NeuroImage 190 (2019) 14–31

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Neuroimaging of stroke recovery from aphasia – Insights into plasticity of the human language network

Gesa Hartwigsen [a,*], Dorothee Saur [b,**]

[a] Research Group Modulation of Language Networks, Department of Neuropsychology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[b] Language & Aphasia Laboratory, Department of Neurology, University of Leipzig, Germany

ARTICLE INFO

Keywords:
Reorganization
Speech
Functional magnetic resonance imaging (fMRI)
Non-invasive brain stimulation
Broca
Plasticity

ABSTRACT

The role of left and right hemisphere brain regions in language recovery after stroke-induced aphasia remains controversial. Here, we summarize how neuroimaging studies increase the current understanding of functional interactions, reorganization and plasticity in the language network. We first discuss the temporal dynamics across the time course of language recovery, with a main focus on longitudinal studies from the acute to the chronic phase after stroke. These studies show that the functional contribution of perilesional and spared left hemisphere as well as contralesional right hemisphere regions to language recovery changes over time. The second section introduces critical variables and recent advances on early prediction of subsequent outcome. In the third section, we outline how multi-method approaches that combine neuroimaging techniques with non-invasive brain stimulation elucidate mechanisms of plasticity and reorganization in the language network. These approaches provide novel insights into general mechanisms of plasticity in the language network and might ultimately support recovery processes during speech and language therapy. Finally, the neurobiological correlates of therapy-induced plasticity are discussed. We argue that future studies should integrate individualized approaches that might vary the combination of language therapy with specific non-invasive brain stimulation protocols across the time course of recovery. The way forward will include the combination of such approaches with large data sets obtained from multicentre studies.

Introduction

Language is a key faculty for human communication. Results from a large body of neuroimaging studies have essentially contributed to our understanding of language organization in left-lateralized large-scale networks of closely connected and interacting brain areas in the temporal, frontal and parietal lobe. This also includes areas beyond the "classical" frontal and temporal language regions. This network organization allows the brain to dynamically compensate focal brain lesions such as stroke. In this review, we discuss how neuroimaging studies in patients with post-stroke aphasia have advanced the current knowledge on neuroplasticity in the language network. These studies complement language studies in the healthy brain and might help to refine existing models of language organization and reorganization. We first focus on the neural mechanisms underlying reorganization in the language network after stroke. Here, neuroimaging can be used to unravel the neurobiological bases of behavioural improvement by mapping large-scale changes in neural activity as well as functional and structural connectivity. As discussed in the second section, a better understanding of these processes is highly relevant for a valid neuroimaging based outcome prediction to efficiently plan therapeutic and rehabilitation procedures. The third section discusses how a multi-method combination of functional neuroimaging and non-invasive brain stimulation in the healthy and lesioned brain can be used to advance the current knowledge of adaptive plasticity and long-range effects of interventions in the language network. The final section shows how neuroimaging can map treatment-induced plasticity on the network level by combining different interventions like speech and language therapy, non-invasive brain stimulation and pharmacological treatment with neuroimaging.

Mapping reorganization in the language network after stroke with neuroimaging

Because stroke hits a previously more or less intact system suddenly and focally, it represents a suitable model disease to study the brain's

* Corresponding author. Research Group Modulation of Language Networks, Department of Neuropsychology, MPI for Human Cognitive and Brain Sciences, Stephanstr. 1a, D-04103 Leipzig, Germany.
** Corresponding author. Language & Aphasia Laboratory, Department of Neurology, University of Leipzig, Liebigstraße 20, D-04103 Leipzig, Germany.
E-mail addresses: hartwigsen@cbs.mpg.de (G. Hartwigsen), dorothee.saur@medizin.uni-leipzig.de (D. Saur).

https://doi.org/10.1016/j.neuroimage.2017.11.056
Received 15 August 2017; Received in revised form 2 November 2017; Accepted 22 November 2017
Available online 23 November 2017
1053-8119/

response to focal injury (Carter et al., 2012). To understand loss and recovery of function, the organization of language in large-scale networks is integral. Current models suggest that language functions result from functional interactions of distant temporal, frontal and parietal brain regions within a left-lateralized network which is organized along two processing systems: (i) mapping from sound to meaning is subserved by a bilateral ventral stream connecting middle temporal lobe and ventrolateral prefrontal cortex through the middle longitudinal fascicle and the extreme capsule and (ii) mapping from sound to articulation is implemented in a left lateralized dorsal stream connecting superior temporal lobe and premotor cortex (Friederici, 2012; Hickok and Poeppel, 2007; Rauschecker and Scott, 2009; Saur et al., 2008; Wise, 2003). This domain specific network for language has been suggested to interact with bilateral domain-general networks involved in cognitive control and attention to optimize performance (Brownsett et al., 2014; Davis and Cabeza, 2015). Based on this extended network perspective and given the degeneracy of neural circuits (Price and Friston, 2002), aphasia can be considered a network disorder and language reorganization shares processes within domain-specific and domain-general networks (Corbetta et al., 2015; Fridriksson et al., 2016; Geranmayeh et al., 2014; Kummerer et al., 2013; Siegel et al., 2016; Ueno et al., 2011). In the following, we provide an overview on how neuroimaging contributes to the understanding of major mechanisms of brain reorganization in stroke patients with aphasia. Beyond this neurobiological insight, we believe that a profound understanding of the neural mechanisms underlying recovery from aphasia is mandatory for developing novel strategies for efficient treatment of post-stroke aphasia.

Early network disruption and recovery in acute and subacute stroke

In the context of this review, we will distinguish a hyperacute (up to 24 h), acute (up to one week), subacute (around one week to 6 months) and chronic phase (starting around 6 months) post onset. These phases are paralleled by the clinical observation that the highest functional dynamic of language recovery occurs in the first days to weeks after stroke (i.e. within the (hyper-)acute and early subacute phase). In some patients deficits persist or gradually improve over a longer period of time and eventually plateau after several months resulting in chronic aphasia (Dunn et al., 2016; Pedersen et al., 1995). This dynamic of behavioural improvement suggests that different neural mechanisms support the functional improvement of language after stroke.

Network disruption in the **(hyper-)acute phase** causing acute aphasia is the consequence of both, critical hypoperfusion (penumbra) mapped with perfusion imaging (PI) and parenchymal damage as identified by diffusion-weighted imaging (DWI) of language relevant brain regions (e.g. Fridriksson et al., 2010b; Hillis et al., 2001; Shahid et al., 2017). An important mechanism that contributes to often sudden and impressive improvements in the (hyper-) acute phase is the reperfusion of the ischemic penumbra, i.e. brain tissue that was critically hypoperfused on PI but not infarcted on DWI, regains its functionality through timely reperfusion (Hillis et al., 2006).

Functional magnetic resonance imaging (fMRI) represents an ideal tool to map the changing patterns of language activation in response to the ischemic lesion on a whole brain systems level. Regarding the dynamic evolution of language activation over time, to date, the study by Saur et al. (2006) still represents the only fMRI study investigating the mechanisms of language recovery longitudinally from acute to chronic stroke. This allowed for the description of a comprehensive pattern of changing group activation over time with reduced activation in the acute phase, bilaterally increased activation in the early subacute phase with peak activation in right frontal cortex and subsequently normalized activation in the chronic phase. Reduced activation in the **(hyper-) acute phase** thereby was interpreted in terms of a global network disruption. Damage to critical nodes of the network and/or their connections might lead not only to local dysfunction of the lesioned brain area but also of intact remote, functionally and/or anatomically connected brain regions. This phenomenon of pathophysiological changes distant to a focal brain lesion is termed diaschisis (Monakow, 1906; for a recent review: Carrera and Tononi, 2014). In a large voxel-based lesion-symptom mapping (VLSM) study on acute stroke patients with aphasia, Kummerer et al. (2013) showed that structural damage to ventral and dorsal white matter fibre tracts connecting language areas in the frontal and temporal lobe critically contributes to the acute deficit in terms of structural disconnection. Disconnection as a domain-independent mechanism of functional loss in acute stroke patients was also demonstrated in a recent study by Corbetta et al. (2015). Complementary, Fig. 1A illustrates the widespread *functional* connectivity of the focal lesion in two exemplary patients with frontal and temporoparietal strokes. This demonstrates the functional dependency of remote brain areas from the lesion site as basis for dysfunction of remote areas caused by functional disconnection (Carter et al., 2012; Carrera and Tononi, 2014). In the **subacute phase**, upregulation predominantly in bilateral frontal brain regions might be attributable (i) to the resolution of diaschisis, i.e. preserved parts of the network regain their function (Saur et al., 2006) and (ii) to compensation through extensive recruitment of domain-general frontal networks (Brownsett et al., 2014; Geranmayeh et al., 2014). The exact timing of the resolution of diaschisis, however, must be assumed individually highly different and may range from hours to few days post stroke.

One particular shortcoming of the Saur et al. (2006) study was that the observed pattern of (mean group) activation could not be attributed to the lesion site due to the highly heterogeneous lesion distribution covering all parts of the left middle cerebral artery territory. Fig. 1B displays the longitudinal fMRI language activation of the two exemplary cases with either a left frontal or temporoparietal stroke (Stockert et al., unpublished data). This allows for an exact attribution of changing brain activation to local perilesional tissue as well as remote left and homologous right brain areas. Based on these single cases, the following hypothesis might be put forward: (1) early network disruption with consecutively reduced activation as consequence of diaschisis depends on the lesion site and seems to be more pronounced in temporal lesions while in case of frontal lesions, homotopic and probably bilateral domain-general activation can be observed from early on; (2) lesion-homologue recruitment represents a phenomenon predominantly observed in frontal lesions; (3) perilesional activation increases over time and continues during the chronic phase. These hypotheses need to be confirmed in group analyses of cohorts of patients with isolated infarctions in left frontal and temporoparietal location.

Complementary to task-based fMRI, task-free resting-state fMRI (rsfMRI) represents a promising tool to investigate mechanisms of post-stroke loss and recovery of brain functions based on functional connectivity (FC). In particular in patients with acute aphasia, rsfMRI is advantageous because it is easy to complete even for patients with severe aphasia. In addition, functional networks supporting different cognitive domains can be measured simultaneously across a broad range of impairments with one single rsfMRI acquisition (Carter et al., 2012). This might be of particular interest to disentangle the influence of domain-general and domain-specific deficits on recovery.

The study by Siegel et al. (2016) is the first large-scale rsfMRI study which examined a remarkable population of 132 stroke patients (33 presenting with aphasia) once in the second week (i.e. in the subacute phase) post stroke. They were able to demonstrate a “network phenotype of stroke injury” that explains the general effects of stroke. In comparison to healthy controls, this domain-independent phenotype consisted of (i) decreased interhemispheric lesion-homotopic FC which also best predicted the behavioural deficit, (ii) unchanged ipsi- and contralesional *within* network FC and (iii) increased ipsilesional FC *between* networks that are normally segregated (i.e., the default-mode network and dorsal-attention network).

With respect to language, some distinct features distinguish language from the other domains. First, language represented the only domain, where lesion topography and FC both predicted behavioural variance to a similar degree. Second, unlike other domains, language deficit showed

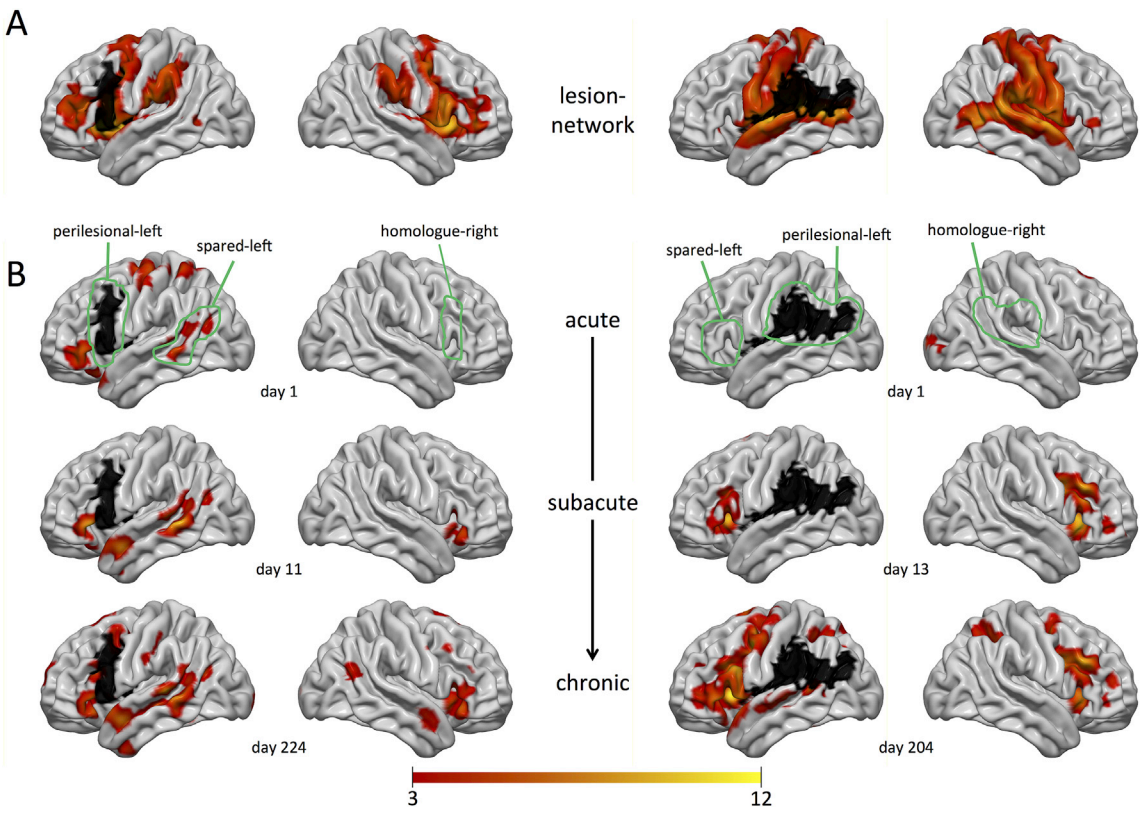

Fig. 1. Two single case studies of patients with acute aphasia caused by either a left frontal (left column) or left temporoparietal (right column) infarction. The lesion is displayed in black. In panel A, the lesion-network calculated from a normative resting state fMRI dataset (n = 100) with the lesion as seed region is displayed showing remote regions with high functional connectivity to the lesion. In panel B, longitudinal task-based (speech compared to reversed speech) fMRI activation is displayed in the acute, subacute and chronic phase post stroke. Green circles indicate domain-specific compartments of interest for language recovery. fMRI activations (t-values) are displayed with a statistical threshold of $p < 0.001$, uncorrected for multiple comparisons.

substantial dependence not only on decreased homotopic inter- but also on decreased left-hemispheric intrahemispheric FC. These findings support the notion that aphasia relies on damage to highly localized brain regions as well as disturbance of bilaterally distributed brain networks (Siegel et al., 2016). Particularly, evidence on the relationship between disturbed interhemispheric FC and aphasia severity, which is in agreement with another study in patients with subacute aphasic stroke (Zhu et al., 2014), is of interest. This relationship displays a specific topology, as it was predominantly present between temporoparietal but rarely between frontal regions. This observation might be interpreted in light of the dual stream model of language processing (see above), which proposes a more bilateral organization for ventral stream regions within the temporal lobes. On the other hand, task-based fMRI activations in right hemisphere regions of patients with aphasia mainly revealed frontal regions (Saur et al., 2006; Turkeltaub et al., 2011). Therefore the interpretation of disturbed homotopic connectivity in the language network after stroke remains unclear – as opposed to the motor system, where post-stroke hemispheric imbalance with transcallosal inhibition of the ipsi-through the contralesional hemisphere is regarded a key concept (Grefkes and Fink, 2014).

In sum, there is good evidence that, in addition to the direct effects of the ischemic lesion, early network disruption is caused by functional and anatomical disconnection resulting in hypoactivation of spared language areas in the left and right hemisphere and decrease of intra- and interhemispheric functional connectivity. There is also good support for the view that early improvement results either from reperfusion of critically hypoperfused but not yet infarcted tissue and resolution of diaschisis resulting in re- and even hyperactivation of bilateral spared brain areas. Future studies should aim at clarifying the influence of the lesion site on these mechanisms, the role of early recruitment of lesion-homologue brain areas and to better disentangle the contribution of domain-specific and domain-general networks for early recovery.

Network reorganization in chronic stroke

In the chronic phase post stroke, the early mechanisms of network disruption and resolution of network failure are completed and mechanisms of intrinsic network reorganization that allow spared components of the network to assume function of the damaged components dominate this phase (Jarso et al., 2013).

The domain of voxel-based symptom-lesion mapping (VLSM) in chronic stroke is to identify sets of brain regions that are critical for a particular function (Rorden and Karnath, 2004), or pointed differently, to explain the chronic impairment based on the observed brain damage. A large body of studies on patients with chronic aphasia correlated either aphasic symptoms (e.g. Pillay et al., 2017; Shahid et al., 2017), syndromes (e.g. Fridriksson et al., 2015b; Henseler et al., 2014) or even clusters of behavioural scores (e.g. Butler et al., 2014; Fridriksson et al., 2016) with the cortical necrosis delineated on structural MRI. Results of these and other studies essentially contribute to our current knowledge on the functional neuroanatomy of language. It is important though to point out that VLSM performed in the chronic stage of stroke is confounded by extensive reorganization (see below) which might have blurred structure-function relationship, leading to possible underestimation of the functional relevance of the lesioned area (Karnath and Rennig, 2017). Furthermore, there is evidence that the chronic post-stroke impairments are due to a wider disruption of neural function than observable on structural neuroimaging alone. In a recent study, Thompson et al. (2017) showed that tissue surrounding the lesion 0–6 mm remains chronically hypoperfused and that this perilesional hypoperfusion is functionally relevant as it correlates with the impairment. In addition, recent methodological advances expanded VLSM to

assess lesions in terms of networks based on either functional (Boes et al., 2015) or structural (Yourganov et al., 2016) connectivity (see also Karnath and Rennig, 2017; in this special issue). This allows for linking the deficit to dysfunctional remote regions or white matter disconnection, even if the structure itself is not affected by stroke. For example, in a recent study, Bonilha et al. (2017) combined VLSM and structural connectome-lesion symptom mapping (CLSM) in chronic stroke patients. CLSM revealed a white matter network in the temporal lobe associated with word comprehension deficits that extended the necrotic lesion in the inferior temporal and fusiform gyrus identified by VLSM. In a similar vein, using deterministic fibre tracking in conjunction with VLSM in patients with chronic aphasia, the same group demonstrated that cortical disconnection is an independent predictor of the impairment, even in patients with chronic aphasia (Bonilha et al., 2014). These results are further complemented by a set of fMRI studies that found altered activation in remote intact but functionally connected areas, again demonstrating that the residual deficit is not only a consequence of local damage but also of altered functional network dynamics (Crinion et al., 2006; Price et al., 2001; Robson et al., 2014). Together, these results provide strong evidence for the conceptualization of aphasia as network disorder.

Mapping the mechanisms of chronic network reorganization is the particular strength of functional neuroimaging studies with fMRI or PET. Taking the heterogeneous study designs and patient cohorts into account, these studies have shown that the chronically reorganized language system comprises spared areas in the left hemisphere (Cao et al., 1999; Fridriksson et al., 2010a; Robson et al., 2014; Saur et al., 2006; Sims et al., 2016; Weiller et al., 1995), perilesional tissue (Rosen et al., 2000; Warburton et al., 1999) as well as (homologous) areas in the right hemisphere (Cao et al., 1999; Crinion and Price, 2005; Leff et al., 2002; Musso et al., 1999; Robson et al., 2014; Weiller et al., 1995). Depending on site and size of the lesion and the residual language impairment, these areas might be more activated as compared to 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, Fridriksson et al. (2010a) found that activation in preserved left frontal and posterior temporal areas was associated with better naming performance in patients with anomia. In a metaanalysis using activation likelihood estimation (ALE) on 12 fMRI studies including 105 chronic stroke patients with aphasia and 129 normal control subjects who performed the same fMRI tasks, Turkeltaub et al. (2011) confirmed these neuroplastic mechanisms. In addition, they found some evidence for recruitment of left hemisphere areas outside the core language network and recruitment of domain-general regions in the dorsolateral prefrontal cortex (middle frontal gyrus). The latter is well in line with the findings of an fMRI study by Brownsett et al. (2014) who showed that residual language performance in chronic aphasia is correlated with activity in domain-general systems in the superior frontal cortex. This supports the view that domain-general cognitive control is an essential factor contributing to the potential for recovery from aphasic stroke.

Although it is reasonable to assume that an intensified integration between spared areas of the reorganized network might contribute to language recovery, so far, only few studies addressed this issue in patients with chronic aphasia. Using partial correlation on time series extracted from functional PET data, Sharp et al. (2010) demonstrated increased functional connectivity between spared parietal and frontal cortex in aphasic patients with chronic left temporal stroke compared to normal subjects. Of interest, similar changes in frontoparietal integration was seen in normal subjects trying to overcome adverse listening conditions. This indicates that patients are mobilizing the same domain-general top-down control resources as healthy subjects if task difficulty increases. In addition to this evidence for the functional importance of intrahemispheric functional connectivity, Warren et al. (2009) demonstrated that aphasic patients with preserved interhemispheric connectivity between bilateral temporal cortices displayed better receptive language function. First attempts with task-free resting state fMRI are reported in a recent study by Sandberg (2017) who found widespread decreases of ipsilesional intra- and interhemispheric functional resting state connectivity in patients with chronic aphasia compared to healthy controls. Since no increases of functional connectivity were observed, this finding reflects the chronic network disorder rather than a mechanism of reorganization.

In addition to this evidence from functional neuroimaging, two recent studies used voxel-based morphometry (VBM) on grey matter to investigate structural plasticity in chronic aphasia. Since the stroke-induced lesion leads to distortion artefacts even when masked out, valid results of VBM can only be obtained for the non-affected right hemisphere. Xing et al. (2016) used a multivariate approach of lesion-symptom mapping in combination with VBM of right hemisphere grey matter volume in chronic aphasic patients. They demonstrated that local grey matter increase (compared to healthy controls) in the right temporoparietal junction correlated with better language production abilities. The study by Hope et al. (2017) is remarkable in the way that aphasic patients were measured twice in the chronic stage with a mean interval of 31 months. Using VBM, they found two clusters in the right middle temporal gyrus where spontaneous improvement of object naming correlated with an increase of grey matter. Both studies carefully controlled for lesion volume, age, time post-stroke and (baseline) performance so that grey matter volume remained as an independent variable explaining either chronic language performance or improvement. These studies provide convincing evidence for the view that structural plasticity in the right hemisphere, at least in the right temporal lobe, supports language recovery. Table 1 summarizes major mechanisms of early and chronic stroke that support language recovery.

In sum, results of neuroimaging studies in chronic post-stroke aphasia indicate that language recovery takes place in domain-specific areas of a pre-existing bilateral network for language with support of domain-general systems in the dorsolateral prefrontal cortex. However, there is only 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 (Zahn et al., 2004). With respect to the right hemisphere, there is converging evidence from functional and structural imaging for a supportive role of the right temporal cortex in language reorganization. Although not systematically investigated, it might be hypothesized that homologue right hemisphere involvement depends on (i) the amount of individual premorbid language lateralization (i.e., patients with a more bilateral premorbid language representation could better utilize homologous right areas), (ii) the lateralization of the language function of interest (i.e., bilaterally organized functions like language comprehension might involve right hemisphere areas to a greater extent compared with left-lateralized functions, e.g. language production) and (iii) the site and size of the left hemisphere lesion (i.e., small strategic or large cortical damage of left hemisphere language zones more likely result in a permanent involvement of right homologue areas). Overall, results from neuroimaging studies favor the concept of reorganization within redundant systems (Price and Friston, 2002) over the concept of reorganization within vicarious systems (Marshall, 1984).

Neuroimaging-based outcome prediction in the language network

Many studies aim at predicting the actual impairment from neuroimaging parameters. For instance, using structural imaging and a probabilistic tractography atlas, Corbetta et al. (2015) showed how the locus of damage and disconnection of white matter contributed to the behavioural deficit 1–2 weeks post stroke. Similar, Yourganov et al. (2015) demonstrated for patients with chronic aphasia that automated multivariate classification based on damage to atlas-defined brain areas could distinguish between aphasia types. These studies are of interest for understanding the neurobiological mechanisms causing the impairment. Here, we will focus on neuroimaging studies that aim at predicting subsequent language recovery from neuroimaging parameters obtained

Table 1
Overview of key neuroimaging studies providing evidence for major mechanisms supporting language recovery in acute, subacute and chronic stroke.

Mechanisms	Phases	Key studies	Methods	n
Early network disruption and recovery				
cortical hypoperfusion and reperfusion	acute	Fridriksson et al. (2010b),	Perfusion imaging	45
		Hillis et al. (2001)		50
		Hillis et al. (2006),		87
		Shahid et al. (2017)		191
remote dysfunction (diaschisis)	acute	Saur et al. (2006)	fMRI-longitudinal	14
structural disconnection	acute	Corbetta et al. (2015),	VLSM	124
		Fridriksson et al. (2010b),		45
		Kummerer et al. (2013)		100
disruption of intra- and interhemispheric functional connectivity	subacute	Siegel et al. (2016)	rsfMRI	132
reactivation of spared left and right language areas	subacute/ chronic	Saur et al. (2006)	fMRI-longitudinal	14
Chronic network dysfunction				
cortical necrosis	chronic	Henseler et al. (2014), many others	VLSM	102
perilesional hypoperfusion	chronic	Thompson et al. (2017)	Perfusion imaging	35
structural disconnection	chronic	Bonilha et al. (2014)	DTI	39
remote dysfunction	chronic	Crinion et al. (2006),	fMRI	17
		Price et al. (2001),	fMRI	4
		Robson et al. (2017)	ASL	12
Chronic network reorganization				
recovery of spared left language areas	chronic	Fridriksson et al. (2010a),	fMRI,	15
		Robson et al. (2014)	fMRI	12
recovery of perilesional brain tissue	chronic	Rosen et al. (2000),	fMRI	6
		Warburton et al. (1999)		6
recruitment of (homologous) right language areas	chronic	(Crinion and Price, 2005),	PET	17
		Robson et al. (2014)	fMRI	12
		Weiller et al. (1995),	PET	6
recruitment of domain-general systems	chronic	Brownsett et al. (2014)	fMRI	16
recruitment of areas outside the language network	chronic	Turkeltaub et al. (2012)	metaanalysis on fMRI	105
increased functional connectivity between spared left hemisphere areas	chronic	Sharp et al. (2010),	PET, partial correlation	9
		Warren et al. (2009)		24
structural plasticity in the right hemisphere	chronic	Hope et al. (2017)	VBM -longitudinal	28
		Xing et al. (2016)	VBM	32

n = number of patients, fMRI = functional MRI; VLSM = voxel-based symptom lesion mapping; rsfMRI = resting state functional MRI; DTI = diffusion-tensor imaging; ALS = arterial spin labelling; VBM = voxel-based morphometry.

in the early phase of stroke (Table 2). This is of particular clinical importance, since early prediction of outcome might influence planning of rehabilitation and future life of patients. The challenge of this task is, however, that neuroimaging parameters are needed that are related to recovery by containing outcome relevant information.

It is well established that initial severity of the language deficit and age are factors that influence later recovery (Pedersen et al., 1995). For neuroimaging being clinically relevant for outcome prediction, this means that parameters must be identified that explain variance in addition to these established parameters. As we elaborated in the previous section, excessive reorganization evolves in the language network within the first weeks after stroke onset. It might therefore be reasonable to assume that the early fMRI signal is relevant for subsequent recovery and thus could be a meaningful predictor of language outcome. In a recent study, Saur et al. (2010) used language fMRI data collected in the second week after stroke onset to predict language outcome in the early chronic phase (6 months after stroke onset). Using multivariate pattern classification techniques, they showed that fMRI language activation in combination with the patients' initial language deficit and age substantially better predicted language outcome than the patients' initial impairment and age alone. In contrast, both, language fMRI as well as diffusion-weighted imaging of the acute lesion acquired in the acute phase (about 2 days post stroke) failed to contribute to language outcome prediction. This demonstrates that fMRI language activation of the subacute phase, for which an upregulation in the remaining intact parts of the language network was observed (Saur et al., 2006), contains most information related to language recovery. An open question still is whether specific early (subacute) activation or connectivity patterns better predict language outcome. For example, in the context of motor recovery, it has been suggested that early ipsilesional effective connectivity between the motor cortex and areas involved in motor control predicts a better outcome in the chronic phase (Rehme et al., 2011a). Although the results from the Saur et al. study were promising, broad clinical application of task-based fMRI is hampered by the rather laborious data acquisition, in particular in case of early-stage stroke patients with aphasia. Related to this, the high demands of task-based fMRI for aphasic patients preclude inclusion of the most severely affected patients for whom outcome prediction is of particular interest. In this context, task-free resting state fMRI could be a promising alternative because of its relatively easy application also in severely affected acute stroke patients (Siegel et al., 2016). However, so far, no studies are published demonstrating that task-free resting state fMRI data acquired in the (sub-) acute phase of stroke contain information related to later language recovery (see also review by Klingbeil et al., 2017).

Complementary to these attempts based on functional neuroimaging, Forkel et al. (2014) examined anatomical predictors of language recovery

Table 2
Overview of studies on early neuroimaging-based prediction of language outcome in the chronic phase after stroke.

Publication	Predictors	Prediction	Patients [n]	Method
Forkel et al. (2014)	tract volume of the right arcuate fascicle	outcome > 6 months	16	DTI tractography
Karbe ei al. (1995)	regional cerebral metabolism in left temporal and frontal brain regions early after stroke	outcome > 2 years	22	FDG-PET
Saur et al. (2010)	fMRI activation in subacute phase, age, deficit	outcome/ improvement > 6 months	23	SVM
Kim and Jang (2013)	integrity of the left arcuate fascicle < 30 days	outcome > 6 months	25	DTI tractography
Seghier et al. (2016)	databank-based individual prediction on structural imaging and behavioural measurements	variable	0	similarity matching

DTI = diffusion-tensor imaging; SVM = support vector machine; FDG-PET = 2-deoxy-2-positron emission tomography.

with diffusion tensor imaging tractography. They observed that the volume of the long segment of the arcuate fascicle in the *right* hemisphere, in addition to other predictive variables including age, gender and lesion size, is an important predictive factor for language recovery six months post-stroke. A similar finding for the *left* hemisphere was reported by Kim and Jang (2013) who found that successful reconstruction of the left arcuate fascicle by means of diffusion-tensor based tractography was associated with better language outcome after six months. These results, in part, underline the functional relevance of the bilateral arcuate fascicles for language recovery. However, with regard to the organization of language along at least two processing streams, as pointed out in the introduction, an approach based on a network perspective seems more promising compared to predicting outcome on a single grey or white matter structure alone.

The PLORAS (predicting language outcome and recovery after stroke) database (Seghier et al., 2016) follows a different strategy. It is a large repository of anatomical and functional imaging as well as a broad range of behavioural scores of more than 760 stroke patients. Based on these data, prediction should be made for individual patients by indicating how other patients with the most similar lesion and behavioural profile recovered their language skills over time. The ultimate goal of this database is to predict language outcome on the basis of a single structural brain scan. In consideration of ongoing multidimensional data acquisition, in the future, this approach seems to be applicable even in the clinical routine. To our knowledge, however, no results on subsequent outcome prediction have been published so far.

In sum, first studies demonstrate that neuroimaging has the potential to add valuable information to improve language outcome prediction after stroke. However, an important prerequisite for broad application is that prediction has to rest upon a measure that can easily be acquired in the clinical routine of acute stroke care. This best applies to structural MRI and, to a lesser degree, task-free resting state fMRI. In conjunction, these methods have the potential to provide essential information on the remaining structural and functional network resources of the lesioned brain that drive recovery. Because different sites (e.g. PLORAS, London, UK; CONSORT, St. Louis, US (Corbetta et al., 2015)) are currently collecting large longitudinal multimodal neuroimaging datasets of stroke patients, major progress in this field could be expected in the near future.

Combining neuroimaging and non-invasive brain stimulation in the language network

Complementary to the above-discussed literature, an increasing number of studies combined neuroimaging with non-invasive brain stimulation (NIBS) to map plastic changes in the language network in response to neuromodulation. To date, most of these studies were performed in healthy volunteers (see Hartwigsen, 2016 for review). Such studies are mandatory to draw valid conclusions on the interaction within and between networks for specific language functions and their compensatory potential for adaptive plasticity after disruption. A better understanding of the neural correlates of the neuromodulatory effects of non-invasive brain stimulation might ultimately help to develop and optimize stimulation approaches for therapeutic purposes and thereby maximize beneficial stimulation effects (cf. section 5.3).

The combination of NIBS and neuroimaging provides an optimal means to map large-scale effects on the systems level that underlie potential behavioural manipulations induced by NIBS. Plasticity-inducing protocols include repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). For an overview of both techniques and their application in the language system, the reader is referred to previous reviews (e.g. Floel, 2012; Hartwigsen, 2016; Hartwigsen and Siebner, 2013; Holland and Crinion, 2012; Turkeltaub, 2015). In general, these protocols can either be inhibitory or facilitatory. Single sessions of plasticity-inducing rTMS protocols usually produce after-effects that outlast the end of stimulation for about 30–45 min (Huang et al., 2005), but lasting effects for up to 50 min were recently reported (Wischnewski and Schutter, 2015). In contrast, animal studies suggest that the after-effects of single tDCS sessions might last for several hours (Bindman et al., 1964).

Mapping NIBS effects in the healthy language network

The underlying idea for the application of inhibitory protocols in the healthy brain is to test the functional relevance of a specific region for a given process and the potential of other regions to compensate for a focal NIBS-induced disruption of this area. Previous combined rTMS-fMRI studies in healthy volunteers demonstrated that after focal disruption of a language region, contralateral homologous regions or other network nodes within the same hemisphere showed compensatory upregulation that might have helped to maintain task processing (e.g. Andoh and Paus, 2011; Binney and Lambon Ralph, 2015; Hallam et al., 2016; Hartwigsen et al., 2013, 2017; Jung and Lambon Ralph, 2016). For instance, we found that rTMS-induced inhibition of the left inferior frontal gyrus decreased activity at the targeted site during speech production and increased activity in the contralateral homologue (Hartwigsen et al., 2013). The upregulation of the right IFG was associated with an increase in the facilitatory influence from the right to the left IFG that predicted rTMS-induced changes in the individual response speed. Specifically, subjects became faster as the influence from the right to the left IFG increased. These results show that right hemisphere regions contribute to language function after focal disruption of the left hemisphere and support the notion of a beneficial role of the right hemisphere in (early) aphasia recovery.

In another recent study (Hartwigsen et al., 2017), we explored rTMS-induced short-term reorganization in parieto-frontal networks for word comprehension in healthy volunteers. In different sessions, inhibitory rTMS was applied over either a key region for semantic processing in the left angular gyrus or a central region for phonological processing in the left supramarginal gyrus. When given over the angular gyrus, rTMS suppressed task-related semantic activity not only at the stimulated site, but in a large network of semantic regions, including the remote anterior inferior frontal gyrus (aIFG). Effective connectivity analyses further showed that after rTMS, the angular gyrus increased its inhibitory influence on the left aIFG during semantic processing. The observed increase in the inhibitory influence predicted the individual semantic response delay after rTMS, demonstrating that inhibition at remote network nodes is functionally relevant. This nicely corresponds to the remote effects of focal lesions on the language network described for early and chronic stroke (see section 2). At the same time, the neighbouring phonological network showed an upregulation of semantic activity that might have reflected partial compensation for the disruptive rTMS effects and helped to maintain task processing. These findings are summarized in Fig. 2. In contrast, after disruption of the phonological region in the supramarginal gyrus, we observed a strong delay in phonological decisions without any compensatory upregulation of semantic regions. These results indicate that lower-level task processing aspects (e.g. phonological or domain-general working memory processes) might to some degree compensate for disruption of higher-level semantic processing but not the other way round. The dynamic regulation of intrahemispheric interactions in the healthy language system observed in this study shows that neighbouring networks might bear the inherent potential to partially support task processing after a strategic lesion of one key region, which might inform models of language reorganization after stroke.

In a complementary approach, other studies combined anodal tDCS with simultaneous fMRI to investigate the neural correlates of stimulation-induced improvements during speech production in the healthy language system (Holland et al., 2011; Meinzer et al., 2012a). For instance, Meinzer et al. (2012a) showed that (facilitatory) anodal tDCS over the left IFG significantly improved semantic fluency in a word generation task in healthy volunteers. The beneficial behavioural effects were underpinned by a decrease in task-related activity at the stimulated

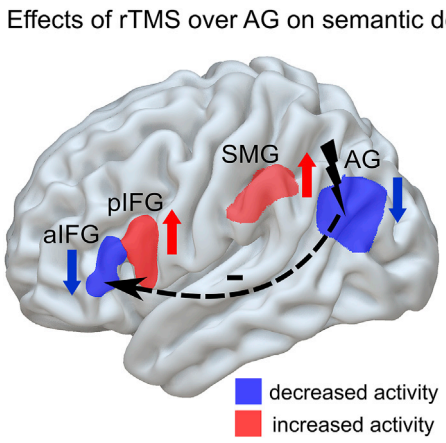

Fig. 2. Schematic overview of rTMS-induced short-term reorganization in the semantic network. rTMS over the left angular gyrus (AG) resulted in task-related decreases in semantic activity at the stimulated site and in the remote anterior inferior frontal gyrus (aIFG) (blue regions). The remote rTMS effect was mediated by an increase in the inhibitory drive (−) from AG to aIFG, as indicated by the dotted arrow. At the same time, task-related activity was increased in neighbouring phonological regions including the left supramarginal gyrus (SMG) and posterior inferior frontal gyrus (pIFG) (red regions). This upregulation of neighbouring regions might have partially compensated for the disruptive rTMS effect in the semantic network. Adapted from Hartwigsen et al. (2017).

area that was interpreted as more efficient task processing. Additionally, the authors found increased functional connectivity between the left IFG and other key regions for language at rest, indicating that the stimulation effect was not restricted to the targeted area but rather modulated functional interactions on a larger network level. Strong modulatory network effects of anodal tDCS are consistent with other studies that also reported decreased task-related activity in the stimulated area (Holland et al., 2011) and increased functional connectivity at rest (Lindenberg et al., 2013, 2016) or during a specific task (Holland et al., 2016). Some of these studies found correlations between the beneficial behavioural effects of tDCS and reduced task-related activity (Holland et al., 2011) or increased task-specific connectivity (Holland et al., 2016). However, it remains unclear how the reported changes in resting state connectivity observed by Meinzer et al. (2012a) were related to the behavioural modulation induced by tDCS. This issue should be addressed in future studies to identify the parameters that are most likely reflecting beneficial behavioural tDCS effects on the neural level.

In summary, combining NIBS and functional neuroimaging in the healthy brain can provide novel insight into general mechanisms of adaptive plasticity and short-term reorganization in the language network and might help to identify critical stimulation sites for application of NIBS to facilitate language recovery in post-stroke aphasia. The above-discussed studies are complementary in their approaches and provide different advantages. Combining inhibitory TMS with subsequent functional neuroimaging is well suited to increase the current understanding of short-term plasticity and changes in network interactions in response to focal perturbation. The relatively high focality of TMS is a main advantage that allows for the dissociation of different neighbouring regions and networks. One methodological disadvantage of this approach is the high technical challenge of combining TMS and fMRI in a simultaneous fashion (see Bestmann et al., 2008) that has precluded its application in the language domain so far. Hence, the neural correlates of immediate "on-line" TMS effects on language processing remain unclear. In contrast, simultaneous application of tDCS during fMRI is easier and particularly suited to investigate the neural underpinnings of stimulation-induced improvements during language (re-) learning. As a disadvantage, tDCS is less focal than TMS and the effects of cathodal tDCS are less stable across studies (Jacobson et al., 2012; Pirulli et al., 2014). Greater focality might be achieved with high-definition tDCS in the future (e.g. DaSilva et al., 2015). Given its easier application and the absence of any severe side effects, tDCS might be generally better suited for rehabilitation purposes in future studies.

With respect to potential novel approaches to facilitate speech and language recovery in post-stroke aphasia, it was recently demonstrated that tDCS might be beneficial when given outside the core language network. Specifically, anodal tDCS over the right cerebellum significantly improved phonemic fluency in healthy volunteers (Turkeltaub et al., 2016). The beneficial tDCS effects were associated with increased functional connectivity between the cerebellum and speech-motor regions as well as remote connections between left hemisphere language regions and speech motor regions at rest. This suggests that cerebellar stimulation might potentially support aphasia rehabilitation in the future.

Mapping NIBS effects in the lesioned language network

Most of the studies on patients with post-stroke aphasia used NIBS techniques to facilitate language recovery (see section 5.1). As discussed below, these studies usually aim at either inhibiting "maladaptive" plasticity in the right hemisphere or facilitating perilesional activity to support language recovery. However, very few studies investigated the functional relevance, interactions and compensatory potential in the reorganized language system to date. In one of the few exceptions, Darkow et al. (2017) applied anodal tDCS during fMRI in 16 patients with chronic aphasia and mild naming impairments to investigate how neuromodulation interacts with the residual language network. Anodal tDCS was applied over the left primary motor cortex, as a previous study had demonstrated improved picture naming in patients with post-stroke aphasia after stimulation of this region (Meinzer et al., 2016). To obtain "pure" stimulation effects independent of performance and language treatment, the authors selectively included items that could be reliably named by the patients without therapy. Relative to sham tDCS, anodal tDCS significantly decreased activity in domain-general brain regions that were previously associated with high-level cognitive control. An independent component analysis further revealed increased activity in a larger language-related network and increased connectivity between these regions. In comparison with un-stimulated healthy controls, tDCS resulted in a normalization of network activity and connectivity in aphasic patients. The overall reduction in task-related activity was taken to reflect enhanced neural efficiency and less effortful processing. Future studies might include more challenging paradigms or more severely affected patients to investigate the neural effects of behavioural improvements after tDCS in the lesioned language network.

In another study, we recently combined inhibitory rTMS with subsequent fMRI in 12 patients with chronic post-stroke aphasia and lesions in the left (temporo)-parietal cortex to investigate how the reorganized language system reacts to focal perturbations of the left inferior frontal gyrus (Hartwigsen et al., unpublished data). Preliminary data revealed a functional-anatomical double dissociation between rTMS region and task. Accordingly, rTMS over the anterior IFG selectively delayed response speed during semantic decisions, whereas rTMS over the posterior IFG strongly affected response speed for phonological decisions. On the neural level, behavioural disruption was underpinned by inhibition at the stimulated area. These results emphasize the functional relevance of different parieto-frontal networks for different aspects of word comprehension (cf. Hartwigsen et al., 2017; Hartwigsen et al., 2016). Fig. 3 illustrates the task-specific inhibitory effects of rTMS over pIFG on phonological decisions ("two or three syllables?") in a representative patient. This patient was a right-handed, 46-year-old German speaker diagnosed with non-fluent aphasia according to the Aachener Aphasia Test (Huber et al., 1984). He had a lesion in the left parietal cortex including the supramarginal and angular gyrus and was included 24 months after stroke.

In this study, additional network analyses might elucidate rTMS-induced changes in intra- and interhemispheric interactions that might reflect potential compensatory efforts after disruption of a key language node in the reorganized brain.

Together, the above-discussed results demonstrate the value of

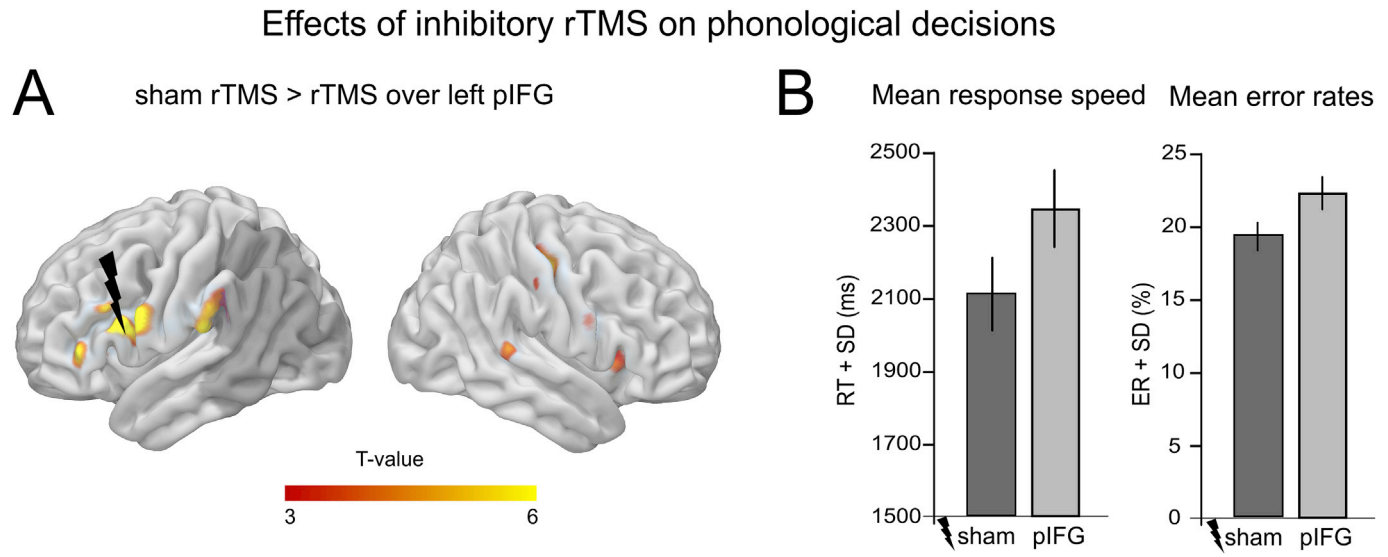

Fig. 3. rTMS-induced disruption of phonological decisions in a representative patient with a lesion in the left parietal cortex (grey region). A. Effects of rTMS on task-related activity during phonological decisions ("two or three syllables?"). Relative to sham rTMS, rTMS over left posterior inferior frontal gyrus (pIFG) significantly decreased task-related activity at the stimulated area and in remote regions. Thresholded at $p < 0.001$ uncorrected, T-values > 3.0 displayed. B. Effects of rTMS on response speed and error rates. rTMS delayed response speed for phonological decisions and increased task-specific error rates.

combining NIBS with neuroimaging to increase the current knowledge of adaptive plasticity and short-term reorganization in the healthy and lesioned language network. However, the current literature on the neural correlates of NIBS-induced plasticity is scarce. In this context, the simultaneous tDCS-fMRI study by Darkow et al. (2017) is particularly interesting as it shows how anodal tDCS modulates neural activity independent of language treatment effects in patients with chronic post-stroke aphasia. Such studies are mandatory to gain insight into differences in the adaptive plasticity of the reorganized relative to the intact language network. One limitation of their approach is that they could not relate the observed changes in task-related activity to tDCS-induced behavioural improvements. In contrast, the above-discussed combined TMS-fMRI study (Hartwigsen et al., unpublished data) aimed at investigating how the reorganized language network reacts to a focal perturbation induced by inhibitory rTMS. As a main advantage, this approach allowed for the association of rTMS-induced behavioural effects with changes in task-related activity that might indicate potential compensatory upregulation of the residual network. However, this study does not provide any translational insight into potential beneficial effects of specific NIBS protocols that might be used to facilitate language recovery.

In summary, the above-discussed studies show that aside from its application to facilitate language recovery, combining NIBS with neuroimaging in patients with post-stroke aphasia might elucidate how the reorganized network changes its computations in response to focal perturbations. Moreover, results from combined NIBS and neuroimaging in healthy volunteers might inform future patient studies and models on reorganization with respect to potential compensatory mechanisms and might help to identify potential sites for NIBS treatment.

Treatment-induced plasticity in the language network

Recent evidence from a large multi-centre study showed that speech and language therapy can significantly improve language functions in the chronic phase after stroke (Breitenstein et al., 2017). In contrast, early treatment in the acute phase after stroke within 2 weeks of onset failed to show significant effects (Nouwens et al., 2017).

Despite the promising findings in the chronic phase after stroke, it is not yet clear to what extent treatment-induced recovery engages spared left hemisphere areas, perilesional regions and contralesional regions as most of the previous studies focused selectively on behavioural treatment outcomes. Deeper insight into the neural and cognitive predictors of treatment success may substantially increase treatment efficacy (Meinzer and Breitenstein, 2008; Pasley and Knight, 2013) and may enhance the current knowledge of the brain's potential for adaptive reorganization. In this section, we discuss the neural correlates of treatment-induced plasticity. We focus on interventions that employed either speech and language therapy alone or in combination with pharmacotherapy or non-invasive brain stimulation to promote language recovery in patients with post-stroke aphasia.

Treatment-induced plasticity after speech and language therapy

An increasing number of studies have investigated treatment-induced plasticity after language therapy (for review see: Crinion and Leff, 2007, 2015; Hillis, 2007; Meinzer and Breitenstein, 2008; Thompson and den Ouden, 2008). Most of these studies applied language therapy in the chronic phase after stroke, as treatment-induced improvements during the early phases after stroke may be confounded by spontaneous recovery.

Overall, it was demonstrated that the efficacy of language therapy depends on treatment intensity (Barthel et al., 2008; Cherney et al., 2008; Meinzer et al., 2004, 2005; Pulvermuller et al., 2001). As recovery from aphasia is a long process that takes place over years (Leger et al., 2002; Meinzer et al., 2008), high-intensity treatment can significantly improve language recovery even several years after stroke (Breitenstein et al., 2017; Carlomagno et al., 2001; Poeck et al., 1989; Pulvermuller et al., 2001; Szaflarski et al., 2008). However, the contribution of left and right hemisphere regions to treatment-induced language recovery remains controversial as different studies associated beneficial effects of treatment with either increases in left or right hemisphere areas, bilateral regions, or decreases in right-hemispheric regions (see Table 3 for a non-exhaustive overview of key studies).

Strikingly, some studies showed that even short-term treatment at high intensities can lead to notable activation shifts in language-related activity. For instance, Musso et al. (1999) reported language improvement after repeated eight-minutes sessions of a language comprehension training to be correlated with activity increases in the right temporal cortex in four patients with left temporal damage. Likewise, Blasi et al. (2002) demonstrated increased activity in the contralesional right frontal

Table 3
Overview of example studies on treatment-induced plasticity in post-stroke aphasia.

Publication	Phase	Method	Intervention type	n	Main outcome (associated with improvement)
Upregulation of right hemisphere regions associated with treatment success					
Crosson et al., 2009	chronic	fMRI	intention treatment (picture naming + intention manipulation)	5	laterality shift to right frontal cortex
Musso et al., 1999	chronic	PET	language comprehension training	4	upregulation of right temporal cortex
Raboyeau et al., 2008	chronic	PET	lexical training (naming retrieval)	10	upregulation of right insula and inferior frontal gyrus
Downregulation of right hemisphere regions associated with treatment success					
Baciu et al., 2016 [a]	chronic	fMRI	visual feedback therapy	3	reduced right hemispheric and increased left hemispheric activity
Heiss et al., 2013	subacute	PET	inhibitory rTMS over right anterior IFG combined with speech and language therapy	29	laterality shift from right to left hemisphere regions
Nardo et al., 2017	chronic	fMRI	anomia treatment (cued picture naming)	18	reduced activity in bilateral frontal regions. Immediate and long-term treatment success directly associated with neural priming (reduced activity) in right frontal cortex
Richter et al., 2008	chronic	fMRI	constraint-induced aphasia therapy	16	downregulation of right hemispheric activity in several regions of interest
Upregulation of bilateral regions associated with treatment success					
Brownsett et al., 2014	chronic	fMRI	home-based computerized auditory discrimination therapy	16	increased activity in language-specific and domain-general regions. Activity in domain-general frontal midline cortex significantly correlated with communicative abilities before and after treatment
Menke et al., 2009	chronic	fMRI	object naming	8	short-term success: increased activity in regions for memory encoding, attention and multimodal integration long-term success: increased activity in right posterior temporal gyrus and left perilesional temporal regions
Mohr et al., 2016	chronic	MEG	intensive language action therapy and constraint-induced aphasia therapy	14	increased word-specific mismatch negativity response in both hemispheres, stronger in perilesional left regions
Pulvermuller et al., 2005	chronic	EEG	constraint-induced aphasia therapy	9	brain activity changes in both hemispheres
Sandberg et al., 2015	chronic	fMRI & graph theory	theoretically-based word-finding treatment with abstract words	10	increased functional connectivity between bilateral regions for abstract word processing, generalization to regions for concrete word processing
Thompson et al., 2010	chronic	fMRI	treatment of underlying forms (auditory sentence verification)	6	increased activity in bilateral superior temporal gyrus and inferior parietal lobe
Upregulation of perilesional or spared left hemisphere regions associated with treatment success					
Breier et al., 2009	chronic	MEG	constraint-induced aphasia therapy	23	upregulation of perilesional regions
Kessler et al., 2000	acute	PET	intensive speech therapy combined with piracetam	12	increased cerebral blood flow in left fronto-temporal regions after piracetam relative to placebo group associated with stronger improvements in the treatment group
Marangolo et al., 2016	chronic	rs-fMRI	intensive language therapy (word repetition) combined with bi-hemispheric tDCS (anode over left, cathode over right IFG)	9	increased functional connectivity in the left hemisphere
Mattioli et al., 2014	acute	fMRI	confrontation naming	12	increased activity in left IFG for treatment group
Meinzer et al., 2004	chronic	MEG	constraint-induced aphasia therapy or model based therapy	28	up- or down-regulation of slow wave activity (different mechanisms of plasticity)
Meinzer et al., 2008	chronic	fMRI	constraint-induced aphasia therapy	11	increased activity in perilesional regions
Van Hees et al., 2014a,b	chronic	fMRI	anomia treatment	8	Increased activity in left superior temporal gyrus
Zhu et al., 2014	subacute	rs-fMRI	mixed conventional therapy	14	increased connectivity in left fronto-parietal network
Downregulation of perilesional or spared left hemisphere regions associated with treatment success					
Abel et al., 2015	Chronic	fMRI	lexical therapy	14	decreased activity in the naming network, including the left inferior frontal gyrus and control regions
Fridriksson et al., 2012a	Chronic	fMRI	speech entrainment therapy	13	decreased activity in left posterior inferior parietal lobe

[a] Ongoing study, preliminary results; EEG = electroencephalography; IFG = inferior frontal gyrus; MEG = magnetoencephalography; PET = positron emission tomography; rs-fMRI = resting state functional magnetic resonance imaging.

cortex associated with learning a word retrieval task using word stem completion. This is consistent with the findings of Crosson et al. (2009) who designed a treatment to specifically engage the right hemisphere by initiating word finding trials with complex left-hand movements (intention treatment). In that study, treatment gain was associated with a laterality shift in the frontal cortex from the left to right hemisphere. These findings were replicated and extended in a follow-up study from the same group (Benjamin et al., 2014). In that study, the rightward shift persisted in a three months follow-up investigation. Moreover, after intention treatment, patients showed behavioural generalization to untrained items. These findings converge with previous studies that also reported correlations between increased activity in homologous right-hemispheric regions and therapy-induced improvements in language performance (Crosson et al., 2005; Raboyeau et al., 2008). Together, these results support the notion of a compensatory role of the right hemisphere in language recovery after brain damage.

However, other studies found therapy-induced improvements in language performance to be correlated with activation decreases in right-hemispheric regions (e.g. Baciu et al., 2016; Richter et al., 2008). These findings are more consistent with a re-shift of language-related activity to perilesional left-hemispheric regions after successful treatment (see Naeser et al., 2010b) and the reported behavioural improvements after

inhibition of the right hemisphere with non-invasive brain stimulation in some previous studies (see section 5.3.). Recent preliminary findings by Baciu et al. (2016) suggest that repeated sessions of visual feedback therapy led to an improvement of speech production in 3 patients with non-fluent chronic aphasia that was associated with a reduction of right-hemispheric activation and a stronger engagement of perilesional regions in the left hemisphere. Congruent with this observation, Richter et al. (2008) also associated behavioural improvements after two weeks of constraint-induced aphasia therapy with decreased activity in several right hemisphere regions. These results were complemented by a recent study (Nardo et al., 2017) that investigated the neural correlates of anomia treatment in patients with chronic post-stroke aphasia. In that study, improvements in picture naming were reported for up to 3 months post treatment. At the neural level, both immediate and long-term facilitation was associated with decreased activity in a bilateral residual frontal network. Treatment outcome was directly related to decreases in task-related activity in the right frontal cortex that were interpreted as neural priming effects due to more efficient task processing. This supports the view of an active and facilitatory role of the right hemisphere in treatment response during speech production.

In this context, it is important to note that therapy outcome and individual recruitment of left and right hemisphere regions might crucially depend on the site, extent and size of a lesion (see Hamilton et al., 2011). To address these inter-individual differences, a recent study by Abel et al. (2015) explored the relation between left-hemispheric lesion site, therapy-induced recovery and beneficial reorganization patterns. To this end, 14 patients with chronic post-stroke aphasia who suffered from word retrieval deficits underwent 4 weeks of lexical therapy. Before therapy, patients showed reduced task-related activity relative to healthy controls in a large-scale network of bilateral language regions and areas for cognitive control processes. Within the group of patients, bilateral upregulation of these regions before therapy was interpreted as compensatory strategy, with the recruitment of non-language regions most likely reflecting alternative control strategies for naming attempts. Moreover, the individual reorganization profiles depended on the individual lesion pattern. Interestingly, in that study, therapy success was associated selectively with activation decreases in the naming network, including the left inferior frontal gyrus, and also decreases in areas for cognitive control processes. These activation decreases were attributed to higher processing efficiency after therapy (see also Breier et al., 2007; Richter et al., 2008). In accordance with this observation, activation decreases in regions associated with learning and attention have been previously reported after successful word-retrieval training in patients with aphasia (Raboyeau et al., 2008).

In another study, Fridriksson et al. (2012a) also associated treatment success with decreases in left hemisphere regions during speech production. In that study, 13 patients with chronic post-stroke aphasia underwent a 6-week treatment with speech entrainment treatment, i.e., the online mimicking of an audio-visual speech model. A single session of speech entrainment prior to treatment engaged a ventral network of brain regions for lexical retrieval. Moreover, relative to healthy control subjects, patients showed increased activity in the left posterior inferior parietal lobe. This region showed a significant treatment-induced decrease after speech entrainment therapy. The decrease of activity after successful therapy again argues for increased processing efficiency. In a follow-up study, the same group (Fridriksson et al., 2015a) demonstrated increased speech fluency in patients with Broca's aphasia after speech entrainment therapy that was absent for other types of aphasia. Congruent with this finding, lesion mapping revealed that damage to the left inferior frontal gyrus was able to predict treatment success.

In contrast to the above-discussed results, several other studies associated therapy-induced language improvement with increased activation in bilateral regions (e.g. Brownsett et al., 2014; Fridriksson et al., 2006; Meinzer et al., 2007; Menke et al., 2009; Mohr et al., 2016; Pulvermuller et al., 2005; Sandberg et al., 2015; Thompson et al., 2010) or selective reactivation of perilesional or spared left-hemispheric areas (e.g. Breier et al., 2009; Kessler et al., 2000; Marcotte et al., 2012; Mattioli et al., 2014; Meinzer et al., 2004, 2008; van Hees et al., 2014a; Zhu et al., 2014). For instance, Fridriksson et al. (2012b) found that activity increases in "classical" perilesional language areas predicted treatment-related increase in naming in patients with post-stroke aphasia.

The observed heterogeneity of results may be best explained by differences in the studied language process of interest, lesion site, treatment strategies, specific language impairments (i.e., aphasia type), as well as intensity of treatment. When interpreting changes in task-related activity in post-stroke aphasia, it is important to bear in mind that increased activation might indicate increased task-demands on the short run as well as (successful) reorganization on the long run (Abel et al., 2015) or, in case of some right hemisphere regions, maladaptive plasticity (Naeser et al., 2005b; see below). The complex interplay of ipsi- and contralesional regions shows that reorganization is a dynamic process that changes across the time course of recovery and might reflect both increased task demands in the acute phase after stroke, disinhibition, as well as rewiring and more efficient processing after therapy or spontaneous reorganization. To draw valid conclusions on the adaptive or maladaptive nature of the observed activity changes, it is thus important to associate changes across the time course of spontaneous or therapy-induced recovery with behavioural improvements. Another important factor that should be considered is the reported large inter-individual variation in activity changes, especially with respect to the recruitment of right hemisphere regions. Moreover, it was argued that since behavioural treatment effects differ across individuals, it is likely that recruitment patterns associated with treatment-induced changes also vary across patients (Kiran et al., 2013). In this context, it should be noted that not all patients show behavioural improvement after therapy. Thompson and den Ouden (2008) emphasized that task difficulty is another important issue that might explain inter-study variability. If the task is too easy, it might not be sensitive to treatment effects. In contrast, a difficult task might reflect processing efforts rather than task processing per se. These authors pointed to the need of including non-language control tasks to confirm normal, reliable activation that can be contrasted with a specific language condition of interest.

Despite the reported variation in the recruitment of contralesional as well as perilesional and spared left hemisphere regions, the majority of the above-discussed studies shows that remodelling of cortical functions is possible even years after stroke and typically targets contralesional homologous regions as well as spared ipsilesional language areas (see also Saur and Hartwigsen, 2012). From these studies, it appears save to conclude that therapy-induced reorganization occurs in the pre-existing bilateral parieto-temporo-frontal language network that was also identified for spontaneous recovery. Future approaches might combine different functional and structural imaging methods to increase the current understanding of treatment-induced plasticity. For instance, besides the relevance of changes in task-related activity, changes in connectivity at rest and during task might be associated with a beneficial remodelling of the language network after therapy.

Combining language therapy with pharmacological interventions

Some previous studies suggested that different pharmacological interventions might improve language and communication deficits in patients with post-stroke aphasia by enhancement of neuroplasticity (e.g. Berthier et al., 2009, 2011; Berthier and Pulvermuller, 2011; Floel and Cohen, 2010). These studies follow the assumption that increased neurotransmitter availability could improve language abilities and facilitate re-learning of language skills (see Turkeltaub, 2015). Pharmacotherapy may have beneficial effects either specifically on language recovery or more generally by improving arousal, attention and working memory function (Pulvermuller and Berthier, 2008). Particularly, drugs affecting glutaminergic, monoaminergic and cholinergic transmitters

may have beneficial effects on language and other cognitive functions after stroke (Meinzer et al., 2012b). However, supporting evidence is scarce, the reported effect sizes are small and the underlying functional and structural correlates of the potentially beneficial effects remain largely unclear. In this context, it should be borne in mind that most of the existing data on the neurophysiological effects of different pharmacological interventions in stroke recovery were obtained from animal studies on motor stroke as no animal model of language recovery exists (Llano and Small, 2016).

To date, very few studies investigated treatment-induced neural changes after combined language therapy and pharmacological interventions (e.g. Cohen et al., 2004; Kessler et al., 2000; Yamada et al., 2016). These studies found treatment-induced language improvements to be correlated with increased cerebral blood flow in the left peri-Sylvian cortex. For instance, Kessler et al. (2000) combined intensive speech and language therapy with the γ aminobutyric acid derivative piracetam in 12 patients with acute post-stroke aphasia. Treatment-induced improvements in speech production were underpinned by increases in cerebral blood flow in left fronto-temporal regions. However, piracetam failed to show benefits for aphasia treatment in the chronic stage after stroke (see Pulvermuller and Berthier, 2008) or in patients with large left-hemispheric lesions (Gungor et al., 2011).

More recently, Berthier et al. (2014) found significantly improved speech production performance in 3 patients with chronic stroke-induced conduction aphasia after combining the cholinesterase inhibitor donepezil with intensive sentence repetition training. It was suggested that the beneficial effects of donepezil might be due to promotion of reorganization of cortical networks (Berthier, 2005) and probably a better regulation of regional cerebral blood flow (Roman and Kalaria, 2006). However, it is not clear whether these preliminary results can be generalized to larger collectives.

In contrast to the above described preliminary weak beneficial effects of donepezil on speech production, a recent study on a larger collective of patients with chronic post-stroke aphasia reported detrimental effects of donepezil on language comprehension when combined with a phonological training (Woodhead et al., 2017). In that study, 20 patients with impaired speech comprehension after left hemisphere stroke were treated with a phonological training and pharmacological interventions in a placebo-controlled crossover design. While phonological training showed small but significant behavioural improvements, donepezil had a negative effect on speech comprehension. Effective connectivity analyses on magnetoencephalography data revealed that phonological training increased self-connectivity as a measure of synaptic plasticity in the left superior temporal gyrus (STG). Interestingly, patients with severe speech impairment showed additional strengthening of the connectivity between left and right STG.

The conflicting results between the few existing studies on the effects of donepezil to support language recovery point to the need of future studies on large collectives to identify the interaction between different pharmacological interventions and specific speech and language deficits and training protocols. Importantly, it should be noted that acetylcholinesterase inhibitors such as donepezil are usually not given in patients with normal cognitive functions but rather used for treatment of Alzheimer's Disease to slow deterioration of cognitive functions (see Marsh and Hillis, 2006). Nevertheless, short- and long-term safety and tolerability has been demonstrated in patients with post-stroke aphasia (see Berthier et al., 2011 or Llano and Small, 2016 for review) and acetylcholinesterase inhibitors may have positive effects on recovery during language rehabilitation (e.g. Berthier et al., 2003; Berthier et al., 2014; Goldstein, 1999, 2000). Other pharmacological treatments that might prove beneficial in aphasia recovery include the noncompetitive N-methyl-D-aspartate receptor antagonist memantine that modulates glutamergic activity and might augment synaptic plasticity in spared language regions (Berthier et al., 2009), and potentially the γ aminobutyric acid derivative piracetam, at least in the acute phase after stroke (e.g. Kessler et al., 2000; see above). Some studies further suggested that stimulant medications like the noradrenergic agonist dextroamphetamine might also have some potential to support aphasia recovery (Walker-Batson, 2000; Walker-Batson et al., 2001; Whiting et al., 2008).

Overall, these preliminary results suggest that some drugs might be useful to augment the beneficial effects of speech and language therapy. However, to date, no pharmacological intervention has been shown to be sufficiently effective to become a standard treatment of language deficits after stroke (see Marsh and Hillis, 2006). Future studies might provide deeper insights into the modulation of structural and functional plasticity induced by the combination of speech and language therapy with pharmacological treatment.

Combining language therapy with non-invasive brain stimulation

As a complementary approach, recent studies also used NIBS to enhance language recovery after stroke. Due to the heterogeneity of results obtained from neuroimaging studies on plastic changes after speech and language therapy discussed above, clear predictions with respect to most promising stimulation sites to facilitate language recovery are difficult to make at the moment (see below for details). Most of the previous NIBS studies focused on behavioural improvements after either rTMS or tDCS (see Hamilton et al., 2011; Hartwigsen and Siebner, 2013; Turkeltaub, 2015 for review). Some studies combined NIBS with speech and language therapy, although it is currently unclear whether NIBS (especially rTMS) might be more efficient when combined with language therapy (Coslett, 2016).

While the results of several NIBS treatment studies in patients with aphasia are generally promising (Coslett, 2016; Otal et al., 2015; but see Elsner et al., 2013b), most of the previous studies were limited by the small number of patients included and the relatively small effect sizes. Moreover, the neurobiological mechanisms of the reported beneficial effects remain largely unclear. Recently, the first studies on larger collectives were started (e.g. Abo et al., 2012; Jung et al., 2011; Khedr et al., 2014; Kindler et al., 2012; Seniow et al., 2013; Thiel et al., 2013) and a controlled multi-centre study was launched (Thiel et al., 2015).

Only very few studies investigated the neural correlates of beneficial NIBS effects on aphasia recovery and most of them focused on potential changes in language laterality after NIBS treatment. In general, the majority of NIBS studies on aphasia treatment aimed at either inhibiting the contralesional homologous inferior frontal gyrus (e.g. Hamilton et al., 2010; Kindler et al., 2012; Martin et al., 2009; Naeser et al., 2010a, 2005a, 2005b) or facilitating perilesional and spared left hemisphere regions (Baker et al., 2010; Fridriksson et al., 2011; Szaflarski et al., 2011), including the motor cortex (Meinzer et al., 2016). Such studies are usually performed in the chronic phase after stroke, but some groups also applied NIBS in the subacute phase (e.g. Jung et al., 2011; Kindler et al., 2012; Polanowska et al., 2013; Seniow et al., 2013; Weiduschat et al., 2011). Importantly, these studies differ not only with respect to the NIBS approach that aimed at contralesional inhibition or perilesional facilitation, but also considered different outcome measures and experimental approaches. Specifically, a number of previous studies on perilesional facilitation (i.e., Baker et al., 2010; Fridriksson et al., 2011; Szaflarski et al., 2011) used an fMRI localizer to define the stimulation site for each subject individually based on the strongest task-related activity during picture naming or semantic processing prior to treatment. This approach accounts for potential inter-subject variability in lesion site and size as well as network reorganization. Consequently, such an approach might avoid strong variability in NIBS effects as reported in previous studies that used standardized stimulation sites across patients (see de Aguiar et al., 2015). However, individual fMRI localization is expensive and time consuming and might be better suited for specific research questions rather than for implementation in the daily routine of rehabilitation settings. Hence, a more pragmatic approach as introduced by Meinzer et al. (2016) might be more appropriate for therapeutic purposes in future studies. Based on the previously reported tight link between language functions and action related motor activity (e.g., Pulvermuller and

Fadiga, 2010), these authors applied anodal tDCS over the left primary motor cortex as determined by the 10–20 EEG system in patients with chronic post-stroke aphasia. The reported strong facilitation in picture naming after tDCS over the motor cortex in that study shows that this approach might be particularly promising to support aphasia recovery. In contrast to the above mentioned studies on perilesional facilitation (i.e., Baker et al., 2010; Fridriksson et al., 2011; Szaflarski et al., 2011), Meinzer et al. (2016) reported a transfer effect to untrained items, long-term stability in a six month follow-up and, probably most important, generalization to measures of everyday communication. Based on these findings, we would argue that a pragmatic approach that demonstrates long-term stability and improvements in functional communication is currently the most promising treatment strategy.

Studies following the second approach rather aimed at inhibiting the contralesional right inferior frontal cortex with low-frequency rTMS. It was argued that the observed behavioural improvements after inhibition of neuronal activity with repeated sessions of inhibitory rTMS in the right hemisphere likely reflect a suppression of maladaptive "over-activation" which in turn may allow for a better modulation in the remaining left hemisphere networks (Naeser et al., 2004, 2005a, 2005b, 2010a). In this context, it is important to note that the observed upregulation of the contralesional homologue is not specific for language functions but rather represents a common phenomenon after stroke-induced lesions that is probably best studied in the motor cortex. However, the role of the contralesional homologue in stroke recovery remains a debated issue (see Buetefisch, 2015; Grefkes and Ward, 2014). Indeed, some studies argue for a supportive role of the contralesional hemisphere in motor recovery (e.g. Lotze et al., 2006; Rehme et al., 2011b), while others emphasize a potentially maladaptive influence of the contralesional motor cortex which may exert functionally relevant inhibition on the ipsilesional motor cortex and thereby cause deterioration of motor function of the paretic hand (Grefkes et al., 2010; Takeuchi et al., 2012). These contradictory findings might be explained by differences in lesion sites, degree of motor impairment and time points after stroke (see Grefkes and Ward, 2014; Volz et al., 2017). Accordingly, there is some evidence that inhibition of the "overactive" contralesional motor cortex by means of NIBS might be beneficial for motor recovery in some patients (e.g. Dafotakis et al., 2008; Hummel et al., 2008; Takeuchi et al., 2005). However, the existing evidence in the motor domain is not conclusive yet (Buetefisch, 2015; see also Elsner et al., 2013a) and the role of the right hemisphere in aphasia recovery might even be less clear.

Following the assumption of a maladaptive contribution of the right hemisphere to language recovery, Heiss et al. (2013) applied inhibitory rTMS over the contralesional right anterior IFG in a relatively large group of 29 right-handed and two left-handed aphasic patients in the subacute phase after left-hemispheric stroke. 10 sessions of 1 Hz effective or sham rTMS were combined with speech and language therapy. Congruent with other rTMS studies that applied rTMS to the right IFG in patients with post-stroke aphasia (Naeser et al., 2005b; Rubi-Fessen et al., 2015; Thiel et al., 2013; Tsai et al., 2014; see Ren et al., 2014 for review), the authors reported improvement of language functions after rTMS over the right IFG but not over a control site. Behavioural improvements were associated with a re-shift of language-related activity towards the left hemisphere in treated patients. These findings are compatible with the notion that, after left-hemispheric stroke, the right hemisphere is released from transcallosal inhibition and might in turn suppress (beneficial) language related activity in perilesional regions (Hamilton et al., 2011). However, it should be noted that not all patients benefit from suppression of right hemisphere activation. Accordingly, some studies found deterioration in task performance after both left- or right-hemisphere rTMS in some patients with left hemisphere brain lesions (Thiel et al., 2006; Winhuisen et al., 2005). Turkeltaub et al. (2012) argued that the involvement of some right hemisphere regions may support recovery while others may interfere. As discussed above, the contribution of the right hemisphere might crucially depend on the time after stroke (Saur et al., 2006). Hence, it is likely that the beneficial effect after suppression of "maladaptive" plasticity in the right hemisphere might be limited to frontal activity in the late subacute and chronic phase after stroke (see section 6 below). This might be tested in future studies.

Notably, a re-shift of activity to language related regions in the left hemisphere was also found in the study by Szaflarski et al. (2011) that reported behavioural improvements in semantic fluency after 8 patients with chronic aphasia had received facilitatory intermittent theta burst stimulation over the left IFG. This might indicate that a re-activation of perilesional or spared language regions in the left hemisphere might indeed represent a neurobiological marker of successful treatment. In addition, the findings by Khedr et al. (2014) suggest that the combination of contralesional inhibition and ipsilesional facilitation might be beneficial. This is congruent with a study by Marangolo et al. (2016) that represents the first investigation of the underlying neural correlates of treatment-induced improvements after combining language therapy and facilitatory tDCS in patients with aphasia. That study demonstrated increased resting-state connectivity in the left hemisphere after repeated sessions of bilateral tDCS with the anode placed over the left and the cathode over the right IFG in 9 patients with chronic aphasia after stroke. However, these results are preliminary and it remains unclear whether the reported increase in resting-state connectivity is behaviourally relevant.

As a third main finding, some studies also reported language improvements after facilitatory NIBS over the right hemisphere (Floel et al., 2011; Vines et al., 2011). For instance, Floel et al. (2011) found that anodal tDCS over the right temporo-parietal cortex significantly improved picture naming in a sample of 12 patients with chronic aphasia and different left hemisphere lesion patterns 2 weeks after treatment. Yet, the neural correlates of these improvements were not investigated.

Finally, as a somehow paradoxical result, two studies reported beneficial effects of inhibitory NIBS over the ipsilesional left inferior frontal gyrus (Jung et al., 2011; Monti et al., 2008). However, these findings might be related to specific methodological details (e.g., high stimulation intensity, small sample size, lack of a control group). As neither of these studies performed a long-term follow-up or neuroimaging, it remains unclear what these results reflect.

In summary, the number of studies applying non-invasive stimulation techniques to enhance plasticity in the lesioned language network is currently very limited and results remain equivocal. The neurobiological and behavioural long-term effects of different NIBBS protocols on aphasia recovery are largely unclear. From the current results, it can be concluded that the effects of NIBS techniques critically depend, among others, on the applied stimulation protocols, the task itself and the time of the intervention. Future studies on larger collectives are needed that should test for potential long-term and generalization effects of NIBS in combination with speech and language therapy. Overall, the most important goal is to improve language recovery at a level that is clinically relevant. Consequently, future studies should include outcome measures that are relevant for everyday communication (see Meinzer et al., 2016) and long-term assessments of improvements. So far, it appears most promising to either facilitate remaining residual left-hemispheric activity and/or inhibit contralesional right hemispheric regions. However, future studies are required to identify how the contribution of perilesional and contralesional regions changes across the time course of recovery to identify the most efficient therapeutic strategy in each phase.

Moreover, NIBS treatment should be complemented with functional and structural neuroimaging techniques to associate behavioural improvement with specific changes in language related activity and connectivity. In this context, one previous study reported an increase in the fractional anisotropy of the underlying white matter close to the stimulation site after excitatory rTMS to the left IFG (Allendorfer et al., 2012). The observed changes in fractional anisotropy were not restricted to the stimulation site but also occurred in distant right hemisphere regions, probably indicating remote effects of the stimulation. These preliminary findings suggest that a complementary approach of combining structural and functional imaging might be suited to provide more

insights into the plastic effects of non-invasive brain stimulation in aphasia recovery.

Future studies might also optimize the individual target site(s) for NIBS based on the individual recovery map and/or lesion site (cf. Abo et al., 2012; Shah-Basak et al., 2015; Szaflarski et al., 2011). Another promising approach, at least for overt production training, might be the implementation of an individualized "site finding approach" that tests for the most sensitive region among different stimulation sites to increase stimulation efficiency (e.g. Hamilton et al., 2010; Medina et al., 2012). Moreover, some findings implicate that the montage of the tDCS-electrodes might have a strong influence, with a bi-hemispheric montage being preferable over classical uni-focal tDCS (Marangolo et al., 2014, 2016). As improvements in language are fastest in the first few months after stroke and then gradually decrease (Lendrem and Lincoln, 1985), it might be most efficient to modulate language-related activity with NIBS in the subacute phase after stroke.

Using NIBS for outcome prediction and prediction of therapy response

Lorca-Puls et al. (2017) recently presented a novel rTMS-guided lesion-deficit mapping approach to demonstrate how NIBS results obtained from healthy volunteers might inform outcome prediction in post-stroke aphasia. In that study, stimulation sites identified in the healthy language system could increase the accuracy of outcome prediction in patients with chronic post-stroke aphasia. Accordingly, the classification accuracy of phonological impairments in patients was highest when regions of interest for outcome prediction in the lesioned brain were limited to functionally defined "positive" rTMS sites (i.e., sites where rTMS disrupted behaviour) obtained from healthy subjects. Strikingly, classification accuracy in a large set of 108 chronic patients was better for rTMS-guided mapping than fMRI-guided regions, lesion overlap or regions identified from voxel-based lesion symptom mapping. These results help to identify regions where damage might cause persistent behavioural deficits, indicating that the rTMS-identified regions in the healthy brain are indeed critical for a specific language process.

These results were complemented by Campana et al. (2015) who used voxel-based lesion symptom mapping to identify regions that are predictable of language recovery after anodal tDCS treatment in patients with chronic post-stroke aphasia. To this end, 20 non-fluent patients received 5 sessions of language therapy combined with anodal or sham tDCS (2 mA for 20 min) over the left perilesional inferior frontal gyrus. A 14-day intersession-interval was included between the two stimulation types to avoid carry-over effects. Lesion mapping showed that damage to distinct regions in the left hemisphere predicted lower response to tDCS. In particular, these regions included the basal ganglia, the superior and inferior longitudinal fasciculi and the insula. Despite the small sample size, these results suggest that the structural integrity of language pathways in the left hemisphere might be a central predictor for therapy response after treatment with non-invasive brain stimulation.

Finally, Rosso et al. (2014) demonstrated that the individual response to inhibitory tDCS depends on the lesion site. In their study, a single session of (inhibitory) cathodal tDCS (1 mA for 15 min, compared with sham tDCS) over the contralesional right inferior frontal gyrus improved picture naming accuracy in patients with chronic post-stroke aphasia and lesions in the left IFG. Resting-state connectivity analyses at baseline revealed that these patients had decreased levels of functional inter-hemispheric balance, probably reflecting abnormally increased transcallosal inhibition from the contralesional to the ipsilesional cortex. tDCS-induced improvement was associated with integrity of the left arcuate fasciculus. In contrast, patients with left hemisphere lesions outside the IFG did not respond to tDCS and had normal levels of inter-hemispheric balance. These results might help to identify patients who might benefit from a stimulation-induced suppression of right hemisphere activity during language recovery.

Together, the above-discussed results show how results from NIBS studies might be used to inform outcome prediction and ultimately increase treatment efficiency. Since the number of studies is small and NIBS-informed outcome prediction is still at its infancy, future studies are required to identify critical predictors.

Conclusions and future directions

Across the last two decades, an increasing number of neuroimaging studies in patients with post-stroke aphasia has substantially advanced the current knowledge on loss and recovery of specific language functions after stroke. The main mechanisms are summarized in Fig. 4. In particular, longitudinal studies provide insights into the dynamic changes of language related activity and the contribution of left and right hemisphere regions. However, many issues remain unsolved. For instance, the contribution of the right hemisphere across the time course of recovery is still a hotly

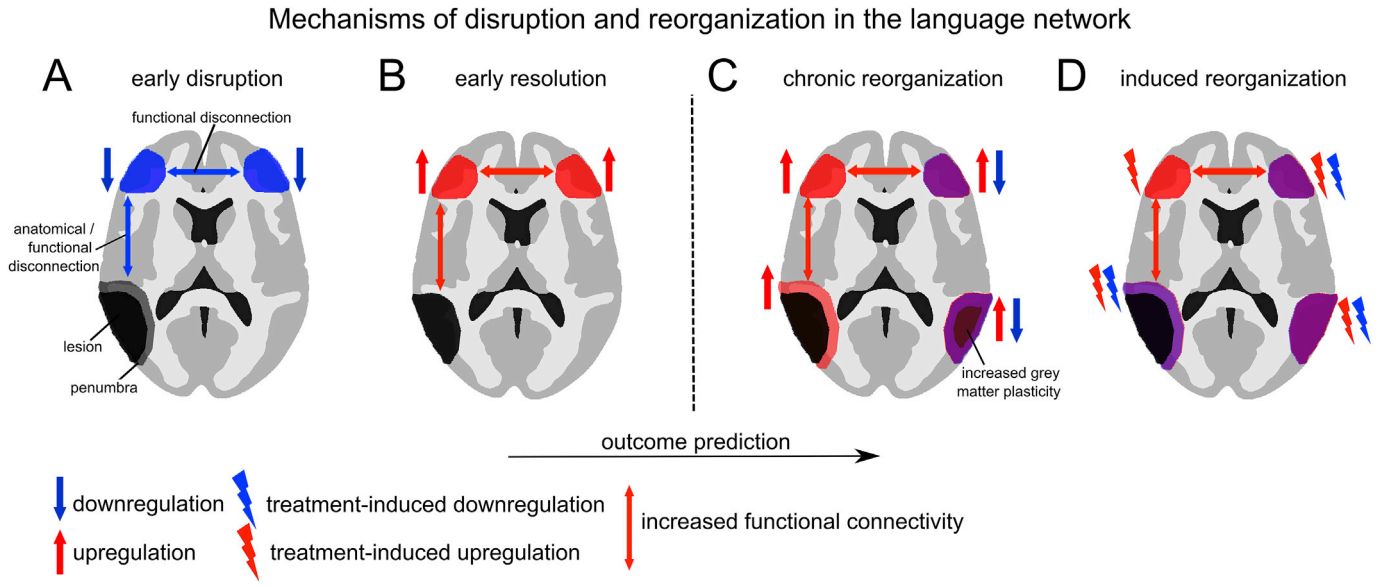

Fig. 4. Schematic overview of mechanisms of disruption and reorganization in the language network. Acute stroke-induced network disruption and early resolution of the network failure is displayed on the left side, chronic spontaneous and treatment-induced reorganization (after behavioural therapy or non-invasive brain stimulation) is shown on the right side. Note that some studies combined inhibition of contralesional right hemisphere regions and facilitation of perilesional left hemisphere regions with non-invasive brain stimulation.

debated topic. Previous studies suggest that the role of right hemisphere regions may change across time, potentially arguing for a phase-specific modulation approach with non-invasive brain stimulation to improve language recovery that might facilitate or inhibit right hemisphere regions in different phases after stroke. In this context, it remains to be explored whether the observed upregulation of the contralesional right frontal cortex in the subacute phase after stroke is mainly associated with the contribution of language-specific or more domain-general processes like attentional resources, working memory or other executive capacities that might be helpful for recovery at earlier stages.

Another open question concerns the neurobiological mechanisms of treatment-induced plasticity. The existing literature on patients with post-stroke aphasia shows that treatment can induce large-scale plastic changes in the chronic stage after stroke. Future studies on larger cohorts are needed to test the generalizability of treatment effects to non-trained items and the long-term stability of the reported improvements. This is important as the dynamics of recruitment might change over time, suggesting that different brain regions might be associated with immediate and long-term treatment effects (see Meinzer et al., 2011). However, given the large inter-subject variability with respect to lesion site, size and symptoms after stroke, the selection of homogeneous patient groups remains a major challenge. To account for these issues, future studies might define subgroups that are balanced with respect to these criteria to identify common mechanisms for specific lesion patterns or aphasic syndromes.

While most of the previous studies on treatment-induced plasticity selectively focused on changes in task-related neural activity, only a few studies considered plastic changes in the white matter connectivity of the language network in response to treatment (e.g. McKinnon et al., 2017; Meinzer et al., 2010; Schlaug et al., 2009; Wan et al., 2014). For instance, McKinnon et al. (2017) recently showed that therapy success in naming was correlated with re-strengthening of the inferior longitudinal fasciculus, suggesting that speech recovery is related to structural plasticity of specific linguistic components of the residual language network. These results demonstrate that measures of structural connectivity might complement results obtained from functional MRI and provide a better understanding of plastic changes induced by treatment. Moreover, recent applications of resting state fMRI (Marcotte et al., 2013; van Hees et al., 2014b; Zhu et al., 2014) and graph theory (Bonilha et al., 2016; Sandberg et al., 2015) indicate that treatment induced changes in neuroplasticity might modulate functional connectivity between language regions in a large network rather than in isolated areas (see also Crinion et al., 2013; Schofield et al., 2012). This is supported by the few existing studies that investigated treatment-induced changes in task-related effective connectivity (e.g. Abutalebi et al., 2009; Vitali et al., 2010). A better understanding of the changes in the interaction between language regions due to spontaneous or treatment-induced recovery might substantially advance the current knowledge about large-scale plasticity in the language network.

Hence, future studies on large collectives should systematically investigate changes in structural, functional and effective connectivity across the time course of recovery and after treatment. The way forward will be the integration of data obtained from multimodal and complementary approaches such as functional and structural neuroimaging and non-invasive brain stimulation. Such data should be linked with assessments of long-term improvements in everyday communication. Finally, while previous studies mainly focused on univariate approaches to map plasticity in the reorganized language network, multivariate analyses might be more sensitive and thus better suited to capture brain changes that drive recovery from aphasia.

References

Abel, S., Weiller, C., Huber, W., Willmes, K., Specht, K., 2015. Therapy-induced brain reorganization patterns in aphasia. Brain 138, 1097–1112.

Abo, M., Kakuda, W., Watanabe, M., Morooka, A., Kawakami, K., Senoo, A., 2012. Effectiveness of low-frequency rTMS and intensive speech therapy in poststroke patients with aphasia: a pilot study based on evaluation by fMRI in relation to type of aphasia. Eur. Neurol. 68, 199–208.

Abutalebi, J., Rosa, P.A., Tettamanti, M., Green, D.W., Cappa, S.F., 2009. Bilingual aphasia and language control: a follow-up fMRI and intrinsic connectivity study. Brain Lang. 109, 141–156.

Allendorfer, J.B., Storrs, J.M., Szaflarski, J.P., 2012. Changes in white matter integrity follow excitatory rTMS treatment of post-stroke aphasia. Restor. Neurol. Neurosci. 30, 103–113.

Andoh, J., Paus, T., 2011. Combining functional neuroimaging with off-line brain stimulation: modulation of task-related activity in language areas. J. Cogn. Neurosci. 23, 349–361.

Baciu, M., Acher, A., Kauffmann, L., Cousin, E., Boilley, C., Hueber, T., Badin, P., Perrier, P., Fabre, D., Jaillard, A., Detante, O., Perennou, D., 2016. Effect of visual feedback on speech recovery and language plasticity in patients with post-stroke non-fluent aphasia. Functional MRI assessment. Ann. Phys. Rehabilitation Med. 595, e67–e79.

Baker, J.M., Rorden, C., Fridriksson, J., 2010. Using transcranial direct-current stimulation to treat stroke patients with aphasia. Stroke 41, 1229–1236.

Barthel, G., Meinzer, M., Djundja, D., Rockstroh, B., 2008. Intensive language therapy in chronic aphasia: which aspects contribute most? Aphasiology 22, 408–421.

Benjamin, M.L., Towler, S., Garcia, A., Park, H., Sudhyadhom, A., Harnish, S., McGregor, K.M., Zlatar, Z., Reilly, J.J., Rosenbek, J.C., Gonzalez Rothi, L.J., Crosson, B., 2014. A behavioral manipulation engages right frontal cortex during aphasia therapy. Neurorehabil Neural Repair 28, 545–553.

Berthier, M.L., 2005. Poststroke aphasia : epidemiology, pathophysiology and treatment. Drugs Aging 22, 163–182.

Berthier, M.L., Dávila, G., Green-Heredia, C., Moreno Torres, I., De Mier, R., De-Torres, I., Ruiz-Cruces, R., 2014. Massed sentence repetition training can augment and speed up recovery of speech production deficits in patients with chronic conduction aphasia receiving donepezil treatment. Aphasiology 28, 188–218.

Berthier, M.L., Green, C., Lara, J.P., Higueras, C., Barbancho, M.A., Davila, G., Pulvermuller, F., 2009. Memantine and constraint-induced aphasia therapy in chronic poststroke aphasia. Ann. Neurol. 65, 577–585.

Berthier, M.L., Hinojosa, J., Martin Mdel, C., Fernandez, I., 2003. Open-label study of donepezil in chronic poststroke aphasia. Neurology 60, 1218–1219.

Berthier, M.L., Pulvermuller, F., 2011. Neuroscience insights improve neurorehabilitation of poststroke aphasia. Nat. Rev. Neurol. 7, 86–97.

Berthier, M.L., Pulvermuller, F., Davila, G., Casares, N.G., Gutierrez, A., 2011. Drug therapy of post-stroke aphasia: a review of current evidence. Neuropsychol. Rev. 21, 302–317.

Bestmann, S., Ruff, C.C., Diver, J., Blankenburg, F., 2008. Concurrent TMS and functional magnetic resonance imaging: methods and current advances. In: Wassermann, E.M., Epstein, C.M., Ziemann, U., Walsh, V., Paus, T., Lisanby, S.H. (Eds.), The Oxford Handbook of Transcranial Stimulation. Oxford University Press, New York.

Bindman, L.J., Lippold, O.C.J., Redfearn, J.W.T., 1964. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J. Physiol. 172, 369–382.

Binney, R.J., Lambon Ralph, M.A., 2015. Using a combination of fMRI and anterior temporal lobe rTMS to measure intrinsic and induced activation changes across the semantic cognition network. Neuropsychologia 76, 170–181.

Blasi, V., Young, A.C., Tansy, A.P., Petersen, S.E., Snyder, A.Z., Corbetta, M., 2002. Word retrieval learning modulates right frontal cortex in patients with left frontal damage. Neuron 36, 159–170.

Boes, A.D., Prasad, S., Liu, H., Liu, Q., Pascual-Leone, A., Caviness Jr., V.S., Fox, M.D., 2015. Network localization of neurological symptoms from focal brain lesions. Brain 138, 3061–3075.

Bonilha, L., Gleichgerrcht, E., Nesland, T., Rorden, C., Fridriksson, J., 2016. Success of anomia treatment in aphasia is associated with preserved architecture of global and left temporal lobe structural networks. Neurorehabil Neural Repair 30, 266–279.

Bonilha, L., Hillis, A.E., Hickok, G., Den Ouden, D.B., Rorden, C., Fridriksson, J., 2017. Temporal lobe networks supporting the comprehension of spoken words. Brain 140 (9), 2370–2380.

Bonilha, L., Rorden, C., Fridriksson, J., 2014. Assessing the clinical effect of residual cortical disconnection after ischemic strokes. Stroke 45, 988–993.

Breier, J.I., Juranek, J., Maher, L.M., Schmadeke, S., Men, D., Papanicolaou, A.C., 2009. Behavioral and neurophysiologic response to therapy for chronic aphasia. Arch. Phys. Med. Rehabil. 90, 2026–2033.

Breier, J.I., Maher, L.M., Schmadeke, S., Hasan, K.M., Papanicolaou, A.C., 2007. Changes in language-specific brain activation after therapy for aphasia using magnetoencephalography: a case study. Neurocase 13, 169–177.

Breitenstein, C., Grewe, T., Flöel, A., Ziegler, W., Springer, L., Martus, P., Huber, W., Willmes, K., Ringelstein, E., Haeusler, K., Abel, S., Glindemann, R., Domahs, F., Regenbrecht, F., Schlenck, K., Thomas, M., Obrig, H., de Langen, E., Rocker, R., Wigbers, F., Rühmkorf, C., Hempen, I., List, J., Baumgaertner, A., Group, F.E.s, 2017. Intensive speech and language therapy in patients with chronic aphasia after stroke: a randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. Lancet 389, 1528–1538.

Brownsett, S.L., Warren, J.E., Geranmayeh, F., Woodhead, Z., Leech, R., Wise, R.J., 2014. Cognitive control and its impact on recovery from aphasic stroke. Brain 137, 242–254.

Buetefisch, C.M., 2015. Role of the contralesional hemisphere in post-stroke recovery of upper extremity motor function. Front. Neurol. 6, 214.

Butler, R.A., Lambon Ralph, M.A., Woollams, A.M., 2014. Capturing multidimensionality in stroke aphasia: mapping principal behavioural components to neural structures. Brain 137, 3248–3266.

Campana, S., Caltagirone, C., Marangolo, P., 2015. Combining voxel-based lesion-symptom mapping (VLSM) with a-tDCS language treatment: predicting outcome of recovery in nonfluent chronic aphasia. Brain Stimul. 8, 769–776.
Cao, Y., Vikingstad, E.M., George, K.P., Johnson, A.F., Welch, K.M., 1999. Cortical language activation in stroke patients recovering from aphasia with functional MRI. Stroke 30, 2331–2340.
Carlomagno, S., Pandolfi, M., Labruna, L., Colombo, A., Razzano, C., 2001. Recovery from moderate aphasia in the first year poststroke: effect of type of therapy. Arch. Phys. Med. Rehabil. 82, 1073–1080.
Carrera, E., Tononi, G., 2014. Diaschisis: past, present, future. Brain 137, 2408–2422.
Carter, A.R., Shulman, G.L., Corbetta, M., 2012. Why use a connectivity-based approach to study stroke and recovery of function? Neuroimage 62, 2271–2280.
Cherney, L.R., Patterson, J.P., Raymer, A., Frymark, T., Schooling, T., 2008. 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. 51, 1282–1299.
Cohen, L., Chaaban, B., Habert, M.O., 2004. Transient improvement of aphasia with zolpidem. N. Engl. J. Med. 350, 949–950.
Corbetta, M., Ramsey, L., Callejas, A., Baldassarre, A., Hacker, C.D., Siegel, J.S., Astafiev, S.V., Rengachary, J., Zinn, K., Lang, C.E., Connor, L.T., Fucetola, R., Strube, M., Carter, A.R., Shulman, G.L., 2015. Common behavioral clusters and subcortical anatomy in stroke. Neuron 85, 927–941.
Coslett, H.B., 2016. Non-invasive brain stimulation in aphasia therapy: lessons from TMS and tDCS. In: Hickok, G., Small, S. (Eds.), Neurobiology of Language. Elsevier, Oxford, pp. 1035–1054.
Crinion, J., Holland, A.L., Copland, D.A., Thompson, C.K., Hillis, A.E., 2013. Neuroimaging in aphasia treatment research: quantifying brain lesions after stroke. Neuroimage 73, 208–214.
Crinion, J., Price, C.J., 2005. Right anterior superior temporal activation predicts auditory sentence comprehension following aphasic stroke. Brain 128, 2858–2871.
Crinion, J.T., Leff, A.P., 2007. Recovery and treatment of aphasia after stroke: functional imaging studies. Curr. Opin. Neurol. 20, 667–673.
Crinion, J.T., Leff, A.P., 2015. Using functional imaging to understand therapeutic effects in poststroke aphasia. Curr. Opin. Neurol. 28, 330–337.
Crinion, J.T., Warburton, E.A., Lambon-Ralph, M.A., Howard, D., Wise, R.J., 2006. Listening to narrative speech after aphasic stroke: the role of the left anterior temporal lobe. Cereb. Cortex 16, 1116–1125.
Crosson, B., Moore, A.B., Gopinath, K., White, K.D., Wierenga, C.E., Gaiefsky, M.E., Fabrizio, K.S., Peck, K.K., Soltysik, D., Milsted, C., Briggs, R.W., Conway, T.W., Gonzalez Rothi, L.J., 2005. Role of the right and left hemispheres in recovery of function during treatment of intention in aphasia. J. Cogn. Neurosci. 17, 392–406.
Crosson, B., Moore, A.B., McGregor, K.M., Chang, Y.L., Benjamin, M., Gopinath, K., Sherod, M.E., Wierenga, C.E., Peck, K.K., Briggs, R.W., Rothi, L.J., White, K.D., 2009. Regional changes in word-production laterality after a naming treatment designed to produce a rightward shift in frontal activity. Brain Lang. 111, 73–85.
Dafotakis, M., Grefkes, C., Wang, L., Fink, G.R., Nowak, D.A., 2008. The effects of 1 Hz rTMS over the hand area of M1 on movement kinematics of the ipsilateral hand. J. neural Transm. 115, 1269–1274.
Darkow, R., Martin, A., Wurtz, A., Floel, A., Meinzer, M., 2017. Transcranial direct current stimulation effects on neural processing in post-stroke aphasia. Hum. Brain. Mapp. 38, 1518–1531.
DaSilva, A.F., Truong, Truong, D.Q., DosSantos, M.F., Toback, R.L., Datta, A., Bikson, M., 2015. State-of-art neuroanatomical target analysis of high-definition and conventional tDCS montages used for migraine and pain control. Front. Neuroanat. 9, 89.
Davis, S.W., Cabeza, R., 2015. Cross-hemispheric collaboration and segregation associated with task difficulty as revealed by structural and functional connectivity. J. Neurosci. 35, 8191–8200.
de Aguiar, V., Paolazzi, C.L., Miceli, G., 2015. tDCS in post-stroke aphasia: the role of stimulation parameters, behavioral treatment and patient characteristics. Cortex 63, 296–316.
Dunn, L.E., Schweber, A.B., Manson, D.K., Lendaris, A., Herber, C., Marshall, R.S., Lazar, R.M., 2016. Variability in motor and language recovery during the acute stroke period. Cerebrovasc. Dis. Extra 6, 12–21.
Elsner, B., Kugler, J., Pohl, M., Mehrholz, J., 2013a. Transcranial direct current stimulation (tDCS) for improving function and activities of daily living in patients after stroke. Cochrane Database Syst. Rev. CD009645.
Elsner, B., Kugler, J., Pohl, M., Mehrholz, J., 2013b. Transcranial direct current stimulation (tDCS) for improving aphasia in patients with aphasia after stroke. Cochrane Database Syst. Rev. CD009760.
Floel, A., 2012. Non-invasive brain stimulation and language processing in the healthy brain. Aphasiology 26, 1082–1102.
Floel, A., Cohen, L.G., 2010. Recovery of function in humans: cortical stimulation and pharmacological treatments after stroke. Neurobiol. Dis. 37, 243–251.
Floel, A., Meinzer, M., Kirstein, R., Nijhof, S., Deppe, M., Knecht, S., Breitenstein, C., 2011. Short-term anomia training and electrical brain stimulation. Stroke 42, 2065–2067.
Forkel, S.J., Thiebaut de Schotten, M., Dell'Acqua, F., Kalra, L., Murphy, D.G., Williams, S.C., Catani, M., 2014. Anatomical predictors of aphasia recovery: a tractography study of bilateral perisylvian language networks. Brain 137, 2027–2039.
Fridriksson, J., Basilakos, A., Hickok, G., Bonilha, L., Rorden, C., 2015a. Speech entrainment compensates for Broca's area damage. Cortex 69, 68–75.
Fridriksson, J., Bonilha, L., Baker, J.M., Moser, D., Rorden, C., 2010a. Activity in preserved left hemisphere regions predicts anomia severity in aphasia. Cereb. Cortex 20, 1013–1019.
Fridriksson, J., Fillmore, P., Guo, D., Rorden, C., 2015b. Chronic Broca's aphasia is caused by damage to Broca's and Wernicke's areas. Cereb. Cortex 25, 4689–4696.
Fridriksson, J., Hubbard, H.I., Hudspeth, S.G., Holland, A.L., Bonilha, L., Fromm, D., Rorden, C., 2012a. Speech entrainment enables patients with Broca's aphasia to produce fluent speech. Brain 135, 3815–3829.
Fridriksson, J., Kjartansson, O., Morgan, P.S., Hjaltason, H., Magnusdottir, S., Bonilha, L., Rorden, C., 2010b. Impaired speech repetition and left parietal lobe damage. J. Neurosci. 30, 11057–11061.
Fridriksson, J., Morrow-Odom, L., Moser, D., Fridriksson, A., Baylis, G., 2006. Neural recruitment associated with anomia treatment in aphasia. Neuroimage 32, 1403–1412.
Fridriksson, J., Richardson, J.D., Baker, J.M., Rorden, C., 2011. Transcranial direct current stimulation improves naming reaction time in fluent aphasia: a double-blind, sham-controlled study. Stroke 42, 819–821.
Fridriksson, J., Richardson, J.D., Fillmore, P., Cai, B., 2012b. Left hemisphere plasticity and aphasia recovery. Neuroimage 60, 854–863.
Fridriksson, J., Yourganov, G., Bonilha, L., Basilakos, A., Den Ouden, D.B., Rorden, C., 2016. Revealing the dual streams of speech processing. Proc. Natl. Acad. Sci. U. S. A. 113, 15108–15113.
Friederici, A.D., 2012. The cortical language circuit: from auditory perception to sentence comprehension. Trends Cogn. Sci. 16, 262–268.
Geranmayeh, F., Brownsett, S.L., Wise, R.J., 2014. Task-induced brain activity in aphasic stroke patients: what is driving recovery? Brain 137, 2632–2648.
Goldstein, L.B., 1999. Pharmacological approach to functional reorganization: the role of norepinephrine. Rev. Neurol. Paris. 155, 731–736.
Goldstein, L.B., 2000. Effects of amphetamines and small related molecules on recovery after stroke in animals and man. Neuropharmacology 39, 852–859.
Grefkes, C., Fink, G.R., 2014. Connectivity-based approaches in stroke and recovery of function. Lancet Neurol. 13, 206–216.
Grefkes, C., Nowak, D.A., Wang, L.E., Dafotakis, M., Eickhoff, S.B., Fink, G.R., 2010. Modulating cortical connectivity in stroke patients by rTMS assessed with fMRI and dynamic causal modeling. Neuroimage 50, 233–242.
Grefkes, C., Ward, N.S., 2014. Cortical reorganization after stroke: how much and how functional? Neuroscientist 20, 56–70.
Gungor, L., Terzi, M., Onar, M.K., 2011. Does long term use of piracetam improve speech disturbances due to ischemic cerebrovascular diseases? Brain Lang. 117, 23–27.
Hallam, G.P., Whitney, C., Hymers, M., Gouws, A.D., Jefferies, E., 2016. Charting the effects of TMS with fMRI: modulation of cortical recruitment within the distributed network supporting semantic control. Neuropsychologia 93, 40–52.
Hamilton, R.H., Chrysikou, E.G., Coslett, B., 2011. Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. Brain Lang. 118, 40–50.
Hamilton, R.H., Sanders, L., Benson, J., Faseyitan, O., Norise, C., Naeser, M., Martin, P., Coslett, H.B., 2010. Stimulating conversation: enhancement of elicited propositional speech in a patient with chronic non-fluent aphasia following transcranial magnetic stimulation. Brain Lang. 113, 45–50.
Hartwigsen, G., 2016. Adaptive plasticity in the healthy language network: implications for language recovery after stroke. Neural Plast. 2016:9674790. Epub 2016 Oct 18. Review.
Hartwigsen, G., Bzdok, D., Klein, M., Wawrzyniak, M., Stockert, A., Wrede, K., Classen, J., Saur, D., 2017. Rapid short-term reorganization in the language network. Elife 6.
Hartwigsen, G., Saur, D., Price, C.J., Ulmer, S., Baumgaertner, A., Siebner, H.R., 2013. Perturbation of the left inferior frontal gyrus triggers adaptive plasticity in the right homologous area during speech production. Proc. Natl. Acad. Sci. U. S. A. 110, 16402–16407.
Hartwigsen, G., Siebner, H.R., 2013. Novel methods to study aphasia recovery after stroke. Front. Neurology Neurosci. 32, 101–111.
Hartwigsen, G., Weigel, A., Schuschan, P., Siebner, H.R., Weise, D., Classen, J., Saur, D., 2016. Dissociating parieto-frontal networks for phonological and semantic word decisions: a condition-and-perturb TMS study. Cereb. Cortex 26, 2590–2601.
Heiss, W.D., Hartmann, A., Rubi-Fessen, I., Anglade, C., Kracht, L., Kessler, J., Weiduschat, N., Rommel, T., Thiel, A., 2013. Noninvasive brain stimulation for treatment of right- and left-handed poststroke aphasics. Cerebrovasc. Dis. 36, 363–372.
Henseler, I., Regenbrecht, F., Obrig, H., 2014. Lesion correlates of patholinguistic profiles in chronic aphasia: comparisons of syndrome-, modality- and symptom-level assessment. Brain 137, 918–930.
Hickok, G., Poeppel, D., 2007. The cortical organization of speech processing. Nat. Rev. Neurosci. 8, 393–402.
Hillis, A.E., 2007. Aphasia: progress in the last quarter of a century. Neurology 69, 200–213.
Hillis, A.E., Kleinman, J.T., Newhart, M., Heidler-Gary, J., Gottesman, R., Barker, P.B., Aldrich, E., Llinas, R., Wityk, R., Chaudhry, P., 2006. Restoring cerebral blood flow reveals neural regions critical for naming. J. Neurosci. 26, 8069–8073.
Hillis, A.E., Wityk, R.J., Tuffiash, E., Beauchamp, N.J., Jacobs, M.A., Barker, P.B., Selnes, O.A., 2001. Hypoperfusion of Wernicke's area predicts severity of semantic deficit in acute stroke. Ann. Neurol. 50, 561–566.
Holland, R., Crinion, J., 2012. Can tDCS enhance treatment of aphasia after stroke? Aphasiology 26, 1169–1191.
Holland, R., Leff, A.P., Josephs, O., Galea, J.M., Desikan, M., Price, C.J., Rothwell, J.C., Crinion, J., 2011. Speech facilitation by left inferior frontal cortex stimulation. Curr. Biol. 21, 1403–1407.
Holland, R., Leff, A.P., Penny, W.D., Rothwell, J.C., Crinion, J., 2016. Modulation of frontal effective connectivity during speech. Neuroimage 140, 126–133.
Hope, T.M.H., Leff, A.P., Prejawa, S., Bruce, R., Haigh, Z., Lim, L., Ramsden, S., Oberhuber, M., Ludersdorfer, P., Crinion, J., Seghier, M.L., Price, C.J., 2017. Right

hemisphere structural adaptation and changing language skills years after left hemisphere stroke. Brain 140, 1718–1728.
Huang, Y.Z., Edwards, M.J., Rounis, E., Bhatia, K.P., Rothwell, J.C., 2005. Theta burst stimulation of the human motor cortex. Neuron 45, 201–206.
Huber, W., Poeck, K., Willmes, K., 1984. The aachen aphasia test. Adv. Neurology 42, 291–303.
Hummel, F.C., Celnik, P., Pascual-Leone, A., Fregni, F., Byblow, W.D., Buetefisch, C.M., Rothwell, J., Cohen, L.G., Gerloff, C., 2008. Controversy: noninvasive and invasive cortical stimulation show efficacy in treating stroke patients. Brain Stimul. 1, 370–382.
Jacobson, L., Koslowsky, M., Lavidor, M., 2012. TDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp. Brain Res. 216 (1), 1–10.
Jarso, S., Li, M., Faria, A., Davis, C., Leigh, R., Sebastian, R., Tsapkini, K., Mori, S., Hillis, A.E., 2013. Distinct mechanisms and timing of language recovery after stroke. Cogn. Neuropsychol. 30, 454–475.
Jung, I.Y., Lim, J.Y., Kang, E.K., Sohn, H.M., Paik, N.J., 2011. The factors associated with good responses to speech therapy combined with transcranial direct current stimulation in post-stroke aphasic patients. Ann. Rehabil. Med. 35, 460–469.
Jung, J., Lambon Ralph, M.A., 2016. Mapping the dynamic network interactions underpinning cognition: a cTBS-fMRI study of the flexible adaptive neural system for semantics. Cereb. Cortex 26, 3580–3590.
Karbe, H., Kessler, J., Herholz, K., Fink, G.R., Heiss, W.D., 1995. Long-term prognosis of poststroke aphasia studied with positron emission tomography. Arch. Neurol. 52, 186–190.
Karnath, H.O., Rennig, J., 2017. Investigating structure and function in the healthy human brain: validity of acute versus chronic lesion-symptom mapping. Brain Struct. Funct. 222, 2059–2070.
Kessler, J., Thiel, A., Karbe, H., Heiss, W.D., 2000. Piracetam improves activated blood flow and facilitates rehabilitation of poststroke aphasic patients. Stroke 31, 2112–2116.
Khedr, E.M., Abo El-Fetoh, N., Ali, A.M., El-Hammady, D.H., Khalifa, H., Atta, H., Karim, A.A., 2014. Dual-hemisphere repetitive transcranial magnetic stimulation for rehabilitation of poststroke aphasia: a randomized, double-blind clinical trial. Neurorehabil Neural Repair 28, 740–750.
Kim, S.H., Jang, S.H., 2013. Prediction of aphasia outcome using diffusion tensor tractography for arcuate fasciculus in stroke. AJNR Am. J. Neuroradiol. 34, 785–790.
Kindler, J., Schumacher, R., Cazzoli, D., Gutbrod, K., Koenig, M., Nyffeler, T., Dierks, T., Muri, R.M., 2012. Theta burst stimulation over the right Broca's homologue induces improvement of naming in aphasic patients. Stroke 43, 2175–2179.
Kiran, S., Ansaldo, A., Bastiaanse, R., Cherney, L.R., Howard, D., Faroqi-Shah, Y., Meinzer, M., Thompson, C.K., 2013. Neuroimaging in aphasia treatment research: standards for establishing the effects of treatment. Neuroimage 76, 428–435.
Klingbeil, J., Wawrzyniak, M., Stockert, A., Saur, D., 2017. Resting-state functional connectivity: an emerging method for the study of language networks in post-stroke aphasia. Brain Cogn. https://doi.org/10.1016/j.bandc.2017.08.005, 2017 Aug 30. pii: S0278–2626(17)30107-0.
Kummerer, D., Hartwigsen, G., Kellmeyer, P., Glauche, V., Mader, I., Kloppel, S., Suchan, J., Karnath, H.O., Weiller, C., Saur, D., 2013. Damage to ventral and dorsal language pathways in acute aphasia. Brain 136, 619–629.
Leff, A., Crinion, J., Scott, S., Turkheimer, F., Howard, D., Wise, R., 2002. A physiological change in the homotopic cortex following left posterior temporal lobe infarction. Ann. Neurol. 51, 553–558.
Leger, A., Demonet, J.F., Ruff, S., Aithamon, B., Touyeras, B., Puel, M., Boulanouar, K., Cardebat, D., 2002. Neural substrates of spoken language rehabilitation in an aphasic patient: an fMRI study. Neuroimage 17, 174–183.
Lendrem, W., Lincoln, N.B., 1985. Spontaneous recovery of language in patients with aphasia between 4 and 34 weeks after stroke. J. Neurol. Neurosurg. Psychiatry 48, 743–748.
Lindenberg, R., Nachtigall, L., Meinzer, M., Sieg, M.M., Floel, A., 2013. Differential effects of dual and unihemispheric motor cortex stimulation in older adults. J. Neurosci. 33, 9176–9183.
Lindenberg, R., Sieg, M.M., Meinzer, M., Nachtigall, L., Floel, A., 2016. Neural correlates of unihemispheric and bihemispheric motor cortex stimulation in healthy young adults. Neuroimage 140, 141–149.
Llano, D.A., Small, S.L., 2016. Pharmacotherapy for aphasia. In: Small, D.S., Hickok, G. (Eds.), The Neurobiology of Language. Elsevier, pp. 1067–1083.
Lorca-Puls, D.L., Gajardo-Vidal, A., Seghier, M.L., Leff, A.P., Sethi, V., Prejawa, S., Hope, T.M.H., Devlin, J.T., Price, C.J., 2017. Using transcranial magnetic stimulation of the undamaged brain to identify lesion sites that predict language outcome after stroke. Brain 140, 1729–1742.
Lotze, M., Markert, J., Sauseng, P., Hoppe, J., Plewnia, C., Gerloff, C., 2006. The role of multiple contralesional motor areas for complex hand movements after internal capsular lesion. J. Neurosci. 26, 6096–6102.
Marangolo, P., Fiori, V., Gelfo, F., Shofany, J., Razzano, C., Caltagirone, C., Angelucci, F., 2014. Bihemispheric tDCS enhances language recovery but does not alter BDNF levels in chronic aphasic patients. Restor. Neurol. Neurosci. 32, 367–379.
Marangolo, P., Fiori, V., Sabatini, U., De Pasquale, G., Razzano, C., Caltagirone, C., Gili, T., 2016. Bilateral transcranial direct current stimulation language treatment enhances functional connectivity in the left hemisphere: preliminary data from aphasia. J. Cogn. Neurosci. 28, 724–738.
Marcotte, K., Adrover-Roig, D., Damien, B., de Preaumont, M., Genereux, S., Hubert, M., Ansaldo, A.I., 2012. Therapy-induced neuroplasticity in chronic aphasia. Neuropsychologia 50, 1776–1786.
Marcotte, K., Perlbarg, V., Marrelec, G., Benali, H., Ansaldo, A.I., 2013. Default-mode network functional connectivity in aphasia: therapy-induced neuroplasticity. Brain Lang. 124, 45–55.
Marsh, E.B., Hillis, A.E., 2006. Recovery from aphasia following brain injury: the role of reorganization. Prog. Brain Res. 157, 143–156.
Marshall, J.F., 1984. Brain function: neural adaptations and recovery from injury. Annu. Rev. Psychol. 35, 277–308.
Martin, P.I., Naeser, M.A., Ho, M., Doron, K.W., Kurland, J., Kaplan, J., Wang, Y., Nicholas, M., Baker, E.H., Fregni, F., Pascual-Leone, A., 2009. Overt naming fMRI pre- and post-TMS: two nonfluent aphasia patients, with and without improved naming post-TMS. Brain Lang. 111, 20–35.
Mattioli, F., Ambrosi, C., Mascaro, L., Scarpazza, C., Pasquali, P., Frugoni, M., Magoni, M., Biagi, L., Gasparotti, R., 2014. Early aphasia rehabilitation is associated with functional reactivation of the left inferior frontal gyrus: a pilot study. Stroke 45, 545–552.
McKinnon, E.T., Fridriksson, J., Glenn, G.R., Jensen, J.H., Helpern, J.A., Basilakos, A., Rorden, C., Shih, A.Y., Spampinato, M.V., Bonilha, L., 2017. Structural plasticity of the ventral stream and aphasia recovery. Ann. Neurol. 82 (1), 147–151.
Medina, J., Norise, C., Faseyitan, O., Coslett, H.B., Turkeltaub, P.E., Hamilton, R.H., 2012. Finding the right words: transcranial magnetic stimulation improves discourse productivity in non-fluent aphasia after stroke. Aphasiology 26, 1153–1168.
Meinzer, M., Antonenko, D., Lindenberg, R., Hetzer, S., Ulm, L., Avirame, K., Flaisch, T., Floel, A., 2012a. Electrical brain stimulation improves cognitive performance by modulating functional connectivity and task-specific activation. J. Neurosci. 32, 1859–1866.
Meinzer, M., Breitenstein, C., 2008. Functional imaging studies of treatment-induced recovery in chronic aphasia. Aphasiology 22, 1251–1268.
Meinzer, M., Darkow, R., Lindenberg, R., Floel, A., 2016. Electrical stimulation of the motor cortex enhances treatment outcome in post-stroke aphasia. Brain 139, 1152–1163.
Meinzer, M., Djundja, D., Barthel, G., Elbert, T., Rockstroh, B., 2005. Long-term stability of improved language functions in chronic aphasia after constraint-induced aphasia therapy. Stroke 36, 1462–1466.
Meinzer, M., Elbert, T., Wienbruch, C., Djundja, D., Barthel, G., Rockstroh, B., 2004. Intensive language training enhances brain plasticity in chronic aphasia. BMC Biol. 2, 20.
Meinzer, M., Flaisch, T., Breitenstein, C., Wienbruch, C., Elbert, T., Rockstroh, B., 2008. Functional re-recruitment of dysfunctional brain areas predicts language recovery in chronic aphasia. Neuroimage 39, 2038–2046.
Meinzer, M., Harnish, S., Conway, T., Crosson, B., 2011. Recent developments in functional and structural imaging of aphasia recovery after stroke. Aphasiology 25, 271–290.
Meinzer, M., Mohammadi, S., Kugel, H., Schiffbauer, H., Floel, A., Albers, J., Kramer, K., Menke, R., Baumgartner, A., Knecht, S., Breitenstein, C., Deppe, M., 2010. Integrity of the hippocampus and surrounding white matter is correlated with language training success in aphasia. Neuroimage 53, 283–290.
Meinzer, M., Obleser, J., Flaisch, T., Eulitz, C., Rockstroh, B., 2007. Recovery from aphasia as a function of language therapy in an early bilingual patient demonstrated by fMRI. Neuropsychologia 45, 1247–1256.
Meinzer, M., Rodriguez, A.D., Gonzalez Rothi, L.J., 2012b. First decade of research on constrained-induced treatment approaches for aphasia rehabilitation. Arch. Phys. Med. Rehabil. 93, S35–S45.
Menke, R., Meinzer, M., Kugel, H., Deppe, M., Baumgartner, A., Schiffbauer, H., Thomas, M., Kramer, K., Lohmann, H., Floel, A., Knecht, S., Breitenstein, C., 2009. Imaging short- and long-term training success in chronic aphasia. BMC Neurosci. 10, 118.
Mohr, B., MacGregor, L.J., Difrancesco, S., Harrington, K., Pulvermuller, F., Shtyrov, Y., 2016. Hemispheric contributions to language reorganisation: an MEG study of neuroplasticity in chronic post stroke aphasia. Neuropsychologia 93, 413–424.
Monakow, C.v., 1906. Aphasie und diaschisis. Neurol. Cent. 25, 1026–1038.
Monti, A., Cogiamanian, F., Marceglia, S., Ferrucci, R., Mameli, F., Mrakic-Sposta, S., Vergari, M., Zago, S., Priori, A., 2008. Improved naming after transcranial direct current stimulation in aphasia. J. Neurol. Neurosurg. Psychiatry 79, 451–453.
Musso, M., Weiller, C., Kiebel, S., Muller, S.P., Bulau, P., Rijntjes, M., 1999. Training-induced brain plasticity in aphasia. Brain 122 (Pt 9), 1781–1790.
Naeser, M.A., Martin, P.I., Baker, E.H., Hodge, S.M., Sczerzenie, S.E., Nicholas, M., Palumbo, C.L., Goodglass, H., Wingfield, A., Samaraweera, R., Harris, G., Baird, A., Renshaw, P., Yurgelun-Todd, D., 2004. Overt propositional speech in chronic nonfluent aphasia studied with the dynamic susceptibility contrast fMRI method. Neuroimage 22, 29–41.
Naeser, M.A., Martin, P.I., Lundgren, K., Klein, R., Kaplan, J., Treglia, E., Ho, M., Nicholas, M., Alonso, M., Pascual-Leone, A., 2010a. Improved language in a chronic nonfluent aphasia patient after treatment with CPAP and TMS. Cogn. Behav. Neurol. 23, 29–38.
Naeser, M.A., Martin, P.I., Nicholas, M., Baker, E.H., Seekins, H., Helm-Estabrooks, N., Cayer-Meade, C., Kobayashi, M., Theoret, H., Fregni, F., Tormos, J.M., Kurland, J., Doron, K.W., Pascual-Leone, A., 2005a. Improved naming after TMS treatments in a chronic, global aphasia patient–case report. Neurocase 11, 182–193.
Naeser, M.A., Martin, P.I., Nicholas, M., Baker, E.H., Seekins, H., Kobayashi, M., Theoret, H., Fregni, F., Maria-Tormos, J., Kurland, J., Doron, K.W., Pascual-Leone, A., 2005b. Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study. Brain Lang. 93, 95–105.
Naeser, M.A., Martin, P.I., Treglia, E., Ho, M., Kaplan, E., Bashir, S., Hamilton, R., Coslett, H.B., Pascual-Leone, A., 2010b. Research with rTMS in the treatment of aphasia. Restor. Neurol. Neurosci. 28, 511–529.
Nardo, D., Holland, R., Leff, A.P., Price, C.J., Crinion, J.T., 2017. Less is more: neural mechanisms underlying anomia treatment in chronic aphasic patients. Brain. Sept. 27, 2017, awx234. https://doi.org/10.1093/brain/awx234.

Nouwens, F., de Lau, L.M.L., Visch-Brink, E.G., van de Sandt-Koenderman, M.W., Lingsma, H.F., Goosen, S., Blom, D.M., Koudstaal, P.J., Dippel, D.W., Investigators, o.b.o.t.R., 2017. Efficacy of early cognitive-linguistic treatment for aphasia due to stroke: a randomised controlled trial (Rotterdam Aphasia Therapy Study-3). Eur. Stroke J. 0, 1–11.
Otal, B., Olma, M.C., Floel, A., Wellwood, I., 2015. Inhibitory non-invasive brain stimulation to homologous language regions as an adjunct to speech and language therapy in post-stroke aphasia: a meta-analysis. Front. Hum. Neurosci. 9, 236.
Pasley, B.N., Knight, R.T., 2013. Decoding speech for understanding and treating aphasia. Prog. Brain Res. 207, 435–456.
Pirulli, C., Fertonani, A., Miniussi, C., 2014. Is neural hyperpolarization by cathodal stimulation always detrimental at the behavioral level? Front. Behav. Neurosci. 8, 226.
Pedersen, P.M., Jorgensen, H.S., Nakayama, H., Raaschou, H.O., Olsen, T.S., 1995. Aphasia in acute stroke: incidence, determinants, and recovery. Ann. Neurol. 38, 659–666.
Pillay, S.B., Binder, J.R., Humphries, C., Gross, W.L., Book, D.S., 2017. Lesion localization of speech comprehension deficits in chronic aphasia. Neurology 88, 970–975.
Poeck, K., Huber, W., Willmes, K., 1989. Outcome of intensive language treatment in aphasia. J. Speech Hear Disord. 54, 471–479.
Polanowska, K.E., Lesniak, M.M., Seniow, J.B., Czepiel, W., Czlonkowska, A., 2013. Anodal transcranial direct current stimulation in early rehabilitation of patients with post-stroke non-fluent aphasia: a randomized, double-blind, sham-controlled pilot study. Restor. Neurol. Neurosci. 31, 761–771.
Price, C.J., Friston, K.J., 2002. Degeneracy and cognitive anatomy. Trends Cogn. Sci. 6, 416–421.
Price, C.J., Warburton, E.A., Moore, C.J., Frackowiak, R.S., Friston, K.J., 2001. Dynamic diaschisis: anatomically remote and context-sensitive human brain lesions. J. Cogn. Neurosci. 13, 419–429.
Pulvermuller, F., Berthier, M.L., 2008. Aphasia therapy on a neuroscience basis. Aphasiology 22, 563–599.
Pulvermuller, F., Fadiga, L., 2010. Active perception: sensorimotor circuits as a cortical basis for language. Nat. Rev. Neurosci. 11, 351–360.
Pulvermuller, F., Hauk, O., Zohsel, K., Neininger, B., Mohr, B., 2005. Therapy-related reorganization of language in both hemispheres of patients with chronic aphasia. Neuroimage 28, 481–489.
Pulvermuller, F., Neininger, B., Elbert, T., Mohr, B., Rockstroh, B., Koebbel, P., Taub, E., 2001. Constraint-induced therapy of chronic aphasia after stroke. Stroke 32, 1621–1626.
Raboyeau, G., De Boissezon, X., Marie, N., Balduyck, S., Puel, M., Bezy, C., Demonet, J.F., Cardebat, D., 2008. Right hemisphere activation in recovery from aphasia: lesion effect or function recruitment? Neurology 70, 290–298.
Rauschecker, J.P., Scott, S.K., 2009. Maps and streams in the auditory cortex: nonhuman primates illuminate human speech processing. Nat. Neurosci. 12, 718–724.
Rehme, A.K., Eickhoff, S.B., Wang, L.E., Fink, G.R., Grefkes, C., 2011a. Dynamic causal modeling of cortical activity from the acute to the chronic stage after stroke. Neuroimage 55 (3), 1147–1158.
Rehme, A.K., Fink, G.R., von Cramon, D.Y., Grefkes, C., 2011b. The role of the contralesional motor cortex for motor recovery in the early days after stroke assessed with longitudinal FMRI. Cereb. Cortex 21, 756–768.
Ren, C.L., Zhang, G.F., Xia, N., Jin, C.H., Zhang, X.H., Hao, J.F., Guan, H.B., Tang, H., Li, J.A., Cai, D.L., 2014. Effect of low-frequency rTMS on aphasia in stroke patients: a meta-analysis of randomized controlled trials. PLoS One 9, e102557.
Richter, M., Miltner, W.H., Straube, T., 2008. Association between therapy outcome and right-hemispheric activation in chronic aphasia. Brain 131, 1391–1401.
Robson, H., Specht, K., Beaumont, H., Parkes, L.M., Sage, K., Lambon Ralph, M.A., Zahn, R., 2017. Arterial spin labelling shows functional depression of non-lesion tissue in chronic Wernicke's aphasia. Cortex 92, 249–260.
Robson, H., Zahn, R., Keidel, J.L., Binney, R.J., Sage, K., Lambon Ralph, M.A., 2014. The anterior temporal lobes support residual comprehension in Wernicke's aphasia. Brain 137, 931–943.
Roman, G.C., Kalaria, R.N., 2006. Vascular determinants of cholinergic deficits in Alzheimer disease and vascular dementia. Neurobiol. Aging 27, 1769–1785.
Rorden, C., Karnath, H.O., 2004. Using human brain lesions to infer function: a relic from a past era in the fMRI age? Nat. Rev. Neurosci. 5, 813–819.
Rosen, H.J., Petersen, S.E., Linenweber, M.R., Snyder, A.Z., White, D.A., Chapman, L., Dromerick, A.W., Fiez, J.A., Corbetta, M.D., 2000. Neural correlates of recovery from aphasia after damage to left inferior frontal cortex. Neurology 55, 1883–1894.
Rosso, C., Perlbarg, V., Valabregue, R., Arbizu, C., Ferrieux, S., Alshawan, B., Vargas, P., Leger, A., Zavanone, C., Corvol, J.C., Meunier, S., Lehericy, S., Samson, Y., 2014. Broca's area damage is necessary but not sufficient to induce after-effects of cathodal tDCS on the unaffected hemisphere in post-stroke aphasia. Brain Stimul. 7, 627–635.
Rubi-Fessen, I., Hartmann, A., Huber, W., Fimm, B., Rommel, T., Thiel, A., Heiss, W.D., 2015. Add-on effects of repetitive transcranial magnetic stimulation on subacute aphasia therapy: enhanced improvement of functional communication and basic linguistic skills. A randomized controlled study. Arch. Phys. Med. Rehabil. 96, 1935–1944 e1932.
Sandberg, C.W., 2017. Hypoconnectivity of resting-state networks in persons with aphasia compared with healthy age-matched adults. Front. Hum. Neurosci. 11, 91.
Sandberg, C.W., Bohland, J.W., Kiran, S., 2015. Changes in functional connectivity related to direct training and generalization effects of a word finding treatment in chronic aphasia. Brain Lang. 150, 103–116.
Saur, D., Hartwigsen, G., 2012. Neurobiology of language recovery after stroke: lessons from neuroimaging studies. Arch. Phys. Med. Rehabil. 93, S15–S25.
Saur, D., Kreher, B.W., Schnell, S., Kummerer, D., Kellmeyer, P., Vry, M.S., Umarova, R., Musso, M., Glauche, V., Abel, S., Huber, W., Rijntjes, M., Hennig, J., Weiller, C., 2008. Ventral and dorsal pathways for language. Proc. Natl. Acad. Sci. U. S. A. 105, 18035–18040.
Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., Weiller, C., 2006. Dynamics of language reorganization after stroke. Brain 129, 1371–1384.
Saur, D., Ronneberger, O., Kummerer, D., Mader, I., Weiller, C., Kloppel, S., 2010. Early functional magnetic resonance imaging activations predict language outcome after stroke. Brain 133, 1252–1264.
Schlaug, G., Marchina, S., Norton, A., 2009. 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. 1169, 385–394.
Schofield, T.M., Penny, W.D., Stephan, K.E., Crinion, J.T., Thompson, A.J., Price, C.J., Leff, A.P., 2012. Changes in auditory feedback connections determine the severity of speech processing deficits after stroke. J. Neurosci. 32, 4260–4270.
Seghier, M.L., Patel, E., Prejawa, S., Ramsden, S., Selmer, A., Lim, L., Browne, R., Rae, J., Haigh, Z., Ezekiel, D., Hope, T.M., Leff, A.P., Price, C.J., 2016. The PLORAS database: a data repository for predicting language outcome and recovery after stroke. Neuroimage 124, 1208–1212.
Seniow, J., Waldowski, K., Lesniak, M., Iwanski, S., Czepiel, W., Czlonkowska, A., 2013. Transcranial magnetic stimulation combined with speech and language training in early aphasia rehabilitation: a randomized double-blind controlled pilot study. Top. Stroke Rehabilitation 20, 250–261.
Shah-Basak, P.P., Norise, C., Garcia, G., Torres, J., Faseyitan, O., Hamilton, R.H., 2015. Individualized treatment with transcranial direct current stimulation in patients with chronic non-fluent aphasia due to stroke. Front. Hum. Neurosci. 9, 201.
Shahid, H., Sebastian, R., Schnur, T.T., Hanayik, T., Wright, A., Tippett, D.C., Fridriksson, J., Rorden, C., Hillis, A.E., 2017. Important considerations in lesion-symptom mapping: illustrations from studies of word comprehension. Hum. Brain Mapp. 38, 2990–3000.
Sharp, D.J., Turkheimer, F.E., Bose, S.K., Scott, S.K., Wise, R.J., 2010. Increased frontoparietal integration after stroke and cognitive recovery. Ann. Neurol. 68, 753–756.
Siegel, J.S., Ramsey, L.E., Snyder, A.Z., Metcalf, N.V., Chacko, R.V., Weinberger, K., Baldassarre, A., Hacker, C.D., Shulman, G.L., Corbetta, M., 2016. Disruptions of network connectivity predict impairment in multiple behavioral domains after stroke. Proc. Natl. Acad. Sci. U. S. A. 113, E4367–E4376.
Sims, J.A., Kapse, K., Glynn, P., Sandberg, C., Tripodis, Y., Kiran, S., 2016. The relationships between the amount of spared tissue, percent signal change, and accuracy in semantic processing in aphasia. Neuropsychologia 84, 113–126.
Szaflarski, J.P., Ball, A., Grether, S., Al-Fwaress, F., Griffith, N.M., Neils-Strunjas, J., Newmeyer, A., Reichhardt, R., 2008. Constraint-induced aphasia therapy stimulates language recovery in patients with chronic aphasia after ischemic stroke. Med. Sci. Monit. 14, CR243–250.
Szaflarski, J.P., Vannest, J., Wu, S.W., DiFrancesco, M.W., Banks, C., Gilbert, D.L., 2011. Excitatory repetitive transcranial magnetic stimulation induces improvements in chronic post-stroke aphasia. Med. Sci. Monit. 17, CR132–139.
Takeuchi, N., Chuma, T., Matsuo, Y., Watanabe, I., Ikoma, K., 2005. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. Stroke 36, 2681–2686.
Takeuchi, N., Oouchida, Y., Izumi, S., 2012. Motor control and neural plasticity through interhemispheric interactions. Neural Plast. 2012, 823285.
Thiel, A., Black, S.E., Rochon, E.A., Lanthier, S., Hartmann, A., Chen, J.L., Mochizuki, G., Zumbansen, A., Heiss, W.D., Group, N.s, 2015. Non-invasive repeated therapeutic stimulation for aphasia recovery: a multilingual, multicenter aphasia trial. J. Stroke Cerebrovasc. Dis. 24, 751–758.
Thiel, A., Habedank, B., Herholz, K., Kessler, J., Winhuisen, L., Haupt, W.F., Heiss, W.D., 2006. From the left to the right: how the brain compensates progressive loss of language function. Brain Lang. 98, 57–65.
Thiel, A., Hartmann, A., Rubi-Fessen, I., Anglade, C., Kracht, L., Weiduschat, N., Kessler, J., Rommel, T., Heiss, W.D., 2013. Effects of noninvasive brain stimulation on language networks and recovery in early poststroke aphasia. Stroke 44, 2240–2246.
Thompson, C.K., den Ouden, D.B., 2008. Neuroimaging and recovery of language in aphasia. Curr. Neurol. Neurosci. Rep. 8, 475–483.
Thompson, C.K., den Ouden, D.B., Bonakdarpour, B., Garibaldi, K., Parrish, T.B., 2010. Neural plasticity and treatment-induced recovery of sentence processing in agrammatism. Neuropsychologia 48, 3211–3227.
Thompson, C.K., Walenski, M., Chen, Y., Caplan, D., Kiran, S., Rapp, B., Grunewald, K., Nunez, M., Zinbarg, R., Parrish, T.B., 2017. Intrahemispheric perfusion in chronic stroke-induced aphasia. Neural Plast. 2017, 2361691.
Tsai, P.Y., Wang, C.P., Ko, J.S., Chung, Y.M., Chang, Y.W., Wang, J.X., 2014. The persistent and broadly modulating effect of inhibitory rTMS in nonfluent aphasic patients: a sham-controlled, double-blind study. Neurorehabil Neural Repair 28, 779–787.
Turkeltaub, P.E., 2015. Brain stimulation and the role of the right hemisphere in aphasia recovery. Curr. Neurol. Neurosci. Rep. 15, 72.
Turkeltaub, P.E., Coslett, H.B., Thomas, A.L., Faseyitan, O., Benson, J., Norise, C., Hamilton, R.H., 2012. The right hemisphere is not unitary in its role in aphasia recovery. Cortex 48, 1179–1186.
Turkeltaub, P.E., Messing, S., Norise, C., Hamilton, R.H., 2011. Are networks for residual language function and recovery consistent across aphasic patients? Neurology 76, 1726–1734.
Turkeltaub, P.E., Swears, M.K., D'Mello, A.M., Stoodley, C.J., 2016. Cerebellar tDCS as a novel treatment for aphasia? Evidence from behavioral and resting-state functional connectivity data in healthy adults. Restor. Neurol. Neurosci. 34, 491–505.

Ueno, T., Saito, S., Rogers, T.T., Lambon Ralph, M.A., 2011. Lichtheim 2: synthesizing aphasia and the neural basis of language in a neurocomputational model of the dual dorsal-ventral language pathways. Neuron 72, 385–396.
van Hees, S., McMahon, K., Angwin, A., de Zubicaray, G., Copland, D.A., 2014a. Neural activity associated with semantic versus phonological anomia treatments in aphasia. Brain Lang. 129, 47–57.
van Hees, S., McMahon, K., Angwin, A., de Zubicaray, G.I., Copland, D., 2014b. Neural activity associated with semantic versus phonological anomia treatment in aphasia. Brain Lang. 129, 47–57.
Vines, B.W., Norton, A.C., Schlaug, G., 2011. Non-invasive brain stimulation enhances the effects of melodic intonation therapy. Front. Psychol. 2, 230.
Vitali, P., Tettamanti, M., Abutalebi, J., Ansaldo, A.I., Perani, D., Cappa, S.F., Joanette, Y., 2010. Generalization of the effects of phonological training for anomia using structural equation modelling: a multiple single-case study. Neurocase 16, 93–105.
Volz, L.J., Vollmer, M., Michely, J., Fink, G.R., Rothwell, J.C., Grefkes, C., 2017. Time-dependent functional role of the contralesional motor cortex after stroke. NeuroImage. Clin. 16, 165–174.
Walker-Batson, D., 2000. Use of pharmacotherapy in the treatment of aphasia. Brain Lang. 71, 252–254.
Walker-Batson, D., Curtis, S., Natarajan, R., Ford, J., Dronkers, N., Salmeron, E., Lai, J., Unwin, D.H., 2001. A double-blind, placebo-controlled study of the use of amphetamine in the treatment of aphasia. Stroke 32, 2093–2098.
Wan, C.Y., Zheng, X., Marchina, S., Norton, A., Schlaug, G., 2014. Intensive therapy induces contralateral white matter changes in chronic stroke patients with Broca's aphasia. Brain Lang. 136, 1–7.
Warburton, E., Price, C.J., Swinburn, K., Wise, R.J., 1999. Mechanisms of recovery from aphasia: evidence from positron emission tomography studies. J. Neurol. Neurosurg. Psychiatry 66, 155–161.
Warren, J.E., Crinion, J.T., Lambon Ralph, M.A., Wise, R.J., 2009. Anterior temporal lobe connectivity correlates with functional outcome after aphasic stroke. Brain 132, 3428–3442.
Weiduschat, N., Thiel, A., Rubi-Fessen, I., Hartmann, A., Kessler, J., Merl, P., Kracht, L., Rommel, T., Heiss, W.D., 2011. Effects of repetitive transcranial magnetic stimulation in aphasic stroke: a randomized controlled pilot study. Stroke 42, 409–415.
Weiller, C., Isensee, C., Rijntjes, M., Huber, W., Muller, S., Bier, D., Dutschka, K., Woods, R.P., Noth, J., Diener, H.C., 1995. Recovery from Wernicke's aphasia: a positron emission tomographic study. Ann. Neurol. 37, 723–732.
Whiting, E., Chenery, H.J., Chalk, J., Darnell, R., Copland, D.A., 2008. The explicit learning of new names for known objects is improved by dexamphetamine. Brain Lang. 104, 254–261.
Winhuisen, L., Thiel, A., Schumacher, B., Kessler, J., Rudolf, J., Haupt, W.F., Heiss, W.D., 2005. 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 36, 1759–1763.
Wischnewski, M., Schutter, D.J., 2015. Efficacy and time course of theta burst stimulation in healthy humans. Brain Stimul. 8, 685–692.
Wise, R.J., 2003. Language systems in normal and aphasic human subjects: functional imaging studies and inferences from animal studies. Br. Med. Bull. 65, 95–119.
Woodhead, Z.V., Crinion, J., Teki, S., Penny, W., Price, C.J., Leff, A.P., 2017. Auditory training changes temporal lobe connectivity in 'Wernicke's aphasia': a randomised trial. J. Neurol. Neurosurg. Psychiatry 88 (7), 586–594.
Xing, S., Lacey, E.H., Skipper-Kallal, L.M., Jiang, X., Harris-Love, M.L., Zeng, J., Turkeltaub, P.E., 2016. Right hemisphere grey matter structure and language outcomes in chronic left hemisphere stroke. Brain 139, 227–241.
Yamada, N., Kakuda, W., Yamamoto, K., Momosaki, R., Abo, M., 2016. Atomoxetine administration combined with intensive speech therapy for post-stroke aphasia: evaluation by a novel SPECT method. Int. J. Neurosci. 126, 829–838.
Yourganov, G., Fridriksson, J., Rorden, C., Gleichgerrcht, E., Bonilha, L., 2016. Multivariate connectome-based symptom mapping in post-stroke patients: networks supporting language and speech. J. Neurosci. 36, 6668–6679.
Yourganov, G., Smith, K.G., Fridriksson, J., Rorden, C., 2015. Predicting aphasia type from brain damage measured with structural MRI. Cortex 73, 203–215.
Zahn, R., Drews, E., Specht, K., Kemeny, S., Reith, W., Willmes, K., Schwarz, M., Huber, W., 2004. Recovery of semantic word processing in global aphasia: a functional MRI study. Brain Res. Cogn. Brain Res. 18, 322–336.
Zhu, D., Chang, J., Freeman, S., Tan, Z., Xiao, J., Gao, Y., Kong, J., 2014. Changes of functional connectivity in the left frontoparietal network following aphasic stroke. Front. Behav. Neurosci. 8, 167.