

# Brain Plasticity in fMRI and DTI

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## Abstract

This chapter describes what kind of neuroplastic information may be generated by functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) after brain damage. Clinical neuroplasticity may be defined as an active reorganization contrary to loss of activation or connectivity simply due to brain damage. After giving an overview about general aspects of clinical neuroplasticity, this chapter introduces specific benefits of neuroplasticity investigations for patient care. These include better definition of the patients' functional state, better individual prognosis, improvement of treatment strategies, and progress in understanding how the nervous system acts in response to disease. Since fMRI and DTI are restricted to detecting neuroplastic changes on the level of neuronal populations and their connections, some important molecular and cellular mechanisms driving these effects are also discussed. Further, a review is given about previously described neuroplastic responses of the diseased brain. This focuses on neuroplasticity evoked by pathomorphological changes of a previously healthy nervous system. It allows an illustration of the complexity and limitations of neuroplasticity research. To ease a critical evaluation of published data, this chapter also includes methodological considerations, which deal with the limitations of the technical or neurophysiological interpretation of neuroplasticity investigations. Finally, some clinical examples illustrating the potential of fMRI and DTI are given.

## 1 Introduction

Clinical neuroplasticity may be defined as functional or structural alterations of the nervous system in the sense of active reorganization after damage. This functional and structural reorganization is possible throughout the entire life span and also occurs as nonclinical neuroplasticity. The latter is a physiological response within the healthy brain to adapt to changing individual demands or changing physiological states.

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Defining nervous system alterations as neuroplastic is not always a trivial task. For example, changes in functional connectivity after a major traumatic brain injury leading to coma may be an immediate consequence of the brain damage itself but not of reorganization. For instance, changes in structural connectivity like reductions in fiber tract integrities may be a result of tract damage but not of structural reorganization (where weakening of non-damaged tracts may also occur (Simões et al. 2012)). Correspondingly, reduced local brain activity may also be a consequence of damage to connecting tracts but not of functional reorganization (e.g., Hamzei et al. 2008). Moreover, clinical improvements after brain damage may occur independently of functional reorganization. Within the first days after a functionally relevant brain damage, secondary effects regress spontaneously, and accordingly, their disturbing influence on brain function disappears (Seitz and Donnan 2010; Buma et al. 2010). Such secondary (non-neuroplastic) effects include inflammation, edema, compromised perfusion close to pathology, and diaschisis (malfunctioning of disconnected brain areas distant from the pathology).

Another important issue with regard to the clinical neuroplasticity literature concerns the functional outcome. The ultimate goal of clinical neuroplasticity is the *regeneration of function* in terms of a reestablishment of the compromised function. However, *physiologic compensation* of the lost function may also occur, and this may induce a (non-neuroplastic) brain activation change, simply due to altered functioning. Examples include compensation of a distal paresis by recruitment of more proximal muscles or increased activity associated with mirror movements of the non-affected limb. A differentiation is possible via repeated functional magnetic resonance imaging (fMRI) measurements and simultaneous documentation of motor performance. Importantly, worsening of function (maladaptation) is also a possible outcome.

All these interrelationships need to be considered when functional or structural alterations are described with fMRI or diffusion tensor imaging (DTI). However, the current literature is not always consistent. This is partly due to the methodological constraints of the individual study. Therefore, a critical question is, what can be measured with clinical fMRI or DTI? Generally, these techniques enable in vivo assessment of spatial and temporal patterns of functional and structural changes. In recent years, an impressive extension of the MR armamentarium suited for neuroplasticity investigations has been established. Detailed descriptions of these methodologies can be found in the methodological chapters of this book. In brief, classical fMRI allows the detection of local increases and local decreases of brain activity. It is possible to monitor brain activation changes occurring spontaneously (resting-state or task-free fMRI), occurring in response to a task (task-based fMRI), or occurring in response to medication (pharmacological fMRI). A correct reflection of neuronal activity by the fMRI blood oxygen level-dependent (BOLD) signal requires an

undisturbed vascular situation. Disturbed situations may be found in early stages after ischemic stroke, where vessels are maximally dilated. It should also be kept in mind that an increase in BOLD signal can reflect excitatory as well as inhibitory neuronal activity. Concerning spatial reorganization, increase in BOLD signal may occur within a typical task active area or in a nontypical but functionally related area due to activation of additional resources. This may be seen as increased activity in spared brain areas close to the pathology or as increased activity in secondary brain areas remote from the pathology. For example, in the motor network the secondary premotor cortex is extensively connected to the primary motor cortex (M1) and can partly substitute M1 via projections to the spinal cord. Increase of local neuronal activity (overactivation) may be locally driven or be a consequence of disinhibition mediated by remote connected areas. Decrease of local neuronal activity (underactivation) may also be mediated by remote areas (inhibition). However, underactivation may also be a consequence of damage to local or distant (diaschisis) tissue. The monitoring of such changes in brain activation can also be used to investigate how brain areas are functionally connected to each other, that is, which brain areas form networks and how these networks do neuroplastically change. The most published measures are functional connectivity, effective connectivity, and graph theory networks. Functional connectivity defines networks of brain areas by integrating all areas which show similar signal behaviors. Effective connectivity determines which brain areas may change the activity of other brain areas. Graph theoretical approaches classify brain areas according to the hierarchy they represent within the global brain connections. All these methods may be applied to describe functional alterations of the nervous system.

For description of structural alterations, DTI techniques are used (for review see Huston and Field 2013). They allow the estimation of the structural integrity and connectivity of white matter tracts at a level that cannot be achieved with anatomical imaging or volumetric white matter analysis. To some extent it is also possible to characterize tissue architecture (e.g., cellular density, vasculature, necrosis, extent, or margins of a neoplasm). The DTI results indicate local increases or decreases of tract integrity and tract volume, dislocation of white matter tracts or alterations of structural connectivity between brain areas.

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## 2 What Are the Clinical Benefits of Neuroplasticity Investigations?

Information about neuroplastic alterations generated by fMRI and DTI is important to improve patient care. By extending standard clinical findings, fMRI/DTI information allow a better definition of the patients' functional state, better individual prognosis, improvement of treatment strategies, and

progress in understanding how the nervous system acts in response to disease (for recent reviews, see Grefkes and Ward 2014; Wahl and Schwab 2014; Gillebert and Mantini 2013; Havsteen et al. 2013; Jiang et al. 2013; Rehme and Grefkes 2013; Shah et al. 2013; Stinear and Ward 2013; Dijkhuizen et al. 2012; Gale and Pearson 2012; Saur and Hartwigsen 2012; Smits et al. 2012; Hamberger and Cole 2011; Westlake and Nagarajan 2011; Buma et al. 2010; Chen et al. 2010; Rowe 2010; Seghier et al. 2010; Seitz and Donnan 2010). Importantly, the information generated by different fMRI/DTI techniques – brain activation, functional or effective connectivity, and structural connectivity – often complement one another or complement other diagnostic techniques. For instance, connectivity analyses may detect disease or treatment effects even when brain activation techniques are insensitive (Rowe 2010). Tractography may allow assessment of Wallerian degeneration better than conventional MR imaging (Huston and Field 2013). Tractography may be even more sensitive than recording of motor evoked potentials – as described in a study of clinically critical disruptions of the posterior limb of the internal capsule (Stinear et al. 2007).

## 2.1 Better Evaluation of the Patients' Functional State

fMRI/DTI benefits for evaluating the patients' functional state are evident from the motor system plasticity literature. A change of motor lateralization to the contralesional hemisphere often indicates a reduced functional competence in the lesioned hemisphere (which does not need to correlate with the extent of morphological destruction!). As also evidenced by brain stimulation data (O'Shea et al. 2014), patients with functionally compromising ipsilateral lesions depend more on their contralesional hemisphere than those with good residual ipsilateral function. Compensatory lateralization changes are informative about the stage of rehabilitation and may be transient (Grefkes and Ward 2014).

## 2.2 Better Individual Prognosis

fMRI/DTI neuroplasticity investigations help to improve the individual prognosis. In pediatric epilepsy, for example, the chronic nature of epileptic activity can result in a shift of language from the left to the right hemisphere or rerouting of language pathways from traditional to nontraditional areas within the dominant left hemisphere. The capability to reorganize may correlate with a better prognosis (evidence for stroke patients exists (Ovadia-Caro et al. 2013)). However, clinical variables have not been reliable predictors of altered language networks in individual patients (Hamberger and Cole 2011), whereas fMRI/DTI data are promising with this respect

(see Sect. 4.2). For stroke patients, Puig et al. (2011) showed that DTI data about corticospinal tract damage correlate better with clinical recovery than baseline clinical scores or even lesion volume. Improved prognosis generates further clinical benefits by enabling adequate setting of rehabilitation goals and more efficient allocation of resources. For example, Appel-Cresswell et al. (2010) showed that clinical performance of patients with Parkinson's disease could be maintained when intact cerebellar circuits were detected which were able to compensate for basal ganglia deficits. In contrast, despite adequate therapy the goal of maintaining performance may be unrealistic when neuroplastic compensation cannot be evidenced. Recently, some prognostic indices have been suggested which combine MR data with clinical data: the PLORAS system (Predicting language outcome and recovery after stroke, Price et al. 2010) combines anatomical images of a lesion with clinical data. The PREP system (Predicting recovery potential, Stinear et al. 2012) combines DTI results about structural integrity with clinical data. Both try to help clinicians to estimate the prognosis of an individual patient. Help for prognostic judgments can also be provided by fMRI data (Marshall et al. 2009) or combinations of fMRI data with clinical data (Zarahn et al. 2011; Saur et al. 2010). In these studies, the fMRI results were classified with various data analysis methods, including multivariate machine learning techniques. Such analyses try to extract fMRI patterns typical for good or bad later recovery.

## 2.3 Improvement of Treatment Strategies

Improvement of treatment strategies concerns any type of intervention, be it behavioral, pharmacological, surgical, or brain stimulation therapies. For example, the definition of typical reorganizational profiles with fMRI/DTI may guide the development of brain stimulation protocols that focus on brain regions most relevant for functional recovery. Such protocols can then be applied across the respective group of patients. Improvement of treatment strategies may also be possible for surgical interventions. Robles et al. (2008) suggested the monitoring of brain reorganization after a first incomplete tumor resection in essential eloquent brain areas, where complete initial tumor removal is mostly not possible due to the danger of generating a nonreversible functional deficit (e.g., aphasia, paresis). The expectation of this approach is that after postsurgical functional reorganization a reoperation allows an optimization of the residual tumor resection. This concept is supported by other data which indicate that tumors within essential brain areas like Broca's area can indeed be removed without generation of clinical deficits, when previous neuroplastic reorganization has been occurred, and there is no clinical aphasia despite Broca's lesion (Benzagmout et al. 2007; Ius et al. 2011). For optimizing

treatment strategies fMRI/DTI neuroplasticity investigations allow the evaluation of the interaction of therapies with learning-dependent and non-learning-dependent mechanisms of recovery. For example, in a brain stimulation study in patients with Parkinson's disease, González-García et al. (2011) found that clinical improvement after repetitive transcranial magnetic stimulation was associated with caudate nucleus activity increases and functional connectivity changes. This kind of studies will allow clinicians to learn which type of neuroplastic changes need to be evoked by therapeutic interventions when they shall be effective.

## 2.4 Progress in Understanding How the Nervous System Acts in Response to Disease

A very important benefit of neuroplasticity investigations concerns the progress in understanding how the nervous system acts in response to disease. For this, the most valuable clinical data are provided by longitudinal measurements. In contrast to cross-sectional data representing the neuroplastic state of the nervous system at a single time point, longitudinal data allow the clarification of nonlinear, time-dependent dynamics and recognition of adaptive compensation strategies. The latter is important to distinguish the restitution of original function from the establishment of a new compensatory function to accomplish the requested task. Longitudinal measurements are also important for understanding which neuroplastic changes are physiological (e.g., compatible with normal aging) as opposed to a pathological response (Heitger et al. 2013; Marchand et al. 2011). Further, descriptions of longitudinal changes allow the recognition of typical reorganizational profiles of neural networks post damage (Turkeltaub et al. 2011). Knowledge about typical reorganization profiles allows the identification of the critical degenerative and restorative processes and the definition of the brain regions most relevant for functional recovery. This may generate new possibilities for a better subclassification of diseases (Richiardi et al. 2012). Also, knowledge about typical reorganization profiles is the basis for the determination of individual anomalies. On the other hand, even if neuroplastic changes are absent, important clinical information may be generated by the fMRI/DTI techniques. They allow the documentation of which networks are still functional and may serve as a therapeutic target (Enzinger et al. 2008).

## 3 Mechanisms of Neuroplasticity

Neuroplasticity as detectable with fMRI/DTI may be driven by molecular changes, cellular changes, or changes concerning the action and interaction of neuronal populations

(for reviews see references in Sect. 2). The latter may also be a consequence of the molecular and cellular changes following brain lesions.

### 3.1 Molecular Changes

On the molecular level, changes for the expression of growth-associated genes resulting in increased growth-promoting factors, decreased growth-inhibiting factors and expression of maturation regulating proteins have been described (e.g., Anderson et al. 2013; Carmichael et al. 2005). These gene expressions are associated with axonal sprouting in peri-infarct cortex and with synapse formation. In addition, the level of glutamate and gamma amino butyric acid (GABA) may change as may the expression and responsiveness of cholinergic and GABA receptors with the latter resulting in a loss of inhibitory interneurons (Clarkson et al. 2010; Zepeda et al. 2004).

### 3.2 Cellular Changes

On the cellular level, a major neuroplastic mechanism concerns the changes in the function or number of synapses. This includes reinforcement of existing but functionally silent synapses (particularly at the periphery of lesions) and formation of new synapses. Further neuroplastic changes concern the dendritic arborization and axonal sprouting which may happen over considerable distances. These mechanisms may be influenced by changed inhibitory and excitatory inputs on local neurons. It is important to realize that the cellular changes may occur not only perilesionally but also in functionally/structurally connected brain areas remote from a lesion. Cellular neuroplasticity may also be modulated by glial cells which have been shown to affect excitability and synaptic transmission and to coordinate activity across networks (Araque and Navarrete 2010; Fields and Stevens-Graham 2002). Furthermore, recent research indicates that brain lesions may also stimulate neurogenesis and migration of neuroblasts (Kernie and Parent 2010). Neurogenesis in the adult brain persists in the subventricular zone, the olfactory bulb region, and the subgranular zone of the dentate gyrus of the hippocampus. These neurogenetic areas may be stimulated by brain injury with the consequence of a proliferation of neural progenitor cells which then migrate to the injured region (Kernie and Parent 2010; Ohab et al. 2006).

### 3.3 Neuronal Population Changes

Concerning neuronal populations, their action and interaction is influenced by the neuroplastic mechanisms described above. The molecular and cellular alterations change inhibitory

and excitatory influences on the neuronal populations and lead to altered anatomical connections. The consequences are functional and structural network changes on a local (changed activity of a network node) or global (changed network configuration) level. These comprise local overactivations or deactivations, increase or decrease of functional connectivity, and increase or decrease of modulatory influences between neuronal populations. Concerning structural network changes, the most important mechanisms are the reduction or increase of preexisting fiber tracts and the generation of new axonal connections. Detailed examples for resulting patterns of functional and structural network changes are described in context with specific diseases below.

## 4 Review of the Literature

Previous literature about clinical neuroplasticity detectable by fMRI and DTI may be divided in general patterns of neuroplastic changes – irrespective of the functional outcome and therefore including maladaptation – and neuroplastic changes leading to recovery. The latter relate clinical outcome with specific neuroplastic effects. Neuroplastic changes detectable with fMRI or DTI concern either local brain activation measures or functional/structural network measures. A problem for the classification of neuroplastic findings is the large number of factors which may affect neuroplasticity. These include type and stage of the disease, location and size of the lesions, type and intensity of clinical interventions (standard treatment, special training techniques, pharmacological interventions, brain stimulation techniques, surgery), age, biological characteristics of the individual, type of the investigated function, and particularly the method used for the detection of neuroplasticity. Knowledge how these factors influence fMRI/DTI findings is still rather limited.

For the investigated diseases, most of the clinical neuroplastic literature relates to neuroplasticity evoked by pathomorphological changes of a previously healthy nervous system. This review will therefore focus on this type of disease. However, descriptions of clinical neuroplastic effects also exist for other diseases like genetic diseases, or psychiatric disorders, or inborn morphological defects. For illustration of the large variety of diseases already studied, interesting recent publications include neuroplastic changes in schizophrenia (e.g., Palaniyappan et al. 2012), dementia (e.g., Jacobs et al. 2012), Parkinson's disease (e.g., van Nuenen et al. 2012), Huntington's disease (e.g., Scheller et al. 2013), focal dystonia (e.g., Altenmüller and Müller 2013), amyotrophic lateral sclerosis (e.g., Mohammadi et al. 2011), traumatic brain injury (e.g., Caeyenberghs et al. 2012a, b), spinal cord injury and spinal cord plasticity (e.g., Cadotte et al. 2012), agenesis of the corpus callosum (e.g., Wolf et al. 2011), congenital blindness (e.g., Collignon et al. 2011),

effects of therapeutic immobilization (e.g., Langer et al. 2012), systemic lupus erythematosus (e.g., Hou et al. 2013), fibromyalgia (e.g., Craggs et al. 2012), small vessel disease (e.g., List et al. 2013), hepatic encephalopathy (e.g., Qi et al. 2013), tinnitus and hearing loss (e.g., Schmidt et al. 2013), and Mal de Debarquement syndrome (e.g., Cha et al. 2012).

To give an overview of previously described neuroplastic responses of the diseased brain, we here discuss exemplary findings based on important neurological diseases which are represented in a relatively large body of published data. This allows an illustration of the complexity and limitations of clinical neuroplasticity research but cannot be comprehensive. We will start with neuroplasticity after stroke. Most data about clinical neuroplasticity have been published for this disease, and several of the neuroplastic effects described here can also be found in other diseases. To present other findings related to differing disease conditions, we will then review studies on epilepsy, tumor, multiple sclerosis, and peripheral nervous system disorders. All these illnesses include largely different pathophysiologies which affect neuroplasticity. Typical stroke consists of a single event which generates neuronal destructions followed by a regeneration period without the influence of additional pathologies. Typical epilepsy is characterized by the perseveration of pathological neuronal activity which may function as a continuous neuroplastic driving factor – and this may happen within a brain without morphological abnormalities (based on routine clinical imaging). Classical brain tumors continuously increase the area of brain destruction at a single specific site at different speeds. Multiple sclerosis is typically caused by the accumulation of new brain lesions over many years but not at a single specific site but in a multitopic fashion. With peripheral nervous system disorders, brain neuroplasticity is not induced by brain lesions. Instead, the changed information flow between the somatic periphery and the brain constitutes the driving factor.

### 4.1 Stroke

#### 4.1.1 General Patterns of Neuroplastic Changes

##### 4.1.1.1 Local Brain Activation Changes

The literature about neuroplastic changes following stroke is very heterogeneous. Early spontaneous reorganization and repair is largely variable within the first months and the speed of spontaneous (non-neuroplastic, see Introduction) neurological recovery correlates with the final outcome. Therefore, the majority of studies investigated neuroplastic changes in a chronic stage of stroke starting after about 6 months post tissue damage. After a stroke neuroplastic changes typically lead to improvement of the disturbed function. However, in some cases neuroplasticity may also result

in functional disturbance – called maladaptation. Besides preventing optimal motor performance (Bütefisch et al. 2008; Grefkes et al. 2008), maladaptation may also be found for other senses. Dilks et al. (2007) reported a case study of a patient whose fiber tracts providing input for the primary visual cortex were partly disconnected due to a stroke. The patient was blind in the deafferented part of the visual cortex (upper left visual field) and suffered from distorted perception in the unaffected lower left visual field. For example, he perceived a square presented in the lower left visual field as a rectangle extending upward (toward and into the blind part of the visual field). fMRI data revealed activation of the deafferented area when stimulating the lower left visual field and thus confirmed maladaptive reorganization of the primary visual cortex leading to perceptual distortion. Beauchamp and Ro (2008) described maladaptive neuroplasticity after a thalamic lesion which resulted in sound-touch synesthesia. They found abnormal brain activity to sounds in the parietal operculum, an area belonging to secondary somatosensory cortex. Only with sounds activating this somatosensory area, a sound-touch synesthesia occurred.

Criteria determining regeneration or maladaptation are not well understood. This is due to the large number of factors which may affect neuroplasticity. One such factor is the level of destruction of a primary brain area. Primary brain areas consist of functionally essential eloquent cortex. In contrast to lesions affecting nonessential cortex, neuroplastic reorganization cannot completely recover the disturbed function of a lesioned *primary* brain area. It is important to note that classical definitions of what constitutes a primary brain area have recently been challenged by results from voxelwise lesion-behavior mapping (Bates et al. 2003) or resections guided by intraoperative direct electrical stimulation (Ius et al. 2011). The latter data also emphasize that besides essential cortex there also are essential white matter tracts. An illustrative example how neuroplasticity may depend on the level of essential cortex destruction has been given by Vitali et al. (2007) in two aphasic patients with Broca's area lesions. After speech training, the patient with the smaller lesion showed left perilesional reactivation; however, the patient with complete destruction of Broca's area showed activation in the right Broca's homologue and therefore a lateralization change. Saur and Hartwigsen (2012) summarized factors which might influence right hemisphere language involvement in the chronic phase after stroke: (1) the amount of individual premorbid language lateralization (i.e., patients with a more bilateral premorbid language representation could better use homologue right areas), (2) the lateralization of the language function of interest (more bilaterally organized functions like language comprehension might involve right hemisphere areas to a greater extent compared with left-lateralized functions, like language production or syntax), and (3) 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). In general, the literature indicates that the chronically reorganized language system post stroke comprises undamaged areas and perilesional tissue in the left hemisphere as well as homologue areas in the right hemisphere and that these reorganization networks are largely consistent across studies (Turkeltaub et al. 2011). However, the concrete distribution of activity depends on the elapsed time after stroke. A plausible model suggests that language recovery proceeds in three phases: first, a strongly reduced activation of remaining left language areas in the acute phase; second, an upregulation with recruitment of homologue contralateral language zones – which correlates with language improvement – and third, a normalization of activation (Saur et al. 2006). A similar interhemispheric time course has been found for the motor network in rodent stroke models (Dijkhuizen et al. 2012) and patients (Binkofski and Seitz 2004). The description of these temporal and localizational factors affecting neuroplasticity is extended by findings concerning effects of biological age and white matter lesions. Age at brain damage influences the extent of poststroke reorganization and the clinical outcome with extraordinary reorganizational capabilities early in life (e.g., Guzzetta et al. 2008; Rath et al. 2008). The amount of corticospinal tract lesions also affects reorganization, with more damage resulting in less neuronal activation (e.g., Hamzei et al. 2008). Altogether, the neuroplastic patterns described above argue for reorganization in preexisting redundant systems in which preserved ipsilesional and homotopic contralesional areas compensate for the damage. There is little evidence for takeover of areas previously completely unrelated to the specific brain function (e.g., takeover of motor functions by the visual system). An exception exists for cases where a functionally unrelated brain area is intact but deafferented. This has been described for early blind subjects where somatosensory or auditory processing has been found in the “visual” occipital cortex (e.g., Collignon et al. 2011).

#### 4.1.1.2 Network Changes

Several studies investigated neuroplastic changes of functional and structural network connections after stroke. Concerning the principles of neuroplastic reorganization, an interesting dissociation between interhemispheric decoupling but increased local (intrahemispheric) coupling was described in animal studies by van Meer et al. (2010a, b). They found that strong interhemispheric correlations between resting-state fMRI signals of primary sensorimotor regions disappear in the first days after unilateral stroke in rats. In the subsequent weeks and coinciding with recovery of sensorimotor function, interhemispheric functional connectivity partially recovered. On the other hand, intrahemispheric functional connectivity did not deteriorate: connections

between primary somatosensory and motor cortices were preserved in the lesion's border zone and moderately enhanced within the contralesional hemisphere. In humans, persistence of intrahemispheric functional connectivity post stroke has also been described. Within the affected hemisphere excitatory interactions between frontoparietal areas and primary motor cortex exist (Rehme and Grefkes 2013). Concerning the interhemispheric interactions in humans, it is well known that primary motor cortex generally inhibits its contralateral homologue. If lesioned, this inhibitory influence is reduced resulting in a disinhibition of the contralesional motor cortex. In contrast, contralesional primary motor cortex still inhibits the lesioned area what may be maladaptive (Bütefisch et al. 2008; Grefkes et al. 2008). Interestingly, some studies indicate that connectivity changes persist even long time after stroke. For example, Mintzopoulos et al. (2009) investigated patients more than 6 months post stroke and found decreased effective connectivity between the primary motor cortex (M1) and the cerebellum. However, connectivity between the supplementary motor area (SMA) and the cerebellum was increased – as was the SMA-M1 connectivity. The authors conclude that this kind of neuroplasticity compensates for a dysfunctional M1. Using motor imagery tasks Sharma et al. (2009) reported that connectivity changes persisted even despite good recovery and normal local brain activity. Complementing the investigations about functional and effective connectivity, a few studies investigated network reorganization using Graph theory. For example, Wang et al. (2010) found that the motor execution network gradually shifted toward a random mode during the stroke recovery process. The authors conclude that a less optimized reorganization is involved in regaining function in the affected limbs. Although methodological limitations have to be considered (see Sect. 5), it is possible that some of the described connectivity changes do have structural correlates. For example, Jang et al. (2010) described a new motor pathway posterior to a lesion in the midbrain and upper pons.

#### 4.1.2 Neuroplastic Changes Driving Recovery

##### 4.1.2.1 Evidence with Standard Therapy

Several studies extend pure descriptions of poststroke neuroplasticity by correlating neuroplastic effects with clinical outcome. The results however are not unequivocal and the neuroplastic findings critically depend on disease duration. For the motor system, there is evidence that – after initial compensatory overactivations – the reconstitution of physiological brain activation patterns is a consistent predictor of a favorable recovery. Initial compensatory overactivations may be found in ipsilesional motor areas but also in contralesional areas from which uncrossed fibers may activate paretic muscles. Activation changes go along with functional and structural connectivity changes which also contribute to recovery. For example in chronic stroke patients, Schaechter

et al. (2009) found an association between the integrity of ipsilesional corticospinal tracts (as a result of degeneration and remodeling) and improved motor function. Further, brain stimulation findings indicate that enhanced excitability of disinhibited contralesional motor cortex typically normalizes within 90 days in patients with good recovery. Persistent recruitment of contralesional primary and bilateral secondary motor areas is often found in poorly recovered patients. In these patients, enhanced contralesional motor cortex excitability also persists (Buma et al. 2010; Bütefisch et al. 2008), and maladaptive inhibitory coupling from the contralesional upon the ipsilesional M1 may be found (Rehme et al. 2011). The importance of a physiological interhemispheric connectivity has been demonstrated by Carter et al. (2010, 2012): disruption of resting-state functional connectivity between left and right sensorimotor areas correlated with motor impairment (compare van Meer et al. 2010a, b, above). Within this context contradictory results of some studies can be understood. For example, two investigations of chronic paretic stroke patients found larger brain activations either with poor (Enzinger et al. 2008) or good (Laible et al. 2012) recovery. Enzinger et al. (2008) reported that particularly in the contralesional hemisphere, the extent of activation was increased, being compatible with an earlier “overactivation stage” of individual recovery. Laible et al. (2012) reported larger brain activation for the ipsilesional hemisphere, indicating that these patients were investigated at a later stage of individual recovery with a more typical (recovered) brain activation pattern. Consistent with this interpretation, Laible et al. described their patients as only moderately paretic at the time of the fMRI investigation. Besides primary and secondary sensorimotor cortices, also cerebellar activation changes contribute to successful recovery. In a longitudinal study over the first 6 months of stroke recovery, Small et al. (2002) found that increased activation in the contralesional cerebellum during rehabilitation supports a good recovery. From the data of Mintzopoulos et al. (2009, see above), it can be inferred that this goes along with an increased connectivity between the cerebellum and SMA and between the SMA and M1. Indeed, evidence for a positive correlation between SMA-M1 coupling and clinical outcome exists (Rehme et al. 2011; Grefkes et al. 2008).

As for the motor system, data for the language system are not unequivocal but several studies indicate that – again, after initial compensatory overactivations – reconstitution of physiological brain activation correlates with favorable recovery. This goes along with functional and structural connectivity changes. An instructive example is given by Papoutsi et al. (2011) who found that good recovery of syntactic function after left hemisphere damage was associated with an enhanced left frontotemporal effective connectivity and tract integrity. Correspondingly, in the patient population described by Warren et al. (2009), a reconstituted (or

preserved) physiological connectivity between the left and right temporal cortex correlated with receptive language performance, and Marcotte et al. (2012) found a better language recovery with reduced compensatory overactivations. For the early phase of recovery, it seems particularly positive if the brain is flexible enough to generate neuroplastic changes: Ovadia-Caro et al. (2013) described a correlation between lesion-induced connectivity changes and clinical outcome (the more, the better). Despite the general notion that normalization of brain activity drives recovery, there are indications that persistence of some residual neuroplastic deviations may be supportive to restore or maintain function. In a longitudinal study, Elkana et al. (2013) performed language fMRI scans years apart. They found that right hemisphere activation was associated with a better recovery in this extended chronic stage. In a typical left-dominant patient, a successful neuroplastic response of the language system might therefore consist of two factors: reconstitution of the typical left hemispheric activation pattern and ongoing right hemispheric activity supporting further recovery in the later chronic stage. These and other data generally challenge the classical view of recovery as ending within the first year after onset.

#### 4.1.2.2 Evidence with Specific Interventions

The abovementioned correlations between neuroplastic changes and clinical outcome result from clinical standard interventions like physiotherapy, ergotherapy, logopedics, and standard medications. Various publications indicate that functional recovery can be enhanced or modified by specific interventions. Sawaki et al. (2008) showed that constraint-induced movement therapy may considerably improve reconstitution of physiological brain activation patterns and thereby clinical recovery. Ertelt et al. (2007) reported that observation of action generated widespread cerebral overactivations despite the patients being in a chronic (stable) phase. These neuroplastic overactivations correlated with improved motor function. Increased functional connectivity in motor and visuospatial networks of stroke patients has been reported by Várkuti et al. (2013) using very sophisticated behavioral interventions (robot-assisted upper-extremity training and brain computer interface with motor imagery). The individual gain in motor scores over 12 weeks could be predicted from functional connectivity changes. Very recent data render it likely that these correlations between functional neuroplastic findings and recovery are accompanied by structural brain changes. For example, in a longitudinal study describing the application of a novel MR-compatible hand-induced robotic device in chronic stroke patients (Lazaridou et al. 2013a, b), structural neuroplasticity after 8 weeks of hand training was found with the appearance of new corticospinal tract fibers, increased fiber number and tract length, and cortical thickness gain in the postcentral gyrus. Corresponding to Mintzopoulos et al. (2009) (see above), the authors also found that effective

connectivity between the SMA and M1 as well as between the SMA and cerebellum were increased by robotic training. The importance of an increased SMA-M1 coupling during motor rehabilitation is further underlined by an exemplary fMRI study of Wang et al. (2011) using a pharmacological intervention. With a placebo-controlled, double-blind crossover design, they showed that noradrenaline specifically improved the ipsilesional SMA-M1 coupling and the motor performance by the application of an oral noradrenaline reuptake inhibitor. Examples for nonstandard interventions with neuroplastic consequences exist also within the brain stimulation literature (Stagg and Johansen-Berg 2013). Inhibition of the contralesional motor cortex by repetitive transcranial magnetic stimulation (TMS) with 1-Hz for 10 min improved motor performance of the affected hand but also generated a contralesional overactivation (Nowak et al. 2008). Grefkes et al. (2010) reported that motor improvement after inhibitory TMS of the contralesional primary motor cortex correlated with a reduction of the negative influences originating from the contralesional M1 during paretic hand movements.

Concerning the language domain, Marcotte et al. (2013) reported that a special aphasia therapy (semantic feature analysis) improved integration in the posterior areas of the default-mode network and this correlated with language recovery. Zipse et al. (2012) described an interesting case of an adolescent aphasia lacking further language improvement despite intense and long-term standard speech-language therapy. After changing to a therapy which specifically involves right hemispheric functions (Melodic Intonation Therapy), language performance improved. This was associated with fMRI activation changes in the right frontal lobe and increased volume of white matter pathways in the right hemisphere. Similarly, associations between TMS evoked white matter changes and improvements in cortical function have also been postulated by Allendorfer et al. (2012). They found increased white matter integrity in the left frontal lobe as a result of excitatory TMS stimulation over the ipsilesional left hemisphere in aphasics.

## 4.2 Epilepsy

In general, MR signal changes related to the neuroplastic principles described for stroke – for example, compensatory overactivations or functional connectivity changes – are also found in epilepsy. For example, in temporal lobe epilepsy patients with normal structural MRI, Schwarze et al. (2009) described that hippocampal overactivation was necessary for a successful encoding of face-name associations. Intra- and interhemispheric functional connectivity for language tasks was found to be reduced in patients with both left- and right-sided epileptogenic foci (Pravata et al. 2011). Since a characteristic feature of epilepsy is the perseveration of pathological neuronal activity,



in some patients this may hinder the reconstitution of a physiological brain state as described for recovery from stroke. In other patients, successful control of epilepsy may eliminate the neuroplastic driving factor, and reconstitution of physiological activation and connection patterns may follow (Helmstaedter et al. 2006). Several specific patterns of functional reorganization in patients with epilepsy have previously been described. In a multicenter study of pediatric localization-related epilepsy, You et al. (2011) identified three language activation patterns: first, a typical left hemispheric language network with left inferior frontal gyrus (Broca's area) and left superior temporal gyrus (Wernicke's area) activity; second, a variant left-dominant pattern with greater activation in Broca's area, mesial left frontal lobe, and right cerebellum; and third, activation in the right counterparts of the first pattern particularly in Broca's area. In a study on localization-related epilepsy with adults, Mbwana et al. (2009) found similar types of reorganization. In addition, they provided evidence for intra-hemispheric reorganization of language limited to the margins of typical left temporal activation.

Structural reorganization with epilepsy has also been investigated. In a study with patients with temporal lobe epilepsy (TLE), Powell et al. (2007) found that patients with more lateralized functional activation had also more lateralized connecting pathways within the functionally dominant hemisphere, compatible with a compensatory structural process. On the other hand, the epileptic seizure focus may disturb white matter tracts as shown by interhemispheric comparisons in children with focal cortical dysplasia (Kim et al. 2013) and patients with TLE (Liacu et al. 2012). They demonstrated increased DTI abnormalities ipsilateral to the seizure focus.

Due to the therapeutic option of epilepsy surgery, various studies investigated neuroplastic changes in this context. Weaver et al. (2013) investigated the potential of functional connectivity techniques for presurgical seizure focus identification in non-lesional focal epilepsy and concluded that it is possible to reliably predict its location. Results from studies which compare pre- and postsurgical neuroplastic changes are rather complex. Some studies indicate that neuroplastic reorganization patterns depend on the lateralization of the seizure focus. Wong et al. (2009) describe preoperatively increased right frontal activation with language tasks in both patients with right- and left-sided TLE. After anterior temporal lobectomy, however, only the left lobectomy patients showed a reduction of the right frontal overactivation. Similarly, Bonelli et al. (2012) found a postoperative fMRI activation change and stronger functional connectivity between frontal lobes only in the left lobectomy patients (and not in right TLE). Structural changes related to surgery have been described in the sense of loss of fiber tract integrity ipsilateral to the side of surgery (Faber et al. 2013) and in the sense of simultaneous decreases and increases of fiber tract integrity in different parts of the brain (Yogarajah et al. 2010).

### 4.3 Tumor

Again, the typical MR indices for neuroplastic changes described above can also be detected with different tumor types. The majority of data concerns compensatory overactivations and changed functional/structural connectivity. Both may be influenced by a large variety of factors. In a study with 68 patients with diffuse glioma, Harris et al. (2014) investigated changes of the default-mode network (DMN). In an evaluation of the influence of tumor grade, tumor volume, postsurgical clinical status, and tumor location, they found tumor grade to be the most significant predictor of DMN integrity with lower integrity in high-grade tumors. Effects on the DMN were also found for prior surgery. Although – as in other studies (e.g., Briganti et al. 2012) – tumor location influenced connectivity, the fact whether a tumor resided within or outside the DMN nodes did not influence the results.

A special feature of the various types of brain tumors is the fact that they continuously increase the area of brain destruction but do this with differing speed. Slow-growing lesions may generate less clinical symptoms and less neuroplastic changes. The infiltrative character of low-grade gliomas makes it even possible that function persists within the tumor (Duffau 2006). These facts may account for some of the discrepancies previously reported for the neuroplastic reorganization in tumoral lesions. An example is provided by a comparison of two patient groups with similar surgical lesions to the right medial temporal lobe (Braun et al. 2008). The groups differed clinically with respect to the preoperative course of disease. One group suffered from benign brain tumors with a slow but continuous increase of brain destruction; the other group suffered from hippocampal sclerosis, a stable pathology. The authors found a significant memory deficit for the tumor group only. They concluded that a stable pathology (hippocampal sclerosis) can yield significant functional reorganization which is not possible with a progressive pathology (tumors).

### 4.4 Multiple Sclerosis

Whereas earlier imaging studies with patients with multiple sclerosis (MS) predominantly described brain activation changes, recent literature focused on connectivity changes. Again the findings for this disease are not unequivocal and there is a large number of factors which may affect neuroplasticity in MS. These include age (effective connectivity increases with age, Rocca et al. 2010) and MS subtype (increased cerebellar-frontal effective connectivity with benign MS course, Rocca et al. 2012a). Given that the disease is characterized by a process which typically adds new lesions continuously over many years, and this in a multi-topic fashion, neuroplastic changes specifically depend on

the stage of the disease (Rocca and Filippi 2007). Therefore, brain activation changes which represent compensatory overactivations are common but variable. Concerning functional connectivity and disease stage, Cruz-Gómez et al. (2014) found that connectivity was reduced in four resting-state networks in cognitively impaired patients but only in one resting-state network in cognitively preserved patients. Rocca et al. (2012b) described a correlation between reduced resting-state connectivity and clinical disability and lesion volumes on T2-weighted MR images. In contrast, in a study investigating effective connectivity, Forn et al. (2012) described stronger connectivity for more cognitively impaired patients (relapsing-remitting MS). This is compatible with an increased demand on some brain areas to modulate others, which theoretically could even happen when general connectivity is reduced. Richiardi et al. (2012) suggested using functional connectivity analysis as a biomarker for the prognosis of the disease. Comparing a whole-brain connectivity matrix between minimally disabled MS patients and healthy controls, they found decreased connectivity for patients which correlated with white matter lesion load. Concerning structural neuroplasticity an interesting DTI study of Calabrese et al. (2011) described increased fractional anisotropy of normal-appearing gray matter in 168 patients with relapsing-remitting MS. This possibly reflects activation of microglia which then changes morphology in the sense of a more bipolar-oriented structure which would give rise to fractional anisotropy increase in gray matter. This finding was correlated with disease stage (i.e., clinical disability). Another study about structural connectivity of relapsing-remitting MS patients used graph theoretical methods (Shu et al. 2011). The authors found decreased white matter network efficiencies which correlated with the expanded disability status scale scores, disease duration, and total white matter lesion load. Correlations between altered structural and altered functional connectivity have also been described. In the study of Rocca et al. (2009), altered effective connectivity (increased and decreased) was correlated with structural damage of task specific fiber bundles, that is, fiber bundles involved in the tested cognitive performance. In contrast, no correlation between altered effective connectivity and fiber damage was found for bundles not directly related with the task.

#### 4.5 Peripheral Nervous System Disorders

The special feature of peripheral nervous system lesions concerns the fact that brain neuroplasticity is not induced by brain lesions. Instead, the changed information flow between the somatic periphery and brain constitutes the driving factor. As with central nervous system lesions, a typical initial response to peripheral damage constitutes compensatory

overactivations. Fornander et al. (2010) and Rath et al. (2011, see Sect. 6.1 below) described an initial increase in the volume of the cortical activation in secondary brain areas after surgical restoration of complete median nerve injury. This overactivation subsequently declined during the following course of rehabilitation. For later recovery phases, Taylor et al. (2009) reported a correlation of decreased fMRI amplitude with gray matter loss 1.5 years after peripheral nerve transection and surgical repair. Initial overactivation is not only required to reestablish previous function but also to learn new functions. This has been shown by Chen et al. (2006) after transplanting a toe for replacement of a lost finger and by Eickhoff et al. (2008) for heterotopic hand replantation. In the latter study, effective connectivity between the healthy and affected (contralateral to the replanted hand) primary motor cortices was also determined. The results showed a maladaptive inhibition of the healthy on the affected motor cortex (see Sect. 6.3 below). Further examples for neuroplastic maladaptation can be found in amputees, where intact somatotopic representations extend into the representation area of the amputated limb and generate phantom limb pain. For instance, in a study of upper limb amputees, MacIver et al. (2008) found that cortical activation with lip movements extended to the area of the denervated hand and correlated with phantom limb pain. After special mental imagery training, overactivation was reduced and this correlated with a reduction of pain intensity, demonstrating that maladaptive neuroplasticity is reversible. This type of functional reorganization may also be accompanied by the structural reorganization of callosal fiber tracts (Simões et al. 2012).

Another feature consistently described is the fact that somatotopic brain activation typically corresponds to the peripheral nervous system output, but not to the effector activated by the output. Bitter et al. (2011) compared three types of peripheral surgical reorganization after facial nerve damage: classical hypoglossal-facial nerve anastomosis, hypoglossal-facial nerve jump anastomosis, and facial nerve interpositional graft. With all operations the effector (mimic musculature) is the same; however, the peripheral nervous system output required for identical movements changes. Lip movements after facial nerve interposition led to selective brain activation in the original facial motor cortex. Lip movements after hypoglossal-facial anastomosis were associated with activation in the hypoglossal motor cortex. For the jump anastomosis, however, overlapping activation encompassing both the original facial and the hypoglossal motor cortex was found. Another impressive example of brain activation corresponding to peripheral nervous system output (and not the changed effector) is presented in patients with brachial plexus lesions. In case of a complete avulsion of a brachial plexus, it is possible to connect the denervated biceps with fibers of the contralesional C7 root. The brain is then required to control flexion of the diseased arm with the

ipsilesional motor cortex. Functional imaging data have shown that this is achieved via activation of the typical ipsilesional C7 arm area (controlling the contralesional C7 root), though initially a bilateral activation pattern may occur (Hua et al. 2013; Beaulieu et al. 2006). More complex neuroplastic effects can be found when biceps reinnervation is done via a connection to the side of the phrenic nerve (Beisteiner et al. 2011, see Sect. 6.2 below).

An instructive example that evocation of cortical neuroplasticity is not restricted to macroscopic nerve changes but may also be induced by affections of terminal nerve endings and mechanoreceptors was provided by Kapreli et al. (2009). In patients with complete right unilateral anterior cruciate ligament rupture, afferent information flow from mechanoreceptors to the brain is disturbed. Despite the central and peripheral nervous system being undamaged otherwise, the authors found cortical reorganization in sensorimotor and other brain areas (as determined relative to healthy controls).

## 5 Methodological Considerations

As with every neurophysiological technique, there are also limitations and pitfalls for fMRI and DTI (compare book chapter, Clinical BOLD fMRI and DTI: Artifacts, Tips, and Tricks). Some limitations are of special importance for neuroplasticity investigations. These relate to the technical and neurophysiological interpretation of findings.

### 5.1 Technical Interpretation of Findings

Technically, it is important to realize that sensitivity and specificity of fMRI and DTI are limited, so that false-negative and false-positive findings can be encountered. With standard fMRI methods major risk factors for false findings include limited signal to noise and contrast to noise ratios, image artifacts (e.g., ghosting, signal voids, motion artifacts, registration errors), effects of data analysis thresholds (e.g., statistical thresholds set for “true” activation), altered hemodynamic responses due to changed neurovascular coupling in pathological tissue, and inadequate patient compliance. With standard DTI methods major risk factors for false findings are similar: limited signal to noise ratio, image artifacts, and effects of data analysis thresholds (e.g., anisotropy thresholds set to define tract endings). Specific DTI problems concern the variability and limitations of current DTI techniques: deterministic vs. probabilistic tractography, Gaussian vs. non-Gaussian model of diffusion, number of diffusion-weighted gradient directions, and specific effects of spatial resolution.

### 5.2 Neurophysiological Interpretation of Findings

Even when the fMRI/DTI data are technically perfect according to the state of the art, the neurophysiological interpretation is not always unequivocal. Particularly with fMRI data one has to bear in mind that results are correlative in nature and causal conclusions are limited. If there is information provided with fMRI only, it is also difficult to differentiate activations of essential primary cortical areas from modulatory secondary activity within neuroplastically changed activation patterns. Further, the results may be specific for the given MR methodology and incongruent to findings with other techniques. For example, in patients with temporal lobe epilepsy, Bettus et al. (2011) found lower functional connectivity in regions with epileptiform abnormalities based on intracerebral electroencephalography (EEG). However, an opposite pattern resulted from fMRI data of the same patients. As already discussed in the chapters above, possible reasons for fMRI activation changes are manifold. fMRI overactivations may indicate both beneficial functional compensation and maladaptation. Lateralization changes may be due to contralateral overactivation or ipsilateral underactivation. The dependence of lateralization on experimental (e.g., task difficulty) and patient factors (e.g., cognitive efforts, epileptic activity) also needs to be considered. Further, altered fMRI signals may result from a changed vascular situation (e.g., preexisting vasodilation or stenosis) instead of a changed functional organization.

For the neurophysiological interpretation of DTI data, it is important to realize that DTI “tracts” are an imperfect model-based construct which typically does not directly correspond to a physical fiber. Due to the methodological difficulties named above, current DTI techniques are limited with regard to a complete identification of the true fiber situation. Particularly in areas with many intersecting pathways like the centrum semiovale, fractional anisotropy values may be artificially low. Also, for pathological tissue like edema or infiltrating tumor, involved tracts may show reduced anisotropy despite not being destroyed. They may also show complex directional tensor changes. Clinicians should therefore be careful with qualitative and quantitative conclusions. It is also mandatory to include the known intraindividual (homologue tracts may differ between hemispheres, Smits et al. 2012) and interindividual tract variability from healthy subject studies in the interpretation.

### 5.3 Consequences for Neuroplasticity Investigations

The foremost consequence for achieving significant neuroplasticity data is to consider all known pitfalls with performance of fMRI/DTI patient investigations. This includes optimization of patient cooperation, patient performance, and adequate task

selection including patient training. Exploring tasks of different complexity may help to clarify the role of overactivated brain areas. For sound associations of clinical outcome with neuroplastic findings, meaningful outcome measures are required – for example, specific testing of the disturbed function (maximum rate, range, force, and accuracy of a recovered movement) instead of a constrictor to gross clinical scales. Outcome measures should capture all relevant functions (e.g., determination of dexterity in a paretic limb, detection of possible mirror movements) to separate behavioral compensation from recovery of the original function. To allow a valid interpretation, the neuroplastic findings need to be reported with an intrascan behavioral documentation and in relation to the location and extent of the lesion. Further, it is important to capture possible confounding factors for neuroplasticity like medication and co-interventions. Concerning the setup of new investigations, it should be regarded that the comprehensive detection of neuroplastic transformations requires longitudinal studies in homogeneous patient populations starting at an early stage of the disease. Currently, such data are sparse (e.g., most stroke studies investigated patients in a chronic stage).

From the technical viewpoint it is beneficial to apply the latest methodological developments like ultrahigh-field MR for functional imaging (Beisteiner 2013) and new diffusion imaging methods for DTI (compare Huston and Field 2013). This is also true for new data-driven analysis strategies which reduce the amount of model assumptions (e.g., Robinson et al. 2013). Validation and an improved interpretation of fMRI/DTI findings can be achieved by multimethodological approaches. For example, arterial spin labeling may be used to detect abnormal brain perfusion and alternative neurophysiological techniques (EEG, magnetoencephalography, positron emission tomography, intraoperative electrical stimulation) can provide independent functional data. Brain stimulation techniques (transcranial magnetic stimulation, transcranial direct current stimulation) allow controlled variation of the brain's functional state.

## 6 Clinical Examples

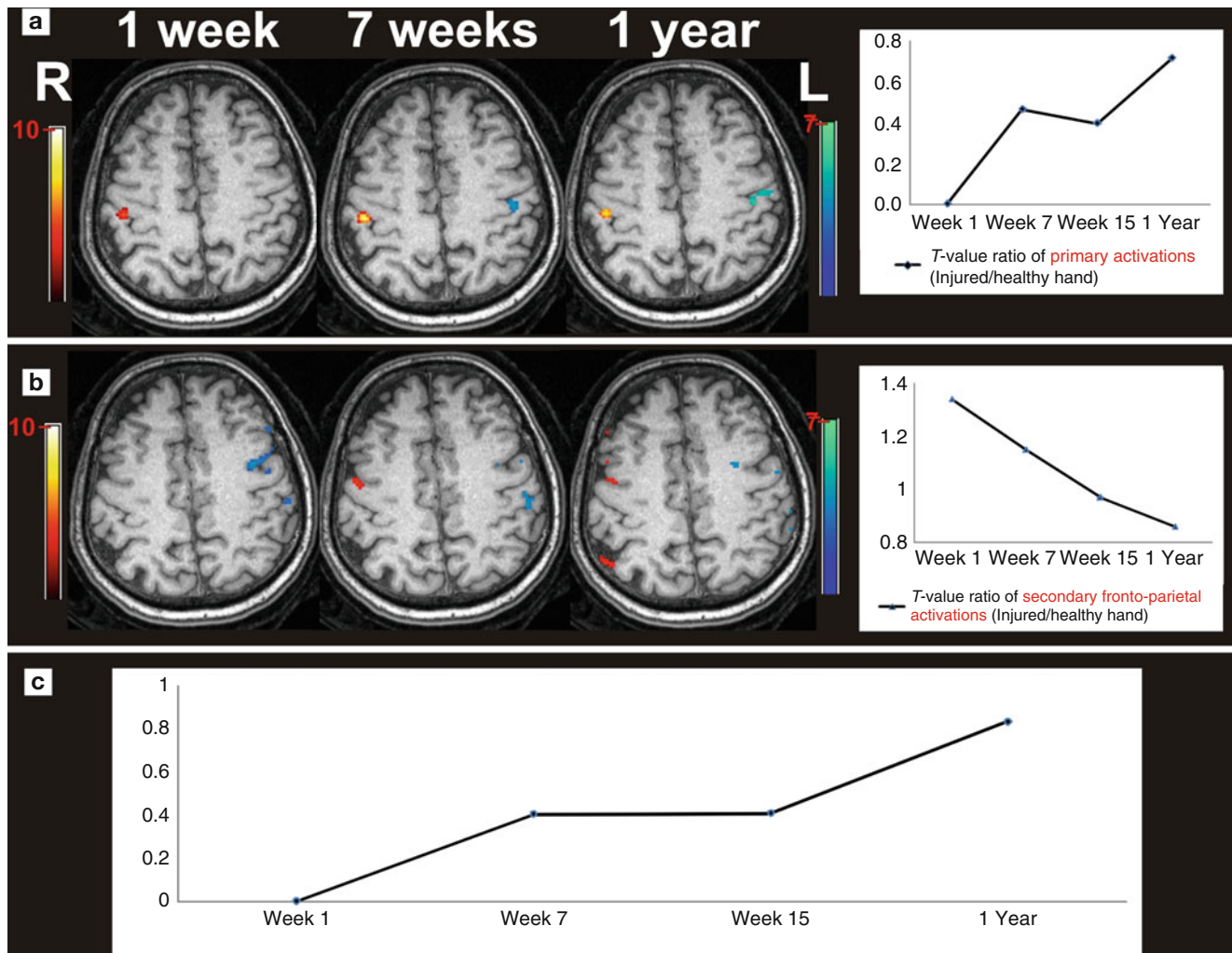
### 6.1 Longitudinal Neuroplasticity Associated with Peripheral Nerve Regeneration

Surgical repair of a transected peripheral nerve is usually followed by a regeneration process involving neuroplastic changes. Rath et al. (2011) provided the first longitudinal fMRI study of cortical somatosensory reorganization following peripheral nerve repair. They presented a case report of a 43-year-old man with isolated complete transection of the right median nerve at the volar side of the wrist who underwent an immediate end-to-end coaptation of the affected nerve.

Clinical assessment revealed initial sensory and motor deficits typical for this nerve lesion with distal loss of sensation of digits II and III, loss of thumb opposition, and weakening of thumb abduction. The patient received an intensive sensory relearning treatment, and his sensory and motor functions were regularly clinically evaluated. Functional imaging was performed at 1, 7, and 15 weeks as well as 1 year after surgery by using a somatosensory stimulation paradigm that consisted of vibrotactile stimulation of digits II and III on the affected and healthy hand, respectively. Functional regions of interest (ROIs) were defined according to previous literature and comprised bilateral primary somatosensory cortices and bilateral frontoparietal areas. Peak *t*-values within these ROIs were used to calculate ratios comparing the injured with the healthy hand. While the patient exhibited no functional activation in the primary somatosensory cortex in the first week after surgery, this activity recovered steadily within a year (compare Fig. 1a). Further, initial frontoparietal overactivation of the affected hemisphere diminished within the same time period (Fig. 1b). This recovery of physiological fMRI patterns corresponded with the clinical recovery of the operated hand. One year after surgery, the diseased hand had recovered 66 % of the sensory and motor function level compared to the healthy hand. Rath et al. proposed to embrace the neuroplastic changes in the primary somatosensory cortex and frontoparietal areas in a regeneration index for the restoration of somatosensory functions (Fig. 1c).

### 6.2 Neuroplasticity After Nerve Repair in Brachial Plexus Lesions

Complete brachial plexus lesions lead to a total paresis of the affected arm resulting in a significant impairment in everyday life. Reinnervation of the affected musculocutaneous nerve via an intact C7 root or via the ipsilateral phrenic nerve can be performed to regain elbow flexion. In an fMRI study, Beisteiner et al. (2011) analyzed functional activation in three patients with complete brachial plexus lesions and in three healthy controls. Two patients underwent an end-to-side nerve reconstruction of the musculocutaneous nerve with the ipsilateral phrenic nerve and one patient received an end-to-end coaptation of the healthy contralateral C7 root with the musculocutaneous nerve. The advantage of the end-to-side technique is the preservation of the donor nerve function – that is, the control of the diaphragm persists via the modified phrenic nerve. However, after establishing an end-to-side connection, the phrenic nerve and its cortical projection area are required to perform a new double function: independent control of breathing and elbow flexion. In contrast, in the control patient (C7 – musculocutaneous connection) the phrenic nerve remained unchanged. FMRI tasks comprised elbow flexion of the healthy arm, elbow flexion of the diseased arm, forced abdominal inspiration, and foot flexion



**Fig. 1** Functional magnetic resonance imaging brain activations with vibrotactile hand stimulation shown on anatomical images. The patient was investigated after complete median nerve transection of the right hand and immediate epineural end-to-end coaptation. Vibrotactile stimulation was separately applied to the left and right hands. **(a)** Representative anatomical slice illustrating the time course of maximum  $t$ -values in the primary somatosensory cortex (injured hand: blue

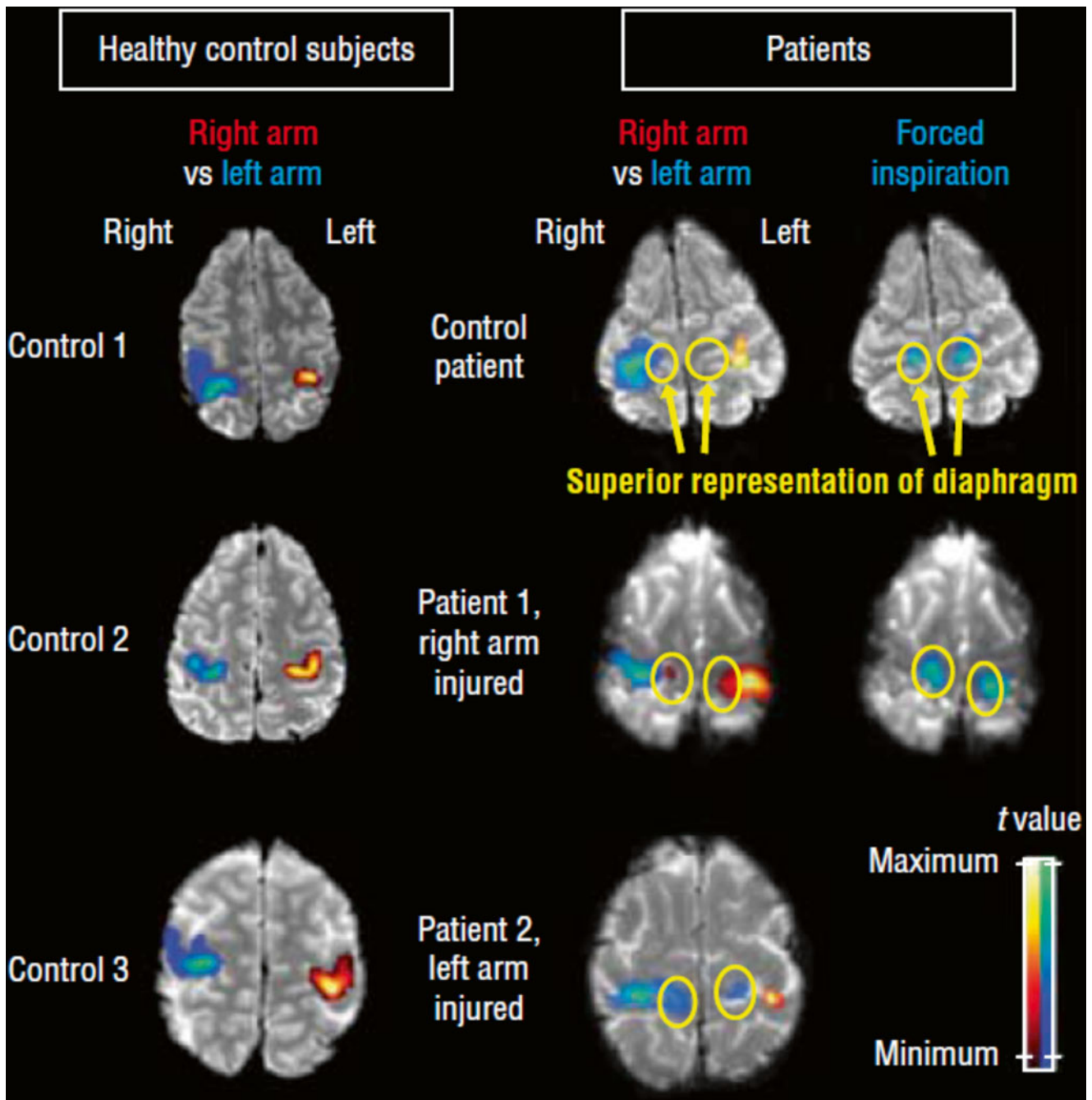
voxels; healthy hand: red voxels). The graph illustrates the peak  $t$  value ratios of the injured/healthy hand ( $p < .01$  uncorrected). Only top 150  $t$  value voxels per brain volume are shown for display purposes and color bars indicate  $t$ -values. **(b)** Same illustration for frontoparietal cortex. **(c)** Proposed regeneration index calculated from graphs A and B (ratio primary cortex)/(ratio frontoparietal cortex) (Reproduced with permission from Rath et al. (2011)) (Color figure online)

on the affected side. Clinical documentations such as electromyographic recording, chest radiography, and fluoroscopy of the thorax confirmed that end-to-side patients were able to control the diaphragm and the arm independently. In Fig. 2, functional imaging findings in patients and controls are summarized. Forced inspiration activated the diaphragm (phrenic nerve) area of the primary motor cortex bilaterally in all participants. In patients with end-to-side anastomoses, elbow flexion of the diseased arm resulted in unilateral activation of the arm area in the primary motor cortex and in an additional activation of the diaphragm area. This recruitment of the diaphragm area was absent when these patients performed movements of the healthy arm or the foot. As expected, neither the control patient nor the healthy control subjects showed activations in the

phrenic nerve area during arm movement. These findings suggest that neuroplasticity may even transform a healthy monofunctional cortical area into a bifunctional area – here shown for the diaphragm area.

### 6.3 Neuroplastic Changes of Effective Connectivity in Patients with Heterotopic Hand Replantation

Eickhoff et al. (2008) investigated cortical plasticity in two patients that underwent a resection of parts of the forearm including the elbow joint due to a malignant soft tissue tumor and a subsequent reimplantation of the amputated distal



**Fig. 2** Original functional magnetic resonance images showing brain activation in the diaphragm area (*circles*) in the superior primary motor cortex and in the adjacent arm areas. The right hemisphere is shown on the left side. Only primary motor cortex activations are depicted, and colors indicate  $t$  value distributions within depicted activation clusters (relative scaling according to local maxima and minima). All images are thresholded at  $p < .001$  uncorrected. Representative slices are shown for the three healthy control subjects, the control patient with C7 end-to-end coaptation, and the two patients with phrenic nerve end-to-side

coaptation. The columns labeled “right arm vs left arm” show significant activation differences of right > left arm (*red*) and left > right arm (*blue*). In the patients with phrenic nerve end-to-side coaptation, the diaphragm area is activated only with flexion of the injured arm, not with flexion of the healthy arm. In all controls, arm flexion did not activate the diaphragm area. Forced abdominal inspiration selectively activated the diaphragm area in all subjects (*rightmost column, blue activation clusters*) (Reproduced with permission from Beisteiner et al. (2011)) (Color figure online)

forearm including the hand. Thereby, tendons of the finger flexors and extensors were attached to upper arm muscles, and distal forearm nerves were coaptated with the nerve trunks of the upper arm.

The 2 patients and 14 healthy control subjects performed a motor fMRI task comprising fist-closing movements with the right, left, or both hands simultaneously. Dynamic causal modeling (DCM) was applied to explore effective

connectivity within an anatomically and functionally defined bilateral motor network consisting of the primary motor cortex (M1), the supplementary motor area (SMA), the ventral premotor cortex (PMC), and extrastriatal visual cortex (V5). The latter region was defined as the input region for the bilateral SMA and PMC as movements were visually paced in the fMRI task. All regions were defined for the affected hemisphere (hemisphere contralateral to the side of peripheral surgery) and the healthy hemisphere (hemisphere ipsilateral to the side of peripheral surgery). Effects of interest analysis revealed a significantly increased activation during tasks compared to the baseline in the motor ROIs. Intrinsic connectivity, that is, task-independent connectivity, was symmetrically organized in controls (Fig. 3, top panel) with a positive influence (green arrows) of the SMA and PMC on M1 and an inhibition (red arrows) between bilateral M1 and SMA. In contrast, both patients showed altered influence of the PMC of the affected hemisphere. However, the actual patterns of intrinsic connectivity differed between both patients as depicted in Fig. 3 (bottom panel). When moving the healthy hand, the PMC of the affected hemisphere was inhibited by the PMC and M1 of the healthy hemisphere in both patients. Eickhoff and colleagues interpreted this result as an enhanced suppression of the influence of the affected hemisphere on the control of the healthy hand. In both patients, movements of the replanted hand resulted in increased activation of the affected PMC that might reflect an increased effort required to perform the task. In addition, a pathological inhibition of the healthy M1 on the affected M1 was present in both patients when moving the replanted hand. The most prominent difference between the two patients was present in the affected PMC (Fig. 3, bottom panel). In patient J.H., the affected PMC had an increased positive influence (compared to controls) on the M1 of the same hemisphere at rest (intrinsic connectivity) as well as during movements of the replanted hand, while in patient G.M., the M1 was inhibited by the PMC. Correspondingly, motor performance of G.M. was worse than that of J.H. Eickhoff et al. concluded that different neuroplastic connectivity changes were related to clinical progress and behavioral performance stressing the importance of an early and intense rehabilitative exercise as it was the case for patient J.H.

#### 6.4 Neuroplastic Reorganization of Hand Functions After Hemispherectomy

Rath et al. (2008) reported a single-case fMRI study of a 27-year-old man who underwent a functional hemispherectomy at the age of 11. The patient suffered from an infarction of the right middle cerebral artery at 2 years of age. After the stroke he showed considerable improvements of motor functions of the left paretic hand; however, he developed intrac-

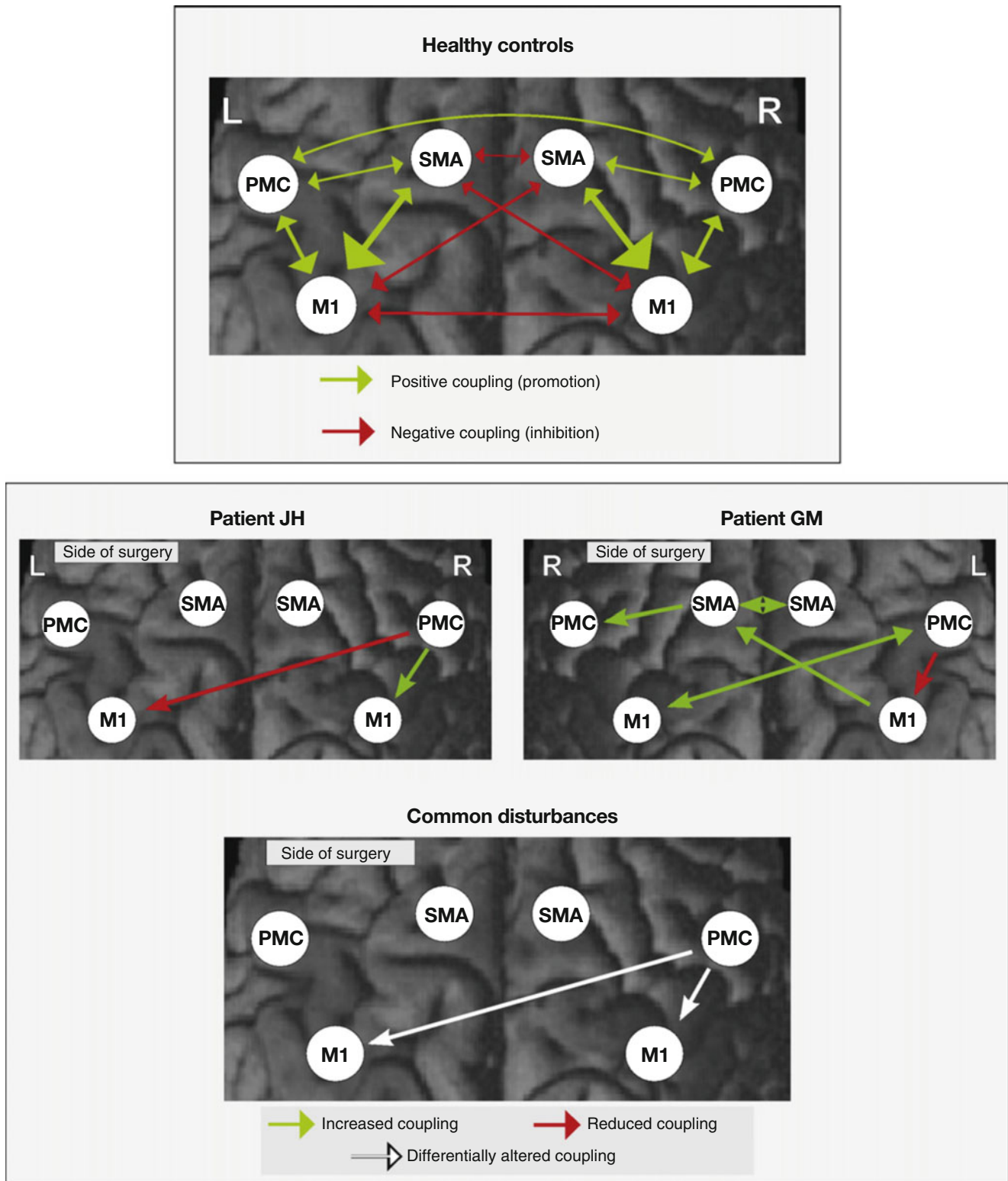
table generalized epilepsy that required a resection of the affected right hemisphere. Although his hemiparesis worsened after hemispherectomy, hand function recovered again after physiotherapy and orthopedic surgeries. At the time of the MR investigation, the patient had spastic hemiparesis but voluntary control and sustained weak motor functions in the hemiparetic arm. Anatomical MRI revealed no pathological findings in the remaining left hemisphere. Functional imaging showed that movements of both hands induced significant activation in the remaining primary motor cortex. Movements of the healthy hand corresponded to activation in the typical hand motor area, whereas movements of the paretic hand produced two activation clusters in the periphery of the hand motor area (Fig. 4). This reorganization is likely to be induced by the hemispherectomy rather than by the initial stroke since hemiparesis showed an initial worsening after hemispherectomy and a secondary improvement after rehabilitation. This single case demonstrates that functional transition zones (i.e., the periphery of a functional cortical area) in the ipsilateral hemisphere can be used to restore functions when no contralateral functional tissue anymore exists.

#### 6.5 Structural Neuroplasticity in Patients with Chronic Stroke

Acute stroke often leads to impaired motor and cognitive functions that are sought to be improved by rehabilitation. Patients with only partial recovery suffering from residual impairments after rehabilitation are referred as chronic stroke patients.

Lazaridou et al. (2013b) investigated structural neuroplastic changes corresponding to a rehabilitative motor training by assessing cortical thickness with voxel-based morphometry (VBM) and white matter integrity with DTI in four patients with chronic stroke. The time interval between the onset of left-sided ischemic subcortical middle cerebral artery stroke and the participation in the study was more than 6 months. The patients underwent an 8-week-lasting motor training consisting of 1 h squeezing an exercise ball with the paretic hand for 3 days per week. MR scans were performed at baseline (before the training), after 4 weeks of training, at the end of the training period (after 8 weeks), and finally another 4 weeks later. For DTI fiber reconstruction, deterministic tractography was performed and visually inspected for directionality and location. The pons, the posterior limb of the internal capsule, and the motor cortex were selected as seed regions to reconstruct the corticospinal tract (CST).

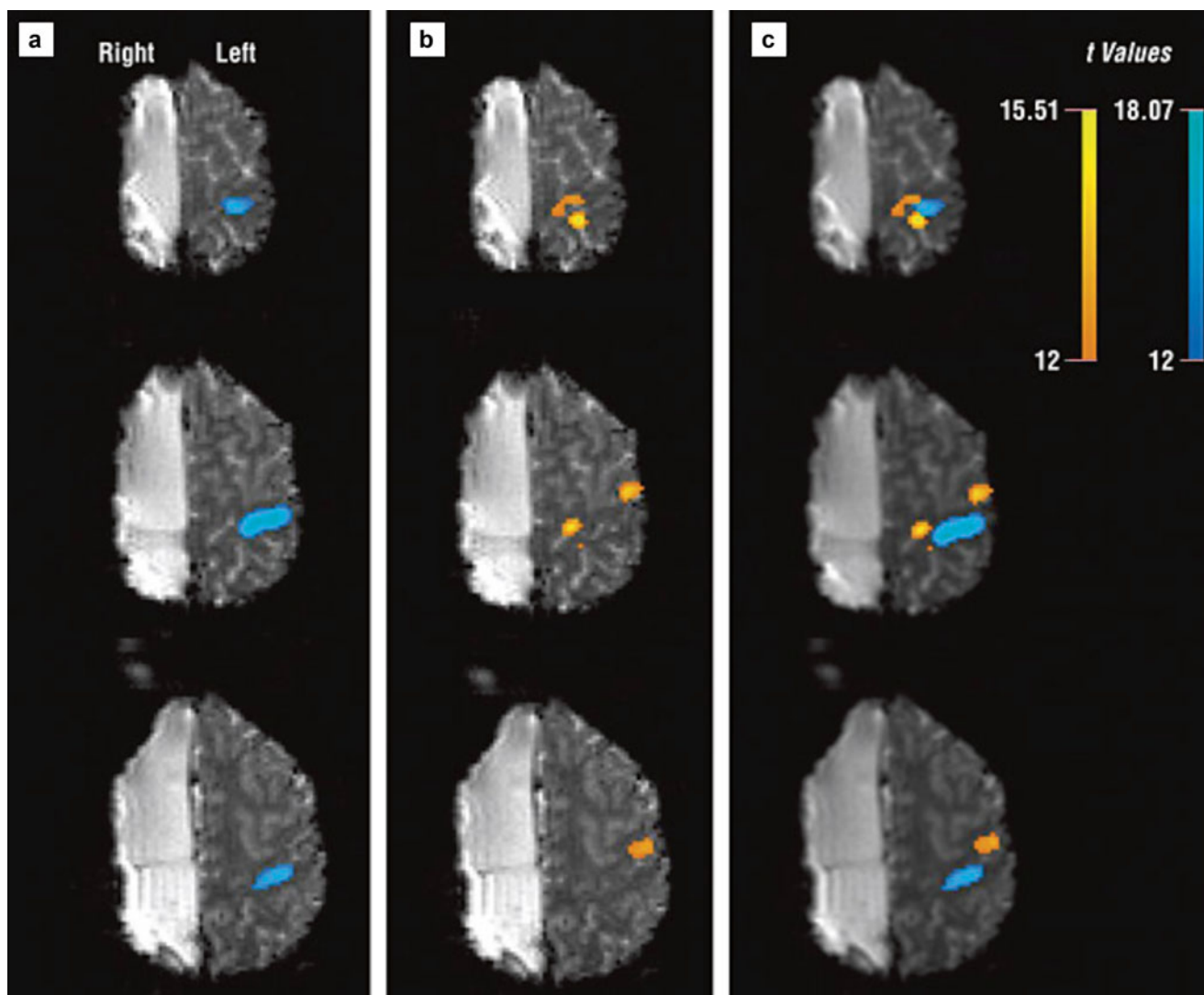
Statistical analysis of CST fibers of the affected hemisphere revealed a significant increase in the number of fibers and average tract length as illustrated in Fig. 5 depicting CST fibers of a representative patient before, during, and after motor training. CST fibers (in blue) projected



**Fig. 3** *Top panel:* regions of interest selected for estimating cortical connectivity shown on a surface rendering of the MNI single-subject template. Displayed regions were significant at  $p < 0.05$  (corrected) in an F-contrast testing for the effects of interest, that is, regions where hand task-related variance was significantly greater than noise. The intrinsic connectivity in healthy controls ( $N = 14$ ) as estimated by means of dynamic causal modeling is displayed. Reciprocal connectivity is assumed for the six motor regions, while visual input is provided via left and right V5 into all four premotor regions. Coupling parameters indicate connection strength, which are coded for size and color. Positive coupling (green arrows) suggests facilitation, whereas negative coupling (red arrows) can be interpreted

as neural inhibition. *Bottom panel:* differences in intrinsic connectivity between the two patients and the control group. Only those connections whose strength was significantly different ( $p < 0.05$  corrected) from those of the controls in a two sample  $T$ -test are displayed. Green arrows denote coupling parameters which were significantly higher (more positive) as compared to normal subjects, red arrows those significantly lower, that is, more negative. In the synoptical panel in the bottom row, white arrows indicated those connections which were significantly altered in both patients but effect changes in opposite directions (Reproduced with permission from Eickhoff et al. (2008)) (Color figure online)





**Fig. 4** Functional echoplanar imaging originals ( $t > 12$ ) showing activation in three slices covering the hand motor area (top row is most superior slice). (a) Contralateral healthy hand activation shown in blue.

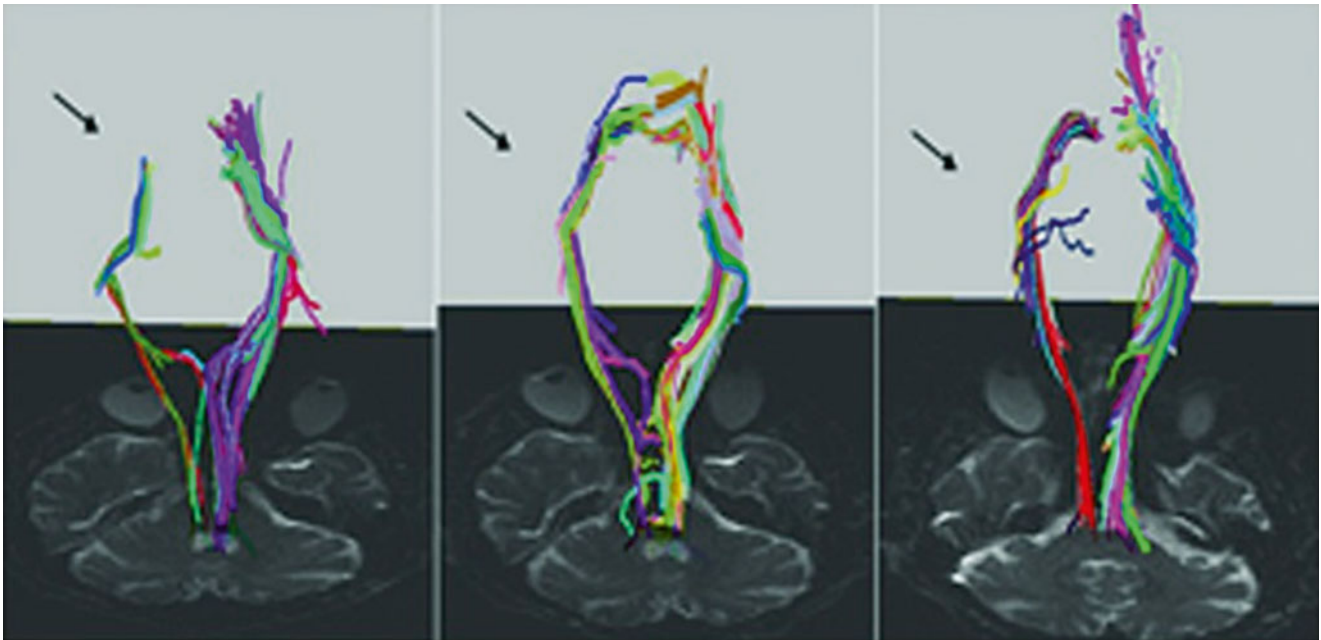
(b) Ipsilateral paretic hand activation shown in orange. (c) Activation in both hands (Reproduced with permission from Rath et al. (2008)) (Color figure online)

progressively closer to the motor cortex and showed increased density with ongoing training progress. In addition, VBM analysis showed a significantly increased cortical thickness of the ventral postcentral gyrus after training compared to the baseline. With this study, Lazaridou et al. could demonstrate that intensive motor training resulted in structural neuroplasticity in the sensorimotor system in chronic stroke patients and provided a new approach for the evaluation of the rehabilitation progress.

## 6.6 Neuroplastic Network Changes in Traumatic Brain Injury

Traumatic brain injury (TBI) is often followed by persistent cognitive deficits affecting several cognitive domains like attention, working memory, speech, and executive functions such as planning, inhibition, and cognitive control.

Caeyenberghs et al. (2012b) addressed the latter issue using a functional imaging approach combined with a graph theoretical analysis. They examined 23 patients with mild to moderate TBI and 26 healthy control subjects applying an event-related fMRI paradigm previously used to investigate cognitive control in young and elderly adults (Coxon et al. 2010) and in TBI patients (Leunissen et al. 2013). Participants performed temporally coupled circular hand movements (either clockwise or counterclockwise) with each hand using a joystick. Visual cues indicated whether to switch the movement patterns from asymmetric to symmetric or vice versa or to continue the prior movement. The authors constructed a switching motor network consisting of 22 regions of interest that were defined as 10 mm spheres centered on peak activation coordinates reported by Coxon et al. (2010) and Leunissen et al. (2013). The network comprised regions of the medial frontal cortex, anterior cingulate cortex, bilateral dorsolateral prefrontal cortex, bilateral inferior frontal cortex



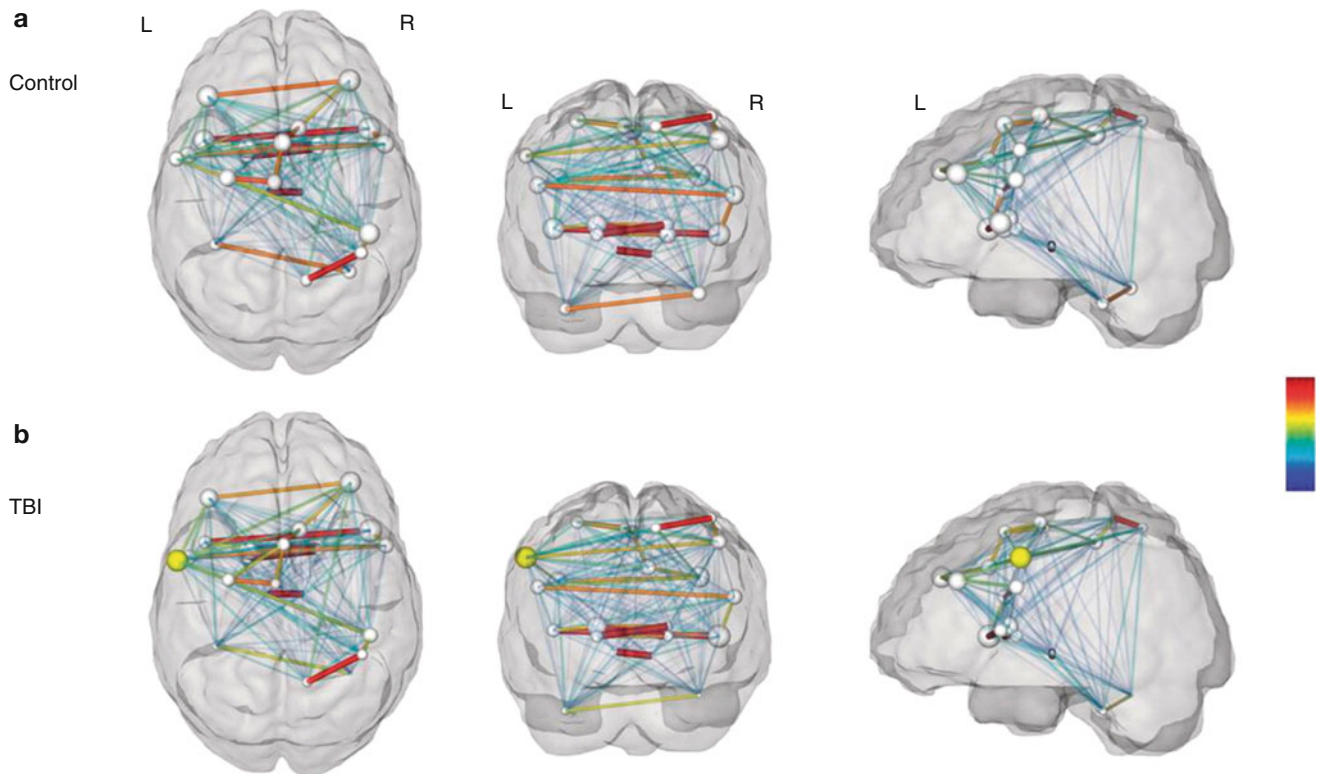
**Fig. 5** Reconstructed corticospinal tracts (CSTs) from the same stroke patient before training (*left panel*), after 4 weeks of training (*middle panel*) and after 8 weeks of training (*right panel*). Note that

reconstructed CST fibers increased dramatically on the right side with training (*arrows*) (Reproduced with permission from Lazaridou et al. (2013b))

(BA 44), basal ganglia, cerebellum, right precuneus, left premotor cortex, bilateral insula, and right superior and inferior parietal cortex. First, a contrast Switch > Continue was conducted to compute the average time series for each ROI of each subject which was then subjected to a partial correlation analysis. This method allowed a quantification of the unique correlation between two ROIs and the content filtering of the effects of all the other ROIs giving an appropriate measure for functional connections. For graph theoretical analysis, matrices with significant connections weighted by the correlation values between nodes (i.e., ROIs) were constructed. Weighted matrices were used to calculate the mean connection strength of the single nodes as well as of the overall network connection strength. The Brain Connectivity Toolbox (Rubinov and Sporns 2010) was employed to assess global network architecture and nodal properties.

TBI patients exhibited slower response times and more disruptions during the switching task than the controls that could not be explained by motor difficulties. Graph theoretical analysis revealed a significantly altered functional network in patients with higher connectivity degree and strength than in controls. Specifically, the patients exhibited a higher connectivity in the left ventral portion of M1 (compare yellow sphere in Fig. 6) possibly reflecting functional

compensation as this area is involved in coordination and is strongly interconnected within the primary motor cortex. In addition, local efficiency was enhanced in patients with TBI which might indicate a compensatory increase of short-range connections between adjacent nodes. Besides, graph theoretical analysis provided information about hubs, that is, regions with a central role in a functional network. In both the patients and controls, the right insula with its critical role in the differentiation between internal and external stimuli presented as a hub, putatively due to the strong directive of a visual input to trigger movement switching. Interestingly, two regions mainly involved in movement planning (right dorsolateral prefrontal cortex and left dorsal premotor cortex) acted as hubs in the TBI group only. Caeyenberghs and colleagues (2012b) concluded that TBI patients might rely more on cognitive control and performance monitoring during the switching task. However, the higher mean connectivity degree in patients was related with poorer switching performance implying that increased connectivity not necessarily improves function. Moreover, higher connectivity degree was positively correlated with injury severity and might therefore be a result of a more severe brain damage reflecting a higher effort to manage cognitive control tasks.



**Fig. 6** Group differences in connectivity degree. **(a)** Controls and **(b)** patients with TBI. The size of the regions of interest (*spheres*) represents connectivity degree. The edge widths represent the strength of the partial correlations between nodes. Notably, the networks shown here were constructed by summing the partial correlation matrices of all subjects in each

group (as shown by the *color bar*). *Yellow sphere* indicates higher connectivity in left ventral premotor cortex ( $p < 0.002$  corrected) in patients with TBI (Reproduced with permission from Caeyenberghs et al. (2012b)) (Color figure online)

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