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Diffusion imaging in post-stroke plasticity: capacity and adequacy of visualization

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ABSTRACT

In recovery from stroke an essential mechanism is plasticity, in which changes in the strength of synaptic connections lead to functional or morphological reorganization. The methods that are commonly used to study post-stroke recovery in the brain predominantly measure brain function, indicating that activation patterns change. However, changing activation patterns do not necessarily reflect plasticity and plasticity is mainly determined by structural connectivity. With diffusion imaging (DI) structural connections can be visualized and quantified and it is suggested that DI is able to determine whether fiber reorganization accounts for changing activation patterns. The objective of the present review was to determine whether the relation between plasticity, DI and recovery is as straightforward as assumed. It is found that the relation between DI, plasticity and recovery is very complex. Changes in DI metrics do not necessarily reflect plasticity mechanisms and occurring plasticity does not always result in (beneficial) recovery changes. Nevertheless, DI is a valuable and necessary tool in investigating the occurrence of plasticity. By combining DI with functional techniques and outcome measures, structural changes can be coupled to changes in activation patterns, and by relating this to functional outcome, more understanding will be gained about the occurrence and significance of plasticity.

KEY WORDS: Stroke, recovery, plasticity, diffusion imaging

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INTRODUCTION

Stroke represents a serious neurological disorder: 15 million people annually suffer a stroke and with a mortality rate of 5 million,[1] it is a leading cause of death worldwide.[2] The most common type of stroke is ischemic stroke,[3] in which reduced blood flow is caused by a blockade of a cerebral artery.[4] This reduced blood flow induces necrosis of tissue within the infarcted area.[5] In the penumbra, adjacent to the infarct, neurons are still alive but dysfunctional due to partial blood flow.[6] In addition to damage around the lesion core, structurally uninjured areas more distant from, but connected to, the infarct may show reduced activity, called diaschisis.[7-9]

In the present review the focus will be on recovery of the motor system, considering that most patients show at least some degree of motor impairment[7, 10] and that the motor system is assumed to be among the most plastic brain regions.[11] In literature, the term *recovery* is not consistently defined; it may indicate improved performance of motor functions in general, without distinguishing underlying processes,[12] or is restricted to pure restitution of brain structures or functions.[13] In accordance with Kreisel et al,[10] in the present review *recovery* will indicate restitution or adaptation on a neurofunctional level, excluding behavioural compensation.

Essential mechanisms in post-stroke recovery are the restoration of reversible damage (the penumbra and diaschisis)[9, 14-16] and brain plasticity.[17] Recovery mechanisms are often revealed by functional MRI (fMRI), transcranial magnetic stimulation (TMS), positron emission tomography (PET) or magnetoencephalography (MEG).[18] These techniques predominantly measure brain *function.*[18] They indicate that activation patterns may change and that the location of activation is imperative for outcome.[6, 7, 12, 19, 20] An attractive explanation for altered activation patterns, is that they reflect reorganization. However, there are potential confounds in this interpretation. Instead of reflecting plasticity, remodelled activation patterns may be caused by behavioural compensation, changed cognitive control or disinhibition of intact areas.[13, 21] In addition, plasticity can be more directly investigated by focussing on supporting structural connectivity.[22] The corticospinal tract (CST) is the main descending pathway from the cerebral cortex to spinal cord motoneurons[23] and there is growing evidence that remapping of the motor system and motor outcome will depend greatly on CST integrity early after stroke.[5, 22, 24-26]

Stroke is assumed to modify structure integrity in the brain[27] and gaining more insight into plasticity in combination with tissue integrity can be very valuable for stroke management and therapeutic interventions.[18, 28] Since diffusion imaging (DI) visualizes and quantifies white matter tract integrity in vivo[18] it is suggested that DI is able to determine whether fiber reorganization accounts for increased brain activaton.[29] However, relating DI to plasticity and recovery is perhaps less straightforward than assumed. The present review will focus on studies that investigated plasticity in post-stroke motor recovery with DI. The first aim is to review whether DI is an adequate technique to visualize plasticity. The second aim is to review how DI metrics relate to recovery and whether possible relations between DI and recovery reflect plasticity.

The key papers that are summarized in table 1 had to meet several inclusion criteria. First of all, all papers claimed demonstration of recovery related post-stroke reorganization or plasticity, with the use of DI. With regard to stroke, no difference was made between hemorrhage or ischemic stroke, but the CST or motor

function (upper or lower extremity) had to be affected. Both human and rat studies were included, disregarding the application of treatment or therapy (the goal was to determine visualization, not occurence, of plasticity). First, the concepts of plasticity and DI will be introduced, after which findings from the key papers will be validated with results from other studies.

PLASTICITY

In order to determine the occurrence of post-stroke plasticity, it is essential to have a clear definition of what plasticity comprises. Nevertheless, in literature plasticity is not consistently defined,[24] which can at least in part be attributed to the fact that plasticity mechanisms are not well-understood[12] and that recovery-related concepts can be used for descriptions on several levels (neuronal, network or behavioural).[14]

Spontaneous recovery is recovery that is not rehabilitation-guided.[7] In accordance with Hallet[17] in the present review two mechanisms (although not mutually exclusive) will be distinguished within spontaneous recovery. The first mechanism is the restoration of a temporary interruption of function, such as restitution of the penumbra or diaschisis.[17] It is assumed that the majority of this takes place in the early phase (e.g. the first weeks) post-stroke.[30] After several weeks, in the subacute and chronic phase, the second mechanism becomes more important, including plasticity mechanisms by which spared brain regions take over functions of damaged areas.[17, 30-33]

Most literature agrees that plasticity refers to changes in the strength of synaptic connections, leading to functional or morphological reorganization.[11, 12, 34] The altered synaptic activity may occur in response to learning and experience,[10, 12, 35] or can be primed by stroke.[10] Most plasticity research is aimed at cortical plasticity (i.e. remapping of motor areas), since functional imaging predominantly visualizes function of grey matter.[36] Nevertheless, subcortical connectivity and organization of white matter tracts are crucial in reorganization. Within subcortical areas plasticity may result from active reorganization of subcortical structures ('anatomical rewiring') or from passive adaptation to cortical remapping.[36]

For understanding plasticity mechanisms, the notion of connectivity in the brain is essential. At present it is assumed that the brain functions as an integrated collection of distributed networks; although regions may have their own specific function, performance of a particular task depends on integrated activity.[12, 37] This in particular holds for the motor cortex, in which the representation of body parts in a topographic fashion (somatotopy) and distributed overlap of movement representations co-occur.[14, 16, 38] In addition to the horizontal fibers that interconnect the distributed representations, each motor area has connections with the spinal cord.[14, 16, 38, 39] This enormous amount of diffuse and redundant connectivity between related cortical regions, combined with the capacity for activity-dependent synaptic strength changes, allows the motor cortex to adapt to changes in the environment.[14, 38-40] Connectivity mainly relies on white matter tracts and orientation and integrity of white matter fibers can be visualized with DI.[41]

DIFFUSION IMAGING

DI is based on the principle of diffusion: the random motion of water molecules. When the movement of water molecules is unrestricted and the same in each direction, diffusion is called *isotropic*.[42] Water molecule movement can, however, be much faster when it is restricted by cell membranes or other molecular structures. The movement will then be in a particular direction, called *ansiotropic*.[42] Ansiotropy is in particular high in white matter, reflecting the fast diffusivity along the fibers and slow diffusivity perpendicular to them. Ansiotropy is mainly determined by the axonal membranes and myelination is assumed to play a primary - although not critical - role.[43] Other contributing factors are: the axonal cytoskeleton of neurofilaments and microtubules, the local-susceptibility-difference induced by gradients and intact membranes.[43] In grey matter and cerebrospinal fluid (CSF) ansiotropy approaches zero as the diffusivity is similar in all directions.[44] Hence, ansiotropic diffusion is assumed to be able to determine fiber tract integrity and orientation within the white matter of the brain.[41]

The average magnitude of water molecule motion (i.e. diffusion) within one voxel is described by the apparent diffusion coefficient (ADC).[42] A drawback of this coefficient is that it is one-dimensional, whereas fiber orientation can be in every direction.[45] A solution is to calculate a mean or average ADC over three dimensions.[27] In addition, diffusion tensor imaging (DTI) is developed, in which diffusion weighted images are obtained in various directions. The tensor is a 3x3 symmetric matrix,[41] which can be visualized with a 3D-ellipsoid illustrating the longest, middle and shortest axes.[42] One of the most widely used metrics based on DTI is fractional ansiotropy (FA), which gives the directional bias of water molecule motion[46] and is scaled from 0: isotropic, to 1: ansiotropic.[42] An even more advanced procedure is fiber tracking. According to the fiber assignment by continuous tracking (FACT) algorithm, fiber pathways are reconstructed from the largest diffusion direction within a voxel.[47]

DI AND POST-STROKE PLASTICITY

DI results

An overview of the results of the included key papers is given in table 1.[48-55] Several of the included papers report ADC and/or FA values.[49, 51, 55] For ADC values Jang et al[51] report an increase in the lesion core, whereas in the degenerated tract no difference in ADC is observed, compared to controls. At five months post-stroke similar ADC values for patients and controls are found.[51] Both Jang et al[51] and Jiang et al[52] report reduced FA values in the lesion core, in the first weeks post-stroke, in patients compared to controls. Over time, however, a gradual increment is seen,[49, 52] with similar FA values for patients and controls at five months post-stroke.[51] The research approach taken by Schaechter et al[55] differs slightly from the other key papers, since good versus poor motor skill performers are investigated (determined by finger tapping and manual dexterity, for details see also *Validation with additional measures*). In this paper, in chronic stroke patients, relative decreased FA combined with increased radial diffusivity is reported for poor performers, whereas in good performers increased FA is combined with decreased radial diffusivity (it should be noted that radial diffusivity is perpendicular to the axons).[55] A closer look at these results shows that the reduced FA regions are predominantly found around the lesion core, whereas elevated FA is found more remote from the lesion.

Within the range of the inclusion criteria, the included papers are quite diverse; all papers investigated plasticity with DI, but in several papers it was only a means for answering questions about a new DI approach,[54] correlations with motor skill[55] or the efficacy of a certain post-stroke therapy.[49, 52] Hence, in most of the included papers DI metrics are interpreted in the light of their research question and not by itself, or with regard to their ability to reflect plasticity. The complexity with interpreting ADC and FA patterns is that it is hard to distinguish the different phases of damage and recovery. Although spontaneous recovery processes are assumed to start during the initial stages post-stroke (1-4 weeks post-stroke),[12] most previous research that investigated DI post-stroke was aimed only at relating white matter *damage* to motor function outcome.[25, 26, 46, 56, 57] Nevertheless, the included key papers all claim investigation of plasticity or white matter recovery over time, and a general pattern can be observed for ADC and FA values in all papers.[48-55] The initial phase of this general pattern is clearly demonstrated by Schaechter et al[55]: the loss of structural integrity is assumed to cause increased diffusion (ADC) and decreased ansiotropy (FA),[27, 43] and these findings are in accordance with a study concerning an experimental murine transient ischemic attack (TIA) model.[58] Plasticity processes are reflected by a development over time, of ADC and FA towards more normal values,[51, 52] or increased FA values.[49]

In addition to the changes over time, two papers indicate that ADC and FA values may also differ depending upon location, both on a shorter[51] and a longer[55] term post-stroke. Previous studies aimed at visualizing white matter damage with DI demonstrate that, besides primary damage caused by the lesion, secondary loss of structural integrity may be caused by wallerian degeneration (WD), especially in chronic stroke patients.[26, 59] WD is commonly observed after stroke and can be defined by the degeneration of axons and their myelin sheaths after injury of a proximal axon or cell body.[46, 56] Jang et al[51] demonstrate the ability of DI to distinguish the primary lesion core from the (secondary) degenerated tract early after stroke. This can be very valuable for outcome predictions, since it provides the opportunity to differentiate irreversibly damaged from salvageable tissue.[27] Schaechter et al[55] investigated DI in chronic patients, and the results show quite clearly that the pattern around the lesion core is different from the pattern in more remote areas. This may indicate the ability to distinguish the irreversibly damaged site from the site where recovery took place on a longer term. In addition, these findings are in accordance with a previous WD study, in which it was shown that diffusion properties differ in the primary and secondary damaged areas.[59]

Several trends in tractography results can be discerned. It is reported that the CST is absent or partly interrupted in the affected hemisphere,[50-52] but possibly regenerates after several months.[51] In addition, the CST is found to pass through the perilesional area.[48, 49, 52, 53] Over time, decreased spatial overlap and an increase in fiber/voxel count in the affected hemisphere is reported, probably reflecting rearranged and increased connectivity.[54]

The initial tract discontinuity presumably reflects damage, whereas the subsequent findings reflect different plasticity mechanisms. The different reorganization mechanisms possibly depend on lesion site and size: from an experimental murine TIA model it is reported that in larger lesions the CST passes through a perilesional area, whereas in smaller lesions new horizontal connections are observed.[60]

Validation with additional measures

Subcortical plasticity can occur at different levels[14] and the advantage of DI is that these different levels are combined: microstructure information is used to visualize connectivity on a network and structure level.[43] In order to validate the DI findings, some of the reviewed papers performed additional measures. Two key papers validated DI findings on a cellular level, with ex vivo histology in mice.[49, 52] Axonal sprouting and co-occuring myelination in the perilesional areas was reported and the correspondence with FA measures and increased fiber count[49, 52] indicates that a recovery process is reflected. These findings are in accordance with a paper in which DI and histology are combined to investigate plasticity after experimental murine TIA.[60] Nevertheless, it should be noted that from murine experimental spinal cord injury (SCI) research it appears to be very difficult to correlate individual diffusion to brain histology; discrepancies are often observed.[29] Moreover, since histological measures are infeasible in humans it is not possible to correlate individual human diffusivities to brain histology.[33]

A technique that is better applicable in humans is in vivo fMRI, which can be combined with DI to indicate reorganization on a network or structure level.[48, 50] At first sight the fMRI post-stroke activation patterns in the key papers seem quite inconsistent. However, the combination with tractography indicates that the inconsistencies can be explained by different reorganization mechanisms. Ahn et al[48] report fMRI activation patterns in which both affected and unaffected hand movement lead to corresponding activation in the contralateral hemisphere, indicating 'normal' activation. In addition, with tractography Ahn et al[48] show that the CST passes through the perilesional area. Taken together, these results suggest reorganization mainly on the level of the CST. Jang et al[50] report fMRI activation patters in which both affected and unaffected hand movement lead to activation only in (the same) unaffected hemisphere. These fMRI findings combined with the reported inability to track the CST in the affected hemisphere[50], indicate a reorganization towards the unaffected hemisphere. As already shortly mentioned, different reorganization patterns may be caused by a difference in lesion size[60]: small lesions induce recovery of perilesional tissue with similar function, whereas for larger lesions tissue with a similar function may be found only at more distant sites.[12] Several other studies used the combination of DI and fMRI: cortical language reorganization is demonstrated[61] as well as a relation between CST damage and changed activation patterns.[26]

In two papers outcome is determined by standardized measures (functional outcome score or behavioural testing), which are related to DI metrics.[54, 55] With regard to functional outcome score, Pannek et al[54] show that FA does not correlate with functional outcome (as determined by National Institutes of Health Stroke Scale (NIHSS) and Barthel's index). However, it should be noted that these outcome measures are regarded as fairly insensitive.[62] Nevertheless, Pannek et al[54] did find a correlations between the measure 'skewness of fiber uncertainty' and functional outcome score. This measure is assumed to be more sensitive to recovery than diffusion ansiotropy, since it gives the certainty of fiber orientation and perhaps repair. With respect to behavioural outcome, Schaechter et al [55] demonstrate that FA correlates with motor skill (speed of finger tapping and manual dexterity, measured with Purdue Pegboard scores).

In sum, the validation of DI findings with other measures leads to several trends in the conclusions: in the subacute to chronic phase, reorganization of damaged white matter tracts into the perilesional area is

seen[48, 49, 53, 54] as well as reorganization of white matter tracts towards the unaffected hemisphere.[50, 52] Diffusion tractography indicates restoration of the damaged CST, which is also supposed to reflect a plasticity mechanism.[51] An intact CST is assumed to be essential for motor remapping,[24, 63] and previous studies show axonal remodelling in the CST, occurring beyond the acute phase.[64] This suggests that the impression of restoration on a tractography level may in fact reflect axonal remodelling. All in all, the distinct reorganization mechanisms all apply to the various organizational principles of the motor cortex: the connections with the spinal cord, the horizontal fibers and the overlapping functional and hierarchical organization.[14, 16, 38, 39] However, the relation with outcome measures remains doubtful.

DI, PLASTICITY AND RECOVERY

DI studies in various patient populations suggest that structural remodelling of functionally-relevant white matter tracts may be an adaptive response that compensates for injury to the human brain.[55] In traumatic brain injury (TBI) research it is presumed that DTI may visualize structural reorganization and is relevant to clinical recovery.[65, 66] In addition, in Broca's aphasia, plasticity of white matter tracts visualized with DTI is assumed to account for better speech outcome.[67] Specifically with regard to the motor system, the correlation between DTI and outcome is suggested to relate the biophysical properties that affect white matter FA (axonal density, diameter, myelination and orientation coherence) to the efficacy of communication along the CST.[55] In the present review all included papers claim to demonstrate a relation between DI, plasticity and post-stroke recovery. Nevertheless, the step from DI, via plasticity, to outcome is quite complicated. Even when a relation between DI and outcome is found, it is hard to determine whether plasticity mechanisms are reflected. In order to make this complex relation better comprehensible, two separate components can be distinguished: first, DI and plasticity mechanisms, and second, plasticity and recovery.

DI and plasticity mechanisms

It is assumed that evolution of possible plastic changes in white matter, related to recovery, can be visualized with DI when used at multiple time points.[18] For fiber tracking in particular, *a priori* knowledge about the white matter system is necessary to determine the regions of interest.[57] In a healthy brain the identification of fiber systems is fairly complex, however, this becomes even more complicated in a brain in which structure is distorted by a lesion.[44] This may pose a difficulty in using 'standard' fiber tracking procedures post-stroke. Pannek et al[54] applied a novel approach, in which the use of a simplified cortical surface model circumvents the *a priori* selection of seeding points.[54] This novel approach may be very promising in future post-stroke fiber tracking.

Previous research indicates that reduced FA correlates with functional deficits, whereas increased FA reflects white matter tract integrity.[25, 27, 43] Nevertheless according to a WD study, it is a widespread misconception that loss of structural integrity is always accompanied by reduced ansiotropy.[59] In only two key papers an attempt is made to directly relate DI metrics to plasticity.[49, 52] Although these conclusions are partly based on structural measures, it is in general hard to determine how well FA values reflect plasticity; it is possible that FA values increase, without the occurrence of plasticity. For example, increased FA values are

found inside the lesion core[58] and it is suggested that FA can be influenced by the astrocytic response to injury; astrocytic hypertrophy is found to influence diffusivity measures and plays a major role as a regulator of water homeostasis.[68] On the other hand, the reverse scenario is also possible: plasticity may occur, without being captured by DI. This may be the case when white matter reorganization involves crossing fibers.[22] Especially in areas in which fibers are not parallel arranged, two factors compete in crossing fibers: increased orientation coherence of the remaining fibers tends to increase ansiotropy, while gliosis and/or accumulation of the extracellular matrix tends to reduce it.[59] The interaction of these two factors may lead to inconsistent ansiotropy outcomes.

Plasticity and recovery

To determine the clinical relevance of applying DI in post-stroke recovery research, it is most interesting to relate DI and (possible) plasticity findings to clinical outcome. Despite the fact that outcome is not always reported in the key papers, and reported time points differ greatly, in general most patients reach at least resistance to gravity, for their affected lower[50, 51] or upper[48, 51, 53] extremity. In addition, several included key papers use (standardized) outcome measures,[54, 55] but hardly any relation between DI metrics and these outcome measures is found, possibly at least in part due to the assumed insensitivity of the used inventories.[62] In addition, it may reflect the complicated relation between plasticity and recovery.[6]

In evaluating the relation between plasticity and recovery it is difficult to determine whether post-stroke plastic changes are adaptive or maladaptive.[69] First of all, not every reorganization seems to have functional meaning.[14] Second, not all plasticity is beneficial; a phenomenon also known as maladaptive plasticity.[6, 35] Compared to a healthy brain, a lesioned brain may be more vulnerable to maladaptive processes;[10] compensatory adjustment can improve function at the short term, while at the same time hindering reactivation of the damaged circuits themselves. In addition, overstimulation of lesioned circuits may hinder neurochemical and physiological repair within these circuits[35] and early intensive therapies may even have a negative effect on eventual outcome.[12] Moreover, persistent activation in the unaffected hemisphere is a sign of maladaptive plasticity[6, 17] and persistence of plasticity is associated with induction of epilepsy, or chronic pain.[7] All these findings indicate that plasticity not always results in functional recovery. Therefore it seems essential to also include (a standardized) degree of functional recovery in assessing the relation between DI, plasticity and recovery.

CONCLUSION

In sum, investigating plasticity is rather complex, since plasticity is no well-defined concept. Taking this into consideration, drawing firm conclusions about the visualization of plasticity with DI is complicated. It can be concluded that DI changes do not necessarily reflect plasticity and plasticity is perhaps not always visualized with DI. In addition, also the relation between plasticity and outcome is not unequivocal: not all plasticity processes are beneficial or meaningful. The step from DI, via plasticity, to outcome is therefore even more complicated; although a relation between DI and outcome may be found, it is hard to determine whether plasticity mechanisms are reflected.

A limitation of the present review is the small amount of key papers that are included. Nevertheless, only these papers met the inclusion criteria, indicating that investigating post-stroke plasticity with DI is still in its infancy. The present review clearly demonstrates that caution is needed with adhering conclusions to plasticity and DI findings; it warrants for wrong conclusions and guides further research into more appropriate directions.

The aims of the present review were to investigate whether DI is an adequate technique to visualize plasticity; how DI metrics relate to recovery and whether possible relations between DI and recovery reflect plasticity. All in all it can be concluded that DI is able to determine whether fiber reorganization accounts for increased brain activation. DI is therefore a valuable and necessary tool in investigating the occurrence of plasticity, and it is suggested that, in order to give a comprehensive analysis regarding plasticity, DI is combined with functional imaging techniques and outcome measures. DI can, for instance, be combined with fMRI; to relate connectivity changes to activation patterns. In addition, it is possible to couple structural brain connectivity to functional brain connectivity, by combining DI with resting state fMRI, in which baseline activity of the brain is investigated.[70] However, in order to give significance to these plasticity findings, it is necessary to determine functional outcome. Instead of using general inventories, such as Barthel's index and NIHSS, it is suggested to use outcome scales that are more specifically related to motor function. Motor function can be determined by, for example, the Action Research Armtest (ARAT), in which upper limb function in hemiplegia is assessed, [71] or the Fugl-Meyer assessment (FMA) for evaluating motor function, balance, sensation qualities and joint function in hemiplegic patients.[72] By any means, obtaining more knowledge about the reorganizational mechanisms that play a role in post-stroke recovery may be very valuable for the treatment of patients.

Table 1. Overview of results of key papers

Reference	Method	Time point	DI measures, strokes versus controls			Combined with other measures?	Outcome?	Conclusion concerning DI& Plasticity
			ADC	FA	Tractography			
Ahn, 2006	2 patients; 6 controls	6 months	x	X	CST from affected hemisphere through different portion pons	**fMRI:** activation contra-lateral SMA during affected and unaffected hand movement	Motor recovery at 9-12 weeks (resistance against gravity)	Reorganization function into peri-infarct area
Ding, 2008	Rats with embolic stroke	24 hours; weekly up to 6 weeks	x	Relative increase FA in affected compared to unaffected hemisphere	Fiber tract present along the ischemic boundary	**Histology:** high density axonal projections ischemic boundary, consistent with DI results	x	Reorganized nerve fibers along the ischemic boundary
Jang, 2005	1 patient; 6 controls	?	x	X	No CST in affected hemisphere of patient	**fMRI**: asymmetric (only unaffected) SM1 activation in patient	Lower extremity: at 10 months independent ambulation	Contralesional SM1 reorgani-zation
Jang, 2006	1 patient; 6 controls	3 weeks	Increased only in ICH region	Reduced only in ICH region	CST discontinuity in affected hemisphere	x	At 5 months complete motor recovery (accomplished with rehabilitation)	Disappearance of interruption indicates recovery of damaged CST
		5 months	No difference with controls	No difference with controls	No CST interruption			
Jiang, 2006	3 patients; rats with MCA occlusion	Patients: 9 months Rats: ex vivo (5 weeks)	x	FA values & FA WM maps: Similar pattern; Initially low in ischemic core, but gradual increment in ischemic recovery regions, such as extended region of CC	Patients: No fibers in lesion core, in boundary region fibers encap-sulated the lesion Rats: orientation changes around the lesion	**Immunohistochemistry:** Reorganization of axons and myelin in ischemic boundary region, corresponds with FA measures	x	Increase in FA in WM of CC indicates that CC promotes WM reorganization

(Continued)

Table 1. Overview of results of Key Papers (Continued)

Reference	Method	Time point	DI measures, strokes versus controls			Combined with other measures?	Outcome?	Conclusion concerning DI& Plasticity
			ADC	FA	Tractography			
Kwon, 2007	3 patients	11-19 weeks; 6 months	x	x	CST from affected hemisphere passed through peri-infarct area	x	At 6 months resistance against gravity	Affected motor function reorganized into posterior portion of infarcted area
Pannek, 2009	10 patients; 6 controls	18 days; 138 days (median)	x	x	- reduced spatial overlap affected hemi-sphere (over time) - difference in voxel count that reflects increase in connectivity in affected hemi-sphere	**Functional outcome**:No correlation with change in FA, but correlation with improved fiber tract repair/recovery	x	Spatial connectivity changes and increased connectivity reflect WM recovery, repair and reorganization in affected hemisphere
Schaechter, 2009	10 patients; 10 controls	2.6 years post-stroke (median)	**Combined approach:** *Voxelwise analysis:* Reduced FA associated with increases in radial diffusivity and poor motor outcome;Elevated FA associated with reduced radial diffusivity and good motor outcome *Tractography based analysis:* CST FA reduced in poor motor skill; trend towards elevated CST FA in better motor skill (not significant)			**Behavioural testing:** Motor skill, determined by manual dexterity and maximum speed of finger tapping, was found to correlate with FA	Sufficient motor skill to perform the measures	Bilateral structural remodelling of WM tracts compensates for injury to human brain

Abbreviations: ADC, apparent diffusion coefficient; FA, fractional ansiotropy; CST, corticospinal tract; SMA, sensorimotor area; SM1, primary sensorimotor cortex; CC, corpus callosum; WM, white matter.

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