Neuroplasticity Associated with Treated Aphasia Recovery

Julius Fridriksson and Kimberly Smith

The Aphasia Lab, Department of Communication Sciences and Disorders, University of South Carolina, Columbia, SC, USA

Aphasia therapy typically refers to clinician-administered behavioral approaches that use language-based drills or the learning of compensatory strategies to ameliorate the effects of impairment. Aphasia treatment is most often administered through didactic interactions between a patient and a clinician—a speech-language pathologist—who provides targeted language stimulation or task instructions focusing on a specific process or communication skill. Other increasingly common forms of treatment administration include group treatment or computerized language therapy. Although its effectiveness has been debated, recent meta-analyses suggest that aphasia treatment is generally beneficial, although much work is needed to better understand which treatment approach might work best for a specific patient (Brady, Kelly, Godwin, & Enderby, 2012; Kelly, Brady, & Enderby, 2010; Robey, 1998). That is, aphasia therapy promotes improved language function even though only a few therapy techniques have been established to tackle the different aspects of aphasic language impairment.

Regardless of treatment mode or maximum efficacy, it is an implicit assumption that treatment-assisted recovery from aphasia is supported by plastic brain changes, either functional or structural. Whether these changes are transient or permanent may determine the long-term effectiveness of aphasia treatment. The brain mechanisms that support aphasia recovery are not clear, and research in this area has yielded seemingly conflicting results (Saur & Hartwigsen, 2012; Saur et al., 2006; Szafarski, Allendorfer, Banks, Vannest, & Holland, 2013). In this chapter, we address treated aphasia recovery in the context of contemporary understanding of neuroplasticity.

80.1 NEUROPLASTICITY

A paramount characteristic of the human brain, among other species, is its ability to continuously adapt its structure and function based on internal and external environmental changes. Typically, this ability is known as neuroplasticity. A generally accepted assumption of neuroplasticity states that to change behavior, the brain must also change. Considerable evidence suggests that structural changes to existing neural circuits or the generation of new circuits at the neuronal level underlie the behavioral changes associated with neuroplasticity (Cramer, 2008; Kolb & Whishaw, 1998). Dendritic morphology (i.e., dendritic form and structure) has been stressed as a critical contributor to these neuronal changes, whereas additional neuronal changes are likely contributory, such as number of synapses, synapse size, and metabolic activity. Neuroplasticity is made possible by coordinating changes of neuronal morphology, glia, and vascular and metabolic processes. These modifications are stimulated by several factors, including sensory-motor experiences, task learning, gonadal and stress hormones, psychoactive drugs, neurotrophic factors, cortical stimulation, aging, and diet (Cramer, 2008; Johansson, 2000; Kolb & Whishaw, 1998; Kleim & Jones, 2008; Ripntjes & Weiller, 2002). In broad terms, synaptic and dendritic changes allow the brain to be structurally and functionally plastic as a response to experiences during development, learning, recovery from injury, and aging (Hebb, 1949).

Typically, neuroplasticity has been considered in the context of behavioral stimulation and response to the external environment. Although it is straightforward to see why this is the case—much of what we know about...
neural plasticity is derived from highly controlled animal studies with optimized experimental manipulations and carefully controlled environments—it is important to consider aphasia recovery in the context of potentially adaptive and maladaptive sequelae of recovery. Most cases of aphasia are caused by ischemic stroke in which the vascular supply to the cortex has been interrupted. Aphasia is often viewed as the consequence of frank brain damage to the cortical language network. However, JohnHughlingsJackson, the eminent English physician who studied many forms of neurological disorders in the late 19th century, suggested that aphasic language impairment should be considered not only the direct behavioral result of the brain damage but also a reflection of the function of remaining brain tissue in the absence of cortical areas damaged by the stroke (Jackson, 1874).

The cortical reorganization and plastic changes after stroke probably occur to optimize function; however, the location and extent of injury dictate what kinds of recovery processes can be engaged and may influence whether cortical maladaptation occurs. In the case of maladaptation, it could be that plastic changes in response to cortical damage actually hinder recovery or promote suboptimal reorganization in the early phases after stroke. Moreover, it is possible that early training (e.g., aphasia therapy) may actually negatively affect long-term recovery. Adverse consequences of acute rehabilitation have been demonstrated in a mouse model after motor stroke (Allred & Jones, 2008) in which early training of the spared forelimb had a negative effect on long-term improvement of the affected limb. Whether the same principle could be attributed to early aphasia treatment is questionable, yet this study demonstrates that we know very little about the effects—positive or negative—of plastic brain changes on recovery, and we also do not know the optimal timing for initiation of aphasia treatment. Several studies have suggested that neuroplasticity is greatest soon after brain damage, with lesser changes seen over time (Hartman, 1981; Kim, Ko, Parrish, & Kim, 2002; Robey, 1998). This could mean that targeted treatment seeking to capitalize on these changes should be dispensed as early as possible after aphasia onset. Clearly, there is an urgent need for a better understanding of the capacity for adaptive neuroplasticity as a consequence of initial brain damage and subsequent aphasia treatment, as well as the risk of maladaptive neuroplasticity that could stifle spontaneous and treated recovery.

80.2 ACUTE AND CHRONIC CONSIDERATIONS

In some cases of acute stroke, the recovery from aphasia can be very substantial in the first few hours and days after onset. As demonstrated by Hillis et al. (2001), Hillis and Heidler (2002), and Hillis et al. (2004), some of this recovery is supported by vascular changes leading to reperfusion of the ischemic penumbra and critical language areas. For patients who make it to the hospital within 4.5 hours of ischemic stroke onset and who are candidates for thrombolysis with tissue plasminogen activator (tPA), the effects of stroke may be partially ameliorated by dissolving the blood clot that caused the stroke. For some of these patients, the return of language function can be quite dramatic and, in some cases, complete (Felberg et al., 2002; Maas et al., 2012; Saur et al., 2006). However, thrombolysis is administered in approximately 10% of cases (Bray et al., 2013; Minnerup et al., 2011; Monks, Pitt, Stein, & James, 2012), which means that many stroke patients do not benefit from early intervention and may ultimately face a life-altering injury to which they must adapt.

Immediate efforts to dissolve or remove the blood clot in acute ischemic stroke are crucial for the preservation of as much neural tissue as possible and to prevent subsequent negative effects on behavior. However, neuroplasticity that occurs after cell death is completed probably takes place over weeks, months, and even years (Cramer, 2008; Johansson, 2000; Kleim & Jones, 2008). Although some of these plastic changes may occur in response to inherent homeostatic factors, it is likely that neuroplasticity supporting aphasia recovery primarily occurs in subacute (e.g., during the first 90 days after onset) and chronic phases of stroke recovery. That is, very early recovery from aphasia may be driven in part by neurovascular changes, whereas later recovery appears to rely more on actual neuroplasticity and, possibly, angiogenesis (the formation of new blood vessels from preexisting ones) (Carmichael, 2008; Cramer, 2008; Wei, Erinjeri, Rovainen, & Woolsey, 2001) as well as neurogenesis (the formation of new neurons) (Carmichael, 2008; Johansson, 2000). At this time, far more work is needed to determine whether and to what extent angiogenesis and neurogenesis play roles in aphasia recovery.

In chronic aphasia, recovery is mediated by relearning lost information, retraining specific processes that were impaired as a result of brain damage, learning compensatory strategies that aid in communication, and psychosocial adaptations such as those afforded by environmental enrichments and increased access to appropriate social environments (Turkstra, Holland, & Bays, 2003). Regardless of the kinds of behavior modifications that take place, neuroplasticity is at the crux of mediating and supporting such changes. Specific patterns of neuroplasticity that support aphasia recovery are being explored and considerable research has been devoted to this issue (Crosson et al., 2005, 2009;
Fridriksson, 2010; Fridriksson et al., 2012; Fridriksson, Morrow-Odom, Moser, Fridriksson, & Baylis, 2006; Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Heiss & Thiel, 2006; Heiss, Thiel, Kessler, & Herholz, 2003; Hillis et al., 2001, 2004; Hillis & Heidler, 2002; Kim et al., 2002; Marcotte et al., 2012; Meinzer & Breitenstein, 2008; Meinzer et al., 2004; Meinzer, Streiftau, & Rockstroh, 2007; Menke et al., 2009; Musso et al., 1999; Postman-Caucheteux et al., 2010; Saur & Hartwigsen, 2012; Saur et al., 2006; Schlaug, Marchina, & Norton, 2009; Szaflarski et al., 2013; Thompson, 2000a, 2000b; Thompson, den Ouden, Bonakdarpour, Garibaldi, & Parrish, 2010.

80.3 STRUCTURAL BRAIN CHANGES AND APHASIA RECOVERY

A few studies have examined structural brain changes associated with aphasia recovery. Probably the first, and perhaps best, known study of this kind was conducted by Schlaug and colleagues (2009), who treated six aphasic patients using Melodic Intonation Therapy (MIT) (Albert, Sparks, & Helm, 1973; Helm-Estabrooks, Nicholas, & Morgan, 1989), a treatment approach that targets nonfluent speech production and emphasizes the patient imitating intoned speech modeled by a clinician. The main idea behind MIT is that it targets activation of the right hemisphere, where melody is thought to be processed (Albert et al., 1973; Conklyn, Novak, Boissy, Bethoux, & Chemali, 2012; Helm-Estabrooks et al., 1989; Norton, Zipse, Marchina, & Schlaug, 2009; van der Meulen, van de Sandt-Koenderman, & Ribbers, 2012; Schlaug et al., 2009). Diffusion tensor imaging (DTI) was used to assess changes in white matter density in the right hemisphere before and after a therapy program consisting of 75 MIT sessions. In summary, this study revealed an increase in volume and number of fibers in the right arcuate fasciculus, suggesting that structural connectivity was increased as a result of aphasia treatment. A case study of a 12-year-old patient with a large left hemisphere lesion and severely nonfluent speech yielded similar results (Zipse, Norton, Marchina, & Schlaug, 2012). That patient underwent 120 hours of treatment using MIT, and DTI was used to assess white matter changes in the right hemisphere. Increased volume was found at the mid-point of the treatment phase and at 1 year after treatment in the right arcuate fasciculus and the uncinate fasciculus, a white matter tract that, in the left hemisphere, is commonly associated with semantic processing (Catani et al., 2013; Harvey, Wei, Ellmore, Cris Hamilton, & Schnur, 2013). Intriguingly, these studies suggest that the type and location of neuroplastic changes associated with treated aphasia recovery might be dependent on the type of treatment. That is, treatments that involve processes that are supported by the right hemisphere (e.g., intonation) are more likely to yield plastic changes in the right hemisphere, whereas approaches that focus more on language processes (which primarily tax the left hemisphere in neurologically intact subjects) may be more likely to recruit preserved areas of the injured left hemisphere.

In another study that specifically examined structural brain changes with DTI, Allendorfer et al. (2012) used intermittent theta burst transcranial magnetic stimulation (iTBS) to target preserved anterior left hemisphere regions in eight patients with different types of chronic aphasia. Although the specific mechanism is unknown, iTBS has been shown to enhance motor-evoked potentials, suggesting that it has excitatory effects on neural tissue. All patients underwent 10 iTBS sessions (without behavioral language treatment), after which increased fractional anisotrophy (FA) was found in the targeted regions, including left inferior and superior frontal gyri, as well as in the right midbrain and several bilateral regions such as the temporal and parietal cortices. With regard to language changes, improvements were found on a semantic fluency test but not on the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 2001) or the Peabody Picture Vocabulary Test (Dunn & Dunn, 2007). Importantly, no relationship was revealed between the extent of FA changes and language improvement. Nevertheless, studies of this kind suggest that treatment of aphasic patients, using either behavioral language treatment or transcranial cortical stimulation, can change the structure of the brain. However, it is far too early to postulate what might be the specific patterns of structural brain changes that support aphasia recovery. More research including a larger number of patients, detailed descriptions of language ability, and consistent methods across studies is needed to better understand structural neuroplasticity in aphasia recovery.

80.4 FUNCTIONAL BRAIN CHANGES AND APHASIA RECOVERY

Compared with studies of structural neuroplasticity, far more research has focused on functional brain changes associated with spontaneous and treated recovery from aphasia. One of the challenges of understanding how functional brain changes support aphasia recovery is that many different approaches, methods, and behavioral tasks have been used to relate cortical modulation to behavioral changes. This can be expected because of the many types and varying
severity levels of aphasia. Future investigations cannot ignore these differences because each may contribute uniquely to plasticity.

It is also a concern that most studies of functional brain changes associated with aphasia treatment have relied on single case studies or very small sample sizes. This is because of the extensive variability that characterizes both the language behaviors and the associated patterns of brain tissue either spared or destroyed by stroke and other causes of aphasia. A case study by Epstein-Peterson, Vasconcellos Faria, Mori, Hillis, and Tsapkini (2012) demonstrates this point well. Their patient had a large left hemisphere stroke affecting most of the structures supplied by the middle cerebral artery, including areas that typically are thought to be crucial for normal language processing (Broca’s area and most of the middle and superior temporal lobe). Despite this severe injury to the left hemisphere, the patient had a relatively mild language impairment characterized mostly by somewhat restricted speech fluency, relatively spared auditory comprehension of canonical sentences, and only very limited anomia. Although the patient was diagnosed with global aphasia (or severe impairment in all language modalities) immediately after stroke, testing at the time of study inclusion (3 years after stroke) indicated fairly mild aphasia. This case is unusual in that most patients with similar damage continue to present with more severe aphasia during the chronic phase, most typically consistent with Broca’s or even global aphasia (Fridriksson, Fillmore, Guo, & Rorden, 2014; Fridriksson et al., 2012). However, such rarities clearly do exist and remain unexplained. Such mild language impairment after extensive left hemisphere damage likely demonstrates premorbid differences in language organization and unique behavioral characteristics. The presence of such patients also demonstrates extensive variability in the process(es) by which recovery from severe brain damage can be achieved. Finally, and not insignificantly, it must be remembered that environmental manipulations, in many guises ranging from the quality, extent, and intensity of treatment to the amount and type of external personal support, also play a role. At the very least, this case and others like it (Berthier, 2001; Heilman, Rothi, McFarling, & Rottmann, 1981; Pulvermüller & Schönlé, 1993) demonstrate the current difficulty and uncertainty of ascribing language recovery to a single process or to specific changes in functional or structural neuroplasticity.

As stated, many different methods have been used to investigate changes in functional activation associated with aphasia treatment. These include functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), positron emission tomography (PET), and transcranial cortical stimulation. Two patterns of functional brain activation have been described to support language recovery in aphasia: (i) functional reactivation, which suggests greater reliance on preserved language areas, including cortex immediately adjacent to the lesion (Cappa, 2000; Heiss et al., 2003); and (ii) functional reorganization, which refers to activation of nontraditional language areas, either residual left hemisphere structures or right hemisphere homologues (Marcotte et al., 2012). Several studies have provided evidence that supports a more favorable outcome when left hemisphere perilesional areas are recruited (Fridriksson, 2010; Fridriksson et al., 2009; Fridriksson, Richardson, Fillmore, & Cai, 2012; Postman-Caucy, Cooke, & Rorden, 2010; Warburton, Price, Swinburn, & Wise, 1999) and, in fact, show detrimental outcomes when right hemisphere regions are recruited (Naeser et al., 2005), whereas others report better outcomes associated with right hemisphere modulation (Crosson et al., 2005; Leff et al., 2002; Musso et al., 1999; Peck et al., 2004). There is also evidence that suggests aphasia recovery is supported by bilateral hemispheric recruitment (Belin et al., 1996; Fridriksson et al., 2006, 2007; Thulborn, Gindin, Davis, & Erb, 1999; Weiller et al., 1995). Saur and colleagues (2006) discussed a plausible explanation for these seemingly incompatible findings in detail, suggesting three phases of language recovery where neural recruitment transitions: weak activation of intact left hemisphere regions in the early acute phase; strong activation of the entire language network—but especially right hemisphere regions—in the subacute phase; and, finally, normalization of activation as peak cortical recruitment returns to the left hemisphere during the chronic phase of recovery. In this study, language recovery systematically improved at each phase of recovery. Thus, there seem to be implications of different patterns of recovery that are potentially adaptive at different times.

Based on the evidence discussed, there is support for functional brain changes associated with both spontaneous and treatment-induced recovery of language in patients with aphasia. Many studies over the past several years have documented recovery in both scenarios, although fewer have looked exclusively at spontaneous recovery during the first few weeks after stroke. Despite the limited research, the studies seem to support a hierarchical model of language recovery during the acute and subacute stages, because dramatic improvements in language function are demonstrated within the first 2 weeks up to a few months after onset (Fernandez et al., 2004; Heiss et al., 1999; Karbe, Herholz, Halber, & Heiss, 1998; Pedersen, Stig Jørgensen, Nakayama, Rasseschou, & Olsen, 1995; Saur et al., 2006). These improvements may be accounted
for by diascisis resolution and strong bilateral activation (Saur & Hartwigsen, 2012). Most patients recruited for these studies received speech-language therapy as part of standard poststroke care, although the details of the implemented therapies were not reported; therefore, it is nearly impossible to identify the functional outcomes that occur purely as a result of spontaneous recovery as opposed to being driven by aphasia treatment.

In contrast, an increasing number of studies have assessed treatment-induced neural plasticity. Treatment approaches associated with neural plastic changes have focused on anomia training (Crosson et al., 2007, 2005, 2009; Fridriksson, 2010; Leger et al., 2002; Menke et al., 2009), semantic feature analysis (Marcotte et al., 2012), auditory comprehension (Musso et al., 1999), and sentence processing (Thompson et al., 2010), and changing activation patterns are most commonly assessed using fMRI. Meinzer and Breitenstein (2008) completed a review of 13 fMRI studies that implemented intervention paradigms to investigate language recovery in patients with chronic aphasia and reported that most studies found treatment-induced neural changes in both hemispheres. Because these findings were predominantly based on word retrieval interventions and not other aspects of impaired language, and because there were only three studies with more than 10 patients in the sample, we must interpret these findings with caution.

MEG, EEG, and PET studies have also documented treatment-based functional brain changes. MEG was used to assess treatment-induced plasticity after constraint-induced language treatment (CILT) (Breier et al., 2009; Meinzer et al., 2004). Results suggest that although the right hemisphere may support language recovery immediately after treatment, recruitment of perilesional regions is fundamental for prolonged, stable effects. This assumption holds true for the majority of studies described, and it supports the premise that treatment-induced changes occurring during the chronic stage of recovery may be attributed to the application of model-based therapies compared with generalized stimulation techniques applied during the acute stage of recovery (Saur & Hartwigsen, 2012).

Further, to optimize neural plasticity post-injury, new approaches to enhance treatment-induced recovery have been explored. Brain stimulation, a class of techniques that modifies cortical excitability, has been coupled with traditional speech-language therapy with the goal of facilitating increased learning and treatment outcomes, either by suppressing or by exciting targeted cortical regions. For example, Baker, Rorden, and Fridriksson (2010) found improved naming outcomes when anomia training was paired with anodal transcranial direct cortical stimulation (atDCS). Similarly, Meinzer and colleagues (2007) paired repetitive transcranial magnetic stimulation (rTMS) with CILT in two patients with aphasia and reported that both patients demonstrated improved outcomes when CILT was paired with rTMS compared with receiving rTMS in isolation.

In summary, the current evidence is encouraging yet nascent. Given the heterogeneity and small sample size, and given the variability in treatment approaches, more controlled group studies are required to confirm the present findings for both spontaneous and treatment-induced recovery. Despite variability in the current literature, as a whole, the implication is that the neural reorganization that occurs during spontaneous recovery is the same as therapy-induced reorganization, which takes place in the bilateral tempo-frontal network (Saur & Hartwigsen, 2012). Future work is necessary to further inform our knowledge of functional language recovery and to contribute to improved treatment efficacy for individuals with aphasia.

References


