Symposium 1: Neuroimaging in Aphasia Treatment Research: Lessons, Challenges and Future Directions

5. Neuroimaging in Aphasia Treatment Research: Lessons, Challenges and Future Directions

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Language function improves in individuals with aphasia, substantiating the now well-known fact that neuroplasticity extends to the adult brain (Merzenich et al., 1996). In the face of damaged neural tissue induced by stroke the brain has the capacity to reorganize. Importantly, as shown in studies of sensory and motor recovery in animals, neural reorganization is directly shaped by experience (Nudo et al., 1996). Reorganizational processes in aphasia are similarly under the influence of the environment even in chronic phases of recovery. That is, treatment directly affects these processes.

Functional neuroimaging has advanced the ability to study the neural mechanisms that support treatment-induced recovery of language processing and there are now a number of studies in the literature addressing this issue. In a recent review, over twenty studies were identified in which fMRI, PET, or MEG has been used to examine the effects of treatment (Thompson & Den Ouden, 2008). In this symposium we discuss this research and address the lessons learned, challenges that remain, and future directions of neuroimaging work examining the effects of treatment for aphasia.

In the first talk, Cynthia Thompson will provide a brief review of the aphasia treatment and neuroimaging literature and summarize the state of the science. Her remarks will provide a scaffolding for the other presentations, which will focus on recommendations for future research. Argye Hillis will address methods for characterizing both structural and functional lesions. Brenda Rapp will discuss the importance of careful quantification of the language deficit that patients present as well as considerations for scan task development. Swathi Kiran will address aspects of treatment research design and implementation in neuroimaging studies, and Dorothee Saur will address challenges in analyzing neuroimaging data derived from lesioned brains, including application of connectivity analyses.

References

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Thompson, C. K., & Den Ouden, D.B. (2008). Neuroimaging and recovery of language in apahsia. Current Neurology and Neuroscience Reports, 8, 475-483.

Presented by: **Rapp, Brenda**

6. Neuroimaging in Aphasia Treatment Research: The State of the Science

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Research examining the neurobiology of recovery from aphasia indicates that treatment impacts brain reorganizational processes. In general two primary patterns of recovery have been noted: (1) language function, premorbidly subserved by the damaged left hemisphere, is shifted to right hemisphere homologous regions, and (2) undamaged neural tissue in the left hemisphere is recruited, extending the functional map to include perilesional regions, perhaps because of functional redundancy. One other possibility is that completely novel brain mechanisms may come into play. Although some suggest that of these possibilities, reorganization within the left hemisphere results in the best recovery, review of studies published using fMRI, PET, or MEG indicate wide heterogeneity in activation patterns from pre- to post-treatment, and even patients who recover well given treatment show both right and left brain activation. This presentation will provide an overview of published studies, highlighting the heterogeneous activation patterns found from pre- to post-treatment across studies and potential reasons for them. There are at lease five factors related to the lack of convergence across studies. The first concerns characteristics of patient lesions and methods used to quantify them. Some studies include patients with aphasia resulting from various etiologies (e.g., stroke, tumor) and the size and extent of patient lesions (both structural and functional) are not always quantified. Because these factors may influence reorganizational processes, for example, patients with similar structural lesions may respond differently to treatment because of hypoperfused perilesional tissue, measures of both structural and functional dimensions of the lesion are important, including evaluation of the integrity of white matter tracts. Another issue concerns heterogeneity with regard to the type of language deficit patients present. Most studies provide information limited to the type of aphasia, but do not discuss aspects of language that are impaired and spared prior to treatment and the precise language functions that improve when treatment is provided. Because the objective of this type of research is to understand the specific neural changes that support recovery of specific language functions, it is important to comprehensively test language function before and after treatment. A third, related factor, is scan task selection and patient performance ability. Some studies have used tasks that at pre-treatment the patients cannot perform, thus it is difficult (if not impossible) to attribute any associated pre- to post-treatment activation with improved language processing ability per se. Another factor related to heterogeneity in neuroimaging treatment research is that the treatment itself varies across studies: treatments are not always clearly described and reliable treatment effects are not always reported. Finally, methods used for analysis of neuroimaging data differ across studies and most have not considered alterations in blood flow that coincide with some stroke-induced aphasias.
Presentations following this introductory talk will provide specific suggestions for addressing these issues, with emphasis placed on developing a set of standards used across researchers. A unified approach to fMRI treatment research will allow the results of studies to be compared to one another and move the neuroscience of aphasia rehabilitation forward.

Presented by: **Thompson, Cynthia**

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7. Functional Neuroimaging of Recovery in Aphasia: Characterizing the Lesion

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Interpreting areas of activation associated with recovered language in aphasic individuals requires characterizing the lesion responsible for the aphasia. The nature, site, size, and age of the lesion must be adequately determined to understand the functional imaging data. This talk will address the reasons why and methods for examining these variables in neuroimaging studies of aphasia treatment effects.
The nature of the lesion is important for several reasons. Some lesions, such as stroke, occur over a short period of

time, followed by potential reorganization of structure/function relationships. However, pre-existing cerebrovascular disease can complicate the hemodynamic response to neural activation; for example, stenosis of major vessels can limit blood flow to their vascular territories, eliminating the hemodynamic response, even if the area is not damaged. Likewise, for days to weeks after acute stroke, areas of hypoperfusion surrounding the acute infarct may be dysfunctional and contribute to the language deficits. These areas may show no hemodynamic response, even when there is some neural activation. Areas of hypoperfusion can be identified with MR perfusion imaging, CT perfusion, PET, or measures of vascular reserve. Some types of stroke (e.g. subarachnoid hemorrhage) have diffuse, poorly localized cognitive effects, even when they also cause areas of focal damage due to vasospasm or treatment. Other lesions cause damage over weeks to months, such as herpes encephalitis and rapidly growing tumors. Others cause damage over months to years, such as primary progressive aphasia, chronic intractable epilepsy, and slow-growing tumors. These progressive lesions can cause reorganization of structure/function relationships even before intervention, influencing the time course and extent of recovery. The nature of the lesion also determines what areas can be evaluated. Some areas are vulnerable to ischemia. Other areas, such as the temporal pole, are rarely affected by stroke. In contrast, herpes encephalitis, Semantic Dementia, and surgery for intractable epilepsy often affect the temporal pole. Thus, the likelihood of seeing activation in these areas during recovery will depend on the nature of the lesion.
The site of lesion can be identified in several different ways, with distinct strengths and weaknesses. The site of focal lesions can be drawn on a template or standardized "atlas", such as the Montreal Neurological Institute atlas or Talairach space, that would also be used to identify the areas of activation. However, the site of dysfunctional tissue (including the area of hypoperfusion discussed above) may be more important than the site of only structural lesion alone. Scans showing the lesion should also be "registered" to the selected atlas, because brains are all different shapes and sizes. Registration methods vary in how well they accommodate large lesions, because these distort the shape of the brain. White matter tracts affected by the lesion can influence functional imaging results. Status of white matter tracts can be evaluated with Diffusion Tensor Imaging and tractography.
Volume of the lesion or dysfunctional tissue will also influence what areas are likely to assume the role of the damaged areas. Finally, age of the lesion is important, as areas of activation during language change over time.

Presented by: **Hillis, Argye**

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8. Characterizing the Language Deficit: Implications for Scan Task Selection

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The goal of functional neuroimaging research on recovery of language function is to characterize and understand the neural changes that support recovery or improvement of specific language functions. Presumably, different language functions will recruit different neural regions in their recovery. For example, recovery of thematic role assignment abilities presumably will involve different neural changes than improvement in the ability to retrieve phonological word forms from a lexical phonological memory store. Therefore, the objective of this type of research is to understand the specific neural changes that support recovery of specific language functions. In the longitudinal approach to this issue, the neural activation patterns of individuals with specific language deficits are evaluated at multiple time points during the course of recovery, either spontaneous or as a result of treatment. Neural changes correlated with the changes in the relevant language functions are assumed to provide information regarding the neural regions and mechanisms that supported the recovery. Simply put, changes in language functions are related to changes in neural activation patterns.
In order to interpret the longitudinal changes within a given study and also to compare and contrast the results of different investigations, it is critical to precisely evaluate language abilities both before and after treatment (or spontaneous recovery). Before treatment, it is necessary to identify the language functions that have been disrupted by the lesion and those that have not; subsequent to treatment, it is necessary to identify the language functions that have improved and those that have not. Only in this way can the longitudinal neural changes that are observed be associated with the appropriate language functions. The pre and post treatment characterization of language abilities will need to be informed by various considerations including the need for comprehensive evaluation, test/re-test

practice effects, etc.
In order to relate the changes in language abilities to changes in neural activation patterns, it is critical to select language tasks to be performed during the functional neuroimaging that will recruit the relevant neural substrates both pre and post treatment. Presumably these tasks will activate the substrates involved in the language functions that have been disrupted by the lesion; in this way changes in language functions can be reflected in changes in activation patterns. The choice of scanner task is a very complex one and will be affected by a number of different factors, including task difficulty.
The quality of the research directed at understanding the neural substrates of recovery of language function will be determined, to an important extent, by the quality of the two "sides of the equation" –our understanding of the affected language functions and our ability to select scanner tasks that will reveal the relevant neural activation patterns. In this talk, the challenges faced by both of these aspects of research design will be discussed.

Presented by: **Rapp, Brenda**

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9. Experimental Treatment Design: What's Important for Neuroimaging Research

Swathi K.
Boston University

Functional neuroimaging is a relatively new methodology that holds promise for detecting physiological processes that underlie learning-related plasticity. A number of studies examining recovery patterns associated with treatment of both groups of (Belin et al., 1996; Musso et al., 1999) and individual patients (Leger et al., 2002; Davis, Harrington, & Baynes, 2006; Small et al. 1998, Thompson et al., 2000) have been published. However, wide heterogeneity has been found with regard to changes in activation from pre- to post-treatment. Although there are a number of factors to consider with regard to this heterogeneity, an important issue relates to the type of treatment provided as well as documentation of how well patients respond to it.
The goal of this paper is to address treatment-related issues relevant to the conduct of neuroimaging studies. First, options for implementing controlled experimental treatment designs will be discussed, including both single subject and group approaches. Topics covered will include measurement of independent and dependent variables, acquisition and generalization, internal and external validity, and reliability. The need for operational definition of the treatment itself will be emphasized. It is now well know that treatment directly impacts reorganizational processes of the brain; thus, it follows that the type of treatment provided also will influence recovery processes. Without careful detailing of the precise experimental treatment manipulations provided, the meaning of any changes in the neurobiology of language will be illusive.
How to integrate treatment dependent variables and fMRI tasks in order to closely inspect the neural regions involved in treatment-induced plasticity will also be discussed. Topics covered will include comparison of task performance inside and outside the scanner, criteria for defining change, and comparisons of improvement and recovery during treatment to that noted during pre-post fMRI scans. It is anticipated that this presentation will promote awareness and interest in using neuroimaging as a tool to document treatment-related changes in the brain and stimulate discussion regarding challenges and recommendations for future research in this area.

Presented by: **Swathi, Kiran**

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10. Analyzing Functional Neuroimaging Data of the Lesioned Brain

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Performing functional imaging in acute and chronic aphasic stroke patients poses a number of challenges but also offers unique insights into the reorganizing brain. In this presentation, the need to consider the lesion extent, derived from both structural and functional (diffusion- and perfusion weighed imaging) in analysis of activation patterns derived from both pre- and post-treatment conditions will be emphasized. In order to understand changes in reorganizational processes derived from functional imaging data these dimensions of the lesion need to be considered. In addition, the results of diffusion tensor imaging, which provides information relative to the functioning of white matter tracts is important to consider in analysis of functional imaging data. Methods for doing this will be emphasized.
Methods for analyzing fMRI data derived from both single subjects as well as groups of aphasic stroke patients also will be discussed, together with methods for evaluating change in activation patterns across all phases of stroke recovery. Data showing changes across phases of recovery with no treatment provided will be presented to demonstrate processes occurring at different phases of language reorganization after stroke. Analysis of treatment-induced recovery will be discussed in consideration of these changes. Furthermore, functional and anatomical network identification procedures used to detect reorganization in terms of a re-coordination of the lesioned language network will be presented. Finally, it will be shown how the application of multivariate analysis techniques to early language fMRI data might be used to predict individual behavioral outcomes of aphasic stroke patients.

Presented by: **Saur, Dorothee**