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Probing rapid network reorganization of motor and language functions via neuromodulation and neuroimaging

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Abstract

Motor and cognitive functions are organized in large-scale networks in the human brain that interact to enable flexible adaptation of information exchange to ever-changing environmental conditions. In this review, we discuss the unique potential of the consecutive combination of repetitive transcranial magnetic stimulation (rTMS) and functional neuroimaging to probe network organization and reorganization in the healthy and lesioned brain. First, we summarize findings highlighting the flexible (re-) distribution and short-term reorganization in motor and cognitive networks in the healthy brain. Plastic after-effects of rTMS result in large-scale changes on the network level affecting both local and remote activity *within* the stimulated network as well as interactions *between* the stimulated and distinct functional networks. While the number of combined rTMS-fMRI studies in patients with brain lesions remains scarce, preliminary evidence suggests that the lesioned brain flexibly (re-)distributes its computational capacities to functionally reorganize impaired brain functions, using a similar set of mechanisms to achieve adaptive network plasticity compared to short-term reorganization observed in the healthy brain after rTMS. In general, both short-term reorganization in the healthy brain and stroke-induced reorganization seem to rely on three general mechanisms of adaptive network plasticity that allow to maintain and recover function: i) interhemispheric changes, including increased contribution of homologous regions in the contralateral hemisphere and increased interhemispheric connectivity, ii) increased interactions between differentially specialized networks and iii) increased contributions of domain-general networks after disruption of more specific functions. These mechanisms may allow for computational flexibility of large-scale neural networks underlying motor and cognitive functions. Future studies should use complementary approaches to address the functional relevance of adaptive network plasticity and further delineate

how these general mechanisms interact to enable network flexibility. Besides furthering our neurophysiological insights into brain network interactions, identifying approaches to support and enhance adaptive network plasticity may result in clinically relevant diagnostic and treatment approaches.

Introduction

The human brain comprises large functional neural networks that exchange information to enable efficient, flexible adaptation to ever-changing environmental conditions. These networks provide the functional basis for a variety of behavior ranging from basic motor control to human interaction and communication. While normal brain function relies on a dynamic balance between local specialization and large-scale integration, the question arises how local changes in functionally specialized areas can influence integrated activity across larger brain networks (Cocchi et al., 2015). In disease, e.g. after stroke, functional recovery has been ascribed to compensatory flexibility of information integration within and between these large-scale networks (e.g. Geranmayeh et al., 2017; Grefkes and Fink, 2014). A prominent way to assess the composition and flexibility of functional networks lies in task-related neuroimaging methods that readily identify key areas for specific functions and delineate their interactions while the brain performs a specific task. Alternatively, functional networks can be characterized via functional connectivity at rest. Such correlative neuroimaging studies are complemented by non-invasive brain stimulation (NIBS) protocols such as transcranial magnetic stimulation (TMS) that allow for testing the functional relevance of specific areas in the healthy and lesioned brain, e.g. by interfering with regional activity underlying task-performance (Pascual-Leone et al., 1999; Siebner et al., 2009; Walsh and Cowey, 2000). More recently, multimodal approaches were introduced that combine functional magnetic resonance imaging (fMRI) with plasticity-inducing repetitive TMS (rTMS) to map plastic after-

effects at the neural network level (e.g. Bestmann and Feredoes, 2013; Cardenas-Morales et al., 2014; Hartwigsen, 2016; Nettekoven et al., 2014). Such combined approaches allow to investigate how a specific network changes its computations in response to neuromodulation and can thereby help to elucidate the flexibility of information processing within and between networks. The goal of this review is to provide an overview of how rTMS and fMRI can be combined to enable a unique empirical perspective into the dynamic functional organization (and lesion-induced reorganization) of neural networks in the human brain. We aim to identify common mechanistic principles of stimulation-induced network dynamics across functional domains. While examples from a range of functional domains will showcase the broad potential utility of combined rTMS-fMRI to shed light on the integrated use of computational brain resources underlying various aspects of cognitive capacities, we will primarily focus on networks involved in motor control or language processing. Importantly, the methodological avenue of network assessment via combined rTMS-fMRI is not limited to the assessment of the healthy brain but has started to be used to address network flexibility and reorganization in diseases such as stroke. Therefore, the goal of this review is to summarize and conceptualize general aspects of network flexibility that can be investigated via combined rTMS-fMRI, bridging cognitive and clinical neuroscience.

The first part of the review introduces recent advances in the combination of TMS and fMRI in the healthy brain. These studies help to identify general mechanisms of short-term reorganization and adaptive plasticity in neural networks for motor and language functions. In the second part, we discuss the combination of these methods in the lesioned brain in patients with motor or language impairment after stroke. The final section provides an outlook on mechanistic commonalities across different functional domains as well as between-network flexibility in health

and disease. From a clinical perspective, a better mechanistic understanding may help to develop more effective therapeutic interventions in the future. This review focuses on the plastic after-effects of rTMS at the network level. For a comprehensive overview of the concurrent combination of TMS and functional neuroimaging, the reader is referred to previous reviews (e.g. Bergmann et al., 2016; Bestmann and Feredoes, 2013; Bestmann et al., 2008).

Mapping rTMS-induced short-term plasticity in the healthy human brain

rTMS can be applied before, during or after a specific task to modulate brain function. When applied during a task (“online“), rTMS may interfere with task-related activity, thereby probing the causal role of the targeted area during performance of a specific function (Pascual-Leone et al., 2000; Walsh and Cowey, 2000). Such a “virtual lesion” approach aims at disturbing neural activity in the stimulated region. If a region’s neural activity is contributing to the performance of a given task, interfering with this region’s neural activity should have a detrimental effect on the performance of this task.

In contrast, rTMS application before or after a task (“offline”) allows for the investigation of longer lasting, plastic after-effects of the intervention. Depending on the stimulation protocol, intensity and stimulation duration, the after-effects of a single session of rTMS may outlast the duration of the stimulation for several minutes (Huang et al., 2005; Siebner and Rothwell, 2003). For instance, continuous theta-burst stimulation (cTBS) applied to the primary motor cortex (M1) is usually classified as inhibitory as it has been shown to decrease the amplitude of the motor evoked potential for up to 60 minutes after the end of stimulation. Conversely, intermittent theta-burst stimulation (iTBS) is typically referred to as facilitatory as it may increase corticospinal excitability for approximately 15-30 minutes (Huang et al., 2005; see

Chung et al., 2016 for review). The exact mechanisms of such lasting after-effects are unknown at the cellular level but likely involve long-term depression (LTD)- or long-term potentiation (LTP)-like plasticity in local and distant but connected areas (Ziemann, 2004; Ziemann et al., 2008). Strong support for this notion derives from the fact that, in line with LTP and LTD *in vitro,* rTMS-induced changes in human cortical excitability are N-methyl-D-aspartate (NMDA) dependent in humans and rats alike (Huang et al., 2007; Labedi et al., 2014). Apart from LTD-/LTP-like changes in synaptic efficiency, plasticity-induction by rTMS may arise from the modulation of cortical inhibition. Combining rTMS and magnetic resonance spectroscopy (MRS) in humans, Stagg and colleagues (2009) showed that inhibiting the motor cortex via inhibitory cTBS resulted in significantly increased levels of GABA within the stimulated motor cortex, thus suggesting that reduced cortical excitability may in fact result from increased GABAergic inhibition. Support for the notion that modulation of cortical inhibition may play an important role in stimulation after-effects stems from animal studies showing that application of rTMS to the rat brain affects specific sub-groups of GABAergic interneurons (Benali et al., 2011; Funke and Benali, 2011; Volz et al., 2013). Of note, such changes in GABAergic interneuron activity have not only been observed in the motor cortex but across various brain regions, suggesting a domain-general effect on cortical inhibition beyond the primary motor cortex (Volz et al., 2013). A third mechanism potentially contributing to the induction of cortical plasticity after rTMS-application lies in stimulation-induced changes in the excitability and ensuing preferential recruitment of specific cortical pathways. When single pulse TMS is applied to the motor cortex at near threshold intensities, the descending volley of activity resulting in a muscle twitch does not typically arise from the direct depolarization of corticospinal neurons, but is rather a product of trans-synaptic activation: the TMS pulse is thought to depolarize neurons projecting onto

corticospinal neurons, which in turn create the descending activity ultimately resulting in muscle activation. These trans-synaptically evoked volleys are referred to as indirect waves (I-waves) and can empirically be tested via the latency of TMS-evoked muscle activity induced by electric fields at distinct orientations and intensities (Day et al., 1989; Di Lazzaro et al., 1998; Lemon, 2008). While a detailed neurophysiological understanding of underlying cortical circuitry remains a matter of ongoing scientific debate (for a recent review see Di Lazzaro et al., 2018), I-wave recruitment varies across subjects and has been shown to be associated with the response to plasticity-inducing TBS across subjects (Hamada et al., 2013). Recently, iTBS has been demonstrated to directly modulate I-wave recruitment, suggesting that a modulation of the excitability of cortical pathways projecting onto the primary motor cortex may contribute to plasticity induction via iTBS in the human motor cortex (Volz et al., 2019). As I-wave recruitment has in turn been shown to relate to motor network connectivity assessed via fMRI across subjects (Volz et al., 2015a), stimulation-induced modulation of pathway recruitment (I-waves) may be assessable via fMRI on a network level. Using multimodal designs to further delineate neural mechanisms of both rTMS induced plasticity and inter-regional interactions represents an important challenge for future research**.**

rTMS and behavioural effects

The lasting after-effects of plasticity-inducing rTMS protocols have been shown to readily impact human behaviour. For instance, a number of studies demonstrated that 1 Hz rTMS or cTBS impaired task accuracy or delayed response speed for simple action selection or motor consolidation tasks (Muellbacher et al., 2002; O'Shea et al., 2007; Robertson et al., 2005). Likewise, inhibitory stimulation protocols can also modulate cognitive functions such as attention, memory, language or social

cognition (Kalbe et al., 2010; Knecht et al., 2002; Krall et al., 2016; Pobric et al., 2010; Prass and de Haan, 2019; Rosero Pahi et al., 2019; Whitney et al., 2012). The number of studies that reported behavioural after-effects of facilitatory protocols remains much smaller to date (e.g. Andoh et al., 2008; Hoy et al., 2015; Restle et al., 2012). The consecutive combination of rTMS with functional neuroimaging (perturb-and-measure approach) offers a unique opportunity to elucidate the mechanistic underpinnings of such behavioural effects. Especially for areas outside the motor cortex, where no direct output (i.e. motor-evoked potential) is caused by TMS, neuroimaging is crucial to provide proof of target engagement, to verify the assumption that the applied TMS protocol has effectively induced the intended neuronal activity in the target region (see Bergmann and Hartwigsen, 2020). This combination thus allows us to gain insight into local and remote effects of different interventions and provides a means to address changes in functional and effective connectivity underlying potential behavioural effects.

Network after-effects of rTMS on resting-state functional connectivity

Recently, a number of studies probed the lasting after-effects of different rTMS protocols via resting-state functional magnetic resonance imaging (rs-fMRI), employing seed-based functional connectivity analyses or independent component analysis (e.g. Seewoo et al., 2018 for review). rs-fMRI allows for detecting temporal correlations in spontaneous blood oxygen level dependent (BOLD) contrast fluctuations between different brain regions (e.g. Fox and Raichle, 2007). While changes in rs-fMRI-based functional connectivity can be highly specific, their neurobiological underpinnings are less clear. One explanation for the emergence of functional connectivity patterns during rest constitutes that temporal correlations are largely shaped by underlying structural connections (O'Reilly et al., 2013), which may

enable higher levels of neural communication between connected brain regions leading to increased interregional activity coherence reflected by functional connectivity (Biswal et al., 1995; van den Heuvel and Hulshoff Pol, 2010). Alternatively, changes in functional connectivity might also be influenced by altered synaptic efficacy, for example through changes in the quantity of neurotransmitter release, astrocyte function or dendritic spine stabilization (see Johnen et al., 2015). Brain regions with coherent spontaneous activity fluctuations are organized in so-called resting-state networks (Biswal et al., 1995). The combination of rTMS with rs-fMRI provides a means to measure stimulation-induced changes in functional connectivity within and between these resting-state networks. The effects of rTMS are thought to propagate trans-synaptically from the stimulation site in a manner constrained by the connectivity of the targeted brain area (Gollo et al., 2017; Muldoon et al., 2016). Consequently, the combination of rTMS and resting-state functional connectivity may help to unravel the physiological processes underlying rTMS-induced changes in the stimulated area and functionally connected nodes (Seewoo et al., 2018) and thereby lead to a better understanding of the network structures and their dynamic reconfiguration after stimulation.

Effects of rTMS on sensorimotor networks

To probe the impact of local changes in brain activity on intrinsic whole brain dynamics, Cocchi et al. (2015) applied cTBS and iTBS over the primary motor cortex prior to rs-fMRI. Local inhibitory stimulation by cTBS led to a selective increase in internal integration in sensorimotor areas and decreased communication with other networks. The observed increased integration within sensorimotor areas is consistent with other work showing increased endogenous functional connectivity with the contralateral motor cortex after inhibitory rTMS of M1 (Watanabe et al., 2014). In

contrast, iTBS neither influenced local network configuration nor interactions with other networks. These results were taken to reflect the existence of selective mechanisms that integrate local changes in neural activity, while preserving ongoing communication in the global network architecture of “rich club“ areas (i.e., areas that are positioned at the highest level of the connectional hierarchy). Such level-specific plasticity in neural dynamics may be critical for containing the impact of locally induced synchronous activity on brain function and preventing it from evolving into epileptic activity that may cause seizures. The absence of any effects of iTBS may be interpreted in line with this assumption and point towards a greater functional resilience of whole brain dynamics to local increases in motor cortical excitability relative to local decreases (Cocchi et al., 2015).

The notion that rTMS protocols thought to increase motor cortical excitability may not exert remote effects is challenged by data from Nettekoven and colleagues (2014) who demonstrated increased functional connectivity between the stimulated M1 and bilateral premotor areas **(including the ipsilateral dorsal premotor cortex) after iTBS. Moreover, functional connectivity between the stimulated M1 and ipsilateral dorsal premotor cortex further increased when further blocks of iTBS were applied, pointing towards a dose-dependency of the stimulation effect.** These results were taken to reflect dense connections between the primary motor cortex and premotor areas that might facilitate simultaneous stimulation of these interconnected brain areas by iTBS, thereby modulating the synchrony of the resting activity in those regions and highlight a dose-dependency of remote stimulation after-effects. In line with the assumed dichotomous nature of iTBS (excitatory) and cTBS (inhibitory) after-effects on motor cortical excitability, cTBS over the somatosensory cortex in turn decreased functional connectivity between the

stimulated area and a network comprising several remote but inter-connected areas, including the dorsal premotor cortex, areas for action observation and execution in the cerebellum and basal ganglia as well as the anterior cingulate cortex (Valchev et al., 2015).

In summary, rTMS applied to primary motor and somatosensory cortex has been shown to result in after-effects in remote but interconnected brain regions that are part of the sensorimotor network. While some evidence has shown a tendency towards decreases in functional connectivity after cTBS and increases in functional connectivity after iTBS, both increased and decreased functional connectivity has also been observed after cTBS applied to M1 (cf. Steel et al., 2016) and future research has to address whether differential network effects are associated with the proposed canonical effects of excitatory and inhibitory rTMS protocols.

Effects of rTMS on domain-general networks

One of the most prominent resting-state networks is the default mode network (DMN), a large-scale network that shows highest activation at rest and generally deactivation in goal-oriented tasks (Raichle et al., 2001). The DMN is anti-correlated with task-positive networks, that is, the cingulo-opercular network and fronto-parietal network. These networks have been demonstrated to strongly interact and control attention, working memory, decision making, and other higher-level cognitive operations (Anticevic et al., 2012; Dosenbach et al., 2007; Sonuga-Barke and Castellanos, 2007). Moreover, the DMN is thought to play an important role for the consolidation and maintenance of brain functions (Marcotte et al., 2013). The DMN thus presents a prime candidate of domain-general computational capacity that may be flexibly attributed to contribute to various demands.

In one of the first studies that combined rTMS with resting-state connectivity, Eldaief and colleagues (2011) provided insight into the functional architecture of the DMN, arguing for at least two subsystems within the larger DMN. In that study, low-frequency (1 Hz) rTMS over the left posterior inferior parietal lobe (IPL) increased functional correlations between the stimulated area and the hippocampal formation. In contrast, high-frequency (20 Hz) rTMS decreased functional connectivity between cortical DMN nodes. These results were taken to reflect the role of the posterior IPL as a key DMN node that possesses multiple, functionally distinct relationships among its distributed partners. These findings further indicate that different stimulation frequencies may not only result in inhibition or facilitation within the same network but may rather change the interaction of a key node with different subnetworks, providing evidence for a dynamic network (re-) configuration at rest. The flexible change in the interaction between network nodes is likely underpinned by a modulation of the underlying neurotransmitter concentration, as reflected in a modulation of remote GABA levels (Vidal-Pineiro et al., 2015). Moreover, rTMS has also been demonstrated to influence the interaction between task-positive and default mode network, indicating that the flexible redistribution of resources is not confined to intra-network interactions (Gratton et al., 2013). Relating such between-network modulations with behavioural rTMS effects may provide insight into the functional relevance of these dynamic interactions for different cognitive functions.

Apart from the potential to increase connectivity with the DMN, several studies have reported *decreased* functional connectivity between the stimulated area and DMN regions **after low-frequency rTMS or cTBS** over the left or right dorsolateral prefrontal cortex (DLPFC) (Mastropasqua et al., 2014; Shang et al., 2019; van der Werf et al., 2010). Accordingly, *increased* functional connectivity between the left DLPFC and DMN regions was reported after high-frequency rTMS over the same

area (Xue et al., 2017). Further work suggests that rTMS-induced changes are not restricted to interactions between the target site and other nodes within a functionally segregated network but also occur between distant nodes in remote networks (Freedberg et al., 2019; Shang et al., 2019).

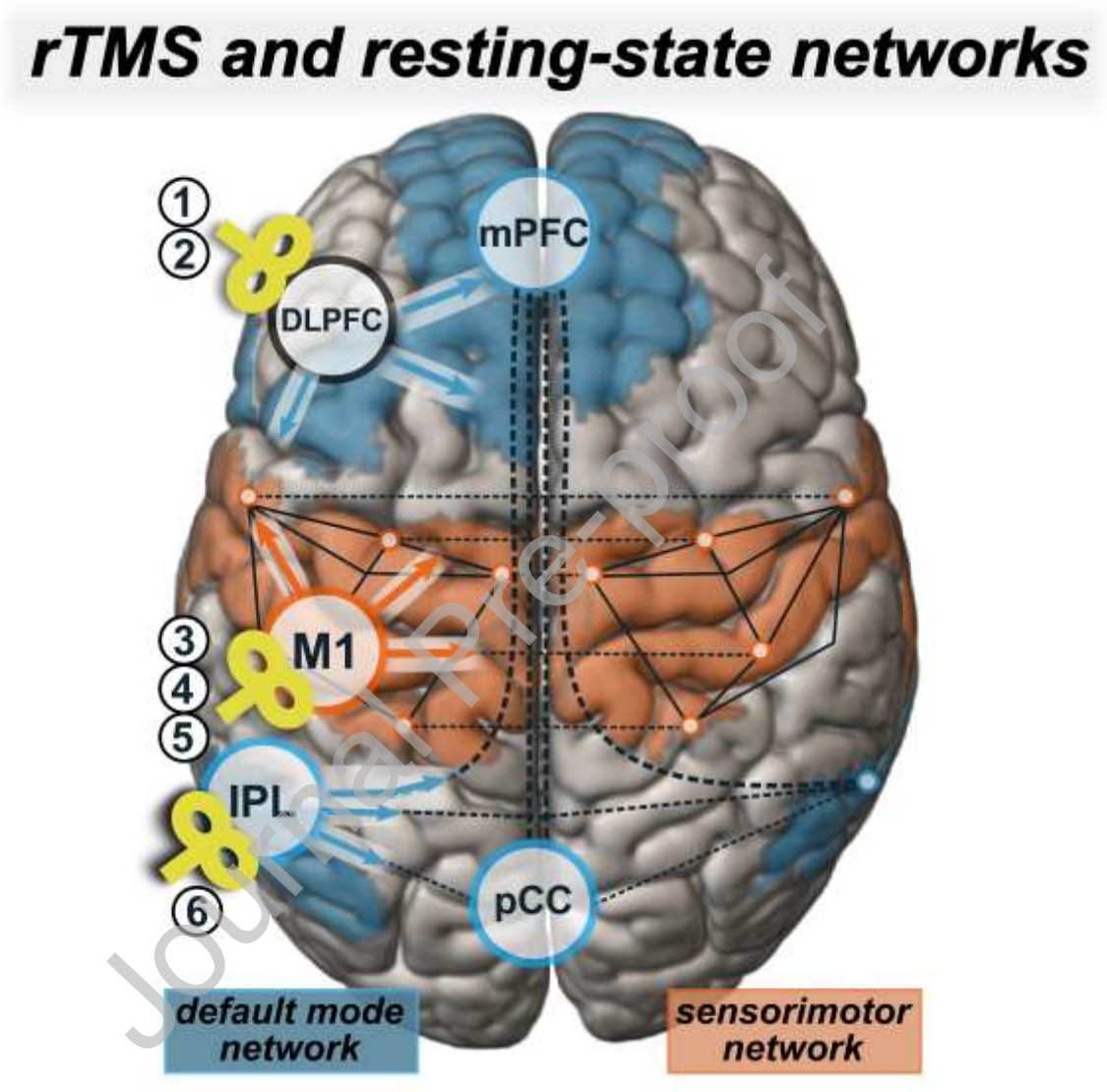

Figure 1: rTMS and resting-state networks: Application of rTMS to target regions within different functional networks has been shown to affect both functional connectivity *within* the stimulated network as well as *between* the stimulated network and distinct functional networks. Inhibitory rTMS applied to the dorsolateral prefrontal cortex (DLPFC) has repetitively been shown to *decrease* connectivity between DLPFC and the default mode network (DMN), (1: Mastropasqua et al., 2014; Shang et al., 2019; van der Werf et al., 2010) while excitatory rTMS *increased* DLPFC-DMN connectivity (2: Xue et al. 2017). Stimulating a node of the DMN by applying inhibitory rTMS to left inferior parietal lobe (IPL) *increased* connectivity between the IPL and the hippocampal formation, while excitatory rTMS *decreased* connectivity between cortical DMN nodes such as the IPL, medial prefrontal cortex (mPFC) and posterior cingulate cortex (pCC) (6: Eldaief et al. 2011). Increased motor network connectivity has independently been observed after rTMS applied to primary motor cortex (M1) using different stimulation protocols (3: Nettekoven et al. 2014; 4: Watanabe et al. 2014; 5: Cocchi et al. 2015). From a mechanistic perspective, changes in functional connectivity may reflect a modulation of information integration within the stimulated network and between distinct networks induced by the stimulation.

In summary, the above-discussed results support the notion that rTMS may affect large-scale network connectivity both within a specific network and across different networks **(Figure 1)**. However, the direction of the induced changes in functional connectivity after different facilitatory or inhibitory rTMS protocols and their functional interpretation is inconsistent across studies. Some studies report *increased* connectivity after inhibitory rTMS protocols over different areas (e.g. Eldaief et al., 2011; Gratton et al., 2013; Watanabe et al., 2014), while others found *decreased* functional connectivity after the same protocols (e.g. Andoh et al., 2015; Rahnev et al., 2013; Shang et al., 2019; van der Werf et al., 2010). Likewise, excitatory rTMS, was also found to either *decrease* (Eldaief et al., 2011; Watanabe et al., 2014) or *increase* functional connectivity (Alkhasli et al., 2019; Nettekoven et al., 2014; Tik et al., 2017; Xue et al., 2017), or resulted in a mixture of both increased and decreased connectivity in large networks at rest (Tang et al., 2019). Yet, other studies did not find any differences in the direction of the modulatory network effects between "classical" inhibitory and excitatory rTMS protocols (Addicott et al., 2019).

Taken together, these findings challenge the simplistic notion that low-frequency rTMS results in inhibition of resting state connectivity while high-frequency rTMS induces facilitation of network interactions (cf. Beynel et al., 2020). The observed differences in the direction and the resulting network modulation across studies may be partly explained by differences in the stimulation site, frequency and stimulation intensity (see also Fox et al., 2012) as well as individual differences in resting-state connectivity (Lynch et al., 2018). One common explanation for the observed inconsistencies across studies arises from potential compensatory mechanisms. For example, increases in functional connectivity after inhibitory rTMS have been interpreted to reflect compensation for the disruption of local activity (Gratton et al., 2013) and both local and global compensatory increases in functional

coupling may explain altered cross-network coupling (Mancini et al., 2017). Following this logic, *decreases* in resting-state functional connectivity after facilitatory rTMS might be interpreted as increased processing efficiency.

Yet, in the absence of behavioural modulations, this remains largely speculative. To date, the number of studies that linked rTMS-induced modulation of resting-state connectivity with behavioural changes in humans is scarce (for a few exceptions, see Hermiller et al., 2019; Ye et al., 2018) and none of the existing studies provides conclusive evidence for the behavioral relevance of local and global network modulations. This issue remains to be investigated in future studies. Likewise, it needs to be shown how changes in resting-state connectivity might be linked to changes in task-related activity and connectivity and whether the former might be used to predict the individual variability in the responsiveness to rTMS during a specific task.

Mapping after-effects of rTMS on task-related activity and connectivity

The combination of offline rTMS with task-related fMRI provides the advantage that task-specific changes can be directly related to behavioural effects, thereby probing the functional relevance of modulatory effects on a network level. In particular, effective connectivity analyses help to gain further insights into the direction and nature of changes in network interactions after neurostimulation. As discussed in the following sections, several offline rTMS-fMRI studies have assessed stimulation effects on effective connectivity, using either undirected psychophysiological interaction approaches (PPI) or directed dynamic causal modelling (DCM).

Effects of rTMS on motor networks

Several studies have investigated rTMS-induced changes in functional connectivity in

motor networks. For instance, Johnen and colleagues (2015) combined paired TMS pulses applied successively to two different areas of the motor system with fMRI recorded at rest and during grasping to investigate the effects of the stimulation of two nodes on the network level. Application of paired TMS over the ventral premotor cortex and the primary motor cortex with a short inter-pulse interval led to increased functional connectivity between both areas selectively during grasping but not at rest. In contrast, paired TMS resulted in larger network effects at rest, including increased connectivity between the premotor cortex and fronto-parietal areas associated with cognitive control and attention, as well as decreased coupling in parts of the dorso-medial sensorimotor circuit. Of note, effects were specific for the short inter-pulse interval and did not occur when the delay between pulses was too long for inducing Hebbian-like plasticity, thus corroborating the notion that increased functional connectivity may reflect short-term changes in synaptic efficacy.

Another study demonstrated task-specific reorganization in the motor network after rTMS over the left dorsal premotor cortex in healthy volunteers (O'Shea et al., 2007). 1 Hz rTMS decreased task-related activity and disrupted task processing in an action selection task. At the same time, widespread increases in other motor areas were observed, including the homologous right dorsal premotor cortex, which were interpreted to be of compensatory nature. Crucially, subsequent rTMS over the reorganized stimulation homologue disrupted task performance, thereby demonstrating the functional relevance of the compensatory upregulation of this area. These data provide evidence for an adaptive recruitment of homologous regions that may help to compensate for the disruption of contralateral key areas.

rTMS-induced changes in task-related motor activity are complemented by a number of studies reporting stimulation-induced changes in the effective connectivity between key areas for motor tasks (e.g. Lee et al., 2003; Moisa et al., 2012; Ward et

al., 2010). For instance, in an early consecutive rTMS-PET study, Lee et al. (2003) showed that 1 Hz rTMS over the left primary motor cortex increased task-related activity in the stimulated area and connected motor regions during finger movements, with the strongest upregulation being observed in the contralateral premotor cortex. Moreover, rTMS affected task-related functional coupling in the motor network, resulting in an increase in the effective connectivity between the stimulated region and anterior motor areas. These findings likely reflect rapid stimulation-induced remodelling of motor representations that may have compensated for the rTMS-induced disruption. The behavioural relevance of rTMS-induced changes in effective connectivity between key network nodes was demonstrated for action reprogramming: changes in the functional coupling between functionally relevant regions predicted the individual rTMS-induced changes at the behavioural level (Ward et al., 2010). Apart from predicting stimulation effects on the behavioural level, task-related activity and connectivity have also been associated with stimulation induced modulation of motor cortical excitability. Specifically, increased corticospinal excitability after iTBS to the left primary motor cortex was negatively associated with task-related activity during a simple hand motor task (Cardenas-Morales et al., 2014). Importantly, subjects who showed better responsiveness to iTBS also revealed stronger effective connectivity between left premotor and motor cortex before TMS. In contrast, initial resting-state connectivity did not predict the individual iTBS-induced after-effects. These results show that plastic changes in response to facilitatory rTMS not only depend on local changes in activity, but also on functional interactions with interconnected regions from the same network. Activity-dependent properties of the motor network may be more predictive of changes in excitability after plasticity-inducing protocols in the motor system relative to individual connectivity profiles at rest. This is congruent with an earlier study that revealed large-scale activity

decreases in the motor network after iTBS over the primary motor cortex during a choice-reaction task, which may have reflected increased processing efficiency, but no changes in regional cerebral blood flow at rest (Cardenas-Morales et al., 2011).

In summary, the above-discussed studies stress the value of combining rTMS with task-based fMRI and measures of effective connectivity to provide insight into short-term plasticity in the motor network. Future research is needed to further disentangle the rTMS after-effects on motor cortical excitability, motor network connectivity and motor behaviour and address how network measures may help to explain the profound level of inter-individual variability of rTMS applied to the motor cortex (Hamada et al., 2013; Hinder et al., 2014).

Effects of rTMS on language networks

Network effects of (mainly inhibitory) rTMS have been studied in a number of cognitive domains, including attention, memory, auditory speech discrimination and language. For instance, stimulation-induced changes in intra- or interhemispheric interactions have been reported during tasks addressing selective attention and visual extinction (Heinen et al., 2014; Petitet et al., 2015), self-referential information processing (De Pisapia et al., 2019a) and meta-memory processing (Ye et al., 2018).

A number of studies reported strong cortical remote effects of offline rTMS on task-related activity in the speech and language network (e.g. Andoh and Paus, 2011; Binney and Lambon Ralph, 2015; Hallam et al., 2016; Hartwigsen et al., 2017; Jung and Lambon Ralph, 2016; Watkins and Paus, 2004). With respect to compensatory short-term reorganization in response to perturbation, some of these studies found increases in task-related activity in ipsilateral regions of the same task-specific network or neighbouring networks for other functions. For instance, Hallam et al. (2016) showed that 1 Hz rTMS over the left inferior frontal gyrus (IFG) decreased

task-related semantic activity in the stimulated area and increased activity in another key node for semantic processing in the left posterior middle temporal gyrus. In contrast, Hartwigsen et al. (2017) reported large-scale inhibition of the semantic network after targeting left angular gyrus with cTBS prior to a semantic judgement task. Effective connectivity analyses showed that the individual increase in the inhibitory influence from the stimulated left angular gyrus to the left anterior IFG after cTBS was correlated with the individual delay in semantic response speed. These results provide evidence for the functional relevance of remote rTMS effects on higher cognitive functions. After cTBS, increased task-related activity was observed in neighbouring regions for phonological processing and domain-general functions, suggesting that large-scale disruption of a domain-specific network might lead to compensatory recruitment of neighbouring areas for specialized functions and domain-general areas for cognitive control and working memory (see Hartwigsen, 2018).

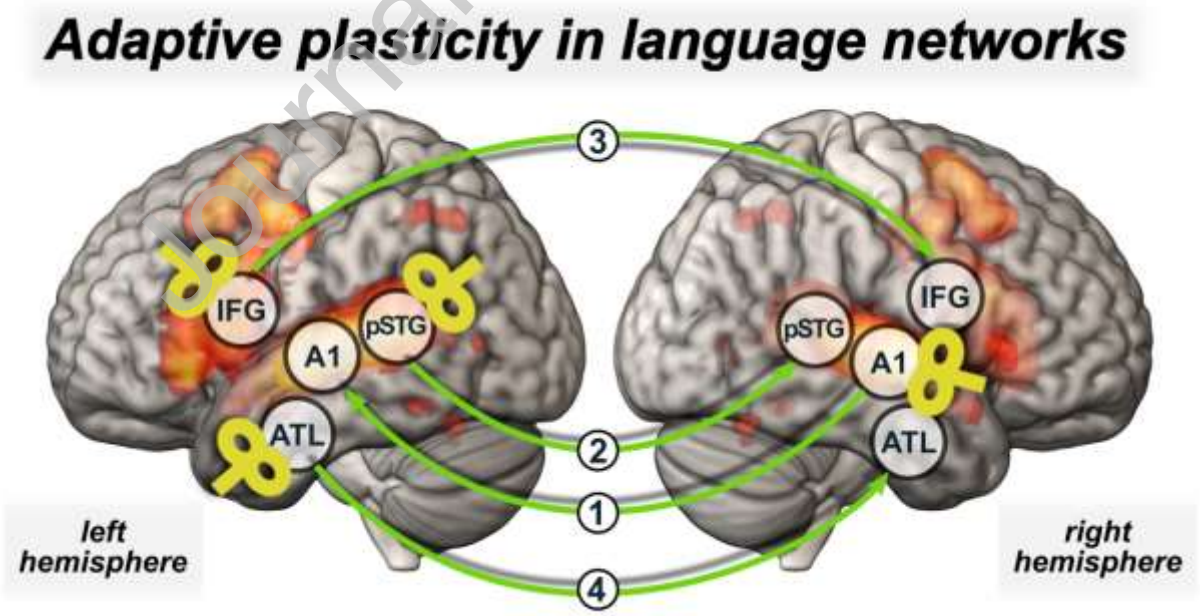

Figure 2: Adaptive plasticity in language networks: rTMS applied to core nodes of the language network has repetitively been shown to result in a typical pattern of altered connectivity and task-related neural activity: a *decrease* in task-related activity in the stimulated region after rTMS is paralleled by an *increase* of neural activity in the homologous contralateral region. This task-dependent recruitment of the homologous region is thought to compensate for the detrimental effects of the stimulation-induced perturbation and support successful

performance. This compensatory mechanism has independently been observed after perturbation of (1) right primary auditory cortex (A1, Andoh and Zatorre, 2013; Andoh and Zatorre 2011), (2) left posterior superior temporal gyrus (pSTG, Andoh and Paus, 2011), (3) left inferior frontal gyrus (IFG, Hartwigsen et al., 2013) and (4) left anterior temporal lobe (ATL, Binney and Lambon Ralph, 2015; Jung and Lambon Ralph, 2015).

Other offline TMS-fMRI studies investigated interhemispheric interactions between homologous regions during auditory melody discrimination or speech and language processing (**Figure 2;** Andoh and Paus, 2011; Andoh and Zatorre, 2011, 2013; Binney and Lambon Ralph, 2015; Hartwigsen et al., 2013; Jung and Lambon Ralph, 2016). These studies provide strong converging evidence for rTMS-induced compensatory short-term plasticity in homologous regions. For instance, Andoh and Zatorre (2013) mapped cTBS-induced modulations of interhemispheric interactions between auditory cortices during a melody discrimination task with fMRI. cTBS over the right auditory cortex resulted in increased activity in the homologous left-hemispheric region. Moreover, a stronger upregulation was associated with better performance, pointing towards the functional relevance of rapid short-term reorganization between auditory key areas. Finally, stronger individual interhemispheric connectivity between the auditory cortices at rest before cTBS was correlated with faster response speed after stimulation. Importantly**,** these results demonstrate the potential of resting-state connectivity to predict TMS-induced modulations of higher cognitive functions at the behavioural level.

Some studies complemented the investigation of task-induced stimulation effects between homologous regions with effective connectivity analyses using DCM (Hartwigsen et al., 2013; Jung and Lambon Ralph, 2016). Increased activity was observed in homologous right-hemispheric areas after disruption of a left-hemispheric language region during speech and language tasks, accompanied by increased facilitatory influences exerted by the homologous region onto the stimulated area. These results reflect a flexible, bilateral (re-)organization of speech

and language functions with a strong degree of adaptive plasticity. The behavioural relevance of these changes was also demonstrated with the individual increase in the functional influence from the right to the left hemisphere being associated with better performance maintenance (Hartwigsen et al., 2013). This supports the notion that the contribution of homologous right hemisphere areas might support language recovery after left hemisphere damage, at least immediately after a focal perturbation (e.g. Saur et al., 2006; Stockert et al., 2020; see below).

In summary, these studies show a strong potential of adaptive short-term reorganization between homologous regions in the language network, enabling the swift recruitment of additional computational resources, which may form the basis for language recovery after stroke. In particular, the above-discussed studies highlight the benefit of combining neurostimulation with functional and effective connectivity analyses to elucidate the behavioural relevance of stimulation-induced changes in network dynamics. However, in most of the previous studies, the behavioural relevance of the observed compensatory recruitment of neighbouring or homologous regions remains unclear. To proof the claim that redistribution of function is reflecting compensatory efforts, future studies need to target the respective “reorganized” area or network, e.g. with inhibitory TMS. Here, the rationale would be that an additional perturbation of the reorganized area should further impair task performance, providing direct evidence for the functional relevance of observed changes in activity.

While the above-discussed results obtained from combined TMS-fMRI studies in healthy volunteers provide insight into the flexible (re-)distribution of network resources, it should be noted that the canonical response dichotomy expected after “inhibitory” (e.g., low-frequency rTMS or cTBS) vs. “facilitatory” (e.g., high-frequency rTMS or iTBS) protocols is not reflected in the present literature on either resting state or task-based fMRI. While a canonical dichotomy of responses was originally

observed on the level of motor cortex excitability (probed via single pulse TMS before and after rTMS), a similar dichotomy is not present across animal studies, e.g., assessing the effect of rTMS on protein expression in the rat cortex (Volz et al. 2013) or regarding behavioral effects of TMS in humans (see Bergmann & Hartwigsen, 2020). In fact, recent work on the inter-individual variability of rTMS effects calls into question the dichotomous concept of canonical rTMS effects on motor cortical excitability (Hamada et al. 2013; Hinder et al. 2014). Yet, this variability is usually ignored in TMS-fMRI studies that selectively focus on group data, although the absence of a clear dichotomy in response to different rTMS protocols complicates the conclusions to be drawn from TMS studies. Moreover, the lack of understanding of rTMS effects at the network level bears the risk of post-hoc explanations for specific response patterns, especially for fMRI data given its informational wealth. For instance, the upregulation of a remote or homologous region after inhibitory rTMS over a specific key area might either reflect an attempt to compensate for the disruption or disinhibition of that area. Again, this emphasizes the need of relating behavioral data with the TMS-induced modulation at the network level. With respect to the strong inter-individual variability in response to plasticity-inducing TMS protocols, it was recently shown that multi-voxel pattern analyses can predict the TMS-induced shift of task-related activity from the stimulated area to neighbouring regions at the single subject level with a high accuracy (Hartwigsen and Bzdok, 2018). These results might be relevant for translational approaches and may help to identify target areas for facilitatory neurostimulation approaches to support recovery of motor and cognitive functions after brain lesions, as discussed in the next sections.

Mapping pathophysiological dynamics: Network reorganization post stroke

While the healthy brain operates within a physiological range of dynamic balance between local specialization and large-scale integration, this balance can be altered by pathology. For example, the sudden loss of specialized neural tissue due to stroke introduces the need for the brain to reorganize its functional architecture in order to regain brain functions impaired after the stroke (for reviews see Alia et al., 2017; Caleo, 2015; Cassidy and Cramer, 2017; Murphy and Corbett, 2009). Such reorganization of functional brain networks is partially accomplished by temporarily entering a state of increased neural plasticity in the first weeks after stroke, a phase often referred to as *"critical period"* (Krakauer, 2015). Besides the need to compensate the loss of specialized neural tissue, the lesion may also affect information integration across distributed functional networks, as often observed in motor and language networks. Therefore, lesions can have functionally detrimental effects on remote (non-lesioned) brain areas, due to changes in interregional communication. This concept coined *"diaschisis"* was first described by von Monakow in 1914 (von Monakow, 1914) and has undergone a renaissance with the advent of the study of brain connectivity via fMRI, allowing the empirical analysis of stroke induced changes on a network-level reflecting both (i) network reorganization and (ii) diaschisis and alleviation thereof (Carrera and Tononi, 2014). While studies directly combining TMS-fMRI in a perturb-and-measure approach in stroke patients remain scarce to date, the multimodal assessment of functional networks via TMS and fMRI has profoundly advanced our understanding of how the brain reorganizes

its functional architecture to recover from stroke induced deficits. This evolving understanding offers the opportunity to (i) understand mechanistic aspects of the pathophysiological network flexibility underlying the remarkable aptitude of the brain to overcome lesion-induced impairments and (ii) use neuromodulatory approaches to amplify reorganization processes in therapeutic approaches.

Motor network reorganization observed during task-performance

With the advent of functional neuroimaging, early studies assessed changes in neural activation observed during movement of the paretic hand (e.g. Chollet et al., 1991; Ward et al., 2003; Weiller et al., 1993). Across studies, changes in neural activation of the motor system have consistently been characterized as "over-activity" of motor areas in both the affected, ipsilesional and non-affected, contralesional hemisphere (Rehme et al., 2012). Importantly, the amount of pathophysiological excess activity typically correlates with severity of impairment, time after stroke and the motor task used in a study (Rehme et al. 2012). A way to further delineate the pathophysiological underpinnings of such patterns of neural "over-activation" during hand movements lies in assessing the connectivity between motor regions showing over-activity. Using DCM for fMRI data, Grefkes and colleagues (**2008**) showed that interhemispheric inhibition exerted by the contralesional ("healthy") primary motor cortex (M1) onto the ipsilesional M1 was observed in subchronic stroke patients but not healthy controls, with this pathophysiological inhibition of the ipsilesional M1 being most pronounced in severely affected patients. Interestingly, a similar mechanism of excess interhemispheric inhibition from the contralesional M1 onto the ipsilesional M1 has also been observed using paired-pulse TMS in subchronic stroke patients featuring an analogous relationship to motor impairment (Murase et al., 2004). Taken together, this multimodal TMS and fMRI evidence thus corroborates

the notion of excessive pathophysiological inhibition of the ipsilesional hemisphere by the contralesional hemisphere, which has been coined *maladaptive.* These observations have resulted in the *model of interhemispheric competition*, which hypothesizes an imbalance of interhemispheric inhibition between hemispheres to result in maladaptive inhibition of the affected and increased excitability of the contralesional hemisphere (for a review see e.g. Volz and Grefkes, 2016). The latter aspect, i.e. a predicted disinhibition of the contralesional M1 has also been observed empirically using a combined assessment of effective motor network connectivity during paretic hand movements via DCM and TMS measures of cortical excitability (Volz et al., 2015b). Chronic stroke patients suffering from most pronounced hand motor deficits also featured a disinhibition of the contralesional M1 (as observed via DCM) and increased levels of cortical excitability of the contralesional M1 (as independently probed via TMS), thus supporting the notion that changes in interhemispheric inhibition and cortical excitability of bilateral M1 are inter-related and occur in association to the level of motor impairment. Directly combining rTMS and fMRI, inhibiting the contralesional M1 via low-frequency rTMS in stroke patients resulted in a reduction of inhibitory influences onto the ipsilesional M1 as assessed via DCM, thus providing empirical support for the notion that the contralesional M1 might exert a maladaptive inhibition over the ipsilesional M1 (Grefkes et al., 2010). Importantly, the level of rTMS-induced reduction of interhemispheric inhibition onto the ipsilateral M1 was associated with stimulation-induced improvement in motor function across patients, highlighting the functional significance and potential therapeutic target of altered interhemispheric inhibition.

While the *model of interhemispheric competition* forms a useful basis of altered interhemispheric interactions post-stroke which have resulted in mechanistic starting points for modulating altered cortical excitability in therapeutic approaches

via non-invasive brain stimulation (e.g. see Volz and Grefkes, 2016; Guggisberg et al., 2019; O'Brien et al., 2018), it certainly represents an oversimplified view of the complex dynamics underlying neural reorganization (c.f. Coscia et al., 2019), neglecting several fundamental aspects such as the state of the motor network independent of the lesion (often referred to as anatomical reserve, Di Pino et al., 2014) or changes observed within hemispheres.

A complementary approach to assess the functional role of a given region lies in using *online-TMS*. Here, short bursts of TMS stimuli are typically applied while the subject performs a specific task. Changes in task performance (compared to a control stimulation condition) are then inferred to arise from the TMS-induced disturbance (or "*virtual lesion"*) of the fine-tuned regional neural activity contributing to task performance (Gerloff et al., 1998; Pascual-Leone et al., 1991). While potential drawbacks of online TMS may result from methodological aspects (e.g., when to apply stimuli for how long and at which frequency in relation to the task performed) and negative results have to be interpreted with caution, using online TMS enables us to investigate the causal role of the stimulated cortical region for the performed motor task. Regarding the debated functional significance of changes in motor regional activation observed via fMRI following stroke, online TMS has helped to further our understanding of potential mechanisms of reorganization (**Figure 3**, cf. Hallett et al., 2020).

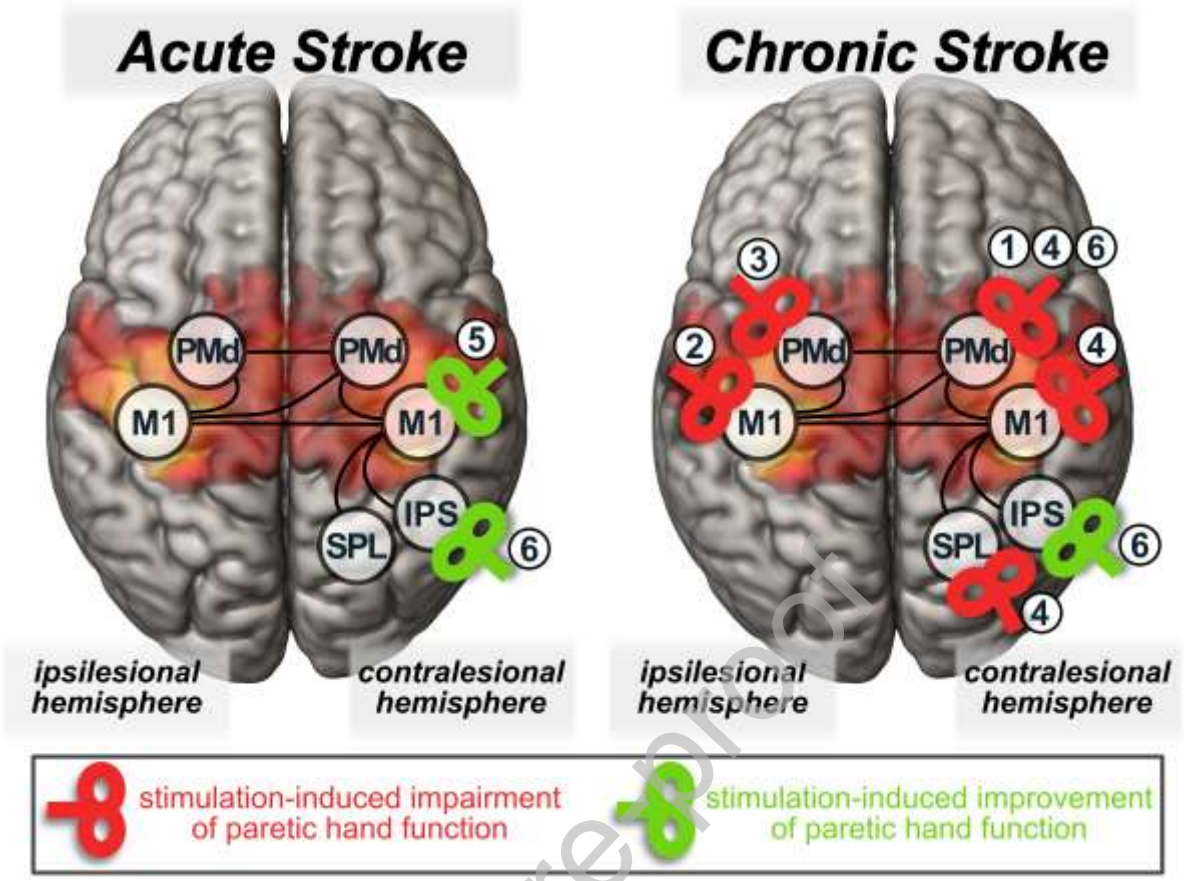

Figure 3: Online TMS and motor function after stroke: Online TMS experiments offer a unique window into functional roles of stimulated cortical regions. In chronic stroke patients (*right panel*), **impaired** motor performance of the paretic hand has been observed when applying online TMS to bilateral primary motor cortex (M1), bilateral dorsal premotor cortex (PMd) or the contralesional superior parietal lobe (SPL) during motor performance (*red coil*). Thus, highlighting a supportive role of these regions on paretic hand motor function in chronic patients. Conversely, online TMS interference applied to the contralesional intraparietal sulcus (IPS) enhanced paretic hand function (*green coil*). In acute stroke patients (*left panel*), interfering with both contralesional M1 and IPS improved paretic hand function, suggesting early maladaptive influences of these regions on specific aspects of paretic hand motor function. (1: Johansen-Berg et al., 2002; 2: Werhahn et al., 2003; 3: Fridman et al., 2004; 4: Lotze et al., 2006; 5: Volz et al., 2017; 6: Tscherpel et al., 2020).

Online TMS experiments in chronic stroke patients have highlighted the supportive functional role of neural activity in ipsilesional M1 (Werhahn et al., 2003), ipsilesional dorsal premotor cortex (Fridman et al., 2004), or contralesional dorsal premotor cortex (Johansen-Berg et al., 2002) contributing to task performance in reaction time and finger sequence production tasks (Lotze et al., 2006) performed with the paretic hand. In mildly to moderately affected acute stroke patients, online TMS applied over contralesional M1 resulted in improved finger tapping frequency, but did not affect grip strength or reaction times of the paretic hand (Volz et al.,

2017). Importantly, no online TMS effects were observed when re-testing patients in the chronic phase (3 months later), highlighting the task- and time-dependence of online TMS results in stroke patients. Extending the scope of reorganization beyond primary and premotor areas, Tscherpel and colleagues recently reported that online TMS interference with the contralesional anterior intraparietal sulcus (IPS) resulted in improved motor task performance both in acute and chronic stroke patients (Tscherpel et al., 2020).

A potential mechanistic explanation for a supportive role of the contralesional parietal cortex stems from a recent DCM study that observed increased effective connectivity between the contralesional superior parietal lobule and ipsilesional M1 during paretic hand movements compared to healthy controls (Pool et al., 2018). Moreover, congruent with earlier data (Johansen-Berg et al., 2002) online TMS interference with contralesional PMd caused deterioration of motor performance in the chronic phase post stroke, but not in the acute phase, suggesting that the supportive role of contralesional premotor cortex might evolve alongside reorganization (Tscherpel et al., 2020). A mechanistic explanation for the pathophysiological role of contralesional PMd stems from a seminal study by Bestmann and colleagues, who used paired-coil TMS of contralesional PMd on ipsilesional M1 to address the direct influence of contralesional PMd on ipsilesional M1 and concurrent TMS-fMRI to characterize the network effect of TMS applied to contralesional PMd (Bestmann et al., 2010). The authors reported a disinhibition of the interhemispheric PMd-M1 connection, which was strongest in patients with greater clinical impairment. More severely affected patients also featured a pronounced increase of neural activity in posterior parts of ipsilesional sensorimotor cortex in response to TMS applied to contralesional PMd. Thus, both paired-pulse TMS and TMS-fMRI findings highlight the influence of PMd

activity onto the ipsilesional motor system and underline its prominent role in cortical reorganization.

In summary, online TMS findings highlight just how much the assessment of reorganization after stroke is impacted on the stage of reorganization (i.e. depending on the severity of initial impairment and time point after stroke) and the task performed in a given experiment. A future combination of online TMS performed shortly before/after or even during fMRI acquisition seems highly desirable to directly address the network effects underlying behavioural online TMS effects.

Motor network reorganization observed at rest

A methodological approach that allows to assess network dynamics bare of the influence of a given task lies in resting-state fMRI. The relative ease of application in clinical populations such as stroke patients has helped resting-state fMRI to become the most popular method to study network reorganization in stroke patients in recent years. While methodological caveats represent unique challenges when interpreting resting-state functional connectivity (rsFC, e.g. see Power et al., 2015; Tagliazucchi and Laufs, 2014), resting-state data is readily comparable across different cohorts and offers the opportunity to study various functional systems at the same time. For a comprehensive overview of the current literature on the motor network alterations observed at rest, the reader is referred to previous reviews (Guggisberg et al., 2019; Thiel and Vahdat, 2015).

Analogous to the rTMS-induced effects on interhemispheric resting-state connectivity between the stimulated region and its contralateral homologue, altered interhemispheric rsFC has frequently been observed after unilateral stroke (Guggisberg et al., 2019; Thiel and Vahdat, 2015)**.** In particular, data from both animal and human studies suggests a characteristic time course of altered

interhemispheric rsFC between bilateral motor cortices after stroke. First, connectivity between the ipsilesional M1 and contralesional M1 typically has been reported to decline in the first two to four weeks after stroke, followed by a subsequent re-increase in interhemispheric connectivity alongside functional recovery (e.g. Park et al., 2011; van Meer et al., 2010).

More recently, studies have started to address changes in the dynamic time course of rsFC in stroke patients, an approach referred to as dynamic functional connectivity (Bonkhoff et al., 2020; Chen et al., 2018; Hu et al., 2018). For example, Bonkoff and colleagues observed that beyond changes in connectivity between distinct functional networks, stroke patients also featured characteristic changes in temporal properties of large-scale network interactions depending on the individual deficit severity: while moderately affected patients spent significantly more time in a weakly connected configuration (i.e. low levels of rsFC) between and within cortical, subcortical and cerebellar motor areas, severely affected patients showed a significant preference for transitions into a spatially segregated connectivity configuration (i.e. high level of rsFC within respective cortical, subcortical and cerebellar motor areas and low level rsFC between these motor clusters) (Bonkoff et al 2020). New analytic approaches such as dynamic rsFC may help to further our insights into pathophysiological mechanisms underlying network reorganization and provide the ability to use such changes as biomarkers to predict the potential for functional recovery and individualize therapies on the level of individual patients.

Besides its role as a potential biomarker, altered rsFC following stroke has inspired a combined use with rTMS in a therapeutic setting. Using iTBS over the ipsilateral M1 to prime the effect of physiotherapy on motor recovery on 5 consecutive days in early subacute stroke patients enhanced motor recovery as assessed via grip-strength of the paretic hand. Importantly, iTBS lastingly increased

rsFC of the stimulated M1 with a network of motor areas comprising the contralesional M1 bilateral premotor areas compared to control stimulation (Volz et al., 2016). These findings highlight the potential of combined rTMS-fMRI approaches to modulate network dynamics with a therapeutic goal.

The question arises, which aspects of reorganization and plasticity may be captured by rsFC compared to changes in task-related activity and connectivity and how rTMS may interact with the network alterations assessable via both techniques. Future research is needed to address whether changes in connectivity at rest and during task performance reflect distinct state-dependent aspects of network reorganization or rather show similar network changes underlying plasticity induced by rTMS or reorganization after stroke.

Reorganization of language networks

As in the motor system, the dynamic changes in network activity and connectivity across the time course of language recovery after stroke have been mapped with both task-based and resting-state fMRI (for review, see Hartwigsen and Saur, 2019; Turkeltaub et al., 2011). In brief, previous resting-state studies have shown that language disruption after stroke is associated with both decreased inter-hemispheric functional connectivity between homologous regions as well as decreased intrahemispheric functional connectivity in the left hemisphere (e.g. Siegel et al., 2016), supporting the notion that aphasia can be characterized as network disorder. Likewise, task-related fMRI revealed a global network dysfunction of the language network in the acute phase after stroke (Saur et al., 2006; Stockert et al., 2020). With respect to spontaneous language recovery, it was demonstrated that upregulation of homologous right-hemispheric language regions in the early subacute phase might

be beneficial for recovery, while a normalization of activity and re-shift towards perilesional left-hemispheric areas was associated with better recovery in the chronic phase (Saur et al., 2006). Aside from the contribution of language-specific regions to recovery, more recent studies argue for a beneficial role of the recruitment of bilateral domain-general areas in the frontal cortex (Brownsett et al., 2014; Geranmayeh et al., 2014), especially in the early subacute phase after stroke (Stockert et al., 2020), highlighting another mechanistic parallel between post-stroke recovery and rapid reorganization induced by rTMS.

Yet, in contrast to the motor system, the number of studies that mapped TMS-induced changes in network plasticity in the lesioned language network is scarce. To date, the majority of studies explored potential beneficial effects of rTMS to support language therapy selectively at the behavioural level (for reviews, see Hartwigsen and Siebner, 2013; Shah et al., 2013; Turkeltaub, 2015). The majority of these studies combined inhibitory offline rTMS over homologous regions in the right hemisphere with picture naming in the late subacute or chronic phase to suppress “maladaptive overactivity” in the right frontal cortex (see Ren et al., 2014 for review). Fewer studies targeted perilesional left-hemispheric regions with facilitatory high-frequency rTMS or combined left-hemispheric facilitation with right-hemispheric inhibition in the subacute and chronic phase after stroke (e.g. Khedr et al., 2014; Szaflarski et al., 2011). In general, these studies show some beneficial effects of combining language therapy with repeated rTMS application, but the effect sizes are small and the clinical relevance remains unclear. Moreover, the neural correlates of these effects remain largely unexplored. Two studies reported a re-shift of language activity towards the left-hemisphere and / or suppression of right frontal activity that was associated with better performance after repeated application of 1 Hz rTMS to the right inferior frontal gyrus in combination with language therapy in subacute

stroke patients (Thiel et al., 2013; Weiduschat et al., 2011). Likewise, a re-shift of language-related activity to the left hemisphere paralleling behavioural improvement in patients with chronic aphasia was observed after facilitatory iTBS over the left IFG (Szaflarski et al., 2011). Together, these studies suggest that late re-activation of perilesional language regions might represent a neurobiological marker of successful treatment. These changes may also be paralleled by changes in the underlying structural connectivity as suggested by preliminary diffusion tensor imaging data (Allendorfer et al., 2012). Based on these studies, one may speculate that different facilitatory and inhibitory protocols may be helpful across the time course of language recovery, with a potential early facilitation of homologous regions (or domain-general areas) and a later inhibition of these areas in combination with perilesional facilitation (see Hartwigsen and Saur, 2019).

To date, only one study explored the potential of the reorganized language network for adaptive plasticity in response to inhibitory rTMS (Hartwigsen et al., 2020). In this study, cTBS was applied to either the anterior or posterior part of the left inferior frontal gyrus (a/pIFG) prior to task-based fMRI to probe short-term reorganization in the right hemisphere in chronic stroke patients with aphasia after temporo-parietal damage. A functional-anatomical double dissociation at the behavioural level was observed, with cTBS over the aIFG selectively affecting semantic processing and cTBS over the pIFG selectively disrupting phonological decisions. These changes were underpinned by site-specific inhibition patterns in task-related activity. The individual cTBS-induced response delay in the phonological task predicted the upregulation of the lesion homologue in the right parietal cortex, which may have reflected an attempt to compensate for the disruption of the phonological network in the left-hemisphere. Moreover, stronger individual tract integrity in the right superior longitudinal fascicle was associated with less cTBS-

induced behavioural disruption, indicating that stronger integrity of the fiber tracts between language homologous regions may reflect a marker of resilience against perturbation. In the semantic network, widespread inhibition in both language-specific and domain-general regions was observed after cTBS, which may explain the absence of any compensatory upregulation. These results provide insight into adaptive short-term plasticity in the reorganized language network and are congruent with a compensatory role of the right hemisphere after combined disruption by a structural lesion and a focal, cTBS-induced perturbation. However, the functional relevance of these changes remains unclear and has to be addressed by future research.

Domain-general plasticity and network reorganization after stroke

The similarity of network dynamics observed in the motor and language network leads to the question whether post-stroke plasticity and network reorganization may represent, at least in part, a domain-general aspect of pathophysiological brain function. If this were the case, functional recovery and network reorganization should be related across different domains: for example, a patient showing substantial motor recovery should also experience more pronounced recovery regarding other functional impairment, such as aphasia. Empirical support for a high degree of inter-domain association of recovery and domain-general reorganization stems from recent work that found behavioural impairment in 132 acute stroke patients measured across different behavioural domains (motor, attention, language, verbal memory) to be strongly correlated (Corbetta et al., 2018; Ramsey et al., 2017). This seems to contradict a traditional “modular brain” perspective, which predicts a strongly localization-dependent functional impact of brain lesions to different functional systems. Conversely, the inter-relation of functional deficits across

domains (i.e. low-dimensionality of functional impairment across domains) may reflect that a high degree of functional integration across functional brain modules, rather than domain-specific changes may drive reorganization after stroke. In other words, rather than the motor system rearranging its specific functional architecture, the brain may alter information integration across various functional networks, potentially increasing its flexibility to tie in computational resources unaffected by the lesion. In line with the notion of domain-general reorganization, disturbances in rsFC more accurately predicted impairment across multiple domains compared to lesion topography or size (Siegel et al., 2016). Thus, the fact that deficits in different domains were highly correlated across patients was mirrored by a similarly "low dimensionality of correlated patterns" of abnormal rsFC, which was characterized by distributed networks of cortical areas rather than specific specialized regions (Corbetta et al., 2018). In line with domain-specific changes observed in the motor and language network, a decrease in inter-hemispheric functional connectivity within functional networks was observed alongside increased intra-hemispheric connectivity between nodes of distinct functional networks. Such domain-general changes in rsFC as a response to focal stroke lesions may reflect a limitation of neural states that the brain can potentially explore with the goal of maximizing the efficiency of information processing (Corbetta et al., 2018).

In summary, the combination of rsFC with the behavioural assessment in different domains has created a new perspective for the study of plasticity suggesting that functional impairment in different domains may arise from a reduction of the brain's capacity to flexibly allocate cortical computational resources to a task at hand. Future work should aim at extending this perspective by combining task-independent rsFC with task-based and perturb and measure approaches using TMS-fMRI to

further elucidate how brain networks modulate their flexibility to adapt to changing demands, both in health and after stroke.

Summary and future directions

The above-discussed consecutive TMS-fMRI studies provide insights into the flexible (re-)distribution and (re-)configuration of large-scale neural networks underlying motor and cognitive functions in the healthy and lesioned brain. The following general conclusions can be drawn from these studies: short-term reorganization after focal perturbation of key nodes for different functions in the healthy brain engages both (i) contralateral homologous regions, (ii) ipsilateral areas from distinct networks that are specialized for other functions as well as (iii) domain-general regions which may help to support disruption of more specific functions in some cases (Figure 4).

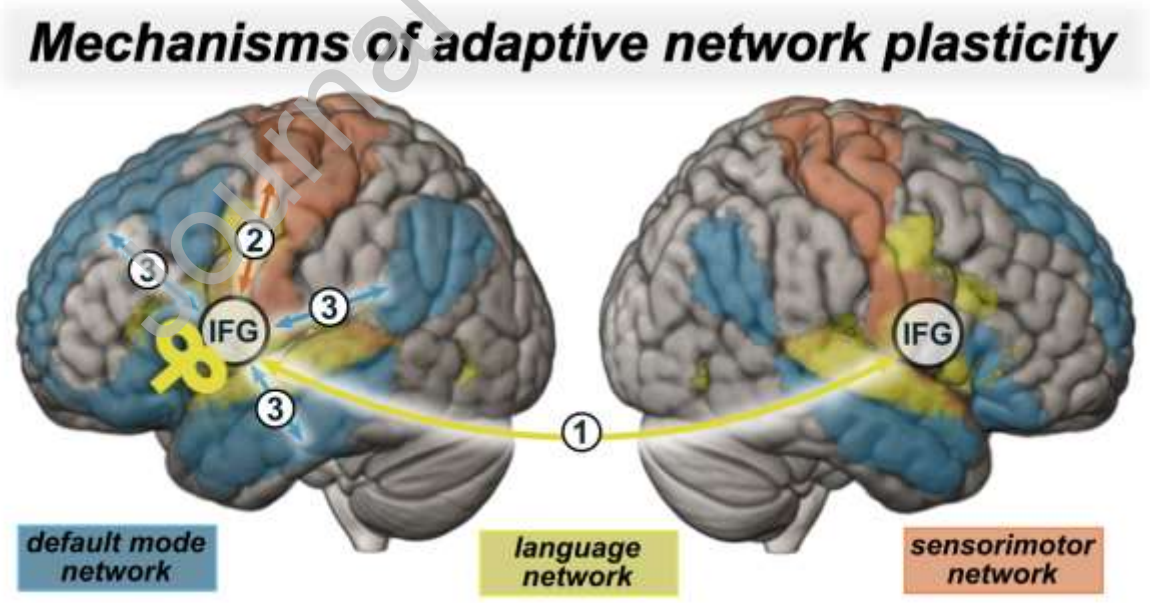

Figure 4: Mechanisms of adaptive network plasticity: Both short-term reorganization in the healthy brain and stroke-induced reorganization seem to rely on three general mechanisms of adaptive network plasticity that allow to maintain and recover function, as schematically illustrated for rapid adaptive plasticity induced by rTMS over left inferior frontal gyrus (IFG). To compensate for the stimulation-induced disturbance of neural activity in the language network (*yellow*) by rTMS application to left IFG: (1) interhemispheric connectivity can be increased and

specialized neural resources in the contralateral homologue (right IFG) can be recruited. (2) Neural resources of other specialized networks such as the motor network (*orange*) and specifically premotor areas can be integrated by increasing *between* network connectivity. (3) The computational capacity of domain-general networks, such as the default mode network (*blue*) can be recruited to ensure specific functions. In combination, these mechanisms may constitute general abilities for computational flexibility of the large-scale neural networks underlying motor and cognitive functions.

This flexible, adaptive plasticity helps to maintain task function after disruption. Secondly, aside from changes in task-related activity patterns, the potential for adaptive plasticity in the healthy brain further includes changes in the functional interactions between large networks both at rest and during different tasks. However, the functional relevance of such changes at the behavioural level is less well understood and future studies should combine TMS-induced perturbation of resting state connectivity with behavioural measures to address this issue. A way forward would include comparative investigations of TMS-induced changes with resting-state and task-based fMRI in the same participants to probe the relationship between both measures and test whether changes in task-related activity after TMS can be predicted by individual resting-state connectivity profiles and their responsiveness to neurostimulation.

Yet, it should be noted that the number of combined consecutive TMS-fMRI studies is overall relatively small, and in particular, the effects of facilitatory rTMS protocols have been rarely mapped with task-based fMRI. While the number of resting state studies that used such protocols is higher, the direction of facilitatory and inhibitory TMS on resting-state connectivity remains unclear, both at the local and global network level.

Independent of the assumed direction of a given protocol, plasticity-inducing rTMS may result in a complex pattern of both inhibitory and facilitatory changes at the local and global network level that may reflect changes in the recruitment and

inhibition of different network nodes or other areas, which may help to support or maintain behaviour.

In the lesioned network, stimulation-induced adaptive plasticity seems to rest on similar network mechanisms but appears to be even more complex. In both motor and cognitive networks, spontaneous recovery after stroke-induced brain lesions seems to be driven by the contribution of both domain-specific and domain-general network nodes. In parallel to perturb-and-measure approaches in healthy subjects, the recruitment of contralateral regions, especially neural resources around the functional homologues of stimulated regions via interhemispheric callosal connections, seems to play a key role in functional reorganization. While recruitment of vicarious computational capacity in the contralesional hemisphere is often assumed to be functionally supportive, the results of some rTMS-studies in the motor and language domain corroborate the concept of “maladaptive plasticity” in the contralesional hemisphere. In particular, inhibition of “over-activation” in the contralesional homologue region has been shown to be associated with better performance in patients with motor or language deficits. In both domains, rTMS-induced offline inhibition of the contralesional homologue seems to be effective in the (late) subacute phase after stroke (e.g. Grefkes et al., 2010; Heiss et al., 2013; Rubi-Fessen et al., 2015). However, the role of lesion-homologous regions in the non-affected hemisphere changes across the time course of recovery and the phase-specific contribution of contralesional regions remains largely unclear. Interestingly, some first TMS evidence suggests that the supportive role of the contralesional primary motor cortex may evolve across the time course of recovery and may be more prominent in later phases of motor recovery. This evidence is mainly driven by online TMS studies that probed the functional relevance of the contralesional homologue in the acute vs. chronic phase after stroke. Similar TMS studies on

language recovery are missing. Based on fMRI studies investigating spontaneous recovery in the language system, it may be concluded that the time course of recruitment patterns may be different in the language compared to the motor network, with an early upregulation of homologous regions being associated with better recovery, while a later normalization of language activity and a re-shift towards the left hemisphere seems to be beneficial (Saur et al., 2006). Yet, early upregulation of the right hemisphere has mainly been observed in patients with lesions in the frontal cortex (Stockert et al., 2020) and thus may reflect the contribution of domain-general areas for cognitive control (Geranmayeh et al., 2014). Consequently, we speculate that the difference in the contribution of the contralesional hemisphere between the motor and language system in the acute phase after stroke potentially reflects the contribution of domain-general networks to higher level domain-specific operations such as language processing.

Additionally, preliminary evidence further suggests that right-hemispheric lesion homologous regions may help to maintain task function after focal TMS-induced perturbation of the reorganized language network. However, the functional relevance of these changes needs to be demonstrated. Combining perturb-and-measure approaches with subsequent online disruption of the observed reorganization patterns in the lesioned brain may help to identify if such upregulation supports motor or language processing. Ultimately, longitudinal studies that map changes in the adaptive recruitment of perilesional and contralesional areas across the time course of recovery are needed to understand changes in the functional contribution of both hemispheres to recovery. Here, task-related changes should be complemented with the investigation of changes in the functional and effective connectivity between key nodes.

To identify domain-global mechanisms of adaptive plasticity and compensation of TMS-induced perturbation or structural lesions, future work should focus on mapping stimulation-induced changes in task-related activity and connectivity across different domains. First hints towards domain-general mechanisms of plasticity and network reorganization have been derived from resting state data in stroke patients. These data support the notion that different domains share several recruitment patterns, such as the increased contribution of domain-general networks to support recovery of domain-specific functions. In particular, recruitment of prefrontal control regions may be functionally beneficial for numerous specific domains under increased control demands in lesioned networks. Likewise, recruitment of premotor regions may be beneficial for both motor and language recovery after stroke since these areas are shared core nodes of networks involved in both motor and language tasks.

Other promising complementary avenues for future research include the concurrent application of TMS during fMRI to map the immediate consequences of the stimulation (e.g. Bestmann and Feredoes, 2013) in the healthy and lesioned brain and asses both regional and remote changes induced by facilitatory and inhibitory neurostimulation. Moreover, the combination of rTMS with novel network approaches such as graph theory for task-based fMRI may increase our understanding of stimulation-induced network effects and may help to identify individual connectivity patterns that may be predictive of compensation in the healthy brain and successful recovery after lesions. Likewise, mapping individual TMS-induced changes during functional recovery may benefit from the use of multivariate approaches that are more sensitive to capture individual differences relative to standard univariate measures of network activity. Finally, complementary approaches such as the combination of TMS with electroencephalography may help to provide new insight

into the underlying mechanisms of plastic after-effects of different rTMS protocols and their interaction with the current brain state during stimulation.

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Figure legends

Figure 1: Figure 1: rTMS and resting-state networks: Application of rTMS to target regions within different functional networks has been shown to affect both functional connectivity *within* the stimulated network as well as *between* the stimulated network and distinct functional networks. Inhibitory rTMS applied to the dorsolateral prefrontal cortex (DLPFC) has repetitively been shown to *decrease* connectivity between DLPFC and the default mode network (DMN), (1: Mastropasqua et al., 2014; Shang et al., 2019; van der Werf et al., 2010) while excitatory rTMS *increased* DLPFC-DMN connectivity (2: Xue et al. 2017). Stimulating a node of the DMN by applying inhibitory rTMS to left inferior parietal lobe (IPL) *increased* connectivity between the IPL and the hippocampal formation, while excitatory rTMS *decreased* connectivity between cortical DMN nodes such as the IPL, medial prefrontal cortex (mPFC) and posterior cingulate cortex (pCC) (6: Eldaief et al. 2011). Increased motor network connectivity has independently been observed after rTMS applied to primary motor cortex (M1) using different stimulation protocols (3: Nettekoven et al. 2014; 4: Watanabe et al. 2014; 5: Cocchi et al. 2015). From a mechanistic perspective, changes in functional connectivity may reflect a modulation of information integration within the stimulated network and between distinct networks induced by the stimulation.

Figure 2: Adaptive plasticity in language networks: rTMS applied to core nodes of the language network has repetitively been shown to result in a typical pattern of altered task-related neural activity: a *decrease* in task-related activity in the stimulated region after rTMS is paralleled by an *increase* of neural activity in the homologous, contralateral region. This task-dependent recruitment of the homologous region is thought to compensate for the detrimental effects of the stimulation-induced perturbation and support successful performance. This compensatory mechanism has independently been observed after perturbation of (1) right primary auditory cortex (A1, Andoh and Zatorre, 2013; Andoh and Zatorre 2011), (2) left posterior superior temporal gyrus (pSTG, Andoh and Paus, 2011), (3) left inferior frontal gyrus (IFG, Hartwigsen et al., 2013) and (4) left anterior temporal lobe (ATL, Binney and Lambon Ralph, 2015; Jung and Lambon Ralph, 2015).

Figure 3: Online TMS and motor function after stroke: Online TMS experiments offer a unique window into functional roles of stimulated cortical regions. In chronic stroke patients (*right panel*), **impaired** motor performance of the paretic hand has been observed when applying online TMS to bilateral primary motor cortex (M1), bilateral dorsal premotor cortex (PMd) or the contralesional superior parietal lobe (SPL) during motor performance (*red coil*). Thus, highlighting a supportive role of these regions on paretic hand motor function in chronic patients. Conversely, online TMS applied to the contralesional intraparietal sulcus (IPS) enhanced paretic hand function (*green coil*). In acute stroke patients (*left panel*), interfering with both contralesional M1 and IPS improved paretic hand function, suggesting early maladaptive influences of these regions on specific aspects of paretic hand motor

function. (1: Johansen-Berg et al., 2002; 2: Werhahn et al., 2003; 3: Fridman et al., 2004; 4: Lotze et al., 2006; 5: Volz et al., 2017; 6: Tscherpel et al., 2020).

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Figure 4: Mechanisms of adaptive network plasticity: Both short-term reorganization in the healthy brain and stroke-induced reorganization seem to rely on three general mechanisms of adaptive network plasticity that allow to maintain and recover function, as schematically illustrated for rapid adaptive plasticity induced by rTMS over left inferior frontal gyrus (IFG). To compensate for the stimulation-induced disturbance of neural activity in the language network *(yellow)* by rTMS application to left IFG: (1) interhemispheric connectivity can be increased and specialized neural resources in the contralateral homologue (right IFG) can be recruited. (2) Neural resources of other specialized networks such as the motor network *(orange)* and specifically premotor areas can be integrated by increasing *between network* connectivity. (3) The computational capacity of domain-general networks, such as the default mode network *(blue)* can recruited to ensure specific functions. In combination, these mechanisms may constitute general abilities for computational flexibility of the large-scale neural networks underlying motor and cognitive functions.