Neuroplasticity and Aphasia Treatments: New Approaches for an Old Problem

A Commissioned Review for Journal of Neurology, Neurosurgery, and Psychiatry

Authors

Bruce Crosson, PhD (corresponding author)
Address: Center for Visual and Neurocognitive Rehabilitation (151-R), Atlanta VA Medical Center, 1670 Clairmont Road, Decatur, GA 30033, USA

Amy D. Rodriguez, PhD
Address: Center for Visual and Neurocognitive Rehabilitation (151-R), Atlanta VA Medical Center, 1670 Clairmont Road, Decatur, GA 30033, USA

David A. Copland, PhD
Address: University of Queensland Centre for Clinical Research, Building 71/918, Royal Brisbane and Women's Hospital Campus, Herston, QLD 4029, Australia

Julius Fridriksson, PhD
Address: Department of Communication Sciences and Disorders, Arnold School of Public Health, University of South Carolina, Columbia, SC 29208, USA

Lisa C. Krishnamurthy, PhD
Address: Department of Physics and Astronomy, 25 Park Place #605, Georgia State University, Atlanta, GA, USA

Marcus Meinzer, PhD
Address: University of Queensland Centre for Clinical Research, Building 71/918, Royal Brisbane and Women's Hospital Campus, Herston, QLD 4029, Australia

Anastasia M. Raymer, PhD
Address: Department of Communication Disorders & Special Education, 240 Lions Club Child Study Center, Old Dominion University, Norfolk, VA, USA

Venkatagiri Krishnamurthy, PhD
Address: Center for Visual and Neurocognitive Rehabilitation (151-R), Atlanta VA Medical Center, 1670 Clairmont Road, Decatur, GA 30033, USA

Alexander P. Leff, MD
Address: Department of Brain Repair and Rehabilitation, Institute of Neurology, 17 Queen Square, University College London, London WC1N 3AR, England, UK

Affiliations:

Center for Visual and Neurocognitive Rehabilitation, Decatur, GA, USA (B Crosson PhD, A Rodriguez PhD, V Krishnamurthy, PhD, LC Krishnamurthy, PhD); Department of Neurology, Emory University, Atlanta, GA, USA (B Crosson PhD, V Krishnamurthy, PhD); Department of Psychology, Georgia State University, Atlanta, GA, USA (B Crosson); School of Health and Rehabilitation Sciences, University of Queensland, St Lucia, QLD, Australia (D Copland PhD, M Meinzer PhD); University of Queensland Centre for Clinical Research, Herston, QLD, Australia (D Copland PhD, M Meinzer PhD); Department of Communication Sciences and Disorders, University of South Carolina, Columbia, SC, USA (J

Fridriksson PhD); Department of Physics and Astronomy, Georgia State University, Atlanta, GA, USA (LC Krishnamurthy); Department of Brain Repair and Rehabilitation, Institute of Neurology, University College London, London, England, UK (AP Leff MD); National Hospital for Neurology and Neurosurgery, University College London, London, England, UK (AP Leff); Department of Communication Disorders & Special Education, Old Dominion University, Norfolk, VA, USA (A M Raymer PhD)

Correspondence to: Bruce Crosson PhD, Center for Visual and Neurocognitive Research (151-R), Atlanta VA Medical Center, 1670 Clairmont Rd, Decatur, GA 30033, USA; bruce.crosson@emory.edu; Telephone: 1-352-219-0769

Abstract

Given the profound impact of language impairment after stroke (aphasia), neuroplasticity research is garnering considerable attention as means for eventually improving aphasia treatments and how they are delivered. Functional and structural neuroimaging studies indicate that aphasia treatments can recruit both residual and new neural mechanisms to improve language function and that neuroimaging modalities may hold promise in predicting treatment outcome. In relatively small clinical trials, both non-invasive brain stimulation and behavioural manipulations targeting activation or suppression of specific cortices can improve aphasia treatment outcomes. Recent language interventions that employ principles consistent with inducing neuroplasticity also are showing improved performance for both trained and novel items and contexts. While knowledge is rapidly accumulating, larger trials emphasizing how to select optimal paradigms for individualized aphasia treatment are needed. Finally, a model of how to incorporate the growing knowledge into clinical practice could help to focus future research.

Introduction

Aphasia, acquired impairment of expression and/or comprehension in spoken and written language, is associated with greater negative impact on quality of life than any other disease or medical condition, including cancer and Alzheimer's disease[1], and its severity predicts functional autonomy after stroke[2]. Hence, assisting persons with aphasia (PWAs) to recover language function is a critical research priority. Understanding how neural changes underlie aphasia treatment, how to induce such neural changes, and the limits of such plasticity is critical for developing effective new treatments. Neuroplasticity is the term used to refer to these neural changes supporting learning, or as applied to the current topic, relearning of language elements and processes. The structural and physiological changes that constitute neuroplasticity occur at the synaptic, cellular, and macrostructural level. Practically, it is only possible to study neuroplasticity in humans at the macrostructural level; hence, this review focuses on this level of measurement. For aphasia rehabilitation, neuroplasticity at this level involves changes in brain systems and how these changes, including damage and reorganization, impact rehabilitation outcome.

Over the past several years, important developments in neuroplasticity research include not only the tools to measure neural mechanisms supporting rehabilitative change but also the means to induce neural changes. Yet, our knowledge regarding neuroplasticity in aphasia is nascent. This review emphasizes the most important developments in the neuroplasticity literature for the last several years as applicable to treatment of stroke-induced aphasia. Our goal is to provide a unique and integrative overview that broadly covers the substantive areas of neuroplasticity relevant to aphasia treatment and is both accessible to generalists and useful for rehabilitation specialists. We start by discussing neuroimaging developments in aphasia treatment research and then turn to research concerning induction of neuroplasticity during aphasia treatment. We summarize findings at the end of each section and discuss the implication of neuroplasticity research for the future of clinical aphasia treatment in our concluding remarks.

Neuroimaging and Neuroplasticity

Functional and structural neuroimaging provide important information about how brain systems change as a result of aphasia therapy. These techniques provide empirical evidence to determine the degree to which different treatments rely on restorative vs. reorganizing processes. Imaging can also provide important clues to therapeutic processes, such as whether patients are relearning words as opposed to reactivating dormant information stores or processes. The information gleaned from imaging studies can help determine how to induce neuroplastic changes supporting therapeutic innovation.

Measuring Neuroplasticity. Functional neuroimaging maps brain activity during a task, revealing areas engaged in language functions, which allows visualization of language system changes from pre- to post-treatment. For aphasia treatment, scans most commonly map activity for a language function of interest vs. some control condition. Recently, scans taken during a resting state (no task) have also been used to measure changes in functional connections between brain regions.

One important question is whether residual learning capacity is supported by brain mechanisms engaged in language-related processing pre-injury (i.e., restorative mechanisms) or whether there is recruitment of mechanisms not previously involved in language processing (i.e., reorganizing mechanisms). A related issue is the overlap in brain structures that support word learning in healthy adults, which engages the medial temporal lobe, and word re-learning in aphasia, which appears to rely on integrity and functional engagement of memory structures such as the hippocampus.[3,4] The implication when patients rely on hippocampal activity, is that they are re-learning as opposed to simply activating latent neural patterns maintained from premorbid encoding, implying reorganization to cortices not previously supporting word retrieval. However, spared networks within the dominant MCA territory also are likely to be relevant. For example, the amount of improvement in naming ability following early intensive therapy has been shown to correlate with increased activation of the left inferior frontal gyrus

(IFG),[5] a structure known to be involved in language for neurologically normal persons.[6-8] Further, recovery patterns revealed in neuroimaging studies may depend on what cognitive processes different therapies engage. For example, after training in producing specific sentence structures, aphasic patients showed increased activity in right-hemisphere structures during verb production that were different from areas neurologically normal groups activate,[9] indicating reorganization of function to new brain regions.

In the largest study to date, Fridriksson[10] identified task-dependent pre- to post-intervention activity increases for picture naming in residual anterior and posterior left-hemisphere regions that were associated with positive treatment response, suggesting that restorative mechanisms were in play. In contrast to these findings of increased activity, Abel et al.[11] demonstrated decreased activity in left and right hemisphere regions that correlated with improved naming ability. This difference in therapy-driven response patterns between studies seems paradoxical. It is reasonable to expect that brain activity will increase in nodes of recovery networks that do more 'neuronal heavy lifting'. However, activity in these nodes also may decrease later in therapy as networks become more efficient with practice and the brain expends less energy performing language functions. Indeed, a recent study used a cued picture-naming task to gain insight into patients' neural response to treatment. A bilateral frontal network including the right anterior insula, inferior frontal and dorsal anterior cingulate cortices, and the left premotor cortex, showed reduced activity from pre- to post-treatment scans for trained vs. untrained words, indicating increasing facilitation by speech-sound cuing as a result of treatment.[12]

Another key finding is that treatment-induced brain changes are not just related to language processing per se. Treatment success may require brain mechanisms involved in multiple cognitive processes, including determining the salience of stimuli, attending to them, and/or regulating cognitive control.[13,14]

Consensus in the field is that complex cognitive processes are mediated by interacting distributed brain systems, indicating that in addition to specific brain regions, we should seek to identify therapeutic effects in network connections.[15] For example, it was recently shown that an increase both in connectivity within sub-networks and segregation between their activity states during resting-state scans over the course of therapy is associated with greater treatment response.[16-18] Another study demonstrated that an auditory therapy for 'Wernicke-type' aphasia induced changes in behaviour and altered network connectivity within the left superior temporal gyrus (STG) as well as connectivity between the left STG and left primary auditory cortex (Heschl's gyrus (HG), Figure 1).[19] Different types of therapy may have differential effects on the nature and extent of neuroplasticity that occurs within these networks and may differentially engage left versus right hemisphere networks. For instance, treatment of word retrieval has been associated with increased functional connectivity in left-hemisphere networks[20] while right-hemisphere sensory-motor networks have shown increased functional connectivity in response to an Action Observation Therapy.[21]

_____

Insert Figure 1 about here.

Compared to functional neuroimaging studies, less research has focused on structural brain changes associated with robust and lasting changes in language function. The first study demonstrating structural brain changes associated with aphasia treatment observed an increase in the number of fibres and volume of the right arcuate fasciculus following melodic intonation therapy (MIT)[22]. This is consistent with the view that MIT leverages right-hemisphere mediated melodic intonation abilities to improve spoken language. More recent studies further support the notion that aphasia recovery relies on changes in brain structure. Allendorfer et al. showed that 10 sessions of excitatory repetitive transcranial magnetic stimulation (rTMS) over the left hemisphere leads to increased fractional anisotropy (FA), a measure thought to reflect axonal density, in left frontal regions as well as the corpus callosum[23]. Interestingly, decreased FA was revealed in the fusiform gyrus and left cerebellum, suggesting that the effects of rTMS were not unidirectional. These two studies did not find a linear relationship between language improvement and changes in white matter density. However, a more recent diffusion tensor imaging (DTI) study demonstrated that the extent of improvement associated with phonologically-based

word retrieval treatment was linearly related to increased white matter structural integrity (FA) for the left arcuate fasciculus,[24] though lower FA in the right arcuate fasciculus was associated with improved speech for MIT[25]. More research is needed to determine the role of white matter changes in aphasia treatment success.

McKinnon et al[26] used diffusion kurtosis imaging, which is thought to be more sensitive than DTI to microstructural changes,[27] to examine white matter changes associated with aphasia treatment. The study revealed that normalization (increase) in mean kurtosis, a measure of microstructural density, in the inferior longitudinal fasciculus was associated with decreased semantic but not phonological naming errors, suggesting that restored integrity of this structure improved semantic processing of words. This finding is consistent with the hypothesized role of the inferior longitudinal fasciculus in language processing.

Studies of aphasia treatment-induced structural changes in gray matter are rare. A recent longitudinal study of natural (rather than treatment-induced) recovery in chronic aphasia used voxel based morphometry (VBM) to assess changes in right-hemisphere gray-matter density across two time-points, which in turn were correlated with changes in language functions[28]. Changes in naming accuracy were associated with both increased and decreased right-hemisphere gray matter density in the anterior temporal lobe and the precentral gyrus, respectively. A different, cross-sectional study, also showed positive correlations between spoken word comprehension and gray-matter density from VBM in the right middle temporal gyrus and insula and between spoken word production and gray-matter density in the right supplementary motor area cortex and insula.[29] These chronic aphasia studies indicate that VBM may have potential for measuring treatment-induced gray-matter changes in aphasia.

In summary, functional neuroimaging studies show differences in brain areas engaged in language processing as a result of therapy. Structural neuroimaging studies show that changes in white and possibly gray matter also occur. Whether therapies restore left perisylvian activity or reorganize activity to right-hemisphere structures seems to be treatment-dependent. However, current studies are limited by small sample sizes and differences in methodologies. Replications of studies with larger samples and more consistent methodology will lend greater confidence to findings. Furthermore, as reliable evidence accumulates, the longitudinal application of neuroimaging to aphasia therapy studies, a relatively new phenomenon, will reveal overarching principles that guide development of more efficient therapies and a greater understanding of neural mechanisms that support them.

Predicting Aphasia Treatment Outcome. The location and degree of damage to language-related brain structures and the impact of that damage on functional systems will place limits on the neuroplasticity necessary for successful aphasia therapy. While functional and structural neuroimaging measures yield insights into how the brain reorganizes during various treatments, using neuroimaging methods to predict treatment change has direct clinical implications. Specifically, regions of brain activity or damage that predict therapeutic outcome could be used as an aid in selecting treatments that are likely to succeed given a specific pattern of activity or damage. Compared to studies of remapping of brain structures and functions as a result of treatment, this is an under-studied area of research.

There are limited examples of functional neuroimaging measures at baseline that predict aphasia therapy outcome. Fridriksson et al.[30] showed that changes in brain activity resulting from therapy within left temporal and parietal regions predicted treatment induced naming improvements and reductions in naming errors, while baseline functional activity alone was less informative. Specifically, functional activity in the residual language network (perilesional frontal lobe) predicted post-treatment changes in semantic paraphasias but not other measures of naming improvement. One recent smaller scale study found that pre-treatment activity in the left caudate nucleus during picture naming predicted positive therapeutic success in a picture-naming treatment relying on semantic feature analysis[31]. In summary, these two studies indicate areas of activity during functional neuroimaging of language have potential for predicting therapeutic outcome, but much more research is needed before such information can be applied clinically.

Voxel-based Lesion Symptom Mapping (VLSM) is a technique used to determine whether presence vs. absence of lesion at the voxel level predicts language abilities. It also can be used to determine if lesion location predicts treatment outcome for aphasia treatment. For example, speech entrainment (SE), an intervention that relies on mimicking speech in real time, may be beneficial for patients with nonfluent aphasias. Using VLSM, Fridriksson et al.[32] found that a positive response to SE was associated with inferior and middle frontal gyri lesions. This finding indicates that SE compensates for damage to language production mechanisms located in the inferior frontal gyrus, provided that alternative neural pathways are still intact to support the function.

Predicting treatment outcome based on the integrity of white matter networks using DTI is another approach. In a recent study[33], diffusion imaging scans were performed prior to 30 hours of a naming therapy that involved semantic and phonemic cuing hierarchies. Not surprisingly, it was shown that a greater global language network integrity of white matter connections led to greater treatment gains in naming, most likely because more of the original connections were preserved and more alternate connections were available for remapping of language function. On a more regional level, this study also showed that preserved integration of the left temporal lobe translated to increased treatment gains.

In summary, a few studies suggest the potential of functional and structural neuroimaging in predicting therapy outcome. Given the increasing availability of neuroimaging data in clinical care, it is straightforward to suggest that future clinical management of aphasia, including its rehabilitation, will rely on measures of brain damage and residual connectivity to predict long-term outcome and eventually to personalize treatment selection.

Inducing Neuroplasticity

While neuroimaging technologies can be used to measure and predict neuroplasticity, the rise of neuroplasticity in aphasia treatment research has raised another critical question: How can we capitalize upon and enhance the brain's natural inherent plasticity that undergirds all forms of learning? Below, three ways to accomplish this goal are discussed: (1) neuromodulation using non-invasive brain stimulation (NIBS), (2) application of behavioural principles shown to stimulate neuroplasticity, and (3) neuromodulation by incorporating non-language behaviours into treatment.

Non-Invasive Brain Stimulation for Neuromodulation: NIBS alters neural excitability which can promote neuroplasticity and render injured brains more receptive to aphasia interventions, either by facilitating activity in recovery-relevant regions or by suppressing dysfunctional neural processes. The two most frequently used NIBS techniques have been repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS)[34,35]. rTMS works by inducing an electrical current from changes in magnetic fields that causes neurons in target cortex to fire. Low frequency stimulation (1 Hz) decreases and high frequency stimulation ($\geq$ 5 Hz) increases cortical excitability.[36] TDCS depolarizes neurons under an anode on the scalp and hyperpolarizes neurons under a cathode[37], though effects can vary depending on current strength[38] (See Figure 2 for typical tDCS protocols). There are differences between these techniques regarding focality of the stimulation, ease of application, and associated costs,[39] but both can promote adaptive neuroplasticity when administered alone (rTMS) or combined with behavioural interventions (rTMS, tDCS).[35]

_____

Insert Figure 2 here.

Stimulation protocols are guided by assumptions about contributions of different brain regions to recovery, which can be derived from functional imaging.[15,40] To date, NIBS approaches have included: (1) excitatory stimulation of spared perilesional left-hemisphere regions recruited to subserve language function after stroke;[40,41] (2) inhibition of right-hemisphere regions that hinder recovery (e.g. pars triangularis in the inferior frontal gyrus);[42,43] (3) combined excitatory left-hemisphere and inhibitory right-hemisphere stimulation,[44,45] (4) facilitation of compensatory right-hemisphere homologues of lesioned

areas by excitatory stimulation;[46] or (5) stimulation of non-language regions that are relevant to language production (e.g., motor regions).[47,48]

 Evidence for efficacy of these approaches to enhance aphasia treatment outcome is mainly limited to relatively small (N<60) experimental trials, but recent meta-analyses suggest that either rTMS or tDCS can enhance treatment outcome in both sub-acute and chronic patients.[49-51] Qualitative appraisal of stimulation effects on naming ability in aphasia suggests that both methods result in similar add-on effects to those of behavioural treatment.[51] However, while the majority of placebo-stimulation controlled trials reported significant enhancement of treatment outcomes across patient groups[52,53] and some also generalize to everyday communication,[47,53] closer inspection of individual patient data reveals substantial heterogeneity of stimulation response.[40,42,47] Because NIBS approaches are most efficacious when combined with behavioural treatment, some of the observed heterogeneity between studies may be attributable to variable efficacy of concurrent treatments. Predicting stimulation effects in aphasia is further complicated by variable and recovery-stage-dependent brain reorganization after stroke[15,35] and the effects that varying lesion locations cause to current flow during tDCS.[54] Therefore, choice of optimal stimulation protocols is not straightforward.

 Recently, there have been efforts to optimize stimulation outcomes: For example, Shah-Basak et al. explored efficacy of different tDCS protocols to modulate naming ability prior to treatment.[51] An alternative approach involves mapping of the residual language network using functional imaging[40,41] to identify stimulation sites vital to recovery.[10,52,55] This approach can induce substantial gains in language performance over that of treatment alone as demonstrated in a large randomised-clinical trial (RCT, N=74); however, it is cost intensive and requires substantial technological expertise. Other approaches exploit known effects of NIBS on functionally connected regions.[56] For example, stimulation of primary motor cortex or the cerebellum modulates neural processing in language regions,[48,57] and motor cortex tDCS improved naming and communication ability in a placebo-tDCS controlled RCT.[57]

 New NIBS techniques are also beginning to emerge in the aphasia literature like theta burst rTMS, that relies on bursts of very high frequency (e.g., 50 Hz) to increase or decrease cortical excitability. Its footprint in the aphasia literature is much too small to objectively evaluate its therapeutic value, but early findings are promising.[58] Likewise, high definition tDCS (Figure 2), which allows for much more focused stimulation than traditional tDCS, is showing some promise for aphasia treatment[53,54,59], but it is too early to fully evaluate its potential. As both of these techniques may be improvements over conventional forms of rTMS and tDCS, respectively, we expect to see more aphasia treatment studies employing them.

 In sum, preliminary evidence from relatively small, methodologically heterogeneous trials suggests that both rTMS and tDCS are promising adjuvant approaches to enhance aphasia treatment outcomes. However, little is known about long-term effects, optimal stimulation parameters (e.g., duration, frequency or intensity) and montages for individual patients, effect of additional variables (e.g., genotype[53]) and whether positive effects from laboratory settings translate into improved everyday communication. Moreover, only a handful of studies investigated the neural mechanisms by which NIBS modulates behavioural performance. How NIBS interacts with the reorganized language network and with the processes engaged during treatment needs to be investigated more systematically to enhance effectiveness of future NIBS trials.[34] Finally, more research regarding prediction variable outcomes for specific NIBS and aphasia treatment combinations would be helpful in selecting best treatments for individual patients.

Principles for Inducing Neuroplasticity through Aphasia Treatment. Animal model studies of rehabilitation after brain injury have identified principles that can facilitate remapping of brain functions, creation of new connections between neurons, and/or engagement of alternative pathways to re-establish function[60,61]. There are striking parallels between these principles and the mechanisms undergirding normal learning and development. Further, application of principles learned in basic neuroscience research to aphasia rehabilitation has been widely acknowledged[62], guiding the understanding of how treatments that aim to restore and/or reorganize language functions work.

For example, use-dependent treatment approaches rely on the principles that neural circuits not actively used for extended periods degrade and that plasticity can be induced through training.[60] Because constraint induced language therapy (CILT) forces patients to rely on verbal language to accomplish goals in various language-action games, it is an example of a use-dependent treatement.[60] Although systematic review[63] showed that early CILT studies yielded positive outcomes compared to alternative interventions, more recent comparative trials have demonstrated that language modality and patient characteristics can determine outcome. For example, Wilssens et al[64] showed that semantic treatment improved comprehension and CILT improved language production, while Rose and colleagues[65,66] demonstrated that a Multi-modality Aphasia Treatment (M-MAT) which engages gesture, drawing, and writing to facilitate verbal production yielded better outcomes for individuals with moderate aphasia and CILT yielded better outcomes for mild aphasia. Three recent clinical trials comparing CILT and conventional treatment in acute and subacute aphasias[67-69] showed significant improvements for both treatments. Collectively, these studies demonstrate the need for more research to understand variables (i.e., severity, stage of recovery) that influence use-dependent learning. Additionally, recent research has called into question[70] the assumption that the neuroplasticity principle of intensity is a fundamental component of CILT. Thus, further studies that systematically manipulate neuroplasticity principles such as intensity and repetition are needed to understand the active treatment components of CILT and their effect on brain structure and function.

Greater repetition of behaviours and higher intensity of treatment schedules have been shown to induce neuroplasticity in animal model rehabilitation studies.[60] Invoking long-term changes following aphasia treatment requires sufficient repetition within sessions (saturated practice) and intensive opportunities to produce target language behaviours over time. One recent study employing cued picture naming demonstrated that saturated practice (400 exposures per session) can lead to word retrieval improvement after only three hours of training[71]. However, a comparative study using a repetition-based treatment demonstrated a mixed pattern of results between patients who received 160 exposures/session and 40 exposures/session[72]. Thus, more research is necessary to define "sufficient repetition" and to understand how treatment and patient-related variables determine which repetitive practice conditions induce lasting behavioural and brain changes.

A number of factors contribute to the cumulative intensity (total amount) of any given treatment, including dose, dose frequency (distribution of sessions over time; massed practice= high dose frequency, distributed practice= low dose frequency), session duration (number of hours per session) and intervention duration (length of intervention over time). A complex relationship exists between factors that contribute to cumulative intensity and treatment outcome in aphasia. There is evidence that higher dose frequency of therapy in early stages of aphasia rehabilitation improves treatment outcomes[73]. Similarly, a recent large-scale study in chronic aphasia demonstrated that massed practice (10 hours per week) was associated with significant improvements in language measures compared to deferred treatment[74]. However, a comparative study of highly intensive (4 hours/day) vs. moderately intensive (2 hours/day) treatment over two 2-week intervals demonstrated that only longer intervention duration (not longer session duration) improved treatment outcomes in chronic aphasia, suggesting there may be a threshold at which greater session duration no longer yields additional benefit.[75] Recent investigations of dose frequency (massed vs. distributed practice) also demonstrated that treatment schedule may influence outcomes. For example, Dignam and colleagues showed that distributed practice (6 hrs/week over 8 weeks) compared to massed practice (16 hrs/week over 3 weeks) yielded larger immediate acquisition and retention of gains[76], while Martins and colleagues demonstrated no difference between massed practice (10 hrs/week over 10 weeks) vs. distributed practice (2 hrs/week over 50 weeks) for acquisition and retention.[77] A review of comparative studies reveals that the advantages afforded by massed vs. distributed practice may equalize when cumulative intensity is >50 hours total[78]. These findings have important clinical implications as distributed practice schedules, which seem to yield enhanced long-term benefit, may be implemented more easily in most clinical settings than massed schedules. More research is necessary to understand the interaction between amount and distribution of therapy across different

stages of recovery and different treatment types, as well as the mechanisms that support response to different treatment schedules.

The overarching goal of aphasia treatment is to transfer gains from trained language behaviours to other language behaviours, tasks, or contexts (i.e., generalization). Since clinicians cannot train every word, patients may use or every context in which they use words, generalization to untrained items and contexts is highly desirable. Treatment studies have demonstrated that generalization across behaviours increases when there is a hierarchical relationship between trained and untrained targets (e.g., within category generalization from abstract words to concrete words[79]), when more complex words or sentences are selected for treatment of word finding or syntax, respectively[9, 80] and when trained words or sentences engage common linguistic rules or principles[81,82]. Furthermore, generalization across tasks occurs when the tasks share psycholinguistic mechanisms (e.g., training novel phoneme sequences to strengthen the phonological system can generalize to improvements in word retrieval[83] and reading[84]). Improvements in discourse, which are important for generalization across contexts, have been found in approaches that treat longer utterances, such as CILT[85] and verb network strengthening treatment[86]. However, the variables that influence different types of generalization and the underlying mechanisms required for generalization to occur remain incompletely understood. Given the importance of generalization for improving everyday communicative function, determining what neuroplasticity principles induce generalization should be a priority.

In brief, neuroplasticity principles derived from animal research have been applied to language rehabilitation with promising results. However, the success of treatments applying such principles depends upon multiple factors, including type or severity of aphasia, the language skill that is targeted in treatment, and stage of recovery. The aim to transfer training effects to untrained items and contexts requires consideration of what linguistic mechanisms and utterance training are addressed. An additional concern is that principles derived from motor rehabilitation in animals may not ultimately encompass, or be fully consistent with, the principles needed to optimize rehabilitation of the uniquely human function of language.

Non-Language Behaviours for Neuromodulation. The idea that non-language behaviours can be used to modulate neural activity for aphasia treatment has also been investigated. As mentioned earlier, use of rhythm and melody in MIT leverages structural changes in right-hemisphere pathways to facilitate word production in Broca's aphasia[22]. Inevitably, investigators have developed other strategies to target specific brain regions for modulation using non-language behaviours.

For example, Intention Treatment, which uses a left-hand movement to initiate word finding efforts, increases right relative to left frontal activity, demonstrating reorganization of word retrieval for picture naming and category member generation.[87] Simple practice in word retrieval without the hand movement does not produce this re-organization. In the relatively fluent patients in this study, the impact of this manipulation on right posterior perisylvian activity correlated with treatment gains. The most desirable outcome of this treatment was that it led to significantly greater improvement on (generalization to) untrained category-member generation items[87] and on word-finding during narrative production.[88] Another recent example of neuromodulation with non-language behaviours capitalized on the observation that mirror neurons, which are activated during observation of others' behaviour, are located in the inferior frontal gyrus and other areas that process language in the dominant hemisphere[89]. In this study, patients with nonfluent aphasia watched videos involving manual manipulation of objects or static videos of objects. Naming performance was significantly greater for objects learned while observing object manipulation during word-finding attempts compared to static videos. There was evidence of generalization to naming of untrained objects and untrained language tasks. Limited evidence indicated that watching the object manipulation videos engaged mirror neuron systems more than watching static object videos[89].

To summarize, initial evidence indicates that specific brain regions or systems can be targeted for neuromodulation using non-linguistic behavioural strategies to enhance therapeutic outcome. The idea that this type of modulation leads to generalization to untrained items and contexts is supported by the

two studies, and because generalization is highly desirable in rehabilitation, whether this strategy facilitates generalization deserves continued attention.

Conclusions

Summaries for this review's topics were given at the end of each section. Here, we concentrate on integrative assessment of the literature and offer a vision for integration of neuroimaging and neuromodulation into clinical aphasia treatment.

The variability in findings using functional and structural neuroimaging does not allow for generalizable conclusions about what changes in neural systems lead to optimal treatment outcomes. While differences in methodologies between studies may account for some of the diversity in findings between studies, it is necessary to consider whether a monolithic pathway to optimize aphasia treatment outcomes ever will emerge. Given the likelihood that patients with different symptom and lesion patterns may require engagement of different mechanisms, future studies should endeavor to identify factors that can predict which treatments are likely to produce clinically significant outcomes for patients with common symptom or lesion patterns. Regarding the latter, structural and functional imaging studies at pre-treatment demonstrate some promise for predicting aphasia treatment outcome. However, this is an under-explored research area. Given the potential to improve treatment outcomes when viable predictions are used for individualized treatment selection, this area deserves greater attention.

Research suggests that it is possible to enhance neuroplasticity during aphasia treatment through the use of NIBS or through linguistic or non-linguist treatment strategies targeting specific cortices and/or processes. Although NIBS studies in aphasia generally have been small with variable findings, one recent large randomized, sham-controlled clinical trial indicates that active tDCS supplements the effects of aphasia treatment compared to sham[52]. Neural activity evoked by linguistic and non-linguistic behavioural strategies also may evoke long-term relearning and brain-system reorganization during aphasia treatment. However, the recent discovery that the val66met brain-derived neurotrophic factor (BDNF) polymorphism affects response to tDCS but not to aphasia therapy[53] indicates that behavioural interventions induce learning and neuroplasticity through different mechanisms than tDCS. If the findings regarding the effect of this BDNF polymorphism hold up to further scrutiny, then this genetic variation would be a good indicator as to whether supplementing aphasia treatment with NIBS will be productive.

The potential contribution of aphasia, lesion, and other patient characteristics to outcome for any particular treatments has been a consistent theme throughout this review. This observation indicates that greater research attention should be given to what patient characteristics predict success of specific treatments, which can vary considerably by treatment. Emphasis on prediction will enable individualization of treatment approaches. Figure 3 provides one vision for future clinical application in which a large database correlating structural and functional neuroimaging features to outcomes of specific treatments is used to facilitate initial selection of the treatment option likely to produce the best outcome for a specific patient. Subsequently, changes in neural substrates and intermediate treatment outcomes are monitored so that adjustments to the treatment plan can be made. This type of vision for integrating and applying accumulating knowledge could be used to guide future research and help bridge the gap between research and clinical practice.

_____

Insert Figure 3 about here.

Declaration of interests

We declare no competing interests.

Acknowledgements

Contributorship Statement

BC and ADR developed the manuscript concept and structure. APL developed the vision for use of neuroimaging in future treatment planning in Figure 3 and its caption . BC and ADR edited the final manuscript. Otherwise, all authors contributed equally to the literature review and preparation of the manuscript, as well as to the preparation/selection of figures.

References

1.   Lam JM, Wodchis WP. The relationship of 60 disease diagnoses and 15 conditions to preference-based health-related quality of life in Ontario hospital-based long-term care residents. *Medical care*. 2010; **48**(4): 380-7.

2.   Koleck M, Gana K, Lucot C, Darrigrand B, Mazaux JM, Glize B. Quality of life in aphasic patients 1 year after a first stroke. *Quality of life research*. 2017; **26**(1): 45-54.

3.   Meinzer M, Mohammadi S, Kugel H, Schiffbauer H, Floel A, Albers J, et al. Integrity of the hippocampus and surrounding white matter is correlated with language training success in aphasia. *NeuroImage*. 2010; **53**: 283-90.

4.   Menke R, Meinzer M, Kugel H, Deppe M, Baumgartner A, Schiffbauer H, et al. Imaging short- and long-term training success in chronic aphasia. *BMC neuroscience*. 2009; **10**: 118.

5.   Mattioli F, Ambrosi C, Mascaro L, Scarpazza C, Pasquali P, Frugoni M, et al. Early aphasia rehabilitation is associated with functional reactivation of the left inferior frontal gyrus: a pilot study. *Stroke*. 2014; **45**(2): 545-52.

6.   Liuzzi AG, Bruffaerts R, Peeters R, Adamczuk K, Keuleers E, De Deyne S, et al. Cross-modal representation of spoken and written word meaning in left pars triangularis. *NeuroImage*. 2017; **150**: 292-307.

7.   Matchin W, Hammerly C, Lau E. The role of the IFG and pSTS in syntactic prediction: Evidence from a parametric study of hierarchical structure in fMRI. *Cortex*. 2017; **88**: 106-23.

8.   Regel S, Kotz SA, Henseler I, Friederici AD. Left inferior frontal gyrus mediates morphosyntax: ERP evidence from verb processing in left-hemisphere damaged patients. *Cortex*. 2017; **86**: 156-71.

9.   Thompson CK, Riley EA, den Ouden DB, Meltzer-Asscher A, Lukic S. Training verb argument structure production in agrammatic aphasia: behavioral and neural recovery patterns. *Cortex*. 2013; **49**(9): 2358-76.

10.   Fridriksson J. Preservation and modulation of specific left hemisphere regions is vital for treated recovery from anomia in stroke. *The Journal of neuroscience*. 2010; **30**(35): 11558-64.

11.   Abel S, Weiller C, Huber W, Willmes K, Specht K. Therapy-induced brain reorganization patterns in aphasia. *Brain*. 2015; **138**(Pt 4): 1097-112.

12.   Nardo D, Holland R, Leff AP, Price CJ, Crinion JT. Less is more: neural mechanisms underlying anomia treatment in chronic aphasic patients. *Brain*. 2017; **140**(11): 3039-54.

13.   Brownsett SL, Warren JE, Geranmayeh F, Woodhead Z, Leech R, Wise RJ. Cognitive control and its impact on recovery from aphasic stroke. *Brain*. 2014; **137**(Pt 1): 242-54.

14.   Geranmayeh F, Leech R, Wise RJ. Network dysfunction predicts speech production after left hemisphere stroke. *Neurology*. 2016.

15.   Ulm L, Copland D, Meinzer M. A new era of systems neuroscience in aphasia? *Aphasiology*. 2016: 1-23.

16.   Duncan ES, Small SL. Increased Modularity of Resting State Networks Supports Improved Narrative Production in Aphasia Recovery. *Brain connectivity*. 2016; **6**(7): 524-9.

17.   Duncan ES, Small SL. Changes in dynamic resting state network connectivity following aphasia therapy. *Brain imaging and behavior*. 2017.

18.   Siegel JS, Seitzman BA, Ramsey LE, Ortega M, Gordon EM, Dosenbach NUF, et al. Re-emergence of modular brain networks in stroke recovery. *Cortex*. 2018; **101**: 44-59.

19.   Woodhead ZV, Crinion J, Teki S, Penny W, Price CJ, Leff AP. Auditory training changes temporal lobe connectivity in 'Wernicke's aphasia': a randomised trial. *Journal of neurology, neurosurgery, and psychiatry*. 2017.

20.   Sandberg CW, Bohland JW, Kiran S. Changes in functional connectivity related to direct training and generalization effects of a word finding treatment in chronic aphasia. *Brain and language*. 2015; **150**: 103-16.

21.   Gili T, Fiori V, De Pasquale G, Sabatini U, Caltagirone C, Marangolo P. Right sensory-motor functional networks subserve action observation therapy in aphasia. *Brain imaging and behavior*. 2017; **11**(5): 1397-411.
22.   Schlaug G, Marchina S, Norton A. Evidence for plasticity in white-matter tracts of patients with chronic Broca's aphasia undergoing intense intonation-based speech therapy. *Annals of the New York Academy of Sciences*. 2009; **1169**: 385-94.
23.   Allendorfer JB, Storrs JM, Szaflarski JP. Changes in white matter integrity follow excitatory rTMS treatment of post-stroke aphasia. *Restorative neurology and neuroscience*. 2012; **30**(2): 103-13.
24.   van Hees S, McMahon K, Angwin A, de Zubicaray G, Read S, Copland DA. Changes in white matter connectivity following therapy for anomia post stroke. *Neurorehabilitation and neural repair*. 2014; **28**(4): 325-34.
25.   Wan CY, Zheng X, Marchina S, Norton A, Schlaug G. Intensive therapy induces contralateral white matter changes in chronic stroke patients with Broca's aphasia. *Brain and language*. 2014; **136**: 1-7.
26.   McKinnon ET, Fridriksson J, Glenn GR, Jensen JH, Helpern JA, Basilakos A, et al. Structural plasticity of the ventral stream and aphasia recovery. *Annals of neurology*. 2017; **82**(1): 147-51.
27.   Glenn GR, Kuo LW, Chao YP, Lee CY, Helpern JA, Jensen JH. Mapping the Orientation of White Matter Fiber Bundles: A Comparative Study of Diffusion Tensor Imaging, Diffusional Kurtosis Imaging, and Diffusion Spectrum Imaging. *AJNR American journal of neuroradiology*. 2016; **37**(7): 1216-22.
28.   Hope TMH, Leff AP, Prejawa S, Bruce R, Haigh Z, Lim L, et al. Right hemisphere structural adaptation and changing language skills years after left hemisphere stroke. *Brain*. 2017; **140**(6): 1718-28.
29.   Lukic S, Barbieri E, Wang X, Caplan D, Kiran S, Rapp B, et al. Right Hemisphere Grey Matter Volume and Language Functions in Stroke Aphasia. *Neural plasticity*. 2017; **2017**: 5601509.
30.   Fridriksson J, Richardson JD, Fillmore P, Cai B. Left hemisphere plasticity and aphasia recovery. *NeuroImage*. 2012; **60**(2): 854-63.
31.   van Hees S, McMahon K, Angwin A, de Zubicaray G, Copland DA. Neural activity associated with semantic versus phonological anomia treatments in aphasia. *Brain and language*. 2014; **129**: 47-57.
32.   Fridriksson J, Basilakos A, Hickok G, Bonilha L, Rorden C. Speech entrainment compensates for Broca's area damage. *Cortex*. 2015; **69**: 68-75.
33.   Bonilha L, Gleichgerrcht E, Nesland T, Rorden C, Fridriksson J. Success of Anomia Treatment in Aphasia Is Associated With Preserved Architecture of Global and Left Temporal Lobe Structural Networks. *Neurorehabilitation and neural repair*. 2016; **30**(3): 266-79.
34.   Hartwigsen G, Saur D. Neuroimaging of stroke recovery from aphasia - Insights into plasticity of the human language network. *NeuroImage*. 2017.
35.   Torres J, Drebing D, Hamilton R. TMS and tDCS in post-stroke aphasia: Integrating novel treatment approaches with mechanisms of plasticity. *Restorative neurology and neuroscience*. 2013; **31**(4): 501-15.
36.   Kapoor A. Repetitive transcranial magnetic stimulation therapy for post-stroke non-fluent aphasia: A critical review. *Topics in stroke rehabilitation*. 2017; **24**(7): 547-53.
37.   Fertonani A, Miniussi C. Transcranial Electrical Stimulation: What We Know and Do Not Know About Mechanisms. *The Neuroscientist*. 2016.
38.   Jamil A, Batsikadze G, Kuo HI, Labruna L, Hasan A, Paulus W, et al. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. *The Journal of physiology*. 2017; **595**(4): 1273-88.
39.   Shah PP, Szaflarski JP, Allendorfer J, Hamilton RH. Induction of neuroplasticity and recovery in post-stroke aphasia by non-invasive brain stimulation. *Frontiers in human neuroscience*. 2013; **7**: 888.
40.   Baker JM, Rorden C, Fridriksson J. Using transcranial direct-current stimulation to treat stroke patients with aphasia. *Stroke*. 2010; **41**(6): 1229-36.
41.   Fridriksson J, Richardson JD, Baker JM, Rorden C. Transcranial direct current stimulation improves naming reaction time in fluent aphasia: a double-blind, sham-controlled study. *Stroke*. 2011; **42**(3): 819-21.
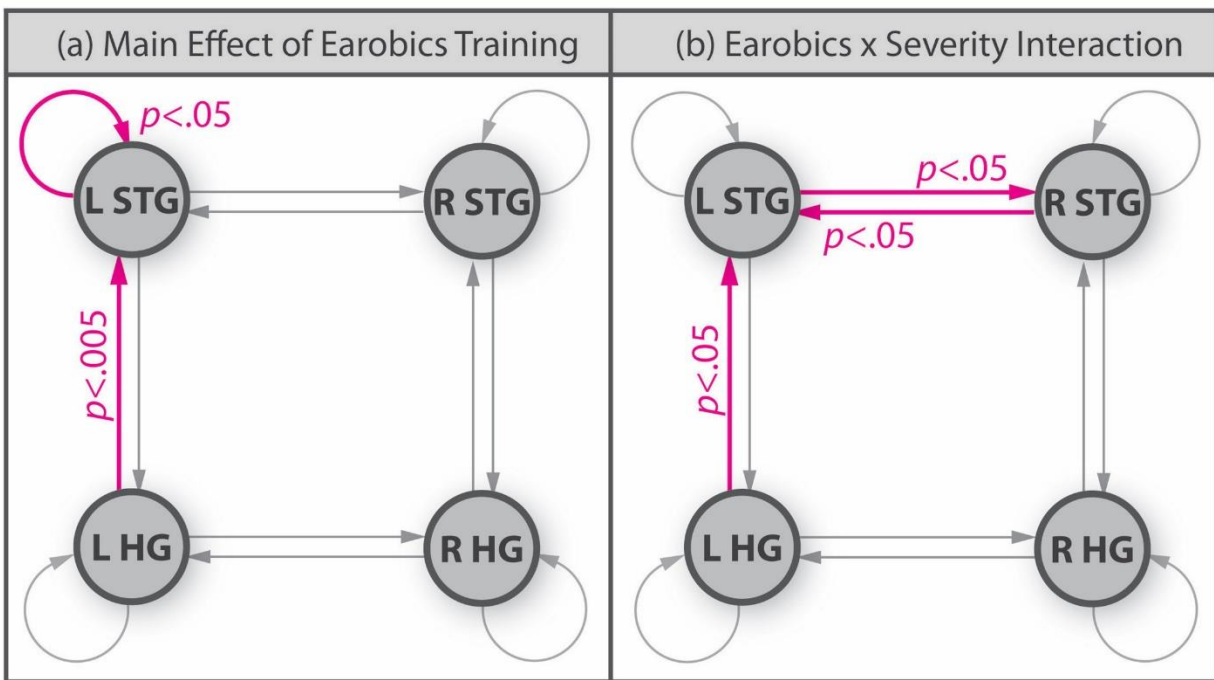
42. Thiel A, Hartmann A, Rubi-Fessen I, Anglade C, Kracht L, Weiduschat N, et al. Effects of noninvasive brain stimulation on language networks and recovery in early poststroke aphasia. *Stroke*. 2013; **44**(8): 2240-6.

43. Rubi-Fessen I, Hartmann A, Huber W, Fimm B, Rommel T, Thiel A, et al. Add-on Effects of Repetitive Transcranial Magnetic Stimulation on Subacute Aphasia Therapy: Enhanced Improvement of Functional Communication and Basic Linguistic Skills. A Randomized Controlled Study. *Archives of physical medicine and rehabilitation*. 2015; **96**(11): 1935-44 e2.

44. Khedr EM, Abo El-Fetoh N, Ali AM, El-Hammady DH, Khalifa H, Atta H, et al. Dual-hemisphere repetitive transcranial magnetic stimulation for rehabilitation of poststroke aphasia: a randomized, double-blind clinical trial. *Neurorehabilitation and neural repair*. 2014; **28**(8): 740-50.

45. Marangolo P, Fiori V, Cipollari S, Campana S, Razzano C, Di Paola M, et al. Bihemispheric stimulation over left and right inferior frontal region enhances recovery from apraxia of speech in chronic aphasia. *The European journal of neuroscience*. 2013; **38**(9): 3370-7.

46. Floel A, Meinzer M, Kirstein R, Nijhof S, Deppe M, Knecht S, et al. Short-term anomia training and electrical brain stimulation. *Stroke*. 2011; **42**(7): 2065-7.

47. Meinzer M, Darkow R, Lindenberg R, Floel A. Electrical stimulation of the motor cortex enhances treatment outcome in post-stroke aphasia. *Brain*. 2016; **139**(Pt 4): 1152-63.

48. Darkow R, Martin A, Wurtz A, Floel A, Meinzer M. Transcranial direct current stimulation effects on neural processing in post-stroke aphasia. *Human brain mapping*. 2017; **38**(3): 1518-31.

49. Ren CL, Zhang GF, Xia N, Jin CH, Zhang XH, Hao JF, et al. Effect of low-frequency rTMS on aphasia in stroke patients: a meta-analysis of randomized controlled trials. *PloS one*. 2014; **9**(7): e102557.

50. Otal B, Olma MC, Floel A, Wellwood I. Inhibitory non-invasive brain stimulation to homologous language regions as an adjunct to speech and language therapy in post-stroke aphasia: a meta-analysis. *Frontiers in human neuroscience*. 2015; **9**: 236.

51. Shah-Basak PP, Wurzman R, Purcell JB, Gervits F, Hamilton R. Fields or flows? A comparative metaanalysis of transcranial magnetic and direct current stimulation to treat post-stroke aphasia. *Restorative neurology and neuroscience*. 2016; **34**(4): 537-58.

52. Fridriksson J, Rorden C, Elm J, Sen S, George MS, Bonilha L. Transcranial Direct Current Stimulation vs Sham Stimulation to Treat Aphasia After Stroke: A Randomized Clinical Trial. *JAMA Neurol*. 2018; 75(12): 1470-1476.

53. Fridriksson J, Basilakos A, Stark BC, Rorden C, Elm J, Gottfried M, George MS, Sen S, Bonilha L. Transcranial direct current stimulation to treat aphasia: Longitudinal analysis of a randomized controlled trial. *Brain Stimul*. 2018, epub ahead of print;1-6.

54. Dmochowski JP, Datta A, Huang Y, Richardson JD, Bikson M, Fridriksson J, et al. Targeted transcranial direct current stimulation for rehabilitation after stroke. *NeuroImage*. 2013; **75**: 12-9.

55. Meinzer M, Flaisch T, Breitenstein C, Wienbruch C, Elbert T, Rockstroh B. Functional re-recruitment of dysfunctional brain areas predicts language recovery in chronic aphasia. *NeuroImage*. 2008; **39**(4): 2038-46.

56. Sale MV, Mattingley JB, Zalesky A, Cocchi L. Imaging human brain networks to improve the clinical efficacy of non-invasive brain stimulation. *Neuroscience and biobehavioral reviews*. 2015; **57**: 187-98.

57. Turkeltaub PE, Swears MK, D'Mello AM, Stoodley CJ. Cerebellar tDCS as a novel treatment for aphasia? Evidence from behavioral and resting-state functional connectivity data in healthy adults. *Restorative neurology and neuroscience*. 2016; **34**(4): 491-505.

58. Griffis JC, Nenert R, Allendorfer JB, Szaflarski JP. Interhemispheric Plasticity following Intermittent Theta Burst Stimulation in Chronic Poststroke Aphasia. *Neural plasticity*. 2016; **2016**: 4796906.

59. Richardson J, Datta A, Dmochowski J, Parra LC, Fridriksson J. Feasibility of using high-definition transcranial direct current stimulation (HD-tDCS) to enhance treatment outcomes in persons with aphasia. *NeuroRehabilitation*. 2015; **36**(1): 115-26.

60.   Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *Journal of speech, language, and hearing research : JSLHR*. 2008; **51**(1): S225-39.

61.   Nudo RJ. Recovery after brain injury: mechanisms and principles. *Frontiers in human neuroscience*. 2013; **7**: 887.

62.   Worrall L, Brandenburg C, Shrubsole K. Neuroscientific Implications in Assessment and Intervention for Aphasia. *Folia Phoniatr Logop*. 2015; **67**(6): 285-92.

63.   Cherney LR, Patterson JP, Raymer A, Frymark T, Schooling T. Evidence-based systematic review: effects of intensity of treatment and constraint-induced language therapy for individuals with stroke-induced aphasia. *Journal of speech, language, and hearing research : JSLHR*. 2008; **51**(5): 1282-99.

64.   Wilssens I, Vandenborre D, van Dun K, Verhoeven J, Visch-Brink E, Marien P. Constraint-induced aphasia therapy versus intensive semantic treatment in fluent aphasia. *American journal of speech-language pathology*. 2015; **24**(2): 281-94.

65.   Attard MC, Rose ML, Lanyon L. The comparative effects of Multi-Modality Aphasia Therapy and Constraint-Induced Aphasia Therapy-Plus for severe chronic Broca's aphasia: An in-depth pilot study. *Aphasiology*. 2013; **27**(1): 80-111.

66.   Rose ML, Mok Z, Carragher M, Katthagen S, Attard M. Comparing multi-modality and constraint-induced treatment for aphasia: a preliminary investigation of generalisation to discourse. *Aphasiology*. 2016; **30**(6): 678-98.

67.   Woldag H, Voigt N, Bley M, Hummelsheim H. Constraint-Induced Aphasia Therapy in the Acute Stage: What Is the Key Factor for Efficacy? A Randomized Controlled Study. *Neurorehabilitation and neural repair*. 2017; **31**(1): 72-80.

68.   Ciccone N, West D, Cream A, Cartwright J, Rai T, Granger A, et al. Constraint-induced aphasia therapy (CIAT): a randomised controlled trial in very early stroke rehabilitation. *Aphasiology*. 2016; **30**(5): 566-84.

69.   Sickert A, Anders LC, Munte TF, Sailer M. Constraint-induced aphasia therapy following sub-acute stroke: a single-blind, randomised clinical trial of a modified therapy schedule. *Journal of neurology, neurosurgery, and psychiatry*. 2014; **85**(1): 51-5.

70.   Mozeiko J, Coelho CA, Myers EB. The role of intensity in constraint-induced language therapy for people with chronic aphasia. *Aphasiology*. 2016; **30**(4): 339-63.

71.   Harnish SM, Morgan J, Lundine JP, Bauer A, Singletary F, Benjamin ML, et al. Dosing of a cued picture-naming treatment for anomia. *American journal of speech-language pathology*. 2014; **23**(2): S285-99.

72.   Off CA, Griffin JR, Spencer KA, Rogers MA. The impact of dose on naming accuracy with persons with aphasia. *Aphasiology*. 2016; **30**(9): 983-1011.

73.   Godecke E, Rai T, Ciccone N, Armstrong E, Granger A, Hankey GJ. Amount of therapy matters in very early aphasia rehabilitation after stroke: a clinical prognostic model. *Seminars in speech and language*. 2013; **34**(3): 129-41.

74.   Breitenstein C, Grewe T, Floel A, Ziegler W, Springer L, Martus P, et al. Intensive speech and language therapy in patients with chronic aphasia after stroke: a randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. *Lancet*. 2017; **389**(10078): 1528-38.

75.   Stahl B, Mohr B, Buscher V, Dreyer FR, Lucchese G, Pulvermuller F. Efficacy of intensive aphasia therapy in patients with chronic stroke: a randomised controlled trial. *Journal of neurology, neurosurgery, and psychiatry*. 2017.

76.   Dignam JK, Copland DA, McKinnon E, Burfein P, O'Brien K, Farrell A, Rodriguez AD. . Intensive versus distributed aphasia therapy: a nonrandomized, parallel-group,dosage-controlled study.. *Stroke*. 2015; 4**6**: 2206–2211.

77.   Martins IP, Leal G, Fonseca I, Farrajota L, Aguiar M, Fonseca J, et al. A randomized, rater-blinded, parallel trial of intensive speech therapy in sub-acute post-stroke aphasia: the SP-I-R-IT study. *International journal of language & communication disorders*. 2013; **48**(4): 421-31.

78.   Patterson JP, Raymer A, Cherney L. Treatment intensity in aphasia rehabilitation. In: Coppens P, Patterson JP, editors. *Aphasia Rehabilitation: Clinical Challenges*. Burlington, MA: Jones & Bartlett Learning; 2018.

79.   Sandberg C, Kiran S. How justice can affect jury: training abstract words promotes generalisation to concrete words in patients with aphasia. *Neuropsychological rehabilitation*. 2014; **24**(5): 738-69.

80.   Riley EA, Thompson CK. Training pseudoword reading in acquired dyslexia: a phonological complexity approach. *Aphasiology*. 2015; **29**(2): 129-50.

81.   Kiran S. Typicality of inanimate category exemplars in aphasia treatment: further evidence for semantic complexity. *Journal of speech, language, and hearing research : JSLHR*. 2008; **51**(6): 1550-68.

82.   Thompson CK, Shapiro LP. Treating agrammatic aphasia within a linguistic framework: Treatment of Underlying Forms. *Aphasiology*. 2005; **19**(10-11): 1021-36.

83.   Kendall DL, Oelke M, Brookshire CE, Nadeau SE. The Influence of Phonomotor Treatment on Word Retrieval Abilities in 26 Individuals With Chronic Aphasia: An Open Trial. *Journal of speech, language, and hearing research : JSLHR*. 2015; **58**(3): 798-812.

84.   Brookshire CE, Conway T, Pompon RH, Oelke M, Kendall DL. Effects of intensive phonomotor treatment on reading in eight individuals with aphasia and phonological alexia. *American journal of speech-language pathology*. 2014; **23**(2): S300-11.

85.   Stahl B, Mohr B, Dreyer FR, Lucchese G, Pulvermuller F. Using language for social interaction: Communication mechanisms promote recovery from chronic non-fluent aphasia. *Cortex*. 2016; **85**: 90-9.

86.   Edmonds LA, Mammino K, Ojeda J. Effect of Verb Network Strengthening Treatment (VNeST) in persons with aphasia: extension and replication of previous findings. *American journal of speech-language pathology*. 2014; **23**(2): S312-29.

87.   Benjamin ML, Towler S, Garcia A, Park H, Sudhyadhom A, Harnish S, et al. A Behavioral Manipulation Engages Right Frontal Cortex During Aphasia Therapy. *Neurorehabilitation and neural repair*. 2014; **28**(6): 545-53.

88.   Altmann LJ, Hazamy AA, Carvajal PJ, Benjamin M, Rosenbek JC, Crosson B. Delayed Stimulus-Specific Improvements in Discourse Following Anomia Treatment Using an Intentional Gesture. *Journal of speech, language, and hearing research : JSLHR*. 2014; **57**(2): 439-54.

89.   Chen W, Ye Q, Ji X, Zhang S, Yang X, Zhou Q, et al. Mirror neuron system based therapy for aphasia rehabilitation. *Frontiers in psychology*. 2015; **6**: 1665.

90.   Kiran S. How Does Severity of Aphasia Influence Individual Responsiveness to Rehabilitation? Using Big Data to Understand Theories of Aphasia Rehabilitation. *Seminars in speech and language*. 2016; **37**(1): 48-59.

91.   Seghier ML, Patel E, Prejawa S, Ramsden S, Selmer A, Lim L, et al. The PLORAS Database: A data repository for Predicting Language Outcome and Recovery After Stroke. *NeuroImage*. 2016; **124**(Pt B): 1208-12.

Figure Captions

Figure 1. The importance of connectivity changes between elements of the language system resulting from aphasia therapy is illustrated by the work of Woodhead and colleagues[30]. Specifically, effects of a phonological therapy ("Earobics", an e-therapy) on the connectivity within the temporal lobes of 20 patients with chronic 'Wernicke-type' aphasia are shown. Phonological training resulted in a small but significant improvement in patients' speech comprehension. (a) The MEG connectivity analysis demonstrated that phonological training increased synaptic gain in the left superior temporal gyrus (L STG) as well as connectivity between the L STG and primary auditory cortex (Heschl's gyrus (HG)). Pink connections showed significantly stronger phonemic sensitivity after Earobics training (main effect of Earobics). (b) Also (not discussed in text), as opposed to increased synaptic gain in the L STG, patients with more severe speech comprehension impairments showed strengthening of bidirectional connections between the left and right STG. This figure is adapted from the original (Figure 5): J Neurol Neurosurg Psychiatry (online first): 04 March 2017. doi: 10.1136/jnnp-2016-314621 (Link to license: http://creativecommons.org/licenses/by/4.0/" and http://jnnp.bmj.com/content/early/2017/03/04/jnnp-2016-314621.info)

Figure 2. Electrode placement and electrical field intensity for traditional and high definition transcranial direct current stimulation (tDCS) at 1 mA current. (a) Placement of traditional 5 X 7 cm electrodes approximately over inferior frontal sulcus with the anode over the left hemisphere and the cathode over the right hemisphere. To date most studies employing tDCS in aphasia have use traditional large electrodes, though with a variety of placements. (b) Placement of one anode (approximately over left inferior frontal sulcus) and four surrounding cathodes for high definition tDCS. Note the current distributes in approximately equal fractions over the four cathodes, while it is at full strength at the anode. (c) Field intensity map showing broad distribution of current over the frontal lobes for the placement of traditional electrodes in panel a. (d) Field intensity map showing more focal stimulation in inferior and middle frontal gyri for the high definition electrode placement in panel b. Even though high definition tDCS produces more focal effects than traditional tDCS, it is still less focal than rTMS. (Current maps were created with HD Explore™ software, Soterix Medical, Inc., New York, NY.)
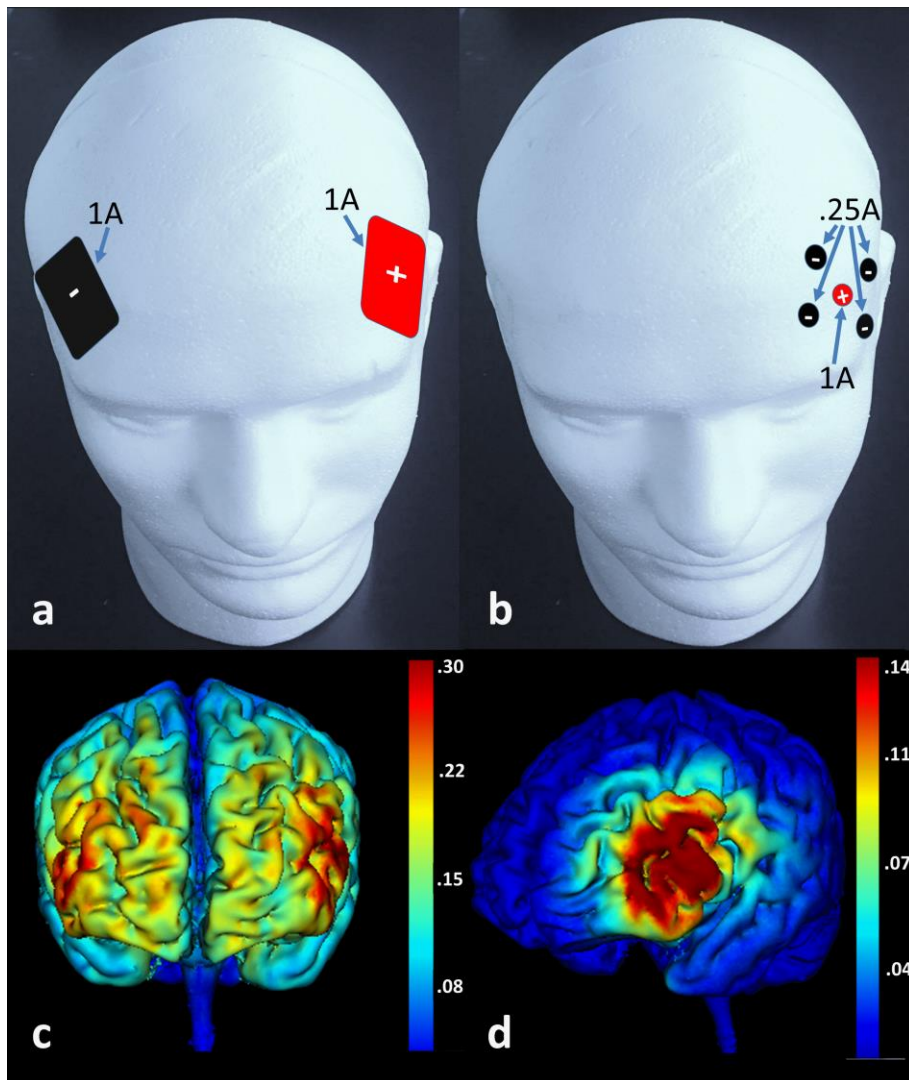
Figure 3. Schematic diagram showing how neuroimaging data eventually could be used clinically for aphasia rehabilitation. The white "i" on a blue field represents information, which refers to baseline behaviour, demographics, and brain scans (blue outlines and arrows). Brain scans may include structural and/or functional magnetic resonance imaging (MRI) scans, diffusion tensor imaging (DTI, which provides information about white matter integrity), or computerized tomography (CT) scans. When this information is fed into an algorithm relying upon a large database, predictions (black boxes and arrows) can be made regarding recovery trajectory and response to various treatments (red boxes and arrows). From these recovery and treatment predictions, the best treatment and dose (i.e., number of hours to achieve a quantifiable treatment outcome) can be prescribed (represented by the white Rx on a red background) for the recovery stage of the patient. Treatments might include application of aphasia interventions (which directly address language functions), other behavioural modulators (such as those described in the text[22,87,89]), or non-invasive brain stimulation (NIBS, such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation) to facilitate neuroplasticity. Prescribed treatments will lead to neuroplastic changes that can be monitored using functional or structural brain scans (signified by the green color above the scan). These measures of neural response to treatment, along with measures of behavioural response, can be used for prediction and prescription of subsequent treatment as the patient progresses through the treatment regimen and various recovery stages. Thus, this kind of algorithm can personalize treatment selection, using neuroimaging to predict best treatments and measure treatment response to interventions involving aphasia therapies accompanied by NIBS and behavioural modulators of neuroplasticity, as algorithmically prescribed. Some groups currently are amassing large-scale databases,[90,91] which might contribute to the kind of aphasia treatment selection envisioned here. Development of more effective treatments through an understanding of how to evoke the necessary neuroplasticity and determining which patients benefit from the treatments that we now have and are developing will greatly expand the benefits of aphasia therapy.