SPECIAL COMMUNICATION

Neurobiology of Language Recovery After Stroke: Lessons From Neuroimaging Studies

Dorothee Saur, MD, Gesa Hartwigsen, PhD

ABSTRACT. Saur D, Hartwigsen G. Neurobiology of language recovery after stroke: lessons from neuroimaging studies. Arch Phys Med Rehabil 2012;93(1 Suppl 1):S15-25.

Language is organized in large-scale, predominantly left-lateralized, temporo-parieto-frontal networks in the human brain. After focal brain damage (eg, ischemic stroke), this network organization enables the brain to adaptively reorganize language functions in order to compensate lesion effects. Here, we summarize how structural and functional neuroimaging methods contribute to the current understanding of loss and recovery of language functions after stroke. This includes voxelwise lesion-behavior mapping, functional imaging for mapping reorganizational mechanisms from acute to chronic stroke, as well as imaging based outcome prediction. The review is complemented by an introductory section on language organization in the healthy brain.

Key Words: Aphasia; Magnetic resonance imaging; Rehabilitation; Stroke.

THIS REVIEW SUMMARIZES how structural and functional neuroimaging methods contribute to the current understanding of loss and recovery of language functions after stroke. For a detailed review on the basic principles of functional magnetic resonance imaging (fMRI), we refer the reader to Smits et al[1] in this issue. We first discuss imaging studies on language networks in the healthy brain and introduce the dual-stream model for language organization. The second part deals with lesion studies using voxelwise lesion-behavior mapping (VLBM). We then review the current literature on functional imaging of spontaneous reorganization mechanisms in acute and chronic stroke. This is complemented by imaging based prediction of language outcome. Finally, we provide an overview of neuroimaging studies dealing with treatment-induced plasticity.

IMAGING LANGUAGE NETWORKS IN THE HEALTHY BRAIN

A profound understanding of language organization in the healthy human brain is mandatory for the interpretation of activation changes due to reorganizational mechanisms in patients with brain damage. While early models of language organization were solely based on behavioral deficits in patients with brain lesions (eg, Broca[2] and Wernicke[3], see Shalom and Poeppel [4] for a review), a new decade of studies on language organization in the human brain has started with the advent of modern functional imaging techniques such as positron-emission tomography (PET), fMRI, electroencephalography, and magnetoencephalography in the late 20th century. In contrast to the lesion-deficit approach, functional neuroimaging studies are not limited to the assumption that cognitive processes or operations are confined to discrete anatomical regions but allow for the investigation of functional specialization which emerges from the interaction between different areas. These studies now focus on the direct correlation between mental operations and indices of brain activity, and thus provide the perfect complement to lesion studies in that the neural systems sufficient for one task compared with another can be identified.

Based on an analogy to the dual-stream model of visual processing,[5] Hickok and Poeppel[6-8] introduced a functional-anatomic model of auditory language processing that distinguishes 2 neuroanatomically segregated routes. A ventral stream, projecting from the core auditory cortices to various temporal lobe regions, is involved in auditory recognition and processes speech signals for language comprehension. The ventral stream thus maps sound onto meaning (ie, lexical-semantic processing). A dorsal stream, projecting from the auditory cortices to temporo-parietal and frontal lobe articulatory networks, is the interface between auditory and motor processing and maps sound onto articulatory-based representations (ie, phonologic processing). A task that consecutively activates the dorsal stream is the verbal repetition of heard speech, during which access to a motor-based representation is necessary.

The framework posits that early cortical stages of language perception involve auditory fields in the bilateral superior temporal gyri.[9] This cortical processing system then diverges into the ventral and dorsal stream. The ventral stream projects ventro-laterally toward posterior and anterior parts of the middle temporal gyrus and serves lexical-semantic processing[9,10] (see[11] for a review). The dorsal stream projects dorso-posteriorly, involving a region in the posterior Sylvian fissure at the parieto-temporal boundary (area Sylvian-parietal-temporal),

List of Abbreviations

DWI	diffusion-weighted imaging
fMRI	functional magnetic resonance imaging
IFG	inferior frontal gyrus
LRS	language recovery score
MRI	magnetic resonance imaging
PET	positron-emission tomography
PLORAS	predicting language outcome and recovery after stroke
PWI	perfusion-weighted MRI
SVM	support vector machine
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation
VLBM	voxelwise lesion-behavior mapping

From the Language and Aphasia Laboratory, Department of Neurology, University of Leipzig, Leipzig, Germany.

Correspondence to Dorothee Saur, MD, Language and Aphasia Laboratory, Dept of Neurology, University of Leipzig, Liebigstraβe 20, 04103 Leipzig, Germany, e-mail: *dorothee.saur@medizin.uni-leipzig.de*. Reprints are not available from the author.

0003-9993/12/9301S-00101$36.00/0
doi:10.1016/j.apmr.2011.03.036

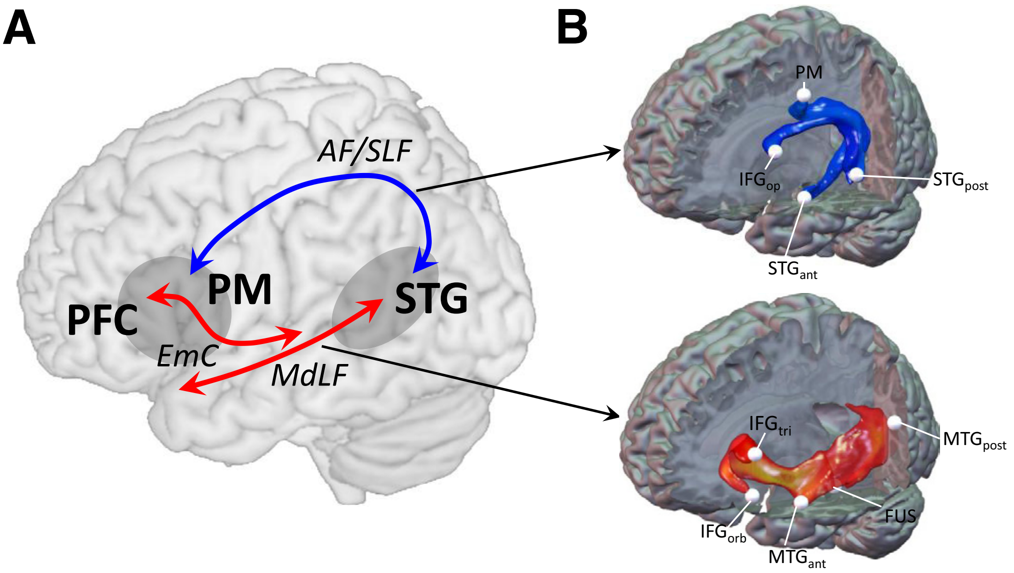

Fig 1. The 2 pathways of auditory language processing. (A) Schematic diagram of the ventral and dorsal streams projecting to the prefrontal and premotor cortices. Regions in gray show Broca's area in the frontal gyrus (left) and Wernicke's area in the temporal gyrus (right). (B) Results from diffusion tensor imaging-based tractography show 2 distinct pathways connecting posterior brain regions with anterior areas via the fasciculus arcuatus/longitudinalis superior (ie, the dorsal pathway) and the fasciculus longitudinalis medialis/capsula extrema (ie, the ventral pathway). Abbreviations: AF/SLF, fasciculus arcuatus/longitudinalis superior; EmC, capsula extrema; FUS, fusiform gyrus; IFG$_{orb}$, pars orbitalis; IFG$_{op}$, pars opercularis of the IFG; IFG$_{tri}$, pars triangularis of the IFG; MdLF, fasciculus longitudinalis medialis; MTG$_{ant}$, anterior middle temporal gyrus; MTG$_{post}$, posterior middle temporal gyrus; PFC, prefrontal cortex; PM, premotor cortex; STG, superior temporal gyrus; STG$_{ant}$, anterior superior temporal gyrus; STG$_{post}$, posterior superior temporal gyrus. Modified from Saur et al.[14] Reprinted with permission. © 2009 National Academy of Sciences, USA.

and ultimately projects to premotor areas in the frontal cortex, including the posterior aspect of Broca's area (ie, pars opercularis of the inferior frontal gyrus [IFG]). Area Sylvian-parietal-temporal is involved in translating acoustic speech signals into articulatory representations in the frontal lobe,[12] which is essential for intact language production as well as for speech development (see[13] for a review). Under normative circumstances, both pathways interact. While the dorsal stream is proposed to be left-hemisphere dominant, the ventral stream is more bilaterally distributed.

In a recent multimodal imaging study, Saur et al[14] used combined fMRI and diffusion tensor imaging-based tractography in healthy subjects to identify the most probable anatomical pathways connecting brain regions preferentially associated with auditory comprehension and repetition, respectively. The authors demonstrated that temporo-frontal interactions are subserved by 2 distinct fiber bundles (fig 1). The repetition of heard pseudowords (ie, meaningless nonwords) is subserved by a dorsal stream connecting the superior temporal lobe and premotor areas in the frontal lobe (including pars opercularis in the IFG) via the arcuate and superior longitudinal fascicle. In contrast, higher-level language comprehension (ie, listening to normative sentences compared with meaningless pseudosentences) is mediated by a ventral pathway connecting the middle temporal lobe and the ventrolateral prefrontal cortex via the extreme capsule. The functional relevance of these anatomical pathways is now widely discussed.[15-19] In sum, these results question the classical view of the temporal lobe (ie, Wernicke's area) being solely connected with frontal regions (ie, Broca's area) via the arcuate fascicle.[20] Rather, these results point toward an organization of language in distinct ventral and dorsal large-scale networks. Further, this implies various routes of compensation after focal brain damage.

VOXEL-BASED LESION STUDIES OF LANGUAGE

Since the days of Broca and Wernicke in the second half of the 19th century, research aims at defining functional-anatomic models of language organization in the human brain. While the modularity assumption (ie, discrete anatomical modules deal with different cognitive functions) of the classical lesion-deficit approach has frequently been criticized (eg,[21,22] for reviews), the recent advent of new techniques offers a complementary approach to the use of imaging studies in healthy volunteers. With modern voxelwise lesion studies, the researcher aims at identifying whether differences in lesion frequency between patients showing a particular disorder and those who do not, might be due to chance or are reliable predictors of behavior.[22] For example, VLBM is a technique to determine whether a specific region is critically contributing to a given task by analyzing the statistical relationship between lesion data and behavioral measures[22-24] (fig 2). In contrast to classical lesion-deficit studies, VLBM is not restricted to specified regions of interest but allows for additional areas to emerge in the exploration of networks that support a given behavior.[23] In VLBM, lesions are manually identified for each patient by marking the damaged region with special software (see[24] for an overview of different techniques) and statistical maps are generated at the group level afterward to reveal patterns of damage associated with the behavioral deficit. Importantly, statistical analyses of the relationship between tissue damage and observed behavior are carried out on a voxel-by-voxel basis by using continuous information both at the behavioral level (ie, avoiding arbitrary cutoffs) and the neuroanatomical level (ie, including patients independent of their lesion location).

An increasing number of studies have used VLBM to identify the critical contribution of different brain areas to specific

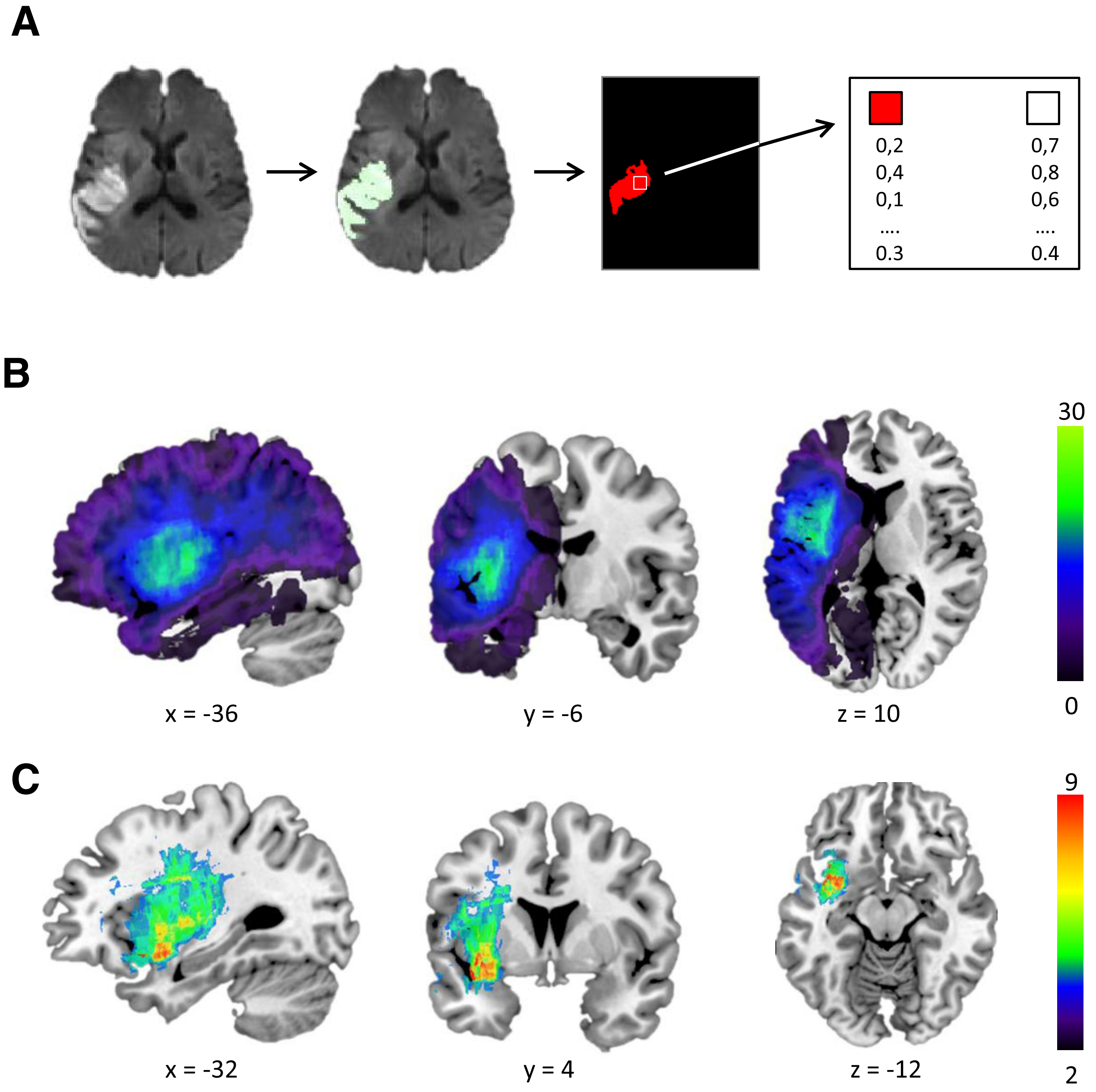

Fig 2. VLBM. (A) Concept of VLBM: the lesion is delineated on structural scans (here: DWI), the resulting map contains either lesioned (red square) or preserved (white square) voxels. Based on this binary classification, behavioral data (here: naming scores ranging from 0–1) are divided into 2 groups and statistical differences in the distribution will be calculated for each voxel with nonparametric tests. (B) Lesion overlap in 70 patients with anomia shows highest lesion overlap around the insular cortex. (C) Statistical lesion map associated with naming deficits in the same 70 patients. This demonstrates that highest lesion overlap and highest T values are not identical. Parts B and C by courtesy of Dorothee Kümmerer.

language tasks in patients with brain damage in the past few years (eg,[23,25-30]).

In an influential study, Bates et al[23] used VLBM in a group of 101 chronic aphasic patients with different degrees of language impairments to identify regions responsible for speech production and speech comprehension in the brain. This study revealed a dissociation of speech production and comprehension. While production was most affected by lesions in the insula and in the arcuate/superior longitudinal fasciculus, speech comprehension was most affected by lesions in the middle temporal gyrus. Although these results support the classical anterior-posterior contrast for speech production and comprehension, those regions historically associated with deficits in both processes, namely Broca's area in the IFG for speech production and Wernicke's area in the temporal lobe for speech comprehension, were not among the areas most reliably associated with deficits in that study.

Dronkers et al[25] further addressed the question of brain regions critically contributing to language comprehension in another study. The authors found that lesions to different left-hemisphere temporal and frontal brain regions affected performance in various language comprehension tests. Those regions included the posterior middle temporal gyrus and underlying white matter, the anterior superior temporal gyrus, the superior temporal sulcus and angular gyrus, mid-frontal cortex, and the anterior IFG. Again, lesions to Broca's (BA 44/45) and Wernicke's areas (posterior portion of BA 22) were not found to significantly alter language comprehension.

More recently, Fridriksson et al[28] investigated brain regions critically involved in speech repetition. That study examined 45 acute stroke patients suffering from aphasia with both diffusion-weighted imaging (DWI) and perfusion-weighted MRI (PWI). Structural damage most closely associated with impaired speech repetition as assessed with DWI was found in the posterior portion of the left arcuate fasciculus. Additionally, results from the PWI revealed that damage of the left inferior parietal lobe was associated with impaired speech repetition. These results were interpreted in terms of the integrity of the left inferior parietal lobe and the underlying white matter being crucial for speech repetition. This study demonstrates the usefulness of a multimodal approach, combining different neuroimaging techniques to describe distinct pathophysiologic aspects of stroke lesions. Several earlier studies demonstrated a correlation between improved language functions and increased perfusion in perilesional regions (eg,[31-33], see[34] for a review), providing further evidence for the value of PWI in lesion studies of acute stroke patients.

These results were complemented by a recent VLBM study providing evidence that the complexity of articulatory movements during the repetition of multisyllabic stimuli, depends on a critical involvement of the superior precentral gyrus of the insula.[35]

In summary, recent VLBM studies provide further evidence for large-scale networks being crucial for language comprehension as well as production, and question the classical view of language functions being predominantly subserved by Broca's and Wernicke's areas. It needs to be born in mind, however, that VLBM also has some limitations. One critical limitation is the impossibility to distinguish whether the lost cognitive function is associated with the lesioned area itself or a (functional and/or anatomical) disconnection of undamaged areas. For instance, in a functional PET study, Crinion et al[36] demonstrated that in addition to the loss of language function in the damaged left posterior temporal cortex, posterior ablation impaired language function in the intact left anterior temporal lobe. Moreover, a causal relationship between a specific lesion pattern and a cognitive deficit may also be obscured after compensatory strategies adopted by the patient to overcome the deficits or changes in the functional topography due to neuronal reorganization in the chronic phase after stroke.

IMAGING LANGUAGE REORGANIZATION AFTER ISCHEMIC STROKE

Dynamics of Language Reorganization in 3 Phases

In a behavioral study, Pedersen et al[37] tested 330 patients with acute aphasia at admission as well as weekly during the hospitalization period (6–12wk poststroke) and 6 months after stroke. The authors found that the highest dynamic of language recovery can be observed in the first 2 weeks after onset, while in the later course, recovery proceeded more prolonged. These different dynamics of functional improvement suggest that different mechanisms contribute to language recovery after stroke. Except for single subject studies,[38,39] very few imaging studies[40-42] investigated the time-course of language reorganization in a longitudinal study design to date. To our knowledge, the study from Saur et al[43] is the only functional neuroimaging study examining language recovery longitudinally from acute to chronic stroke. Fourteen patients presenting with acute aphasia caused by infarctions of different parts of the left middle cerebral artery territory (fig 3A) were examined repeatedly 3 times: in the acute phase (<4d poststroke, examination 1), subacute phase (after about 2wk, examination 2), and chronic phase (after 4–12mo, examination 3). At each examination, an auditory language comprehension task (contrasting speech with reversed speech) was presented during fMRI. Keeping with the dual-stream model of language processing, this paradigm was designed to predominantly activate the ventral stream. In parallel to fMRI investigations, patients were assessed with a set of aphasia tests from which a global language recovery score (LRS) was calculated. At examination 1, the fMRI group analysis (fig 3B) revealed little activation of the left IFG (Broca's area) with a low concomitant mean LRS. At examination 2, patients showed a significant improvement of their language abilities, which was paralleled by a strong up-regulation in the entire language system with strongest activation in the right IFG (Broca's homologue). Thereby, strongest correlation between early improvement of language function and increase of activation from the acute to the chronic phase was observed in the right IFG (fig 3C, right panel). At examination 3, a gradual normalization in the activation pattern was found while patients showed further significant improvement; in particular, activation in the right IFG decreased.

Thus, (preserved) language areas in the left hemisphere showed a more monophasic course of activation with a continuous increase, while right homologue areas showed a more biphasic course with an early increase and later decrease of activation.

Based on these results, Saur et al[43] postulated a model of language reorganization which proceeds in 3 phases: a first, acute phase is characterized by a global breakdown of the entire network. In this early phase, the mechanism of diaschisis plays an important role.[44]

Diaschisis is defined as a dysfunction of preserved cortical brain regions that are remote but functionally connected to the infarcted region. That is, in this early phase, a widespread local and remote dysfunction causes a severe language deficit often resulting in global aphasia. In the second, subacute phase, we observe a resolution of diaschisis. In this phase, preserved areas in the left and homologue areas in the right hemisphere show strong activation. To date, it remains unclear whether this strong right hemisphere activation early after stroke represents functional relevant activation compensating the lesioned left hemisphere areas (as indicated by the correlation analysis shown in fig 3C), or might alternatively be the result of disinhibition. The latter possibility would be consistent with the assumption that left hemisphere areas inhibit their homotopic right hemisphere counterparts in the healthy brain. Animal models of cerebral ischemia suggest that in this phase of hyperexcitation, GABAergic and glutamatergic pathways might be involved.[45] In the third chronic phase, a normalization of activation with a reshift of activation to the left hemisphere areas can be observed, which resembles the pattern in healthy subjects. In this phase, anatomic remodeling, for example dendritic outgrowth and synaptogenesis, likely underlie the reorganization process.[45]

It should be born in mind, however, that this time course of language activation was derived from a heterogeneous group of aphasic stroke patients. Thus, in the individual case, the pattern of reorganization might differ. For example, in case of a large

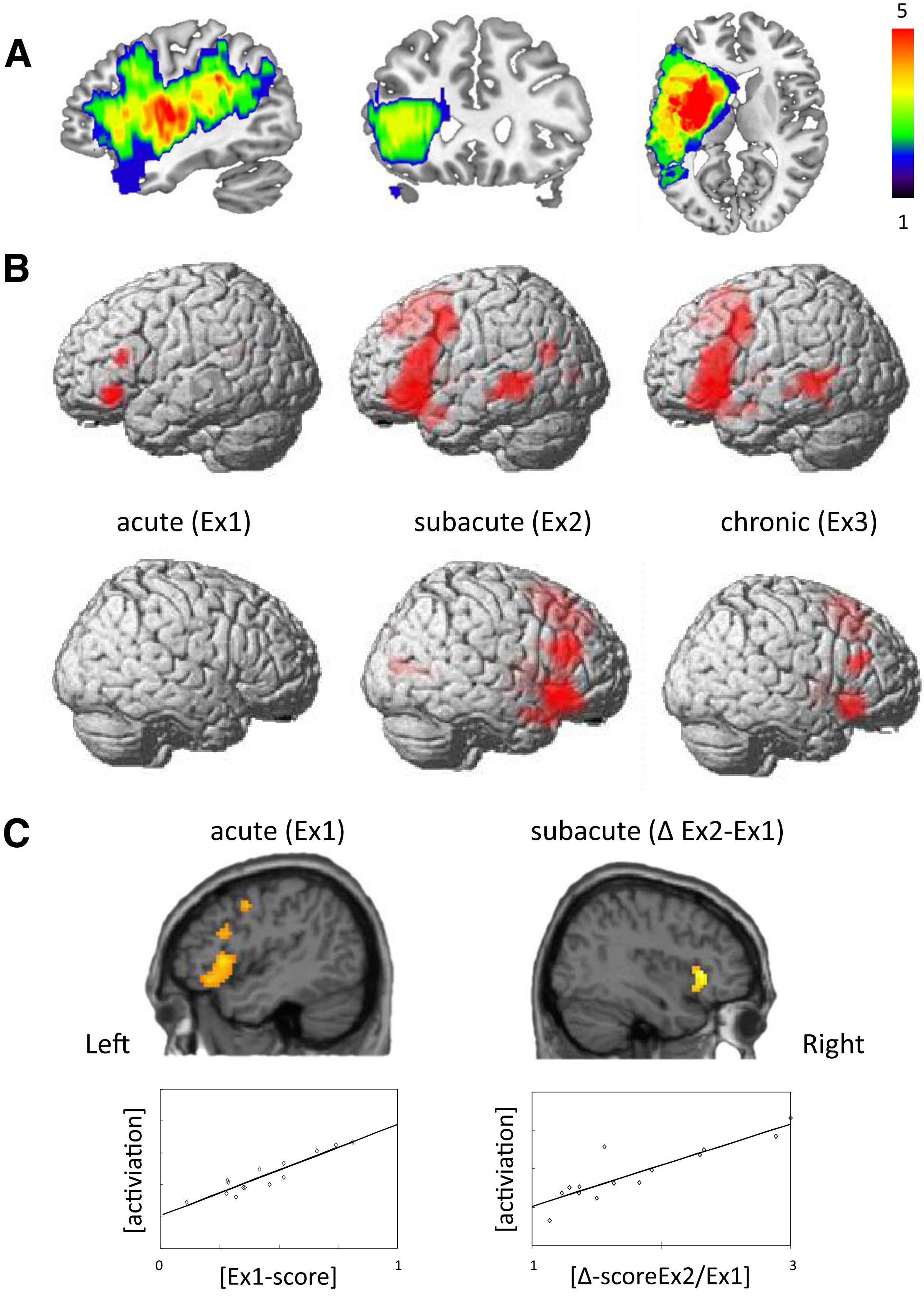

Fig 3. Dynamics of language reorganization in 3 phases. (A) Infarct overlays of 14 patients with acute aphasia. (B) Dynamics of language activation over the time course of recovery from the acute to the chronic phase. Left hemisphere (top) and right hemisphere (bottom) activation in patients during a language comprehension task (speech vs reversed speech). (C) Correlation of language recovery score (LRS_{Ex1}) and fMRI language activation at the first examination (Ex1, left panel); correlation of early language improvement (LRS_{Ex2}/LRS_{Ex1}) with early increase of language activation from Ex1 to Ex2 (right panel). Abbreviations: Ex1, examination 1; Ex2, examination 2; Ex3, examination 3. Modified from Saur et al.[43] Reprinted with permission. © 2006, Oxford University Press.

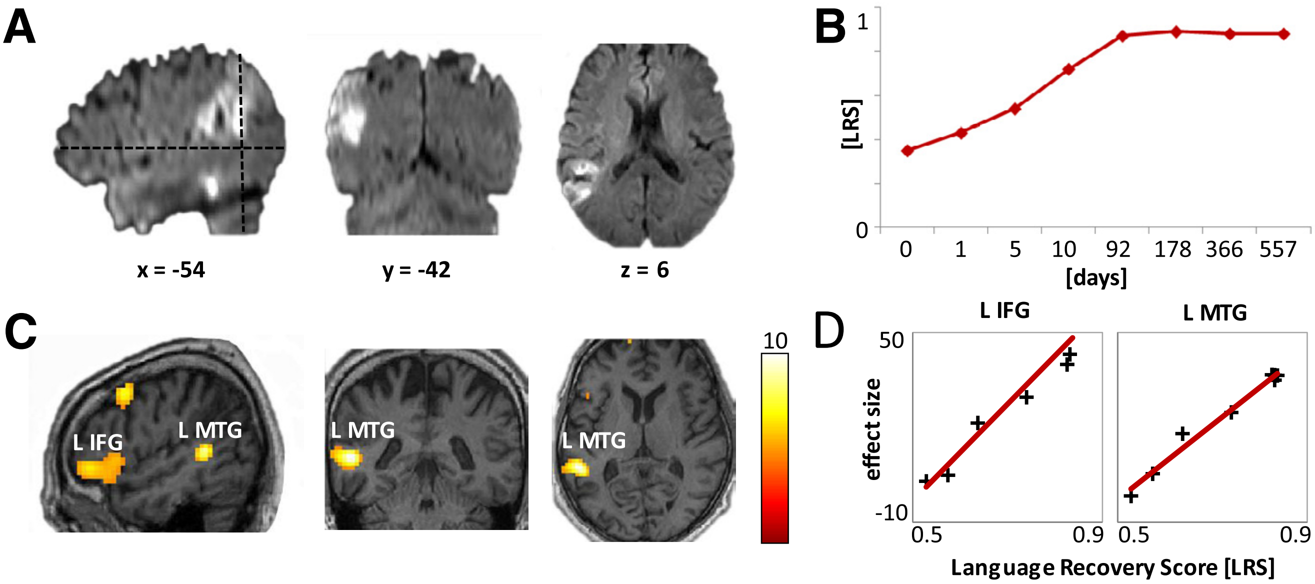

Fig 4. Single case example of a 68-year-old man. (A) Left temporo-parietal ischemic lesion on DWI. (B) LRS at 8 consecutive examinations. (C) The language recovery map reflects the longitudinal correlation of LRS and language activation (speech compared with reversed speech). (D) Correlation plots extracted from the peak activations in the left inferior frontal gyrus (L IFG) and left middle temporal gyrus (L MTG). Modified from Saur.[100] Reprinted with permission. © 2010, Springer, Germany.

left hemispheric stroke, activation in the right hemisphere might still persist in the chronic phase (see Language Reorganization in the Chronic Phase section below).

Figure 4 shows a case study of a 68-year-old man who suffered from a left temporo-parietal stroke. We were able to examine this patient repeatedly 8 times during a period of 18 months using the same language comprehension task as introduced for our group study.[43] He initially presented with a moderate to severe unfluent aphasia with almost complete recovery within the first 6 months (fig 4B). To identify specific brain regions driving language improvement over time in this patient, we correlated language performance and language activation at each examination. As a result, we got an individual recovery map, which is displayed in fig 4C. This recovery map shows that the highest correlation of language activation and language performance over time was found in left posterior temporal perilesional tissue and the left inferior frontal cortex. Hence, we postulate that such an individual recovery map reliably reflects the brain regions most relevant for functional recovery. Consequently, these areas seem to be the most suitable target candidates for brain stimulation techniques like transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) to further facilitate recovery.

Language Reorganization in the Chronic Phase

The majority of imaging studies on language recovery were performed in the chronic phase after stroke. In these studies, patients who more or less recovered from aphasia were examined once with PET or fMRI to identify the pattern of the reorganized language system in the lesioned brain. In sum, these studies with very heterogeneous designs, methods, and patients have shown that the chronically reorganized language system comprises undamaged areas in the left hemisphere,[42,46,47] perilesional tissue,[48,49] as well as homologue areas in the right hemisphere[46,47,50,51] (see[52-54] for reviews). Depending on site and size of the lesion and the residual language impairment, these areas might be more activated as compared with healthy subjects. More specific conclusions on the functional relevance of these activation patterns can be drawn by correlating the patients' proficiency in a particular language task with task-related activation. For instance, Crinion and Price[55] investigated a group of 17 patients with left temporal stroke who presented with different degrees of comprehension impairments. In their study, performance in auditory sentence comprehension was positively correlated with activation in the right lateral superior temporal gyrus. Additionally, Fridriksson et al[56] found that activation in preserved left frontal and posterior temporal areas was associated with better naming performance in 15 patients with anomia.

Together, these results indicate that chronic language recovery takes place in a preexisting bilateral temporo-frontal network in which both preserved left and homotopic right hemisphere areas might compensate for damage. However, there is little evidence for take-over of function in areas previously unrelated to language processing. This also holds true in case of large left hemisphere lesions and severe aphasia.[57] Overall, results from neuroimaging studies favor the concept of reorganization within redundant systems[58] over the concept of reorganization within vicarious systems.[59]

Based on these assumptions, it might be hypothesized that homologue right hemisphere involvement in the chronic phase after stroke depends on (1) the amount of individual premorbid language lateralization (ie, patients with a more bilateral premorbid language representation could better use homologue right areas), (2) the lateralization of the language function of interest (bilaterally organized functions like language comprehension might involve right hemisphere areas to a greater extent [see[55]] compared with left-lateralized functions, like language production or syntax [see[60]]), and (3) the site and size of the left hemisphere lesion (ie, small strategic or large cortical damage of left hemisphere language zones more likely result in a permanent involvement of right homologue areas [see[42]]).

As discussed above, language deficits might be produced not only by local dysfunction through direct effects of ischemia but also by remote dysfunction through disturbed integration of information between connected brain regions. In a recent reanalysis of previously reported PET data,[36] Warren et al[61] compared the organization of left anterior temporal cortex connectivity during speech comprehension in healthy subjects with a group of chronic aphasic patients. The authors found that those aphasic patients with preserved intertemporal connectivity displayed better receptive language function. This study is a first example demonstrating that not only local cortical function but also functional connectivity between language areas is associated with language outcome after stroke.

Imaging-Based Prediction of Language Outcome

To efficiently plan therapeutic and rehabilitation procedures, a precise outcome prediction after stroke is mandatory. Recently, 2 imaging-based methods for (early) prediction of language outcome have been suggested.[62,63]

Price et al[62] introduced a data-led system for predicting language outcome and recovery after stroke (ie, the predicting language outcome and recovery after stroke [PLORAS] system). In this approach, individual outcome prediction for each patient is preinformed by data from other patients with comparable symptoms and distribution of stroke damage who progressed in the years after their stroke. Thus, the PLORAS system relies on a database of structural magnetic resonance imaging (MRI) data, behavioral data from standardized assessments, and demographic information in a large number of stroke patients. Outcome prediction is achieved by comparing the individual lesion site on the patient's MRI with that of all other patients in the database. Accordingly, those patients in the database who are most similar to the new one in terms of their lesions and symptoms can be selected and the language scores over time for these patients are extracted. The PLORAS system thus seems a promising approach to warrant a reliable individual outcome and recovery prediction after stroke in the clinical routine.

Using a complementary approach, Saur et al[63] were the first to demonstrate that early language fMRI data contains substantial outcome-relevant information. The authors used fMRI activation acquired 2 weeks after stroke to predict individual language outcome in the chronic phase (ie, 6mo after stroke) in 21 patients with moderate or severe aphasia. In that study, language outcome was measured by assessing both the absolute and relative outcome in a dichotomic fashion (ie, measured as good vs bad outcome). Additional baseline information included age and language deficit as measured with the LRS. To predict later language outcome, a support vector machine (SVM) was used. A SVM is a multivariate pattern classification technique[64] that is trained to categorize complex high-dimensional data. More specifically, SVMs use training data to predict which of 2 possible classes a new dataset is a member of (fig 5). To account for a nonlinear relationship between fMRI activation and outcome, Saur et al[63] used a nonlinear function in their study, allowing for the possibility that within the same voxel, the same outcome could be coded by either high or low T values. For instance, a bad outcome could be coded by both high and low activation, while medium activation would then predict a good outcome.

For the absolute outcome, classification accuracy was 86% when fMRI data, age, and LRS scores were included for classification. A comparable accuracy was reached for the relative language improvement when fMRI data were restricted to a region of interest in the right frontal gyrus. Classification accuracy decreased to 62% when only age and LRS scores were included. This suggests that the use of fMRI data acquired within the second week after stroke substantially increases the accuracy of the individual outcome prediction.[63] This method has a high potential for application in the clinical routine. For instance, it seems reasonable that after training with a large sample of fMRI data, outcome of newly admitted patients can be predicted to prospectively evaluate their potential of recovery. Furthermore, a setting is conceivable in which the response to a specific treatment could be predicted: if the true responsiveness after therapy is known for some patients, SVMs could be trained with pretreatment data to extract information relevant to predict treatment outcome and apply this to new patients. Such an approach could help assigning a given therapy to those who will benefit the most.

IMAGING TREATMENT-INDUCED PLASTICITY

The results of the longitudinal fMRI study on language recovery from Saur et al[43] implicated that aphasic patients may be able to resort to normative learning mechanisms in the chronic phase after stroke. Consequently, it can be assumed that model-based therapeutic strategies may be best applied in the chronic phase.

Overall, it has been demonstrated that the efficacy of language therapy depends on treatment intensity. Various studies showed that high-intensive short-term interventions can significantly improve language functions even in the chronic phase after stroke (eg,[65-68] for a recent review on the effects of treatment intensity, please refer to[69] or http://www.asha.org/uploadedFiles/EBSR-Updated-CILT.pdf for an update). Accordingly, with therapy, late recovery has been reported up to several years after stroke.[65,70-72]

Many previous studies in chronic stroke patients revealed significant task-related activation changes from pre- to post-treatment fMRI sessions (see[73,74] for review). Even short-term treatment can lead to notable activation shifts. In 4 patients with left temporal damage, Musso et al[51] found improvement after repeated 8-minutes sessions of a language comprehension training to be correlated with activity increases in the right temporal cortex. In another study, Blasi et al[75] demonstrated increased activity in the right frontal cortex associated with learning a word retrieval task using word stem completion in 8 patients with left frontal damage. These results were interpreted to further support the notion of a compensatory role of the right hemisphere in recovery after brain damage. On the other hand, results from studies performing long-term training either showed left hemisphere,[39,76-78] right hemisphere,[79,80] or bilateral activation increases[81-84] associated with treatment-induced improvement.

In contrast to the above mentioned studies, Szaflarski et al[85] investigated recovery processes over a longer time period (ie 10wk). Using a picture identification task in weekly repeated fMRI sessions in 4 chronic aphasic patients and 4 healthy control subjects, the authors also found that left-hemisphere peristroke areas rather than right hemisphere homologues are important for language recovery after stroke. Conversely, Richter et al[86] found no significant changes of fMRI activation after 2 weeks of constraint-induced aphasia therapy.

This heterogeneity of results may be best explained by differences in treatment strategy, language impairment, as well as lesion site and size. In analogy to spontaneous reorganization, Grafman[87] argued that homologous right-hemisphere brain upregulation is most likely when left-hemisphere lesions completely destroy cortical regions that serve a particular function.

It should also be noted that most of the fMRI studies on treatment-induced aphasia recovery included small sample

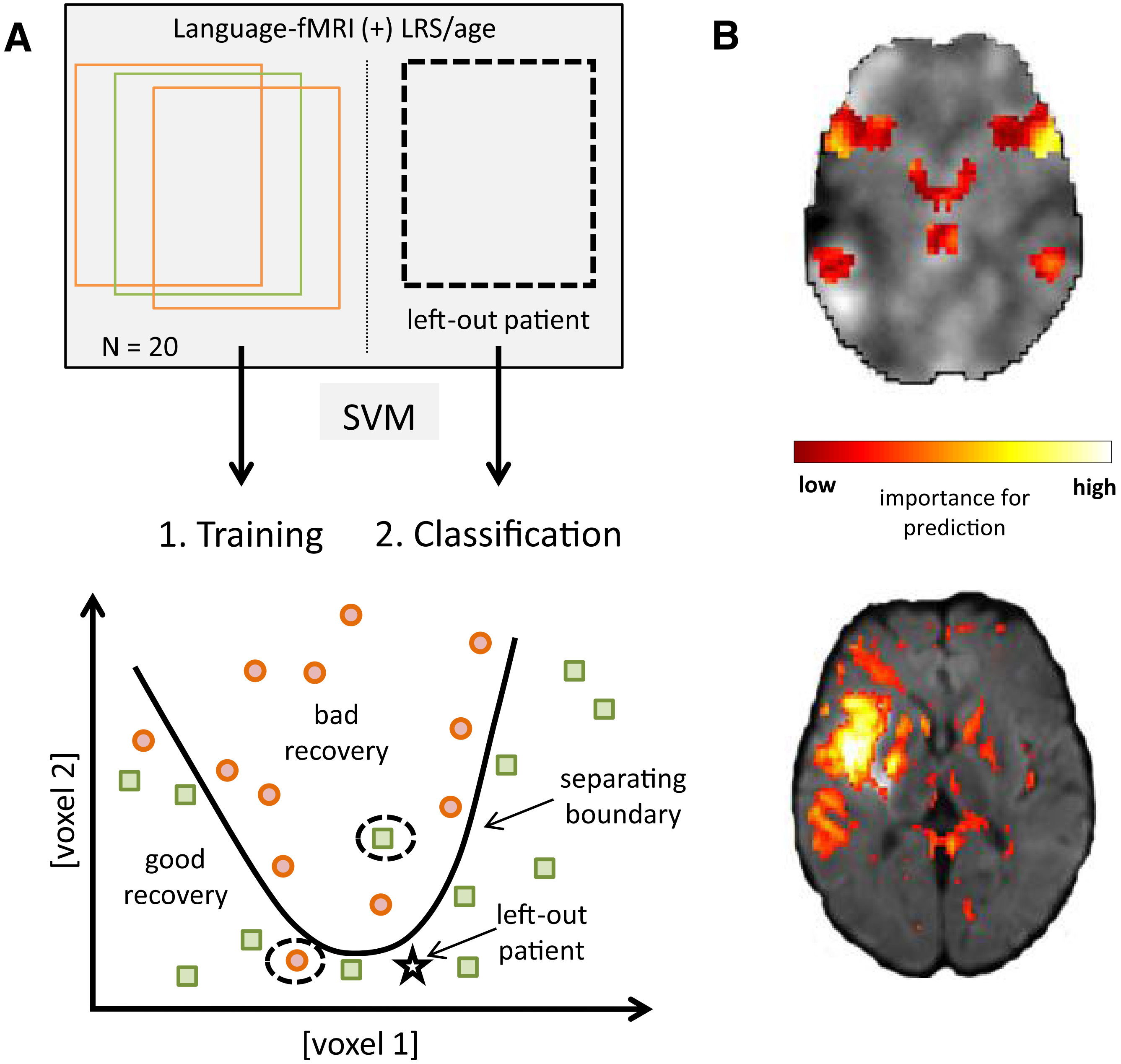

Fig 5. Outcome prediction based on early fMRI data. (A) Concept of data analysis with a SVM: a separating function is calculated from all but 1 dataset. The separating function divides patients with bad (orange circles) from those with good outcome (green squares). Dotted circles indicate 2 cases that are placed on the wrong side of the separating function during training. The star represents the left out patient who is classified by the separating function. (B) Visualization of voxels most relevant for correct classification in a correctly classified subject. The upper panel shows an fMRI parameter image (speech vs reversed speech) with voxels in the right IFG being most relevant for correct classification. The lower panel displays a DWI scan with most-relevant voxels for correct classification located within the ischemia. Modified from Saur.[100] Reprinted with permission. © 2010, Springer, Germany.

sizes, typically less than 10 patients. This may further contribute to the partly contradictory findings on left- versus right-hemisphere language activation during recovery after stroke. Furthermore, various neuroimaging studies reported that cortical language functions are not dichotomously distributed in healthy subjects, but rather represent a continuum between left- and right-hemispheric language distributions[88] thus allowing for the compensation of unilateral brain lesions in some patients (see also the Language Reorganization in the Chronic Phase section).

To summarize, the majority of studies indicate that remodeling of cortical functions is possible even years after stroke and typically targets contralateral homologue regions as well as perilesional language areas. Thus, therapy-induced reorganization occurs in the same preexisting bilateral temporo-frontal network identified for spontaneous recovery. Here, future neuroimaging studies should include longitudinal investigations of larger collectives to shed more light on treatment-induced activation changes in language networks.

While the relationship between task and functional activation, as revealed by fMRI, is correlative in nature, the neurodisruptive effect of stimulation techniques like TMS reflects a causal effect on brain activity. Hence, results from neuroimaging studies have been complemented by recent studies applying TMS to test if the stimulated cortex makes a critical contribution to the brain functions subserving a specific (language) task. In some of these investigations, improved language recovery in aphasic patients was shown after suppression of neuronal processing in the nonlesioned right-hemisphere homologue area.[89-93] The behavioral improvement after suppression of neuronal processing in the right hemisphere has been interpreted as a suppression of maladaptive overactivation, which in turn may have allowed for a better modulation in the remaining left-hemisphere networks.[90] In contrast, other studies found a deterioration in task performance after both left- or right-hemisphere TMS in some patients with brain lesions of the left hemisphere[94,95] or in healthy subjects.[96,97] In a somehow complementary approach, another recent study aimed to increase cortical excitability in perilesional areas by means of transcranial direct current stimulation (tDCS) in 10 chronic stroke patients with aphasia.[98] That study applied effective or sham (control) anodal tDCS for 5 consecutive days over left-hemisphere perilesional areas in the frontal cortex. The authors found a (slight) significant improvement in picture naming abilities for effective relative to sham stimulation that persisted for up to 1 week. These results were taken to provide evidence for a benefical effect of tDCS in aphasia treatment. However, the number of studies applying stimulation techniques to enhance plasticity in language networks is currently very limited and the results remain equivocal. Thus, these results should be interpreted with caution.

FUTURE DIRECTIONS

Within the last years, the use of functional imaging techniques has substantially increased our knowledge about brain organization, loss of functions after brain damage, and reorganizational processes. It should be noted, however, that the results from functional imaging studies are correlative in nature and do not allow for any causal conclusions. Thus, the use of a multimodal approach combining different methods, such as functional and/or structural imaging with transcranial stimulation techniques, seems promising. A multimodal approach allows for the identification of brain areas being involved in specific language functions and enables the researcher to test whether this activation is of functional significance for specific language functions in healthy subjects and patients with brain lesions. Here, it might be worthwhile to apply different stimulation protocols during different phases of reorganization after stroke to advance the current knowledge about critical areas for specific language functions across the time course of reorganization. These results should be further complemented by information about the integrity of the underlying white matter tracts obtained from structural measures like diffusion tensor imaging (eg, Schlaug et al[99]). In sum, such a multimodal approach will further add to our understanding of loss and recovery of language functions on a systems level and might fuel the development of novel, neurophysiologically based treatment strategies.

References

1. Smits M, Visch-Brink EG, van de Sandt-Koenderman, MW, van der Lugt, A. Advanced magnetic resonance neuroimaging of language function recovery after aphasic stroke: a technical review. Arch Phys Med Rehabil 2012;93:S4-14.
2. Broca P. Remarks on the seat of the faculty of articulated language, following an observation of aphemia (loss of speech). [French] Bulletin de la Societé Anatomique de Paris 1861;6:330-57.
3. Wernicke C. The Aphasic Symptom-Complex. [German] Breslau: Cohn and Weigert; 1874.
4. Shalom DB, Poeppel D. Functional anatomic models of language: assembling the pieces. Neuroscientist 2008;14:119-27.
5. Milner AD, Goodale MA. The visual brain in action. New York: Oxford Univ Pr; 1995.
6. Hickok G, Poeppel D. Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. Cognition 2004;92:67-99.
7. Hickok G, Poeppel D. The cortical organization of speech processing. Nature Rev Neurosci 2007;8:393-402.
8. Hickok G, Poeppel D. Towards a functional neuroanatomy of speech perception. Trends Cogn Sci 2000;4:131-8.
9. Scott SK, Blank CC, Rosen S, Wise RJ. Identification of a pathway for intelligible speech in the left temporal lobe. Brain 2000;123 Pt 12:2400-6.
10. Crinion JT, Lambon-Ralph MA, Warburton EA, Howard D, Wise RJ. Temporal lobe regions engaged during normal speech comprehension. Brain 2003;126:1193-201.
11. Scott SK, Johnsrude IS. The neuroanatomical and functional organization of speech perception. Trends Neurosci 2003;26: 100-7.
12. Buchsbaum BR, Olsen RK, Koch P, Berman KF. Human dorsal and ventral auditory streams subserve rehearsal-based and echoic processes during verbal working memory. Neuron 2005;48:687-97.
13. Warren JE, Wise RJ, Warren JD. Sounds do-able: auditory-motor transformations and the posterior temporal plane. Trends Neurosci 2005;28:636-43.
14. Saur D, Kreher BW, Schnell S, et al. Ventral and dorsal pathways for language. Proc Natl Acad Sci U S A 2008;105: 18035-40.
15. Friederici AD. Pathways to language: fiber tracts in the human brain. Trends Cogn Sci 2009;13:175-81.
16. Frey S, Campbell JS, Pike GB, Petrides M. Dissociating the human language pathways with high angular resolution diffusion fiber tractography. J Neurosci 2008;28:11435-44.
17. Saur D, Kellmeyer P, Weiller C. Reply to Yamada: the extreme capsule is the ventral pathway for language. Proc Natl Acad Sci U S A 2009;106:E15.
18. Weiller C, Musso M, Rijntjes M, Saur D. Please don't underestimate the ventral pathway in language. Trends Cogn Sci 2009; 13:369-70; 70-1.
19. Catani M, Jones DK, Ffytche DH. Perisylvian language networks of the human brain. Ann Neurol 2005;57:8-16.
20. Geschwind N. Disconnetion syndromes in animals and man. Brain 1965;88:237-94.
21. Price CJ. The anatomy of language: contributions from functional neuroimaging. J Anat 2000;197 Pt 3:335-59.
22. Rorden C, Karnath HO. Using human brain lesions to infer function: a relic from a past era in the fMRI age? Nat Rev Neurosci 2004;5:813-9.
23. Bates E, Wilson SM, Saygin AP, Dick F, Sereno MI, Knight RT et al. Voxel-based lesion-symptom mapping. Nat Neurosci 2003; 6:448-50.
24. Rorden C, Fridriksson J, Karnath HO. An evaluation of traditional and novel tools for lesion behavior mapping. Neuroimage 2009;44:1355-62.
25. Dronkers NF, Wilkins DP, Van Valin RD Jr, Redfern BB, Jaeger JJ. Lesion analysis of the brain areas involved in language comprehension. Cognition 2004;92:145-77.

26. Baldo JV, Bunge SA, Wilson SM, Dronkers NF. Is relational reasoning dependent on language? A voxel-based lesion symptom mapping study. Brain Lang 2010;113:59-64.
27. Piras F, Marangolo P. Noun-verb naming in aphasia: a voxel-based lesion-symptom mapping study. Neuroreport 2007;18:1455-8.
28. Fridriksson J, Kjartansson O, Morgan PS, et al. Impaired speech repetition and left parietal lobe damage. J Neurosci 2010;30:11057-61.
29. Leff AP, Schofield TM, Crinion JT, et al. The left superior temporal gyrus is a shared substrate for auditory short-term memory and speech comprehension: evidence from 210 patients with stroke. Brain 2009;132:3401-10.
30. Walker GM, Schwartz MF, Kimberg DY, et al. Support for anterior temporal involvement in semantic error production in aphasia: new evidence from VLSM. Brain Lang 2011;117:110-22.
31. Mimura M, Kato M, Sano Y, Kojima T, Naeser M, Kashima H. Prospective and retrospective studies of recovery in aphasia. Changes in cerebral blood flow and language functions. Brain 1998;121:2083-94.
32. Hillis AE, Kane A, Tuffiash E, et al. Reperfusion of specific brain regions by raising blood pressure restores selective language functions in subacute stroke. Brain Lang 2001;79:495-510.
33. Reineck LA, Agarwal S, Hillis AE. ”Diffusion-clinical mismatch” is associated with potential for early recovery of aphasia. Neurology 2005;64:828-33.
34. Hillis AE. Magnetic resonance perfusion imaging in the study of language. Brain Lang 2007;102:165-75.
35. Baldo JV, Wilkins DP, Ogar J, Willock S, Dronkers NF. Role of the precentral gyrus of the insula in complex articulation. Cortex 2011;47:800-7.
36. Crinion JT, Warburton EA, Lambon-Ralph MA, Howard D, Wise RJ. Listening to narrative speech after aphasic stroke: the role of the left anterior temporal lobe. Cereb Cortex 2006;16:1116-25.
37. Pedersen PM, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Aphasia in acute stroke: incidence, determinants, and recovery. Ann Neurol 1995;38:659-66.
38. Fernandez B, Cardebat D, Demonet JF, et al. Functional MRI follow-up study of language processes in healthy subjects and during recovery in a case of aphasia. Stroke 2004;35:2171-6.
39. Léger A, Démonet JF, Ruff S, et al. Neural substrates of spoken language rehabilitation in an aphasic patient: an fMRI study. Neuroimage 2002;17:174-83.
40. Cardebat D, Démonet JF, De Boissezon X, et al. Behavioral and neurofunctional changes over time in healthy and aphasic subjects: a PET Language Activation Study. Stroke 2003;34:2900-6.
41. de Boissezon X, Démonet JF, Puel M, et al. Subcortical aphasia: a longitudinal PET study. Stroke 2005;36:1467-73.
42. Heiss WD, Kessler J, Thiel A, Ghaemi M, Karbe H. Differential capacity of left and right hemispheric areas for compensation of poststroke aphasia. Ann Neurol 1999;45:430-8.
43. Saur D, Lange R, Baumgaertner A, et al. Dynamics of language reorganization after stroke. Brain 2006;129:1371-84.
44. Price CJ, Warburton EA, Moore CJ, Frackowiak RS, Friston KJ. Dynamic diaschisis: anatomically remote and context-sensitive human brain lesions. J Cogn Neurosci 2001;13:419-29.
45. Dijkhuizen RM, Singhal AB, Mandeville JB, et al. Correlation between brain reorganization, ischemic damage, and neurologic status after transient focal cerebral ischemia in rats: a functional magnetic resonance imaging study. J Neurosci 2003;23:510-7.
46. Cao Y, Vikingstad EM, George KP, Johnson AF, Welch KM. Cortical language activation in stroke patients recovering from aphasia with functional MRI. Stroke 1999;30:2331-40.
47. Weiller C, Isensee C, Rijntjes M, et al. Recovery from Wernicke’s aphasia: a positron emission tomographic study. Ann Neurol 1995;37:723-32.
48. Rosen HJ, Petersen SE, Linenweber MR, et al. Neural correlates of recovery from aphasia after damage to left inferior frontal cortex. Neurology 2000;55:1883-94.
49. Warburton E, Price CJ, Swinburn K, Wise RJ. Mechanisms of recovery from aphasia: evidence from positron emission tomography studies. J Neurol Neurosurg Psychiatry 1999;66:155-61.
50. Leff A, Crinion J, Scott S, Turkheimer F, Howard D, Wise R. A physiological change in the homotopic cortex following left posterior temporal lobe infarction. Ann Neurol 2002;51:553-8.
51. Musso M, Weiller C, Kiebel S, Muller SP, Bulau P, Rijntjes M. Training-induced brain plasticity in aphasia. Brain 1999;122:1781-90.
52. Crinion JT, Leff AP. Recovery and treatment of aphasia after stroke: functional imaging studies. Curr Opin Neurol 2007;20:667-73.
53. Crosson B, McGregor K, Gopinath KS, et al. Functional MRI of language in aphasia: a review of the literature and the methodological challenges. Neuropsychol Rev 2007;17:157-77.
54. Zahn R, Schwarz M, Huber W. Functional activation studies of word processing in the recovery from aphasia. J Physiol Paris 2006;99:370-85.
55. Crinion J, Price CJ. Right anterior superior temporal activation predicts auditory sentence comprehension following aphasic stroke. Brain 2005;128:2858-71.
56. Fridriksson J, Bonilha L, Baker JM, Moser D, Rorden C. Activity in Preserved Left Hemisphere Regions Predicts Anomia Severity in Aphasia. Cereb Cortex 2010;20:1013-9
57. Zahn R, Drews E, Specht K, et al. Recovery of semantic word processing in global aphasia: a functional MRI study. Brain Res Cogn Brain Res 2004;18:322-36.
58. Price CJ, Friston KJ. Degeneracy and cognitive anatomy. Trends Cogn Sci 2002;6:416-21.
59. Marshall JF. Brain function: neural adaptations and recovery from injury. Annu Rev Psychol 1984;35:277-308.
60. Tyler LK, Wright P, Randall B, Marslen-Wilson WD, Stamatakis EA. Reorganization of syntactic processing following left-hemisphere brain damage: does right-hemisphere activity preserve function? Brain 2011;133:3396-408.
61. Warren JE, Crinion JT, Lambon Ralph MA, Wise RJ. Anterior temporal lobe connectivity correlates with functional outcome after aphasic stroke. Brain 2009;132:3428-42.
62. Price CJ, Seghier ML, Leff AP. Predicting language outcome and recovery after stroke: the PLORAS system. Nat Rev Neurol 2010;6(4):202-10.
63. Saur D, Ronneberger O, Kummerer D, Mader I, Weiller C, Klöppel S. Early functional magnetic resonance imaging activations predict language outcome after stroke. Brain 2010;133:1252-64.
64. Vapnik V. Statistical learning theory. New York: Wiley Interscience; 1998.
65. Pulvermüller F, Neininger B, Elbert T, et al. Constraint-induced therapy of chronic aphasia after stroke. Stroke 2001;32:1621-6.
66. Barthel G, Meinzer M, Djundja D, Rockstroh B. Intensive language therapy in chronic aphasia: which aspects contribute most? Aphasiology 2008;22:408-21.
67. Meinzer M, Elbert T, Wienbruch C, Djundja D, Barthel G, Rockstroh B. Intensive language training enhances brain plasticity in chronic aphasia. BMC Biol 2004;2:20.
68. Meinzer M, Djundja D, Barthel G, Elbert T, Rockstroh B. Long-term stability of improved language functions in chronic aphasia after constraint-induced aphasia therapy. Stroke 2005;36:1462-6.

69. 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. J Speech Lang Hear Res 2008;51: 1282-99.
70. Carlomagno S, Pandolfi M, Labruna L, Colombo A, Razzano C. Recovery from moderate aphasia in the first year poststroke: effect of type of therapy. Arch Phys Med Rehabil 2001;82:1073-80.
71. Poeck K, Huber W, Willmes K. Outcome of intensive language treatment in aphasia. J Speech Hear Disord 1989;54:471-9.
72. Szaflarski JP, Ball A, Grether S, et al. Constraint-induced aphasia therapy stimulates language recovery in patients with chronic aphasia after ischemic stroke. Med Sci Monit 2008; 14:CR243-50.
73. Meinzer M, Breitenstein C. Functional imaging studies of treatment-induced recovery in chronic aphasia. Aphasiology 2008; 22:1251-68.
74. Thompson CK, den Ouden DB. Neuroimaging and recovery of language in aphasia. Curr Neurol Neurosci Rep 2008;8:475-83.
75. Blasi V, Young AC, Tansy AP, Petersen SE, Snyder AZ, Corbetta M. Word retrieval learning modulates right frontal cortex in patients with left frontal damage. Neuron 2002;36:159-70.
76. Cornelissen K, Laine M, Tarkiainen A, Jarvensivu T, Martin N, Salmelin R. Adult brain plasticity elicited by anomia treatment. J Cogn Neurosci 2003;15:444-61.
77. 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;39:2038-46.
78. Vitali P, Abutalebi J, Tettamanti M, et al. Training-induced brain remapping in chronic aphasia: a pilot study. Neurorehabil Neural Repair 2007;21:152-60.
79. Crosson B, Moore AB, Gopinath K, et al. Role of the right and left hemispheres in recovery of function during treatment of intention in aphasia. J Cogn Neurosci 2005;17:392-406.
80. Raboyeau G, De Boissezon X, Marie N, et al. Right hemisphere activation in recovery from aphasia: lesion effect or function recruitment? Neurology 2008;70:290-8.
81. Fridriksson J, Morrow-Odom L, Moser D, Fridriksson A, Baylis G. Neural recruitment associated with anomia treatment in aphasia. Neuroimage 2006;32:1403-12.
82. Fridriksson J, Moser D, Bonilha L, et al. Neural correlates of phonological and semantic-based anomia treatment in aphasia. Neuropsychologia 2007;45:1812-22.
83. Meinzer M, Obleser J, Flaisch T, Eulitz C, Rockstroh B. Recovery from aphasia as a function of language therapy in an early bilingual patient demonstrated by fMRI. Neuropsychologia 2007;45:1247-56.
84. Menke R, Meinzer M, Kugel H, et al. Imaging short- and long-term training success in chronic aphasia. BMC Neurosci 2009;10:118.
85. Szaflarski JP, Eaton K, Ball AL, et al. Poststroke aphasia recovery assessed with functional magnetic resonance imaging and a picture identification task. J Stroke Cerebrovasc Dis 2011;20: 336-45.
86. Richter M, Miltner WH, Straube T. Association between therapy outcome and right-hemispheric activation in chronic aphasia. Brain 2008;131:1391-401.
87. Grafman J. Conceptualizing functional neuroplasticity. J Commun Disord 2000;33:345-55; quiz 55-6.
88. Knecht S, Flöel A, Dräger B, et al. Degree of language lateralization determines susceptibility to unilateral brain lesions. Nat Neurosci 2002;5:695-9.
89. Naeser MA, Martin PI, Nicholas M, et al. Improved naming after TMS treatments in a chronic, global aphasia patient–case report. Neurocase 2005;11:182-93.
90. Naeser MA, Martin PI, Nicholas M, et al. Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study. Brain Lang 2005;93:95-105.
91. Naeser MA, Martin PI, Lundgren K, et al. Improved language in a chronic nonfluent aphasia patient after treatment with CPAP and TMS. Cogn Behav Neurol 2010;23:29-38.
92. Hamilton RH, Sanders L, Benson J, et al. Stimulating conversation: enhancement of elicited propositional speech in a patient with chronic non-fluent aphasia following transcranial magnetic stimulation. Brain Lang 2010;113:45-50.
93. Martin PI, Naeser MA, Ho M, et al. Overt naming fMRI pre- and post-TMS: two nonfluent aphasia patients, with and without improved naming post-TMS. Brain Lang 2009;111:20-35.
94. Thiel A, Habedank B, Herholz K, et al. From the left to the right: How the brain compensates progressive loss of language function. Brain Lang 2006;98:57-65.
95. Winhuisen L, Thiel A, Schumacher B, et al. Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: a combined repetitive transcranial magnetic stimulation and positron emission tomography study. Stroke 2005;36:1759-63.
96. Hartwigsen G, Baumgaertner A, Price CJ, Koehnke M, Ulmer S, Siebner HR. Phonological decisions require both the left and right supramarginal gyri. Proc Natl Acad Sci U S A 2010;107: 16494-9.
97. Hartwigsen G, Price CJ, Baumgaertner A, et al. The right posterior inferior frontal gyrus contributes to phonological word decisions in the healthy brain: evidence from dual-site TMS. Neuropsychologia 2010;48:3155-63.
98. Baker JM, Rorden C, Fridriksson J. Using transcranial direct-current stimulation to treat stroke patients with aphasia. Stroke 2010;41:1229-36.
99. 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. Ann N Y Acad Sci 2009;1169:385-94.
100. Saur D. [Imaging aphasia] [German] Nervenarzt 2010;81: 1429-37.