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Recent developments in functional and structural imaging of aphasia recovery after stroke

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Abstract

Background—Functional and structural neuroimaging techniques can increase our knowledge about the neural processes underlying recovery from post-stroke language impairments (aphasia).

Aims—In the present review we highlight recent developments in neuroimaging research of aphasia recovery.

Main Contribution—We review (a) cross-sectional findings in aphasia with regard to local brain functions and functional connectivity, (b) structural and functional imaging findings using longitudinal (intervention) paradigms, (c) new adjunct treatments that are guided by functional imaging techniques (e.g., electrical brain stimulation) and (d) studies related to the prognosis of language recovery and treatment responsiveness after stroke.

Conclusions—More recent developments in data acquisition and analysis foster better understanding and more realistic modelling of the neural substrates of language recovery after stroke. Moreover, the combination of different neuroimaging protocols can provide converging evidence for neuroplastic brain remodelling during spontaneous and treatment-induced recovery. Researchers are also beginning to use sophisticated imaging analyses to improve accuracy of prognosis, which may eventually improve patient care by allowing for more efficient treatment planning. Brain stimulation techniques offer a new and exciting way to improve the recovery potential after stroke.

Introduction

With the invention of modern functional and structural imaging techniques (e.g., functional magnetic resonance imaging [fMRI]; diffusion tensor imaging [DTI]) the investigations and discoveries of the neural substrates of language processing increased dramatically. Recently, refinement of existing imaging protocols, development of new techniques and advancement of data analysis strategies opened the door to a more thorough understanding of brain systems supporting cognitive functions. These recent developments have also fostered a dramatic knowledge increase in rehabilitation neuroscience, where researchers are interested in mapping changes in brain systems during spontaneous recovery or during the rehabilitation of patients with neurological injury (for review see Crosson, et al., 2010).

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Mapping these changes over time in larger groups of patients or assessing the impact of specific lesion patterns on behavioral outcomes may lead to improved prognosis or even patient specific treatment prescription early after brain damage. The combination of functional imaging (e.g., fMRI) with information about the integrity of white matter tracts (e.g., DTI) or by modeling functional brain activity at the system level (e.g., connectivity analysis) offers new exciting possibilities to gain insight into the neural substrates of spontaneous or treatment related recovery. Moreover, non-invasive brain stimulation techniques (e.g., transcranial direct current stimulation, tDCS; repetitive transcranial magnetic stimulation, rTMS) guided by functional imaging data may be a viable way to enhance the effectiveness of existing behavioral treatment protocols.

In the present manuscript we aim to highlight recent developments in functional and structural imaging and brain stimulation methods in aphasia research to enhance treatment outcomes. In particular, in four sections we will discuss examples of:

- **A.** cross-sectional findings with regard to local brain functions and functional connectivity and their impact on language functions in aphasia
- **B.** structural and functional imaging findings in aphasia treatment research using longitudinal designs
- **C.** adjunct brain stimulation techniques guided by functional imaging to improve aphasia treatment effectiveness and
- **D.** more recent developments related to the prognosis of language outcome after stroke and treatment responsiveness

In each section below we describe the relevant techniques or methodological advances and how they have improved our understanding of spontaneous recovery and treatment related changes in brain activity or structure in aphasia, the impact of these advances on prognosis and finally we discuss their implications and future directions for research [for a detailed overview of the imaging techniques described in this paper, their main applications in neurorehabilitation and limitations see Crosson, et al. (2010) and Eliassen, et al. (2008)]. Brain stimulation techniques are described in more detail in the respective sections.

(A) Functional imaging findings on aphasia in cross sectional settings

One of the most intensely debated issues in functional imaging research on aphasia recovery concerns the roles of the left (damaged) and right (intact) hemispheres in facilitating recovery. While there is consensus that lesion location and extent contribute to the eventual pattern of functional reorganization (Crosson, Fabrizio, et al., 2007), most studies suggest a more favorable outcome if perilesional areas in the left hemisphere are successfully recruited during language tasks (Heiss & Thiel, 2006; Saur, et al., 2006). Several recent studies further contributed to this discussion by using sophisticated fMRI and positron emission tomography (PET) methods. Both fMRI and PET provide an indirect measure of neural activity and are based on local changes of metabolism (e.g., oxygen consumption) and blood flow in brain areas active during a given task (Crosson, et al., 2010). In these studies aphasia patients were assessed during language production (Fridriksson, Baker, & Moser, 2009; Fridriksson, Bonilha, Baker, Moser, & Rorden, 2010; Postman-Caucheteux, et al., 2010) and comprehension tasks (Thompson, Bonakdarpour, & Fix, 2010; Warren, Crinion, Lambon Ralph, & Wise, 2009).

Neural correlates of anomia—Fridriksson et al. (2009) performed an elegant study that highlighted the important role of left-hemispheric perilesional brain regions to recovery. They assessed 15 patients with chronic aphasia and word-retrieval difficulties (anomia) during an overt picture naming task and fMRI. An age-matched healthy control group was scanned during the same task to provide a reference map of functional activity. The latter is important because increased right hemisphere activity has been found in older vs. younger healthy adults during word-retrieval tasks (e.g., Meinzer, et al., 2009; Meinzer, Seeds, et al., 2010). Initially, the activity patterns of each patient during correct naming trials was determined and then compared to the control group to identify patient specific deviations from the reference pattern of the control group. These differences were then used in a regression model to assess which of these patient specific patterns best predicted naming accuracy. Across the group more pronounced activity in preserved areas in the left hemisphere (inferior occipital and medial/middle frontal cortices and the anterior cingulate cortex) was associated with better naming performance. These activity patterns were located anterior and posterior to the activity pattern of the control group, which was interpreted as evidence of the cortical map expanding beyond areas normally involved in picture naming in healthy subjects. In a post-hoc analysis the authors explored whether activity differences were associated with a particular lesion pattern ("lesion-activation intensity analysis"). Indeed, patients with lesions in the posterior portion of Broca's area (BA 44) had less pronounced compensatory perilesional brain activity. Even though the authors acknowledge the relatively small sample for such an analysis and the lack of correcting for multiple comparisons, this finding suggests that lesions in BA 44 may reduce the potential to recruit perilesional brain areas. In sum, this study highlights the importance of perilesional areas that are not active in healthy controls, but contribute to successful recovery from anomia.

In a second study of the same workgroup, Fridriksson, Bonhila, et al. (2010) assessed overt picture naming in 11 chronic aphasia patients with different types of aphasia and different degrees of word-retrieval problems (anomia). While previous studies had examined differences between correct naming responses and error types in single subject designs (Meinzer, et al., 2006), their goal was to identify areas of activation across the entire group associated with accurate picture-naming, phonemic paraphasias, and semantic paraphasias. As the authors were interested in common areas that differentiate these three types of responses, they did not consider (mask out) lesioned left hemisphere areas in the patients. Successful naming attempts were associated with activity in several right hemisphere areas (e.g., homolog areas of Broca's and Wernicke's area, precentral gyrus, supplementary motor area and other temporo-parietal areas). Interestingly, these areas of activity overlapped with healthy controls' activity in right hemisphere areas and no differences in the activation strength between patients and the control group were found. Thus, successful naming was associated with activity in part of the residual language network, which was also activated by healthy subjects. A subsequent region of interest (ROI) analysis revealed that irrespective of lesion size, activity in the right posterior portion of the homologue of Broca's area was associated with the number of correct naming responses. Thus, the results highlight the importance of right frontal recruitment for successful naming performance in this patient sample with relatively large lesions. However, this does not exclude the possibility that left hemisphere regions contributed to successful naming in some of their patients, as highlighted in the previous study (Fridriksson, et al., 2009).

When compared to successful naming attempts, semantic paraphasias were associated with more pronounced activity in right posterior temporo-occipital areas. This was interpreted as evidence for unsuccessful compensatory recruitment of the right-hemisphere component of the bilateral semantic retrieval network (Hickok & Poeppel, 2007). Phonemic errors were associated with more pronounced activity in left posterior perilesional areas (occipito-parietal regions, inferior temporal), presumably reflecting impaired phonological processing. The important aspect of this work is that irrespective of lesion size and extent or symptom patterns, different types of errors were characterized by activity in a common neural network. This may not necessarily reflect maladaptation of the language network in general (as successful naming attempts were also found and associated with functionally relevant activity in part of the network active in healthy subjects), rather, it may represent "the struggle of the organisms to cope with the damaged language network" (p. 2497).

In an attempt to highlight common activity patterns associated with correct and erroneous naming responses in a heterogeneous sample of patients, including those with severe anomia, Fridriksson et al. (Fridriksson, Bonilha, et al., 2010) excluded large portions of the left-hemisphere from the analysis. Thus, information about perilesional activity, that may have functional significance in individual patients, was not assessed. The specific role of left perilesional vs. contralateral brain areas in aphasia recovery was addressed in a study by Postman-Caucheteaux and colleagues (Postman-Caucheteux, et al., 2010) that also employed an overt picture naming task during fMRI. In an attempt to avoid reduced sensitivity to detect perilesional activity in group studies, they employed a multiple case design and assessed three well recovered patients, who still evidenced a substantial number of errors (24–47% erroneous naming attempts during fMRI, mostly semantic paraphasias or omissions). All three patients showed robust activity mainly in perilesional areas during correct naming trials, which overlapped with the left-lateralized pattern of a healthy control group. On the other hand, naming errors were characterized by strong right frontal activity (inferior and middle frontal gyrus) that was not observed during correct namings. At first, these results seem to be inconsistent with Fridriksson et al. (2010); however, differences in severity and lesion size and extent in these two studies may have contributed to these differences. In particular, the right inferior frontal gyrus (IFG) may play a more important role in language processing with larger lesions and less pronounced ipsilesional activity. Also, differences in the respective designs may have contributed. For example, naming related activity in the healthy control group in the study by Postman-Caucheteaux et al. (2010) was strongly left lateralized, while in the study by Fridriksson et al. (2010) substantial right hemisphere activity was observed in the control group, and similar to that of the patient group during correct naming attempts.

Local cortical activity changes during syntax processing—While the first studies reviewed focused on language production, another recent study (Thompson, Bonakdarpour, et al., 2010) studied verb argument structure processing (VAS) in five patients with chronic aphasia using a lexical decision task and fMRI. Verb production was impaired, but verb comprehension was relatively spared in all patients. A previous study (Thompson, et al., 2007) that used the same paradigm had shown parametric modulation (i.e., more pronounced recruitment) of bilateral posterior temporo-parietal cortex (angular gyrus) with increasingly complex verb argument structure. Thus, in a first step the authors aimed to replicate these findings in older subjects, as aging might be associated with changes in functional activity patterns. Indeed, while similar areas were activated in healthy old and young groups, the old group failed to show the same strong parametric modulation of VAS processing; only differences between 1- and 3-argument verbs were observed highlighting the importance of including an age-matched group of participants in aphasia imaging research.

A second methodological aspect of this study is noteworthy: It had been shown in previous studies (Bonakdarpour, Parrish, & Thompson, 2007) that even in chronic patients the hemodynamic response (HR) may be abnormal (e.g., abnormal shape or delayed peak compared to healthy subjects). However, during data analysis in fMRI a standard approach would comprise correlating a prototypical (standard) HR function (HRF) with the actual data. An abnormal HR in stroke patients (e.g., in perilesional areas) may compromise such an approach and prevent detection of activity in such areas. Indeed, in this sample a close inspection of the response functions revealed abnormal hemodynamic responses in 3/5 patients. As the authors also acquired a measure of the individual patient's hemodynamic response function using a long trial event-related design, they could use this information to model the individual patient's fMRI data. This resulted in increased sensitivity to detect activity in perilesional areas in the patients with abnormal HRFs. With regard to VAS processing, the patients demonstrated relatively preserved task performance associated with activity in posterior brain areas overlapping with those found active in the control group. However, while the control group showed bilateral modulation, activity was found either in the left or right hemisphere in the patients. Thus, the patients showed a similar modulation of task related activity by VAS complexity as the healthy older control group and in some cases (with lesions encroaching in critical left hemisphere areas), the right hemisphere was capable of sustaining processing of VAS. This finding is in line with previous studies (e.g., Crinion & Price, 2005) showing that compensatory right hemisphere activity might be sufficient during relatively simple receptive language tasks (e.g., single word comprehension, lexical decision). However, such compensatory activity may not be sufficient to support performance during more difficult tasks (Crinion & Price, 2005; Warren, et al., 2009).

Functional network correlates of sentence level processing—A different approach to look into the roles of the two hemispheres in language comprehension recovery was carried out by Warren et al. (2009). These authors re-analyzed a previously published data set (Crinion & Price, 2005) that assessed narrative sentence comprehension in aphasia patients during PET using a "functional connectivity analysis". A stroke results in local cortical dysfunction at the lesion site and in perilesional areas, impaired functioning in remote areas and potentially a compensatory up-regulation of other areas. More recent developments in fMRI data analysis allow investigation of not only how local activity changes relate to behavioral outcome (e.g., the above reviewed studies), but also the assessment of functional integration among different regions (i.e., how different brain systems interact with each other during task performance). While functional network approaches are diverse and rely on complex mathematical assumptions (see Price, Crinion, & Friston, 2006 for a review of common techniques), this dynamic network approach has the potential to investigate cortical reorganization of complex brain networks in a more realistic way, as patterns of functional linkage (vs. activity in isolated brain areas) can be studied. This can be accomplished by addressing how (a) interconnectivity of brain areas is modulated by some external stimulus (e.g., an experimental task), in response to a focal lesion or after treatment ("intrinsic connectivity") and (b) how such factors change the modulating influence of one or more brain areas on others ("effective connectivity").

In the study by Warren et al. (2009), functional connectivity of the left anterior superior temporal lobe was assessed; a brain region critical for speech processing. First, connectivity of this region was determined in a group of healthy subjects showing strong interactions with the homolog area in the right hemisphere and left inferior frontal and basal temporal areas. When they analyzed the whole group of aphasia patients, a selective disruption of right- and left anterior superior temporal connectivity was evident and correlated with the degree of behavioral impairment. A subsequent analysis revealed that 50% of the patients exhibited intact functional connectivity of right and left temporal areas, which was associated with better language comprehension recovery. Moreover, compared to the healthy control group, only in this group of patients more pronounced activity in the functionally connected left inferior frontal lobe was found. This suggests effective functional compensation, as this area has been implicated with top-down modulation of language comprehension in previous studies (e.g., Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997).

In sum, this study highlights the important interplay of remote but connected brain areas in normal language comprehension and for language recovery after stroke. However, the type of functional connectivity measure employed in this study basically assessed temporal correlation between different brain areas. This did not assess the directionality of the connections or the influence of a potential modulation input from other brain regions. These issues could be assessed with more advanced connectivity measures (e.g., dynamic causal modelling, DCM, see Price, et al., 2006 for a review) and further corroborated by information about the integrity of fibers connecting a given set of brain regions (e.g., using diffusion tensor imaging, Le Bihan, (2003)).

(B) Functional and structural imaging in aphasia treatment research

An increasing number of studies have used fMRI to assess functional brain activity changes in response to treatment in aphasia (see Meinzer & Breitenstein, 2008 for a recent review). Compared to the above described cross-sectional studies, neuroimaging studies of treatment effects aim to assess treatment-induced plasticity of neural functions in longitudinal designs, typically involving repeated assessments in the same individuals (e.g., prior to and after treatment). So far, however, the literature has been dominated by single- or multiple single-subject research studies and only very recently the first few group studies have been conducted (Meinzer, et al., 2008; Raboyeau, et al., 2008; Richter, Miltner, & Straube, 2008).

Functional and structural correlates of therapy in chronic anomia—The largest sample so far that was studied with fMRI prior to and after anomia treatment was reported in a recent study by Fridriksson (2010). Here, 26 patients received two weeks of phonemic and semantic cueing treatment (3 hrs/day) and were scanned during a picture naming task. Their main analysis was a regression analysis that aimed to predict treatment outcome based on the pre-post change of fMRI activity. In line with previous studies, increased activity in anterior (middle frontal gyrus, pars opercularis, precentral gyrus) and posterior brain regions (inferior and superior parietal lobule, precuneus) in the affected left hemisphere were associated with more pronounced treatment success. In addition, a lesion analysis revealed that damage to posterior brain regions in the middle temporal and occipital lobe was associated with poor treatment outcome. Fridriksson suggests that this might represent first evidence that patients with damage to these areas might be less suited for such a particular cueing treatment approach and other types of inventions may be more appropriate.

Crosson, Fabrizo et al. (2007) had developed a treatment to shift laterality of frontal activity rightward during word production in nonfluent aphasia, and the treatment increased the rate at which patients relearned words more than a control treatment. The active component of the treatment was performing a complex left-hand movement to initiate picture-naming trials. Crosson et al. (2009) imaged five patients before and immediately after this treatment using a word production paradigm (category-member generation) and fMRI to determine whether laterality of frontal activity changed as a result of treatment. Five neurologically age- and gender-matched controls also were scanned. Four of the five patients improved in treatment. Both those four patients and the control subjects showed greater right than left frontal activity before treatment, but frontal laterality indices did not differ between the groups then. After treatment, the patients who improved showed significantly greater right-hemisphere lateralization of activity than controls. Indeed, for three of the four patients who improved in treatment, frontal activity was completely lateralized to the right hemisphere post-treatment. Even though frontal laterality indices increased for the patients who improved, the amount of right frontal activity generally decreased, as did the amount of left frontal activity (note that laterality indices in these patients increased, as activity decreases were more pronounced in left than right frontal areas). Further, right frontal activity became increasingly localized in the posterior, inferior frontal lobe, primarily in motor and premotor cortices. This pattern of decreased right frontal activity suggests increased efficiency of processing from pre- to post-treatment. For some patients, maintenance or increase in posterior left-hemisphere activity appeared necessary for leveraging treatment gains and increased right frontal lateralization. The one patient who did not improve in the treatment showed a leftward shift in laterality. The idea that therapists might engage a specific structure in the service of rehabilitation using a specific behavioral strategy and verifying that engagement with fMRI is intriguing and supports earlier suggestions that treatment aimed at right hemisphere structures can be effective (Burton, Kemp, & Burton, 1987; Code, 1983). While the data of Crosson et al. (2009) are encouraging in providing some support for the mechanism they proposed for their treatment, a larger and better controlled study needs to be done to confirm the mechanism.

Neural correlates of short- and long-term of language therapy outcomes—So far, previous group studies in aphasia treatment functional imaging research in the chronic stage had used a priori defined regions of interest, restricted their analyses to the undamaged right hemisphere or assessed immediate effects of the training on functional activity only (for review see Meinzer & Breitenstein, 2008). These potential shortcomings were addressed in a recent study by Menke et al. (2009). Here, naming performance was assessed during a picture-naming task immediately prior to and after a two week intensive anomia training, and again eight months after the training. Naming improvement was substantial at both post-treatment assessments; however, different brain areas were associated with treatment success at both time points. Immediately after the intervention a whole brain regression analysis revealed that brain areas associated with memory, attentional processes and multimodal integration (e.g., bilateral hippocampal formation and fusiform gyrus, right precuneus, cingulate gyrus) were associated with more pronounced recovery. Retention of the treatment gains during the follow-up scan were correlated with increased activity in posterior parieto-temporal areas of the right hemisphere and left temporal areas, both associated with semantic processing. Thus, similar to longitudinal studies that found a dynamic pattern of language network reorganization across the first year post-stroke (e.g., Saur, et al., 2006), different brain areas might be associated with the immediate treatment response versus consolidation of treatment gains over time.

A second study (Breier, et al., 2009) that included a follow-up assessment used magnetoencephalography (MEG), a noninvasive electrophysiological brain imaging method, to assess short and long term language network plasticity in response to treatment. Electrophysiological techniques, like MEG or electroencephalography (EEG), measure signals generated by ionic currents caused by information exchange between neurons. Synchronized activity of thousands of active neurons generates a small electrical (EEG) or magnetic (MEG) field that can be detected at the surface of the scalp. Complex mathematical algorithms are then used to determine the location of the sources underlying this surface activity (Crosson, et al., 2010). In this study, Breier et al. (2009) trained 23 patients with moderate to severe chronic aphasia according to constraint-induced language therapy (CILT) principles (Meinzer, Elbert, Djundja, Taub, & Rockstroh, 2007; Pulvermueller, et al., 2001). Patients were assessed at three time points (prior to and after CILT, three months after the end of the treatment) using a word recognition task during MEG that had previously been shown to elicit reliable activity in anterior and posterior language areas. Approximately half (N=11) of the patients significantly improved after treatment and treatment gains were maintained in eight patients during the follow-up (f-u) assessment. Based on the immediate treatment response the authors divided the patients into three groups for the MEG data analysis: (1) patients who showed a positive treatment response and maintained these gains at the f-u assessment, (2) patients improved after treatment but lost these gains three months later and, (3) non-responders. Interestingly, group (1) showed a consistent increase of task-related activity in left temporal brain areas at both post-treatment assessments, while non-responders showed the opposite trend (reduced left temporal activity). The small group of patients that benefited initially but did not maintain the treatment gains had more extensive lesions in the left hemisphere and the most pronounced activity in right temporal areas that was sustained across all three scanning sessions. In this group the most pronounced activity increase was found in left parietal areas at the follow-up assessment. Clearly a major accomplishment of this study was the inclusion of a follow-up period. In line with the above mentioned fMRI study by Menke et al. (2009) this demonstrated that activity patterns can change over time and specific patterns of task-related activity may be associated with different types of short- and long-term treatment outcome. Also, the study is in line with previous functional imaging studies of spontaneous recovery (Saur, et al., 2006) or intervention paradigms (Meinzer, et al., 2008) showing that increased (perilesional) left hemisphere activity might be related to more pronounced and stable improvements.

Rehabilitation of sentence level processing—While most studies that assessed the impact of treatment on functional activity patterns used word-retrieval paradigms (category generation, picture naming), very few studies looked at syntactic processes (see Meinzer & Breitenstein, 2008). Thompson, den Ouden, Bonakdarpour, Garibaldi, & Parrsih (2010) studied six chronic aphasia patients who were treated with a linguistically based approach to improve sentence processing (Treatment of underlying form, Thompson, Shapiro, Kiran, & Sobecks, 2003). Similar to the previously described cross-sectional study (Thompson, Bonakdarpour, et al., 2010) the authors obtained information about changes of the hemodynamic response in individual patients using a long-trial design and assessed potentially delayed time-to-peak (TTP) values. Arterial spin labeling (ASL; a non-invasive perfusion imaging technique that does not require an exogenous tracer to evaluate tissue functionality) was performed to assess potential hypoperfusion in the patient sample. Interestingly, prior to treatment, longer TTP of the hemodynamic response was associated with reduced perfusion. Across the entire sample, successful rehabilitation was associated with a shift of activity towards bilateral posterior temporo-parietal areas, which were activated by normal control subjects during the same tasks. Areas with changed activity after treatment, during an fMRI auditory verification task, evidenced higher perfusion levels and more normal TTP values (i.e., reduced latency). Thus, improved performance was associated with a normalization of activity (changed functional activity, reduced TTP and increased perfusion) in brain areas activated during the same task in healthy controls.

Functional network reorganization in response to therapy—As demonstrated above in the cross-sectional study by Warren and colleagues (2009), measures of connectivity may add important information about functional reorganization of the language network in aphasia. However, such analyses may have great value in aphasia treatment research by identifying different patterns of interregional connectivity of language network components. Only recently the feasibility of such a dynamic network approach in aphasia treatment research has been demonstrated in two case reports that used different types of connectivity analyses [for details of the respective procedures see Price, et al., (2006)]: dynamic causal modelling (DCM, Abutalebi, Rosa, Tettamanti, Green, & Cappa, 2009) and structural equation modeling (SEM, Vitali, et al., 2010).

In the study by Abutalebi et al. (2009) patterns of interregional connectivity in a bilingual anomic patient (Spanish/Italian) during an overt picture naming task and fMRI were studied. Language and functional activity were assessed prior to and after six weeks of daily phonological treatment that was performed in Italian (the patient's second language) and again four months after the end of the training. As DCM requires a priori assumptions about the underlying effects of interest, the authors focused exclusively on left hemispheric language areas (inferior temporal gyrus, BAs 19/37 and inferior frontal gyrus, BAs 47/45) and areas associated with language control in bilinguals (head of the caudate nucleus and anterior cingulate gyrus). Behaviorally, the patient's previously less proficient second language (Italian) improved substantially at both post assessments, but a performance decline in his untrained first language (Spanish) was evident after treatment. This observation was mirrored by progressively increased coupling of parts of the naming network for Italian, the reverse pattern was found for Spanish. On the other hand, parts of the control network became more connected over time for the untrained Spanish language, while connections were less prominent at the post assessments in Italian. This fascinating study demonstrated how complex networks may change over the course of treatment, including modulations of the primary naming network (with more connectivity being associated with better performance) and control areas (i.e., the less proficient language requiring more pronounced interplay between these areas and with the naming network, presumably due to greater interference from the more active/better rehabilitated language).

A second study (Vitali, et al., 2010) studied two cases with chronic aphasia and addressed "effective connectivity" changes consequent upon an intensive phonological treatment. As in the previous study, connectivity in several bilateral ROIs (insula; inferior parietal lobule [IPL]; inferior frontal gyrus [IFG]; middle temporal gyrus [MTG]) was assessed. Both patients improved immediately after treatment and delayed generalization of treatment effects were found for untrained pictures during a follow-up assessment six months later. Different patterns of changed effective connectivity were observed in the two patients for successfully trained items. In the patient with a smaller lesion enhanced effective connectivity was found mainly in bilateral IFG and IPL and left MTG. In the second patient with a larger lesion that affected the left IFG and MTG, increased connectivity was observed between the spared left IPL and right sided MTG and insula and within parts of the right hemisphere network. Thus, patterns of changed connectivity clearly depended on the extent and location of the lesion (Crosson, McGregor, et al., 2007) and both patterns were functionally relevant as they were associated with improved naming ability. Interestingly, during the follow-up scan, some improvement was seen for untrained items as well, and this delayed generalization was associated with connectivity changes in a subset of the network associated with successfully trained items immediately after treatment.

In sum, both studies provide valuable information about complex patterns of interregional activity changes in response to treatment and thus complement studies that addressed local cortical functioning only. However, in the future, studies with larger numbers of patients need to be completed to allow for a generalization of the results and to identify beneficial patterns of functional network reorganization at the systems level.

Structural markers of treatment success—While an increasing number of studies used fMRI or other functional imaging techniques to assess language network reorganization, structural changes in response to language treatment had not yet been assessed. Recently, the first study on structural plasticity in response to aphasia treatment has been published by Schlaug, Marchina, & Norton (2009). The authors used diffusion tensor imaging (DTI), a non-invasive MR-based imaging technique that measures the propagation of water molecules in brain tissue. It can be used to asses the microstructural integrity of white matter (i.e., fiber tracts) and provides a measure of structural brain connectivity (Crosson, et al., 2010). In this study patients received a highly intensive intervention (Melodic Intonation Therapy, >75, daily, 1.5 hour sessions) and the authors assessed potential changes in the right arcuate fasciculus (AF), a fiber bundle connecting anterior and posterior language regions, and the premotor cortex (note that all patients had extensive lesions in the left hemisphere and the AF was affected in all patients). Indeed, across the group the number of fibers in the AF increased significantly after treatment and the degree of language improvement tended to correlate with the degree of white matter changes. No changes were observed in a control ROI and for some patients repeated baseline DTI scans were obtained prior to treatment that did not show changes in the AF. Thus, the findings point to a specific treatment induced plasticity of white matter structures connecting critical language areas in the right hemisphere. Future studies may further corroborate these findings by combining DTI analyses with fMRI connectivity analyses.

(C) Adjunct treatments guided by functional imaging

High-frequency intensive speech-and-language therapy is currently the treatment of choice in chronic aphasia (Kelly, Brady, & Enderby, 2010). It has been shown in several studies that short bouts of intensive language intervention (e.g., two weeks duration with several hours of language exercises daily) can significantly enhance linguistic functions, with excellent long-term stability of therapy outcome (e.g., Barthel, Meinzer, Djundja, & Rockstroh, 2008; Meinzer, Djundja, Barthel, Elbert, & Rockstroh, 2005). However, despite its general effectiveness, treatment effect sizes are only low to moderate or are highly variable even within the same study (Beeson & Robey, 2006; Kendall, et al., 2008). Thus, there is a pressing need to explore new strategies to enhance treatment efficacy. This could be achieved by different brain stimulation techniques that modifiy cortical excitability with the goal to enhance learning during therapy.

Transcranial direct current stimulation—One of these new techniques is anodal (excitatory) transcranial direct current stimulation (atDCS) during which a weak constant current (1–2 mA) is applied to the scalp surface. It is used in stroke rehabilitation, because it modulates cortical excitability and plasticity (Schlaug, Renga, & Nair, 2008). Application of atDCS during therapy may enhance the beneficial effects of behavioral training protocols. Safety for stroke patients has been established, and due to the portability of the stimulation device it can be applied during therapy (Floel & Cohen, 2010). Anodal tDCS can enhance motor learning in healthy subjects (Nitsche, et al., 2003) and stroke (Hummel, et al., 2005). In the language domain, improved naming performance (Sparing et al., 2009) and vocabulary and grammar learning in healthy subjects (de Vries, et al., 2010; Floel, Rosser, Michka, Knecht, & Breitenstein, 2008) with atDCS have been shown. A recent study showed that anodal tDCS applied to individually determined perilesional brain areas in the left frontal cortex (based on a pre-treatment fMRI naming task) has the potential to improve the efficacy of language therapy in chronic aphasia. In this study, Baker, Rorden, & Fridriksson (2010) found that naming performance after five days of computerized anomia treatment with concomitant anodal tDCS led to more pronounced improvement than training alone. However, while this first trial showed promising results, mostly well recovered patients with residual anomia were included. Future studies are necessary to determine the best stimulation site for individual patients and patients with more severe aphasia need to be included as well.

Transcranial magnetic stimulation—A different type of non-invasive brain stimulation technique is repetitive transcranial magnetic stimulation (rTMS). During rTMS a fluctuating magnetic field is used to induce an electrical current in discrete cortical regions. The magnetic field is produced by an electrical current discharged through a coil held to the scalp over a brain region of interest. The magnetic field penetrates the scalp and induces a depolarizing electrical current in the underlying cortical surface. Repetitive trains of stimulations at a given frequency can either decrease (low-frequency TMS) or enhance (high-frequency TMS) the excitability of the underlying cortical areas (for review see Pascual-Leone, Walsh, & Rothwell, 2000).

In aphasia patients previous studies used low-frequency rTMS (1 Hz) to reduce excitability of right frontal brain regions. This was based on functional imaging studies suggesting that over activation of right frontal cortices may reduce the recovery potential in some aphasia patients by inhibiting (perilesional) left frontal areas (e.g., Belin, et al., 1996). Indeed, it has been shown that rTMS administered to the anterior portion of Broca's area (pars triangularis) may have beneficial effects on naming performance in chronic non-fluent aphasia (Naeser, et al., 2005). Moreover, a recent study that combined this type of intervention and pre-post fMRI provided first evidence that restoration of left hemisphere activity may underlie the beneficial effects of right frontal rTMS in some patients (Martin, et al., 2009).

However, only recently rTMS intervention has been combined with behavioral treatment to assess the potentially mutual benefits on training outcome. Naeser et al. (2010) reported first preliminary result of the combined effects of slow-frequency rTMS over right frontal areas and two weeks of Constraint-Induced Language Therapy (CILT, Meinzer, et al., 2007). In a crossover design they also compared the results to the effects of rTMS alone. In both patients the combination of the two treatments produced more pronounced improvement of language functions than rTMS alone, which warrants future controlled clinical trials in larger patient samples.

Epidural electrical brain stimulation—A more invasive means of brain stimulation has been studied by Cherney, Erickson, & Small (2010). These authors explored if treatment success can be enhanced by concomitant epidural cortical stimulation. Here, an electrode grid (neurostimulator) is surgically implanted on the dura mater over a given target brain region of interest. The advantage over rTMS and tDCS stimulation is that it allows stimulation with high frequency and high spatial specificity to the targeted area, which has been shown to enhance neuroplasticity in animal studies (Adkins, et al., 2006). In this study, four patients received an implanted stimulator over the left ventral premotor cortex, a region known to be involved in language processing. Location of stimulation was individually determined by pre-surgery fMRI based on three language tasks. Patients also received six weeks of daily language therapy that focused on language production and their results were compared to a matched control group that received language therapy but no stimulation. During treatment high-frequency cortical stimulation (50 Hz) at intensity of 4.75–6.5 mA was administered. The main goal of the study was to determine the safety of such a brain stimulation approach, and indeed, no adverse effects were observed. Language functions improved across the entire group; however, even though the gains in the stimulation group were more pronounced, no significant differences emerged when compared to the no-stimulation group. This could have been related to the small number of patients in this feasibility study. While the lack of adverse events in this highly invasive study is promising, the design did not allow ruling out potential placebo effects and there was a trend for a larger lesion size in the control group, both of which could have contributed to their findings. Thus, future studies need to evaluate the efficacy of such an approach, which may be indicated in severe patients for whom the most pronounced effects were found. However, due to the highly invasive nature, this type of adjunct treatment may be reserved for patients when other brain stimulation techniques or pharmacological interventions fail.

(D) Predicting outcome of recovery/prognosis in acute and chronic aphasia

Neural correlates of impairment in acute aphasia—Impaired repetition (with relatively spared comprehension and fluency) is the primary symptom of conduction aphasia, but impairment in repetition is also common in other aphasia syndromes. However, the neural substrates of impaired repetition are intensely debated. Candidate regions include the left arcuate fasciculus connecting anterior and posterior language areas or the inferior parietal lobe. A recent study by Fridriksson, Kjartansson, et al. (2010) further contributed to this discussion: The authors scanned 39 aphasia patients in the acute stage after stroke (3–20 days post stroke) with and without repetition impairment. They obtained multimodal structural (T1-weighted), diffusion and perfusion weighted imaging data (DWI/PWI) to identify lesion patterns and hypoperfusion in individual patients. In particular, PWI measures blood flow in brain tissue (i.e., perfusion) to obtain information about tissue viability or functionality. It can be used to detect abnormal functioning of brain areas that may appear normal on structural MRI or DTI scans. Lesion patterns and PWI images were subjected to voxel-based lesion-symptom mapping (VLBM, Bates, et al., 2003) to elucidate predictors of impaired repetition. Regions that predicted impaired repetition scores were located in the left inferior supramarginal gyrus and its underlying white matter (posterior rostral portion of the arcuate fasciculus). PWI provided complementary information in that it showed that hypoperfusion of the inferior parietal lobule was the best predictor of impaired repetition. Thus, damage/dysfunction in both grey and white matter of the inferior parietal lobe as indicated by DWI-related changes or hypoperfusion (PWI) can be associated with repetition impairment in aphasia patients.

In the days following a stroke, lesion location is often thought to be unreliably associated with a particular aphasia syndrome because of the variability in day-to-day performance as the brain recovers. A recent study by Ochfeld, et al. (2010) challenged this assumption by assessing language and MRI scans of fifty patients who were hospitalized with acute left hemisphere ischemic stroke. They acquired T2, DWI and PWI scans to identify ischemic lesions or hypoperfusion in Broca’s area (Brodmann areas 44/45). The Western Aphasia Battery was used to classify aphasia syndromes. Thirty chronic patients (>6 months post-stroke) underwent MRI and language testing as well; 20 of whom were of the 30 patients tested acutely and came back for a follow-up. Hypoperfusion or lesion in Broca’s area was significantly associated with Broca’s aphasia or Global aphasia in acute stroke, but not in chronic stroke possibly because of neural reorganization. These findings highlight two important clinical considerations about acute aphasia. First, despite fluctuations in performance during the first few days after a stroke, hypoperfusion in Broca’s area is often manifested as Broca’s aphasia. Second, during the acute phase, when structural imaging shows little or no infarct, classification of aphasia syndromes based on language performance may provide important information about at-risk brain tissue and important changes in blood flow.

Predicting treatment outcome in chronic aphasia—Based on the findings by Menke, et al. (2009) that functional activity increases in the hippocampus may predict anomia treatment success, the same workgroup addressed the specific role of memory related structures in treatment induced recovery of anomia (Meinzer, Mohammadi, et al., 2010). In particular, previous studies had shown that the hippocampus is involved in language learning in healthy subjects (e.g., Breitenstein, et al., 2005) and recovery of language and motor functions in stroke sufferers (Gauthier, et al., 2008; Goldenberg & Spatt, 1994). The main cause for aphasia after stroke is an occlusion of the middle cerebral artery (MCA). More proximal occlusion of the MCA relative to the internal carotid artery may affect the integrity of the hippocampus or surrounding white matter. Proximity in this study was determined retrospectively based on the lesion pattern in ten patients with chronic aphasia. Integrity of the hippocampus was assessed by MR-based volumetry and microstructural integrity of surrounding white matter by fractional anisotrophy derived from DTI. In this study, proximity of the infarct (but not lesion size), relative damage of the hippocampus in the language dominant left hemisphere and impaired integrity of surrounding white matter was associated with less pronounced treatment gains immediately after two weeks of anomia training and eight months later. No correlations were found for a set of untrained pictures, highlighting the importance of the hippocampus and surrounding white matter structures for language re-learning capacity in chronic aphasia. As previous functional imaging group studies in aphasia treatment research only assessed activity changes in predefined ROIs (not including the hippocampus), future studies need to scrutinize whether this finding can be generalized to other treatment protocols.

Additional support that lesion location and extent can have important implications for aphasia treatment outcomes comes from Parkinson, Raymer, Chang, Fitzgerald, & Crosson (2009). Here, they investigated the relationship between degree of lesion in anterior cortical regions, posterior/temporal regions and basal ganglia, and naming abilities. Using a 5-point lesion rating system (0 = no lesion and 5 = total area has solid lesion), the authors correlated lesion extent in each region with action and object naming scores before and after language treatment. Since basal ganglia lesions can exacerbate language disturbances, the authors controlled for extent of such lesions when investigating the relationship between anterior cortical lesions and naming abilities. Interestingly, *larger* anterior cortical lesions were strongly associated with both *better* naming abilities for objects and actions before treatment, as well as *greater* improvements during therapy. The authors hypothesized that residual left frontal activity may interfere with naming by interfering with compensatory right hemisphere activity. Hence, left frontal cortex that is damaged by a large lesion can no longer compete with more productive neural substrates, thus producing better speech. Support offered for this hypothesis comes from studies applying transcranial direct current stimulation to the left frontotemporal region of individuals with post-stroke chronic nonfluent aphasia (Monti, et al., 2008). Suppression of cortical activity by cathodal stimulation improved naming abilities, whereas enhancement of cortical activity by anodal stimulation had no effect. Parkinson and colleagues (2009) also found that when controlling for anterior cortical lesions, degree of basal ganglia lesion was significantly correlated with poorer pretreatment naming scores, as well as fewer treatment gains. Left basal ganglia may suppress left frontal areas that compete with right hemisphere substrates available to take over language function. Thus, when left basal ganglia are impaired, the competition between left and right hemisphere frontal regions to take over language function may result in poorer performance.

Predicting language outcome based on structural and functional imaging— Disruption in the neural networks underlying the multiple cognitive processing steps involved in language tasks can give rise to different aphasia syndromes. However, the location and extent of lesions do not usually correspond to the size and shape of functional areas, rather, they correspond to cerebrovascular factors. Therefore, lesions often overlap different functional areas and are manifest as collections of cognitive, linguistic and motor deficits. Methods to predict prognosis in language rehabilitation after stroke, based on neuroimaging data, would provide valuable utility in determining treatment plans for clinicians, as well as recovery expectations for patients and families. To this end, Price, Seghier, & Leff (2010) developed a database with the anatomical images of 330 stroke patients, as well as scores on a series of standardized language assessments that were given over time. The database predicts language outcomes for a new stroke patient by measuring and comparing the lesion of this patient with other patients in the database, and then selecting the patients who are most similar to the new patient. Output provides a percent likelihood of regaining functions in a particular domain. As more stroke patients are entered into the database and more information regarding which cortical areas and white matter tracts are most important for language, the predictions for aphasia recovery may become enhanced.

Hosomi, et al. (2009) conducted a retrospective study of hospital records and diffusion tensor inaging (DTI) images of 13 individuals with acute left MCA infarcts to examine if arcuate fasciculus fibers that connect Broca's and Wernicke's areas in the left hemisphere were more affected in individuals with persistent aphasia than those without persistent aphasia at time of hospital discharge (mean hospital stay 30.2 days for aphasic patients, 28.6 days for nonaphasic patients). Neurologists made the diagnosis of aphasia using the National Institute of Health Stroke Scale (NIHSS) and subjects were divided into an aphasic group (n=6) and a nonaphasic group (n=7). Ten healthy volunteers served as control participants.

Controls and nonaphasic patients had significantly greater number of arcuate fasciculus fibers on the left than on the right side. However, the persistent aphasic group did not show this leftward asymmetry. The loss of leftward asymmetry predicted persistent aphasia with 0.83 sensitivity and 0.86 specificity. A larger, prospective study with a more extensive language evaluation is necessary, but these results indicate that in left MCA infarcts, leftward asymmetry of arcuate fasciculus fibers could be a potential predictor of aphasia recovery.

In another study, Saur et al. (2010) investigated the predictive value of early functional MRI patterns to language recovery at six months post stroke. Twenty-one patients with moderate-severe aphasia underwent fMRI during an auditory comprehension task two weeks post stroke, as well as extensive language testing two weeks and six months post stroke. A supervised, multivariate classification method (SVM) was used to determine if early post-stroke fMRI activation patterns predicted good versus bad language outcomes. A SVM basically learns about differences between previously classified groups (e.g., characteristics of aphasia patients with known good vs. bad language outcome) and can apply this knowledge to new data to predict outcome (Kloppel, et al., 2008).

In this study, the SVM was trained using fMRI data of an independent sample of aphasia patients to establish patterns of activity that were associated with good vs. bad recovery. This information was used to predict language outcome in a new sample of patients. Key language areas in the left and right frontal and temporal areas were selected as regions of interest. Functional activation patterns (i.e., the degree and location of fMRI signal in the selected language areas) two-weeks after stroke predicted language recovery in these patients with 76% accuracy at six months post stroke. The classification accuracy increased to 86% when age and language scores were also added as predictors; however, age and language scores failed to predict recovery by themselves. Interestingly, fMRI activity at two days post-stroke or diffusion weighted imaging did not predict outcome. Such early classification algorithms may have a great value in clinical practice, e.g., patients with a predicted unfavorable outcome based on early fMRI patterns could be assigned to more intensive treatment schedules.

Summary and conclusion

More recently, advances in neuroimaging data acquisition and analysis have progressively been used to learn about language recovery processes after brain damage. While the analysis of local cortical changes are still the most popular methods used, researchers are beginning to combine different imaging modalities (e.g., structural lesion information, DTI and PWI), which provides complementary information about the neural concomitants of recovery. Different forms of functional connectivity analysis have been shown to be a promising and powerful tool for modeling brain functions and recovery in a more realistic (systemic) way. Even though this has been accomplished at the group level in cross-sectional studies only, the feasibility and usefulness has now been confirmed in treatment studies as well using single subject designs.

The first longitudinal studies using extended follow-up assessments in aphasia treatment research have been accomplished. Similar to studies in early stages of recovery (e.g., the first year post-stroke), dynamic brain activity changes were found and could be linked to more or less favorable outcome. In addition, first preliminary evidence of white matter plasticity in response to successful treatment outcomes has been provided.

Brain stimulation techniques are relatively new tools that may be suited to enhance the recovery potential in aphasia and treatment responsiveness. Functional imaging has been used to guide the application of these new techniques (e.g., by determining areas of perislesional activity to be targeted by stimulation). However, so far only few patients have been treated and future studies need to determine which areas should be targeted for facilitation (or even inhibition) in individual patients.

Finally, neuroimaging techniques are now used to assess predictors of recovery and treatment outcome and the first larger databases are in the process of being established to allow for a more comprehensive understanding of the recovery process. Both may, in the near future, help to predict the language recovery potential at an early stage, thus allowing for patients to begin the most beneficial therapeutic interventions in the initial stages of recovery from brain damage.

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