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Introduction

Neuroplasticity in the language system: Reorganization in post-stroke aphasia and in neuromodulation interventions

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Owing to its critical role in human cognition, the neural basis of language has occupied the interest of neurologists, psychologists, and cognitive neuroscientists for over 150 years. The language system was initially conceptualized as a left hemisphere circuit with discrete comprehension and production centers. Since then, advances in neuroscience have allowed a much more complex and nuanced understanding of the neural organization of language to emerge. In the course of mapping this complicated architecture, one especially important discovery has been the degree to which the map itself can change. Evidence from lesion studies, neuroimaging, and neuromodulation research demonstrates that the representation of language in the brain is altered by injury of the normal language network, that it changes over the course of language recovery, and that it is influenced by successful treatment interventions. This special issue of RNN is devoted to plasticity in the language system and focuses on changes that occur in the setting of left hemisphere stroke, the most common cause of aphasia.

Aphasia—the acquired loss of language ability—is one of the most common and debilitating cognitive consequences of stroke, affecting approximately 20–40% of stroke survivors and impacting approximately a million individuals in the US alone (Siirtola et al., 1977; Pedersen et al., 1995; Berthier, 2005). For most healthy individuals, language is predominantly but not exclusively represented in a network of regions of the left hemisphere surrounding the Sylvian fissure; strokes that result in aphasia typically damage this left perisylvian network. While some degree of recovery occurs in most patients as they transition from the acute to chronic phase of their condition, persistent deficits of language are commonplace (Wade et al., 1986). Currently, speech therapy remains the mainstay of treatment for post-stroke aphasia, but is variable and limited in its efficacy (Robey et al., 1994; Basso & Marangolo, 2000; Bhogal et al., 2006; Brady et al., 2012). Moreover, despite recent advances in the neuroscience of language, it is still difficult to predict long-term outcomes and response to therapy in patients with aphasia (Lazar et al., 2008). These limitations underscore the need to develop novel approaches for understanding and intervening with the language system after it has been affected by brain injury. As the fields of cognitive neuroscience, neuroimaging, and neuromodulation continue to advance, characterization of plastic changes in brain architecture, connectivity, and functional activity after stroke are being explored as both prognostic indicators of language recovery and as targets for intervention. Articles in this issue will highlight both the network changes that emerge spontaneously over time

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in post-stroke aphasia, and the role that neuroplasticity can play in emerging treatments, including behaviorally-based speech and language therapies and noninvasive brain stimulation (NIBS).

1. Language network changes induced by stroke

Understanding how the intact language system is organized is fundamental to elucidating the neuroplastic changes that occur in that system after brain injury. The notion that language is represented in the brain by a network of functionally distinct interacting processing centers dates back to the 19th century with the pioneering discoveries of Broca, Wernicke, and with the development in 1885 of the Wernicke-Lictheim model (Lichtheim, 1885; Wernicke, 1874). While this classical model continues to inform the thinking of clinicians, developments in imaging and cognitive neuroscience have expanded understanding of the language network considerably, revealing components that are integral for processing specific features such as semantic, syntactic, and phonological information (e,g, Hagoort, 2013). Current models of language representation also emphasize the role of dorsal and ventral processing streams, the former of which is critical for mapping sound onto articulation, and the latter of which is integral to mapping sound onto meaning (Hickok & Poeppel, 2012). In this issue of RNN, Thiel and Zumbansen (2016) provide a concise review of these advances in our understanding of the intact language system.

Thiel and Zumbasen (2016) also review the pathophysiology of stroke with respect to the cellular and synaptic events that mediate changes in neural activity and connectivity after injury. As neuroimaging tools become increasingly sophisticated, the ability to translate between these neuronal changes and network-level shifts in brain plasticity is continually being refined. Advances in functional neuroimaging have yielded a number of insights into the changes that occur in brain activity during language tasks in patients with post-stroke aphasia. For instance, seminal work by Saur and colleagues (2006) demonstrates that in the acute phase after stroke, there is diminished activity of left hemisphere perisylvian areas that corresponds to severe decrements in language ability. During the subacute phase of recovery, increased activity is observed in homologous regions of the right hemisphere, whereas in the chronic phase of stroke and aphasia there is a degree of reengagement of left hemisphere areas. Thiel and Zumbasen (2016) also provide an excellent summary of this and other important findings in the imaging literature on language plasticity after stroke.

Post-stroke aphasia is typically associated with infarction in the territory of the left middle cerebral artery (MCA), and the bulk of behavioral and imaging research studies in aphasia are confined to patients whose language deficits are attributable to lesions in this vascular territory. Therefore, work by Sebastian and colleagues (2016), appearing in this issue of RNN, is novel in that it demonstrates network-level imaging changes in patients with aphasia due to strokes of the left posterior cerebral artery (PCA). Using task-based and resting state functional magnetic resonance imaging in conjunction with detailed language testing, the authors studied longitudinal changes in the naming network in four participants with PCA stroke in the acute, sub-acute, and chronic phases of recovery. They found that improvements in naming accuracy from the acute to the chronic stages following stoke corresponded with increased connectivity within and between left and right hemisphere language regions, while one participant who had a persistent naming deficit demonstrated diminished connectivity longitudinally within and between these left and right hemisphere regions. These findings suggest that inter- and intra-hemispheric connectivity between language regions are necessary for optimal naming recovery, and speak directly to the importance of reorganizing patterns of brain activity and connectivity after injury to relevant connections in the language network.

2. Noninvasive brain stimulation (NIBS) leverages language system plasticity

Understanding the course of spontaneous changes associated with post-stroke aphasia allows investigators to devise and optimize novel interventions that enhance the beneficial reorganization of language networks. Several articles in this special issue of RNN address the role of focal NIBS techniques like transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) in the treatment of post-stroke aphasia.

The vast majority of studies employing NIBS as a treatment for aphasia have focused on either regions surrounding injured portions of the left hemisphere (perilesional areas) or contralesional regions of the intact right hemisphere. There is wide agreement that

in the setting of left hemisphere lesions that impair language ability, regions that surround the area of injury (i.e. perilesional) can assume language-related functional roles (Chrysikou & Hamilton 2011). By contrast, the role of increased activity in contralesional right hemisphere remains controversial. By some accounts, the right hemisphere plays a largely compensatory role in the reacquisition of language abilities in persons with aphasia. This is supported by lesion studies that have shown that secondary injury to right perisylvian structures can reverse improvements in language performance experienced by patients with prior left hemisphere lesions (Barlow, 1877; Turkeltaub et al., 2012), as well as by more recent studies that have shown that the integrity of right hemisphere structures is associated with improved language recovery (Xing et al., 2016; Pani et al., 2016). In this issue of RNN, work by Zheng and colleagues (2016) builds upon and extends ideas based on this model. The authors employed MRI-compatible anodal (excitatory) tDCS of the right inferior frontal gyrus (IFG) in healthy adults, paired with arterial-spin labeling MRI (ASL-MRI) before, during, and after stimulation. They found that tDCS of the right hemisphere decreased interhemispheric connectivity, but increased intra-hemispheric connectivity. Saliently, these findings demonstrate that ASL-MRI can be used to detect tDCS-induced modulation of brain connectivity, which the authors posit may play an important role in future trial designs focusing on modulating the non-dominant hemisphere.

A countervailing view regarding the role of the right hemisphere areas is that increased activity may have deleterious effects on aphasia recovery in stroke. This account is predicated on the notion of interhemispheric inhibition. According to this account, when the brain is injured unilaterally, the lesioned side loses the ability to inhibit the intact contralesional hemisphere. Released from inhibition, the nondominant hemisphere exerts enhanced inhibitory inputs to the perilesional areas of the left hemisphere, impeding the language-related activity of these reorganized regions. By this account, an appropriate therapeutic strategy would be to suppress excessive activity of the right hemisphere with the objective of increasing the beneficial activity of left hemisphere perilesional areas. A number of investigators have adopted this premise, and have shown some degree of supportive evidence. In this special issue of RNN, Heiss (2016) presents PET data demonstrating that inhibitory repetitive TMS (rTMS) of the right inferior frontal gyrus results in both clinical improvement in aphasia and a shift from right to left hemisphere activation. Other work has suggested that the role of the right hemisphere in aphasia recovery is not monolithic, that different patients may employ different language recovery mechanisms, and that multiple recovery mechanisms may even be employed within the same individual (Turkeltaub 2012).

Because the heterogeneity of stroke-induced lesions can make identification of ideal left-hemisphere stimulation targets challenging, and because the role of the right hemisphere in aphasia recovery is debated, it would be useful to identify novel sites in the language system that may serve as potential targets for intervention. Novel work presented by Turkeltaub and colleagues (2016) in this issue of RNN is especially germane. In a relatively large cohort of healthy individuals, the authors demonstrated that tDCS applied over the right posterolateral cerebellum improved phonemic fluency. In addition, stimulation increased functional connectivity between the cerebellum and other brain areas involved in the motor control of speech, and enhanced correlations between left-hemisphere language and speech-motor regions. Excitingly, these findings suggest that the cerebellum may serve as a suitable stimulation target in individuals with aphasia.

Finally, the existence of at least two potential noninvasive brain stimulation therapies for aphasia (tDCS and TMS) raises questions about whether one intervention may be more efficacious than the other in treating people with aphasia. To address this, Shah-Basak, Wurzman, and colleagues (2016) conducted a systematic review and comparative meta-analysis of the two NIBS intervention approaches in persons with aphasia. They found that treatment effects were significant for both TMS and tDCS and were overall similar to each other in magnitude. However, while TMS had a significant impact in both chronic and subacute populations, tDCS effects were significant in chronic but not subacute persons with aphasia, suggesting a possible difference in efficacy at different phases of aphasia recovery.

3. Conclusions

The articles included in this special issue of RNN represent only a small sampling of the exciting developments emerging with respect to neuroplasticity in the language system. As the field of neuroscience makes progress toward mapping out the human

connectome, our understanding of the properties that define brain networks, including the language network, becomes increasingly refined (Gu et al., 2015). This may someday allow us to make principled predictions as to how the brain ought to adapt to specific lesions in the language system, how persons with aphasia ought to differ in their recovery potential based on individuals network differences, and how best to target language networks with treatments like speech therapy and brain stimulation in order to optimize clinical outcomes. Meanwhile, ongoing work in human neurophysiology is starting to elucidate measures that can be used as biomarkers of individual differences in neuroplasticity (Di Lazzaro et al., 2010; Pascual-Leone et al., 2011). If such measures can be developed for post-stroke aphasia recovery, it may be possible to predict aphasia outcomes based not only on the features of patients' strokes or their severity of their acute post-stroke deficits, but also potentially based on intrinsic individual differences in the plasticity of patients' brains. Neuroscience has only begun to scratch the surface with respect to understanding behaviorally relevant neuroplasticity. The closer we get to understanding and leveraging this remarkable feature of the central nervous system, to closer we will come to developing truly impactful treatments for aphasia and other cognitive deficits associated with focal brain injury.

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