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Section 3

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Language recovery

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Chapter 10

Functional MRI evidence for reorganization of language networks after stroke

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Abstract

In this chapter, we review fMRI evidence for language reorganization in individuals with poststroke aphasia. Several studies in the current literature have utilized fMRI as a tool to understand patterns of functional reorganization in poststroke aphasia. Consistent with previous models that have been proposed to explain the trajectory of language recovery, differential patterns of language processing and language recovery have been identified across individuals with poststroke aphasia in different stages of recovery. Overall, a global network breakdown typically occurs in the early stages of aphasia recovery, followed by normalization in "traditional" left hemisphere language networks. Depending on individual characteristics, right hemisphere regions and bilateral domain-general regions may be further recruited. The main takeaway of this chapter is that poststroke aphasia recovery does not depend on individual neural regions, but rather involves a complex interaction among regions in larger networks. Many of the unresolved issues and contrastive findings in the literature warrant further research with larger groups of participants and standard protocols of fMRI implementation.

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INTRODUCTION

p0010 Aphasia is an acquired language impairment due to damage to language regions in the brain following brain injury (e.g., stroke). Over the last few decades, there has been growing attention to neuroplasticity in poststroke aphasia with a focus on the reorganization of language processing. The use of functional magnetic resonance imaging (fMRI) originated in the 1990s and since then, it has been widely utilized to understand patterns of functional reorganization in poststroke aphasia. Several studies to date have implemented fMRI to investigate neural changes of language processing and language recovery in individuals with poststroke aphasia. Diverse patterns of neuroplasticity have been revealed among these previous studies, and these contrastive patterns mostly result from heterogeneity across individuals and differences in methodology across studies. In this chapter, we will discuss fMRI evidence for neural reorganization of language in poststroke aphasia. In the first section, we present fMRI as a neuroimaging technique and highlight its applications in language research. In the second section we review current fMRI evidence for poststroke language processing. In the last section, we describe patterns of neural changes based on fMRI studies investigating language recovery as a function of aphasia rehabilitation, then point out limitations of the current literature and directions for future studies.

fMRI IN NEUROIMAGING RESEARCH

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fMRI technique and its overall applications

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p0015 Functional magnetic resonance imaging (fMRI) has widespread application in human research of both basic and clinical neuroscience. Over the last few decades, this

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technique has provided new insight into the investigation of how various cognitive functions (e.g., language, memory, learning) are formed in the human brain. Brain images produced by fMRI reflect local changes in blood flow elicited by cognitive tasks (Ogawa et al., 1992). MRI detects electromagnetic signals (resonant frequency waves) in the brain, which depend on the level of oxygen present in the neural tissue. When neuronal activity increases (i.e., processing a cognitive task), there is an increase in blood flow accompanied by increased oxyhemoglobin concentration in the corresponding brain region. fMRI essentially measures the changes in resonances of the brain tissue based on functionally dependent levels of blood oxygen, which is referred to as the blood-oxygen-level-dependent (BOLD) signals (Biswal et al., 1995).

p0020 There are several advantages of this technique making it unique and valuable in studying human neuroscience. For instance, fMRI is noninvasive and does not involve radiation, and hence is safe for participants. It also has relatively high spatial resolution and good temporal resolution, and is easy for clinicians or researchers to use (Kimberley and Lewis, 2007). Thus, fMRI has become a popular research and, in some cases, clinical tool for studying human brain functions. However, one important aspect to consider about interpreting fMRI research is that the results from these studies are vastly different owing to the large variability in the fMRI methodology used by different studies. While these results provide important insights into the functioning of the brain, implementation of fMRI in clinical settings should be done with caution until fMRI methodologies are standardized across studies (Matthews et al., 2006).

s0025 fMRI in language research

p0025 fMRI has been widely implemented in human studies to understand the neural organization of language, including comprehension and production at the word, sentence, and conversational levels. One clinical application of fMRI is presurgical language mapping, which aims to identify language lateralization, language localization and to predict postsurgical language change (Matthews et al., 2006; Benjamin et al., 2017). Another fMRI application in language research is to identify language processing in both neurotypical individuals and patients with poststroke aphasia. Several characteristics of the fMRI technique make it well-suited for language research (Binder, 2011). For instance, the small size of voxels (on average 3 mm) produces favorable image quality and spatial localization of brain function. The relatively high resolution of fMRI allows us to associate functional foci with anatomic structures via registration of functional data and the structural scan. Additionally, fMRI provides the opportunity to repeatedly measure neural functions in the same individual within and across scanning sessions and runs, leading to increased statistical power and providing the potential for the examination of a range of cognitive functions. A caveat, however, is that even within the same individual, repeated scanning results in variability across different scans, i.e., intrasubject variability. Intrasubject variability could refer to the variability in the performance of a single participant at multiple time points (MacDonald et al., 2006). This intrasubject variability can result from motion (Lund et al., 2005) as well as physiologic processes such as cardiac pulsations (Dagli et al., 1999), respiration (Brosch et al., 2002), or change in accuracy or ease of performance in the task over time. For these reasons, fMRI research in human subjects (McGonigle et al., 2000; Bijsterbosch et al., 2017) needs to be interpreted with these caveats in mind.

p0030 The early fMRI studies assessing language localization and lateralization have provided a solid foundation for recent research to understand human language processing (Wang et al., 2012). Particularly, fMRI work has identified neural regions that are typically activated during language processing. Additionally, fMRI studies have provided evidence for hemispheric asymmetry of language, i.e., the observation that in most right-handed individuals, the left hemisphere is dominant for language functioning (Desmond et al., 1995), a concept that was originally reported by Paul Broca and Carl Wernicke in the 19th century. One early classical theory that fMRI has shed light on is the Wernicke–Lichtheim–Geschwind neuroanatomic model of language (Geschwind, 1965; Geschwind, 1970). This model has posited that certain brain regions are specialized for specific language functions, such as the inferior frontal gyrus (IFG; Broca's area) is important for speech production, and the superior temporal gyrus (STG; Wernicke's area) is associated with language comprehension. This model further assumed that language impairment results from damage to specific brain regions or pathways. For example, language comprehension involves a pathway from the primary auditory cortex to the superior temporal lobe for language decoding. Hence, damage to these regions may cause difficulty with language comprehension or Wernicke's aphasia. These behavioral patterns have been validated for the most part over a broad range of fMRI studies, discussed in detail below.

p0035 Recent fMRI work has further defined the nature of language processing as being more complex and nuanced than the classical Wernicke–Lichtheim–Geschwind neuroanatomic model and may involve complex interactions among different brain regions in language networks (Schwartz, 1984; Price, 2000; Binder, 2011; Hagoort, 2014; Hagoort, 2016). Specifically, semantic processing, which involves storing and retrieving word meanings,

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has been associated with widespread activation in frontal (IFG; prefrontal cortex/PFC), temporal (angular gyrus/AG, middle temporal gyrus/MTG, fusiform gyrus/FUS), and other paralimbic regions such as the parahippocampus and posterior cingulate cortex (Binder et al., 2009; Binder and Desai, 2011). Phonologic processing, by which speech sounds are mapped onto words in abstract form, has been correlated with neural activation in Wernicke's area along with the left IFG (Poldrack et al., 2001). Syntactic processing, by which words are combined to construct sentences, has been observed in the frontal (IFG, middle frontal gyrus/MFG) and temporoparietal tissue (anterior MTG, STG, and AG) in the left hemisphere (Humphries et al., 2006; Caplan et al., 2008). Finally, orthographic processing, by which written characters are represented in reading and writing, has been linked to the recruitment of the left IFG, intraparietal sulcus (IPS), and FUS (Glezer et al., 2009; Szwed et al., 2011). A widely investigated theoretical model, the *Dual Stream Model* (Poeppel and Hickok, 2004a; Hickok and Poeppel, 2007), proposes two large-scale processing streams emphasizing the connections between cortical regions involved in speech and language processing in the healthy brain. One stream represents phonologic processes, which typically rely on a dorsal pathway across left-hemisphere frontal speech regions and at the temporal–parietal junction. The other stream represents lexical-semantic processes that recruit a ventral pathway including the bilateral temporal lobes (Price, 2000; Poeppel and Hickok, 2004b; Hickok and Poeppel, 2007; Price et al., 2010). Importantly, this model suggests that Broca's area and Wernicke's area are no longer viewed as homogeneous pieces of neural tissue in processing language. Rather, regions interact with each other in a larger network, and those, outside of the perisylvian language zone may further be recruited to support different language processes (Poeppel and Hickok, 2004a).

fMRI IN POSTSTROKE APHASIA

While fMRI has been quite ubiquitous in examining language processing abilities in healthy individuals and has correspondingly been extended to study language recovery after stroke, its application in clinical populations and particularly in disorders such as stroke also comes with caveats. First, stroke or ischemic events result in damage to parts of the brain, thereby affecting how blood flows in those parts of the brain. In other words, hemodynamic response function in these regions may be affected (Bonakdarpour et al., 2007). Also, damage to specific parts of the brain influences specific language processing abilities, but there is no one-to-one correspondence between particular brain regions that are damaged and behavioral language impairment (Crinion and Price, 2005; Price and Crinion, 2005). In fMRI studies that examine task-activation, individuals with poststroke aphasia usually complete language-related tasks in the scanner, and functional reorganization is examined by correlating their behavioral performance with task-related brain activation. Inconsistencies in the performance of the task in the scanner (affecting brain activation) can, however, complicate the interpretation (Price and Crinion, 2005). Most importantly, no two-stroke patients have the same lesion, and so it is unclear if results from one patient provide insights regarding other patients, or whether patients can be sensibly grouped to obtain average results. These caveats limit the overall interpretation we can draw about language recovery solely from fMRI studies, but nonetheless, provide us an important perspective on both the modularity and integrative nature of language processing in the brain after a stroke. In this section, we will discuss current fMRI evidence for language processing in poststroke aphasia that addresses language reorganization.

Effect of stroke on the brain

Stroke causes neural cell death and alters cerebral blood flow, which can be reflected in the fMRI BOLD signal. Ischemic stroke occurs when the brain's blood vessels are narrowed or blocked by a clot, causing reduced blood flow (hypoperfusion) and oxygen supply to the brain. Regions where hypoperfusion is severe enough to cause cell death are known as infarcts, and the surrounding region, where there is a lesser degree of hypoperfusion and some cells cease to function but are still viable, is known as the "penumbra." Within the penumbra, there can even be a negative BOLD effect when oxygen consumption exceeds regional cerebral blood flow. Hemorrhagic stroke occurs when a blood vessel ruptures in the brain due to many different factors such as uncontrolled high blood pressure or aneurysms, causing tissue damage. Stroke may further complicate several physiologic parameters of the fMRI BOLD contrast (Lake et al., 2016). For instance, stroke triggers changes in microvascular architecture and influences cerebral blood flow and cerebral blood volume in the brain. Additionally, the cerebral metabolic rate of O_2 consumption may be altered due to neuronal loss, axonal sprouting, and synaptogenesis.

fMRI evidence for poststroke language processing

Several recent studies have provided insights into the nature of language recovery in poststroke aphasia (Saur et al., 2006; Kiran et al., 2019; Kiran and Thompson, 2019). In general, poststroke aphasia recovery involves three phases: (1) the acute phase, (2) subacute phase and (3) chronic phase. Following a nonlinear process,

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the greatest changes in the brain often occur in the early stages of recovery, followed by longer-term recovery in the chronic phase. The dynamics of language reorganization in these three phases have been previously identified via longitudinal group studies (Saur et al., 2006; van Oers et al., 2010; Stockert et al., 2020) and include: (1) reduced activation in left hemisphere language regions in the acute phase, (2) upregulation in right hemisphere homolog language regions that links to language improvement in the subacute phase, and (3) normalization of activation with a shift to left hemisphere language regions in the chronic phase. These studies will be detailed below (see Table 10.1). However, longitudinal fMRI studies of individuals show that different aphasic individuals can show different patterns of recovery, depending on the site and size of stroke and other factors (Jarso et al., 2013; Sebastian et al., 2016).

p0055 Saur et al. (2006) investigated language reorganization during three phases of recovery in 14 patients with aphasia. Participants completed an fMRI auditory sentence comprehension task, in which they were asked to press the button when a sentence was incorrect. In the acute phase (0–4 days poststroke), reduced activation of the left IFG was observed across patients, and the amount of remaining activation in this region was positively correlated with language recovery scores. In the subacute phase (2 weeks poststroke), a strong bilateral activation in the language network with the greatest increase of activation in the right inferior frontal cortex was associated with improved language performance, suggesting that the upregulation of the entire language network and especially the right hemisphere plays a vital role in subacute aphasia recovery. In the chronic phase (4–12 months poststroke), a reshift of peak activation to left hemisphere language regions was observed, which was linked to further significant language improvement.

p0060 Another longitudinal study investigated language reorganization in the first year after stroke (Nenert et al., 2018). In this study, 17 individuals with poststroke aphasia underwent behavioral testing of language abilities and fMRI tasks (semantic decision, covert verb generation) at 2-, 6-, 12-, 26- and 52-weeks poststroke. The results showed over-time language improvement, which was correlated with an initial decrease then an increase of hemispheric lateralization index. Additionally, brain activation was located predominantly in the left hemisphere in stroke patients, which reduced (relative to controls) in the early phase then returned to the level of healthy controls over time. These findings again support normalization of language networks in poststroke aphasia.

p0065 A more recent fMRI study by the Saur group examined language reorganization in 17 individuals with left frontal lesions and another 17 individuals with left temporoparietal lesions (Stockert et al., 2020). These patients performed an fMRI auditory comprehension task and their language scores in comprehension and production were obtained at the acute phase (1–7 days poststroke onset), the subacute phase (8–21 days postonset), and the chronic phase (>6 months postonset). In the acute phase, patients with temporoparietal lesions showed a global network disturbance as characterized by reduced neural activation in areas distant to the lesion (i.e., diaschisis), preserved language activation was only observed in the left IFG. Conversely, patients with left frontal lesions showed activation in several language regions including the left posterior temporal lobe, right anterior temporal lobe, and homotopic right IFG. In the subacute phase, patients with left temporoparietal lesions showed network reactivation in spared left language and bilateral domain-general networks, suggesting resolution of diaschisis. Additionally, significant bilateral activation of domain-general networks (IFG) was observed irrespective of lesion location. In the chronic phase, both groups of patients showed reorganization of left temporal regions. Notably, recruitment of lesion regions was only reported in patients with left frontal lesions. These findings altogether highlight that the dynamics of language reorganization, even over time, depend on lesion location.

Language processing in the acute phase s0045

p0070 Acute aphasia is characterized by reduced neural activation in the left hemisphere (Saur et al., 2006) or even a global breakdown of the entire neural network (Stockert et al., 2020). In addition to the studies described above, other studies examining aphasia recovery in the acute phase indicate the importance of reperfusion and reversal of language deficits in the damaged regions. Current evidence of language recovery in the acute phase is mainly based on magnetic resonance perfusion-weighted imaging (PWI) or diffusion-weighted imaging (DWI). As mentioned previously, hypoperfusion is one hallmark characteristic in the acute phase of stroke recovery, which commonly occurs within the ischemic penumbra (Heiss, 2000). Previous studies using PWI have shown a strong association between language impairment and hypoperfusion or infarct in the corresponding brain region. For instance, one study used PWI to examine the correlation between the severity of word comprehension impairment and the magnitude of delay in perfusion of Wernicke's area in 80 patients with acute stroke (Hillis et al., 2001b). Results revealed a strong correlation between the rate of errors in word comprehension and the mean number of seconds of delay in the time-to-peak concentration of contrast in Wernicke's

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t0010 *Table 10.1*

fMRI evidence in post-stroke language processing.

Study (sample size)	Long.	Intervention	fMRI Task	Key findings	Implications of recovery mechanisms			
					LH	RH	Bil.	Other
Longitudinal studies								
Saur et al. (2006) ($n = 14$)	Y	n/a	Auditory sentence comprehension	*Acute:* minimal activation, better language performance was associated with higher activation in LIFG; *Subacute:* large bil. increase (R Broca and RSMA); *Chronic:* re-shift of peak activation in LH (LIFG, temporal cortex, SMA, RIFG)	x			Activation shifts over time
Nenert et al. (2018) ($n = 17$)	Y	n/a	Semantic decision/tone decision; covert verb generation	*Acute:*↑ L temporal activation, correlation between behavioral improvement and L cerebellar activation over time; *Subacute-chronic:* a shift towards stronger frontal left-lateralization fMRI activation over the 1st year postonset; lack of RH compensation; recovery driven by L frontotemporal activation	x			Nontraditional language regions are involved
Stockert et al. (2020) ($n = 17$ L frontal lesions; $n = 17$ L temporoparietal lesions)	Y	n/a	Auditory sentence comprehension	*Acute:* diaschisis, global breakdown in temporo-parietal patients; *Subacute:* reactivation in temporo-parietal patients; ↑ perilesional and bil. domain-general network activations (DLPFC, IPL, INS, IFG POp, SMA/dACC); RH homologue recruitment in frontal patients; *Chronic:* reorganization of L temporal regions	x			Recovery reorganization depends on lesion location
Subacute and chronic phases								
Perani et al. (2003) ($n = 5$)	N	n/a	Covert semantic fluency	Patients with stronger language skills had greater recruitment of spared and perilesional tissue in the language-dominant hemisphere during the task	x			
Fernandez et al. (2004) ($n = 1$, subacute and chronic)	Y	n/a	Semantic categorization; rhyme judgment	↑ L perilesional activation from subacute to chronic (STG for semantic task; aSTG and MTG for rhyme task) was associated with language improvement	x			
Fridriksson et al. (2010) ($n = 15$)	N	n/a	Overt picture naming	Higher naming accuracy was correlated with more activation in spared L ACC, medFG & MFG, and IOG	x			
Szaflarski et al. (2011) ($n = 4$)	N	n/a	Word-to-picture matching	Positive activation in LIFG, LSTG, LIPL; negative activation in midline/MFG, midline/preCG, R aINS/IFG; reliable activations in LIFG, LMFG, RMOG, RCUN, LMTG, LAG, LPCUN, LIPL	x			
Allendorfer et al. (2012) ($n = 16$)	N	n/a	Semantic covert and overt verb generation and repetition	*Block-design verb generation:* RIFG, LIFG/MFG, LSFG, bil. MTG/STG; *event-related verb generation (noun verb semantics):* LMTG, LSFG/superior cingulate, LMFG; *event-related verb generation (articulation and auditory processing):* RINS, RSTG, R thalamus, bil. cerebellum and visual cortex; positive correlation between verb generation and activation in LMFG, LSFG/cingulate	x			Domain-general and MD networks are essential in aphasia recovery

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Table 10.1

Continued

Study (sample size)	Long.	Intervention	fMRI Task	Key findings	Implications of recovery mechanisms			
					LH	RH	Bil.	Other
Szaflarski et al. (2013) ($n = 27$)	N	n/a	Semantic feature judgment	Recovered patients had greater activation in LSPL and LSFG than nonrecovered patients; per ROI analysis, language performance was positively associated with activation in LSPL and LSFG and negatively associated with RSTG	x			
Griffis et al. (2017a) ($n = 43$)	N	n/a	Auditory semantic decision	Higher L temporoparietal tissue concentration was correlated with higher task-evoked activation in distributed regions associated with the semantic network, which predicted better fMRI task performance and other language tasks	x			
Thompson et al. (2017) ($n = 35$)	N	n/a	Standardized language testing (composite)	Greater perilesional hypoperfusion was associated with poorer language performance; Higher perfusion in RH than LH in aphasic patients	x			RH perfusion indicates autoregulatory changes in blood flow rather than maladaptive language recovery
Purcell et al. (2018) ($n = 1$)	Y	n/a	Reading, spelling, naming	Activation in L dIFG, SMA and mid-ITG was associated with spelling and reading; adaptation effect was found in the L dIFG and visual word form area	x			
Cao et al. (1999) ($n = 7$)	N	n/a	Covert picture naming	↑ activation of R IFL and IPL-STL in picture naming; ↑ R IPL-STL activation in verb generation; Spared LH regions were not observed in patients; Naming score was positively correlated with recovery time and lateralization index in IFL		x		RH activation indicates dysfunction/suboptimal recovery
Thulborn et al. (1999) ($n = 2$)	Y	n/a	Sentence reading	P1: R dominance (lateralization ratio) of the damaged Broca's area and L dominance of Wernicke's area at 76 h and 6 months postonset; P2: R dominance of the damaged Wernicke's area and L dominance of Broca's area at 3- and 9-month poststroke		x		
Gold and Kertesz (2000) ($n = 1$)	N	n/a	Written word semantic association	Task performance was associated with activation in R MFG, STG, SMG, AG, and PCUN		x		
Rosen et al. (2000) ($n = 6$)	N	n/a	Covert word-stem completion	Significantly higher RIFG activation in patients vs. controls in word-stem completion task; no correlation between the strength of RIFG activation and fMRI task performance or WAB-AQ; perilesional LIFG activation observed in two patients with highest aphasia scores and communication skills		x		

Crinion and Price (2005) ($n = 17$)	N	n/a	Narrative comprehension	Better performance was correlated with activation in the R lateral STG, and the L Wernicke's area when L temporal is spared		x		RH recruitment is modulated by lesion location
Fridriksson et al. (2009) ($n = 11$)	N	n/a	Overt picture naming	Correct responses were associated with activation in R PTr, preCG, SMA, MTG, STG, and TP; phonemic paraphasias were associated with L CUN, PCUN, and pITG; semantic paraphasias were associated with R MOG, CUN, and pITG		x		
Postman-Caucheteux et al. (2010) ($n = 3$)	N	n/a	Overt picture naming	Naming errors were associated with activation in R IFG/MFG		x		RH activation indicates dysfunction/suboptimal recovery
van Oers et al. (2010) ($n = 13$)	N	n/a	Picture word matching, semantic decision, verb generation	Naming improvement from time point 1 (subacute) to time point 2 (chronic) was positively correlated with the amount of LIFG activation for semantic decision and verb generation; improvement on the Token Test was positively correlated with the amount of L and R IFG for semantic decision and verb generation.	x	x		RH activation in nonlinguistic task
Robson et al. (2014) ($n = 12$)	N	n/a	Semantic judgement	Bil. activation in the ventral and anterior temporal lobes (FUS, TP, ventral occipito-temporal, aSTG, aMTG); Higher activation in patients vs. controls; activation in R aSTL during semantic processing of written words		x		
Griffis et al. (2017b) ($n = 43$)	Y	n/a	Auditory semantic decision	↑ R frontal regions; activation in RIFG and RSMA were correlated with better language performance in patients with larger lesions		x		RH activation indicates dysfunction/suboptimal recovery in patients with smaller lesions
Lee et al. (2017) ($n = 1$ chronic)	N	n/a	Over naming	*MVPA:* correct naming was associated with activation in R occipito-temporal cortex encompassing FUS, LOC, and MOG; *Univariate between accurate vs. inaccurate:* activation in RSMG		x		
Skipper-Kallal et al. (2017) ($n = 49$; fMRI data reported for 39)	N	n/a	Delayed naming with covert and overt responses	*Covert responses:* lesion volume was associated with activation in R central sulcus, IFG POp, and PTr, and other areas bilaterally (e.g., visual cortex, cingulate). *Overt responses:* activation was R lateralized in PTr, pSTS, and pSTG; lesion volume was associated with activation in bil. central sulcus, cingulate, cerebellum; activation in R motor cortex was correlated with naming accuracy in patients with L motor cortex damage		x		RH recruitment is modulated by lesion size and location
Sebastian and Kiran (2011) ($n = 8$)	N	n/a	Semantic judgment; overt picture naming	*Semantic task:* activation in LIFG in patients without frontal lesions, R homologue activation in patients with frontal lesions, which was not correlated with lesion volume; *Picture naming:* greater activation in LIFGPTr; no difference in RIFG activation between patients and controls; ↑ R frontal and R temporal in patients with larger LH lesions	x	x	x	RH activation when LH lesion size increases

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Table 10.1

Continued

Study (sample size)	Long.	Intervention	fMRI Task	Key findings	Implications of recovery mechanisms			
					LH	RH	Bil.	Other
Sims et al. (2016) ($n = 14$)	N	n/a	Semantic feature judgment or word relatedness judgment	Less damage to LACC and LSFG was correlated with more % signal change in RH (RSFG, RMFG, RACC, RIFG PTr, and RIFG POp); more spared LIFG POrb and LMTG was correlated with more % signal change in LACC and LSFG; less amount of spared LAG/SMG was correlated with more % signal change in LMFG, LSFG, LACC, RSFG, and RACC; larger LH lesion volume predicted more % signal change in RMTG, RAG/SMG; Higher fMRI task accuracy was correlated with more % signal change in LIFG POp and PTr; less severe aphasia was linked to more spared tissue in LIFG POrb, LMTG, LAG/SMG; LIFG regions were positively correlated with one another; RH homologues were positively correlated with one other in patients; RIFG POrb was negatively correlated with RIFG PTr and LIFG POp, and positively correlated with LACC; % signal change of RMFG was positively correlated with other L and R regions	x	x	x	RH activation as LH lesion increases; bil. network assists language recovery
van Oers et al. (2018) ($n = 12$)	Y	n/a	Picture word matching, semantic decision	↑ activation (picture word matching) was associated with language function in L and R pITG over the 1st year postonset; RIFG activation inversely correlated with language recovery on BNT and comprehension			x	Domain-general cognitive control is essential in aphasia recovery
Brownsett et al. (2014) ($n = 16$)	Y	Auditory (phonological) discrimination	Listen-repeat sentence	Midline frontal activation (salience/central executive networks) in PWA during sentence listening; dACC/SFG activation predicted picture description score			x	Domain-general cognitive control is essential in aphasia recovery

Abbreviations: BNT, Boston Naming Test; *MVPA:* multivoxel pattern analysis; *ROI*, region of interest; *WAB-AQ*, Western Aphasia Battery—Aphasia Quotient.
Anatomical indicators and regions: a, anterior; *ACC*, anterior cingulate cortex; *AG*, angular gyrus; *bil*., bilateral; *CUN*, cuneus; *d*, dorsal; *DLPFC*, dorsolateral prefrontal cortex; *FUS*, fusiform gyrus; *IFG*, inferior frontal gyrus; *IFL*, inferior frontal lobe; *INS*, insula; *IOG*, inferior occipital gyrus; *IPL*, inferior parietal lobule; *ITG*, inferior temporal gyrus; *L/LH*, left/left hemisphere; *LOC*, lateral occipital cortex; *medFG*, medial frontal gyrus; *MFG*, middle frontal gyrus; *MOG*, middle occipital gyrus; *MTG*, middle temporal gyrus; *p*, posterior; *PCUN*, precuneus; *POp*, pars opercularis; *POrb*, pars orbitalis; *preCG*, precentral gyrus; *PTr*, pars triangularis; *R/RH*, right/right hemisphere; *SFG*, superior frontal gyrus; *SMA*, supplementary motor area; *SMG*, supramarginal gyrus; *SPL*, superior parietal lobule; *STG*, superior temporal gyrus; *STL*, superior temporal lobe; *TP*, temporal pole; ↑, increased activation.

area, suggesting that hypoperfusion in language areas may predict severity of language impairment in acute aphasia. Studies have also shown that reperfusion (restored blood flow) of the ischemic penumbra may facilitate language recovery (Hillis et al., 2001a, 2006; Hillis and Heidler, 2002). For example, 24 patients with acute stroke who showed impaired picture naming underwent intervention to restore cerebral blood flow in ischemic areas (Hillis et al., 2006). Results showed that reperfusion in the left posterior MTG/FUS, Broca's area, and Wernicke's area significantly predicted naming improvement in these patients. These findings suggest that reperfusion of the damaged language regions in the left hemisphere promotes early language recovery in individuals with poststroke aphasia.

s0050 ## Language processing in the subacute phase

p0075 As highlighted in previous longitudinal studies, recovery in the subacute phase emphasizes the role of bilateral networks of language (Saur et al., 2006; Nenert et al., 2018; Stockert et al., 2020). An early fMRI study examined language reorganization in two patients with aphasia during early stages of recovery (Thulborn et al., 1999). The first patient (Broca's aphasia) was scanned at 76 h and again at 6 months post the onset, and the second patient (Wernicke's aphasia) was scanned at 3- and 9-months poststroke. Both of the patients participated in a sentence-reading fMRI task, in which they silently read sentences and answered true or false questions. Both patients exhibited significant language improvement over time. The laterality ratio of the first patient indicated a strong right dominance of the damaged Broca's area and a left dominance of the undamaged Wernicke's area at both time points. The second patient exhibited right dominance of the damaged Wernicke's area and left dominance of the unaffected Broca's area at both 3- and 9-months poststroke. Findings from both patients suggest recruitment of lesion-homolog regions in subacute aphasia. Another study examined language recovery in a patient with conduction aphasia by comparing it to the language ability in healthy controls. An fMRI word-picture rhyming task and a word-picture semantic matching task were administered at 1 month and 1 year after stroke (Fernandez et al., 2004). At 1-month poststroke, the patient exhibited significantly worse performance in the fMRI tasks relative to controls and revealed increased brain activation in homotopic right hemisphere regions, suggesting that right hemisphere lesion-homolog regions may contribute to recovery in the subacute phase.

p0080 Finally, subacute aphasia recovery may also recruit bilateral domain-general regions. One study examined 27 individuals with poststroke aphasia, who were scanned several days after the stroke and again at 4 months poststroke (Geranmayeh et al., 2014). These participants performed a speech task in which they were asked to describe object nouns, a counting task in which they counted numbers, and a decision task in which they were required to press a button when they saw a target. The behavioral findings showed significant improvement on the speech and count tasks. fMRI revealed that brain activation in the presupplementary motor area (preSMA)/dorsal anterior cingulate cortex (dACC) significantly predicted speech task performance at 4 months poststroke, suggesting domain-general regions, in addition to language regions are important in subacute aphasia recovery.

Language processing in the chronic phase s0055

p0085 During the chronic phase, language recovery continues to involve an interactive relationship between hemispheres as evidenced by (1) activation in spared left hemisphere regions, (2) recruitment of right hemisphere regions and domain-general regions, and (3) engagement of a network of bilateral regions (Kiran et al., 2019). Although the underlying mechanism of how language recovery occurs in the chronic phase remains debatable, ultimately the degree of language recovery in the chronic phase seems to be determined by new pathways and compensatory mechanisms developed for lost function (Hartwigsen and Saur, 2019; Stefaniak et al., 2020). One important factor that drives language recovery is lesion characteristics (Plowman et al., 2012; Hope et al., 2013), which will be first reviewed before we discuss fMRI evidence for chronic aphasia.

Lesion characteristics s0060

p0090 Lesion size or volume is known to be associated with poststroke language recovery. Many studies have revealed an overall negative correlation between lesion size and language performance (Alexander et al., 1990; Kertesz et al., 1993; Goldenberg and Spatt, 1995; Maas et al., 2012; Plowman et al., 2012; Hope et al., 2013). Specifically, smaller lesions are reported to be associated with better language performance, whereas larger lesions result in a smaller volume of tissue available for the reorganization of language and linked to poorer language recovery. Consequently, there is a general consensus that with increased lesion volume in the left hemisphere language regions, there may be increased activation in the homotopic right hemisphere regions (Gold and Kertesz, 2000; Crinion and Price, 2005; Fridriksson et al., 2009; Postman-Caucheteux et al., 2010; Turkeltaub et al., 2011; Griffis et al., 2016; Sims et al., 2016; Skipper-Kallal et al., 2017; Wilson and Schneck, 2020) as well as in bilateral domain-general regions (Gold and Kertesz, 2000; Fridriksson, 2010; Sims et al., 2016;

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Nardo et al., 2017), potentially in response to the increased cognitive effort after stroke.

p0095 In addition to lesion size, there is a wealth of literature indicating lesion location as a significant predictor of aphasia recovery in addition to lesion size (Selnes et al., 1983; Alexander et al., 1990; Kertesz et al., 1993; Naeser and Palumbo, 1994; Turkeltaub et al., 2011; Plowman et al., 2012; Hope et al., 2013). Poorer language performance is more likely associated with damage to language regions central to the specific language function (Fridriksson et al., 2010; Hillis et al., 2018). For instance, Hope et al. (2013) identified 35 relevant lesioned regions as significant predictors of speech production skills in 270 individuals with aphasia, suggesting that lesion location plays a crucial role in aphasia recovery. Moreover, a meta-analysis of fMRI studies in aphasia has revealed the importance of the left IFG in aphasia recovery (Turkeltaub et al., 2011). Specifically, the right IFG was more consistently recruited in individuals with lesions in the left IFG. Further, different patterns of activation were identified in different subregions of the right IFG depending on whether IFG was damaged: activation in the right ventral pars opercularis (POp) was observed across individuals regardless of lesion location, but the right dorsal POp and the right pars orbitalis (POrb) were activated in individuals with left IFG lesions. In sum, all these studies suggest that lesion size and lesion location may contribute to the patterns of activation noted in fMRI studies.

s0065 Activation in spared left hemisphere regions

p0100 Several fMRI studies have shown that spared left-hemisphere regions and perilesional tissue play a vital role in poststroke aphasia recovery (Perani et al., 2003; Saur et al., 2006; Fridriksson et al., 2010; Szaflarski et al., 2013, 2011; Meier et al., 2016; Sims et al., 2016; Thompson et al., 2017; Stockert et al., 2020; see reviews in Fernandez et al., 2004; Sebastian and Kiran, 2011; Turkeltaub et al., 2011; Allendorfer et al., 2012; Griffis et al., 2017a; Wilson and Schneck, 2020). For example, Sims et al. (2016) found several significant relationships between language impairment and spared tissue in individuals with chronic aphasia. In this study, 14 patients completed an fMRI semantic feature verification task in which they decided whether a written semantic feature matched with a picture. They found that less severe aphasia and better picture naming were correlated with larger amounts of spared tissue in the left IFG, MTG, AG, and supramarginal gyrus (SMG). Further, they found that the amount of spared tissue within the left MFG and left superior frontal gyrus (SFG) was linked to better nonverbal semantic processing. For the fMRI task performance, left IFG POp and pars triangularis (PTr) were the only two regions associated with signal change, emphasizing the role of left IFG in poststroke language processing. This finding that spared left hemisphere regions are important in language processing even in the chronic phase has further been substantiated in previous meta-analysis reviews. In the aforementioned review by Turkeltaub et al., relative to when IFG was damaged, studies that reported undamaged/spared IFG also reported activation of the IFG (PTr, POp, POrb) and left posterior MTG (in addition to RMTG and R anterior PTr). Similarly, a recent meta-analysis included 86 task-related fMRI studies in individuals with aphasia and found positive correlations between better language function and activation in preserved left hemisphere language regions (Wilson and Schneck, 2020), including the left anterior temporal lobe, left IFG POrb, and left IFG PTr. Thus, the consistent findings from studies indicate that undamaged regions in the left hemisphere play a vital role in aphasia recovery. Notably, many of these studies have also revealed activation in several domain-general regions such as MFG, which we will return to later in this chapter.

Activation in right hemisphere homotopic regions s0070

As noted by many previous fMRI studies, neural activation may expand to the right hemisphere homotopic regions in chronic aphasia, including the IFG (Cao et al., 1999; Rosen et al., 2000; Fridriksson et al., 2009; Postman-Caucheteux et al., 2010; van Oers et al., 2010; Turkeltaub et al., 2011; Skipper-Kallal et al., 2017; Griffis et al., 2017b), inferior temporal gyrus (ITG) (van Oers et al., 2018), MTG (Fridriksson et al., 2009; Sims et al., 2016), STG (Cao et al., 1999; Gold and Kertesz, 2000; Crinion and Price, 2005; Fridriksson et al., 2009; Robson et al., 2014; Skipper-Kallal et al., 2017), and AG/SMG (Gold and Kertesz, 2000; Fridriksson et al., 2009; Sims et al., 2016; Lee et al., 2017). p0105

The direct relationship between right hemisphere activation and chronic aphasia recovery, however, remains debated (Price and Crinion, 2005; Heiss and Thiel, 2006; Crosson et al., 2007). Perhaps, the question is no longer whether right hemisphere activation contributes to aphasia recovery, but rather under what circumstances and to what extent it does so. As noted above, right hemisphere activation is more frequently observed in individuals with larger lesions relative to those with smaller lesions (Grafman, 2000; Crosson et al., 2007; Turkeltaub et al., 2011; Sims et al., 2016). In terms of whether right hemisphere activation contributes to optimal language recovery, several distinct arguments have been put forth. One line of research suggests a facilitatory role of right hemisphere activation in aphasia recovery, p0110

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as evidenced by a positive correlation between the extent of right hemisphere activation and language performance (van Oers et al., 2010; Robson et al., 2014; Griffis et al., 2017b). Conversely, right hemisphere activation often plays a facilitatory role only in earlier phases of recovery (Saur et al., 2006; Stockert et al., 2020), a point made earlier in the chapter. The third line of research argues that right hemisphere activation plays a "maladaptive" role in aphasia recovery, as higher activation in the right hemisphere has been inversely correlated with language improvement, suggesting dysfunction or suboptimal language recovery (Rosen et al., 2000; Blank et al., 2003; Naeser et al., 2004; Thiel et al., 2006; Postman-Caucheteux et al., 2010; Szaflarski et al., 2013). These mixed findings altogether suggest that different mechanisms may account for right hemisphere activation in individuals with aphasia, which are highly driven by individual differences (i.e., lesion size, time postonset).

s0075 ### Bilateral activation of language regions

p0115 Several studies also document activation in bilateral language regions as a function of language performance in individuals with aphasia. Bilateral regions may be activated due to partial restitution of damaged functions in the left hemisphere language regions and activation of the right hemisphere (Cao et al., 1999). For instance, van Oers et al. (2010) specifically investigated the role of the left and right IFG in aphasia recovery. In this study, 13 individuals with aphasia were assessed for language abilities using the Token Test at the subacute (2 months poststroke) and the chronic (>1-year poststroke) phase, which were then correlated with their fMRI data (picture-word matching, semantic decision, verb generation) in the chronic phase. The results showed a positive correlation between improvement on the Token Test from time-point 1 to time-point 2 and the amount of activity in bilateral IFG for semantic decision and verb generation tasks, suggesting the contribution of homotopic right hemisphere regions to aphasia recovery.

p0120 Thus, in addition to IFG (Gold and Kertesz, 2000; van Oers et al., 2010; Stockert et al., 2020), SFG (Sims et al., 2016), MTG (Fridriksson et al., 2009; Sebastian and Kiran, 2011; Robson et al., 2014), STG (Gold and Kertesz, 2000; Allendorfer et al., 2012; Robson et al., 2014), AG/SMG (Gold and Kertesz, 2000; Crosson et al., 2005; van Hees et al., 2014b; Sims et al., 2016), and cerebellum (Allendorfer et al., 2012) have also been reported in previous fMRI studies.

s0080 ### Activation in domain-general regions

p0125 Regions in domain-general networks may be further recruited as part of the altered network for recovery following damage to traditional language networks. These domain-general regions include the dorsolateral PFC (DLPFC; Stockert et al., 2020), SMA (Geranmayeh et al., 2014), cingulate cortex (Raboyeau et al., 2008; Fridriksson et al., 2010; Brownsett et al., 2014; Geranmayeh et al., 2014; Sims et al., 2016), MFG (Sebastian and Kiran, 2011; Turkeltaub et al., 2011; Allendorfer et al., 2012; Meier et al., 2016; Sims et al., 2016), inferior parietal lobule (IPL; (Stockert et al., 2020), precuneus (PCUN; Gold and Kertesz, 2000; Fridriksson, 2010; Raboyeau et al., 2008), and insula cortex (INS; Szaflarski et al., 2011; Allendorfer et al., 2012; Geranmayeh et al., 2014; Stockert et al., 2020). Importantly, activation in these regions has been frequently reported in stroke patients irrespective of whether their frontotemporal language network is substantially damaged or spared (Kiran et al., 2015; Meier et al., 2016). This finding implies that upregulation of activity in intact domain-general systems may support the increasing demand for cognitive control and attention in aphasia recovery (Geranmayeh et al., 2014). While domain-general regions seem to play an important role in aphasia recovery, it is unclear to what extent these regions are engaged in language processing in patients relative to healthy controls, and thus, future research can examine the relationship between activation in domain-general regions and language recovery in poststroke aphasia. As pointed out by a recent systematic review and meta-analysis of functional neuroimaging evidence of neuroplasticity in poststroke aphasia, much of the current research has been largely constrained by methodologic limitations related to task performance confounds, contrast validity, and correction for multiple comparisons (Wilson and Schneck, 2020). Thus, much more work needs to be done to distinguish the precise role and mechanisms of bilateral language and domain-general regions in language processing after stroke.

fMRI EVIDENCE IN POSTSTROKE TREATMENT-INDUCED LANGUAGE RECOVERY s0085

p0130 Treatment has been seen to be a critical factor influencing aphasia recovery (Kiran and Thompson, 2019). Evidence of treatment-induced language recovery from fMRI studies provides an additional view of how subnetworks change over time after stroke. Language interventions usually target one specific area or a combination of underlying impairments (i.e., phonology, semantics, orthography, or syntax). As highlighted in the first section of this chapter, interventions in these linguistic components are presumably associated with changes in related subnetworks. Much of the fMRI research in aphasia rehabilitation has focused on whether activation in the left hemisphere or the right hemisphere is associated with

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optimal language recovery. Consistent with studies examining language processing in the previous section, the consensus of fMRI evidence from aphasia rehabilitation suggests heterogeneous patterns with some studies reporting activation in the left hemisphere that is associated with favorable treatment outcomes, whereas others argue that right hemisphere activation is associated with treatment-induced language recovery (Price and Crinion, 2005; Vitali et al., 2007; Fridriksson, 2010, 2012; Turkeltaub et al., 2011; Johnson et al., 2019; Wilson and Schneck, 2020). In this section, we will describe current fMRI evidence of treatment-induced language recovery in poststroke aphasia (see Table 10.2 for summaries and implications of studies).

p0135 Anomia (i.e., difficulties in naming or retrieving words) is a hallmark characteristic in individuals with poststroke aphasia. This symptom can be characterized by different types of speech errors, such as semantic errors (e.g., producing the word "cow" in response to the picture of a "horse") and phonologic errors (e.g., producing the word "hat" in response to the picture of a "cat"). According to previous models of lexical production (Dell, 1986; Levelt et al., 1999; Foygel and Dell, 2000), there are three levels (nodes) of linguistic representation: (1) semantic-conceptual level, (2) lemma/lexical selection level, and (3) morpho-phonologic level. Lexical retrieval is achieved in two stages—the lemma is accessed in the first stage, and phonologic information is accessed in the second. In aphasia, overt speech errors may occur at any of these three levels.

p0140 Most fMRI rehabilitation studies have targeted semantics, phonology, or a combination of both to help patients improve their naming abilities (Schevenels et al., 2020). The first treatment-induced recovery pattern is that neural activation is commonly observed in the left hemisphere and perilesional regions (Fridriksson et al., 2006, 2010, 2012; Vitali et al., 2007; Marcotte and Ansaldo, 2010). For instance, Fridriksson (2010) examined changes in cortical activation as predictors of recovery outcomes in 26 individuals with anomic aphasia who received 30-h of treatment targeting naming difficulty and performed an overt naming task before and after treatment. The fMRI results showed increased activation in the anterior and posterior regions of the left hemisphere and a negative correlation between damage to the left temporal lobe and naming performance. These findings suggest that treatment-induced brain changes rely on the preservation of the left hemisphere regions that are commonly involved in lexical retrieval and phonologic processing.

p0145 The second pattern of neural changes following naming treatment is the recruitment of the right hemisphere, including both homologous regions to the damaged left-hemisphere (Vitali et al., 2007; Nardo et al., 2017; Johnson et al., 2019) and other domain-general regions (Fridriksson et al., 2006; Nardo et al., 2017; Johnson et al., 2019). One recent study from our own lab investigated neural changes using an fMRI overt picture naming task in 26 individuals with chronic aphasia, who received a 12-week of semantic-based naming treatment (Johnson et al., 2019). Before treatment, patients showed higher activation in the bilateral IFG and lower activation in the bilateral AG relative to healthy controls; following treatment, these patients exhibited increased activation in bilateral IFG and the right MFG. These findings suggest that language treatment engages preserved tissue in left-hemisphere language regions as well as right-hemisphere homologs for language processing, further substantiating earlier observations that both left and right hemispheres may be critical for rehabilitation-induced language recovery in individuals with anomic aphasia.

Agrammatism is another symptom frequently p0150 observed in individuals with aphasia, which can be characterized by deficits in producing and comprehending complex and noncanonical sentences, such as passive sentences (e.g., a girl is pushed by a boy). Individuals with agrammatism may also exhibit difficulties with verb production, which is critical in sentence construction. Neural changes have been observed following language treatment targeting syntactic and morphosyntactic deficits in patients with poststroke agrammatism (Cherney and Small, 2006; Wierenga et al., 2006; Thompson et al., 2010, 2013). One treatment study examined patterns of neural activation associated with treatment-induced improvement of complex sentence production. Six individuals with poststroke agrammatism completed a course of Treatment of Underlying Forms (TUF; Thompson and Shapiro, 2005) that aimed to target object relative clause constructions, and also participated in an fMRI auditory verification task pre- and posttreatment. The fMRI results showed a shift of activation from the left superior temporal lobe before treatment to bilateral posterior temporoparietal regions after treatment (Thompson et al., 2010). In another study, eight individuals with poststroke agrammatism participated in a course of verb argument structure training that targeted the production of three-argument verbs in sentence contexts. After the treatment, performance in an fMRI action naming task revealed upregulation in the frontal and temporoparietal regions, which are typically activated in normal verb and argument structure processing (Thompson et al., 2013). Findings from these aphasia rehabilitation studies suggest there is the reinstitution of normal-like language processing in poststroke aphasia recovery, and consistent with naming treatments, neural tissue in both left and right hemispheres contribute to optimal language recovery.

Difficulties in reading and writing (i.e., dyslexia p0155 anddysgraphia) are additional common symptoms in

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t0015 *Table 10.2*

fMRI evidence for treatment-induced language recovery.

Study (sample size)	Long.	Intervention	Scan task	Key findings	Implications of recovery mechanisms			
					LH	RH	Bil.	Other
Léger et al. (2002) ($n = 1$)	Y	Phon.-artic. memory training	Overt picture naming	↑ L POp and SMG was associated with naming improvement	x			
Davis et al. (2006) ($n = 1$)	Y	Computerized semantic tx	Semantic covert verb generation	↑ L inferior frontal and R posterior inferior temporal/ occipitotemporal ROIs.			x	
Fridriksson et al. (2006a) ($n = 3$)	Y	Spaced retrieval, errorless learning, masses practice	Overt picture naming	↑ bil. L temporal and parietal and RH			x	
Meinzer et al. (2006) ($n = 1$)	Y	CIAT	Overt picture naming	Post-tx activation for correct responses: ↑ R IFG and thalamus and bil. putamen		x		
Fridriksson et al. (2007 ($n = 3$)	Y	Phonemic and semantic cueing hierarchy	Overt picture naming	*Nonfluent PWA:* ↑ bil. PCUN; *Fluent PWA:* ↑ R entorhinal and posterior thalamus			x	Other nontraditional language regions are involved in language recovery
Vitali et al. (2007) ($n = 1$ stroke)	Y	Phonological cueing	Overt picture naming	↑ L MFG, SFG and SMG; RIFG	x	x		
Meinzer et al. (2008) ($n = 11$)	Y	CIAT	Overt picture naming	↑ L-perilesional tissue was correlated with post-tx naming improvement	x			
Raboyeau et al. (2008) ($n = 10$)	Y	Phonological/ orthographic cueing	Overt picture naming	↑ R IFG, INS, PCC, and cerebellum; ↓ L PCC, PCUN, posterior parietal cortex, and R motor cortex		x		
Crosson et al. (2009) ($n = 5$)	Y	Intention manipulation	Category-member generation	*Post-tx activation in responders:* ↓ frontal with increased concentration of activity in R frontal (posterior motor); L ≥R perisylvian activity		x		
Menke et al. (2009) ($n = 8$)	Y	Computerized semantic tx	Overt picture naming	*Post-tx:* L hippocampus, R PCUN and PCC, and bil. FUS and occipital lobe; *8 months post-tx:* L MTG and STG and R posterior middle/superior temporal cortex			x	
Fridriksson (2010) ($n = 26$)	Y	Cueing hierarchy	Overt picture naming	↑ anterior and posterior LH was associated with improved naming; Damage to L posterior middle temporal lobe and temporo-occipital junction had negative effect on tx outcome	X			

Continued

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Table 10.2

Continued

Study (sample size)	Long.	Intervention	Scan task	Key findings	Implications of recovery mechanisms: LH	RH	Bil.	Other
Marcotte and Ansaldo (2010) ($n = 1$)	Y	SFA	Object and Verb Naming	Post-tx: *Object naming:* R preCG; bil. SFG and IOG, and L GP;LH activation > RH; *Trained verbs:* bil. activation in L ITG, MOG, STG, MTG, and R CUN, preCG, MFG, DLPFC, cingulate gyrus, and PHipG			x	
Rochon et al. (2010) ($n = 3$ treated, $n = 3$ untreated)	Y	PCA	Semantic association judgment	↑ L IFG, MTG, and SMG	x			
Fridriksson et al. 2012 ($n = 30$)	Y	Phonological or semantic cueing	Overt picture naming	*Post-tx for improved naming:* ↑ L frontal lobe *Post-tx for reduced paraphasias:* smaller ↑ in L temporal lobe	x			
Abel et al. (2014, 2015) ($n = 14$)	Y	Semantic or phonological cueing	Overt picture naming	↓ bil. activation; Better tx outcomes were associated with smaller ↓ in L temporoparietal regions (STS, SMG, paracentral lobule, and MTG); Effective tx was associated with ↓; LIFG POp predicted positive tx gains; R CN was a negative predictor	x			RH activation indicates suboptimal recovery
van Hees et al. (2014) ($n = 8$)	Y	PCA and SFA	Overt picture naming	*Group results:* PCA-trained items activation: ↑L SMG, R PCUN *Individual results:* PCA-trained items activation: ↑L IFG, SMG, AG, ITG ($n = 5$); ↑ R AG ($n = 1$); ↓ bil. IFG, MTG, STG (subsets); *SFA-trained items activation:* ↑ L IFG, SMG, AG ($n = 3$); ↑ RAG ($n = 1$); ↓ R MTG, STG, IFG, LMTG (subsets)	x			
Kiran et al. (2015) ($n = 8$)	Y	SFA	Overt picture naming & semantic feature judgment	↑ bil. IFG, MFG and MTG, and L preCG			x	
Sandberg et al. (2015) ($n = 10$)	Y	Complexity-based tx targeting abstract words	Word judgment task	*Concrete words:* ↑ LSMG, RMCC, LMOG, R preCG, RSTG, LPCUN, LINS, LIPL, RSFG; *Abstract words:* ↑ LMCC, RMTG, LAG, RAG, LCUN, LPCUN, LITG, RSOG, LSMA, LIPL, LSMG, LIFG PTr, LCN, LMFG, RSFG, RSMG, LSFG; ↑ LIFG PTr activation in tx responders			x	

Nardo et al. (2017) ($n = 18$)	Y	Phonemic cueing	Overt picture naming with/without phonemic cueing	RIFG POp, aINS, dACC, LPMC activation; Effective tx was associated with ↓		x	x
Marcotte et al. (2018) ($n = 2$; 1 intensive, 1 standard)	Y	PCA	Object naming	*Postintensive PCA tx activation:* ↑ RCN, LMFG;↓ RPCC, preCG and medFG in the LH; Changes in RPCUN; *Poststandard, nonintensive, PCA tx activation:* ↑ bil. STG, R preCG, LIFG; ↓ MTG, L preCG and putamen, R postCG			x
Johnson et al. (2019) ($n = 26$)	Y	SFA	Overt picture naming	*Post-tx activation:* ↑ bil. IFG and RMFG in PWA than controls; *Effect of tx on % of signal change:* ↑ in general activation, ↓ L IFGPTr, IFG POp, MFG, preCG, ↑ RH; Less spared tissue in L AG, MFG, IFG POrb, SMG was associated with larger ↑ from pre- to post-tx; Averaged ↑ from pre- to post-tx in responders but not in nonresponders			x
Thompson et al. (2010) ($n = 6$ agrammatic speakers; $n = 12$ healthy controls)	Y	TUF	Sentence picture matching	General shift from L superior temporal to bil. posterior temporoparietal areas; General shift to bil. posterior perisylvian and superior parietal cortices, outside of the network primarily activated by healthy controls			x
Thompson et al. (2013) ($n = 8$)	Y	Verb argument structure training	Action naming	Upregulation in cortical regions implicated for verb and argument structure processing in healthy controls	x		
Barbieri et al. (2019) ($n = 19$)	Y	TUF	Sentence comprehension (picture verification)	*Passive > Control condition:* PWA showed upregulation in R SPL extended to AG, posterior SMG, and superior LOC; in R aSMG and postCG; in R MFG extended to preCG		x	

Abbreviations: CIAT, constraint-induced aphasia therapy; *PCA*, phonological components analysis; *PWA*, patients with aphasia; *ROI*, regions of interest; *SFA*, semantic feature analysis; *TUF*, treatment underlying forms; *Tx*, Treatment.

Anatomical indicators and regions: a, anterior; *ACC*, anterior cingulate cortex; *AG*, angular gyrus; *bil*., bilateral; *CN*, caudate nucleus; *CUN*, cuneus; *d*, dorsal; *DLPFC*, dorsolateral prefrontal cortex; *FUS*, fusiform gyrus; *GP*, globus pallidus; *IFG*, inferior frontal gyrus; *INS*, insula; *IOG*, inferior occipital gyrus; *IPL*, inferior parietal lobule; *ITG*, inferior temporal gyrus; *L/LH*, left/left hemisphere; *LOC*, lateral occipital cortex; *MCC*, middle cingulate cortex; *medFG*, medial frontal gyrus; *MFG*, middle frontal gyrus; *MOG*, middle occipital gyrus; *MTG*, middle temporal gyrus; *PCC*, posterior cingulate cortex; *PCUN*, precuneus; *PHipG*, parahippocampal gyrus; *PMC*, premotor cortex; *POp*, pars opercularis; *POrb*, pars orbitalis; *postCG*, postcentral gyrus; *preCG*, precentral gyrus; *PTr*, pars triangularis; *R/RH*, right/right hemisphere; *SFG*, superior frontal gyrus; *SMA*, supplementary motor area; *SMG*, supramarginal gyrus; *SPL*, superior parietal lobule; *STG*, superior temporal gyrus; *STS*, superior temporal sulcus; ↑, increased activation; ↓, decreased activation.

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individuals with poststroke aphasia. Nevertheless, few studies to date have investigated the treatment effects of reading and writing, and even fewer have implemented fMRI to examine treatment-induced neural changes. One study (Purcell et al., 2019) examined neural changes in 21 individuals with poststroke aphasia following a 12-week treatment targeting written language impairment. Their results revealed increased neural activation in the ventral occipital-temporal cortex of the left hemisphere including the STG, IFG, ITG, and FUS. Further, higher brain activation in these regions before treatment was associated with less severe writing impairment and also predicted better treatment outcomes. Recall that normal spelling involves regions including the left IFG, IPS, and FUS (Purcell et al., 2011; Martin et al., 2015), and these regions are typically damaged in individuals with orthographic and lexical processing (Tsapkini et al., 2011; Rapp et al., 2016). These findings again partially align with the underlying mechanisms of recovery in individuals with naming and syntactic deficits, suggesting upregulation of "traditional" regions that are frequently involved in the targeted language processes.

p0160 Taken together, language recovery in poststroke aphasia involves a complex interplay between the left and right hemispheres. Previous fMRI studies have revealed the importance of spared left hemisphere regions in aphasia recovery and highlighted that regions in the right hemisphere or domain-general networks may be recruited as lesion size increases in the left hemisphere. Ultimately, language recovery in poststroke aphasia is not mediated by specific regions in one or both hemispheres but rather is driven by complex interactions between brain regions within larger networks. These findings substantiate the hypothesis of hierarchic models of recovery (Kiran et al., 2019; Heiss and Thiel, 2006), which postulate that: (1) optimal language recovery is observed when there are spared regions in the left hemisphere, and (2) in cases of larger lesions or poor language recovery, homotopic right hemisphere regions and bilateral domain-general regions may support language recovery. Essentially, these underlying mechanisms seem to be applied to aphasia recovery with or without explicit language treatment.

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CONCLUSIONS

p0165 Functional MRI has been widely implemented in the current literature to investigate language processing in healthy individuals and language recovery in individuals with poststroke aphasia. Collectively, fMRI evidence implies crucial roles of spared tissue and perilesional tissue in the left hemisphere. Depending on lesion characteristics and other factors, recruitment of the right hemisphere likely occurs in lesion-homolog regions in addition to bilateral domain-general regions. Yet, inconsistent findings in the current literature suggest that the dynamics of poststroke language recovery are closely associated with individual heterogeneity as well as differences in methodologic designs across studies. Many of the previous fMRI studies have very small sample sizes, leading to contrastive results across studies. Therefore, although the fMRI technique has provided us with a fair insight into the neural processes involved in aphasia recovery, it is important to know that this is not a complete picture, and results from fMRI studies need to be interpreted with caution. Further research in this field demands studies following consistent guidelines in terms of implementing fMRI paradigms (Meinzer et al., 2013), and many of the unresolved issues warrant future investigations using fMRI or a combination of different neuroimaging techniques.

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