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12

Impact of White Matter Damage After Stroke

Robert Lindenberg[1,2] and Rüdiger J. Seitz[3,4]
[1]*Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts,*
[2]*Department of Neurology, Charité – Universitaetsmedizin Berlin, Berlin,*
[3]*Department of Neurology, University Hospital Düsseldorf and Biomedical Research Centre, Heinrich-Heine-University Düsseldorf*
[4]*Florey Neuroscience Institutes, Melbourne, Victoria,*
[1]*USA*
[2,3]*Germany*
[4]*Australia*

1. Introduction

Ischemic stroke is one of the leading causes of persistent disability in Western countries (Bejot *et al.*, 2007). It results from cessation of blood supply due to an occlusion of a cerebral artery. Many patients benefit from thrombolysis with the approved drug recombinant tissue plasminogen activator (rtPA). Nevertheless, the clinical effect of intravenously administered rtPA is variable (Hallevi *et al.*, 2009; Wahlgren *et al.*, 2008) which is of particular importance for middle cerebral artery (MCA) stroke: It has been demonstrated that early artery recanalisation yields unevenly distributed, circumscribed infarct lesions within the MCA territory with a great potential for functional recovery; in contrast, failed recanalisation results in large infarcts with a limited potential for functional recovery (Figure 1). Accordingly, an important factor contributing to recovery from stroke is the early restoration of cerebral blood flow. Spontaneous recovery is known to continue for the subsequent weeks to months (Cramer, 2008). Furthermore, recovery can be facilitated by dedicated rehabilitative training with greater effects in greater dosing of training (Kwakkel, 2006) even years after the stroke (Stinear *et al.*, 2007).

Animal studies (Dancause *et al.*, 2005) as well as imaging and electrophysiological studies in humans (Butefisch *et al.*, 2006) have suggested that recovery is brought about by cerebral plasticity. Cerebral plasticity pertains to *functional* changes such as synaptic efficiency as well as *structural* changes such as synaptic sprouting (Dancause *et al.*, 2005; Nudo *et al.*, 1996). Even in the adult brain, a loss of hand motor function due to small cortical lesions within the sensorimotor cortex can be completely restored (Binkofski and Seitz, 2004). However, there are limits to plasticity. For example, severe damage to major pathways such as the pyramidal tract (PT) can be compensated for to some extent, but full functional recovery is often not possible (Lang and Schieber, 2004).

To date, neuroimaging studies of brain infarcts have mostly examined grey matter alterations. Recent advances in diffusion tensor imaging (DTI) and lesion-symptom

mapping techniques provided novel ways to investigate the white matter in the context of recovery from stroke (Johansen-Berg *et al.*, 2010). The crucial role of the white matter for functional outcome can be illustrated by the observation that small cortical infarcts, e.g. in the precentral gyrus, typically allow for profound recovery from stroke, whereas infarcts of similar volume in the peri-ventricular white matter or the internal capsule may induce a severe and persistent hemiparesis (Kretschmann, 1988; Wenzelburger *et al.*, 2005). Focusing on DTI and lesion mapping, we will discuss recent studies that established white matter damage as an important factor for functional outcome in the acute stroke phase. Furthermore, alterations of fibre tracts will be presented as a critical determinant of functional recovery due to cerebral plasticity in the subacute and chronic phases after stroke.

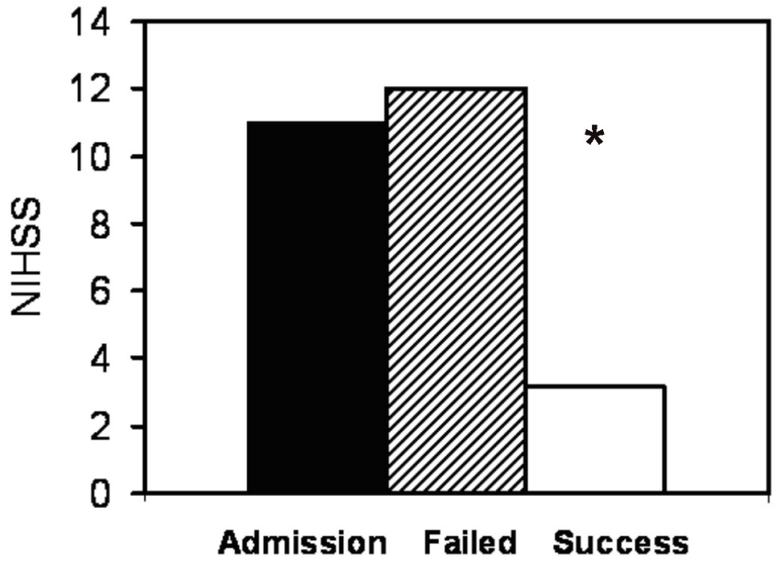

Fig. 1. Neurological deficit as assessed with the NIHSS in 108 MCA stroke patients. Successful thrombolysis with early MCA recanalization resulted in a significant neurological improvement (*: $p<0.0001$). Adapted from (Seitz *et al.*, 2009).

2. Lesion mapping in the acute phase after stroke

Different modalities of magnetic resonance imaging (MRI) are widely used to visualise brain lesions. In acute stroke, perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) can identify the area of acute ischemia. After reperfusion, PWI deficits can be resolved (Davis *et al.*, 2008; Seitz *et al.*, 2005), and also DWI alterations are partly reversible (Kranz and Eastwood, 2009). By use of lesion mapping it has been found that the hemispheric white matter is preferentially affected in patients with major MCA stroke as compared to patients with lesion regression (Stoeckel *et al.*, 2007). Similarly, patients with a lacking response to rtPA and no recanalization of the MCA, showed larger brain lesions with greater hemispheric white matter damage than those with successful thrombolysis (Seitz *et al.*, 2009). The large infarct lesions in patients non-responsive to thrombolysis occurred adjacent to the insular cortex and basal ganglia in the internal capsule and periventricular white matter and were predicted by the maximal perfusion deficit in the acute phase of stroke. These infarcts corresponded to the type II.2 MCA infarcts as described

recently (Seitz and Donnan, 2010). Note the close topographic correspondence of the mean area of the most severe perfusion deficit, the DWI abnormalities, and the lesion overlap in the periventricular white matter found in the patients with severe MCA stroke (Figure 2). Since the structural alterations project onto the corona radiate, the corresponding damage of well-defined fibre bundles—such as corticospinal motor tracts—can be assessed specifically by electrophysiology and MRI techniques such as DTI in order to correlate imaging measures with parameters of functional outcome.

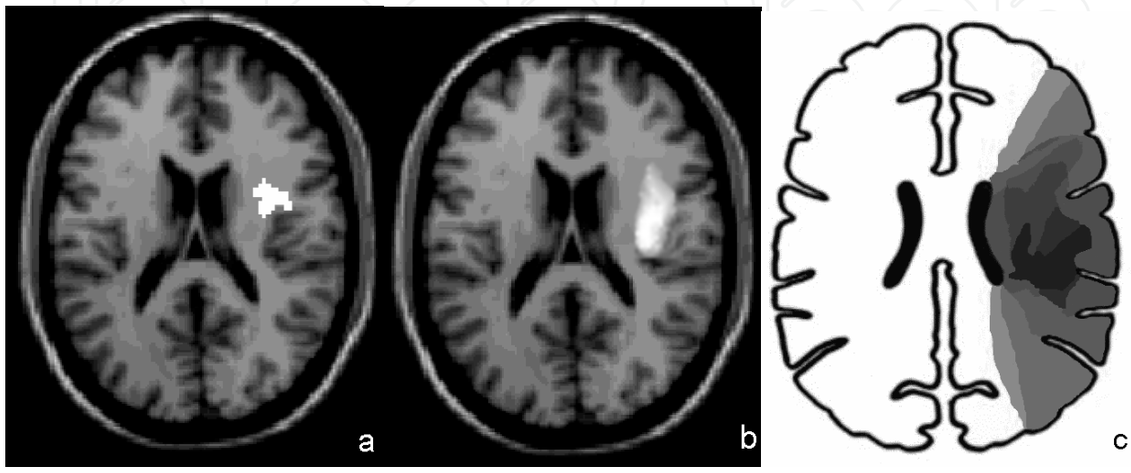

Fig. 2. Lesion pattern in severe MCA stroke. a) Area of the maximal PWI deficit in severely as compared to slightly affected patients. b) Area of common DWI-changes before acute stroke therapy (n=64). c) Overlap of the residual infarct lesions in hemispheric white matter (n=13). Adapted from (Seitz *et al.*, 2009; Stoeckel *et al.*, 2007).

3. Diffusion tensor imaging: Methodological considerations

DTI allows for inferences of the microstructural status of regions of interest in the white matter or reconstructed tracts (Beaulieu, 2009). DTI is a DWI technique that uses the measurement of Brownian motion of water molecules in different directions to reconstruct three-dimensional images of diffusivity (Jones, 2008). Whereas molecules can diffuse relatively freely in water, structural boundaries such as cell membranes or myelin sheaths cause restrictions and yield anisotropic diffusion (Beaulieu, 2002). The degree of diffusion anisotropy can then be used to characterise neural tissue and reveal potential pathological processes (Beaulieu, 2002; Jones, 2008). As an example, Figure 3 shows images of fibre distributions according to the main directions of diffusivity in each voxel of the image. Here, the colour-coding allows for the detection of diffusion abnormalities. Main diffusion directions of single voxels also provide the basis for deterministic tractography, which reconstructs trajectories through a combination of adjacent voxels with similar main directions. Probabilistic tractography, in contrast, propagates numerous pathways through the tensor field so that each voxel can be coded with a number that reflects its likelihood of being connected with a given seed region from which the tracking is started (see (Jones, 2008) for a review).

With both the deterministic and probabilistic approaches, major fibre bundles can be reliably reconstructed (Mori and Zhang, 2006; Wakana *et al.*, 2004). Furthermore,

tractography not only allows for the visualisation of tract alterations after lesions, but can be used to quantify those alterations (Johansen-Berg and Behrens, 2006). Furthermore, fractional anisotropy (FA) has been used to describe microstructural abnormalities of white matter. FA indicates the coherence of aligned fibres and is calculated from directional diffusivities (axial and radial). Based on animal experiments, axial diffusivity is thought to primarily reflect axonal integrity whereas radial diffusivity has been suggested to relate to myelin degradation (Acosta-Cabronero *et al.*, 2009; Naismith *et al.*, 2009; Sidaros *et al.*, 2008; Song *et al.*, 2003; Sun *et al.*, 2008). However, the model of a specific relationship of directional diffusivities with discrete pathological processes such as axonal damage or demyelination is controversial, especially in regions of complex fibre architecture (Wheeler-Kingshott and Cercignani, 2009). Interpretations of these parameters with respect to "fibre integrity" should therefore be made with caution.

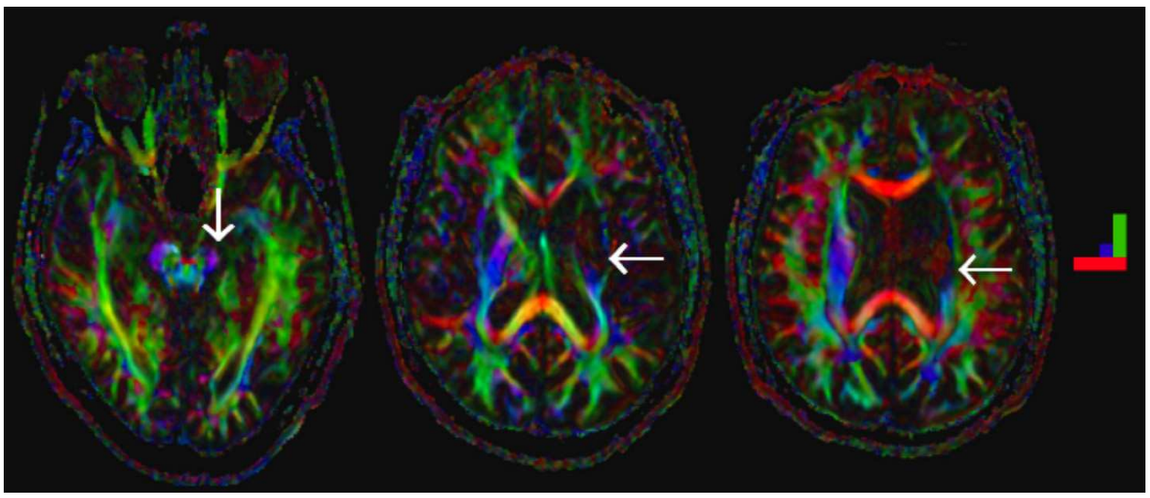

Fig. 3. DTI image of a patient with persistent hemiplegia in a striatocapsular infarct. Arrows point to severe diffusion alteration of corticospinal fibres descending in the posterior limb of the internal capsule and the cerebral pedunculus. The colour bar indicates the spatial orientation of fibres; blue: predominantly inferior—superior orientation, green: predominantly anterior—posterior orientation, red: predominantly left—right orientation.

4. Assessing the impact of white matter damage on motor function using DTI

Although the concept of disconnection syndromes is well established and helps explaining functional deficits after lesions (Geschwind, 1965a; Geschwind, 1965b), the involvement of the white matter in stroke has not received much attention until recently (e.g., (Catani and ffytche, 2005). White matter damage has been found to be particularly prominent in large cerebral infarcts with hemispatial neglect, apraxia and severe hemiparesis (Karnath *et al.*, 2009; Pazzaglia *et al.*, 2008; Seitz *et al.*, 2009; Stoeckel *et al.*, 2007). However, it is not merely the size of the infarct but preferentially its location that determines the functional outcome after stroke (Binkofski *et al.*, 1996; Chen *et al.*, 2000; Zhu *et al.*, 2010).

The importance of corticospinal fibres for recovery of motor function after stroke has been demonstrated with different imaging modalities as well as electrophysiological measures (Binkofski *et al.*, 1996; Fries *et al.*, 1991; Schaechter *et al.*, 2008; Stinear *et al.*, 2007). Based on animal studies, it has been suggested that so-called alternate motor fibres (aMF) can

compensate for motor impairment after severe damage to the PT (Lang and Schieber, 2004). In monkeys and cats, the cortico-reticulo-spinal and cortico-rubro-spinal tracts may mediate motor functions in case of PT lesions (Canedo, 1997), whereas these tracts have been described as functionally redundant in healthy animals (Kennedy, 1990). In more detail, it has been observed that damage to the PT and the rubro-spinal tract of monkeys yielded therapy-refractory impairment of the contralateral upper extremity, but monkeys with lesions to the PT that spared the rubro-spinal tract were able to recover considerably (Lawrence & Kuypers, 1968a; Lawrence & Kuypers, 1968b). Furthermore, changes in the synaptic organization of rubro-spinal neurons in response to PT lesions have been reported in monkeys (Belhaj-Saïf & Cheney, 2000).

The first neuroimaging study that translated these findings into motor recovery after human stroke combined structural MRI and electrophysiology to demonstrate that, despite severe degeneration of the PT, motor evoked potentials (MEP) could still be elicited from the ipsilesional motor cortex in patients who had recovered from stroke (Fries *et al.*, 1991). Similarly, patients with hemiparesis due to focal PT lesions were still able to execute individuated finger movements contralateral to the lesion, but with reduced selectivity (Lang and Schieber, 2004). These studies in humans illustrate the role of aMF after stroke similar to that observed in non-human primates.

Using diffusivity parameters and tractography, researchers can examine fibre degeneration at different stages of motor recovery after stroke (Kang *et al.*, 2000; Lindberg *et al.*, 2007; Thomalla *et al.*, 2004; Werring *et al.*, 2000). In the chronic stage, structural damage to the PT could be related to measures of functional impairment (Schaechter *et al.*, 2009; Stinear *et al.*, 2007). Besides the PT, DTI has been applied to reconstruct aMF using deterministic fibre tracking algorithms and, thereby, to explore their role for motor recovery after stroke (Lindenberg *et al.*, 2010). Consistent with previous animal and human studies mentioned above, the differential affection of PT and aMF yielded a three-tier classification system suggesting that (1) when both PT and aMF could be reconstructed, patients showed only mild impairment, (2) when damage occurred to the PT but aMF remained relatively preserved, patients were only moderately impaired, and (3) when pronounced damage to both the PT and aMF was visible, patients was most severely impaired (Figure 4). In addition, DTI-based tractography allows to topographically relate lesions to corticospinal fibres and provides insights into their somatotopic organisation (Konishi *et al.*, 2005; Kunimatsu *et al.*, 2003; Lee *et al.*, 2005; Nelles *et al.*, 2008; Newton *et al.*, 2006; Yamada *et al.*, 2004). Furthermore, the calculation of the overlap between lesion and tracts can explain some of the variance in motor outcome after stroke (Zhu *et al.*, 2010).

5. Predicting functional potential for motor recovery using DTI

One of the most important clinical questions after stroke is a patient's potential for recovery from stroke-induced deficits. Small cortical infarcts in the precentral gyrus typically allow for a profound recovery from hemiparesis. In contrast, infarcts of similar volume in the periventricular hemispheric white matter or the posterior limb of the internal capsule may induce a severe persistent hemiparesis (Kretschmann, 1988). Electrophysiological studies suggest that the functional integrity of ipsilesional motor circuits as well as interhemispheric interactions play a major role in motor recovery from hemiparesis after stroke (Perez and Cohen, 2009). Although transcranial magnetic stimulation (TMS) has been shown to strongly correlate with motor impairment in the acute and subacute phase after stroke, its

predictive value appears unclear in the chronic stage (Talelli *et al.*, 2006). However, a combination of TMS and DTI-derived parameters of corticospinal tracts proved to be useful in estimating a patient's potential for recovery when undergoing motor rehabilitation even years after the stroke (Stinear *et al.*, 2007). Similarly, DTI in the acute stroke phase helped predicting outcome at three months (Jang *et al.*, 2008).

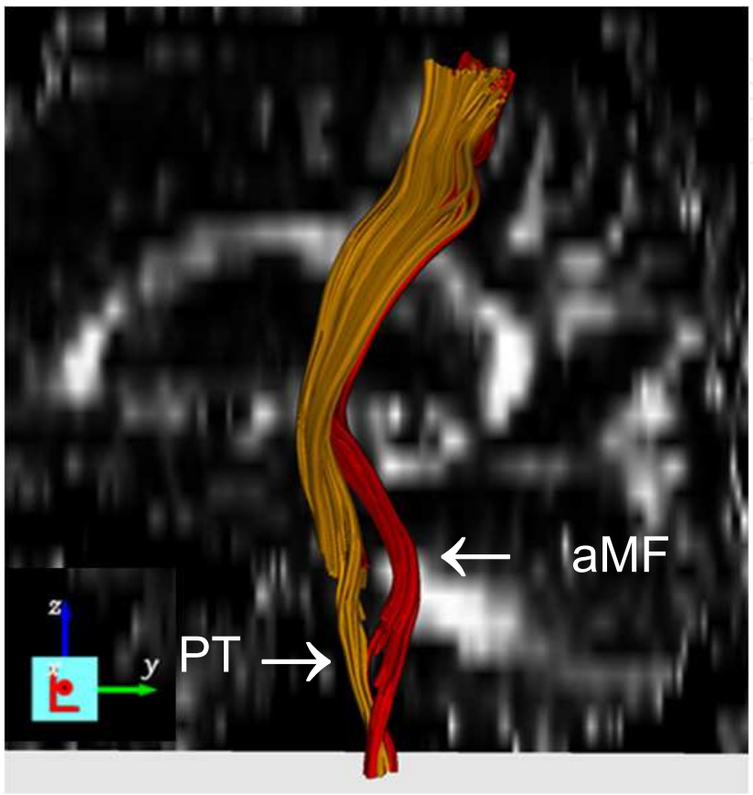

Fig. 4. The course of the pyramidal tract (PT) and alternate motor fibres (aMF) from the white matter underlying the precentral gyrus to the brainstem in a healthy subject.

In order to define predictors of therapeutic response to novel rehabilitation techniques such as non-invasive brain stimulation, it may be useful to examine transcallosal motor fibres as well. Using transcranial direct current stimulation (tDCS) or repetitive TMS, it has been demonstrated that both the up-regulation of intact portions of the ipsilesional and down-regulation of contralesional motor cortices facilitates motor recovery after stroke (Schlaug *et al.*, 2008). Together with evidence from electrophysiological investigations (Perez and Cohen, 2009) and functional MRI (Carter *et al.*, 2009; Grefkes *et al.*, 2008), there is ample evidence for the importance of inter-hemispheric interactions in functional recovery from a stroke. To complement these findings, a study in healthy subjects revealed an association of function and microstructure of transcallosal motor connections (Wahl *et al.*, 2007). In chronic stroke patients, DTI-derived measures of transcallosal motor fibres as well as ipsilesional corticospinal tracts (PT and aMF) could be used to explain the therapeutic response to rehabilitation: the more the diffusivity profiles resembled those observed in healthy subjects, the greater a patient's potential for functional recovery (Lindenberg *et al.*, 2011). Thus, diffusivity profiles of motor tracts, particularly, in combination with electrophysiological

measures can serve as predictors of a patient's potential for spontaneous recovery as well as in response to different types of neurorehabilitation techniques.

6. Impact of white matter damage for functional deficits beyond hemiparesis

Brain infarcts with white matter involvement lead to disconnection of areas in perilesional tissue, but also remote locations. This has been shown using positron emission tomography of cerebral blood flow and metabolism as well as with MRI (Feeney and Baron, 1986). Lesion analysis by use of statistical parametric mapping revealed that cortical infarcts result in remote changes in the ipsilesional thalamus, while striatocapsular infarcts induce changes in the contralesional cerebellum (Seitz *et al.*, 1994). Consequently, functional changes occur in regions spatially distant from the area of infarction, an event which has been termed diaschisis. In the chronic phase after stroke, scar formation and fibre degeneration have been shown to result in brain atrophy (Kraemer *et al.*, 2004). Many patients retain functional impairments which can be documented by dedicated investigations including neuropsychology, electrophysiology and DTI. A clinical example is ataxic hemiplegia resulting from infarct lesions around the internal capsule with cortico-cerebellar disconnection (Classen *et al.*, 1995). Similarly, callosal infarcts can induce a lasting decoupling of both hands (Seitz *et al.*, 2004). Infarcts in the frontal parasagittal white matter can produce a deficit of visual face processing probably due to disruption of fronto-occipitotemporal projections (Schafer *et al.*, 2007). Lesion studies in neglect have demonstrated subcortical white matter involvement in the peri-insular area and the internal capsule (Karnath *et al.*, 2004). In Gerstmann's syndrome it has been shown recently that the different parietal cortical subareas which process finger naming, colour naming, right-left orientation, and calculation can all be impaired by a single subcortical white matter lesion affecting the point of convergence of their subcortical projections (Rusconi et al. 2009). These data are of considerable interest given the impact of white matter abnormalities for cognitive decline and the development of dementia after stroke (Dufouil *et al.*, 2009). Taken together, many clinically well-established syndromes are likely to result from cortico-cortical and cortico-subcortical disconnections.

7. Fibre tract changes in white matter and cerebral plasticity

As observed in lesion experiments, intensive rehabilitation allowed animals with damage of corticospinal tracts to recover considerably (Maier *et al.*, 2008). In these animals, collateral fibres increased their innervation density and extended toward the ventral and dorsal horn in response to forced limb use. In contrast, animals that were impeded in their usage of the affected limbs remained impaired and did not show such plastic changes. This highlights the importance of examining white matter structures to determine the extent of potential recovery. In monkeys it has been found that damage of white matter adjacent to lesions in the visual cortex determined the extent of remote and transneural degeneration in the dorsal geniculate and retina (Cowey *et al.*, 1999). Preliminary results in humans undergoing intonation-based speech therapy for chronic aphasia suggest plastic changes in the contralesional arcuate fasciculus associated with improvement in speech production (Schlaug *et al.*, 2009). In healthy subjects, it has already been demonstrated that DTI allows for the detection of white matter changes in response to training, as indicated by an increase in FA after training (Scholz *et al.*, 2009). Taken together, homologous contralesional regions

or partially preserved perilesional areas and their associated fibre tracts seem to exhibit plastic reorganisation upon dedicated training. However, more work in experimental animals is needed to come to a better understanding which microstructural and physicochemical changes underlie the signal changes assessed with DTI in men. In the future, DTI may serve as a surrogate marker of cerebral plasticity and help evaluating a patient's response to rehabilitation.

8. Conclusions

White matter changes after stroke are important determinants for presentation and severity of the neurological deficits as well as for prospects of recovery or secondary cognitive decline. Notably, DTI appears to be a valuable tool for predicting the individual patient's perspective for recovery in order to tailor an optimized rehabilitation regime.

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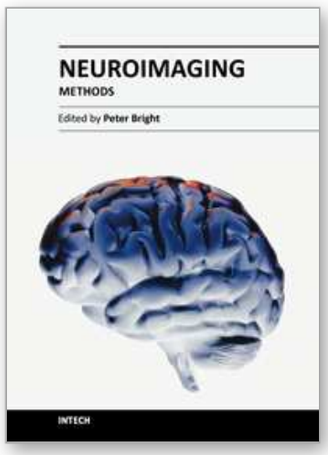

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Neuroimaging methodologies continue to develop at a remarkable rate, providing ever more sophisticated techniques for investigating brain structure and function. The scope of this book is not to provide a comprehensive overview of methods and applications but to provide a 'snapshot' of current approaches using well established and newly emerging techniques. Taken together, these chapters provide a broad sense of how the limits of what is achievable with neuroimaging methods are being stretched.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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