UNIVERSITY OF CALIFORNIA,
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Neurological and Behavioral Predictors of Aphasia Recovery

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Psychology

by

E. Susan Duncan

Dissertation Committee:
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DEDICATION

Do mo mháthair. Sláinte, táinte agus áthas! Tá grá agam leat.

Airson m' athair. Wha's like us? Tha gaol agam ort.

To the questions:

So what is this mind of ours: what are these atoms with consciousness?
Last week's potatoes!
They now can remember what was going on in my mind a year ago – a mind which has long ago been replaced. To note that the thing I call my individuality is only a pattern or dance, that is what it means when one discovers how long it takes for the atoms of the brain to be replaced by other atoms. The atoms come into my brain, dance a dance, and then go out – there are always new atoms, but always doing the same dance, remembering what the dance was yesterday.

Richard P. Feynman
What Do You Care What Other People Think?

and the answers:

New knowledge is the most valuable commodity on earth.
The more truth we have to work with, the richer we become.

Kurt Vonnegut, Jr.
Breakfast of Champions

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ABSTRACT OF THE DISSERTATION

Neurological and Behavioral Predictors of Aphasia Recovery

By

E. Susan Duncan

Doctor of Philosophy in Cognitive Neuroscience

University of California, Irvine, 2016

Professor Steven L. Small, Chair

This thesis reports behavioral and neurological results of a novel form of aphasia therapy – based on imitation of audiovisual speech – that was motivated by neurophysiological findings in human and non-human primates. The six-week intensive therapy program was completed by nineteen participants with post-stroke aphasia.

Participants demonstrated significant improvement on the practiced repetition task and generalization to other tasks. Measures included subtests of the Western Aphasia Battery-Revised (Aphasia Quotient, Cortical Quotient, Repetition, Naming and Word Finding) and specific characteristics of narrative production (number and percent correct information units).

This research investigated the role of performance variability within individuals during repetition to predict improvement with practice. We found that individuals demonstrating greater variability at baseline made greater improvement following treatment. Additionally, changes in variability over the course of treatment were negatively correlated with changes in performance. The more participants improve, the more consistent (less variable) their performance.

On the narrative task, significant improvement was positively correlated with the number of

therapy sessions that were completed, a result not explained by other traits that are often associated with aphasia recovery, such as lesion size and time since onset. The imitation therapy generalizes to other tasks, and more practice confers greater benefit.

With functional neuroimaging during the resting state, we discovered two inter-related functional predictors of improvement in narrative production. Using a sliding window approach, we investigated the dynamic nature of resting state networks (RSNs) as they change over the course of therapy. An increase in the amount of time spent in one of the states – a state characterized by minimal correlation among the identified RSNs – predicted improvement on the narrative task. We interpreted this finding as evidence for adaptive segregation among the RSNs.

Using a graph theoretical approach, we found a second functional predictor. By grouping the RSNs into communities, we examined network changes representative of segregation in the brain, and found increased RSN modularity to be positively correlated with behavioral improvement.

These findings of previously unexplored behavioral and neurological changes and predictors associated with post-therapy recovery are consistent with an emerging approach to personalized (precision) aphasia treatment.

Chapter 1: Introduction

1.1 Aphasia

Aphasia is a multimodal disorder resulting from injury to parts of the brain – particularly in the left hemisphere – that contribute to our human capacity for language. Such damage is most commonly caused by stroke affecting the distribution of the left middle cerebral artery yet can have other etiologies such as tumor or trauma, and in rare cases, right hemisphere injury (e.g., (Lee et al., 2016)). Although the presence of aphasia is not indicative of a generalized intellectual impairment, it is associated with deficits in other cognitive domains, such as working memory (Kasselimis et al., 2013) and problem solving (Baldo, Paulraj, Curran, & Dronkers, 2015).

Approximately one third of individuals with acute ischemic stroke (Engelter et al., 2006) and one fifth of those in chronic stages (Wittenauer & Smith, 2012) are afflicted. One million Americans currently have aphasia (NIDCD, 2010), and this number is increasing as life expectancy extends and new medical interventions offer greater probability of survival following neurological injury (Code, 2010). People with aphasia are less likely to return to work than other stroke survivors (Tanaka, Toyonaga, & Hashimoto, 2014), contributing significantly to the 33 billion dollars of direct and indirect expenses that stroke costs the American public annually (Mozaffarian et al., 2016).

There is much variability in aphasia recovery and limited ability to predict duration or severity from acute to chronic stages. Severity during the first three days following stroke has been reported to predict performance three months later (Lazar et al., 2010), although individuals with initially severe deficits are more heterogeneous in their recovery (Lazar, Speizer, Festa, Krakauer, & Marshall, 2008). Improvement is greatest in the first three months (Laska,

Hellblom, Murray, Kahan, & Von Arbin, 2001) and plateaus approximately one year following onset (Basso, 1992), although patients can demonstrate measurable gains with intervention even a decade post onset with speech-language therapy (Duncan, Schmah, & Small, 2016; Szaflarski et al., 2008). Aphasia is, today, still incurable, and therapy typically provides only modest benefit (Brady, Kelly, Godwin, & Enderby, 2012). Yet the field of aphasia intervention remains relatively young; it has only been for the past century that aphasia has been seen as a treatable condition with established pathophysiology, despite several millennia of documented cases.

1.2 History of Aphasia

1.2.1 Ancient Egypt

The earliest record of the written word "brain", and the earliest descriptions of aphasia, can be found in the Edwin Smith surgical papyrus (see Figure 1.1), dating from 1700 BCE (Minagar, Ragheb, & Kelley, 2003). This ancient medical text describes a patient who is frustrated by the inability to speak following traumatic head injury. This disorder is described as untreatable.

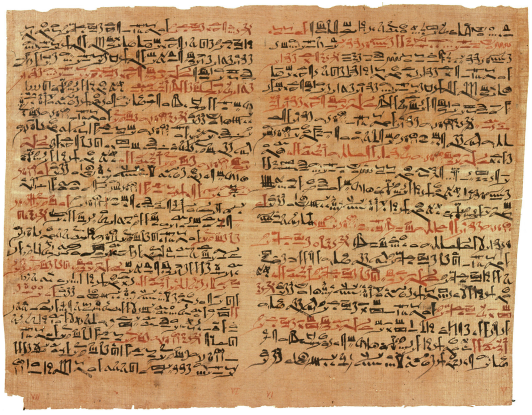

Figure 1.1 The Edwin Smith Papyrus. Document containing the oldest known references to aphasia. Image in public domain.

1.2.2 Ancient Greece

"Speechlessness" was first connected to brain injury in the Hippocratic Corpus of the late fifth/early fourth century BCE (Prins & Bastiaanse, 2006), although the contemporary Aristotle believed the brain to simply be a cooling unit for the passions of the heart, which in turn was thought to be the source of the nerves (Finger, 2000). Around 200 CE, the Greek physician Galen better developed this understanding through vivisection. Galen found that severing the laryngeal nerves and compressing the exposed brains of live animals caused their cries and squeals to cease, leading him to believe that the soul, housed in the ventricles, traveled through hollow nerves to move the body (Prins & Bastiaanse, 2006).

1.2.3 Europe: Middle Ages and Early Modern Period

While there are many descriptions of aphasic symptoms between the fifth and nineteenth centuries, there are a few of particular note in demonstrating the emergence of a more accurate biological understanding of the disorder.

The first of these is the Renaissance description of Italian physician and professor Antonio Guainerio. He described two patients with aphasia. In keeping with the tradition of Galen, he attributed their deficits to a phlegmatic blockage of the posterior ventricle, thereby disrupting memory (Benton, 1964). Biological inaccuracy notwithstanding, Guainerio's fifteenth century diagnosis may be the earliest known localization of a language deficit within the brain.

German physician Johann Schenck von Grafenberg was the first figure to record a clear distinction between motor speech, as lingual paralysis, and language, conceptualized as a function of memory (Luzzatti & Whitaker, 1996). Despite this, treatment of the tongue for the purposes of curing aphasia was widely practiced until the middle of the nineteenth century (Prins

& Bastiaanse, 2006). While by no means the only example, Schenck's sixteenth century work is also notable for a shift from a ventricular to a brain tissue basis for language (Eling & Whitaker, 2009).

In 1770, another German physician, Johann Gesner, wrote a landmark work entitled Die Sprachamnesie (language amnesia), which provided extensive behavioral descriptions of aphasia as well as attempts to elucidate pathogenic contributions (Prins & Bastiaanse, 2006). He described and connected impairments of speech with impairments of writing, addressing the existence of a shared language system underlying both skills (Luzzatti, 2002). Gesner's work may be viewed as a landmark in aphasiology, and one that paved the way for the better-known, and more biologically grounded, work of the following century.

1.2.4 Europe: Nineteenth Century

1.2.4.1 Phrenology

The true origins of the neurobiology of aphasia may be found in the work of nineteenth century European physicians. One of the earliest of these was Viennese neuroanatomist Franz Joseph Gall around the turn of the century. Gall interpreted bumps and depressions on the surface of the skull as indications of the development of the underlying neural tissue, and thus as evidence of the presence of personality traits attributable to the underlying brain region (Gall, 1825). While Gall's phrenological methods have been rightly discredited as pseudoscience, he deserves credit for introducing the idea that various regions of the brain provide unique contributions to different forms of information processing. Phrenology served as a precursor to the cerebral localization of mental processes, including language, then thought to be situated behind the eye (see Figure 1.2).

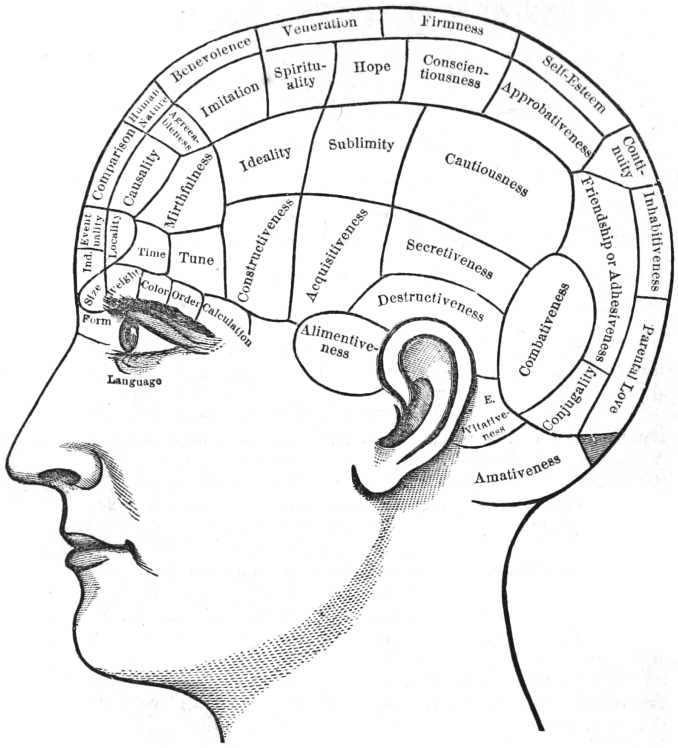

Figure 1.2 Phrenological Chart. Published in Fowler & Fowler (1859); image in public domain.

1.2.4.2 Lesion Studies

It should be acknowledged that French neurologist Marc Dax made the discovery of left hemisphere dominance for language in the early nineteenth century, although this was not published until 1863 (Cubelli & Montagna, 1994). Thus, the next significant development was Pierre-Paul Broca's presentation of a case study of a patient with nonfluent aphasia before the Anthropological Society of Paris in 1861, in which he reported a lesion primarily occupying the posterior portion of the third convolution of the left frontal lobe (Broca, 1861; see Figure 1.3), citing the error of the phrenologists and declaring this area (now named Broca's area) to be the seat of spoken language.

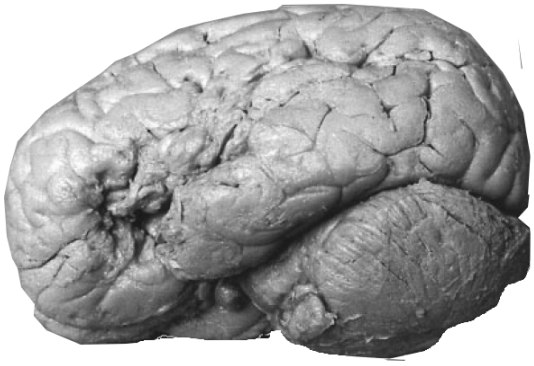

Figure 1.3 Brain of Louis Victor Leborgne, Broca's Original Patient. Reproduced from Dronkers, Plaisant, Iba-Zizen, & Cabanis (2007) with permission from Oxford University Press.

The German anatomist and neuropathologist Theodor Meynert expanded on Broca's findings through autopsies documenting that aphasia could be associated with damage to other left hemisphere brain regions in the vicinity of the Sylvian fissure, including a region now named for his student, Carl Wernicke. Wernicke, in turn, expanded on this by conceptualizing the perisylvian cortex and insula as a "speech center" and developing a model of regions critical to language with connecting association pathways (Wernicke, 1874), pioneering the first of the connectionist theories of language (see Figure 1.4).

Figure 1.4 Carl Wernicke's Language Network. Primary auditory cortex is represented by a, Broca's area by b. These regions are shown as connected to each other and to cranial nerve nuclei in the brainstem. One of several language networks drawn in Wernicke (1874). Image in public domain.

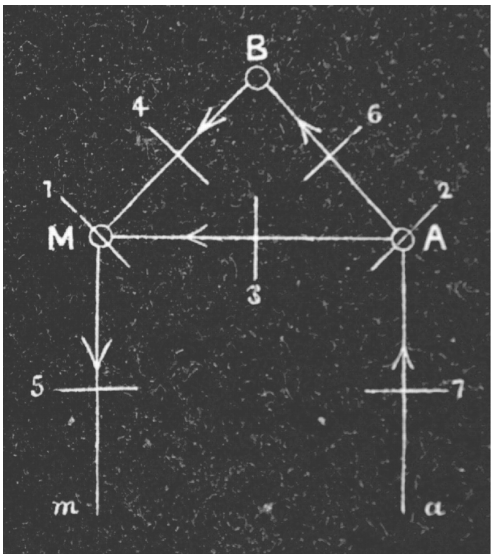

Figure 1.5 Lichtheim's "House" Model. Language system conceptualized through the following regions/functions: B= concept center (broadly distributed); M= motor image center (Broca's area); m= motor output (speech motor cortices); A= auditory image center (Wernicke's area); a= acoustic-sensory input (primary auditory cortices). Lesions at numbered sites are conceptualized as: 1= Broca's aphasia; 2= Wernicke's aphasia; 3= conduction aphasia; 4= transcortical motor aphasia; 5= apraxia/ dysarthria; 6= transcortical sensory aphasia; 7= pure word deafness. Figure from Lichtheim (1885). Image in public domain.

Further evolution of this idea was demonstrated by Ludwig Lichtheim's "house" model (1885), which elaborated the role of cortical connections and identified "disconnection" syndromes (See Figure 1.5) and Joseph Jules and Augusta Déjerine's identification of the role of white matter connections in his writing on pure alexia without agraphia (Déjerine & Déjerine-Klumpke, 1895). Pioneering French neurologist Jean Martin Charcot developed his own anatomical scheme for localizing various aphasia symptoms (Bernard, 1889; see Figure 1.6). Sigmund Freud objected to these conceptualizations of language as a property arising from isolated centers and their interspersed connections, positing that aphasia does not result in the absolute deficits such models predict and that the entire perisylvian cortex provides crucial, if heterogeneous, contributions to language (Freud, 1891), although this work was largely ignored.

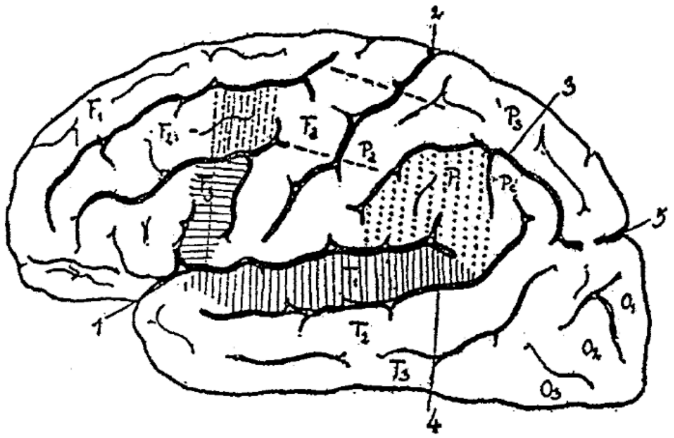

Figure 1.6 Localization of Aphasia Symptoms According to Charcot. Labeled sulci: 1= Sylvian fissure; 2= central sulcus; 3= intraparietal sulcus; 4= superior temporal sulcus; 5= parietoccipital sulcus. Labeled gyri: F1/2/3 = superior/middle/inferior frontal gyrus; Fa= precentral gyrus; T1/2/3= superior/middle/inferior temporal gyrus; Ps/i= superior/inferior parietal lobule; Pa= postcentral gyrus; Pc= angular gyrus. Shaded areas corresponding to deficits: F2=agraphia; F3= Broca's aphasia; T1= pure word deafness/Wernicke's aphasia; Pi= alexia. Figure from Bernard (1889). Image in public domain.

1.2.5 Twentieth Century

French neurologist Pierre Marie began the twentieth century with the declaration that "the third left frontal convolution plays no special role in language", citing cases of damage to this region without associated aphasia as well as cases of Broca's aphasia in which this region was spared (Tesak & Code, 2008). Still, in the mid-twentieth century, the Wernicke-Lichtheim model was resurrected by Norman Geschwind (Geschwind, 1970), and it remains perhaps the predominant model in aphasia theory today. The behavioral classifications (see Table 1.1) associated with the model can be identified using clinical tools such as the Boston Diagnostic Aphasia Examination (BDAE; Goodglass & Kaplan, 1983) and the Western Aphasia Battery (WAB; Kertesz, 1982). While the correlation is imperfect, the various classifications are often associated with different lesion patterns (Willmes & Poeck, 1993).

	Fluency	Content	Comprehension	Repetition	Naming
Broca's	Poor	Good	Fair-Good	Poor-Fair	Fair-Good
Wernicke's	Good	Poor-Fair	Poor-Fair	Poor-Fair	Poor-Fair
Conduction	Good	Good	Good	Poor-Fair	Fair
Global	Poor	Poor	Poor	Poor	Poor
Trans. Motor	Poor	Good	Fair-Good	Good	Fair-Good
Trans. Sensory	Good	Poor-Fair	Poor-Fair	Good	Poor-Fair
Mixed Trans.	Poor	Poor	Poor	Fair-Good	Poor
Anomic	Good	Good	Good	Good	Fair

Table 1.1 Typical Aphasia Taxonomy. Classifications based on Goodglass & Kaplan (1983), Hillis (2007), and Kertesz (1982). Trans= Transcortical.

The importance of the lesion studies of the nineteenth century and the neuropsychological classifications of the twentieth century to the study of aphasia cannot be overstated. Yet, the types of questions we ask will always inform the types of answers we find. Lesion studies will invariably present us with localizationalist answers, as lesions are inherently localized. Similarly, neuropsychological classifications impose categories on behavioral continua.

In the latter part of the twentieth century, functional neuroimaging revolutionized our thinking about language and aphasia. Positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG) demonstrated activation during language tasks that was both bilateral and present in cortical and subcortical regions not traditionally associated with language, underscoring the complexity of even the most basic tasks (Hillis, 2007). Further, intraoperative cortical stimulation mapping (Ojemann, Ojemann, Lettich, & Berger, 1989) and noninvasive transcranial magnetic stimulation (Epstein, 1998) allowed the introduction of "virtual lesions" and the investigation of anatomical hypotheses not previously testable in humans. These relatively new methods have significantly informed our understanding of aphasia and the neural organization of language.

1.3 Present Day

Ongoing advances in neuroimaging techniques and statistical methods are changing the kinds of questions we can answer, and perhaps more importantly, ask, about aphasia. Early neuroimaging studies demonstrated a tendency to pinpoint circumscribed regions of activation correlated with language and other higher-order functions by using high activation thresholds, such that a single region might remain (e.g., Small et al., 1996). Many early studies that did not force such localized activation through statistical means nevertheless described their results in focal terms (e.g., Binder et al., 1994). Currently, these perspectives are evolving.

Beyond localizationalism lies an appreciation of the brain as the product of overlapping and interconnected circuits. As our analytical methods advance in tandem with our theoretical conceptualization, our investigations become more complex, reflective of the characteristics of the subject matter. Thus, the study of the brain basis of aphasia can now transition from strictly region of interest (ROI) analyses to the realm of connectivity. We can assess structural connectivity by examining white matter pathways through use of diffusion tensor imaging (DTI) on an individual basis and through atlases derived from multi-subject DTI. In functional connectivity, the brain is typically understood through correlations between the time courses of anatomically separate regions, similarities of which are believed to reflect functional integration. The resulting connectivity measures commonly reflect average statistical dependencies collapsed across time, while more advanced analyses yield dynamic measures that express how functional connectivity varies as a function of time. Additionally, graph theoretical analysis of neural networks, whether functional or structural, allows insights into organizational principles that govern the flow of information by modeling pairwise relationships among brain regions (Bullmore & Sporns, 2009). Such quantitative methods, with their focus on interconnections

rather than isolated regions, currently represent our strongest tools for investigations into the neurobiology of language and aphasia.

1.4 Rationale for this Thesis

With consideration of the changing nature of our understanding of aphasia and our methods for investigating the brain, this dissertation identifies neurological and behavioral predictors and correlates of an individual's ability to benefit from aphasia therapy. The finding that all aphasia therapies offer essentially equivalent benefit (Brady et al., 2012) may be due, in part, to the lack of individualized criteria for selecting a particular type of therapy or the failure to track progress on a biological, as well as behavioral, basis. Thus, treatment studies that apply the same therapy to a sample of stroke patients and offer a single effect size as summary may be attenuating findings by averaging results across a diverse group. Consistent with contemporary notions of precision (personalized) medicine, it is likely that we will make significant strides in the ability to benefit those with aphasia when we have explanatory power for the considerable heterogeneity in individual recovery and response to treatment.

It is increasingly recognized that, as a biological disorder, attention must be paid to the role of biology in aphasia treatment (Small & Llano, 2009), with a potential for the most significant gains when we are able to regrow brain tissue. At that point, the purpose of therapy will be to re-establish adaptive circuits incorporating new tissue into the existing system. Until this time, however, we continue to expand our mechanistic understanding of aphasia recovery for the purpose of enhancing current benefit, as well as laying the groundwork for future intervention.

The imitation-based aphasia treatment work described in this thesis is based on a biological rationale described in Chapter 2. The therapy itself, and the methods with which it has been

investigated, are described in Chapter 3. Chapter 4 describes a behavioral analysis focused on the role of intra-individual variability in improvement on a practiced task. Chapter 5 discusses the generalization of benefit associated with the therapy to a narrative production task. Chapter 6 focuses on a data-driven investigation into the dynamic functional connectivity of resting state networks as it relates to behavioral gains post-therapy, and Chapter 7 describes a hypothesis-driven validation of the findings described in Chapter 6 through the use of graph theoretic methods. Chapter 8 concludes the dissertation with a summary of findings and a brief exploration of future directions motivated by the present work.

Chapter 2: Imitation-Based Aphasia Therapy

2.1 Repetition and Imitation in Aphasia

In 1683, the German physician Peter Rommel was the first to write about repetition deficits in a patient with nonfluent aphasia (Benton & Joynt, 1963). Imitation has since been a key diagnostic and treatment tool for such acquired language disorders. All popular standardized instruments for the assessment of aphasia, such as the Western Aphasia Battery-Revised (WAB; Kertesz, 2006), Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983), and Aachen Aphasia Test (Huber, Poeck, & Willmes, 1984) include repetition ability in their classification scheme.

Imitation was fundamental to the nascent field of aphasia therapy at the turn of the 20th century, and it remains so today (Duffy, 1995). This chapter describes the neurobiological rationales for, and current implementations of, imitation in aphasia therapy. "Imitation" and "repetition" are used interchangeably, and modes of stimulus presentation are clarified as needed. Additionally, it should be noted that acquired apraxia of speech, a motor planning deficit frequently accompanying nonfluent aphasia (Duffy, 1995), is not specifically addressed in this chapter.

2.2 Neurobiological Approaches to Language and Aphasia

The earliest approaches were based on behavioral and educational principles, and this philosophy dominates aphasia therapy today (Small, 2004). Although aphasia is a neurological impairment resulting from brain damage, typically stroke (Ellis, Dismuke, & Edwards, 2010), treatment programs are rarely biologically motivated. Since the end of the 20th century, studies

in aphasia have been relying less on applied psychology and linguistic models, instead seeking to link observed deficits to impairments in the underlying neural systems (Blumstein, 1997). Rehabilitation of the behavioral deficits of aphasia must target the plasticity and repair of affected biological systems. Two main biological models characterizing these systems are considered here, the human mirror system and the dual-stream hypothesis for speech.

2.3 Mirror Neuron System

2.3.1 Macaque

Mirror neurons were discovered serendipitously during single-cell recordings of hand motor representations in the macaque. Rizzolatti and colleagues found neurons firing in premotor cortex (area F5) in a monkey during observation of the experimenter (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992), although the monkey itself was motionless (see Figure 2.1). Further investigation found that individual neurons were active during observation and execution for specific hand or mouth movements (Ferrari, Gallese, Rizzolatti, & Fogassi, 2003; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996). Additional mirror neurons possessing such visuomotor properties were subsequently identified in the inferior parietal region of the macaque (Fogassi, Gallese, Fadiga, & Rizzolatti, 1998), primarily in subcomponents PF and PFG (Rozzi, Ferrari, Bonini, Rizzolatti, & Fogassi, 2008), which have strong anatomical projections to the ventral premotor cortex (F5). These findings led to the suggestion of a functional "mirror" network (Rozzi et al., 2006).

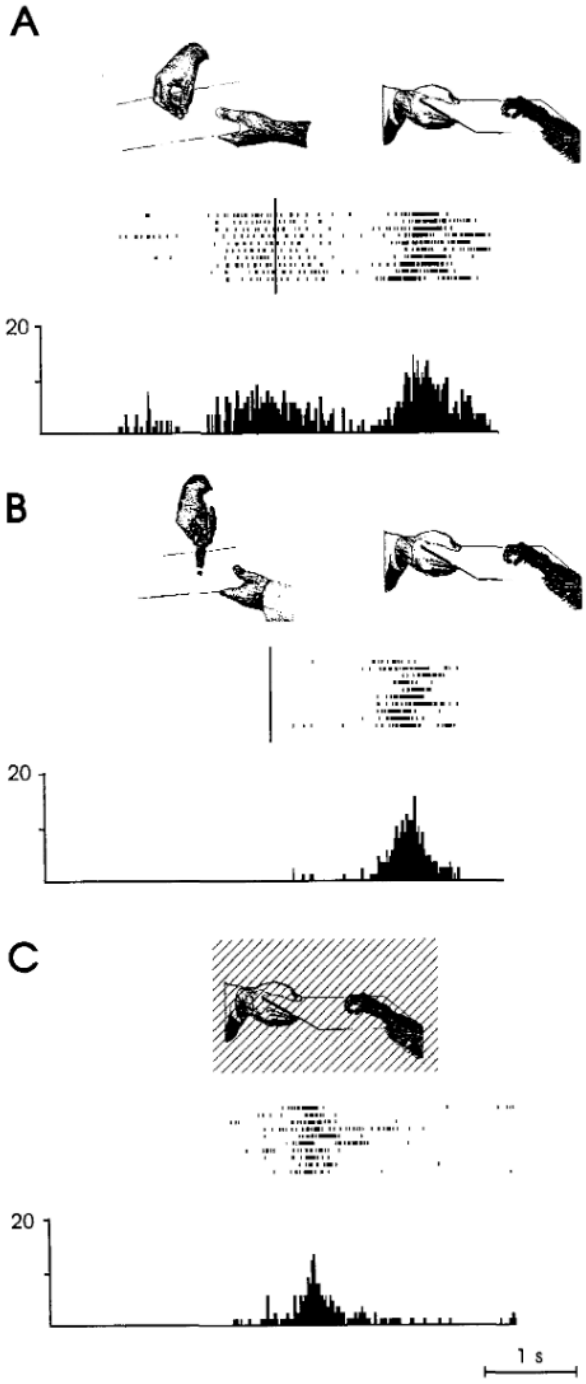

Figure 2.1 Visual and Motor Responses of a Mirror Neuron. Behavioral situations are depicted in upper panels, raster plots representing neural discharge in middle panels, and histograms of relative response in lower panels. A, neuron discharging for monkey's observation and execution of grasping of food. B, neuron does not discharge when observing grasping food using tool. C, neuron discharges for monkey grasping food in darkness. Reproduced from Gallese et al., (1996) with permission from Elsevier.

The existence of mirror neurons immediately prompted hypotheses about their role in action recognition (Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). Further support for this has been provided by the discovery that some mirror neurons in macaque F5 have auditory as well as visual and motor properties (Kohler et al., 2002), firing in response to observation and execution of actions, as well as for sounds associated with those actions. This multimodal integration at the level of a single cell may form the basis for action understanding and motor learning (Jeannerod, 1994).

2.3.2 Human

Ethical considerations prohibit systematic human studies investigating individual mirror neurons. However, support for the existence of a human parieto-frontal mirror neuron system is converging from behavioral, neurophysiological, and brain imaging studies (Small, Buccino, & Solodkin, 2012). The "direct matching hypothesis" postulates that imitation is subserved by simple neural mechanisms mapping observed actions onto internal motor representations of the same action by neurons with mirror properties, populations of which are more strongly activated for actions elicited by preceding observations of the same action (Iacoboni et al., 1999).

2.3.2.1 Behavioral

Behavioral studies demonstrate motor facilitation when action execution immediately follows observation, supporting the existence of a mirror system in humans. Finger movements are faster if the stimulus cue is a modeled finger movement compared to an unrelated symbol (Brass, Bekkering, Wohlschlager, & Prinz, 2000). Response speed further increases as the modeled movement more closely resembles the target, even when the stimulus image is flipped

upside-down (Brass, Bekkering, & Prinz, 2001). Grasping response speed increases when subjects are shown a picture of a hand with optimal orientation for their own final hand position (Craighero, Bello, Fadiga, & Rizzolatti, 2002). On language tasks, response times for plausibility judgments are faster when the action response required is similar to the action described in the stimulus sentence (Glenberg & Kaschak, 2002). These behavioral findings suggest that action perception influences the functioning of one's own motor system.

2.3.2.2 Neurophysiology

2.3.2.2.1 Electroencephalography

Studies using electroencephalography (EEG) demonstrate a central mu rhythm in the alpha frequency range (8–13 Hz) that is present when a subject is at rest. This rhythm, detected in electrodes overlying sensorimotor cortices, is suppressed during action observation as well as motor activity, as was first described in 1954 (Cohen-Séat, Gastaut, Faure, & Heuyer, 1954). These findings have since been replicated for observation, imitation, and execution of actions with EEG (Altschuler et al., 2000; Cochin, Barthelemy, Roux, & Martineau, 1999). Responses measured via implanted subdural electrodes also show a reduction in absolute power in the alpha band over primary motor cortex and Broca's area during both observation and execution of finger movements (Tremblay et al., 2004).

Suppression of this mu rhythm is stronger for object grasping than for movements that are not goal-oriented in adults (Muthukumaraswamy & Johnson, 2004) and in children (Lepage & Theoret, 2007). A precursor to the mu rhythm, that is similarly reduced during both observed and executed grasping movements, is also found in infants, albeit in a lower frequency range (6–9 Hz; Marshall, Young, & Meltzoff, 2011). It has been proposed that such early-developing mirror

neurons may underlie childhood imitation, language acquisition, and the development of other social and cognitive functions (Williams, Whiten, Suddendorf, & Perrett, 2001).

2.3.2.2.2 Magnetoencephalography

Magnetoencephalography (MEG) permits neurophysiological monitoring of a band of activity (15–25 Hz) that is present in the precentral motor cortex during rest. This activity is suppressed during movement and can also be suppressed by stimulating the median nerve of the upper extremity, which allows the study of its rebound in varying contexts. This rebound is extinguished when stimulation is followed by object manipulation and is also significantly reduced when stimulation is followed by passive observation of the same task (Hari et al., 1998). The rebound is not affected by viewing other moving stimuli, linking action observation to the motor system.

2.3.2.2.3 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) manipulates cortical responses by either inducing or inhibiting action potentials in populations of neurons. Excitatory TMS applied over the contralateral cortical region that optimally induces contractions of hand or arm muscles produces measurable motor-evoked potentials (MEPs; Kamen, 2004), which provide an objective measure of motor excitability. TMS-induced MEPs increase when observing grasping actions and arm movements that use the same muscles that are being measured (Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995), as demonstrated in Figure 2.2. These results have been replicated using observation of handwriting and arm movements compared to rest (Strafella & Paus, 2000).

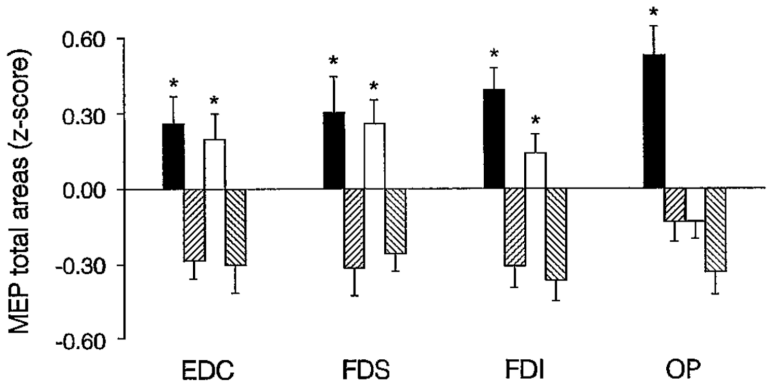

Figure 2.2 Motor Evoked Potentials (MEPs) During Action Observation. MEPs induced by transcranial magnetic stimulation (TMS) were recorded from four hand muscles under four different conditions. From left to right, the four muscles are: EDC= extensor digitorum communis; FDS= flexor digitorum superficialis; FDI= first dorsal interosseous; OP= opponens pollicis. Within each muscle, from left to right, the four conditions are: grasping observation, object observation, arm movement observation, and detection of dimming of a visual stimuli. Reproduced from Fadiga et al. (1995) courtesy of the American Physiological Society.

2.3.2.2.4 Single-cell Recording

These neurophysiological findings suggest the influence of mirror properties on the human motor system extends to primary motor areas, in addition to the postulated premotor homologues of the frontal regions where macaque mirror neurons have been identified. Greater extension still has been proposed. In single-cell recordings from subjects with medically intractable epilepsy, a significant number of neurons in the supplementary motor area (SMA) and the medial temporal lobe (MTL) respond to the observation and execution of a single action (Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010). These regions, with clinical rather than theoretical determination of electrode placement, have not previously shown mirror properties in animal experimentation. Additionally, some neurons change their baseline firing rates but in a manner paradoxical to macaque studies; they respond with increased excitation for execution and suppressed firing rate for observation. The authors propose that these findings may provide

evidence of multiple mirroring systems in the brain, with reduced activity of some neurons during observation playing a role in suppressing socially inappropriate imitation.

2.3.2.3 Brain Imaging

Brain imaging studies permit greater spatial localization of mirror properties in humans. Early evidence for these properties comes from a positron emission tomography (PET) study contrasting object observation with action observation (Rizzolatti, Fadiga, Matelli, et al., 1996), which demonstrates activation in response to observation of grasping movements in Broca's area and left hemisphere temporal regions (middle temporal gyrus, superior temporal sulcus). Mirror properties have since been demonstrated via functional magnetic resonance imaging (fMRI) in two regions of the human brain active during both passive observation and imitation of finger movements, the left frontal operculum of Broca's area and the right anterior parietal region (Iacoboni et al., 1999).

Broca's area, the putative frontal oral-motor and speech area in localizationist language models, plays a role in hand motor representation (Binkofski et al., 1999) and is typically identified as the human homologue of macaque F5 in which mirror neurons have been recorded (Rizzolatti, Fadiga, Gallese, et al., 1996). However, the consistent finding of activation in response to observation of hand and arm actions (Decety et al., 1997; Grafton, Arbib, Fadiga, & Rizzolatti, 1996) in Broca's region, in combination with its long history in the neuroscience of language, has raised the question of whether this increased neural response is perhaps an epiphenomenal artifact of internal speech during these tasks.

To resolve this issue, fMRI tasks have explored brain activation patterns when actions are performed by various body parts. Investigation of response to observation of actions performed

by the hand, foot, or mouth reveals a somatotopic organization of premotor cortex similar to that found in the primary sensory and motor cortices, with ventral mouth movements and dorsal foot movements (Buccino et al., 2001). Similar organization is found in the posterior parietal lobe for object-related actions (see Figure 2.3). These findings ground single neuron measures from macaque in a broader network of motor circuitry underlying both action observation and execution in humans.

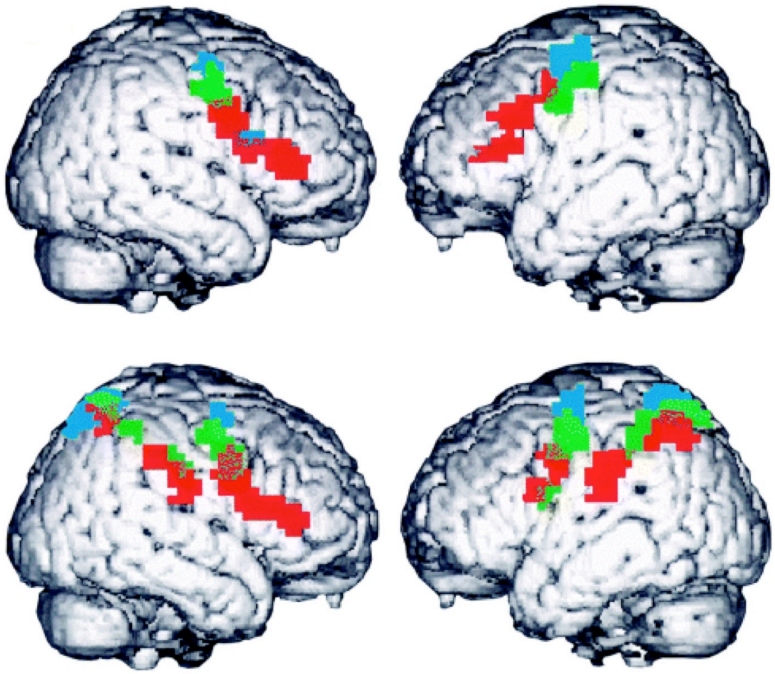

Figure 2.3 Somatotopic FMRI Activation During Action Observation. Above, observation of non-object-related actions. Below, observation of object-related actions. Color scheme is as follows: red= activation foci during observation of mouth movements; green= activation foci during observation of hand movements; blue= activation foci during observation of foot movements. Somatotopically organized activation is present in premotor and parietal cortices. Figure reproduced from Buccino et al. (2001) with permission from John Wiley and Sons.

Macaque studies find that mirror neurons fire for observation of grasping only in the presence of a graspable object, even if it is not visible (Umilta et al., 2001). It has therefore been

suggested that this system is not simply encoding movements, but goal-oriented motor acts (Gallese et al., 1996). In support of this, left frontal and temporal regions are activated for meaningful, but not meaningless, actions in human PET scans (Decety et al., 1997). Similarly, actions embedded in contexts show increased fMRI activation in the posterior inferior frontal gyrus (IFG) and ventral premotor cortex (PMv) compared to viewing either the action or the context alone (Iacoboni et al., 2005). This is especially pertinent to the discussion of language, a goal-directed behavior in which we use our motor systems to transmit meaningful messages, with mirror neurons bridging the gap between "doing" and "communicating" (Rizzolatti & Arbib, 1998).

2.4 Mirror Neuron System and Language

Language, as a uniquely human property, lacks an ideal animal model, and biological theories of language cannot be directly tested. However, indirect evidence supports a role for the mirror neuron system in human language ability, both phylogenetically through evolutionary selection processes (Rizzolatti & Arbib, 1998) and ontogenetically in facilitating child language acquisition (Kuhl & Rivera-Gaxiola, 2008). It is suggested that mirror deficits may underlie developmental disorders of language and social interaction, notably autism (Williams et al., 2001), although such issues are controversial and beyond the scope of this text.

2.4.1 Perception and Production of Articulated Speech

The observation–execution or direct matching hypothesis suggests that perception of an action, including speech, depends on previous experience with producing that actions or sound (Iacoboni et al., 1999). One model of this is the "inverse-forward model pairs" (IFMPs; Skipper,

Nusbaum, & Small, 2006) . These are mechanistic components of the mirror system, in which speech sounds, whether heard or observed, are transformed into corresponding articulatory gestures (inverse) as well as predictions of motor behaviors to be observed next (forward) with resultant sensory consequences affecting perception (see Figure 2.4). These IFMPs operate in the multisensory contexts in which we experience language, consisting of acoustic signals and also the visual cues of oral, facial, manual, and body gestures, particularly when auditory information is distorted or ambiguous. The inverse modeling in this theory predicts that speech perception should produce measurable responses of the speech motor system similar to how it would be engaged during production of that observed speech.

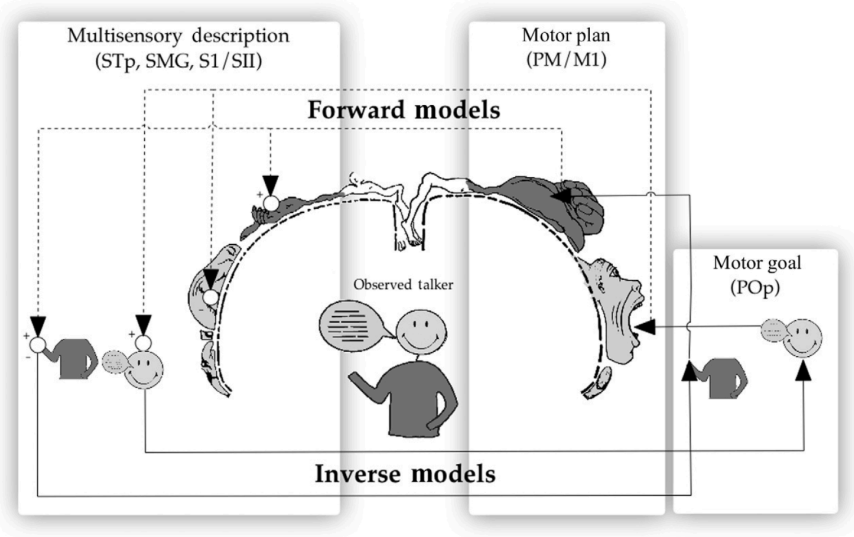

Figure 2.4 Diagram of Inverse-Forward Model Pairs. Observed talker in center. Inverse models (solid lines) are derived from seeing and hearing the talker's facial (light gray) and hand (dark gray) gestures; these models specify the motor goals of the observed movements, facilitated by mirror properties, and can map the talker's behaviors to a plan in the observer's own motor system. Forward models (dashed lines) predict the sensory consequences of implementing those motor plans. Combining these two models into an inverse-forward model pair disambiguates sensory input and improves speech perception. STp= posterior superior temporal areas; SMG= supramarginal gyrus; SI/SII= primary /secondary somatosensory cortices; PM/M1= premotor/primary motor cortices; POp= pars opercularis. Reproduced from Skipper et al. (2006) with permission from Cambridge University Press.

2.4.1.1 Neurophysiology

Listening to the lingual trill /r/ results in significantly increased amplitude in tongue muscle MEPs in neurologically intact participants compared to observation of the nonlingual labiodental phoneme /f /, and also when MEPs are measured from a thumb muscle rather than the tongue (Fadiga, Craighero, Buccino, & Rizzolatti, 2002). This response is more pronounced for real words compared to pseudowords, suggesting that past experience with perception and production influence the motor system. Similarly, increased MEPs in oral muscles, but not finger muscles, are found during either listening to connected speech or viewing silent video of speech-related lip movements (Watkins, Strafella, & Paus, 2003), highlighting multisensory contributions to speech perception. This contrast is not found for nonspeech control conditions, including nonverbal sounds and observation of eye movements. Consistent with widely accepted lateralization theories of speech and language, this follows stimulation of the left, but not the right, hemisphere.

2.4.1.2 Brain Imaging

2.4.1.2.1 Motor Regions Engaged During Speech Perception

Brain imaging studies provide indirect evidence of a relationship between speech observation and execution. Speech motor regions are engaged in response to audiovisual (Skipper, van Wassenhove, Nusbaum, & Small, 2007; Watkins et al., 2003), visual (Nishitani & Hari, 2002), and auditory (Fadiga et al., 2002; Tettamanti et al., 2005) speech perception. Figure 2.5 shows regions active during both syllable production and passive observation of audiovisual, visual, or auditory speech. Bilateral brain activation is present in premotor regions and Broca's area during

silent lip-reading (Buccino et al., 2004), indicating that frontal motor cortices are activated in response to multimodal aspects of language.

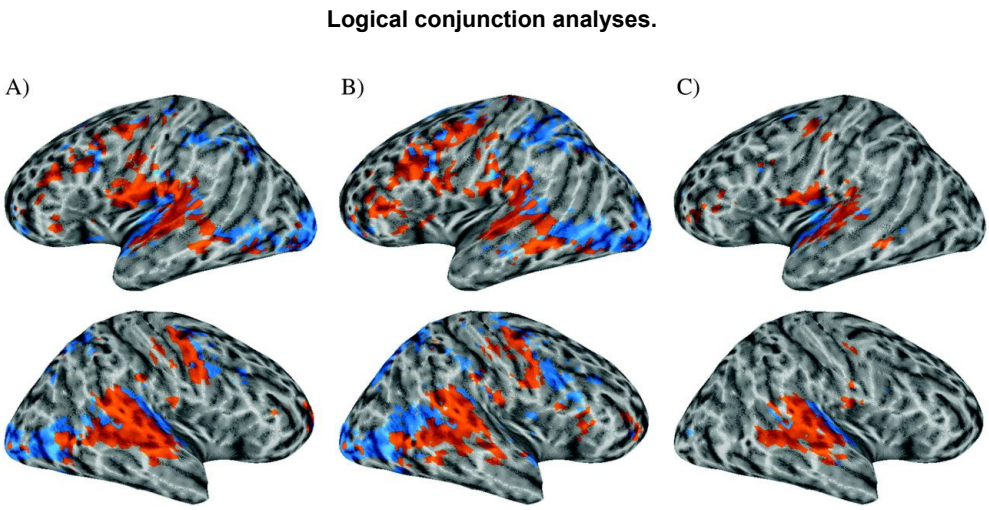

Figure 2.5 Regions of Overlap for Speech Perception and Production. Logical conjunction analyses from fMRI acquired during production and perception of the same syllables. Orange indicates regions of activation overlap between production and perception (thresholded at $p<0.05$). Blue indicates regions active during passive perception but not during production (thresholded at $p<0.05$). Stimuli for speech perception were audiovisual (A), visual only (B), or auditory only (C). Reproduced from Skipper et al. (2007) with permission from Oxford University Press.

Structural equation modeling (SEM) applied to neuroimaging permits the determination of covariances, or weights, among brain regions with known anatomical connectivity (McIntosh & Gonzalez-Lima, 1994). SEM of these effective paths during observation and imitation of audiovisual syllables during fMRI shows common functional connections shared for both these tasks, differing in connection strength but sharing the same essential structure (Mashal, Solodkin, Chen, Dick, & Small, 2012). Like imitation, speech observation engages dorsal and ventral premotor cortices and primary motor cortex.

2.4.1.2.2 Temporal and Auditory Regions Engaged During Speech Production

Regions in posterior auditory cortex are active during speech production, including covert speech, as well as speech perception (Okada & Hickok, 2006; Papathanassiou et al., 2000). Further, posterior lesions of the left temporal cortex, as in Wernicke's aphasia, are associated with errors in verbal expression as well as comprehension deficits (Damasio & Geschwind, 1984). Temporal regions have classically been excluded from the putative mirror neuron system, because there has been no finding of motor activation in the temporal lobe in macaque studies (Keysers & Perrett, 2004). Still, the existence of individual mirror neurons remains poorly defined in humans due to limitations of appropriately noninvasive methods. It is possible that their cortical distribution is more extensive than that in our primate cousins (Mukamel et al., 2010).

2.4.2 Comprehension of Action Language

The human mirror system operates in tandem with low-level sensorimotor aspects of speech, discussed above, and also higher-level language comprehension (Barsalou, 2008). Listening to sentences describing motor activity activates a broad left-lateralized network of frontal, temporal, and parietal regions, as do action observation and execution, which does not occur for sentences that do not encode action (Tettamanti et al., 2005). Listening to or reading action-related language evokes somatotopic motor cortex activation consistent with the described effector performing the action (Aziz-Zadeh, Wilson, Rizzolatti, & Iacoboni, 2006; Hauk, Johnsrude, & Pulvermuller, 2004).

Theories proposing that cognition is grounded in – or superimposed on – basic sensory and motor processes also apply to language. Priming effects are found for objects sharing

affordances, such as a piano and a typewriter, even when the task does not address the object's use (Myung, Blumstein, & Sedivy, 2006). Subjects receiving verbal or visual cues to assume certain hand shapes are faster to respond to the plausibility of action–object pairings congruous with the simulated grasp (Klatzky, Pellegrino, McCloskey, & Doherty, 1989). This difference disappears when a verbal response replaces the motor response, suggesting that the interplay between language processing and the motor system confers the advantage, rather than the semantic relationship.

2.5 Dual Streams for Speech

The dual-stream theory of vision has long been dominant (Mishkin, Ungerleider, & Macko, 1983), with a ventral "what" pathway for object identification and a dorsal "where" or "how" pathway for visuomotor integration (Goodale, 1993). More recently, two stream models have been identified in the study of audition (Rauschecker & Tian, 2000), speech perception (Hickok & Poeppel, 2004), speech production (Hickok & Poeppel, 2007), and sentence comprehension (Friederici, 2009). There is considerable debate among varying theories regarding specific functions, regions, connections, and the role of feedback. Broadly, however, the dorsal stream progresses from temporoparietal regions to frontal premotor areas, whereas the ventral stream progresses through temporal lobes to prefrontal cortex.

The present discussion only superficially describes the putative roles of the two streams to elucidate their role in imitation (see Figure 2.6). The interested reader is referred to the original sources, including those cited here. The streams are typically discussed separately, but it should be understood that this division is an artificial one made for the sake of simplicity rather than accuracy. In actuality, the streams must be integrated for successful functioning, operating

through “cooperative computation” (Fagg & Arbib, 1998). The strongest neurobiological models underpinning language processing in the brain presently comprise the dual-stream model and the mirror neuron system.

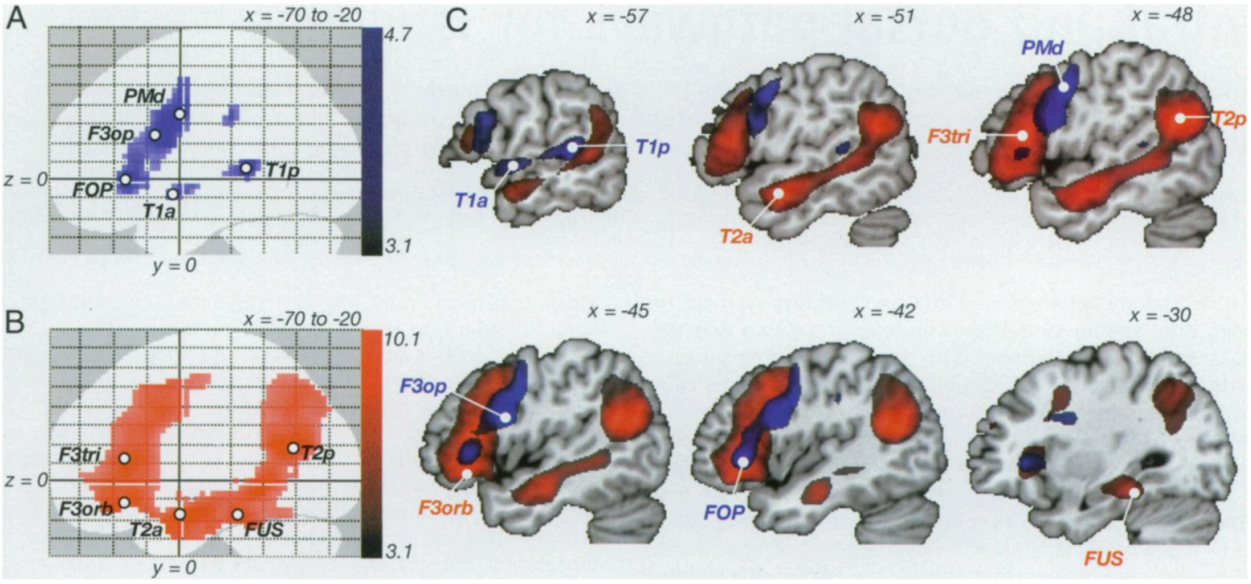

Figure 2.6 Dorsal and Ventral Streams for Language. Functional magnetic resonance imaging (fMRI) results for A, repetition (pseudowords > words); B, comprehension (sentences > pseudosentences); and C, both contrasts (colors as in A,B). FOP= deep frontal operculum; F3op/orb/tri= pars opercularis/orbitalis/triangularis of the inferior frontal gyrus; FUS= fusiform gyrus; T1a/p= anterior posterior superior temporal gyrus; T2a/p= anterior posterior middle temporal gyrus. Figure reproduced from Saur et al. (2008) with permission from The National Academy of Sciences.

2.5.1 The Ventral Stream

The ventral pathway is conceived in terms of semantics, extracting meaning from the communicative signal (Saur et al., 2008). It is considered to be bilateral in some models (Hickok & Poeppel, 2007), whereas others identify ventral auditory language pathways only in the left hemisphere (Parker et al., 2005). In the temporal lobe, it includes anterior portions of the superior temporal gyrus and sulcus, the middle and inferior temporal gyri, and the temporal poles

(Skipper et al., 2006). In the macaque, these areas connect to frontal regions including orbitofrontal cortex and pars orbitalis via the uncinate fasciculus, and pars opercularis and pars triangularis via the extreme capsule (Petrides & Pandya, 2009).

Imitation of familiar and meaningful actions is positively correlated with ventral activity in the inferior temporal cortex (Decety et al., 1997). This is consistent with the object identification, or "what," role of the visual ventral stream, which may share connectivity analogous to that of the auditory ventral stream (Seltzer & Pandya, 1978). In contrast, imitation of novel and meaningless actions do not activate these ventral cortices, instead resulting in activation in dorsal parietal and occipital regions (Rumiati et al., 2005).

Words and sentences, which can be conceived of as meaningful "gestures" or speech "objects," also represent the domain of the ventral stream. Consistent with this, temporal lobe atrophy (predominantly anterior and ventral) is associated with semantic dementia, a variant of frontotemporal dementia characterized by progressive deficits in confrontation naming and single word comprehension, as well as loss of the underlying concepts associated with the language (Mummery et al., 2000), while speech repetition remains intact (Gorno-Tempini et al., 2011). This would suggest at most a minimal role for the ventral stream in imitation, although the stimuli used might differentially engage regions and enhance connectivity in ventral areas depending on semantic meaning and social relevance (Kilner, Marchant, & Frith, 2006), such as personal significance, ecological validity, and familiarity.

2.5.2 The Dorsal Stream and Parietal Cortical Connectivity

In contrast with the semantic role of the ventral stream, and analogous to the "where" or "how" role of the visual dorsal stream, the dorsal stream for speech is proposed as a

sensorimotor network mapping sounds onto motor plans to support production (Hickok & Poeppel, 2007). Repetition, especially of meaningless pseudowords, is the prototypical task of dorsal stream function (Saur et al., 2008), as demonstrated in Figure 2.6.

The dorsal stream projects from primary auditory regions to posterior superior temporal and inferior parietal regions, and then to more posterior regions of the frontal lobe compared with ventral stream projections, including pars opercularis of the IFG and premotor and motor cortices (Skipper et al., 2006). At a gross anatomical level, the dorsal stream supporting speech and language functions shares temporal and parietal regions associated with the dorsal stream for vision. These regions show strong fMRI activation during action observation, especially in the left hemisphere (Decety & Grezes, 1999). Some of these shared dorsal stream regions, specifically pars opercularis and inferior parietal cortex, are considered the human homologues of macaque F5 and PF/PFG in which mirror neurons have been identified (Rizzolatti, Fogassi, & Gallese, 2001; Rozzi et al., 2006). Some dual-stream models consider the dorsal stream for speech to be strongly left-dominant (Hickok & Poeppel, 2007).

In conduction aphasia, the ability to repeat is disproportionately impaired. This is classically attributed to damage of the left arcuate fasciculus (Geschwind, 1965), traditionally thought to serve as the primary dorsal pathway (Anderson et al., 1999), although this role is debated due to recent anatomical work implicating the superior longitudinal fasciculus (Schmahmann & Pandya, 2009). Further, voxelwise lesion symptom mapping with perfusion and diffusion-weighted imaging shows damage involving the left supramarginal gyrus and underlying white matter is most strongly related to repetition deficits in aphasia (Fridriksson et al., 2010). Other investigators have implicated damage to temporoparietal regions in conduction aphasia (Buchsbaum et al., 2011), supporting the critical role of the dorsal stream in repetition and the

potential presence of mirror neurons within this functional network. This also suggests that the arcuate fasciculus may not serve the crucial role once suggested for the interconnection of Broca's and Wernicke's areas.

2.6 Aphasia Therapy: Speech Imitation as Therapeutic Tool

Imitation has a long history in therapy for communication disorders, including aphasia. Reducing language formulation demands and using visual input to complement other sensory modalities typically enhances a patients' ability to produce accurate speech output (Duffy, 1995). Early approaches to aphasia therapy were developed prior to the fundamental work of the twentieth century in learning theory and the unfortunate consequences of World War II, which produced many young veterans with head injuries, and often relied solely on repetition and drilling (Basso, 2003). Later researchers continued to use repetition in aphasia rehabilitation, but within a better-defined theoretical framework. For example, in the Helm Elicited Language Program for Syntax Stimulation (Helm-Estabrooks, 1981) designed to treat agrammatism, increasingly more complex syntactic forms are introduced by imitation at level A before the same forms are elicited in context at level B.

Imitation elicits the most accurate picture naming in patients with severe Broca's aphasia (Love & Webb, 1977), and repetition is often the simplest level of a cueing hierarchy (Linebaugh, Shisler, & Lehner 2005). Although imitation is sometimes promoted as a technique to be used only when no other prompts cue correct responses, its ability to facilitate speech output makes it inherently error reducing. Thus, it is a useful tool and desirable starting point in errorless learning designs, in which every response, regardless of accuracy, is viewed as self-reinforcing, and the therapy environment is structured to produce the greatest possible successes

(Sigurðardóttir & Sighvatsson, 2006). However, the benefit of errorless learning remains debated in aphasia rehabilitation (Fillingham, Sage, & Lambon Ralph, 2005).

Many aphasia therapies used in research do not cite imitation as a rationale for their use or theorized effectiveness, yet they still rely heavily on imitation or choral reading (online imitation) in their implementation. Semantic Feature Analysis (SFA) seeks to improve word retrieval by targeting conceptual connections of individually trained words, using modeling and repetition of the target word and its semantic associations when these are not produced independently (Boyle & Coelho, 1995). Melodic Intonation Therapy (MIT), recommended for patients with nonfluent aphasia and poor repetition, uses melody and rhythm to increase speech output, relying on choral productions of intoned targets before progressing to imitation and more naturalistic contexts (Helm-Estabrooks, Morgan, & Nicholas, 1989). Conversational script training introduces scripts to be learned via online and delayed imitation (Youmans, Holland, Muñoz, & Bourgeois, 2005). Choral reading and imitation are also paired with written stimuli in some therapy programs, such as Oral Reading Treatment (Orjada & Beeson, 2005) and Oral Reading for Language in Aphasia (Cherney, 2004).

2.7 Mirror Neuron System and Rehabilitation

Given evidence for motor system activation during action observation (Buccino et al., 2001), and given identification of neural circuits active during both observation and execution of oral movements (Ferrari et al., 2003), there is a sound biological basis for speech imitation as an aphasia rehabilitation technique. Connections between inferior parietal and ventral premotor regions are active during observation and imitation of syllables, as seen in Figure 2.7, and may represent a human mirror neuron network for speech (Mashal et al., 2012). Although the most

straightforward implication of engaging this system may be for the direct motor act of speech production, the role of this network in speech perception (Mottonen & Watkins, 2012) and comprehension of action language (Tettamanti et al., 2005) could result in a broader impact on more general aspects of language rehabilitation (Small et al., 2012).

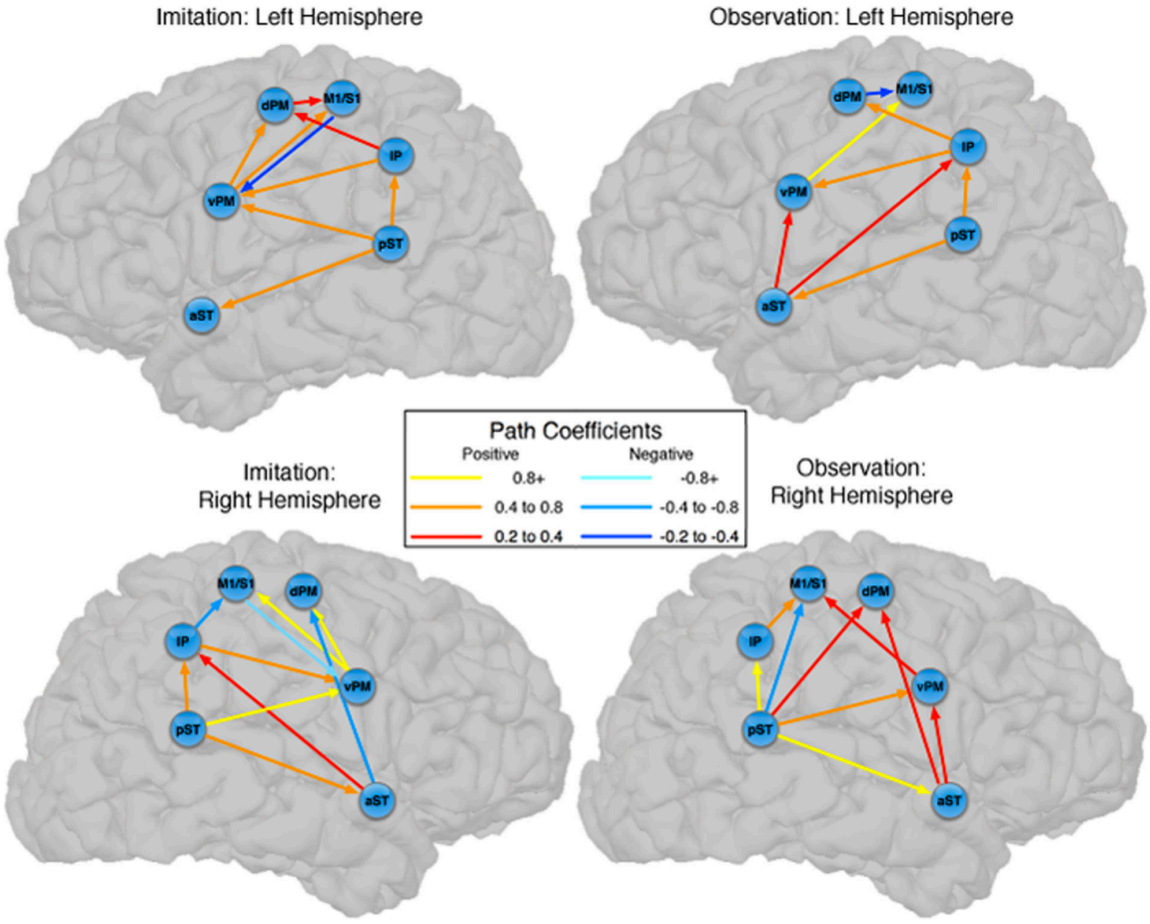

Figure 2.7 Common Network for Speech Observation and Imitation. Weighted connections obtained from SEM of fMRI during observation (right) and imitation (left) of audiovisual syllables. Connections are shown for the left (top) and right (bottom) hemispheres. Both models share connections between pST, aST, IP, vPM, dPM, and M1S1. Abbreviations are as follows: IP, inferior parietal lobule; M1S1, primary motor/somatosensory cortex; pST, posterior superior temporal gyrus and sulcus; aST, anterior superior temporal gyrus and sulcus; vPM, ventral premotor cortex; dPM, dorsal premotor cortex; M1/S1, primary motor/somatosensory cortex. Figure reproduced from Mashal et al. (2012) courtesy of Frontiers.

A similar approach undertaken in hand motor rehabilitation following stroke comprises viewing videos of daily actions followed by therapist-assisted performance of observed actions with the impaired upper extremity (Ertelt et al., 2007). Patients demonstrate significant improvement following therapy compared to baseline performance or controls, with maintenance of at least 8 weeks after intervention. Increased fMRI activation during object manipulation was found in contralateral supramarginal gyrus and bilateral ventral premotor cortices, consistent with human correlates of the macaque mirror neuron system (Small et al., 2012).

2.8 Aphasia Therapy: Speech Imitation as Therapeutic Theory

2.8.1 IMITATE

The following chapters describe the design and results of a therapy study using IMITATE (Intensive Mouth Imitation and Talking for Aphasia Therapeutic Effect), a novel computer-based aphasia therapy program designed to improve communication skills in aphasia by repetition of audiovisual words and phrases, motivated by neurophysiological findings of mirror properties in human and nonhuman primates (Lee, Fowler, Rodney, Cherney, & Small, 2010). The stimuli are presented by video featuring a view of the speaker's head and shoulders. The therapy is intense and uses ecologically valid stimuli presented by a variety of human talkers, and difficulty increases are graded overall yet are variable within a level. Additional information about the therapy and the study design can be found in Chapter 3.

The control therapy, REPEAT, uses similar principles but audio-only stimuli with a still image of the talker. This therapy also varies the stimulus presentation, such that subjects hear a single presentation by a single talker before each cued repetition, in contrast with the IMITATE group, which hears six consecutive talkers present each stimulus before repeating the target word

or phrase several times. Each group hears the same overall number of stimuli and the same number of presentations.

Nineteen subjects completed a 6-week course of therapy (9 h weekly). As there were no significant differences between groups, results for both forms of imitation-based therapy were pooled (Duncan et al., 2016). The lack of significant differences between the two groups may be attributable to the overlap between cortical regions supporting both production and audio-only perception (Skipper et al., 2007), as well as the existence of neurons with auditory-motor as well as visual-motor properties (Kohler et al., 2002). Behavioral and neuroimaging findings are discussed in Chapters 4 through 7.

In a sleep study, high-density EEG recordings were taken for subjects with aphasia on two consecutive nights, before and after participating in a single, highly intensive 3.5-h session of IMITATE (Sarasso et al., 2014). Findings indicate a significant increase in slow wave activity (SWA), associated with synaptic plasticity (Huber, Ghilardi, Massimini, & Tononi, 2004), in regions active during observation–execution of speech in healthy controls (Mashal et al., 2012) in the right (intact) hemisphere. A positive correlation was found between increased SWA over the left ventral premotor cortex and improvement on the Repetition subtest of the WAB. This finding is of interest due to premotor cortex involvement in imitation and the inclusion of this region in the lesion extent of most of the participants.

2.8.2 Speech Entrainment

Citing previously mentioned findings of activation in left frontal speech-motor areas when visual observation accompanies auditory speech, Fridriksson et al. (2009) hypothesized that better performance would be elicited when a computer-based naming treatment for patients with

nonfluent aphasia included audiovisual compared to auditory-only stimuli. Statistically significant gains are made for audiovisual treatment only (see Figure 2.8), including trained and untrained items.

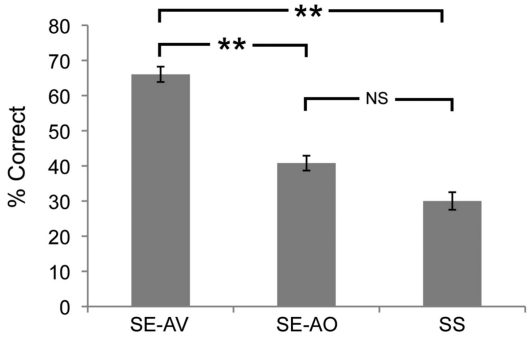

Figure 2.8 Post-therapy Production of Correct, Novel Words. Bar graph showing percent of novel words produced correctly in each of 3 experimental conditions. SE-AV= speech entrainment-audiovisual; SE-AV= speech entrainment-audio only; SS= spontaneous speech. Asterisks indicate $p < .01$; NS= not significant. Figure reproduced from Fridriksson et al. (2012) with permission from Oxford University Press.

Fridriksson et al. (2012) coined the term "speech entrainment" to describe the ability of some subjects with nonfluent aphasia to produce more fluent speech with an audiovisual model compared to spontaneous speech. Subjects perform online imitation of scripts, which are heard while viewing the speaker on an iPod screen. Only the speaker's mouth is visible to emphasize visual perception of the speech act. This therapy results in production of twice as many words during entrainment for patients with Broca's aphasia. Significant increases in word variety are maintained for at least one week following treatment termination for production of practiced scripts during both entrainment and spontaneous speech. Entrainment of untrained scripts remains significantly improved compared to baseline for at least six weeks.

Using fMRI to explore the neural mechanisms underlying these behavioral findings, Fridriksson et al. (2012) find greater activation in left BA 37 and bilateral anterior insula/BA 47

for the speech entrainment condition compared to spontaneous speech. The authors propose that imitation of speech may facilitate word retrieval (BA 37) and visceral speech support (anterior insula/BA 47) for rapid, online lexical processing and/or airflow modification or for lexical prediction and anticipation of respiratory demands. Broca's area may serve as an internal temporal gating device, which, although injured, can be compensated for by the external temporal gating offered by real-time imitation of an observed speaker, entraining the requisite regions to again function as part of a coordinated network.

2.9 Aphasia Therapy: Nonspeech Motor Observation and Imitation

Speech is a motor activity and gestures are a rich aspect of human communication, whether for independent information transmission or to supplement spoken language (Goldin-Meadow, 1999). Verbal communication among humans may have evolved on top of existing gestural communication systems relying on the observation–execution matching system (Rizzolatti & Arbib, 1998). Gesture has thus been targeted as a means of treatment for aphasia.

2.9.1 Visual Action Therapy

Visual Action Therapy is a nonverbal therapeutic intervention for global aphasia, using real and drawn objects in a hierarchy (Helm-Estabrooks, Fitzpatrick, & Barresi, 1982). The patient imitates manipulation of real objects or pantomimed gestures associated with the use of these objects, with the ultimate goal that the patient is able to produce a pantomimed action as a representation of an unseen object. The rationale is that gestures, requiring only unilateral gross motor control compared to the more precise bilateral motor control required for speech, may be used symbolically (Helm-Estabrooks et al., 1982). Although Visual Action Therapy is not a

contemporary subject of research, similar gesture-based therapies continue to be investigated in aphasia rehabilitation.

2.9.2 Action Observation Treatment

Patients with nonfluent aphasia improve in verb retrieval abilities after training with gesture labels paired with either imitation or observation of the target gesture, but not when they observe the gesture while producing a meaningless movement (Marangolo et al., 2010). There is no significant difference between therapy using observation alone and therapy using meaningful imitation, with improvement maintained for 2 months. These findings support the existence of a bilateral distribution of frontoparietal connections that can be engaged by action observation or execution when there is damage to regions associated with the human mirror neuron network in the left hemisphere (Aziz-Zadeh, Koski, Zaidel, Mazziotta, & Iacoboni, 2006). While either action observation or execution engages this network, addition of a meaningless gesture interferes with this process and eliminates the beneficial result of observation and the resultant therapeutic gains in verb retrieval.

However, observation therapy only improves verb production for actions within the human motor repertoire, such as dancing compared to printing (Marangolo, Cipollari, Fiori, Razzano, & Caltagirone, 2012). FMRI findings also demonstrate differences between activation patterns resulting from observation of actions within the realm of human behavior, even when performed by nonhumans (e.g., a dog biting), compared to those that are not (Buccino et al., 2004). These findings further reinforce the role of a mirror neuron network implicated in action observation and execution that subserves language production.

2.10 Conclusion

Although aphasia is a biological disorder resulting from neurological damage, aphasia rehabilitation has traditionally neglected biological approaches to treatment in favor of behavioral and educational models. However, increasing understanding of the neurobiology underlying language is shifting the discourse toward biological mechanisms.

The two main biologically based models for language that have empirical support at this time are the human mirror neuron system and the dual-stream hypothesis. These models support imitation as a powerful tool to rehabilitate the speech and language deficits of aphasia. Action observation engages mirror properties of the same neural networks that are activated during execution, which is as true for speech and oral motor actions as for the grasping behaviors for which they were initially discovered. Higher-level language skills are also grounded in motor systems. Both observation and imitation of speech engage a similar network including components of the dorsal and ventral pathways for language.

Imitation has long been, and continues to be, used in many aphasia interventions. More recently, several researchers have developed neurophysiologically motivated aphasia therapy programs targeting online or delayed imitation as a strategy to improve speech output and language function. Some aphasia therapies have also used nonspeech imitation of actions to enhance gestural communication and production of action labels.

Chapter 3: Participants and Study Design

3.1 Participants

Nineteen native English speakers with aphasia following single, left hemisphere ischemic stroke, confirmed by neurological examination and MRI, were recruited (age range= 31-72; mean= 53.5; SD= 11.7; 4 female (21%)). All had sustained a single stroke 5 to 130 months prior to enrollment (mean= 41.6; SD= 42.9). Select demographic and neurological information can be found in Table 3.1. Lesion overlap can be seen in Figure 3.1.

Subject	Sex	Age	Months Post-Onset	Treatment Group	# of Sessions Completed	Lesion Size (% LH)	Lesion Location	Aphasia Classification
1	F	72	17	I	88	9.64	FIPT	Broca's
2	M	60	5	R	84	9.72	FI	Broca's
4	M	63	7	I	54	7.52	FIPT	Broca's
5	M	56	16	R	90	3.31	FPT	Broca's
6	M	65	8	I	90	6.36	TP	Conduction
9	F	46	28	I	108	17.86	FPT	Broca's
10	F	31	11	I	106	10.62	FIPT	Anomic
11	M	58	13	R	101	19.78	FIPT	Trans. Motor
12	F	55	22	R	108	0.95	BG	Anomic
13	M	36	78	R	108	12.35	FIPT	Broca's
14	M	37	51	R	105	10.06	TIPO	Broca's
15	M	70	120	I	99	26.34	FIPT	Anomic
16	M	58	29	I	108	3.25	FI	Anomic
17	M	57	130	I	107	13.52	FIPT	Anomic
18	M	55	81	R	79	11.54	FIPTO	Wernicke's
19	M	42	124	R	53	5.21	FI	Anomic
20	M	60	7	I	103	11.42	TPO	Trans. Sensory
21	M	43	15	I	108	12.44	FIT	Broca's
22	M	49	29	I	108	11.24	FIPT	Broca's

Table 3.1 Individual Data for Each of the 19 Subjects. The fourth column gives months post stroke onset at time of enrollment. The fifth column gives treatment group (IMITATE or REPEAT). Lesion size is given as the percentage of left hemisphere (LH) voxels included in the lesion mask. Lesion location is abbreviated as follows: F- Frontal, P- Parietal, T-Temporal, I-Insular, O-Occipital, BG- Basal Ganglia. Aphasia classifications are as determined by the Western Aphasia Battery-Revised (WAB) and Transcortical is abbreviated (Trans). Table reproduced from (Duncan et al., 2016) online supplement courtesy of Sage Publications.

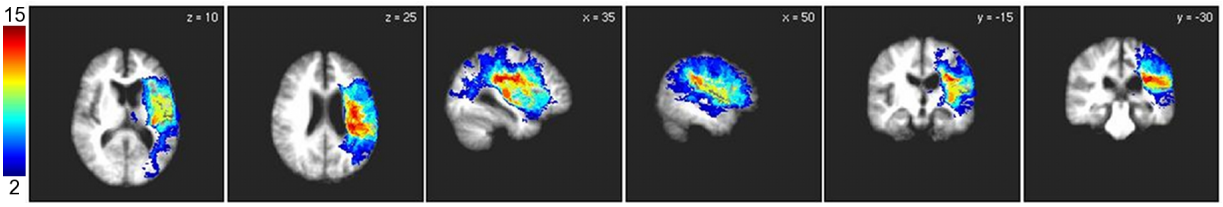

Figure 3.1 Lesion Overlap for All Subjects.

3.2 Experimental Summary

The intensive imitation-based therapy (IMITATE or REPEAT; Lee et al., 2010) was administered 6 days per week for three 30 minute sessions each day. Both therapies required participants to listen to words and phrases presented by six different speakers and to repeat them multiple times. Half of the participants also saw a video of the speaker during the presentation. Because there was no statistical difference in any measure between those subjects who saw the speaker and those who did not, all data have been aggregated for the studies described in Chapters 4 through 7.

Over the six-week therapeutic period (Weeks 1-6 of the overall study), participants undertook the specialized speech therapy on a preprogrammed, dedicated laptop. Participants underwent behavioral assessments (WAB, repetition test, narrative production; described in Section 3.4 below) that were administered twice before and twice after therapy, with all evaluations six weeks apart (Weeks -6, 0, 6, and 12). These measures were administered twice pre-therapy to establish a stable baseline, and twice post-therapy to establish immediate changes and maintenance. Figure 3.2 depicts the timing of these assessments relative to therapy.

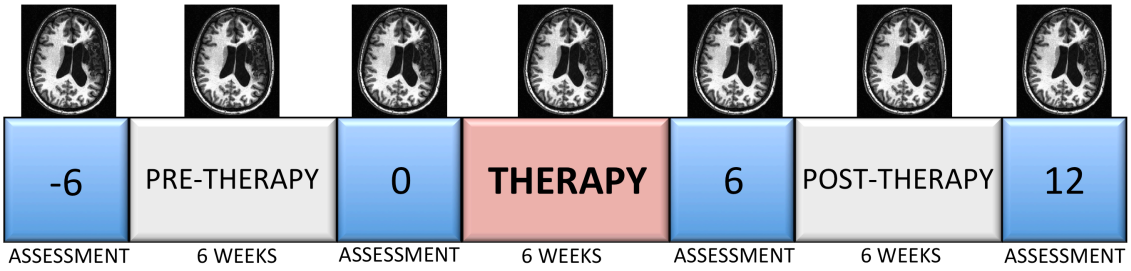

Figure 3.2 Visual Depiction of Experimental Design. Two pre-therapy assessments (Weeks -6,0) were separated by a 6-week interval during which no therapy was provided. Between Weeks 0 and 6, subjects participated in six weeks of therapy. No therapy was provided in the interval between the two post-therapy sessions (Weeks 6,12).

3.3 Therapy Description

3.3.1 Therapy Features

The important therapeutic features in IMITATE include visual observation, oral repetition, speaker variability, ecologically valid stimuli, high intensity, graded incremental learning and variability in gradation (Lee et al., 2010; Small & Llano, 2009). Visual observation refers to the use of audiovisual stimuli in which the speaker's moving face, lips and mouth are visible, in contrast to the control REPEAT therapy, in which the patients viewed a static image of each speaker while simultaneously hearing their voice utter the target word or phrase. Oral repetition was performed during both IMITATE and REPEAT therapy sessions. Speaker variability was implemented by the presentation of each target word or phrase by each of six different talkers, seen in Figure 3.3. This was used for both therapies and was theorized to aid in generalization to a wider variety of talkers. Ecological stimuli refers to the use of real words and phrases that might be used by an English speaker in the course of daily activities (rather than non-speech oral movements, isolated syllables or nonsense words), as well as to the display of a visible talker such as one might engage with in normal communicative interactions. The use of real words and

phrases was common to both groups, but visual observation (video) was used only for patients receiving IMITATE. Use of ecologically valid stimuli was physiologically motivated by the shared substrates found for observation and execution of action, including oral communicative actions, on a cellular level in studies of macaque cortex (Ferrari et al., 2003; Rizzolatti, Fadiga, Gallese, et al., 1996) and in a motor cortical network model supported by fMRI findings in neurologically intact human subjects (Mashal et al., 2012). Such stimuli may enhance the efficacy of neural connectivity by matching observed actions, such as speech, to internal motor representations existing within the viewer's repertoire of action performance (Kohler et al., 2002).

Figure 3.3 Six Talkers Presenting Therapy Stimuli.

High intensity was implemented by requiring patients from both groups to participate in 90 minutes (3 30-minute sessions) daily, 6 days a week, for 6 weeks. This level of intensity, far greater than the level that can typically be provided by a trained therapist, was chosen based on

the positive correlation between intensity and therapeutic outcome (Bhogal, Teasell, & Speechley, 2003). This massed practice used in both the experimental and control therapies is consistent with other biologically motivated behavioral therapies for aphasia rehabilitation, notably Constraint Induced Aphasia Therapy (CIAT; Pulvermüller et al., 2001). The IMITATE subjects were also exposed to the entire stimulus block of a target before producing a block repetitions, while the REPEAT group had a shorter period for repetition following each of the 6 presentations. The massed stimulation of the IMITATE therapy has been theorized to prime synaptic connections and facilitate the generation or re-instatement of neural pathways (Ferguson, 1999).

Graded incremental learning was addressed by advancing patients in both groups through levels featuring successively more difficult stimuli, such as longer words, more complex phonology, more varied word classes, and longer word sequences (phrases and sentences). Each patient started the therapy at a level that was judged to be appropriate to pre-treatment repetition capability, and advanced through a level each week, unless the clinician performing the weekly repetition test (described in Section 3.4.2) judged that repetition of a level was necessary. Finally, variability in gradation was implemented in both therapies by occasionally providing simpler stimuli at higher levels as well as more difficult stimuli at lower levels according to a probabilistic algorithm. In addition to being consistent with the variability of daily communicative demands, this approach sought to combine two conflicting bodies of evidence on learning strategies that suggest that either a simple (Elman, 1993) or a complex (Kiran & Thompson, 2003) origin (i.e., initial level of difficulty) yields maximum benefit. An example of the therapy interface can be seen in Figure 3.4.

Figure 3.4 Example of Therapy Interface.

3.3.2 Selection of Lexical and Phrasal Stimuli

Therapy items for IMITATE were selected by an algorithm that was designed to consider parameters including number of letters, phonemes, and syllables, part of speech, written frequency, familiarity, frontal and total visibility, and phonemic complexity. These values were derived from the MRC Psycholinguistic Database (Coltheart, 1981), the Kucera and Francis corpus (Kucera & Francis, 1967), the Hoosier mental lexicon (Nusbaum, Pisoni, & Davis, 1984), and various measures of viseme content (Bement, Wallber, DeFilippo, Bochner, & Garrison, 1988; Owens & Blazek, 1985). Measures of phonemic complexity were calculated by coding stimuli for presence of consonant blends in the initial position. Visibility of consonants and vowels was assessed on a 4-point scale that assigned high values to high-visibility productions,

like consonants /p/, /b/, /m/, /f/, and /v/. Combining all criteria yielded a final pool of 2568 words, which was augmented by the addition of 68 words that were added due to high functional utility (e.g., “blue”, “March”, “chair”, “Monday”). Words contained between 1 and 4 syllables (mean = 1.42) and between 1 and 12 phonemes (mean = 4.09).

The stimulus set also included 405 phrases that were chosen due to common use and high functional utility for people with aphasia (e.g., “sit down”, “watch out”, “nice to see you”, “please pass the salt”). These were selected from a large variety of English language textbooks, travel guides, and intuition. Phrases were assigned a value on the basis of the number of words and syllables, as well as verb and preposition frequency. Phrases contained two to nine syllables (mean = 4.03) and two to five words (mean = 3.36).

Twelve treatment levels were developed, which increased gradually in complexity. Individual patients were assigned to a treatment level based on their level of functioning. The stimuli analyzed for the study described in Chapter 4 were selected on the basis of the level to which the individual was expected to advance over the course of therapy. This higher level was selected to diminish ceiling effects.

3.4 Behavioral Measures

3.4.1 Western Aphasia Battery

The Western Aphasia Battery-Revised (WAB; Kertesz, 2006) was used as the primary outcome measure, as it was anticipated that benefits of our imitation-based therapy would generalize to other domains of language (Duncan & Small, 2015; Lee et al., 2010; Small & Llano, 2009). The WAB was administered at each of the four main behavioral assessment sessions by a speech-language pathologist (SLP) blind to treatment group. We analyzed the

WAB Aphasia Quotient (WAB-AQ), Cortical Quotient (WAB-CQ), and the four subcomponents of the WAB-AQ (Spontaneous Speech, Auditory Verbal Comprehension, Repetition, and Naming and Word Finding). Paired t-tests were used to compare differences between pre-therapy (Week -6,0) WAB scores and between post-therapy (Week 6,12) WAB scores.

3.4.2 Repetition Test

Tests of repetition accuracy were administered during all four pre- and post-treatment behavioral assessments. These were administered by an SLP using words and phrases randomly selected from the pool of IMITATE therapy stimuli. Repetition tests and other behavioral assessments were performed by different SLPs, blinded to the other's findings.

Repetition test stimuli, as included in Chapter 4, consisted of words and phrases of high difficulty, based on the level to which the subject was expected to advance. Each block of words contained 10 words. Each block of phrases contained 10 phrases with a varying number of words (2-6) depending on level. For both blocks, each word was scored on a 5-point scale (0 signifying no vocalization; 5 indicating accurate, prompt repetition). Scoring was performed once offline by a single SLP for all subjects, and therefore reliability rates are not reported. Performance on these measures was combined in a single repetition score for each time point (mean score for Words and Phrases). Paired t-tests were used to compare differences between pre-therapy (Week -6,0) repetition scores and between post-therapy (Week 6,12) repetition scores.

3.4.3 Narrative Production

At each of the four behavioral assessments, narratives were elicited by having participants tell the story of the fairy tale Cinderella (Saffran, Berndt, & Schwartz, 1989). These narratives

were recorded, transcribed, and subsequently analyzed for number of correct information units (CIUs) produced (Nicholas & Brookshire, 1993). Words were scored as CIUs if they were intelligible, novel during the narrative task, and relevant to the story. Paired t-tests were used to compare number (and percent) of CIUs produced pre- vs. post-therapy, between the two baseline sessions, and between the two post-therapy sessions.

3.5 Neuroimaging

3.5.1 Acquisition

Magnetic resonance imaging (MRI) was acquired at three time points before therapy (Weeks -6, -3, 0) and three time points after its conclusion (Weeks 6, 9, 12). Images were acquired using a 3T Siemens Trio MRI scanner (Siemens Medical Solutions USA Inc., Malvern, PA) at Northwestern University. Anatomical images were acquired with a T1-MPRAGE sequence with TR=2300 ms, TE=3.36 ms, TI=900 ms, flip angle=9°, and 1 mm isotropic voxel size. Resting state fMRI (rsfMRI) images were acquired with an EPI sequence with TR=1500 ms, TE=20 ms, FA=71°, FOV=220x220 mm^2, matrix size=64x64, 29 axial slices with 4 mm thickness (1 mm gap), and inplane voxel size of 3.75 x 3.75 mm. During 5 minutes of scanning, 200 volumes were acquired. Participants were instructed to get into a comfortable position prior to the rsfMRI scan in order to minimize motion, and to stay awake and keep their eyes open during the scan.

3.5.2 Virtual Brain Transplant and FreeSurfer

One of the difficulties of working with neuroimaging in aphasia is that the presence of large cortical lesions can cause catastrophic failure when attempting to use many neuroimaging tools designed for the analysis of brain imaging data. In order to improve registration and to facilitate

the use of standard software packages, such as FreeSurfer (Fischl, 2012), we performed a Virtual Brain Transplant (VBT; Solodkin et al., 2010) on the T1-weighted anatomical scans of individual participants. In VBT, imaging data from the intact hemisphere is morphed to fit into the lesioned space in the left hemisphere, in which tissue is damaged or absent. The workflow for this technique is depicted in Figure 3.5.

In VBT, a lesion mask is first manually drawn on the anatomical scan. The original brain scan is then extracted from the skull and divided into two separate hemispheres. This allows the nonlesioned hemisphere to be flipped into the mirrored space of the lesioned hemisphere, followed by nonlinear warping using symmetric diffeomorphic image registration via ANTS (Avants, Epstein, Grossman, & Gee, 2008) with cost function masking of the lesioned region. Once the nonlesioned hemisphere is aligned to the shape of the lesioned hemisphere, the lesion mask is used to extract an image of intact tissue from the flipped nonlesioned hemisphere. This image is enlarged by a few millimeters in order to better capture the expanded sulci of the lesioned hemisphere. It is then used to replace the region overlaid by the lesion mask in the left hemisphere of the whole brain image, and this transplanted region is morphed with the surrounding area to blur the border between images.

Performing VBT permitted the use of FreeSurfer (Fischl, 2012) for the segmentation of brain scans. With FreeSurfer, we were able to reconstruct individual cortical surfaces for each of our participants. We used individual volumes, surfaces, and curvatures to construct a common template (see Figure 3.6) for use in group analysis, in order to facilitate more accurate registration compared to a standard atlas comprising neurologically intact brains.

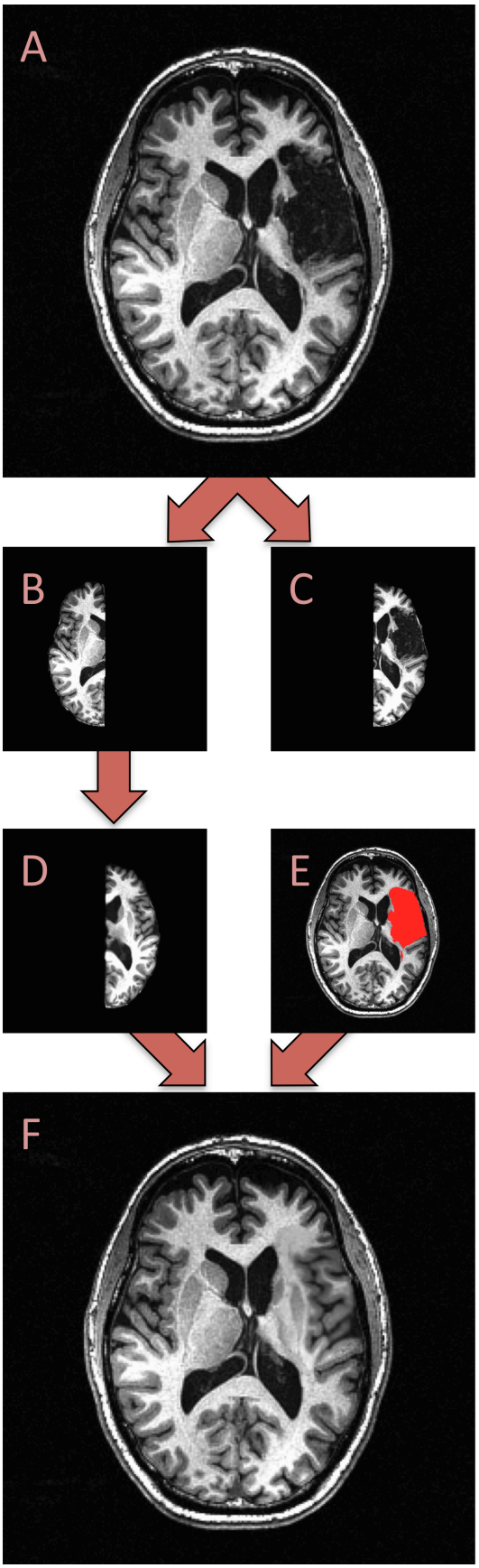
A
B
C
D
E
F

Figure 3.5 Virtual Brain Transplant (VBT) Workflow. (A) shows an axial view of the original brain with large left hemisphere lesion. This brain is split into nonlesioned right (B) and lesioned left (C) hemispheres. In (D), the nonlesioned right hemisphere (B) has been flipped around the x axis and aligned to the lesioned left hemisphere (C) using a nonlinear warp. Note the size of the horns of the lateral ventricle in (D), compared to (B) and (C). (E) shows a mask that has been hand drawn on the original image (A) to demarcate the limits of the lesion. In (F), the lesion mask from (E) has been used to extract an image from the flipped right hemisphere (D) for use in the virtual transplant, and the original lesion appears filled by intact tissue.

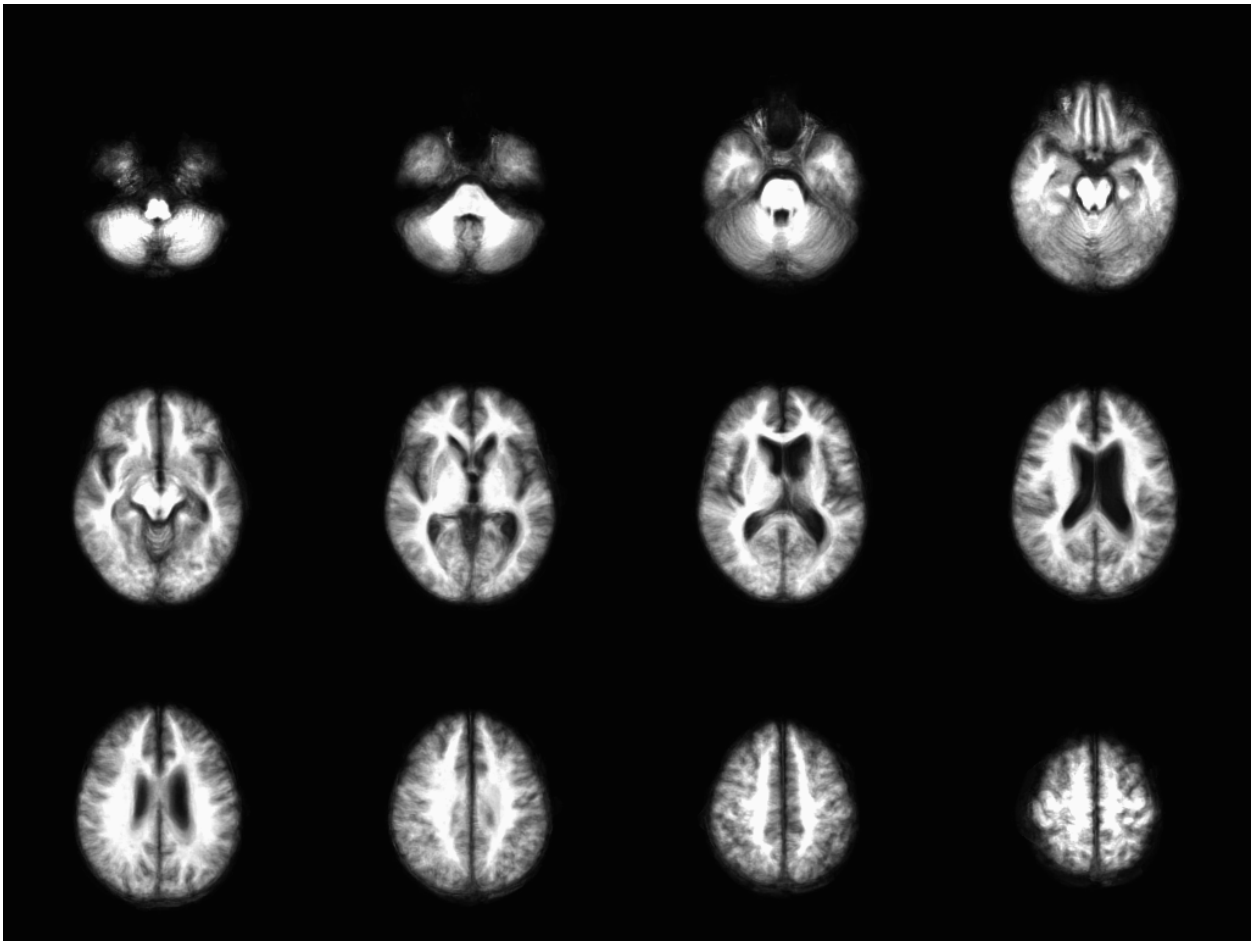

Figure 3.6 Group Template. Created from the brains of all participants using FreeSurfer (Fischl, 2012). Montage shows axial slices from inferior (top left) to superior (top right).

3.5.3 Brain Parcellation

Following VBT and FreeSurfer, each participant's brain was parcellated into 463 regions using the Connectome Mapping Toolkit (Hagmann et al., 2008), including 448 right hemisphere cortical regions, 14 subcortical nuclei, and the brainstem. Parcellated surfaces can be seen in Figures 3.7 to 3.10.

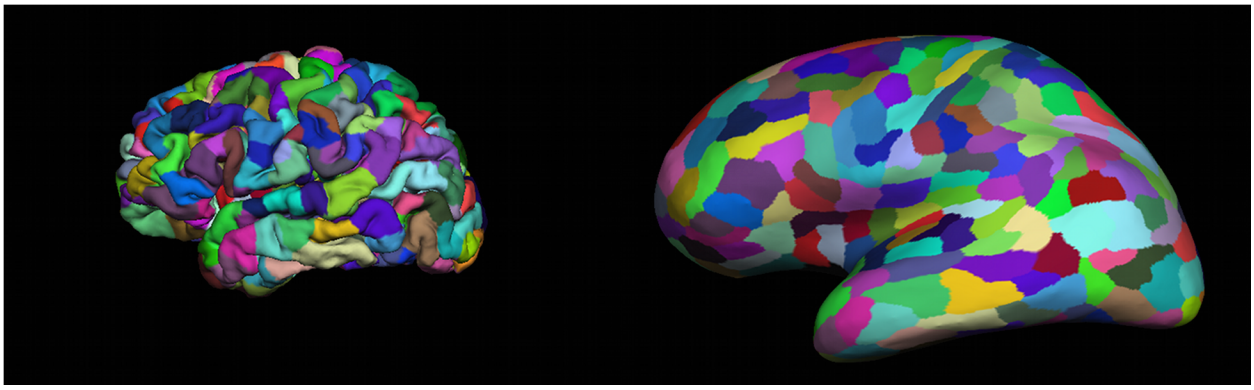

Figure 3.7 Lateral View of the Parcellated Left Hemisphere. Left image shows pial surface, right image shows an inflated surface permitting viewing of surfaces within the sulci.

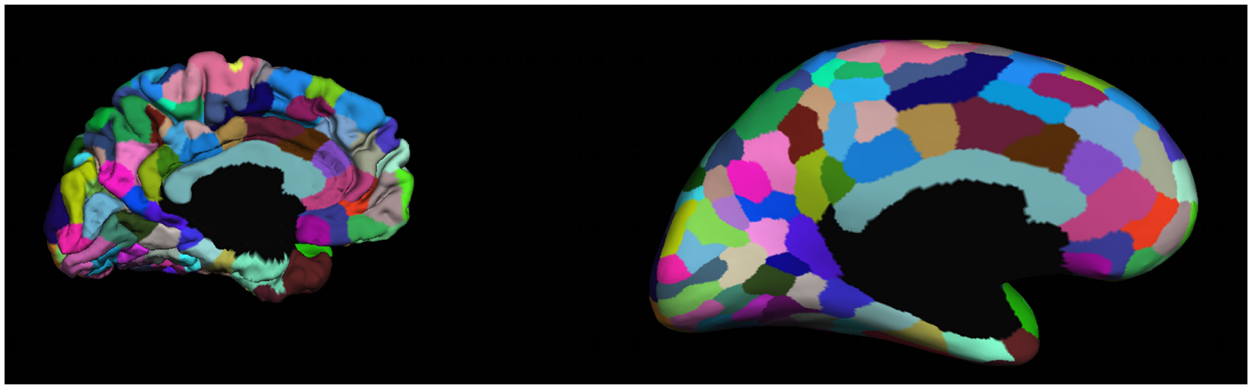

Figure 3.8 Medial View of the Parcellated Left Hemisphere. Left image shows pial surface, right image shows an inflated surface permitting viewing of surfaces within the sulci.

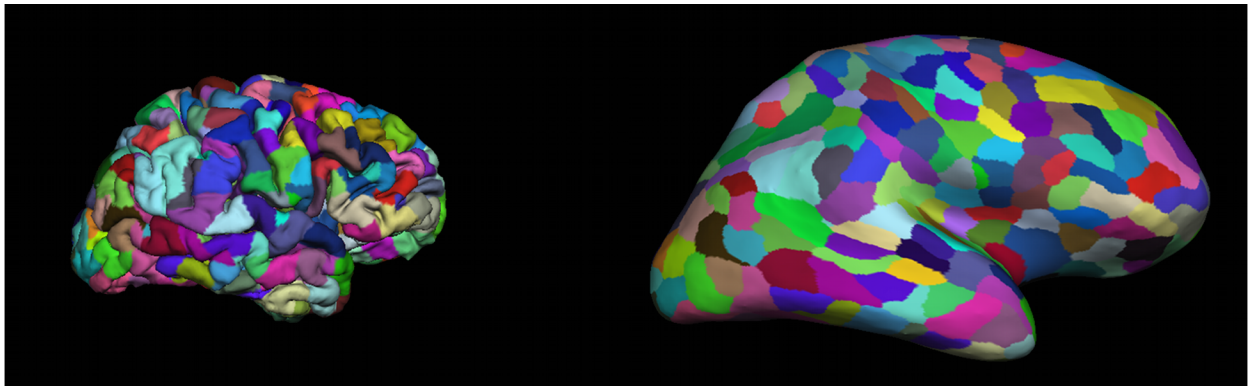

Figure 3.9 Lateral View of the Parcellated Right Hemisphere. Left image shows pial surface, right image shows an inflated surface permitting viewing of surfaces within the sulci.

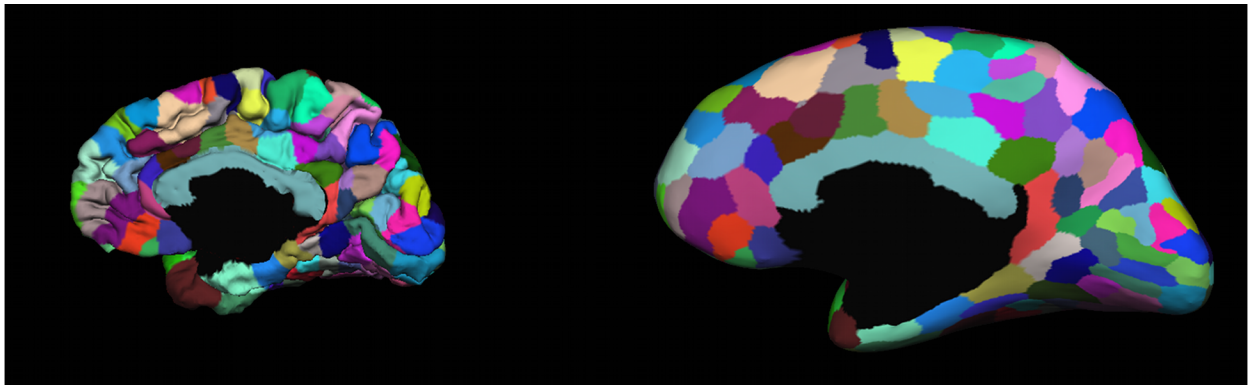

Figure 3.10 Medial View of the Parcellated Right Hemisphere. Left image shows pial surface, right image shows an inflated surface permitting viewing of surfaces within the sulci.

3.5.4 Preprocessing

Further details about the preprocessing and analysis of structural and functional MR images can be found in the Materials and Methods sections of Chapters 6 and 7.

Chapter 4: Performance Variability as a Predictor of Response to Aphasia Treatment

4.1 Introduction

4.1.1 Background

Therapeutic research in aphasia typically characterizes baseline and improved language skills in terms of mean scores on a specific task or assessment battery. Whereas this approach succeeds at capturing variability across individuals, it fails to capture such variability within individuals. Performance fluctuations within a single individual (intra-individual variability) are typically perceived as an inconvenient impediment to reaching the desired general conclusions about a new therapy. But treating intra-individual variability as a nuisance parameter or measurement error (e.g., of the same magnitude and significance as inter-individual variability; Van Geert & Van Dijk, 2002), may be giving up important and highly relevant information about the therapy. In fact, short-term performance inconsistency on a particular task may represent a characteristic feature of – and a metric to gauge – an individual's functional status. Particularly in the context of large variability, mean performance may oversimplify the true nature of behavior and inadequately capture the range of ability (Nesselroade, 2002), obscuring insight into potential therapeutic benefit and outcome assessment on an individual basis.

4.1.2 Intra-individual Variability in Cognitive and Motor Function

Existing limited research on intra-individual variability in cognitive and perceptual-motor function in healthy aging (Garrett, Macdonald, & Craik, 2012; Li, Lindenberger, & Sikström, 2001; Lövdén, Li, Shing, & Lindenberger, 2007; Nesselroade & Salthouse, 2004) and dementia (Duchek et al., 2009; Gamaldo, An, Allaire, Kitner–Triolo, & Zonderman, 2012; MacDonald,

Hultsch, & Dixon, 2003) suggests a relation between increased intra-individual variability and decreased performance. Yet other, seemingly contradictory, findings suggest that greater intra-individual variability has positive implications for acquiring skills with practice or training. For example, increased intra-individual variability in a cognitive or motor skill during learning precedes (and presages) mastery of that skill during development (Courage, Edison, & Howe, 2004), and in cognitive training of healthy older adults, the pre-treatment degree of intra-individual variability predicts higher response accuracy and performance improvement (Allaire & Marsiske, 2005).

These data suggest that performance variability may suggest susceptibility to change and/or the potential for learning. Fluctuations representing adaptive variability (Li et al., 2004) may be conceived of not as vulnerability, but as potential. Further, distinguishing between adaptive and maladaptive variability may be key to understanding the significance of these measures in predicting future outcomes.

4.1.3 Intra-individual Variability in Aphasia

In the realm of stroke recovery, extensive investigation has addressed differences between individuals, yet little work studying performance variability within individuals (although important work has explored the role of attention in intra-individual variability in aphasia (e.g., Erickson, Goldinger, & LaPointe, 1996; Tseng, McNeil, & Milenkovic, 1993)). In the recovery of language functions after stroke, intra-individual performance variability has not been investigated, either as a correlate of present functioning or as a predictor of post-treatment ability (but see Small, Holland, Hart Jr, Forbes, & Gordon (1995) for a theoretical study). The implications are far-reaching. From a research standpoint, our knowledge of language recovery

in aphasia is limited to mean scores and effect sizes using pooled standard deviations, thus neglecting individual parameters of variability. Such data may represent fundamentally incomplete metrics, substituting a crude numerical proxy for the more nuanced complexity of performance, and thus profoundly affecting our understanding of recovery. From a clinical standpoint, such omission could have graver consequences, since the most desirable measure of rehabilitation success is a patient's consistent performance in the real world, not maximal performance in the clinic or the possibility of good performance under ideal conditions.

4.1.4 Motivation for the Present Study

We hypothesize that intra-individual variability on a language task is predictive of the ability of an individual with aphasia to improve mean performance on that task through training. We investigate this hypothesis in a clinical trial of an intensive, imitation-based aphasia therapy motivated by neurophysiological evidence (Lee et al., 2010; Small, 2009) that uses a computer interface to prompt repetition of words and phrases to engage a frontal-parietal motor cortical network involved in both observation and execution of speech (Hari et al., 1998). In this paper, we report on an experiment testing the hypothesis that pre-treatment intra-individual variability predicts therapeutic outcome.

4.2 Materials & Methods

4.2.1 Participants

Participants are nineteen subjects as described in Section 3.1. Select demographic and neurological information is listed in Table 3.1, and lesion overlap is depicted in Figure 3.1.

4.2.2 Experimental Summary

The details of the study are described in Section 3.2 and visually depicted in Figure 3.2. Features of the IMITATE therapy and stimuli selection are described in Section 3.3.

4.2.3 Behavioral Measures

4.2.3.1 Assessment Tools

Two measures are described in this study, the WAB and the repetition test (see Section 3.4).

4.2.3.1.1 Western Aphasia Battery-Revised

Additional information about WAB administration can be found in Section 3.4.1. Six WAB measures were used: WAB Aphasia Quotient (WAB-AQ), Cortical Quotient (WAB-CQ), and the four subcomponents of the WAB-AQ (Spontaneous Speech, Auditory Verbal Comprehension, Repetition, and Naming and Word Finding). There was no significant difference in any of these measures between the two pre-treatment sessions or between the two post-treatment sessions ($p > 0.05$ on two-tailed paired t-tests).

4.2.3.1.2 Repetition Test

Additional information about the repetition test can be found in Section 3.4.2. One subject (2) was excluded from this analysis due to missing data, leaving 18 subjects. There were no significant differences between Week -6 and Week 0 repetition scores, or between Week 6 and Week 12 repetition scores ($p > 0.05$ on two-tailed unpaired t-test).

4.2.3.2 Changes in Behavioral Performance

Seven measures of language performance were studied: WAB-AQ, WAB-CQ, the four

subcomponents of the WAB-AQ, and the score from the repetition test (defined as the average percent correct for blocks of words and phrases). For each measure, the pre-treatment score was taken to be the mean of Week -6 and Week 0 scores, and the post-treatment value is the Week 6 score (post-therapy repetition). We did not use scores from Week 12 (fourth behavioral assessment) as two subjects missed this assessment. Therefore, our definition of improvement, for all measures, is the Week 6 score minus the mean for Weeks -6 and 0.

Pre-treatment scores were compared with post-treatment scores using two-tailed paired t-tests. All significance tests use $\alpha = 0.05$. Due to the nested nature of the WAB measures (i.e., four subcomponents of the WAB-AQ are used, which also contribute to WAB-CQ), Bonferroni correction with $n = 5$ was applied for the repetition assessment and the four subcomponents of the WAB-AQ (Spontaneous Speech, Auditory Verbal Comprehension, Repetition, and Naming and Word Finding).

4.2.3.3 Intra-individual Variability as Predictor of Improvement

The repetition test based on stimuli from the pool of IMITATE items (see Sections 3.3 and 3.4 for further detail) was used to test directly the hypothesis that intra-individual variability in a language task is predictive of the ability of an individual with aphasia to improve performance on that task through training. This single measure was selected for two reasons: (1) there were two days on which the repetition test was administered at least twice (Week 0 and Week 6), allowing a robust assessment of individual variability before and after treatment, and (2) these stimuli were developed to be grossly equivalent in complexity, in contrast with the hierarchical ordering of increasing complexity on the WAB subtests. We chose not to pool data from Weeks -6 and 0 when computing intra-individual variability to avoid confounding variability on

different time scales; our intra-individual variability scores measure performance variability within a given day only. We computed a repetition intra-individual variability measure pooling variances of words and phrases blocks. Details about the calculation of this measure can be found in Section 4.2.3.3.1.

Our specific question was the extent to which pre-treatment repetition intra-individual variability predicted improvement in repetition mean, which we determined by computing a Pearson correlation coefficient. We used Week 0 and Week 6 repetition mean scores as the pre- and post-treatment values, ignoring Week -6 scores for consistency with intra-individual variability calculations. There was no significant difference between pre-treatment repetition mean calculations regardless of whether Week -6 repetition test scores were included (two-tailed paired t-test, $p > 0.05$).

We used stepwise linear regression to identify those pre-treatment variables that best predicted improvement. In addition to pre-treatment repetition intra-individual variability, these variables included participant age, months post stroke onset (MPO), number of sessions completed (NSC), aphasia type (fluent vs. nonfluent), and pre-treatment repetition mean. NSC was tracked by automated video recording of patient participation during each session via the built-in laptop camera, and then verified by review of these recordings. Stepwise regression was performed with the MATLAB `stepwise` function, using the default settings: a new predictor is selected if its regression coefficient would be significantly nonzero at the 0.05 level, and an existing predictor is removed if its coefficient is not significantly nonzero at the 0.10 level.

4.2.3.3.1 Intra-individual Variability Measure

For each time point (Week 0 or Week 6) and each subject, we computed the variance of the

per-word scores in the pooled Word blocks, and the same for the pooled Phrase blocks. Our intra-individual variability measure for repetition score is the square root of the mean of the variances in the two blocks (words and phrases), which is comparable to a pooled standard deviation but gives equal weight to the words and phrases blocks. This is analogous to our definition of the repetition mean (see Section 4.2.3.2), which gives equal weight to words and phrases, despite the phrases block containing a larger, and more variable, number of words than the words block.

4.2.3.3.2 Exclusion of Subjects from Intra-individual Variability Analysis

Beginning with all 18 subjects for which intra-individual variability data was available (i.e., all except Subject 2), we calculated full and partial Pearson correlation coefficients for the relationship between pre-treatment intra-individual variability and improvement. The full correlation coefficient was r= 0.79. The partial correlation coefficient, controlling for age, months post onset and number of sessions completed as potential confounding variables, was r= 0.78. The partial correlation coefficient, with these confounding variables plus an additional one of pre-treatment repetition mean performance, was r= 0.76.

We then excluded Subject 4 as an outlier, since its pre-treatment mean performance lies more than 3 standard deviations below the group mean (see Figure 4.1B). Excluding this subject only, we recalculated the correlation coefficients between intra-individual variability and improvement in post-therapy repetition mean, with results shown in Table 4.1. Note that the full correlation coefficient of r= 0.75 (excluding subject 4) is very similar to the value r= 0.79 obtained using all subjects. The same is true of the partial correlation coefficient, with age, months post onset, and number of sessions completed as confounding variables: r= 0.76 (excluding subject 4) versus r=

0.78 using all subjects. However, with the additional confounding variable of pre-treatment mean, the partial correlation coefficient is now r= 0.48 (excluding subject 4) versus r= 0.76 using all subjects, and is not significant at the p= 0.05 level. This means that, when subject 4 is excluded, pre-treatment mean and the other confounding variables listed predict improvement well enough that including pre-treatment intra-individual variability as an additional predictor does not significantly improve the prediction.

Repetition measures:	r	p
Intra-individual variability vs. improvement	0.75	0.0005
(controlling for age, MPO, aphasia type, NSC)	0.73	0.0050
(controlling for age, MPO, NSC, aphasia type, and mean)	0.48	0.1153
Mean vs. improvement	-0.64	0.0055

Table 4.1 Full and Partial Correlation Coefficients for Pre-treatment Intra-Individual Variability and Improvement in Mean Accuracy for the Repetition Test. Partial correlations control for age, months post onset (MPO), aphasia type (fluent vs. nonfluent), and number of sessions completed (NSC) and pre-treatment mean. The full correlation between pre-treatment mean and improvement is also included. Subject 4 has been excluded as an outlier from all calculations. Table reproduced from Duncan et al. (2016) online supplement courtesy of Sage Publications.

Noting the effect of controlling for pre-treatment mean in the context of the overall high performance scores (group mean 79.4%, SD 18.8%), we considered that ceiling effects might have artificially constrained both intra-individual variability and improvement scores. The asymptotic appearance of Figure 4.1B, showing pre-treatment repetition mean vs. intra-individual variability, further reinforces this possibility. This scatter plot shows several near-ceiling means, and also a strong negative association (excluding the outlier, subject 4) between mean and intra-individual variability. Therefore, our intra-individual variability measure may be artificially low for subjects with high mean performance, due purely to a ceiling effect,

especially since our intra-individual variability measure is based on variance, the estimation of which gives high weight to extreme values. In order to compensate partially for this, we recalculated the above correlation coefficients using a restricted set of subjects. We calculated the overall mean of the per-subject standard errors of the repetition mean, which was 2.2% pre-treatment and 1.9% post-treatment, and excluded those subjects with a repetition mean, either pre- or post- treatment, within one mean standard error of the ceiling (100%). (Note that the standard error of the repetition mean score (SEM) equals one half of the square root of the sum of squared SEMs for words and phrases separately.) The subjects excluded are listed in the main text, and marked with crosses in Figures 4.1 and 4.2. Table 4.2 contains results analogous to Table 4.1, but with the listed subjects excluded.

4.3 Results

4.3.1 Changes in Behavioral Performance

Statistically significant improvements were demonstrated in five of the seven language measures assessed, with correction for multiple comparisons. Results of two tailed t-tests are summarized in Table 4.2 with uncorrected p values. We used Bonferroni correction (n = 5; see Section 4.2.3.2) for the six WAB measures vs. repetition test to determine significance. Significant improvement was measured for the repetition test, WAB-AQ, WAB-CQ, and two of the four WAB-AQ subcomponents (Repetition, Naming and Word Finding). The two remaining subcomponents of the WAB-AQ (Spontaneous Speech, Auditory Verbal Comprehension) did not demonstrate significant change.

MEASURE	Mean Pre (SD)	Mean Post (SD)	Mean Improvement (SD)	p value (uncorrected)
WAB-AQ	67.72 (20.00)	70.34 (18.33)	2.61 (3.73)	.0068*
WAB-CQ	71.27 (16.50)	73.89 (15.44)	2.62 (2.72)	.0005*
WAB-SS	12.42 (4.49)	12.81 (3.89)	0.47 1.36	.1460
WAB-AVC	164.40 (26.94)	166.42 (25.78)	2.02 (7.67)	.5186
WAB-Rep	67.16 (26.64)	72.00 (24.85)	4.84 (6.49)	.0044*
WAB-NWF	64.62 (29.21)	67.00 (29.19)	2.39 (3.13)	.0037*
Repetition Test	79.40 (19.03)	86.19 (19.11)	6.58 (5.90)	.0002*

Table 4.2 Performance Measures for All Subjects. The asterisk (*) marks significant values after Bonferroni correction for 5 comparisons (* $p < 0.05/5$). SD: standard deviation; WAB: Western Aphasia Battery-Revised; AQ: Aphasia Quotient; CQ: Cortical Quotient; SS: Spontaneous Speech; AVC: Auditory Verbal Comprehension; Rep: Repetition; NWF: Naming and Word Finding. Table reproduced from Duncan et al. (2016) courtesy of Sage Publications.

4.3.2 Intra-individual Variability as Predictor of Improvement

In this section, only the repetition test results are used. In contrast to Table 4.2, pre-treatment results are from Week 0 only, for reasons explained in Section 4.2.3.3. Pre-treatment repetition mean ranged from 20.5% to 99.5% (overall mean 79.4%, SD 18.8%). Improvement in repetition mean from pre-treatment to post-treatment (Week 0 to Week 6) ranged from -3.8% to 16.5% (median 5.3, mean 6.7, SD 5.7), representing a mean improvement of 0.34 points on the 5-point scale used to rate the repetition performance.

Figure 4.1A shows pre-treatment intra-individual variability versus improvement in repetition mean performance, and Figure 4.1B shows pre-treatment repetition mean vs. pre-treatment intra-individual variability.

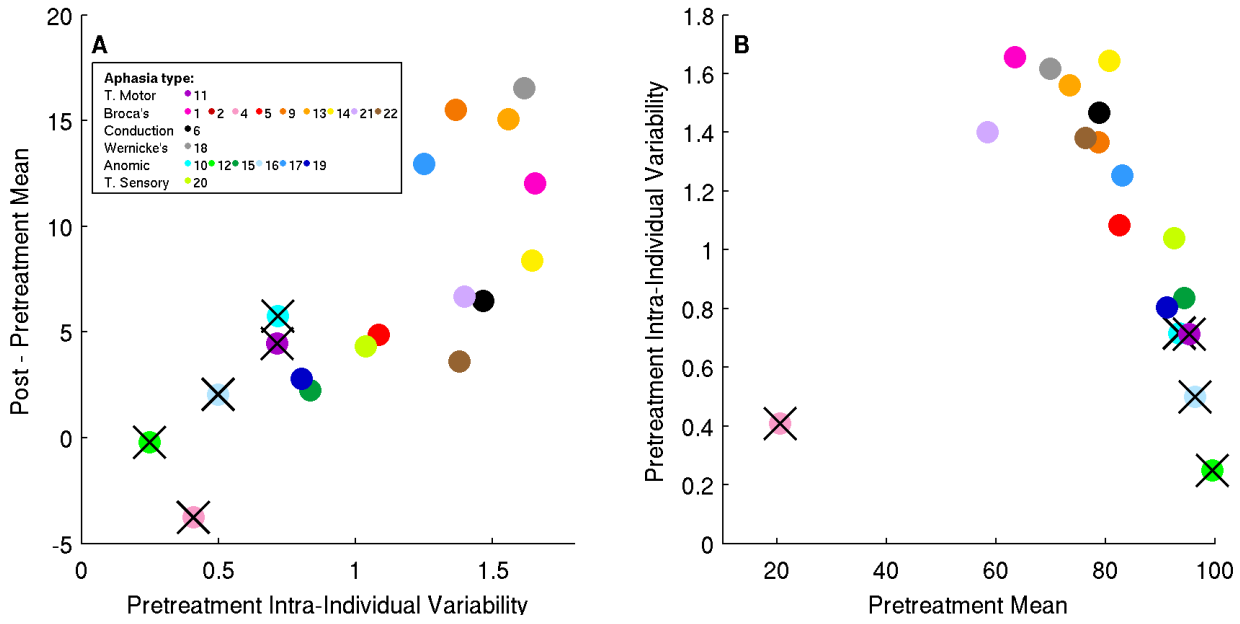

Figure 4.1 Pre-treatment Intra-Individual Variability, Mean, and Improvement on the Repetition Test. Data shown for repetition test: A, improvement plotted against intra-individual variability; B, intra-individual variability plotted against pre-treatment mean. Participant 2 was excluded because of missing data, leaving 18 participants. Those marked with black crosses are excluded from further analysis (see Section 4.2.3.3.2). Figure reproduced from Duncan et al. (2016) courtesy of Sage Publications.

We removed several subjects from further analysis due to outlier status (4) and possible ceiling effects (i.e., subjects near threshold pre- or post-therapy: 10,11,12,16), as detailed in Section 4.2.3.3.2. For the remaining subjects, there is a positive correlation (r= 0.68, p= 0.01 uncorrected) between pre-treatment intra-individual variability and improvement – i.e., higher pre-treatment intra-individual variability is associated with greater improvement. We then considered all of the pre-treatment variables listed earlier (age, MPO, NSC, aphasia type, pre-treatment intra-individual variability and pre-treatment mean) as possible predictors of improvement in post-therapy repetition accuracy. In a stepwise regression, the optimal regression model found intra-individual variability to be the only predictor of improvement (p = .01, as noted above). With all subjects included, the relationship remains highly significant (p = .0001),

with no additional predictors selected. Repeating this stepwise regression without variability included in the model resulted in the selection of no variables, whether for the entire group or with near-threshold subjects excluded.

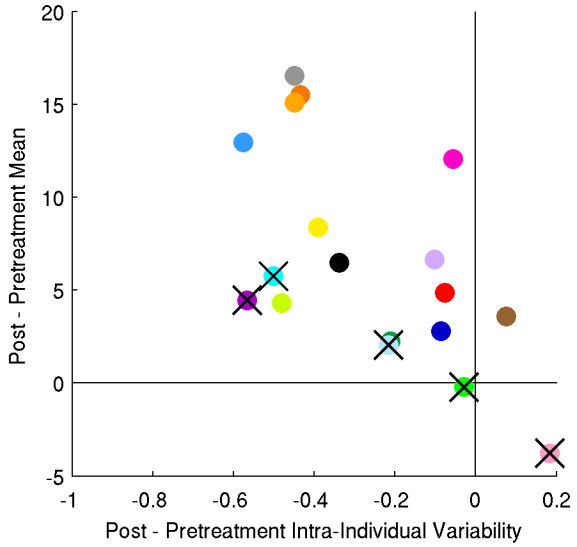

Figure 4.2 Changes in Intra-Individual Variability and Mean on the Repetition Test. Participants shown are as in Figure 4.1. Figure reproduced from Duncan et al. (2016) courtesy of Sage Publications.

Finally, we examined intra-individual variability in repetition accuracy immediately post-treatment (Week 6). This decreased significantly over the course of treatment (two-tailed paired t-test, $p < 0.05$), regardless of whether we consider all subjects or exclude near-threshold subjects (as detailed in Section 4.2.3.3.2). Post-treatment intra-individual variability in repetition accuracy is positively correlated with change in repetition mean when we consider all 18 subjects (Pearson's $r = 0.49$, $p = 0.04$ in a 2-tailed t-test). However, it is no longer significant when we exclude subjects who were near-threshold either before or after therapy ($r = 0.25$, $p = 0.41$). The change in intra-individual variability in repetition accuracy over the course of treatment has a significant negative correlation with improvement, whether considering all subjects ($r = -0.48$, p

=0.053) or excluding near-threshold subjects (r =-0.57, p =0.04), as shown in Figure 4.2. This effect remains if we control for all of the confounding variables (age, MPO, NSC, aphasia type, pre-treatment mean, pre-treatment intra-individual variability; r = -0.69, p = 0.018). Put another way, reduction in intra-individual variability is positively correlated with improvement.

4.4 Discussion

The present study reviews outcomes of a clinical trial of imitation-based therapy for chronic aphasia, and explores a new hypothesis about the role of intra-individual variability in predicting benefit from language therapy following stroke.

This study showed positive effects of the IMITATE system of repetition based, computer assisted speech-language therapy for patients with chronic aphasia. In particular, participants undergoing the therapy had statistically significant gains on composite language and cognitive measures on a standard test for aphasia (WAB), as well as on two repetition accuracy measures. Significant gains were made over a relatively short treatment period (6 weeks) in subjects who, in some cases, were more than a decade removed from their stroke. Future investigation will refine the IMITATE therapeutic protocol in view of the results from the current study, related research (Fridriksson et al., 2012), and other theoretical considerations.

Our analysis suggests that subjects demonstrating higher levels of performance variability prior to therapy are likely to experience greater improvement over the course of treatment. Specifically, subjects demonstrating greater intra-individual variability during repetition before therapy demonstrated greater improvement in repetition than those with lower intra-individual variability. Perhaps most interestingly, intra-individual variability declined over the course of treatment, and there was a significant correlation between performance improvement and intra-individual variability reduction.

The finding that intra-individual variability is a positive predictor of language improvement appears to conflict with existing literature on the relation between intra-individual variability and task performance in cognitive and perceptual-motor domains. In healthy aging and dementia, intra-individual variability has generally been negatively correlated with both short-term performance (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000) and long-term variables (Lövdén et al., 2007), including time until death (MacDonald, Hultsch, & Dixon, 2008). On the other hand – and perhaps most relevant here – evidence also suggests that increased variability in a particular cognitive or motor domain may be associated with greater potential for change following training specific to that domain (Li et al., 2004).

Correlation of task-specific variability with performance improvement has been attributed to influences of learning and strategy use in development (Siegler, 2007). During skill acquisition, changes occur in execution of strategies, even in the absence of changes in strategy selection (Siegler & Lemaire, 1997). These subtle changes may result in adaptive variability while learning specific tasks. Thus as an individual achieves maximal potential on a task, variability decreases. In expert motor control, when an individual is performing a highly practiced skill at or near peak level, performance variability is reduced, and this consistency is reflected in precise activation of neural networks during motor planning (Milton, Solodkin, Hlustik, & Small, 2007). Our finding that intra-individual variability decreased over the course of therapy provides further support for this proposition, especially given the significant correlation between improvement on the repetition test and intra-individual variability reduction. Within the limitations of their language impairment, our participants became more expert at the practiced task, thus demonstrating more consistent and more accurate performance. Although it is impossible to determine from the present study, it would be of great interest to explore whether such variability

might continue to play a predictive role in the outcome of further therapy or with the introduction of new or more difficult tasks.

That increased variability has been found at dynamic periods of cognitive decline and development suggests, not surprisingly, that these transitions do not occur uniformly. It seems probable that such variability indicates a lack of system stability that is influenced by opposing tendencies. On one hand, in a progression towards overall decline, increased variability results as the valleys of performance drop more deeply; on the other, in the case of development, or recovery, the heightening of peaks is responsible for the observed fluctuation. In support of this, increasing latency for an individual's slowest reaction times is related to increasing variability for older adults (Williams, Hultsch, Strauss, Hunter, & Tannock, 2005). Nevertheless, cognitive enhancement can occur with training and stimulation programs, with functional gains reported in daily life despite increasing age (Willis et al., 2006). As in development and recovery, when older subjects realize increased potential, greater intra-individual variability is correlated with improved learning (Li et al., 2004).

In the present study, it is possible that individuals demonstrating less variability are at or near an asymptote of their abilities, given their neurological status, the extent of lesion damage, and the degree to which they have already experienced recovery. While it is generally accepted that individuals with aphasia encounter a plateau within the first year following stroke (Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1995), intra-individual variability may serve as a more sensitive, individualized measure of potential than time post stroke, as well as an immediate and cost efficient means of prediction.

The implications for language rehabilitation are of great significance, as predictors of response to aphasia treatment are presently limited. Specifically, it may be productive for

clinicians to target skills in which patients demonstrate high performance variability prior to treatment, rather than areas in which limited variability suggests a reduced capacity for gains with therapy. It may also be productive to periodically re-assess patient performance on a variety of tasks, in order to determine whether cycling through treatment goals, selected on the basis of variability as a proxy for potential, may be beneficial. However, such possibilities should be interpreted with caution, as the present study represents a new avenue of inquiry, and little is yet known about how intra-individual variability changes over the course of recovery. Although the present analysis considered time post onset, subjects participating in this study were all at chronic aphasia stages. Therefore, there is no suggestion that findings would be identical or even similar in acute phases of recovery. Additionally, several measures that may impact variability in task performance were not included in our assessment, such as attention, mood, and fatigue. Future studies would benefit from operationalization and inclusion of these variables.

Further limitations of our study include the potential for practice effects, given the relatively short time over which these tests were administered. However, we believe that the lack of significant differences between the two pre-therapy time points and the two post-therapy time points suggests that this is not a major confound for the present study. While our inclusion of fluent vs. nonfluent aphasia classifications did not indicate significant differences in benefit between these groups, there was not adequate power in our sample to address the differential effects of repetition therapy that may exist for different aphasia types. It is also worth noting that our imitation-based therapy was heavily dependent on motor processes, as was our repetition outcome measure. Therefore, it is not possible to definitively state that intra-individual variability would predict improvement on purely cognitively based tasks.

While extrapolation from the present study to clinical guidelines would be premature, if the relationship between behavioral intra-individual variability and post-treatment performance withstands further exploration, it may suggest that those demonstrating higher levels of baseline variability are good candidates for intervention. Intra-individual variability, in this conception, could represent a measure of plastic potential, the extent to which an individual's present neurological status is conducive to the kind of recovery or reorganization necessary to manifest improvement with practice and stimulation. However, individuals performing consistently at the same level may require different types of intervention if they are to realize enhanced function, and these patients may be better candidates for referral to clinical trials, pharmacology or more invasive forms of treatment.

Chapter 5: Effects of Imitation-Based Aphasia Therapy on Narrative Content

5.1 Introduction

Generalization has long been recognized as one of the most significant challenges to the treatment of disorders of speech and language (e.g., Ingham, 1980; Palyo, Cooke, Schuler, & Apolloni, 1979; Wambaugh, Kalinyak-Fliszar, West, & Doyle, 1998). Typically, a patient trained on one task, such as orally producing the word "hammer" when shown a hammer, demonstrates improvement for that same item and task with practice. Generalization refers to the ability for an individual trained in one behavior to demonstrate improvement on a different, untrained behavior, such as being able to verbally label a screwdriver or to write the word "hammer".

With aphasia, as with other language deficits, generalization is both a primary concern and an often unrealized goal. This is true across various measures, including naming (Nickels, 2002), discourse comprehension (Kiran, Des Roches, Villard, & Tripodis, 2015), and the production of scripts (Cherney, Kaye, Lee, & van Vuuren, 2015). For the roughly one million Americans diagnosed with aphasia (NIDCD, 2010), there is no cure, although speech therapy provides some benefit (Brady et al., 2012). Despite this prevalence, similar to that of Parkinson's disease, aphasia is little known outside the spheres of neurologically trained medical professionals, aphasia patients, and their families.

Unlike Parkinson's disease, aphasia is not an organic disease per se. Rather, the deficits that we observe in aphasia are the result of a biological process such as stroke, traumatic brain injury, or brain tumor that results in injury to neural circuits supporting language behaviors. Thus, aphasia may be more accurately conceived of as symptomatic, rather than causal. As aphasia results from biological damage, the greatest benefits in its treatment may be achieved through

interventions that are biologically informed (Small, 2000).

Imitation has historically been incorporated into many different treatment protocols and used with many types of aphasia (Duncan & Small, 2015). More recent discoveries in neurophysiology have given rise to a biological motivation for the use of imitation in language rehabilitation, as mirror neurons in macaque (di Pellegrino et al., 1992) and analogous mirror properties in humans (Buccino et al., 2001) have been found to underlie both observation and execution of mouth actions, including speech (Skipper et al., 2007). This suggests that we may be able to harness the stimulatory effects elicited by observing speech to support a consequent increase in the production of speech.

IMITATE therapy was motivated by this concept, that engagement of the shared anatomical network underlying the observation and execution of speech (Mashal et al., 2012) would enhance the ability of individuals with aphasia to produce verbal output (J. Lee et al., 2010). In the therapy, individuals with aphasia repeat words and phrases presented by human speakers on a laptop. We have previously shown (Chapter 4; Duncan et al., 2016) therapeutic benefit on a standard test of aphasia, with particular effects on repetition, but additional effects on naming and word finding tasks from the Western Aphasia Battery (Kertesz, 2006). These findings suggest that improvement following imitation-based treatment extends beyond trained items and is not restricted to the practiced task.

The current investigation hypothesizes that the imitation-based therapy will generalize to narrative production. In particular, we examine the changes of our patients on the "Cinderella" task (Saffran et al., 1989), i.e., their ability to produce this well-known fairytale. We also seek to investigate the relationship of select demographic, behavioral, and neurological variables with this benefit.

5.2 Materials & Methods

5.2.1 Participants

Participants are nineteen subjects as described in Section 3.1. Select demographic and neurological information is listed in Table 3.1, and lesion overlap is depicted in Figure 3.1.

5.2.2 Neuroimaging

Structural magnetic resonance imaging (MRI) was acquired prior to therapy to assess lesion size and location. Details about acquisition of T1-weighted anatomical scans can be found in Section 3.5.1. Lesions were drawn by hand under the supervision of a trained neuroanatomist in order to assess lesion location and calculate lesion volume.

5.2.3 Behavioral Measures

Behavioral evaluations were performed at two separate time points before therapy (baseline assessment) and two time points after therapy. Baseline evaluations occurred 6 weeks (Week -6) and immediately (Week 0) before therapy. Post-therapy evaluations occurred immediately following the 6-week therapy interval (Week 6) and 6 weeks following the conclusion of treatment (Week 12). At each time point, narratives were elicited by having participants tell the story of the fairytale Cinderella (Saffran et al., 1989) and analyzed for correct information units (CIUs) as described in Section 3.4.3. One subject (20) was excluded due to missing data, leaving 18 subjects.

One-tailed paired t-tests ($\alpha = 0.05$) were used to compare number and percent of CIUs produced pre- vs. post-therapy due to our strong *a priori* hypothesis that the therapy would increase productive output. Two-tailed paired t-tests were used to compare number and percent

of CIUs produced between the two baseline sessions, and between the two post-therapy sessions. One subject (10) missed the Week 12 assessment and was therefore excluded from the t-test comparing the two post-therapy sessions, leaving 17 subjects.

Pre-therapy and mean scores for both number and percent of CIUs as well as post-therapy (Week 6) scores for both measures are shown in Table 5.1. This table also includes select demographic variables (age and sex; see Table 5.2 for additional variables).

Subject	Sex	Age	Pre-therapy CIUs (#)	Week 6 CIUs (#)	Pre-therapy CIUs (%)	Week 6 CIUs (%)
1	F	72	0.0	0	0	0
2	M	60	10.0	0	15.0	0
4	M	63	0.0	0	0	0
5	M	56	30.5	119	30.0	38.3
6	M	65	146.5	244	38.6	43.8
9	F	46	22.5	33	40.7	48.5
10	F	31	92.0	178	43.0	42.5
11	M	58	2.5	10	5.2	20.4
12	F	55	145.0	160	70.4	70.8
13	M	36	41.5	45	49.9	57.7
14	M	37	30.0	32	18.0	30.0
15	M	70	91.5	200	61.4	65.2
16	M	58	146.5	270	56.1	70.0
17	M	57	248.0	190	54.0	67.4
18	M	55	16.5	3	9.0	1.1
19	M	42	254.0	383	63.2	60.0
20	M	60	2.0	---	3.2	---
21	M	43	7.0	14	7.3	10.3
22	M	49	4.5	26	7.9	15.7

Table 5.1 Select Demographic Information and Pre-/Post-therapy Performance on Cinderella Narrative Task. CIUs correct information units; # = number; % = percent.

Two separate stepwise regression analyses were used to identify variables associated with changes in number of CIUs and percent of CIUs following treatment (Week 6 compared to baseline). Regression was performed using the MATLAB `stepwise` function with the default settings using a criterion of $\alpha = 0.05$ to select new predictors and $\alpha = 0.10$ to exclude existing predictors. Variables included as potential predictors in the regression model included age,

months post stroke onset (MPO), number of therapy sessions completed (NSC), fluency (fluent vs. nonfluent), lesion size, and baseline performance (i.e., mean number or percent of CIUs produced pre-therapy). Values for these variables are shown in Tables 5.1 and 5.2.

Subject	MPO	NSC	Aphasia Classification	Fluency	Lesion Size (cm^3)	Lesion Location
1	17	88	Broca's	N	61.88	FIPT
2	5	84	Broca's	N	50.46	FI
4	7	54	Broca's	N	45.38	FIPT
5	16	90	Broca's	N	49.21	FPT
6	8	90	Conduction	F	42.12	TP
9	28	108	Broca's	N	130.58	FPT
10	11	106	Anomic	F	158.29	FIPT
11	13	101	Trans. Motor	N	137.13	FIPT
12	22	108	Anomic	F	14.11	BG
13	78	108	Broca's	N	86.93	FIPT
14	51	105	Broca's	N	90.69	TIPO
15	120	99	Anomic	F	219.06	FIPT
16	29	108	Anomic	F	48.66	FI
17	130	107	Anomic	F	82.35	FIPT
18	81	79	Wernicke's	F	162.10	FIPTO
19	124	53	Anomic	F	36.58	FI
20	7	103	Trans. Sensory	F	100.62	TPO
21	15	108	Broca's	N	81.98	FIT
22	29	108	Broca's	N	100.62	FIPT

Table 5.2 Potential Predictors of Maintenance Used in the Regression Model. These include age, months post stroke onset (MPO), number of therapy sessions completed (NSC), aphasia classification and fluency (F=fluent; N=nonfluent), lesion size (in cubic centimeters), and lesion location. Lesion location is abbreviated as follows: F- Frontal, P- Parietal, T-Temporal, I-Insular, O-Occipital, BG- Basal Ganglia. Aphasia classifications are as determined by the Western Aphasia Battery-Revised (Kertesz, 2006) and Transcortical is abbreviated (Trans).

Pearson correlation coefficient was calculated for any variable found to be significantly predictive of either outcome (i.e., change in number or percent CIUs) with the predicted outcome measure.

5.3 Results

5.3.1 Neuroimaging Findings

The mean lesion size was 89.4 cm^3 (range= 14.1 – 219.1, SD= 52.4). Lesion sizes for individual participants are included in Table 5.2.

5.3.2 Behavioral Measures

The mean change in number of CIUs produced for the narrative task from pre- to post-therapy (Week 6) was 34.36 (SD = 55.15; range -58 to 129). This increase was significant at α= 0.05 ($t(17) = -2.64$, p= 0.009) with an effect size of 0.377. There were no significant differences between the two pre-therapy sessions ($t(17) = -0.17$; p = 0.864) or the two post-therapy sessions ($t(16) = -0.50$; p = 0.622).

The mean change in percent of CIUs produced for the narrative task from pre- to post-therapy (Week 6) was 3.99 (SD= 7.88; range -15.01 to 15.20). This increase was significant at α= 0.05 ($t(17)= -2.14$, p= 0.023) with an effect size of 0.215. There were no significant differences between the two pre-therapy sessions ($t(17) = 0.375$; p = 0.712) or the two post-therapy sessions ($t(16) = -1.08$; p= 0.294).

Stepwise regression performed to identify variables significantly predictive of the change in number of CIUs produced following therapy selected no variables. For the change in percent of CIUs produced following therapy, the sole variable selected was the number of sessions completed (F= 6.67; p = 0.020; MSE= 6.82).

This variable was found to have a significant positive correlation with post-therapy change in percent of CIUs produce during the narrative task (r= 0.542; p = 0.020). Figure 5.1 shows the relationship between these variables.

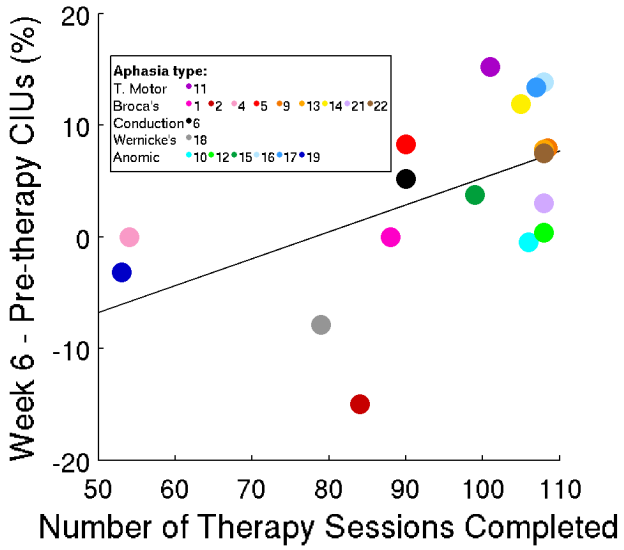

Figure 5.1 Number of Sessions Completed and Percent Change in CIU Production. Y axis shows the change in percent of words produced that were CIUs during the Cinderella narrative task immediately following therapy (Week 6) compared to baseline. Figure legend indicates individual subjects by aphasia type. CIU= correct information unit.

5.4 Discussion

The present analysis examines the effects of imitation-based aphasia therapy on generalization of therapeutic effect. We find that patients with aphasia demonstrate significant improvement on a narrative task following a 6-week period of intensive therapy involving repetition of words and phrases. This behavioral outcome is of particular interest as the practiced task is quite dissimilar to the measure on which improvement was demonstrated. Failure to achieve generalization is a significant obstacle in aphasia treatment, and it is most common for benefits of therapy to be restricted to precisely the task and items that are explicitly trained, with no effect on untrained items, even on the identical task (Pring, Hamilton, Harwood, & Macbride, 1993). However, recent studies exploring speech entrainment, or online imitation, have found generalization to untrained scripts as well as to spontaneous speech (Fridriksson et al., 2012). These findings may suggest a unique benefit of imitation-based therapy.

Our two outcome measures on the narrative task are the number and percent of CIUs produced following therapy. Overall, our participants demonstrate significant increases for both of these measures. These changes indicate that individuals with aphasia are able to produce narratives that are more informative and efficient following intensive imitation practice, despite the fact that neither the narrative task nor the specific words and phrases used in the task are related to the content of training. Additionally, that there were no significant differences found for these measures six weeks following the termination of treatment suggests that they are able to maintain these benefits once achieved. Maintenance of treatment effects, similar to generalization to untrained behaviors, is an infrequently met treatment goal (Dechene et al., 2011; Fridriksson et al., 2012), making this finding of particular practical interest.

None of the demographic, behavioral, or neurological measures included in our regression model predicts the change in number of CIUs produced following therapy. However, individual compliance with the requested therapy intensity does vary in our sample, and we do find a positive correlation between change in percent of CIUs produced and the number of sessions completed over the course of treatment. This is perhaps unsurprising, as more treatment (Carpenter & Cherney, 2016) and higher intensity (Bhogal et al., 2003) are associated with better outcomes following therapy. However, it may be unexpected that this measure trumps other variables previously found to be associated with aphasia prognostication, such as time since onset (Pickersgill & Lincoln, 1983) and lesion size (Plowman, Hentz, & Ellis, 2012).

High intensity was a key design feature of IMITATE. It is theorized that the sort of massed stimulation provided by our treatment program supports implicit learning through the repeated engagement of neural pathways which are consequently strengthened, or that lead to the formation of new pathways (Ferguson, 1999). While the present study does not explore the brain

changes underlying our findings, generalization following aphasia therapy, such as that demonstrated by our participants, is associated with changes in functional connectivity as measured by functional magnetic resonance imaging (Sandberg, Bohland, & Kiran, 2015). Further suggestion that synaptic changes facilitate generalization can be found in the literature on transcranial direct current stimulation, a form of noninvasive brain stimulation that is found to promote generalization, as well as maintenance, when paired with aphasia therapy (de Aguiar et al., 2015; Meinzer, Darkow, Lindenberg, & Floel, 2016).

There is strong evidence for causality in the relationship between our therapy and changes on the narrative task, as significant changes occur only over the duration of therapy. No significant changes occur during the two equally spaced pre-therapy assessments, or during two similar post-therapy sessions, allowing us to be quite confident that it was indeed the therapy that produced the observed effect. Our findings of a significant positive correlation between the number of sessions completed and the change in percent CIUs produced may or may not be causal. It is possible that participants who did not feel that the therapy was benefiting them were therefore less motivated to complete as many sessions, and thus the poor performance actually caused fewer sessions to be completed. This explanation is judged to be unlikely, however, as individuals with poor compliance completed fewer sessions throughout the entire 6-week duration of treatment, rather than reducing participation over the course of the program as might be expected in the case of waning enthusiasm for the therapy. However, it remains possible that another factor such as attention – known to be impaired in aphasia (Tseng et al., 1993) – may have resulted in both limited participation and lesser benefit of therapy.

The present treatment study uses a biologically motivated approach to aphasia therapy and finds significant generalization beyond the practiced task of imitation. Further, the more therapy

sessions that are completed, the greater is the therapeutic benefit. This is interpreted as support for our hypothesis that through the engagement of populations of neurons active during the observation and execution of speech, we are strengthening those networks' ability to support the production of speech. By using a general approach that targets the processes subserving imitation, we are able to achieve generalized benefits in the domains of speech and language.

Chapter 6: Changes in Dynamic Resting State Network Connectivity Following Aphasia Therapy

6.1 Introduction

Resting state functional magnetic resonance imaging (rsfMRI) permits observation of neural networks produced by correlated low frequency activity across the brain when not engaged in any particular task. These low frequency fluctuations in the hemodynamic response found in rsfMRI are believed to serve as proxy for estimating baseline neuronal activity in the brain, and the relationships that emerge reflect networks that typically are engaged in some shared function (Damoiseaux et al., 2006). Resting state networks (RSNs) have been investigated extensively in healthy controls, and to a lesser extent in neurological disease, including Alzheimer's disease and schizophrenia (Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005; Woodward, Rogers, & Heckers, 2011). Examination of RSNs in the study of acute and chronic stroke has been less common, and there is limited understanding of how these networks are associated with functional behavioral deficits and recovery. Characterizing RSNs in chronic stroke, and in particular, individuals with post-stroke deficits such as aphasia, could lead to important biomarkers for therapeutic selection and prognosis, or as an objective measure of rehabilitation.

In aphasia, treatment with any of myriad traditional approaches has some benefit although there is no scientific basis for choosing an appropriate therapy for a given individual, and scant evidence that it even makes a difference (Brady et al., 2012). There is also little insight thus far into the considerable variability in treatment outcomes among patients. Further, the mechanisms of plasticity underlying functional gains experienced with therapy remain debated. Models of plasticity associated with aphasia recovery are typically localizational in nature, focusing on

increasing or decreasing activation in regions thought, respectively, to underlie compensatory or maladaptive reorganization of cortices involved in language tasks (Abel, Weiller, Huber, Willmes, & Specht, 2015; Marcotte et al., 2012). As the field of neuroscience increasingly recognizes the brain as the sum of its connections to a greater extent than its parts, it is appropriate that investigation of aphasia recovery should likewise refocus on the interrelationship of neural networks associated with gains in language ability following therapy. This could lead to novel approaches to solving the problems related to therapy selection, explaining variability, and providing prognosis.

Previous investigation in rsfMRI indicates disrupted functional connectivity following stroke that is significantly associated with degree of language impairment (Zhu et al., 2014) and also suggests that RSNs change with aphasia therapy. Intensive treatment with semantic feature analysis results in increased integration within the default mode network, and this increased integration is positively correlated with better treatment outcome (Marcotte, Perlbarg, Marrelec, Benali, & Ansaldo, 2013). Increased functional connectivity has also been found within language networks, with reorganization following treatment to appear more similar to healthy controls (van Hees et al., 2014).

Appreciation of the interconnected nature of the brain is not without its own controversies. Graph theoretic analyses of the brain suggest that its complex composition simultaneously requires segregation of functions, and therefore of regional activations and their connectivity, as well as integration of these units to form a cohesive whole capable of directing behavior (Sporns, 2013). Thus, segregation promotes specialization within a unit, while integration facilitates the unification necessary to coordinate interaction among these specialized units. Stroke necessarily disrupts both of these processes to some extent, and functional recovery may hinge on their

return to a relative balance (Falcon et al., 2015).

Currently, most investigations of functional connectivity collapse across scan time, using a single statistic to represent the aggregate interactions within a network or between regions of interest. While this work is of significant importance, the dynamic nature of brain function, perhaps most acutely assessed by electroencephalography (EEG) or electrocorticography (ECoG), but also informative at the lower temporal resolution of rsfMRI, permits unique insight into the time-dependent roles of neural networks (Calhoun, Miller, Pearlson, & Adali, 2014). Sliding window approaches to functional connectivity examine time-varying correlations among RSNs. Such approaches can extend our understanding of brain function by providing more nuanced measurement of network dynamics, which are particularly valuable in deciphering the neural underpinnings of human behavior (Hutchison et al., 2013).

The present study interrogates the changing nature of the relationships among RSNs over the course of a novel, computer-based imitation therapy program (IMITATE; Duncan et al., 2016; Lee et al., 2010) as it relates to behavioral gains in the production of meaningful language. We analyze rsfMRI scans acquired before and after treatment to better understand the mechanisms of plasticity underlying recovery of language functions. We hypothesize that aphasia patients will demonstrate changes in the correlations of RSNs associated with behavioral changes following therapy.

6.2. Materials & Methods

6.2.1 Participants

The nineteen patients recruited for participation in the study are described in Section 3.1 and Table 3.1, with lesion overlap depicted in Figure 3.1. From this group, twelve participants were

selected for the present analysis on the basis of participation in three baseline rsfMRI scans prior to initiation of therapy (excluding subjects 1,2,5,18,20). Of the fourteen participants who qualified, two additional subjects (14, 17) were excluded due to excessive motion, leaving the twelve subjects included in this analysis. These subjects were overall similar to the larger sample (age range 31-70; mean= 52.08; SD= 11.75; 3 female (25%)). All participants had sustained a single stroke 7 to 124 months prior to enrollment (mean = 40.33; SD 42.55). Additional information about the therapy can be found in Sections 3.3 and 3.4.

6.2.2 Behavioral Measures

The behavioral task and related significant results are reported in Chapters 3 and 5, respectively. Participants were recorded telling the story of the Cinderella fairytale (Saffran et al., 1989) twice before and twice following six weeks of intensive aphasia therapy (see Section 3.2 and Figure 3.2 for study design). The number of correct information units (CIUs; (Nicholas & Brookshire, 1993)) produced was calculated for each time point (see Sections 3.4.3 for methods and 5.3.2 for results). One subject (10) missed the second post-therapy (Week 12) behavioral evaluation.

6.2.3 Neuroimaging

6.2.3.1 Acquisition

Magnetic resonance imaging (MRI) was acquired at three time points before therapy (Weeks -6, -3, 0) and one to three time points after its conclusion (Weeks 6, 9, 12). Study description can be found in Section 3.2 and acquisition details can be found in Section 3.5.1. Both high resolution anatomical and five minutes of functional resting state data were acquired.

6.2.3.2 Preprocessing

The first four rsfMRI volumes were discarded to ensure the steady state of the scanner. Preprocessing of rsfMRI images consisted of slice timing correction, despiking, and registration using AFNI (Cox, 1996) and FSL (Smith et al., 2004). A Gaussian smoothing kernel of 4 mm FWHM was applied to increase signal-to-noise ratio. White matter, ventricle and hand-drawn lesion masks were used to create nuisance time series that were regressed out of the signal along with motion and polynomial (linear and quadratic) trends using AFNI's 3dDeconvolve. For time points containing motion greater than 3 mm, neither the volume containing the movement nor the one following it were included in the regression. After deconvolution using AFNI's 3dDeconvolve, these censored time points were filled using a cubic spline interpolation to facilitate the continuity required for the sliding window analysis described below. Band-pass filtering (0.01 to 0.1 Hz) was then performed in order to identify the low frequency fluctuations of interest.

Anatomical scans were used to create a common template following reconstruction of the cortical surface with FreeSurfer (Fischl, 2012) facilitated by Virtual Brain Transplant (Solodkin et al., 2010). For each time point, an anatomical scan was registered to the rsfMRI for individual preprocessing, and then to this common template, with individual transformation matrices applied to the band-pass filtered rsfMRI data to permit group analysis.

Two subjects (11,19) missed the scan immediately post-therapy (Week 6). Two subjects (4,10) missed the scan at the 6-week maintenance interval (Week 12).

6.2.4 Dynamic Functional Network Connectivity

Spatial independent component analysis (ICA) and dynamic functional network connectivity

(dFNC) were performed using the Group ICA of fMRI Toolbox (GIFT; Calhoun, 2004).

Time series were initially mean-centered, and then whitening and dimension reduction were achieved using subject-specific principal component analysis (PCA) to extract the first twenty eigenvectors (low-order Gaussian features). Group ICA was then performed using the Infomax algorithm to identify twenty independent higher-order non-Gaussian features of the reduced data. ICASSO (Himberg, Hyvarinen, & Esposito, 2004) was used to ensure the stability of the extracted features, repeating the decomposition ten times using random initiation and bootstrapping.

Of the twenty components yielded via ICA, eight were identified as true components that did not overlap with regions of known vascular, motion, and susceptibility artifacts and that were consistent with RSNs previously identified in the literature (Damoiseaux et al., 2006; Lee et al., 2012). These components were used to compute dynamic functional network connectivity via a sliding window approach using windows of twenty volumes (30 s) in steps of one volume (1.5 s). Edges were tapered by convolving a rectangular window with a Gaussian function using the standard deviation of three windows (i.e., the window of interest and surrounding windows). Due to the brevity of the window (30 s) and concomitant risk of increased influence of noise, sparsity was induced by applying graphical LASSO (Friedman, Hastie, & Tibshirani, 2008), with lambda value optimized for each scan using cross-validation. Following estimation of covariance among these eight RSNs, values were Fisher-Z transformed to permit valid comparison across individuals.

Normalized covariance relationships between networks within a given window were then grouped into ten states using k-means clustering. The number of states was selected based on the amount of variance accounted for by each added state in order to control for overfitting. The

cutoff (k) was selected as the largest number of clusters that explained more variance (measured by sum of squared L_1 distances) than did k-1 clusters.

6.2.5 Individual Correlations in Functional Connectivity States and Behavioral Measures

Differences in the amount of time (number of 30-second windows) spent in each of the ten functional network connectivity states ("dwell time") were correlated with differences in number of CIUs produced before and after therapy to identify states that are facilitative or obstructive to treatment benefit. Pre-therapy dwell times were calculated as the mean number of windows clustered in a particular state during the three baseline scans (Weeks -6, -3, 0). Post-therapy dwell times were calculated as the mean number of windows clustered in a particular state during the one to three scans acquired after conclusion of therapy (Weeks 6, 9, 12). The pre-therapy CIU measure was defined as average number of CIUs for the two pre-therapy assessments. These correlations were corrected for multiple comparisons (α=0.05/10 states).

If a state was significantly correlated with behavioral change, three further correlations were calculated to examine the relationship between changes in dwell time and number of CIUs produced for each individual post-therapy time point (Week 6 vs. baseline, Week 12 vs. baseline), as well as between the two post-therapy time points (Week 12 vs. Week 6). Pearson correlation coefficients were corrected for multiple comparisons (α=0.05/3 comparisons). These comparisons were also repeated using a partial correlation controlling for number of CIUs produced pre-therapy.

A repeated measures ANOVA was used to compare baseline dwell times to ensure that connectivity states did not significantly differ among pre-therapy scans.

6.3. Results

6.3.1 Resting State Networks (RSNs)

The eight RSNs identified via group ICA are pictured in Figure 6.1 (highest 5% of Z scores for mean components for the group). They are most consistent with a dorsal attention network (DAN), frontoparietal control network (FPC), default mode network (DMN), language network (LAN), left ventral attention network (LVAN), right ventral attention network (RVAN), sensorimotor network (SMN), and visual network (VIS) (Lee et al., 2012). Four of these networks (DAN, DMN, LAN, SMN) appear to be more right lateralized than those found in healthy controls, consistent with left hemisphere lesion. Figures showing the overlap of these components with those from healthy controls can be seen in Appendix B (Figures B.1 – B.8).

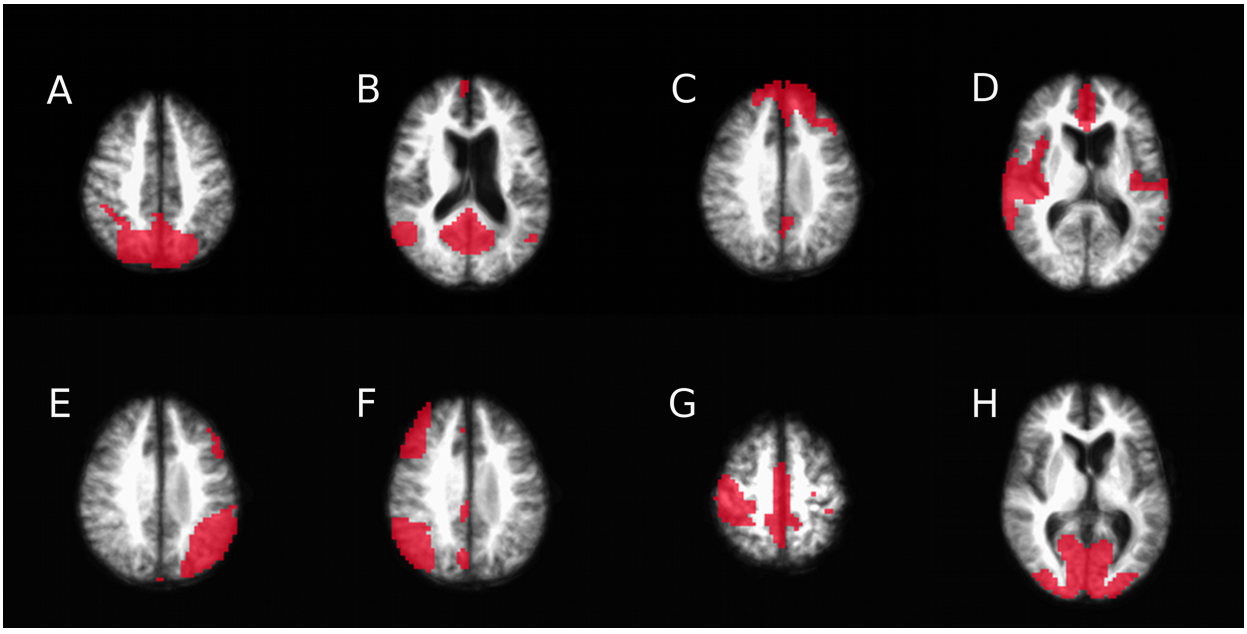

Figure 6.1 Resting State Networks (RSNs) Displayed on a Group Template. A: dorsal attention network (DAN); B: default mode network (DMN); C: frontoparietal control network (FPC); D: language network (LAN); E: left ventral attention network (LVAN); F: right ventral attention network (RVAN); G: sensorimotor network (SMN); H: visual network (VIS). As radiological convention is used, left hemisphere is depicted on right side.

The twelve artifactual ICA components that were excluded from further analysis can be seen in Appendix A (Figures A.1 – A.12). Similarity estimates for the ten repetitions of ICA can be seen for all components in Figure 6.2, with identified RSNs labeled.

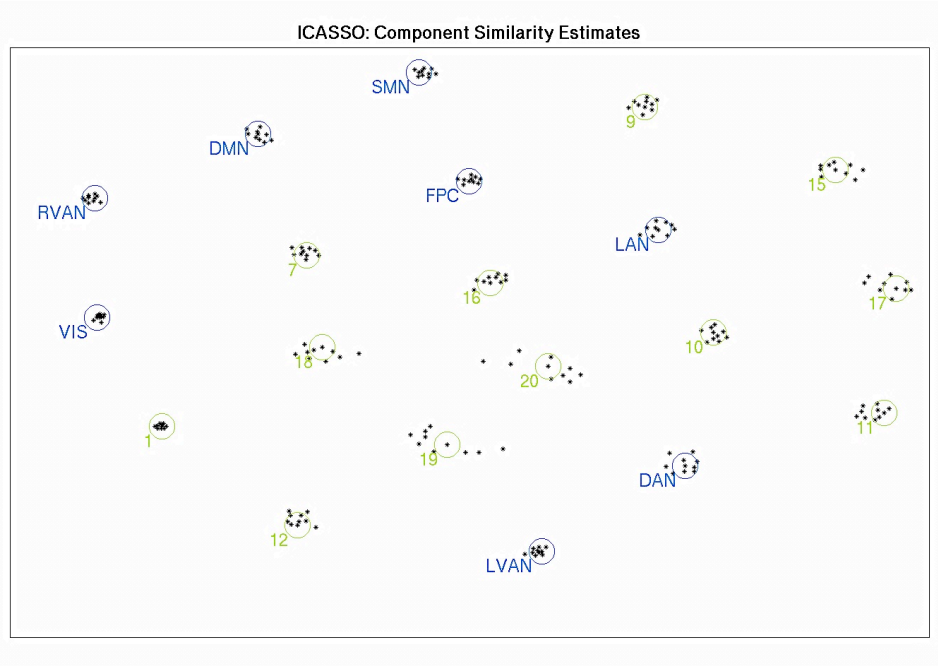

Figure 6.2 Similarity Graph for ICASSO Estimates. Each of the ten repetitions of ICASSO (Himberg et al., 2004) for each of the twenty components detected with independent component analysis (ICA), visualized as a unitless two-dimensional plot. Each dot represents a component estimate from one repetition of the ICA decomposition. A circle estimates the centroid of each individual component cluster. Tighter clusters indicate more reliable components. Numbers represent components that were identified as artifactual (see Appendix A). Acronyms represent components identified as resting state networks (RSNs) and are abbreviated as follows: DAN= dorsal attention network; DMN= default mode network; FPC= frontoparietal control network; LAN= language network; LVAN= left ventral attention network; RVAN= right ventral attention network; SMN= sensorimotor network; VIS= visual network. RSNs can be seen in Figure 6.1.

6.3.2 Dynamic Functional Network Connectivity

Figure 6.3 shows the correlation matrix for the single dynamic functional network connectivity state (state 10) found to correlate significantly with changes in behavior ($\alpha = 0.05/10$; see below).

State 10 may be described as a state of near zero correlation among RSNs (mean = 0.014; range -0.105 to +0.134). An ANOVA comparing baseline dwell times in state 10 indicated no significant differences among the three pre-therapy sessions (p = 0.376).

6.3.3 Individual Correlations in Functional Connectivity States and Behavioral Measures

Dwell time in a single state (state 10; See Figure 6.3) was found to change in tandem with changes in number of CIUs produced ($\alpha = 0.05/10$) when pre- and post-therapy measures were compared. Pearson correlation coefficient between increased number of CIUs produced and increased dwell time in state 10 was significant (r = 0.785; p = 0.004).

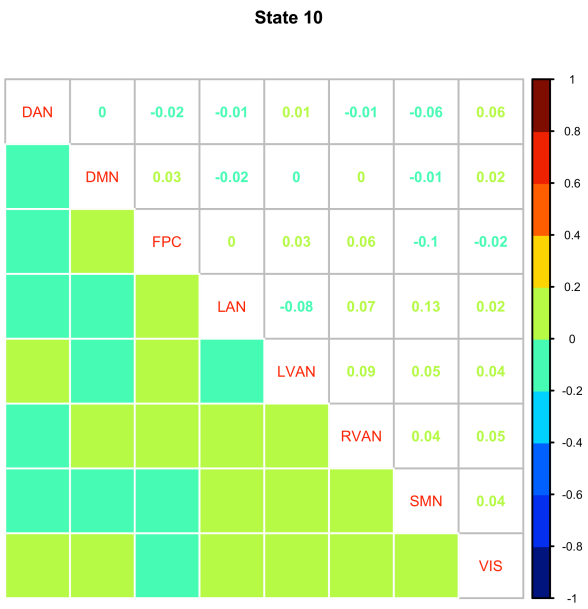

Figure 6.3 Correlation Matrix Representing State 10. Increased time spent in state 10 was positively correlated with increase in correct information units (CIUs) on the narrative production task at the maintenance interval compared to baseline (p = 0.002) and immediately post-therapy (p = 0.012). From left to right on the x axis and top to bottom on the y axis, resting state networks (RSNs) are: dorsal attention (DAN), default mode (DMN), frontoparietal control (FPC), language (LAN), left ventral attention (LVAN), right ventral attention (RVAN), sensorimotor (SMN), and visual (VIS). Color bar shows binned correlation values, upper triangle shows actual Pearson correlation coefficients (r).

The nine additional states dynamic functional network connectivity states that were not significantly correlated with behavioral change can be seen in Appendix C (Figure C.1).

When each of the post-therapy CIU scores and state 10 dwell times were compared to baseline, the Week 6 comparison was significant at $\alpha = 0.05$ ($p = 0.033$), but did not withstand correction for multiple comparisons. The Week 12 comparison was significant when corrected for multiple comparisons ($r = 0.842$; $p = 0.002$), as was the comparison between Week 6 and Week 12 ($r = 0.821$, $p = 0.012$). Figure 6.4 shows the relationship between changes in dwell time in state 10 and changes in number of CIUs produced post-therapy compared to pre-therapy and at Weeks 6 and 12 compared to baseline. Comparison using partial correlation to control for pre-therapy CIU production remained significant at $\alpha=0.05$ for Week 12 performance compared to Week 6 ($r= 0.819$, $p= 0.024$; see Figure 6.5), with trends for post- vs. pre-therapy ($r= 0.565$, $p= 0.089$) and for Week 12 compared to baseline ($r= 0.650$, $p= 0.058$).

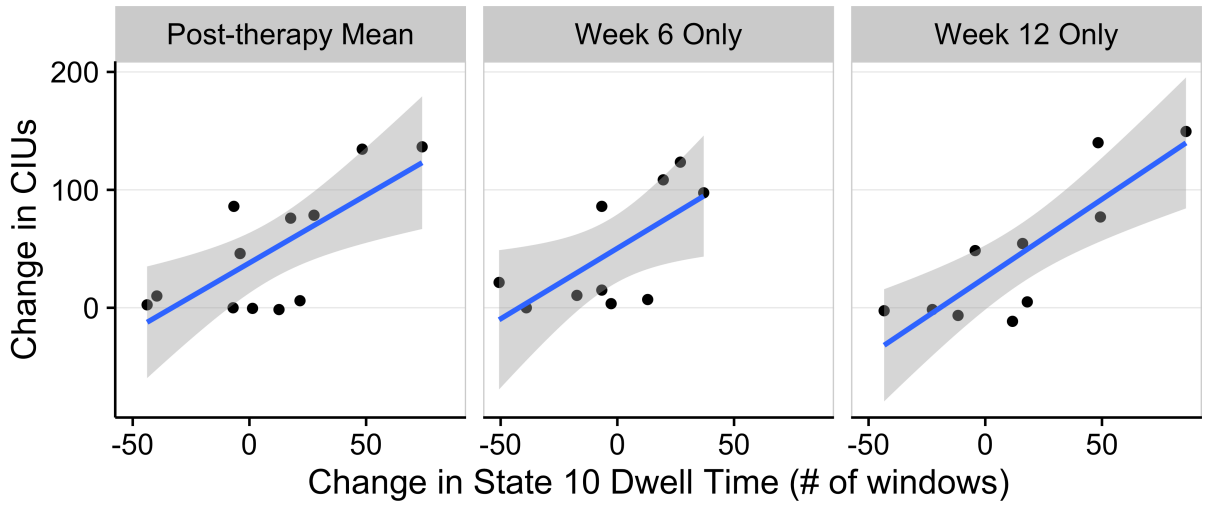

Figure 6.4 Changes from Baseline in State 10 Dwell Time and CIU Production. Left panel averages across all post-therapy behavioral and neuroimaging measures (including Week 9, at which time no behavioral measures were recorded). Middle panel indicates differences between Week 6 and baseline. Right panel indicates differences between Week 12 and baseline. CIU= correct information unit.

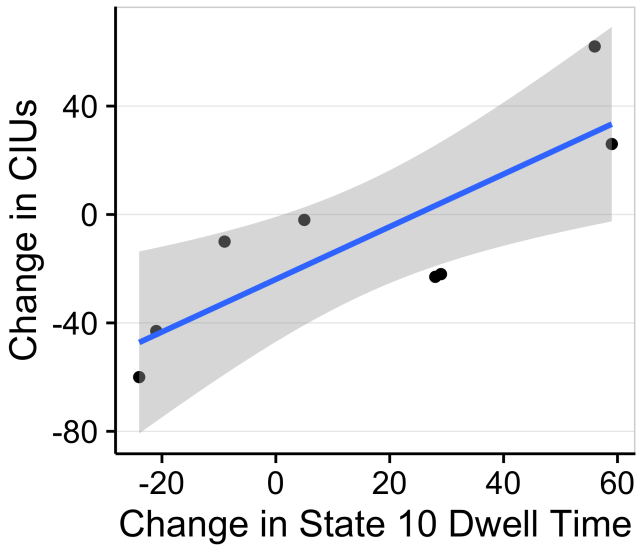

Figure 6.5 Post-therapy Changes in State 10 Dwell Time and CIU Production. Both x and y axis show contrasts between Week 12 (6 weeks following therapy) and Week 6 (immediately post-therapy). As two subjects (11,19) missed the scan immediately post-therapy and two subjects (4,10) missed the scan at the maintenance interval, this analysis includes only 8 participants. CIU= correct information unit.

6.4 Discussion

The present study finds a shift in dynamic functional resting state connectivity associated with improvement on a narrative production task. Individuals demonstrating behavioral change (i.e., number of novel, correct information units produced during a narrative task) also demonstrated change in the amount of time spent in one particular state of brain functional connectivity. Improvement on the language task was associated with concomitant increase in the amount of time spent in a functional connectivity state best characterized by its minimal correlation between any of the RSNs identified here. This finding suggests that it may be increasing segregation among RSNs that drives recovery, at least in response to the imitation-based behavioral treatment used in this study.

In graph theoretic models of brain connectivity, the RSNs described here might be conceived of as distinct modules. In this conceptualization, a greater proportion of intermodular

connections (i.e., among RSNs) would represent increased integration, and a greater number of intramodular connections (i.e., within RSNs) would represent increased segregation. The driving force behind the tendency towards increased segregation, as observed in this investigation, might relate to the connectivity of specific hubs, or regions in the network. Connector hubs link different modules to a greater extent than any one single module, and thus promote integration, whereas provincial hubs, which are highly interconnected within a module and have few or no connections outside of it, increase segregation (Sporns, Honey, & Kotter, 2007).

Following this model, improvement in accurate, qualitative narrative production is driven by an increased ability to isolate those networks necessary to perform the task for individuals with chronic aphasia. This suggests that integration may be increasing within individual networks, as has been found previously (Marcotte et al., 2013; van Hees et al., 2014), yet with the global balance consequently shifting towards segregation of functional units. This is consistent with findings of more focal, efficient and presumably specialized activation that is observed in expert compared to novice motor control (Milton et al., 2007) and is associated with functional gains in motor (Ward, Brown, Thompson, & Frackowiak, 2003) and language (Abel et al., 2015) in stroke recovery.

When the architecture of the brain is disrupted by a focal lesion, many connections are necessarily lost. Processes of homeostatic plasticity attempting to ensure that surviving neurons continue to receive adequate input may cause inappropriate connections to form (Murphy & Corbett, 2009), and proximity will dictate that short-range connections are the most likely. The increased segregation associated with improvement in the present study is believed to represent the loss of short-range connections (Fair et al., 2007) that were not adaptive. The IMITATE therapy, designed to engage a cortical network underlying both observation and execution of

speech (Lee et al., 2010), induces experience-dependent Hebbian plasticity that likely increases synaptic weights within individual RSNs via long-term potentiation, while other (maladaptive) connections become weaker or are lost entirely.

Decreased segregation among brain networks is observed in healthy aging, and greater segregation predicts superior episodic memory across the lifespan (Chan, Park, Savalia, Petersen, & Wig, 2014), suggesting a positive role for specialization of neural networks in cognitive ability. Decreased clustering and local efficiency, both measures of segregation, have also been found for somatosensory and visual motor networks in Parkinson's disease (Tinaz, Lauro, Hallett, & Horovitz, 2016). These findings suggest that segregation of neural networks decreases with normal and pathological degeneration, and that this deterioration underlies the loss of functional skills.

This association between RSN segregation and improved verbal communication has a number of potentially significant clinical implications. For example, if segregation plays an adaptive role, behavioral interventions might seek to engage isolated functional RSNs through specific tasks, aiming to enhance network segregation through experience-dependent plastic changes. Further, it may be possible to enhance such segregation through pharmacotherapy or genetic intervention, to the extent that these distinct brain networks have different characteristics at a cellular level (e.g., dopamine in the default mode network). Although this line of reasoning requires considerable further investigation, we anticipate that the functional distinctions in the organization of these intrinsic RSNs may reflect important cellular and molecular differences that can provide therapeutic targets – that is, that there are neurotransmitters or receptors that can be targeted to induce integration within RSNs and thus promote segregation between them. Noninvasive brain stimulation techniques, such as transcranial magnetic stimulation and

transcranial direct current stimulation, may also be used to target regions included in one network that are anatomically distinct from regions in other networks. The most effective treatment might be a highly specified behavioral program seeking to target individual networks in combination with both physiological stimulation and pharmaceutical intervention, which in aggregate are designed to enhance synaptic plasticity in the individual networks.

Although the clinical possibilities are exciting, the present study does have several limitations. One is the small sample size and heterogeneity of the patient group in measures of age, aphasia type, baseline performance, and lesion size/location. Additionally, while the findings of reduced network coupling associated with behavioral improvement are provocative, the nature of this analysis does not permit exploration of intra-network dynamics. Future investigations will focus on understanding the roles of specific network relationships and the regions that contribute most significantly.

While a task as complex as narrative production certainly engages multiple networks, including those supporting sensorimotor, attention and cognitive control as well as language capacities, it is of great interest that it may be the functional integrity of the individual networks, rather than the strengthening of the connections between them, that underlies improvement on this task. Although the entire network requires integration of its constituent pieces in order to function, segregation of these components into synchronized individual units is paramount. Enhancing the specialization of distinct neural networks is key to achieving optimal functioning of the unified brain in chronic aphasia.

Chapter 7: Network Properties Underlying Changes in Narrative Production

7.1 Introduction

Graph theoretic approaches provide simplified metrics to characterize complex networks. By defining regions as nodes and the (functional or structural) connections between them as edges, the brain can be modeled as a graph and analyzed through the pairwise relationships among its component parts (Rubinov & Sporns, 2010). As measured by resting state functional magnetic resonance imaging (rsfMRI), our brains demonstrate the same types of topological properties found in other complex networks across various systems (Bullmore & Sporns, 2009).

Modularity is one key organizational principle found in social and biological systems (Girvan & Newman, 2002), including the human brain. To characterize the modularity of a network, individual nodes are first assigned to discrete communities by various methods. The modularity value of the network quantifies how many of the edges connected to a given node are also connected to another node within the same community, compared to if those edges had been distributed randomly (Newman & Girvan, 2004). Thus, modularity is essentially an index of how cleanly a network can be subdivided with a given partition, with higher values indicating more distinct subnetworks, or a greater level of segregation.

Figure 7.1 shows two different graphs that share many network characteristics. Each has 34 nodes. They share a similar number of edges connecting those nodes (7.1A = 81, 7.1B = 78). They also share a similar degree distribution, with each node having, on average, just under five connections to other nodes (7.1A = 4.59, 7.1B = 4.76). Each graph has been separated into five communities, indicated by node color, as this was determined to be the optimal number of communities for maximizing modularity for each of these networks individually. However, the

communities in Figure 7.1A overlap and share many edges among them, whereas the communities in Figure 7.1B are more discrete, and their modularity scores reflect this difference (0.29 and 0.41, respectively). This major difference in their organization is not surprising as the graph in 7.1A is a random construction, whereas the graph in 7.1B represents data from a social network (Zachary, 1977).

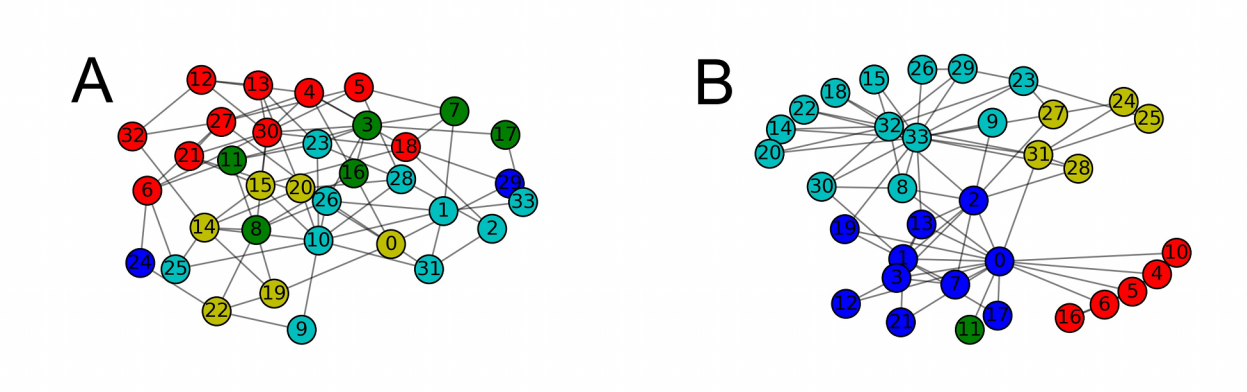

Figure 7.1 Visual Depiction of Two Graphs. A and B share similar network properties, including number of nodes, edges, communities, and average degree, yet the modularity of B (0.41) is much higher than that of A (0.29). A is a random network; B depicts data from a social organization (Zachary, 1977).

As modularity is a basic characteristic of complex networks under normal circumstances, it might be expected that a disruption to that network would result in a decrease in its modularity. In the brain, deprivation of blood flow results in changes in both cognitive function and functional connectivity and modularity as assessed by rsfMRI. For patients with unilateral carotid stenosis, modularity is negatively correlated with performance on neuropsychological tasks, including the Mini-Mental Status Examination (MMSE) and measures of reading and memory (Chang et al., 2016), and positively correlated with better post-operative cognitive outcomes (Soman et al., 2016). Focal lesions are also found to reduce measures of modularity (Gratton, Nomura, Pérez, & D'Esposito, 2012).

In healthy adults, higher modularity is associated with better working memory performance, a finding thought to reflect efficient organization and transmission of information throughout the brain (Stevens, Tappon, Garg, & Fair, 2012). It may, therefore, be unsurprising that measures of modularity are decreased in patients with Alzheimer disease (AD). This is also true for cognitively intact individuals demonstrating preclinical biomarker pathology suggestive of AD (Brier et al., 2014) when compared to controls without such pathology. However, even in healthy aging, brain changes are associated with alteration in its modular organization. Whole brain modularity declines with aging across the life span (Onoda & Yamaguchi, 2013), including when examining the modularity of intrinsic resting state networks (RSNs) exclusively (Song et al., 2014).

In a recent investigation of changes in dynamic functional network connectivity (dFNC) in patients with aphasia (see Chapter 6), we investigated the amount of time spent by each participant in one of a small number of states determined by clustering the dynamic network correlations. We found that imitation-based aphasia therapy led to improvement in narrative production that is associated with an increasing amount of time spent in one of these states, a state characterized by minimal correlations among resting state networks (Duncan & Small, under review). We interpret these findings as evidence for an association between greater functional segregation and better performance, as previously demonstrated in healthy aging (Chan et al., 2014) and Parkinson's disease (Tinaz, Lauro, Hallett, & Horovitz, 2016). They are also consistent with the finding that diffuse patterns of activation are replaced by more focal, and presumably efficient, organization as behavior improves, as has been found in motor learning (Milton et al., 2007), as well as post-stroke motor (Ward et al., 2003) and language (Abel et al., 2015) rehabilitation.

In the present study, we examine the hypothesis that assigning community structure based on membership in well-established resting state networks will result in changes in modularity that are positively correlated with behavioral changes in narrative production, as found in dynamic functional connectivity. Such findings would support the notion that successful therapy leads to increased network segregation, and would provide insight into the mechanism underlying behavioral improvement following treatment.

7.2. Materials & Methods

7.2.1 Participants

Nineteen native English speakers with chronic aphasia secondary to ischemic stroke participated in a larger study of intensive, imitation-based aphasia therapy (Duncan et al., 2016; Lee et al., 2010), as described in Section 3.1. Fourteen subjects were selected from that superset based on participation in three baseline rsfMRI scans prior to the initiation of therapy (see Section 6.2.1 for excluded subjects). Two additional subjects were excluded due to excessive motion during scanning (see Section 7.2.3.2 for details). The remaining group included in this analysis consisted of twelve individuals (3 female; 25%) ages 31 to 70 years (mean= 52.08; SD= 11.75) who had sustained a single stroke 7 to 124 months prior to enrollment (mean= 40.33; SD 42.55). Further information about the therapy is included in Sections 3.3 and 3.4.

7.2.2 Behavioral Measures

A full description of the Cinderella task and associated behavioral results are reported in Chapters 3, 5, and 6. Participants were recorded telling a narrative (Cinderella; Saffran et al., 1989) four times over an eighteen week span (Weeks -6,0,6,12) during which the middle six

weeks (Weeks 0 to 6) consisted of the IMITATE therapy (see Sections 3.3 and 3.4). The recorded narratives were scored for number of correct information units (CIUs) produced on the basis of whether words were novel, intelligible, and appropriate to the context (see Sections 3.4.3 for methods and 5.3.2 for results). Figure 3.2 depicts the study design. One subject (10) missed the fourth behavioral evaluation.

7.2.3 Neuroimaging Measures

7.2.3.1 Acquisition

Magnetic resonance imaging (MRI) was acquired at three baseline time points prior to six weeks of therapy (Weeks -6, -3, 0) and at up to three time points following the end of treatment (Weeks 6, 9, 12). Figure 3.2 depicts the study design, and study description can be found in Section 3.2. Acquisition details for structural and functional scans are included in Section 3.5.1. Five minutes (200 volumes) of functional resting state data were acquired.

7.2.3.2 Preprocessing of Resting State fMRI

RsfMRI preprocessing consisted of discarding the first four volumes, slice timing correction, despiking, and registration performed using AFNI (Cox, 1996) and FSL (Smith et al., 2004). The AFNI function 3dDeconvolve was used to regress out signals of no interest (from white matter, ventricles, lesion) as well as motion and polynomial (linear, quadratic) trends. If a volume had >3 mm displacement from the volume to which it was being registered, both that volume and the following one were censored and not included in the regression. A scan needed to have ≥ 55% of volumes uncensored (108) to be included in the analysis. These cleaned time series were then band-pass filtered (0.01 to 0.1 Hz) to identify the low frequency fluctuations of interest. As some

participants missed or had excessive motion during one or two scanning sessions, a total of 76 scans were included in this analysis (rather than 12 subjects x 7 scans = 84).

7.2.3.3 Anatomical Preprocessing

Lesion masks drawn on the high-resolution structural scans were used to perform a Virtual Brain Transplant (Solodkin et al., 2010) to facilitate reconstruction of each participant's cortical surface with FreeSurfer (Fischl, 2012), brain parcellation into 463 regions (Hagmann et al., 2008), and the creation of a common template. Each participant's preprocessed and band-pass filtered rsfMRI was registered to the common template to permit group analysis.

7.2.3.4 Independent Component Analysis (ICA)

Spatial ICA was performed using the Group ICA of fMRI Toolbox (GIFT; (Calhoun, 2004)). In a preprocessing step prior to ICA, the time series underwent mean centering followed by whitening and dimension reduction using subject-specific principal component analysis (PCA) to extract the first twenty eigenvectors (low-order Gaussian features). Group ICA using the Infomax algorithm then identified twenty independent higher-order non-Gaussian features of the reduced data. ICA was repeated ten times with random initiation and bootstrapping to ensure the stability of the identified components (ICASSO; Himberg et al., 2004).

7.2.3.5 Graph Construction

Eight of the twenty identified components were selected as components of interest (Duncan & Small, under review) that did not overlap with regions of known vascular, motion, and

susceptibility artifacts and that were consistent with RSNs previously identified in the literature (Damoiseaux et al., 2006; Lee et al., 2012). The twelve components that were discarded can be seen in Appendix A (Figures A.1 through A.12).

We took the inverse of the transformation that registered individual scans to the group template and applied it to these eight RSNs in order to bring them from standard space into the native space in which the rsfMRI data were acquired. We then identified the anatomical regions included for all subjects as part of a given component (i.e., the intersection) through the use of the parcellation scheme applied during preprocessing of the anatomical volume (Hagmann et al., 2008). Each RSN included between 24 and 40 regions, for a total of 230 regions among the eight RSNs.

After identifying the peak voxel for each region included any one of the eight RSNs for each scan, we mean centered the time series and constructed a joint covariance matrix for all time series in all 230 regions. Sparsity was induced using the graphical lasso (Friedman et al., 2008) implemented in R (Friedman, Hastie, & Tibshirani, 2014), and the resulting inverse covariance matrix was used to construct a graph for each scan using NetworkX (Hagberg et al., 2004). In these graphs, each region is a node, and the edges are weighted by the strengths of the functional connectivity (covariance).

7.2.3.6 Modularity

Processing of the functional connectivity graphs included first removing all negative edges and then binarizing the remaining positive edges. We assigned each node of these resulting graphs to a module based on its membership in one of the original eight RSNs, and then computed a modularity value for each scan. A modularity measure (Q) was calculated through

use of the NetworkX `community.modularity` function (Hagberg, Schult, & Swart, 2008) based on a well-established metric (Newman & Girvan, 2004).

To control for graphs simply changing in modularity without any consideration of RSNs, nodes were also assigned to modules based on a separate partition determined via application of a community detection algorithm using the Louvain method (Blondel, Guillaume, Lambiotte, & Lefebvre, 2008), with a separate modularity score calculated.

7.2.4 Correlation of Modularity and Behavior

Differences in modularity (Q) were correlated with differences in number of CIUs produced before and after therapy. Pre-therapy modularity was calculated as the average Q of the three baseline scans (Weeks -6, -3, 0). Post-therapy modularity was calculated as the average Q for the scans (from 1 to 3 total) acquired after therapy (Weeks 6, 9, 12). The pre-therapy CIU score was defined as the average number of CIUs for the two pre-therapy assessments. The post-therapy CIU score was averaged across the two post-therapy testing sessions (Week 6, 12). Four comparisons were made for the changes that occurred in behavior and functional RSN modularity: post-therapy vs. pre-therapy, Week 6 vs. pre-therapy, Week 12 vs. pre-therapy, and Week 12 vs. Week 6. Due to our strong *a priori* hypothesis that increased RSN modularity would subserve improvement, based on our previous analysis (see Chapter 6), one-tailed t-tests were used. These correlations were corrected for the three independent comparisons being made ($\alpha=0.05/3$).

Significant comparisons were repeated twice: (i) using partial correlations controlling for pre-therapy CIU production, and (ii) using a separate community assignment partition (see Section 7.2.3.6) to control for changes in modularity unrelated to RSNs.

A repeated measures ANOVA was used to compare baseline Q values to ensure that RSN modularity did not significantly differ among pre-therapy scans.

7.3 Results

There was a positive correlation between change in CIUs and change in RSN modularity comparing pre- and post-therapy measures (r= 0.687; p= 0.007) and comparing Week 6 measures to baseline (r= 0.760; p= 0.006). Figure 7.2 shows these relationships. Neither the correlation of Week 12 with baseline (r = 0.549; p = 0.05) nor Week 12 with Week 6 (r = +0.237; p = 0.286) was significant following correction for multiple comparisons. Reduced power due to missed scans (leaving 8 or 10 subjects) may have played a role in the failure of these comparisons to reach significance.

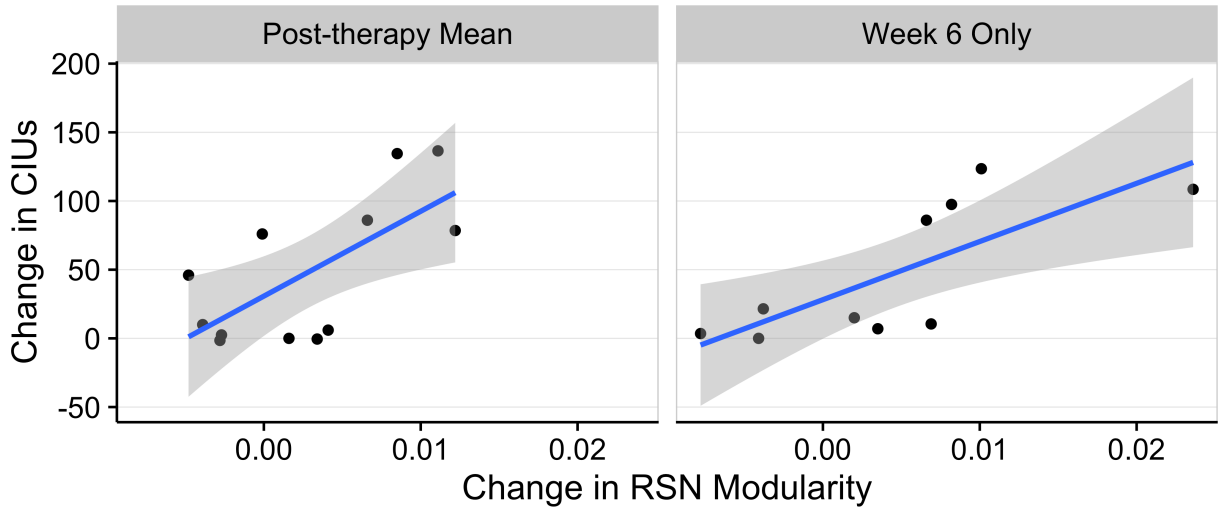

Figure 7.2 Correlations Between Changes in CIU production and RSN Modularity. Significant positive correlations for post- compared to pre-therapy measures (left) and for immediately post-therapy (Week 6) compared to pre-therapy. CIU= correct information unit; RSN= resting state network.

Controlling for pre-therapy CIU production, the pre- vs. post-therapy partial correlation ($r= 0.758$; $p= 0.004$) and the Week 6 partial correlation ($r= +0.676$; $p= 0.023$) remained significant at $\alpha=0.05$. There were no significant results for the control comparisons, in which nodes were assigned to communities based on an independent algorithm, rather than RSN membership ($|r|< 0.484$; $p> 0.110$).

An ANOVA comparing baseline modularity indicated no significant differences among the three pre-therapy sessions ($p = 0.273$).

7.4 Discussion

The present analysis provides confirmatory evidence for the hypothesis that individuals demonstrating behavioral improvement in narrative production following imitation-based aphasia therapy demonstrate increased segregation among functional networks. We interpret this to mean that increased functional segregation supports better ability to communicate a narrative. The present finding, that of improved behavioral performance and increased network modularity when a node's community is assigned based on RSN association, also supports that notion of an adaptive role for increased segregation.

Decreased modularity is associated with functional deficits in a variety of disorders, including Alzheimer's disease and carotid stenosis (Brier et al., 2014; Chang et al., 2016). However, it should be noted that higher modularity is also associated with decreased performance in some studies. Increased modularity is found in patients with multiple sclerosis (Muthuraman et al., 2016), for whom it is negatively correlated with working memory (Gamboa et al., 2014). In Parkinson's disease, results have been mixed (Baggio et al., 2014; Ma et al., 2016). These findings may indicate that, as with essentially all biological properties, there is an inverse U-shaped curve associated with the modularity of functional brain connectivity. If the

modular organization of the brain is either too weak or too strong, the behavior of the organism is maladaptive.

However, for the present findings, it is believed that there is explanatory power associated with the observed changes in brain connectivity. Studies of healthy controls indicate that modularity decreases when task-based fMRI is compared to rsfMRI (Di, Gohel, Kim, & Biswal, 2013), as well as when task demands increase (Vatansever, Menon, Manktelow, Sahakian, & Stamatakis, 2015). Given that individuals with aphasia demonstrate deficits in cognitive domains outside language (Murray, 2012), the observed recovery in narrative production may be associated not only with language-specific improvement but also with cognitive benefit, resulting in better behavioral performance as well as less required effort. Additionally, connectivity changes in the language system secondary to stroke can ripple throughout other brain subnetworks not directly related to language (Warren, Crinion, Lambon Ralph, & Wise, 2009), causing connectivity changes both within and between modules.

While graph theoretical analyses are generally underutilized in the study of aphasia and other sequelae of stroke, a few prior studies use such methods to illuminate behavioral changes occurring following injury and therapy. In aphasia, local increases in network connectivity are found in bilateral angular gyrus and left pars triangularis, part of Broca's area, in individuals demonstrating benefit from a word finding treatment (Sandberg et al., 2015). Aphasia severity is associated with disruption of regions serving as connector hubs in the language network and a global reduction in the rich club coefficient (Gleichgerrcht et al., 2015), a measure of the tendency for highly connected nodes to be highly interconnected with each other. Patients with the semantic variant of primary progressive aphasia demonstrate lower global efficiency, or more remote functional connections, compared to controls (Agosta et al., 2014), as do those with post-

stroke motor deficits (Falcon et al., 2015). These findings suggest, similar to those of the present investigation, that the ability to effectively manage and transmit information throughout the brain is compromised following stroke, that these changes underlie behavioral impairment, and that the restoration of these properties may facilitate functional gains.

How to restore normal network topology in the brain is a question distinct from these collected findings of disturbance, however. Targeted stimulation or inhibition of nodes and modules demonstrating deviant patterns of connectivity, with the aim of reinstating network balance, can currently be explored through transcranial magnetic stimulation or transcranial direct current stimulation. Future insight into the neural mechanisms through which these changes occur may come from "build to understand" approaches, such as modeling with The Virtual Brain (Jirsa, Sporns, Breakspear, Deco, & McIntosh, 2010). Better understanding the biological underpinnings of network disruption and reorganization will stimulate more informed and effective interventions that, in turn, will promote greater recovery.

Chapter 8: Conclusion

In this dissertation, we examined behavioral and neuroimaging measures associated with changes in performance following a six-week intensive course of imitation-based aphasia therapy. The therapy was motivated by specific neurobiological findings about motor function from primate physiology and human neuroimaging, in which certain neurons, called mirror neurons, and their network connections are active during both the observation and execution of motor acts, such as speech. The heterogeneous group of nineteen individuals with post-stroke aphasia who completed the therapy program underwent behavioral and neuroimaging assessment at multiple time points before and after therapy. This research design allowed us to establish a definitive baseline and to examine the often elusive maintenance of therapeutic effects following the termination of treatment.

In Chapter 4, we find that an individual's baseline variability in performance is a behavioral predictor of improvement on a practiced task, in particular, that intra-individual variability decreases in tandem with improvement on an audiovisual speech imitation task. Speech-language pathologists have long used this concept informally through the assessment of stimulability during initial diagnostic sessions, and it is intuitive, in hindsight, that one's performance on a task should become more consistent with practice. However, the work described in Chapter 4 provides formal evidence for this practice in targeting a skill based on the variability with which it is performed at baseline. It also represents a clear departure from the vast majority of the literature on intra-individual variability, which suggests that increases mark vulnerability and precede decline. As most of this work has been done in aging, it is noteworthy that a different trajectory applies in stroke recovery.

One of the most significant goals of virtually all therapeutic interventions, and also one of the greatest challenges, is the generalization of treatment effects. Chapter 5 explores generalization by investigating the impact of the practiced imitation task on a task that is very different functionally, specifically the retelling of a well-known fairytale. Participants are found to increase in two measures of narrative production, both the number and the percent of correct information units (CIUs) produced before compared to after therapy. The study described in Chapter 5 also explores maintenance of therapeutic benefit through comparisons between performance immediately after therapy and assessment six weeks later. Maintenance is a second major goal of, and challenge in, aphasia therapy, as treatment effects tend to be extinguished following the termination of treatment, yet our participants demonstrated no significant differences between performance immediately after and six weeks following therapy. The results of these behavioral findings are particularly striking, in which there is a strong generalization from the therapeutic task (audiovisual imitation) to a quite different one (story retell).

The studies described in Chapters 6 and 7 are highly inter-related, as it was the data-driven analysis in the former that gave rise to the hypothesis-driven analysis in the latter. Both studies examine changes in resting state functional connectivity to determine signatures facilitative of behavioral gains on the narrative production (story retell) task, and both use the same intrinsic resting state networks (RSNs) identified via independent component analysis (ICA). In Chapter 6, a sliding window approach is used to examine the amount of time participants spent in various states, characterized by correlations among the identified RSNs. The study of Chapter 6 showed improvement to be positively associated with an increase in time spent in a state in which RSNs were minimally correlated with each other. Thus, in Chapter 7, we conducted a graph theoretic

analysis to determine whether the network of RSNs was, in fact, becoming increasingly segregated. We assigned communities within the larger network based on membership in the subcomponent RSNs, thus assessing the overall modularity of the larger network. Improvement on the narrative task was positively correlated with RSNs evolving to be more differentiable modules, supportive of the hypothesis of increased segregation advanced in Chapter 6. Taken together, these two investigations offer powerful support for a new finding about brain changes enabling successful post-stroke language rehabilitation.

In its entirety, the work performed in this dissertation offers both practical insight into aphasia therapy (e.g., targeting goals based on variability) in addition to novel avenues for future research. The clearest starting point going forward is continued investigation of the changing network properties supporting language recovery through further graph theoretic analyses. Understanding which RSNs, and which particular nodes within them, are the most influential in producing the behavioral changes measured here could inform future anatomical targets for high-precision brain stimulation, such as transcranial magnetic stimulation (TMS). Lower resolution brain modulation with transcranial direct current stimulation (tDCS) could also be used with one of the more anatomically distinct networks, such as the visual network, to determine whether altering the connectivity in one RSN induces comprehensive changes throughout the larger network.

Finally, despite the biological motivation for this imitation-based therapy, it was not found to be significantly more (or less) effective than other existing aphasia therapies – whether currently accepted or experimental – with an effect size of 0.38 on the narrative task. Future development of a new aphasia intervention using imitation will further consider personal relevance, ecological validity, and the context-dependent nature of communication. Just as mirror neurons tuned to

grasping in macaque premotor cortices require a graspable object to fire, human language is a fundamentally goal-driven behavior, and it is believed that incorporating purpose into speech imitation will optimize the neural activation, network engagement, and behavioral efficacy achieved with therapy. Further study will also recruit a new and larger pool of participants in order to better validate extrapolation of the current findings and to more precisely identify biomarkers indicative of patients with predictable benefit from imitation-based intervention.

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Appendix A: Artifactual ICA Components

The following components were not selected as components of interest for the analyses described in Chapters 6 and 7 due to their overlap with regions of known artifact (e.g., brainstem, ventricles, venous sinuses) and their lack of consistency with RSNs identified in the literature. Each of these twelve components is displayed on the group template (highest 5% of Z scores for mean components for the group) and at the coordinates (upper right corner) of its peak voxel (highest Z score).

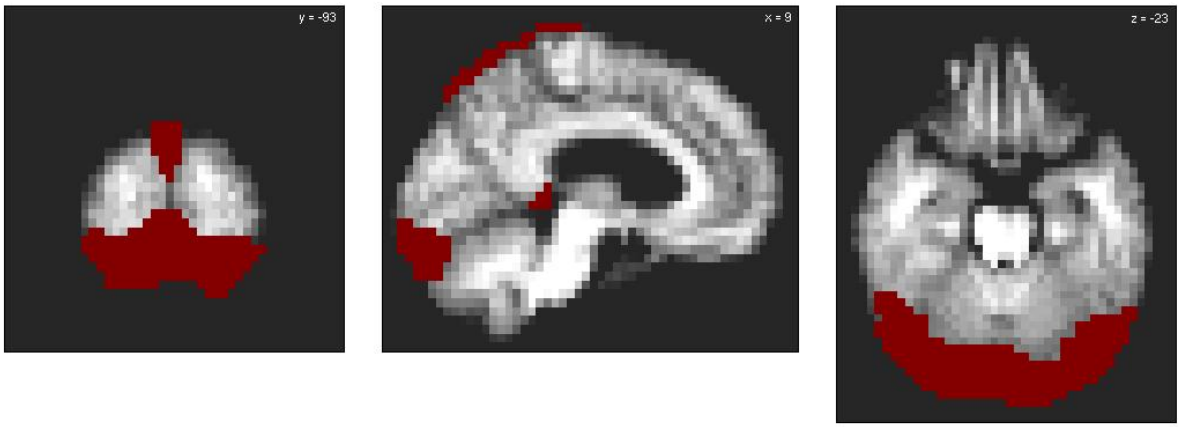

Figure A.1 Component 1. Left= coronal; middle= sagittal (right hemisphere); right= axial.

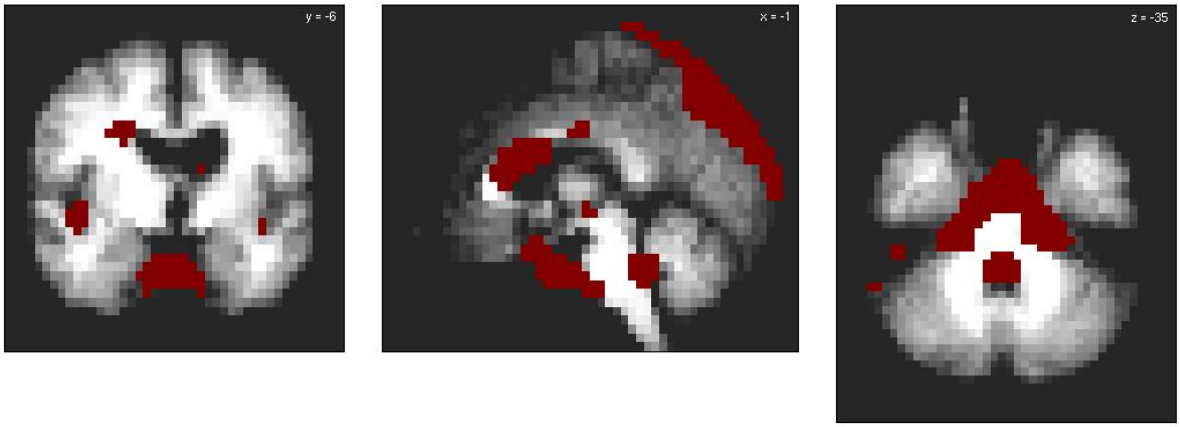

Figure A.2 Component 7. Left= coronal; middle= sagittal (left hemisphere); right= axial.

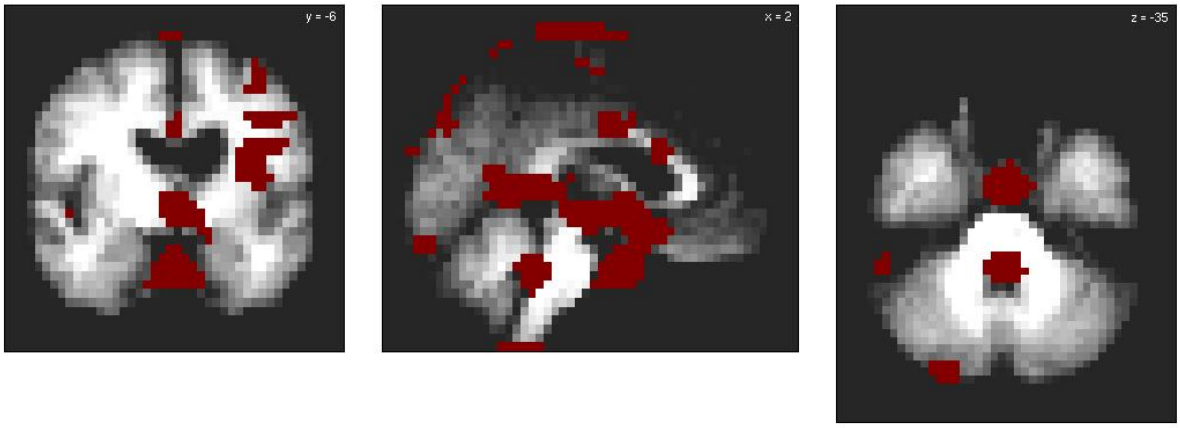

Figure A.3 Component 9. Left= coronal; middle= sagittal (right hemisphere); right= axial.

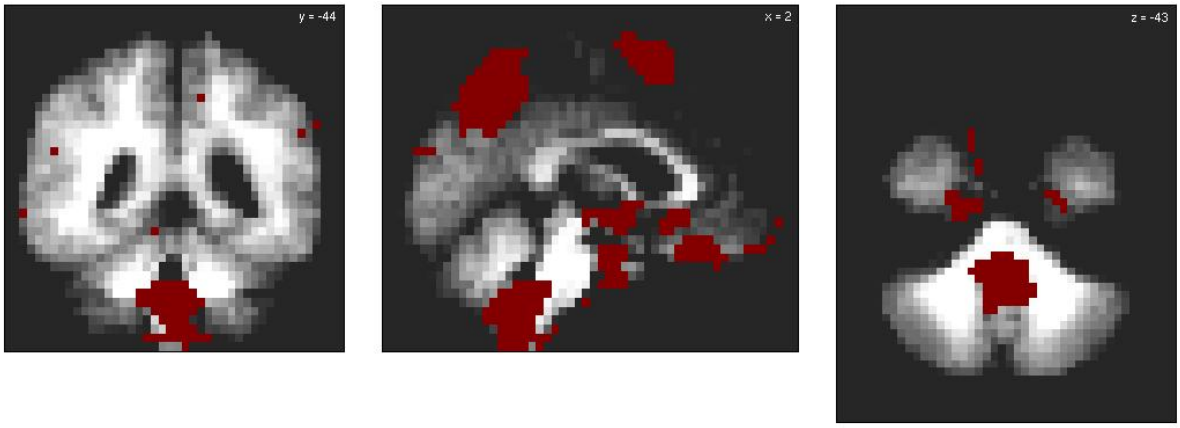

Figure A.4 Component 10. Left= coronal; middle= sagittal (right hemisphere); right= axial.

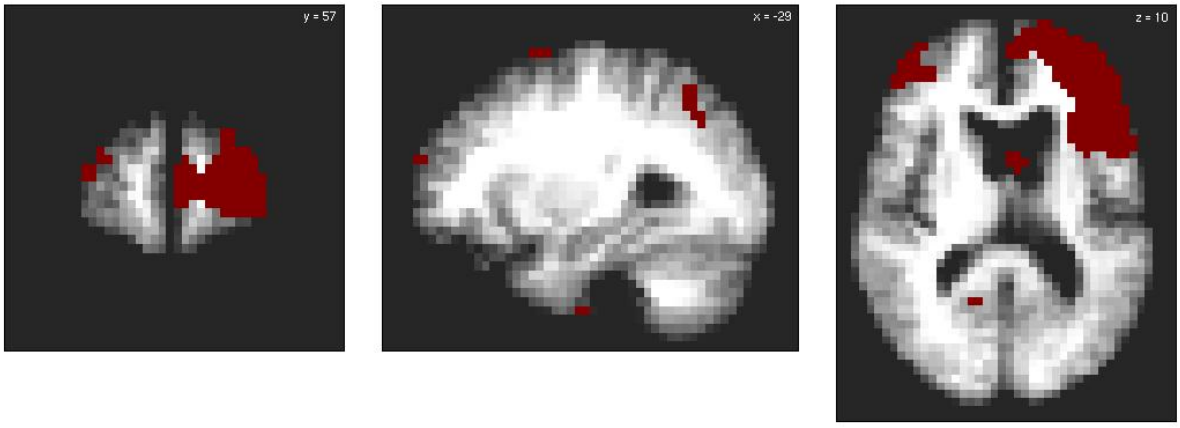

Figure A.5 Component 11. Left= coronal; middle= sagittal (left hemisphere); right= axial.

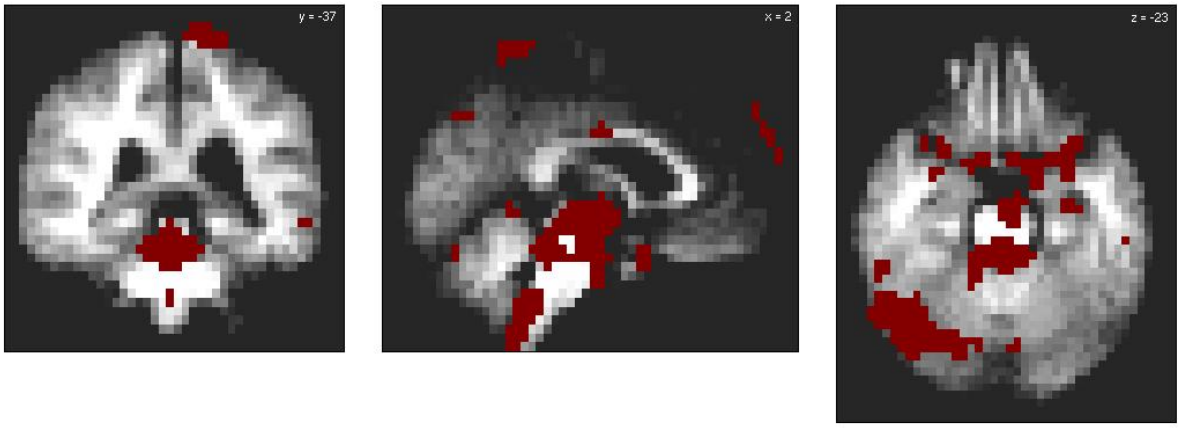

Figure A.6 Component 12. Left= coronal; middle= sagittal (right hemisphere); right= axial.

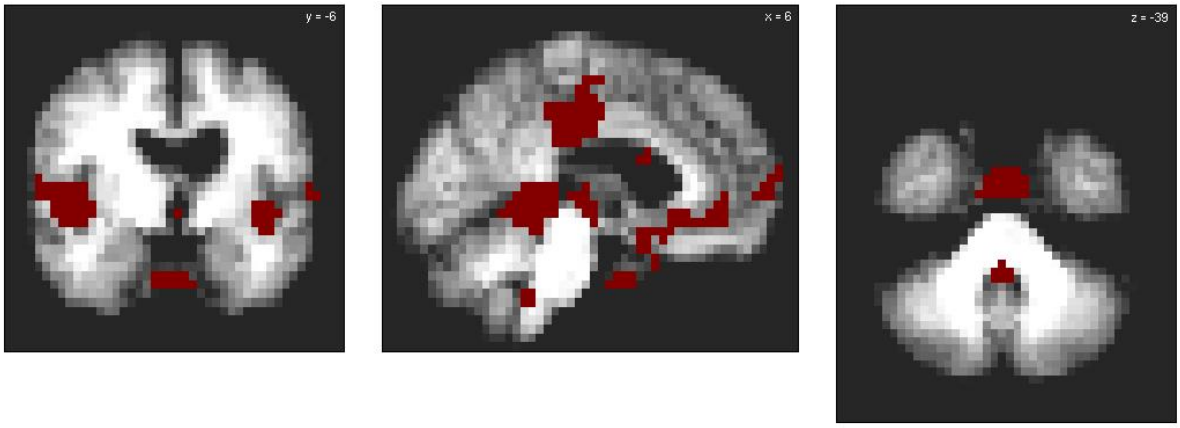

Figure A.7 Component 15. Left= coronal; middle= sagittal (right hemisphere); right= axial.

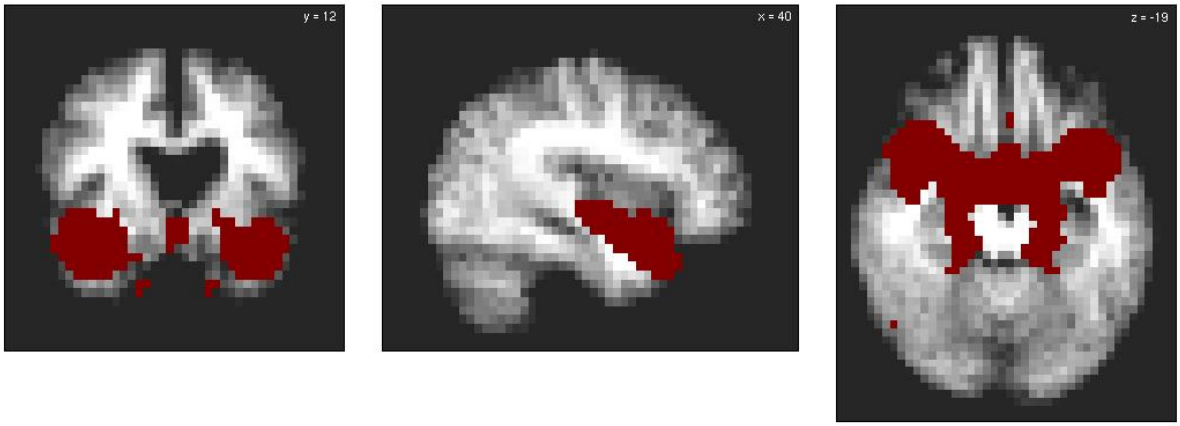

Figure A.8 Component 16. Left= coronal; middle= sagittal (right hemisphere); right= axial.

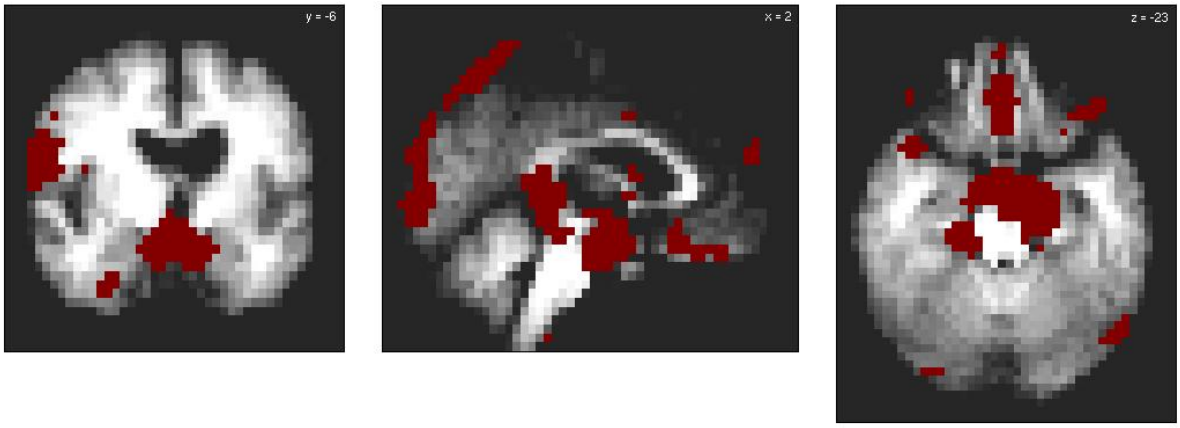

Figure A.9 Component 17. Left= coronal; middle= sagittal (right hemisphere); right= axial.

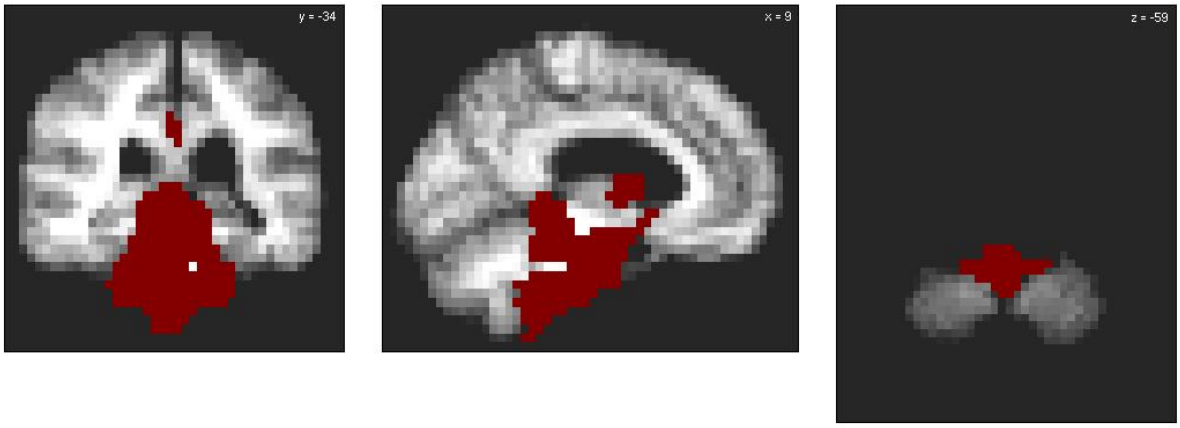

Figure A.10 Component 18. Left= coronal; middle= sagittal (right hemisphere); right= axial.

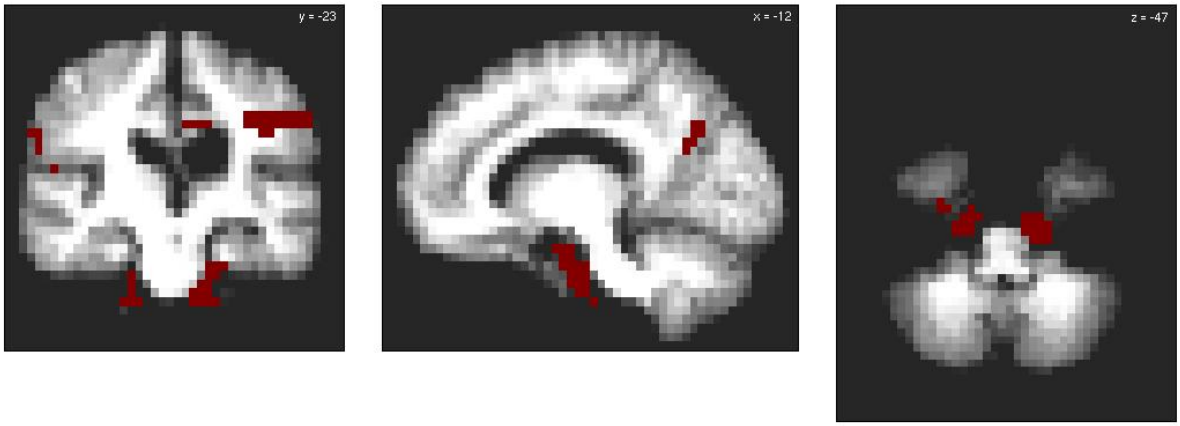

Figure A.11 Component 19. Left= coronal; middle= sagittal (left hemisphere); right= axial.

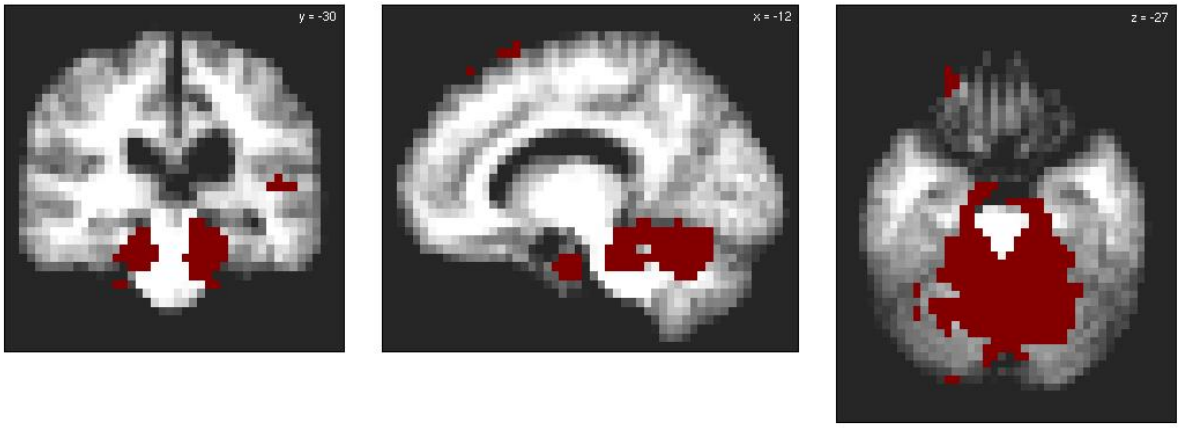

Figure A.12 Component 20. Left= coronal; middle= sagittal (left hemisphere); right= axial.

Appendix B: Overlap Of Resting State Networks with Healthy Controls

The following figures (B.1 – B.8) show the overlap between the resting state networks (RSNs) used in the analyses with participants with post-stroke aphasia, as described in Chapters 6 and 7, and RSNs from a group of healthy controls (n=27; 16 female; mean age= 38; SD=20.38; range=18-70). Healthy control data specs: Preprocessing steps and independent component analysis (ICA) were identical to those described in Sections 7.2.3.2 and 7.2.3.4, with the exception of the use of a lesion mask in the regression used to clean the time series of nuisance signals. Figures below show the eight components for each group (highest 5% of Z scores for mean components for the group) that were identified as RSNs (vs. artifact; see Appendix A). RSNs are displayed on the group template (participants with aphasia; see Section 3.5.2) and at the coordinates (upper right corner) of the peak voxel for the healthy controls group (highest Z score). RSNs for healthy control group are shown in blue. RSNs for participants with aphasia are shown in red. Overlap for both groups is shown in purple.

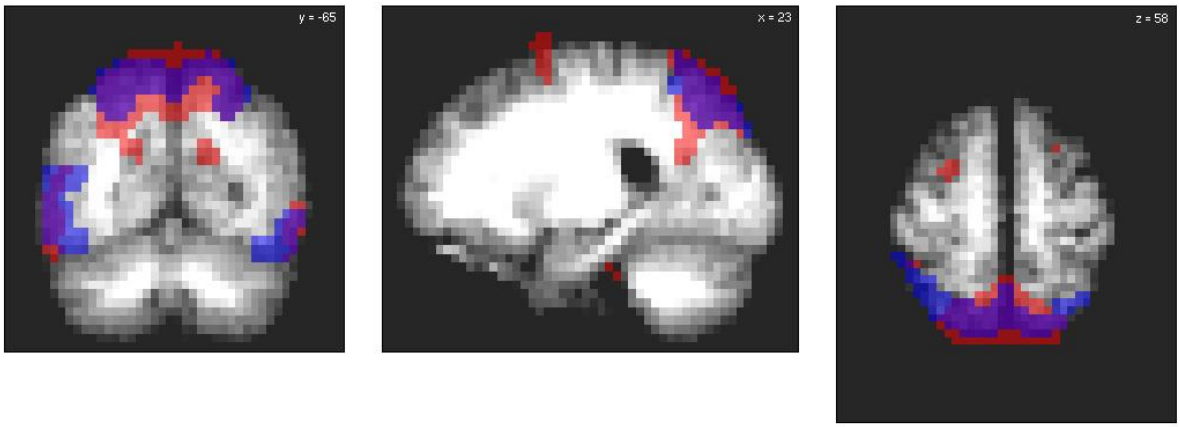

Figure B.1 Overlap for dorsal attention network (DAN). Healthy controls (blue) and participants with aphasia (red); overlap shown in purple. Left= coronal; middle= sagittal (right hemisphere); right= axial.

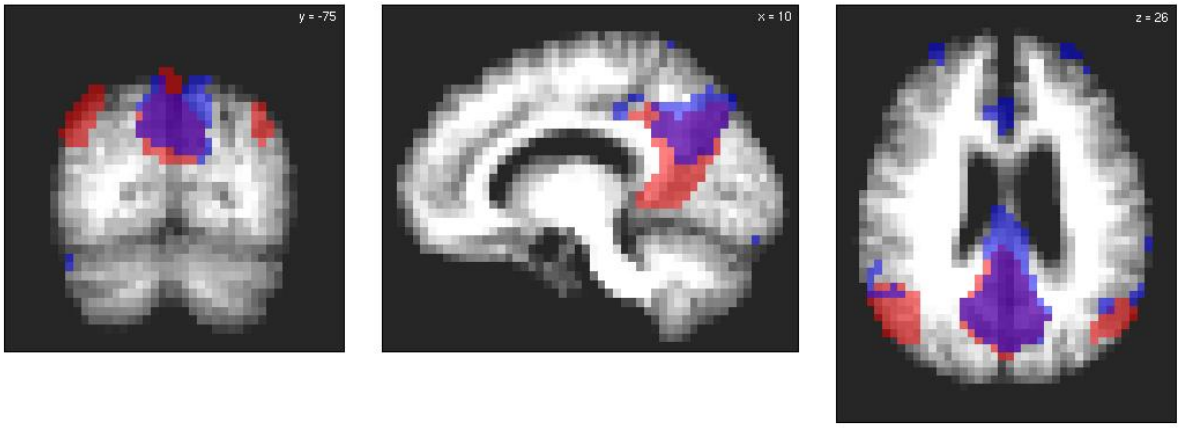

Figure B.2 Overlap for default mode network (DMN). Healthy controls (blue) and participants with aphasia (red); overlap shown in purple. Left= coronal; middle= sagittal (right hemisphere); right= axial.

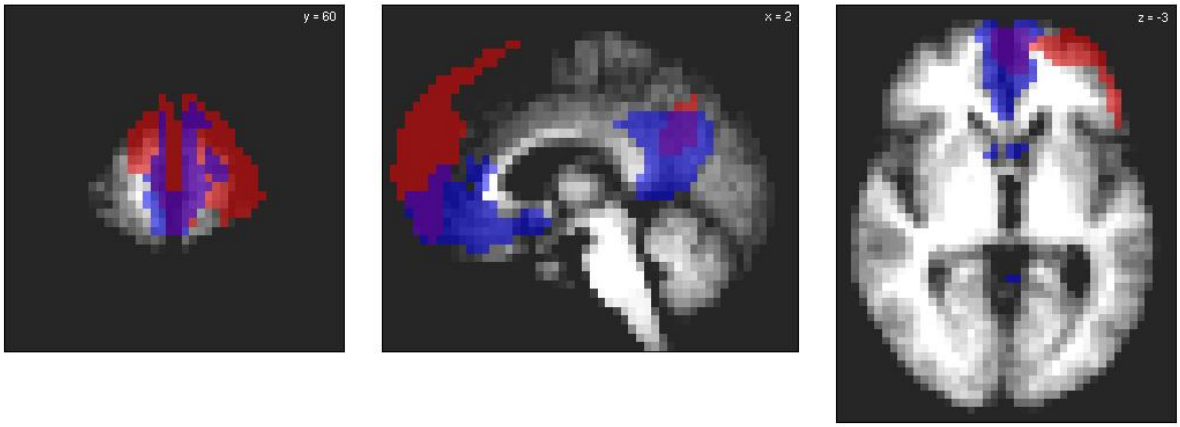

Figure B.3 Overlap for frontoparietal control network (FPC). Healthy controls (blue) and participants with aphasia (red); overlap shown in purple. Left= coronal; middle= sagittal (right hemisphere); right= axial.

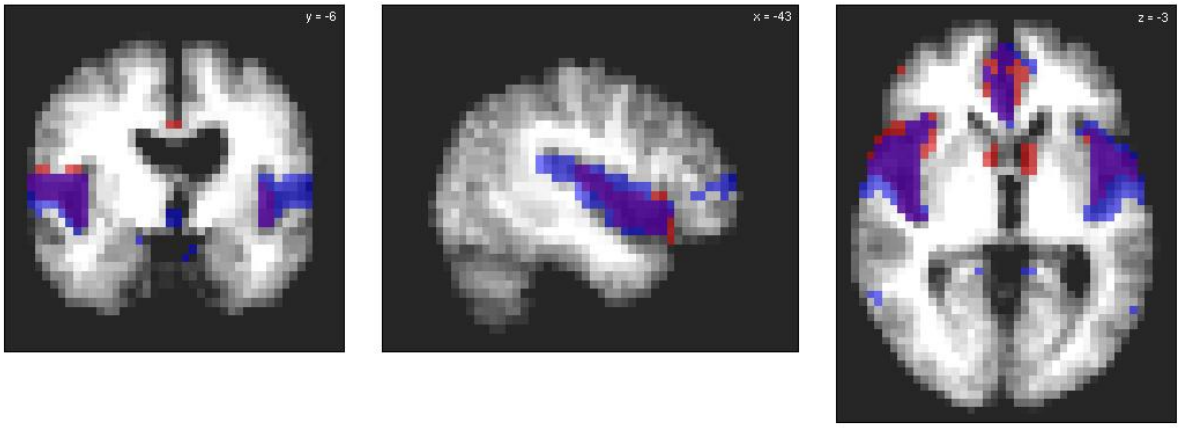

Figure B.4 Overlap for language network (LAN). Healthy controls (blue) and participants with aphasia (red); overlap shown in purple. Left= coronal; middle= sagittal (left hemisphere); right= axial.

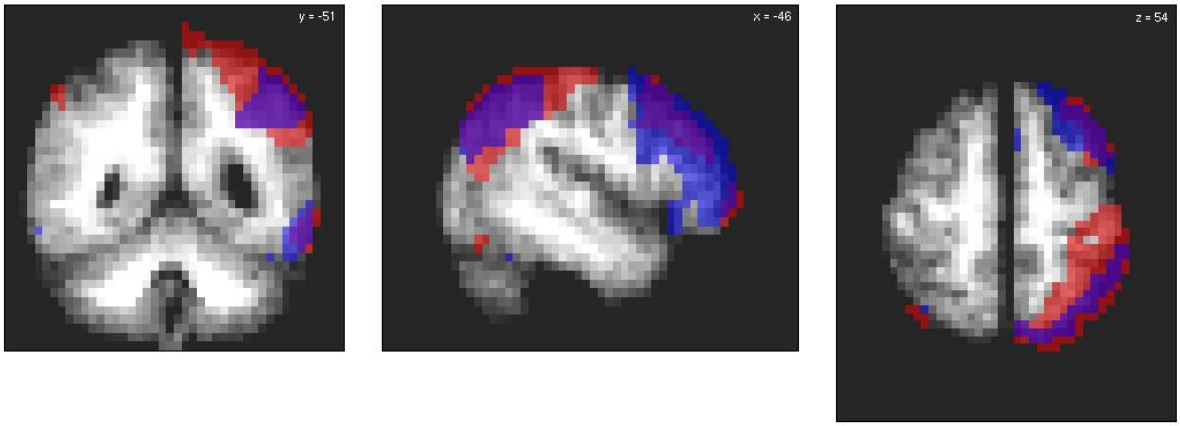

Figure B.5 Overlap for left ventral attention network (LVAN). Healthy controls (blue) and participants with aphasia (red); overlap shown in purple. Left= coronal; middle= sagittal (right hemisphere); right= axial.

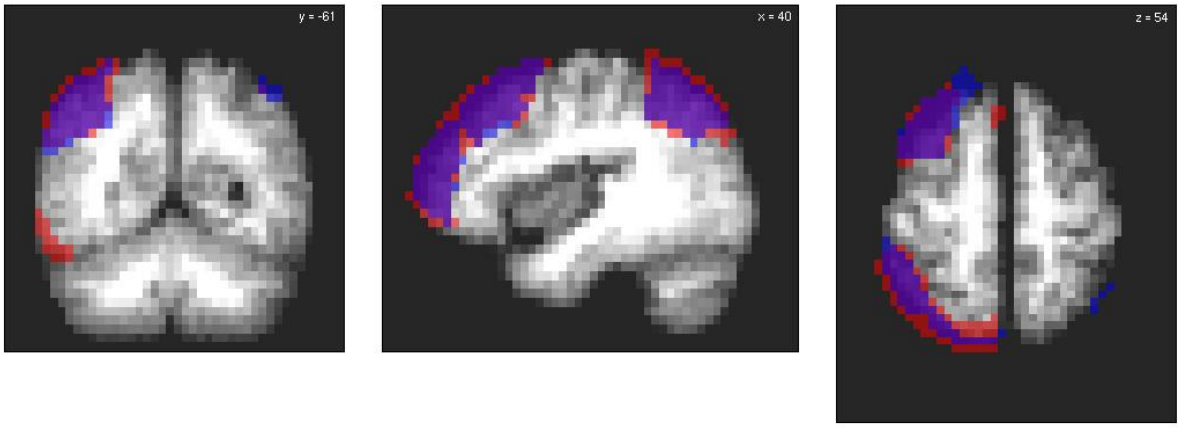

Figure B.6 Overlap for right ventral attention network (RVAN). Healthy controls (blue) and participants with aphasia (red); overlap shown in purple. Left= coronal; middle= sagittal (right hemisphere); right= axial.

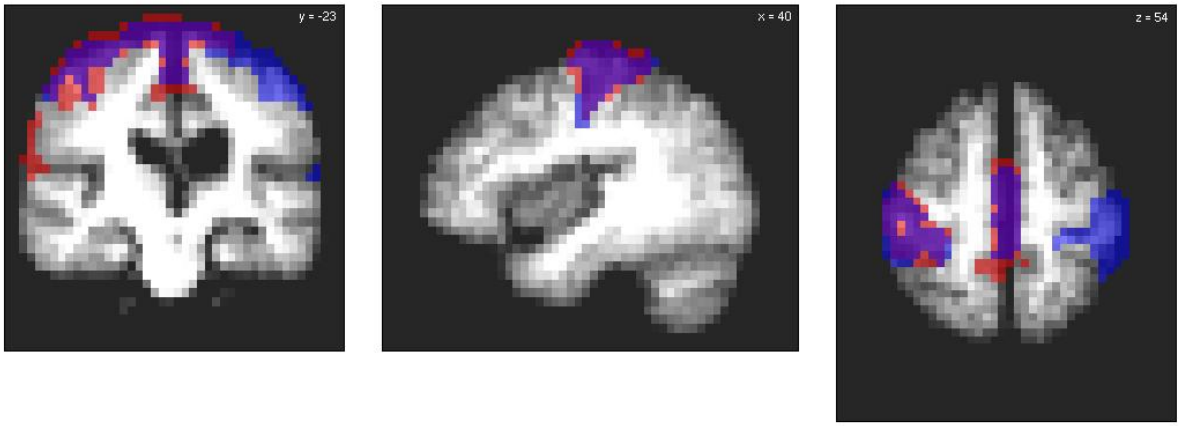

Figure B.7 Overlap for sensorimotor network (SMN). Healthy controls (blue) and participants with aphasia (red); overlap shown in purple. Left= coronal; middle= sagittal (right hemisphere); right= axial.

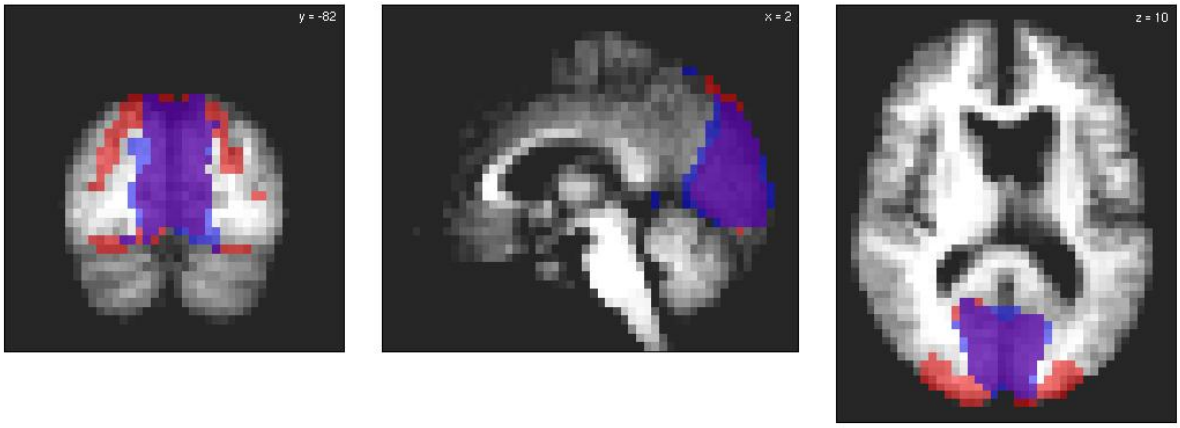

Figure B.8 Overlap for visual network (VIS). Healthy controls (blue) and participants with aphasia (red); overlap shown in purple. Left= coronal; middle= sagittal (right hemisphere); right= axial.

Appendix C: Non-Significant Dynamic Functional Connectivity States

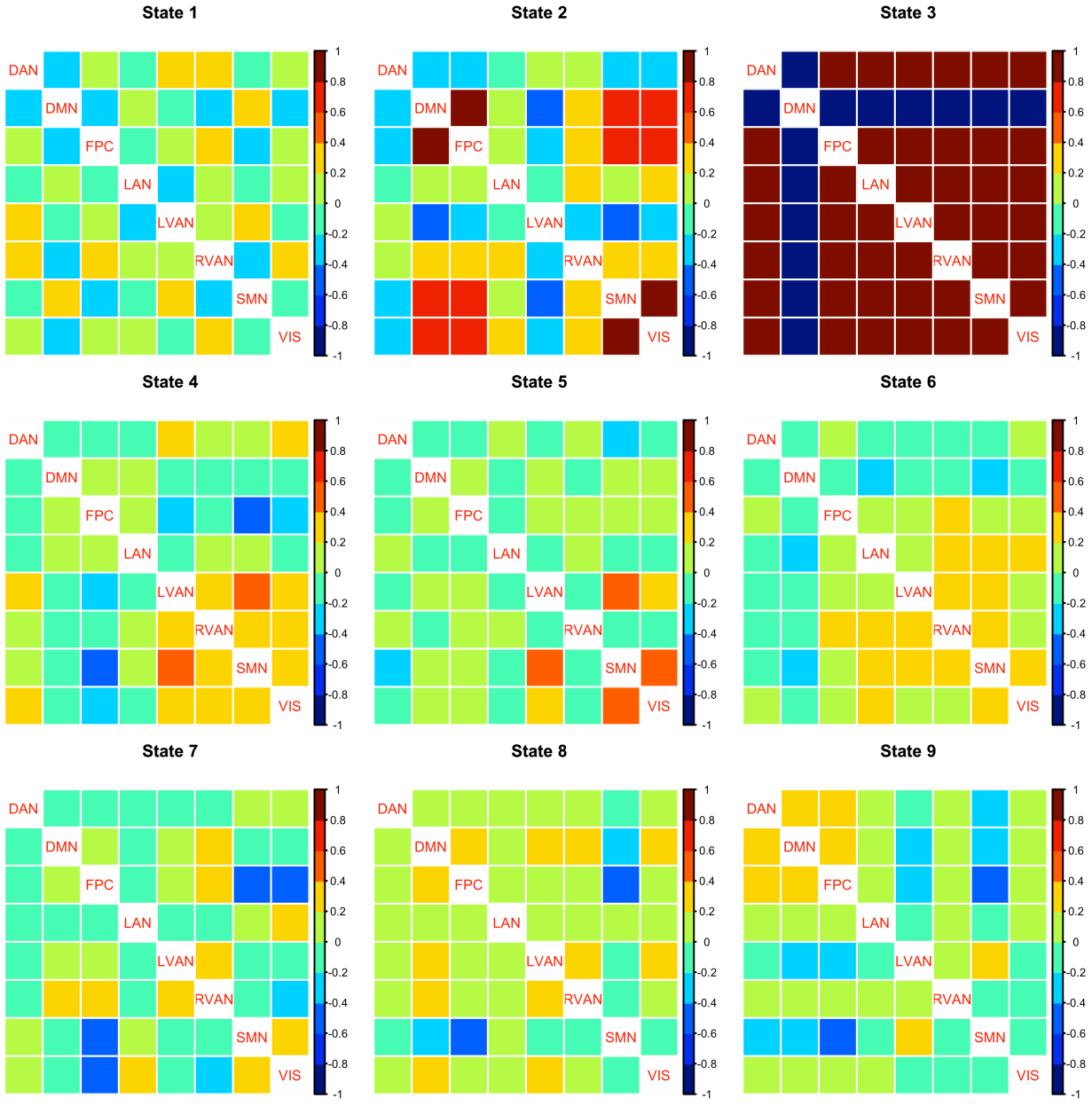

Figure C.1 Correlation matrices for the nine dynamic states not significantly correlated with changes in behavior on the narrative production task, as reported in Chapter 6. From left to right on the x axis and top to bottom on the y axis, resting state networks (RSNs) are: dorsal attention (DAN), default mode (DMN), frontoparietal control (FPC), language (LAN), left ventral attention (LVAN), right ventral attention (RVAN), sensorimotor (SMN), and visual (VIS). Color bars show binned correlation values.