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MRI Characterization of Progressive Brain Alterations After Experimental Traumatic Brain Injury: Region Specific Tissue Damage, Hemodynamic Changes and Axonal Injury

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1. Introduction

In this chapter we describe magnetic resonance imaging (MRI) findings in a rat model of traumatic brain injury (TBI). Although studied in a rodent model, these findings correspond closely to those seen in patients. The experimental study setup allows mapping of the spatio-temporal interrelations of different pathological features in the injured brain as well as correlation of non-invasive MRI results with tissue histochemistry data. We combine the information provided by some selected MRI techniques to characterize the interplay between structural and hemodynamic changes.

1.1 Non-invasive imaging and animal models are needed for understanding the complex and progressive brain alterations that occur after traumatic brain injury (TBI)

TBI is a devastating disease with a variety of cognitive and motor function deficits that manifest from immediately after the impact and even up to several years later. The mechanisms of TBI are complex and there is a great unmet medical need to find neuroprotective treatments. Primary TBI damage is caused by the shear forces of the impact itself, which initiates ionic, molecular, and cellular alterations within seconds (McIntosh et al., 1994; Rink et al., 1995) followed by immediate cytotoxic edema and later vasogenic edema (Faden et al., 1989). Thereafter, the secondary injury begins to develop and continues to worsen for days, months, or even years. The neurodegenerative cascades of secondary injury are composed of complex combinations of cellular and metabolic alterations (Pitkänen et al., 2009). The cortical contusion site suffers most, but other cortical areas and sub-cortical gray matter regions are exposed to the destructive cascades as well. The impact forces stretch the white matter tract network and adjacent vasculature, which causes microbleeds within the white matter bundles. These microbleeds are one early indicator of diffuse axonal injury (DAI), which involves progressive demyelination and axonal damage throughout the brain. DAI is recognized as a key factor in the consequential progressive cognitive impairment. Histological studies of TBI report the co-occurrence of chronic inflammation, glial hypertrophy, and axonal injury (Lenzlinger et al., 2001; Morganti-Kossmann et al., 2002; Soares et al., 1995). We know that eventually the combination of these gray matter and white matter associated cascades leads to functional disabilities including

motor impairment, cognitive decline, emotional disturbance, or epilepsy (Kharatishvili et al., 2006; Thompson et al., 2005), but the exact mechanisms remain unrevealed.

Animal studies permit control of the inter subject variability, elimination of environmental un-known factors, long-term follow-up of the same subject, multimodal testing, and accurate correlation of radiological, behavioural, histological and molecular findings. The following chapter focuses on describing the multimodal MRI findings in a *rat model of lateral fluid percussion injury (LFPI) induced TBI*, which is the most widely used and best characterized experimental model of human closed head injury (Kharatishvili et al., 2006; Thompson et al., 2005).

Magnetic resonance imaging (MRI) methods offer a variety of approaches to study the different features of brain pathologies non-invasively. Particularly, in complex nervous system diseases that progress slowly and carry unknown mechanisms, the application of multimodal MRI techniques that target different underlying phenomena can provide crucial information about the spatio-temporal developments of the tissue damage and thereby provide added insights into the disease mechanisms.

2. Multimodal MRI of the injured brain: Access to morphology and tissue atrophy, transient edema, neurodegeneration, white matter damage, intracerebral hemorrhages and hemodynamics

2.1 Characterization of damage extent and region specific pathological features

MRI has an important role after head injury in detecting the primary lesion, tissue atrophy and lysis, microbleeds and hematomas, transient oedema coverage and other morphological features. In particular, ultra high magnetic fields (such as 7 T – 16 T) can access the fine details in cortical and sub-cortical structures and map the entire brain of a mouse in, for example, a resolution of tens of micrometers. Clinical scanners (1.5 T - 3 T) are able to pick up the same features in patients at the sub-millimeter scale. Figures 1 and 2 demonstrate the extent and sparse distribution of pathological morphological MRI findings post experimental TBI and therefore stress the importance of both the whole-brain coverage and high resolution agenda in imaging.

In the lateral fluid percussion injury rat model, the direct damage caused by the impact forces (pressure and shear stress) depends upon the impact pressure and exact direction. Figures 1 and 2 show example cases of severe injury caused by higher than 3 atm fluid mediated pressure. Figure 1 shows how the atrophy gradually worsens at 3 hours, 3 days, 9 days, 23 days, 2 months, 3 months and 6 months after injury in one representative animal. Figure 2 shows a higher resolution image set of another example animal at 2 months post injury and how the hematomas, atrophy and calcifications extend through the brain rostro-caudally. Immediately after impact the integrity of the blood brain barrier (BBB) is compromised both in gray matter at the contusion site and inside/next to major white matter tracts that are exposed to and transduce the mechanical shear forces. This creates hematomas in cortical gray matter at the contusion site and microbleeds along more distal white matter bundles. Thereafter, the contusion site and ipsilateral surrounding regions suffer from transient edema (hyperintense, swollen cortical area in Figure 1, visible already at 3 hours, maximal at 3 days and partially resolving after 9 days). The impact launches destructive cellular cascades, and the area of neurodegeneration and subsequent atrophy can be first identified at the core of the contusion site as very high intensity (i.e. high free water content) T_2 weighted signal. The tissue degradation area expands from 23 days post

injury onwards and is called here 'the focal lesion'. At later time points a glia scar is found to be outlining this cerebrospinal fluid filled cavity. Macroscopically, it is evident that the hippocampus ipsilaterally to the impact is deformed as atrophy progresses. Microscopically, very pronounced and well described loss of hilar interneurons has been reported in this model (Lowenstein et al., 1992; Hunt et al., 2011). In long follow-up studies of rats, repeated MRI scans have shown that the atrophy volume continues to increase up to 6 months post injury, which correspond to decades in humans (when comparing the relative age).

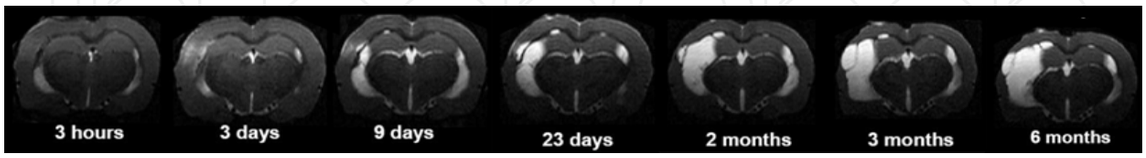

Fig. 1. Progressive atrophy mapped by non-invasive MRI. T_2 weighted MRI made at a 4.7 T scanner. Long-term follow-up studies of the LFPI rat model for TBI demonstrate how tissue atrophy continues until 6 months. This is one time series from the same animal imaged from 3 hours to 6 months post-injury. Sub-acute progression continues for over 2 months and a 'plateau' state is reached 6 months post-injury. The corresponding time scale for humans could be from years to decades. (Immonen et al., 2009b)

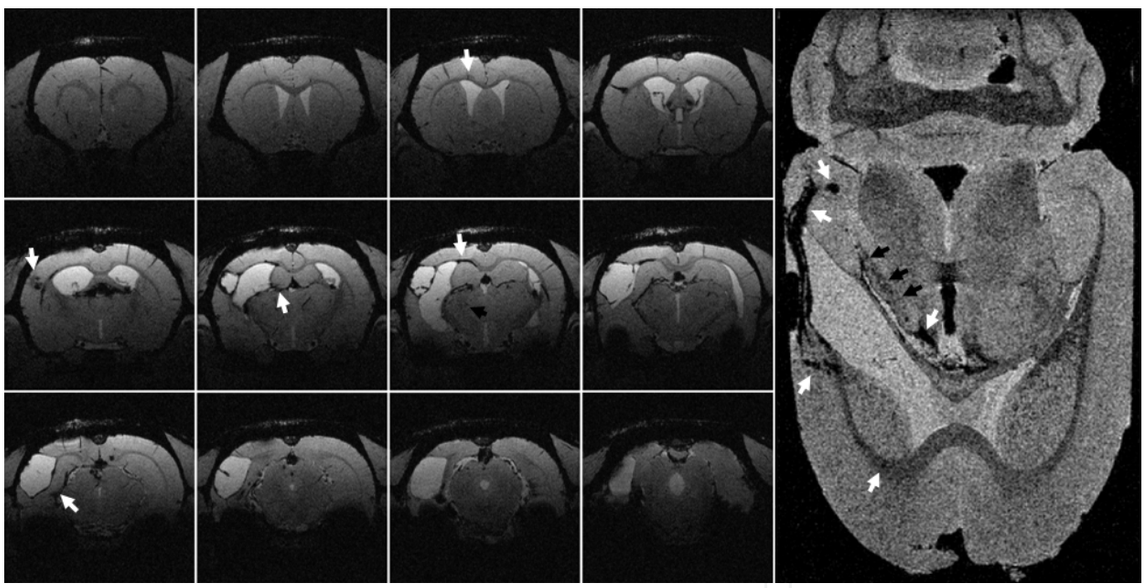

Fig. 2. T_2/T_{2*} weighted images of a rat brain after TBI. The high resolution achievable in an ultra high 9.4 T magnetic field with small animal models characterizes the morphological brain pathology in detail. Left: In vivo MRI of a living mouse at 5 weeks after fluid percussion injury: a series of transverse images showing every fifth slice of 200 μm-thick slices that cover the entire brain (in-plane resolution 70*70 μm). Right: Ex vivo MRI of an intact, fixed rat brain 12 weeks post injury acquired at 50*50*60 μm resolution, coronal view. Anatomical high resolution MRI demonstrates the extent of atrophy (tissue lysis at the primary lesion site and enlargement of ventricles, cerebrospinal fluid appears bright), hematomas and microbleeds (white arrows) and thalamic calcifications (black arrows)

The literature concerning clinical and experimental MRI findings as well as histological correlates after TBI shows good compatibility with our data. In patients, intracerebral hemorrhage, lesion and edema formation at the acute phase are common clinical MRI findings (Caroli et al., 2001; Kurth et al., 1994; Morais et al., 2008; Scheid et al., 2007). Axonal damage following TBI has been frequently detected using diffusion tensor imaging (DTI) and the changes in diffusion anisotropy have been reported in both acute and chronic TBI patients (Sidaros et al., 2008).

In experimental studies, MRI findings resemble the clinical findings with accelerated temporal progression. MRI alterations associated with edema and hemorrhage have been reported (Graham et al., 2000b; Iwamoto et al., 1997) and axonal damage has been linked to changes in diffusion MRI (Mac Donald et al., 2007). Studies in rats have described prolonged relaxation times due to increased water content and decreased cell density. For example, the hyperintensity in T_2 weighted images has been used to show edema, neuronal loss or, the consequence of tissue atrophy and partial volume effect. The hippocampal T_2 relaxation time has been reported to increase during the first 7 days after TBI induced by controlled cortical impact (Obenaus et al., 2007). A 3 month follow-up showed enlarged ventricles, cisterns, and that the necrotic tissue in the primary contusion site was absorbed and replaced by cerebrospinal fluid (Iwamoto et al., 1997). Diffusion weighted imaging has shown decreased apparent water diffusion (ADC) acutely (<24 hours) after TBI followed by increased diffusion days or weeks after TBI (Albensi et al., 2000; Obenaus et al., 2007; Onyszchuk et al., 2007; Van Putten et al., 2005; Vink et al., 2001).

Histological studies in rat models have verified these aforementioned MRI findings and the robust cellular loss and cavity formation in the primary cortical contusion site during the early weeks post-injury, the degeneration has been found to be selective for certain cell types and brain regions (Conti et al., 1998; Cortez, McIntosh, Noble 1989a; Hallam et al., 2004; Raghupathi et al., 2002; Rink et al., 1995; Sato et al., 2001) and it has been demonstrated to go on up to 1 year (Bramlett et al., 1997; Pierce et al., 1998; Smith et al., 1997).

2.2 Progressive brain alterations: Quantitative mapping of relaxation properties

Slow degradation and plastic neuronal processes after trauma may not show in anatomical images in their early phase but they cause alterations in magnetic relaxation properties of tissue locally and can thereby be detected and followed by quantitative MRI. Particularly the gray matter areas surrounding the primary contusion site appear visually completely normal in conventional anatomical images (both in T_2 or T_1 weighted MRI) but the quantitative mapping is sensitive enough to pick out the regions that are undergoing microstructural changes. Figure 3 shows how the perifocal area and ipsilateral hippocampus can appear healthy initially and then later display increased relaxation and diffusion values at 23 days post-injury. Only a 5-10% change in absolute relaxation and diffusion values in perilesional cortical regions at the sub-acute phase (secondary increase after resolution of edema) post injury reveals regions that later progress to atrophy. Maps of T_1, T_2, $T_{1\rho}$ and diffusion (ADC/D_{av}) parameters discern regions of irreversible and reversible tissue damage, and are sensitive enough to monitor the progression and potential treatment responses in different brain regions. Both the magnitude and the temporal pattern of the observed MRI changes differ between the primary lesion site (irreversible damage) and in the perilesional regions (tissue at risk but potentially salvageable), including the hippocampus. Figures 3 and 4 describe the alteration pattern of quantitative MRI data in the acute phase 3 hours post-trauma associated with the immediate mechanical consequences of

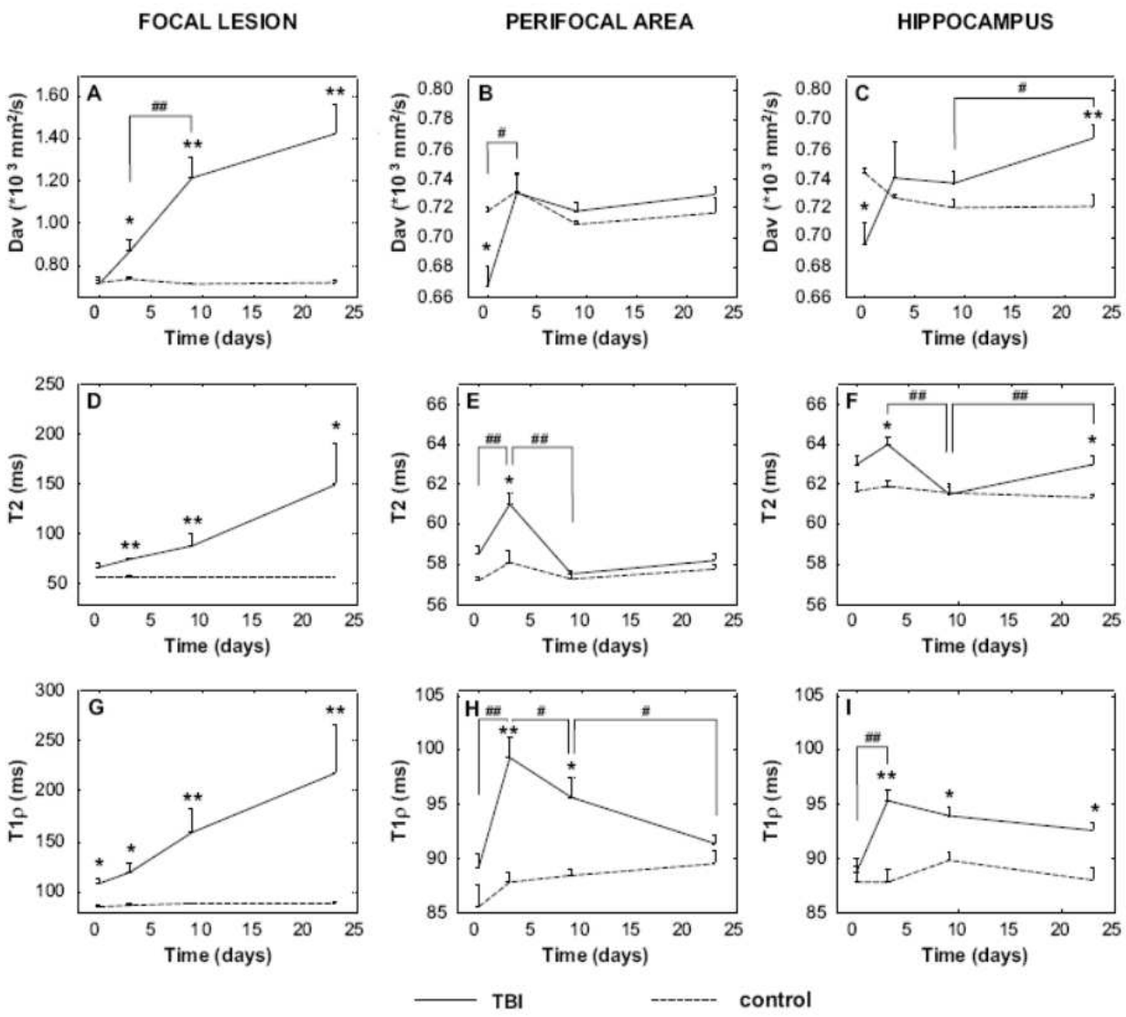

Fig. 3. Early progression of D_{av}, T_2 and $T_{1\rho}$ in the lesion (left column), in the perifocal area (middle column) and in the ipsilateral hippocampus (right column). Graphs compare the quantitative relaxation and average diffusion values from TBI and sham groups at 3 hours, 3 days, 9 days and 23 days after TBI induction. Data points are group averages from region of interest (ROI) analysis of quantitative maps. Each ROI shows a characteristic pattern. **The lesion:** D_{av} increased rapidly in the lesion area starting from day 3. Both T_2 and $T_{1\rho}$ also increased steadily, and $T_{1\rho}$ was significantly elevated already at 3 hours after TBI induction. **The perifocal area** (*i.e.* ipsilateral cortex excluding the lesion): D_{av} dropped acutely (3 hours) after TBI. T_2 and $T_{1\rho}$ show a transient peak at day 3 post-TBI, but unlike T_2, $T_{1\rho}$ remained elevated still at day 9. **The ipsilateral hippocampus**: D_{av} dropped acutely (3 hours) after TBI and increased 23 days later. Both T_2 and $T_{1\rho}$ peaked at day 3 post TBI and were elevated at day 23, but T_2 recovered at day 9 while $T_{1\rho}$ remained elevated. Differences between groups are indicated as **, $p<0.01$ and *, $p<0.05$ (Mann Whitney *post hoc* test), and the differences between time points as #, $p<0.05$ and ##, $p<0.01$ (Wilcoxon *post hoc* test). Note that the scale on lesion graphs differs from that on the perifocal and hippocampus graphs. (Immonen et al., 2009ab)

impact injury and cytotoxic edema (1), in the sub-acute phase 1-5 days after trauma associated with some recovery processes and vasogenic edema (2), during secondary injury cascades associated with neurodegeneration, gliosis and inflammation (and more) that become detectable around 2 weeks after trauma by quantitative MRI and show persistent progression up to 6 months (3), and in the chronic, apparently stable stage 7-12 months after trauma (4). Note again, that this time scale in rats can correspond to a period of tens of years in patients.

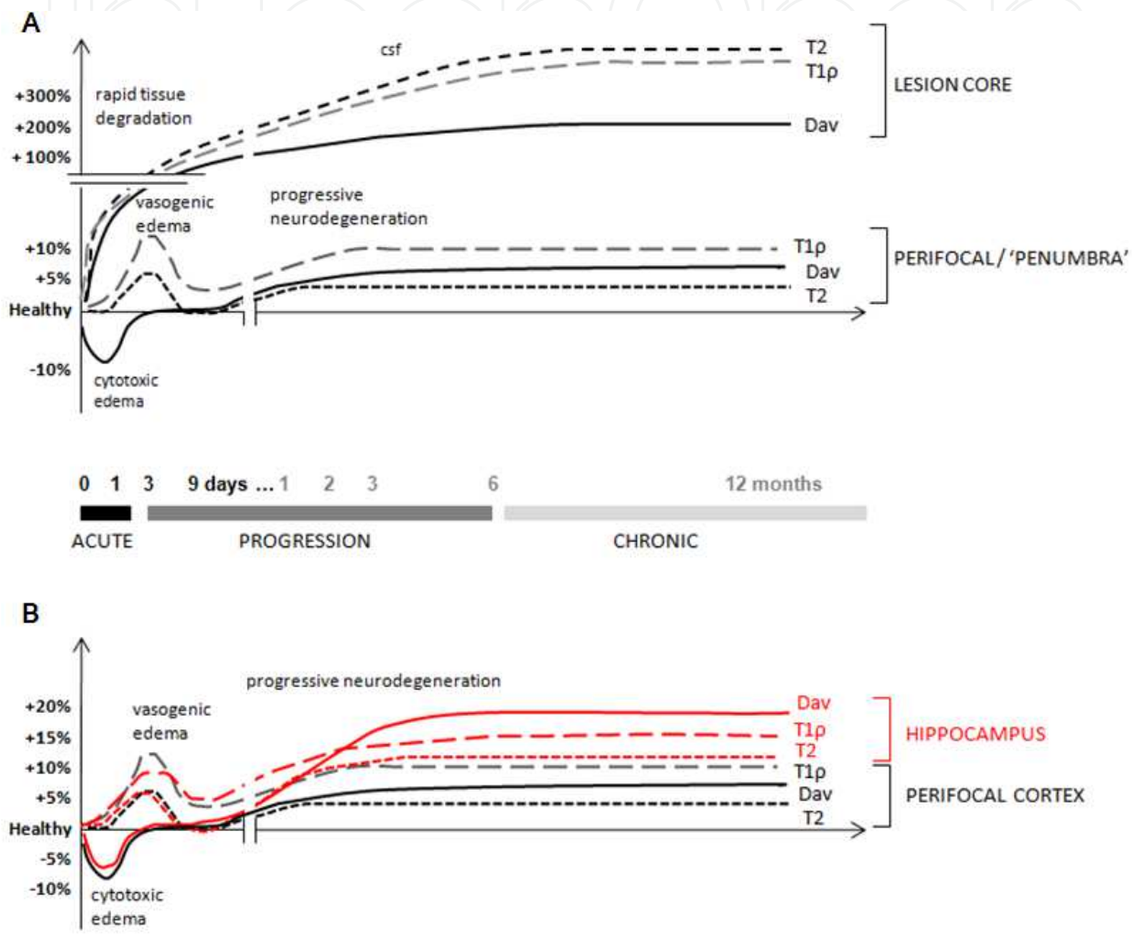

Fig. 4. Schematic graph of the temporal development of average diffusion (D_{av}), T_2 and $T_{1\rho}$ relaxation times over a 1 year period. **A)** Note the differences in both the magnitude and the temporal pattern at the lesion core (irreversible fast damage, values increase by 100-400%) compared to the perilesional region (initial fluctuating values due to transient edema, secondary increase with slow progression, potentially reversible, values increase 5-10%). **B)** When comparing the two main regions at risk: perifocal cortex and ipsilateral hippocampus, the patterns are very similar. The observation that the hippocampus displays somewhat higher secondary alterations (values increase 10-20%) than the perifocal cortical region may partly be a consequence of the perifocal ROI selection (the ROI may include some well preserved cortical tissue). In both cases, the D_{av} and $T_{1\rho}$ seem to be more sensitive than T_2, and when focusing on the time point around day 9 (edema is resolving), the only parameter that does not appear normal is $T_{1\rho}$.

Thus, quantitative MRI has the capability to probe two important characteristics of TBI. First, it is sensitive enough to detect that gray matter alterations continued for several months. While the volume of the primary focal lesion continued to expand for 3 months, the quantitative MRI observations showed progressive changes at the primary cortical lesion site for 6 months. In the perifocal region and in the hippocampus the slow secondary increase in quantitative D_{av}, T_2 and $T_{1\rho}$ continued steadily for the first 2-3 months (significant further increase in the hippocampus until 3 months and in the perifocal area until 2 months).

Secondly, the quantitative MRI is specific enough to discern the irreversible damage and tissue at risk. In the lesion site the drastic increase of all T_2, $T_{1\rho}$ and D_{av}, detectable already 3 hours or 3 days post-injury and rapidly increasing henceforth, was several fold in magnitude as compared to the more subtle alterations detected in the perilesional regions. For example, when considering the situation 9 days after injury, the observed changes at that time in the perilesional regions were maximally +8% (for $T_{1\rho}$) or even undetectable (for T_2 and D_{av}) while in the primary lesion the irreversible damage was revealed by a 70% increase in diffusion, 54% increase in T_2, and 80% increase in $T_{1\rho}$. Thereafter, the lesion values rose up to the values equal to those in CSF, that is, the tissue was absorbed and the cavity filled with CSF was generated (Fig. 4). In addition to the magnitude differences the temporal pattern of MRI changes differed between lesion and surroundings. In the primary lesion the T_2, $T_{1\rho}$ and D_{av} values simply shot up, continuing the rapid irreversible increase, while in the perilesional regions (the perifocal cortical area and the hippocampus) the values first displayed acute edema related increase, recovery, and then a delayed, slow, persistent secondary increase. The magnitude of quantitative MRI contrast parameter deviations during the delayed secondary increase remained around 10-13% for the relaxation times in the ipsilateral hippocampus (4-7% in the contralateral hippocampus and 3-9% in the perifocal area) and around 7-15% for the diffusion in the ipsilateral hippocampus (6-8% in the contralateral hippocampus and 4-6% in the perifocal area). (Immonen et al., 2009ab)

2.3 Diffuse axonal injury

After studying the visually detectable morphological and more subtle gray matter alterations post-TBI, the next major subject of interest is the white matter integrity. White matter shear injury and myelin damage can be selectively probed by MRI. One MRI technique that provides information about diffuse axonal injury (in addition to diffusion tensor imaging and magnetization transfer imaging that are not discussed here) is susceptibility weighted imaging (SWI) that has been reported to detect diffuse axonal injury associated microbleeds after TBI, detailed vascular properties, fine structure of lesions and myelin content related features (particularly in high > 3Tesla field strengths) (Haacke, 2004; Akiyama, 2009). It also distinguishes calcifications due to their diamagnetic properties. SWI utilizes the phase information of MR images in combination with magnitude information, but this phase content can be presented separately to provide phase contrast images or phase maps. This phase contrast is one hot topic in current experimental MRI method development, and even though it is easily transferable to clinical scanners, it is not yet in general use for patient care. Figure 5 shows some recent unpublished preliminary data (by Immonen) with a very robust phase mapping approach in the fluid percussion injury rat model for TBI, and Figure 6 compares the MRI magnitude and phase information to tissue myelin histochemistry of brain sections.

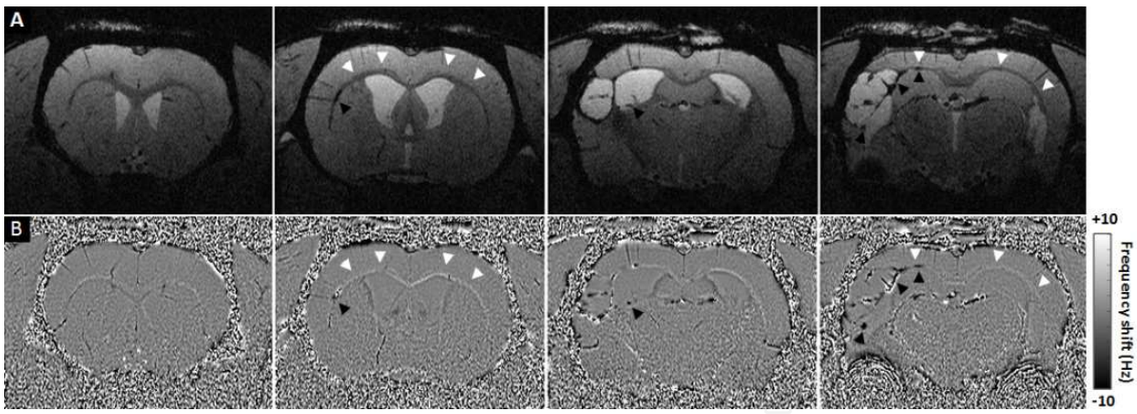

Fig. 5. A) T_2/T_{2^*} weighted magnitude images of a representative rat made one month after lateral fluid percussion injury, and B) corresponding phase maps. The contrast in the phase maps highlights the major white matter tracts (positive frequency shift, white arrowheads) and picks out dark hematomas and microbleeds (negative frequency shift, black arrowheads), while the contrast in surrounding tissue and accross ventricles appears very flat. The main magnetic field B_0 orientation is through the plane and the shown axial slices are 0.2 mm thick.

2.4 From morphology to function - Hemodynamic alterations after TBI

Autoregulation of brain perfusion is impaired after traumatic brain injury. The immediate and focal effects of the impact pressure and stretching of the vessels cause tears and BBB leakage. Blood clots can form and they may cause occlusions that seize the delivery of blood to some regions, which causes ischemia. Both the acute and sub-acute tissue edema and the later developing hydrocephalus can apply extra compression locally or through elevated intracranial pressure. The later changes in regional circulation can be beneficial if they are a controlled physiological response to the increased metabolic demands of the recovery processes. However, if the vascular system is unable to respond to these needs then the situation further deteriorates and can launch adverse cascades. The causal relations and exact mechanisms of autoregulation failure, structural tissue degradation, and functional brain injury development over the course of TBI are still largely unknown.

A valuable MRI method that probes cerebral hemodynamics non-invasively is arterial spin labeling (ASL) technique. This technique yields cerebral blood flow (CBF) maps. In ASL, no exogenous contrast agent is used because the protons in the blood-stream are labeled by an 180° inversion RF-pulse applied at a location covering the incoming vasculature upstream from the level of interest. This technique determines the perfusion rate by quantifying the labeled portion of blood that moves into/through the region of interest (Williams et al., 1992).

In severely brain injured patients three distinct cerebral hemodynamic phases have been recognized based on cerebral blood flow (CBF) changes (Martin et al., 1997): hypoperfusion (decreased CBF during the day of the injury), hyperemia (i.e. increased perfusion in the tissue capillary bed and vasculature during the next 3 days), and vasospasm that invokes a fall in the CBF that lasts for the next two weeks. Particularly, decreased CBF acutely after impact has been documented (Kelly et al., 1996; Kelly et al., 1997; Martin et al., 1997). Long term deviations from the normal CBF level have been depicted, and even patients with symptomatic mild traumatic brain injury but without any other abnormal MRI findings have shown persistent regional hypoperfusion (Bonne et al., 2003).

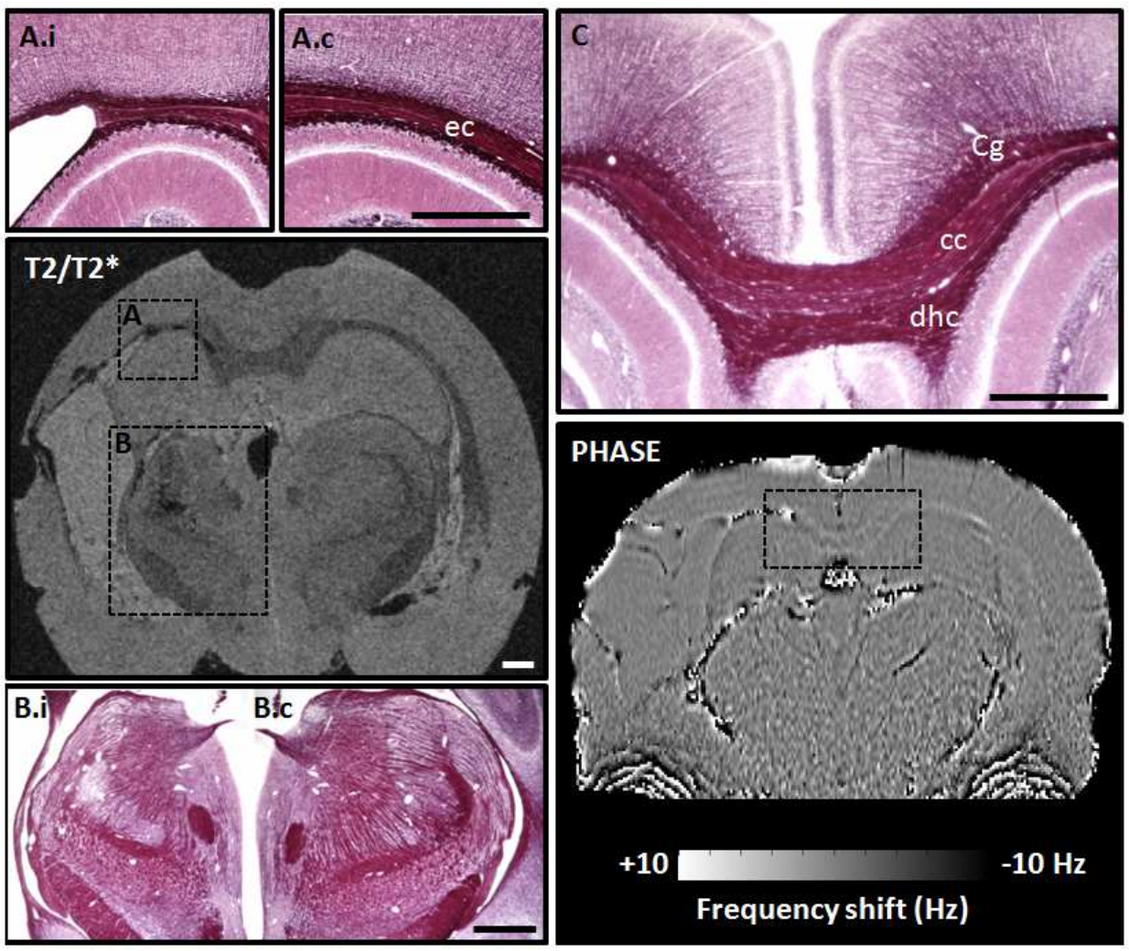

Fig. 6. Histology of the myelinated structures and how they appear in MRI: findings in a TBI rat model. T_2/T_{2*} weighted contrast of fixed trauma brain and myelin stained brain sections of the same animal are shown on the left. The two regions selected (dashed squares on top of T_2/T_{2*} weighted MRI) are highlighting **A**: microbleeds within white matter and associated myelin damage in corpus callosum and external capsule ipsilaterally (A.i) as compared to the contralateral corresponding region (A.c). **B**: Loss of thalamic white matter and myelin structures and formation of calcifications ipsilaterally (B.i) while no myelin pathology occurs contralaterally (B.c). The right side column of the figure shows an in vivo phase map (PHASE) of the same situation and demonstrates the differences in frequency shift between closely located white matter bundles (dashed square in phase map and corresponding region in myelin stained section (C), note the higher frequency shift in cingulum (Cg), dorsal hippocampal commissure (dhc), and external capsule (ec) as compared to the corpus callosum (cc) in between them). The phase contrast reflects the myelin content but depends also on the structure orientation in respect to the main magnetic field B_0 (here, B_0 orientation is through the plane). Abbreviations of indicated white matter bundles: Cg, cingulum; cc, corpus callosum; ec, external capsule; dhc, dorsal hippocampal commissure. Scale bar equals 1 mm.

Hemodynamic disturbances found in experimental models of TBI include local CBF decrease from 15 minutes to 4 hours post-injury close to the LFP site (Ginsberg et al., 1997; Muir et al. 1992; Ozawa et al., 1991) and transient hypoperfusion also in the contralateral hemisphere (Pasco et al., 2007). Perfusion deficits after traumatic impact can lead to a local ischemic state of the tissue where the oxygen and glucose delivery is so severely impaired that it causes disturbances in energy metabolism and mitochondrial function. Dietrich and collaborators report severe ischemia (i.e., mean local CBF < 25 ml/100g/min) after severe TBI (fluid percussion rat model) within lateral parietal cortex, moderate reductions in CBF throughout the traumatized hemisphere, including the frontal and occipital cortices, hippocampus, thalamus, and striatum, along with milder decreases in CBF also throughout the contralateral cerebral cortex. Their parallel histological studies report subarachnoid hemorrhage, blood-brain barrier (BBB) breakdown overlying the pial surface and superficial cortical layers of the injured hemisphere, focal leakage at the gray-white matter interface of the lateral cortex, petechial hemorrhages associated with small venules and focal platelet accumulation. (Dietrich et al., 1994a, 1994b, 1996, 1998).

Although the initiation mechanisms of TBI are more complex than those of ischemia the thresholds for tissue perfusion reductions and adjacent cellular consequences are common for both. The tissue in the ischemic core region suffers irreversible damage when the blood supply drops below a threshold level of around 10-15 ml/100g/min, corresponding to the anoxic cell depolarization (Hossmann and Schuier 1980), and is not restored immediately. The surrounding region, the ischemic penumbra, is hemodynamically compromised and suffers from protein synthesis inhibition [CBF between 35-55 ml/100g/min] and impaired glucose metabolism [CBF 22-35 ml/100g/min] which promotes anaerobic glycolysis, and lactic acidosis (Allen et al., 1993; Obrenovitch et al., 1988). Once the CBF declines below 20 ml/100g/min the adenosine triphosphate (ATP) levels reduce markedly and functional impairment (cessation of evoked potentials and electroencephalographic (EEG) activity) follows. The ischemic penumbra is hemodynamically defined as the region between this functional impairment and anoxic depolarisation, thus it is salvageable if the blood supply is restored acutely. The aforementioned perfusion thresholds are estimates and the factors such as the variability between measurement techniques, tissue types and animal species must be kept in mind (Baron 2001; Takasawa et al., 2008). Regarding the ischemic state of the tissue, perfusion findings are complemented by data from diffusion studies. Diffusion values reduce about 40-50% within hours after severe focal ischemia in experimental models, while thereafter some normalization of values precedes a gradual secondary increase in diffusion (Hoehn-Berlage et al., 1995). The diffusion-perfusion mismatch is a recognized marker for the ischemic penumbra. The mismatch means that the acute diffusion decrease indicates the ischemic core and the region of reduced perfusion extends further to include the penumbra (Baird et al., 1997; Finelli et al., 1992; Pierce et al., 1997; Roberts et al., 1993; Sorensen et al., 1996). Local ischemia can be one consequence of traumatic impact, due to the vascular damage at the primary contusion site or due to blood clots, but otherwise the role of perfusion and blood supply changes in traumatic head injury mechanisms are largely unknown.

Our recent studies in the rat LFPI rat model have highlighted region specific CBF alterations at acute, sub-acute and chronic time points post-injury. Blood flow alterations vary remarkably between perilesional, hippocampal, thalamic, and contralateral areas. Importantly, the animal data shows temporal developments of the autoregulation status that are much like those seen in TBI patients. The three observed phases of the

hemodynamic profile around the lesion are acute hypoperfusion, normalization, and secondary hypoperfusion. The CBF map series in Figures 7 and 8 display the regional perfusion patterns (Hayward et al., 2010).

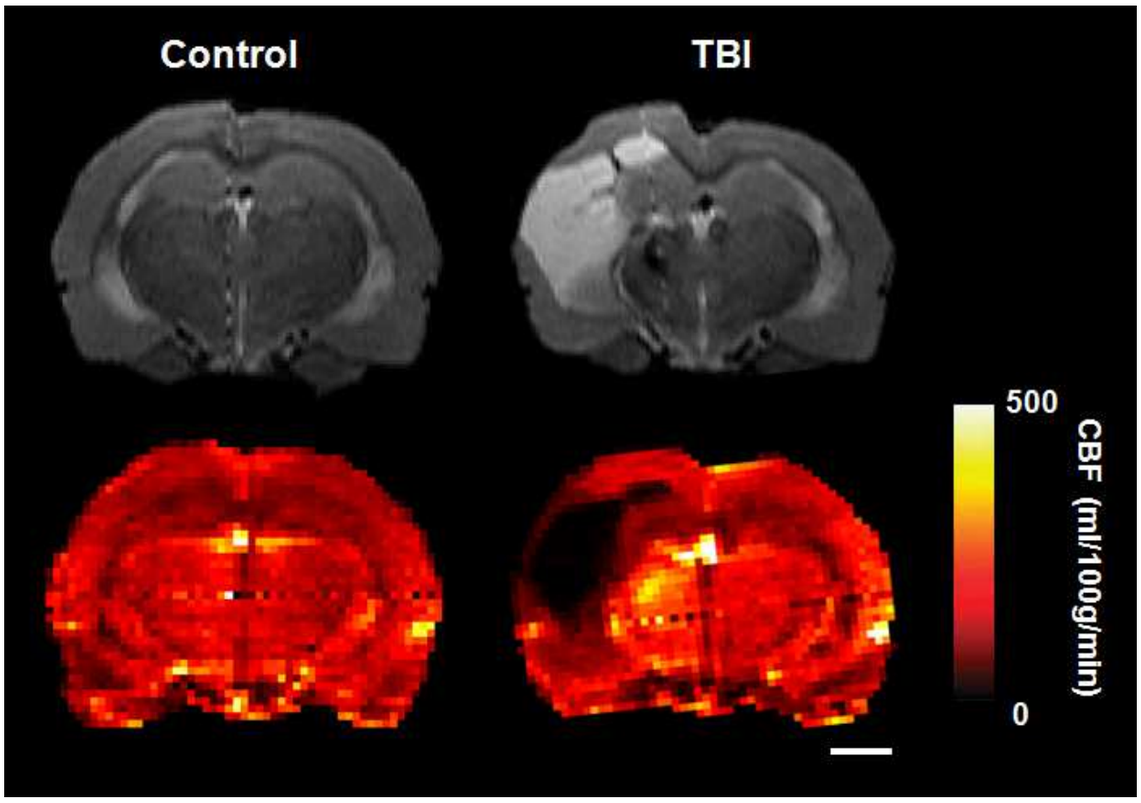

Fig. 7. T_2 weighted images (top row) and cerebral blood flow (CBF) maps measured by arterial spin labeling (bottom row) from a healthy (left) and chronic trauma animal (right, 8 months post LFPI). Note hypoperfusion in the ipsilateral cortex surrounding the cerebrospinal fluid filled cavity (lesion & hydrocephalus) and hyperperfusion in the ipsilateral thalamus in the chronic TBI rat. Scale bar equals 2 mm. (data by Hayward, see further details in Hayward et al., 2010)

It has been shown that immediately after TBI the cytotoxicity leads to increased cerebral glucose utilization while CBF remains low (Ginsberg et al, 1997; Richards et al, 2001). After TBI the decreased CBF results from vasoconstriction induced by endothelium-derived signaling (reviewed in Golding, 2002). This may explain the initial cerebral hypoperfusion we observed after experimental TBI induction. Later, cellular efforts to reestablish ionic gradients (Hovda et al, 1995) lead to hyperglycolysis (Martin et al, 1997) and this may lead to hyperemia. Furthermore, gliosis begins ~24 hours after TBI (Gehrmann et al, 1995; Graham et al, 2000), and demands energy, which may in part be the reason for the recovery of CBF observed at this time point in many regions. Thereafter, vasospasm (Martin et al, 1997) or vasoconstriction caused by delayed vasogenic edema (Rangel-Castilla et al, 2008) may lead to the second hypoperfusion phase we observed.

We compared CBF findings with the immunohistochemistry of the vascular reorganization and density alterations that may be due to post-traumatic angiogenesis (RECA-1 staining).

Each of the investigated brain areas had a unique pattern of vascular abnormalities, but they did not explain the observed MRI CBF results (Figures 7 and 8). At 8 months after TBI in the perilesional cortex, chronic hypoperfusion co-occurred with increased vascular density, while in the ipsilateral hippocampus we observed mild hypoperfusion despite no blood vessel changes. Differently again, hyperperfusion the ipsilateral thalamus was associated with a considerably increased vascular density. Although regional CBF has long been suggested to correlate positively with regional blood vessel density in healthy tissues (Gross et al., 1986), these results indicated very few links between CBF and chronic vascular reorganization after trauma. The fact that we found that the lower the CBF in the perilesional cortex, the higher the vascular density implies that cortical angiogenesis after TBI may not provide new vessels with sufficient vascular integrity to recover the chronic perfusion deficit. Due to the mixed cerebrovascular results from the thalamus and hippocampus, chronic alterations in CBF 8 months post-injury could not be attributed to changes in vascular density.

We have found even fewer links between vascular reorganization and CBF in acute and sub-acute phases after TBI. We reported an acute loss of blood vessel density and subsequent increase between 6 hours and 2 weeks after TBI in the stratum oriens and perilesional cortex. In the perilesional cortex, CBF measures did not correlate with vessel density and it is possible that newly formed vessels may not be fully functional at 2 weeks after TBI. A recent immunohistochemistry study by Park and colleagues (Park et al., 2009) demonstrated cortical blood vessel loss 24 hours after LFPI, which recovered by 2 weeks in moderately injured rats but not in severely injured rats (the TBI rats in Hayward's study all have severe injury). We also observed hypoperfusion in regions without significant vessel loss, such as the thalamus.

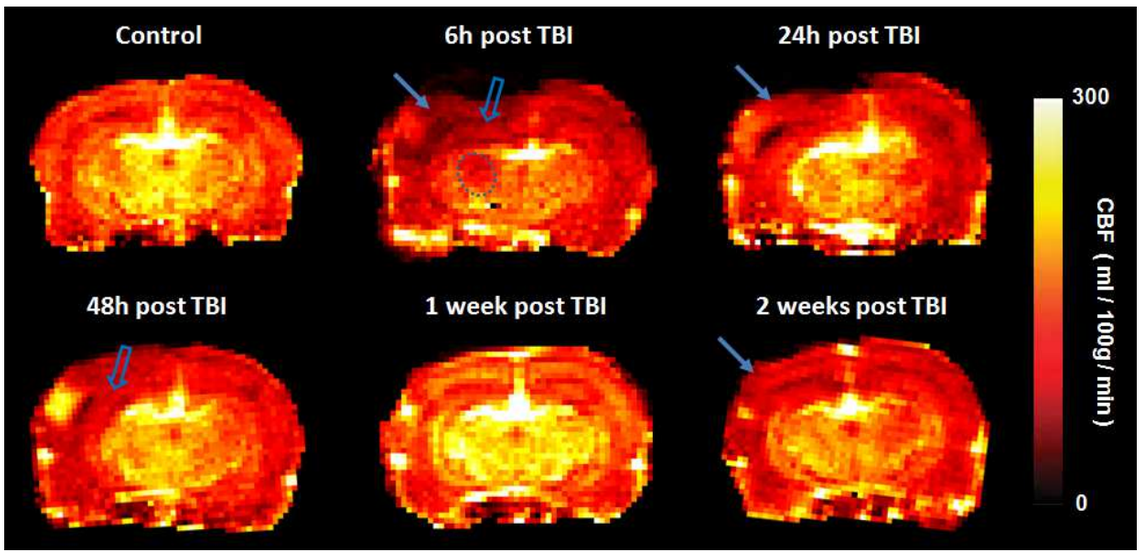

Fig. 8. CBF maps of a control rat (top left) and time series of a representative TBI rat during 2 weeks follow-up after LFPI induction. In the perilesional cortex around the lesion, the flow alterations over time have three phases: acute decrease to 54% of the CBF in controls, recovery, and secondary decrease to 75% of control measures (solid arrows). The ipsilateral hippocampal (open arrows) CBF changes show a similar pattern, but secondary hypoperfusion appears sooner at 48 h. The ipsilateral thalamus suffers from acute hypoperfusion at 6 hours after injury (dashed oval) and displays hyperperfusion 2 weeks later in its subregions. (data by Hayward, see further details in Hayward et al., 2011)

3. Correlation of MRI findings with cognitive deficits and hyperexcitability: can early MRI predict behavioral outcome?

It is of course essential to understand the cellular changes and histologically determined correlates that underlie the observed MRI abnormalities. But equally or even more important is the ability to use MRI as a direct predictor or marker for brain functionality. The morphological MRI findings, alterations in quantitative MR relaxation and diffusion properties and cerebral blood flow changes could all potentially have a role in predicting long-term TBI outcomes such as cognitive impairment, motor deficits or the development of epilepsy. The chance of head injury patients presenting with epilepsy later in life is 16% after moderate brain injury and may be as high as 53% after ballistics or blast injuries (Lowenstein 2009).

In clinical head trauma studies, intracranial and intracerebral hemorrhages have been found to be associated with poor long-term outcome, as assessed with the Glasgow Outcome Scale (Chieregato et al., 2005). Increased diffusivity of white matter structures has been reported to correlate with later impairment of learning and memory functions (Salmond et al., 2006; Sidaros et al., 2008). Magnetization transfer ratio decrease in the corpus callosum and abnormal fractional anisotropy values in several major white matter tracts (obtained by techniques called magnetization transfer imaging and diffusion tensor imaging, respectively) are used to estimate the myelin loss and axonal injury. The severity of these DAI related changes have been found to correlate with cognitive recovery in mild TBI (Belanger et al., 2007). Herniation, due to a swollen ipsilateral hemisphere can be seen as midline shift in MRI and it has been listed as a risk factor for human post traumatic epilepsy (Pitkänen et al., 2011). Metting and colleagues reviewed the early MRI findings with predictive values for chronic outcome in mild-to-moderate head injury (defined by having Glasgow Coma Score > 8) (Metting et al., 2007). The list included the number of lesions (detected by a T_2* weighted gradient echo technique), lesion size, perfusion abnormalities and reduced cerebral blood volume observed days to weeks (< 3 weeks) post-injury. These early findings could be linked to outcome at 3 to 12 months later.

In experimental research, many of the factors contributing to long term outcome after brain injury can be controlled for and monitored. Our follow-up studies in the LFPI rat model have yielded many potential MRI surrogate markers for neurodegeneration, memory deficits and epileptogenesis. As outcome measures, the final atrophy extent 6 months post-injury, spatial memory and learning ability tested in Morris Water maze 7 months post-injury, and histopathological neuronal loss 12 months post-injury were assessed. At the chronic phase after TBI the animals displayed largely expanded lesion cavities, the ipsilateral hippocampal volume was decreased by 21%, the number of hilar neurons was decreased by 63% and the hippocampus related learning and memory performance was impaired in trauma animals. Non-invasive MRI was performed frequently over the course of disease progression. The lesion volume measured and the amount of intracerebral hemorrhage in the acute (3 hours) and sub-acute (3-23 days) phases after injury correlated with the final lesion extent 6 months later. The $T_{1\rho}$ increase in the perifocal area surrounding the lesion at 9 days post-injury correlated with the final cortical lesion volume. The edema related transient increase in $T_{1\rho}$ and T_2 in the ipsilateral hippocampus 3 days post-injury correlated with the chronic volume reduction of the ipsilateral hippocampus and with the hilar neuron loss (in the dentate gyrus of the hippocampus) - and so did the $T_{1\rho}$ increase 9 days post-injury. The delayed secondary increase 23 days post-injury in $T_{1\rho}$, T_2 and D_{av} in

the ipsilateral hippocampus, which was already an indicator of the severity of the secondary injury cascades, correlated with the later hippocampal volume decrease at 6 months and with the final hilar neuron loss. This same delayed diffusion increase (in the ipsilateral hippocampus 23 days post-injury) correlated also with the long-term learning impairment 7 months post-injury. Also, the severity of hemorrhage at the sub acute phase was indicative of long-term learning impairment. See the behavioural test and correlation details in Immonen et al., 2009a. Upon assessing the risk for posttraumatic epilepsy, we have shown that acute diffusion drop 3 hours post lateral fluid percussion injury has predictive value for seizure susceptibility one year later (Kharatishvili et al., 2007).

The causal relationship between hemodynamic alterations and behavioral symptoms is still under investigation and the studies presented here, using arterial spin labeling technique for CBF mapping (Hayward et al., 2010), touched the surface by showing that enhanced seizure susceptibility post TBI was associated with reduced CBF in the ipsilateral hippocampus ($r = 0.78$, $p < 0.05$) and increased vascular density in the thalamus ($r = 0.69$, $p < 0.05$). Although the perilesional cortex may generate ictal activity after LFPI (D'Ambrosio et al., 2004, 2005, Kharatishvili et al. 2006), we did not find any association between the hypoperfusion or increased vascular density in the perilesional cortex and seizure susceptibility. This might be because injury to more caudal cortical areas associates with hyperexcitability, while the cortical regions close to the lesion may not be involved (Kharatishvili and Pitkänen 2010a). More importantly, we found that a reduction in the ipsilateral hippocampal CBF at 8 months after TBI was associated with increased seizure susceptibility at 9 months such that the lower the CBF, the higher the seizure susceptibility. Circuitry alterations and cerebrovascular responses in the hippocampus are common in experimental epilepsy and in epilepsy patients (Pitkänen and Lukasiuk 2009, Ndode-Ekane et al. 2010) and the ipsilateral hippocampus is involved in electrographic activity during spontaneous seizures after TBI (Kharatishvili et al. 2006). Indeed, previous reports have used ASL together with other neuroimaging techniques to delineate the ictogenic zone (Rougier et al. 1999, Lim et al. 2008). Further studies are needed, however, to discern whether chronic hippocampal hypoperfusion after TBI can be used as a surrogate marker for epileptogenesis.

Our study did not yield any correlations between CBF changes and memory and learning impairment, but poor performance in the Morris water maze was found to correlate with enhanced thalamic vessel density ($r = -0.81$, $p < 0.01$). The thalamus is often found to be damaged in moderate and severely injured TBI patients as well as in animal models (Pierce et al. 1998, Maxwell et al. 2004, 2006, Tollard et al. 2009, Little et al. 2010), but the role of the thalamic pathology in epileptogenesis after acquired etiologies like TBI is poorly understood (Bonilha et al. 2004, Blumenfeld et al. 2009). We also found that a high vessel density in the ipsilateral thalamus was associated with increased CBF and enhanced seizure susceptibility in injured rats. A recent clinical report measured increased thalamic CBF during secondary generalization of focal onset seizures (Blumenfeld et al. 2009). Still, one must be cautious with the interpretation of such clinical and preclinical correlations and keep in mind that in most of the cases it is still unclear whether the cerebrovascular sequelae is the cause or the consequence of abnormal neural activity.

4. Conclusions

This chapter introduced several different MRI techniques and how each of them aid in probing TBI pathology. Techniques target features at the micro- and macro size scales, gray

matter pathology, white matter injury, and hemodynamic disturbances. Non-invasive MRI has been demonstrated to be a highly sensitive and valuable tool in progressive brain disease research and care. The temporal pattern and magnitude of measured T_2, $T_{1\rho}$, D_{av}, and CBF changes varied substantially between brain regions highlighting how quantitative MRI can be used to differentiate the regions with risk of delayed secondary damage from those of continuously progressing irreversible damage or from the normal areas. Importantly, quantitative MRI can also identify how advanced the pathological processes in each region are, which is a major advantage in targeting treatments and following the treatment response.

Considering the prognostic value of early MRI findings in evaluating long term outcomes, many of the promising singular MRI findings and their correlations with outcome are lacking in specificity, and thus we must continue to search for more robust MRI markers. In particular, the multimodal approach and utilization of a combination of different MRI parameters for more sensitive and specific prediction paradigm is on the rise. A series of reviews emphasized the need for predictive markers (Belanger et al., 2007; Catroppa et al., 2008; Gallagher, Hutchinson, Pickard 2007; Kharatishvili and Pitkänen 2010b, Lewine et al., 2007; Metting et al., 2007, Pitkänen et al., 2009a, 2009b, 2011).

The MRI techniques discussed in this chapter are only a fraction of all available non-invasive MRI 'probes'. Furthermore, there is a wealth of information about the metabolic alterations in TBI accessible by variety of MR spectroscopy techniques.

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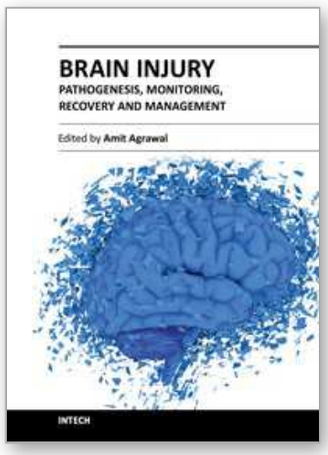

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The present two volume book "Brain Injury" is distinctive in its presentation and includes a wealth of updated information on many aspects in the field of brain injury. The Book is devoted to the pathogenesis of brain injury, concepts in cerebral blood flow and metabolism, investigative approaches and monitoring of brain injured, different protective mechanisms and recovery and management approach to these individuals, functional and endocrine aspects of brain injuries, approaches to rehabilitation of brain injured and preventive aspects of traumatic brain injuries. The collective contribution from experts in brain injury research area would be successfully conveyed to the readers and readers will find this book to be a valuable guide to further develop their understanding about brain injury.

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