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Traumatic brain injury and the frontal lobes: What can we gain with diffusion tensor imaging?

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ABSTRACT

Traumatic brain injury (TBI) is a leading cause of death in the young population and long-term disability in relation to pervasive cognitive–behavioural disturbances that follow frontal lobe damage. To date, emphasis has been placed primarily on the clinical correlates of frontal cortex damage, whilst identification of the contribution of subjacent white matter lesion is less clear. Our poor understanding of white matter pathology in TBI is primarily due to the low sensitivity of conventional neuroimaging to identify pathological changes in less severe traumatic injury and the lack of methods to localise white matter pathology onto individual frontal lobe connections. In this paper we focus on the potential contribution of diffusion tensor imaging (DTI) to TBI. Our review of the current literature supports the conclusion that DTI is particularly sensitive to changes in the microstructure of frontal white matter, thus providing a valuable biomarker of the severity of traumatic injury and prognostic indicator of recovery of function. Furthermore we propose an atlas approach to TBI to map white matter lesions onto individual tracts. In the cases presented here we showed a direct correspondence between the clinical manifestations of the patients and the damage to specific white matter tracts. We are confident that in the near future the application of DTI to TBI will improve our understanding of the complex and heterogeneous clinical symptomatology which follows a TBI, especially mild and moderate head injury, which still represents 70–80% of all clinical population.

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1. Introduction

Traumatic brain injury (TBI) is reported at all ages and is a leading cause of disability among citizens younger than 45 years of age, affecting about 235 cases per 100,000 individuals each year in most Western societies (Tagliaferri et al.,

2006). In 1990, estimates of worldwide TBI requiring medical care or resulting in death were reported at 9,500,000 persons (Thurman et al., 2007), attributed to enormous public health costs and burdens. Despite its frequency, pathophysiological mechanisms of TBI remain poorly understood (Zappalà, 2008; Jennett, 1978; Gualtieri, 1995).

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TBI produces rapid deformation of the brain, resulting in a cascade of specific pathological events. The resulting changes in the anatomy and neurophysiology of the brain can disrupt multiple cerebral networks affecting cognitive, autonomic and emotional functions, as well as other aspects of behaviour (Eslinger et al., 2007). Damage to brain connections, involving widely distributed brain networks, is a crucial factor in the development of cognitive impairment (Mesulam, 1998). Diffuse axonal injury, more recently referred to as traumatic axonal injury, occurs in most TBI after motor vehicle collisions and falls, in which deceleration and rotational forces cause a shearing of the brain's white matter, especially within the frontal lobes (Marquez de La Plata et al., 2011). After a TBI, the integrity of white matter is correlated with the severity of the injury, as well as the outcome. Kraus et al. (2007) documented that reduction in the integrity of various white matter structures was associated with poorer performance on measures of attention, memory and executive functions. TBI produces a complex pattern of diffuse axonal injury at variable locations across individuals, rendering it difficult to localise white matter disruption (Kinnunen et al., 2011). Although, white matter disruption is an important determinant of cognitive impairment after TBI, conventional neuroimaging underestimates its extent.

Diffusion tensor imaging (DTI) is a novel neuroimaging method for studying *in vivo* the anatomy and integrity of white matter tracts in the human brain (Lawes et al., 2008; Beaulieu, 2009; Thiebaut de Schotten et al., 2011). Recent studies suggest that DTI may provide more sensitive measurements of discrete axonal injury in TBI compared to other neuroimaging methods not only in the acute phase but also after the traumatic injury in the chronic stage (Thomas et al., 2009, 2011; Rimrodt et al., 2010; Charlton et al., 2010; Arfanakis et al., 2002; Assaf and Pasternak, 2008). Anatomical information derived from DTI atlases can also be used to assess the extension of the white matter damage in TBI. In this article we focus on the impact of physical and neuropathological causes of TBI on white matter damage and describe three single cases representatives of the typical clinical profiles observed following TBI. We then use a recently published white matter atlas of human brain connections derived from DTI tractography to identify the extension of the injury to underlying white matter tracts (Catani and Thiebaut de Schotten, *in press*). Finally, we briefly review the preliminary results reported in studies employing DTI to measure axonal injury in TBI.

2. Physical and neuropathological causes of TBI

Traumatic injury mechanisms encompass a cascade of events, that produce widespread, multifocal, diffuse damage that varies according to the severity of the impact. Three mechanisms have been described.

A combination of *physical and mechanical forces* following a *coup-contrecoup* blow causes lacerations mostly in the frontal, temporo-polar and occipital areas due to the brain impacting against the base of the skull. The resulting damage is greater for closed TBI where the skull is not fractured and the pressure waves are directed inwardly towards discrete areas of impact. These lacerations can cause localised contusions, bruising of tissue and damage to the vessels, leading to bleeding.

Shearing and stretching forces lead to traumatic axonal injury (TAI), which includes petechial hemorrhages and deep white matter degeneration. Changes to vessels' membranes in brain regions at the junction between gray and white matter (WM) contribute to axonal injury in the chronic stage (Li and Feng, 2009).

Finally, *angular and rotational forces* lacerate the brain tissue due to a centrifugal acceleration, with significant damage to the mid-sagittal anterior and ventral cortical regions and underlying deep white matter connections to the striatum and the brainstem.

The neuropathological changes of TBI are directly related to the initial severity of the injury classified according to the Glasgow Coma Scale (GCS) in: (i) *severe injury* (GCS between 3 and 8), (ii) *moderate injury* (GCS between 9 and 12), and (iii) *minor (or mild) injury* (GCS between 13 and 15). Brain abnormalities in severe injury are easily detected with conventional neuro-radiologic scans (CT scan or MRI). These include "primary" cerebral insults like focal contusions, skull fractures, subdural haematomas and white matter damage. "Secondary" damage follows hypoxia, focal ischaemic injury, and occasionally anoxia of sensitive cerebral areas like the hippocampus (Sidaros et al., 2009; El-Sayed et al., 2008; Gaetz, 2004; Gennarelli et al., 1982; Zappalà and Trexler, 1992). In mild injury, brain damage is often not visible on conventional MRI, despite diffuse axonal injury being responsible for most of the behavioural and neurocognitive consequences (Arfanakis et al., 2002; Hashimoto et al., 2007; Inglese et al., 2005; Pontifex et al., 2009; Wilde et al., 2008; Lee and Newberg, 2005; Levine et al., 2006).

3. Clinical profiles following TBI

Clinical profiles of TBI are highly variable and present themselves along a spectrum of severity that depends on the intensity and site of the injury. In mild and moderate TBI, the traumatic forces are more frequently localised to the orbito-frontal and temporal polar zones including the amygdala and anterior hippocampus. These regions are interconnected via the *uncinate fasciculus*, a bilateral tract involved in memory, inhibition and emotion processing. The clinical manifestations associated with damage to the fronto-temporal connections are often a mixture of behavioural, cognitive and affective symptoms that include personality disintegration, coping disturbances and impulsive control of behaviour. Attentional impairment and executive function deficits are also frequently observed. Disinhibited behaviour is the distinctive feature of the 'pseudo-psychopathic syndrome', which is often observed in patients with orbitofrontal damage. In these patients disinhibited behaviour is accompanied by irritability, egocentrism, childishness, stubbornness as well as tactless, aggressive and abusive behaviour. Many of these symptoms are difficult to assess with current test batteries (Zald and Andreotti, 2010). Usually a combination of behavioural examinations and clinical analysis of real-world functioning is necessary to reveal the functional impairment.

In more severe TBI, patients are more likely to present with an abulic or a dysexecutive syndrome in which, the traumatic damage can extend either towards more cortical and subcortical medial frontal regions (including the descending

frontostriatal and ascending thalamo-frontal projections, head of the caudate, putamen, pallidum and their connections) or towards dorsolateral convexity of the frontal lobes and underlying associative and projection fibres (Trexler and Zappalà, 1988; Zappalà, 2008). When damage involves predominantly medial and subcortical frontal regions, including the anterior cingulum, corticostriatal and thalamo-frontal projection systems, TBI patients develop disinterest, lethargy, reduced drive and lack of initiative, clinically resembling an abulic, amotivational or pseudo-depressed state. When traumatic lesions involve the dorsolateral frontal cortex and association and projective connections, patients show significant impairments of executive functions, including working memory deficits, lack of insight, reduced reasoning and set-shifting, defective linguistic or visuospatial abilities. These patients are cognitively severely impaired, a clinical profile that often mimics a condition of ‘pseudo-dementia’. The correspondence between lesion location and clinical manifestations is, however, influenced by other factors such as, pre-morbid personality and other demographic characteristics including education, gender, and age (Gouick and Gentleman, 2004; Henry et al., 2006; Lucas, 1999; Mateer and Sira, 2006; McDonald and Flanagan, 2004).

With regard to age most TBI victims are in their second decade of life, presumably in their last phase of cerebral maturation where myelination of prefrontal tracts has not yet been completed. Hence, TBI in this young victims affects “crucial zones” of behavioural regulation, still in the final phase of their maturation. For this reason Kolb and Whishaw (1990) highlighted that cognitive and behavioural abilities in youngest victims of TBI are not just lost, but not yet developed. On the other end of the life-span, TBI occurs more frequently as a consequence of a fall. In these cases, the TBI can compound age-associated neural and cognitive changes, damaging fragile neural networks, and leading to more complex symptoms and slower recovery rate (Bhullar et al., 2010; Senathi-Raja et al., 2010).

In summary, the predominant patterns of behavioural, abulic and dysexecutive syndromes have a close correspondence with orbitofrontal, medial and dorsolateral frontal damage respectively. Syndromes have been classically correlated with cortical damage to these regions and little is known on the contribution of white matter damage to specific syndromes. There is evidence that the study of frontal white matter involvement in TBI could be an important predictive factor for recovery (Eslinger et al., 1995). In the following section we propose an atlas approach to TBI for the exact localisation of the injury to specific white matter bundles underlying cognitive, affective and behavioural functions.

4. An atlas approach to TBI

In the last 10 years the advent of DTI has permitted to create normalised average maps of the major white matter connections. These atlases allow to identify affected tracts in patients with lesions extending into the deep white matter. In this section we describe three single cases of TBI representative of each clinical syndrome described above. To identify frontal white matter damage induced by TBI, the T1 or T2 structural images of these three subjects with TBI were normalized in the MNI with SPM5 using affine (12 degrees of freedom) and elastic

(16 iterations) transformation and superimposed onto the corresponding slices from a recently published DTI Atlas (for more details see Thiebaut de Schotten et al., 2008; Thiebaut de Schotten et al., 2011). The overall visualization and screenshots were performed in Anatomist (<http://brainvisa.info>). The cases are presented and discussed to highlight the advantages and limitations of the atlas approach to TBI.

4.1. A.M.: a case of minor TBI – behavioural – “pseudo-psychopathic” syndrome

A 28-year-old right-handed male, highly educated, came to our attention after an apparent minor accident, which occurred 10 years earlier. He reported a brief loss of consciousness at the time of the injury and a short period of hospitalisation. Neuro-radiologic examination demonstrated a linear skull fracture of the right occipital squama, a minor right frontal contusion and a thin subdural haematoma on right fronto-parietal area. He was discharged after a few days without showing clinical signs or cognitive disturbances. After some time, he noticed hyposmia (reduced smell) and hypogeusia (reduced taste), irritability, strange tactile misperceptions on the left side of his body, mood swings, depression and, above all, distractibility and social inappropriateness.

Neurocognitive examination did not reveal any significant disturbances, except on the interference trial of the Stroop test. His Digit span was equal to 6 (forward) and 4 (reverse) denoting a mild impairment given his high education; the Corsi span was equal to 6 (forward) and 6 (reverse); The California verbal learning test (CVLT) and Rey’s Figure were within normal range; and semantic fluency was broadly average (20 words in 1 min). Low performances in complex attention and psychomotor performance tasks were reported when using computerised attentional assessment. Problems with his sense of smell and taste, irritability, and tactile misperceptions on his left side, especially in his face and neck were also noticed during the clinical examination. An anatomical MRI clearly demonstrated a significant area of residual bilateral damage in the region of the piriform cortex (responsible for his hyposmia and hypogeusia) and TAI involving bilateral fronto-basal and fronto-polar areas (see Figure below) affecting frontolimbic and frontostriatal pathways. He was placed on low-dose of Carbamazepine (100 mg/b.i.d), given its psychotropic activity on fronto-temporal association cortex (see Fig. 1; yellow arrows pinpoint to residual focal damage). The MRI shows a residual damage in the anterior frontal lobe area still visible 10 years after the injury. This damage enclosed the bilateral piriform cortex (orbitofrontal area) and predominantly left polar frontal cortex. Given the very small visible residual damage in the anteriormost aspect of the frontal lobes, we did not use the DTI atlas in this case.

4.2. P.M.: a case of moderate TBI victim – “abulic” syndrome

A 47-year-old male (5 years of schooling) accidentally fell during the night, whilst in his house during March 2009. His fall was followed with a prolonged loss of consciousness and a post-traumatic amnesia (PTA), which lasted more than 6 h. When he awoke, the patient showed an agitated behaviour and his GCS was equal to 11/15. An MRI scan revealed a TAI

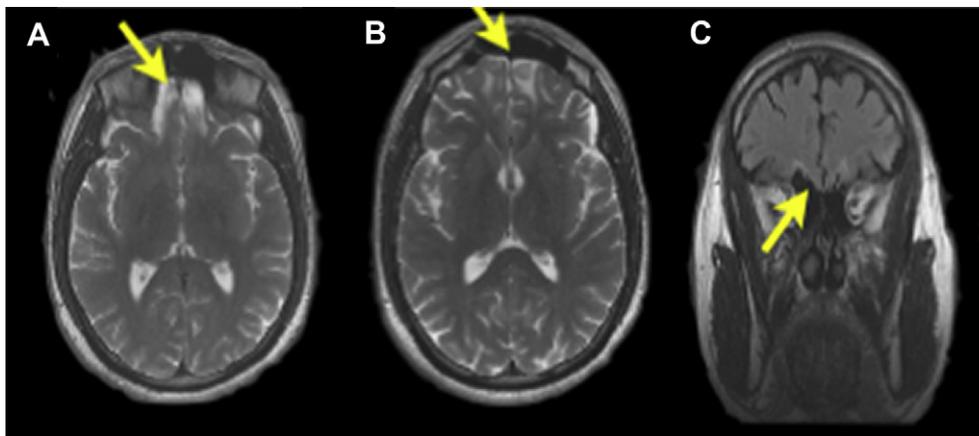


Fig. 1 – A case of minor TBI with a behavioural syndrome. Conventional MRI scans illustrating the identifiable damages (yellow arrows) using T1 (A and B) T2 (C) contrasts.

bilaterally situated in anterior frontal and medial frontal areas (Left > Right); there was evidence of brain contusions and small hemorrhages in left medio-frontal region (see MRI below). His clinical examination revealed a depressive mood, the presence of anxiety, a lack of initiation, a reduced sexual drive, reduced self-esteem, a lack of interest (which did not improve after antidepressant therapy) and the loss of the senses of smell and taste. He was aware of his reduced work competence and ability, not being able to keep track of his activity, duties, work orders, etc. He was discovering significant short-term memory problems and felt discouraged, not being able to change his mood or performance.

A neurocognitive exam revealed a reduced attention span (5/3 verbal and 5/4 spatial); a flat learning curve on the CVLT (total of 26/80 words recalled and 4, 3, 6, 6, 7 free recalls over the five trials; very defective clustering capacity with only 4/60 possible clusters; STM 3; LTM 3; Recognition 13/16) good visuospatial skills on Rey's Figure copy but very poor performance on recall attempt (see Fig. 2).

The patient was re-evaluated 1 year later. Re-adaptation in competitive world was still lacking; he was pursuing workmen's compensation. He still complained of hyposmia and hypogeusia, low desire and drive, mood swings, fatigue, a lack of initiative, low attentional skills and "memory loss". His performance in the working environment was never satisfactory due to easy distractibility and low stress tolerance. He was on medications, with low-dose of Carbamazepine, which helped with his mood swings and sertraline for his depressed mood and apathy. The overlap of the MRI scan with a probabilistic atlas of the white matter pathway (Thiebaut de Schotten et al., 2011) suggests an impairment of left anterior cingulate cortex (in red) and left uncinate fasciculus (in blue) (Fig. 2D).

4.3. A.G.: a case of severe TBI victim – cognitive "dysexecutive" syndrome

A 48-year-old right-handed male (low schooling) following 3 days of high-fever, suddenly collapsed last year on the floor and crushed the back of his head, without a skull fracture. He entered a coma and was hospitalised with a large left frontal

intracerebral haematoma (see Fig. 3). Two weeks later he was still stuporous, mildly aphasic, mildly hemiparetic on the right side. He was aware, although densely amnesic from the sudden fall. His retrograde amnesia was long-lasting but his behaviour remained very appropriate.

His Neurocognitive examination revealed a low verbal span (F4/B3); an average spatial span (F6/B4); a flat learning curve on the CVLT (6, 5, 6, 6, 7 over the five learning trials; total words: 30; STM 4; LTM 4; Recognition 9/16 – demonstrating a clear problem during the learning phase where clusters were almost absent, showing severe semantic strategy defect); he also presented with 8 errors on the Stroop test; a low score of 40 out of 60 on confrontation naming (Boston naming test); psychomotor speed, verbal memory and reaction times were defective on a computerized test (CNS-VS). He was placed on low-dose of Carbamazepine and a low-dose of an antidepressant. The patient was re-evaluated 1 year later. He regained confidence and resumed his position in his firm, but still necessitates help from his wife in handling complex organisation and money issues. The patient feels improved, but not yet at his pre-morbid usual capacity. No medico-legal or insurance controversies interfered with his recovery. The overlap of the MRI scan with a probabilistic atlas of the white matter pathway (Thiebaut de Schotten et al., 2011) suggests an impairment of left anterior cingulate cortex (in red), the corpus callosum (in blue) and the LEFT inferior fronto-occipital fasciculus (IFOF in green).

5. DTI in TBI

Based on the aforementioned cases, as well as available clinical literature, it is clear that imaging of the damage resulting from TBI remains limited. Thus patients with diffuse cerebral damage, secondary to TBI, often chronically exhibit cognitive and behavioural disorders, although CT and conventional MRI scans can be frequently normal or show lesions poorly related to the nature and severity of cognitive post-traumatic disturbances (Fig. 4) (Sugiyama et al., 2007).

DTI is a less conventional and relatively new MRI modality that provides in vivo indices (i.e.: average diffusion

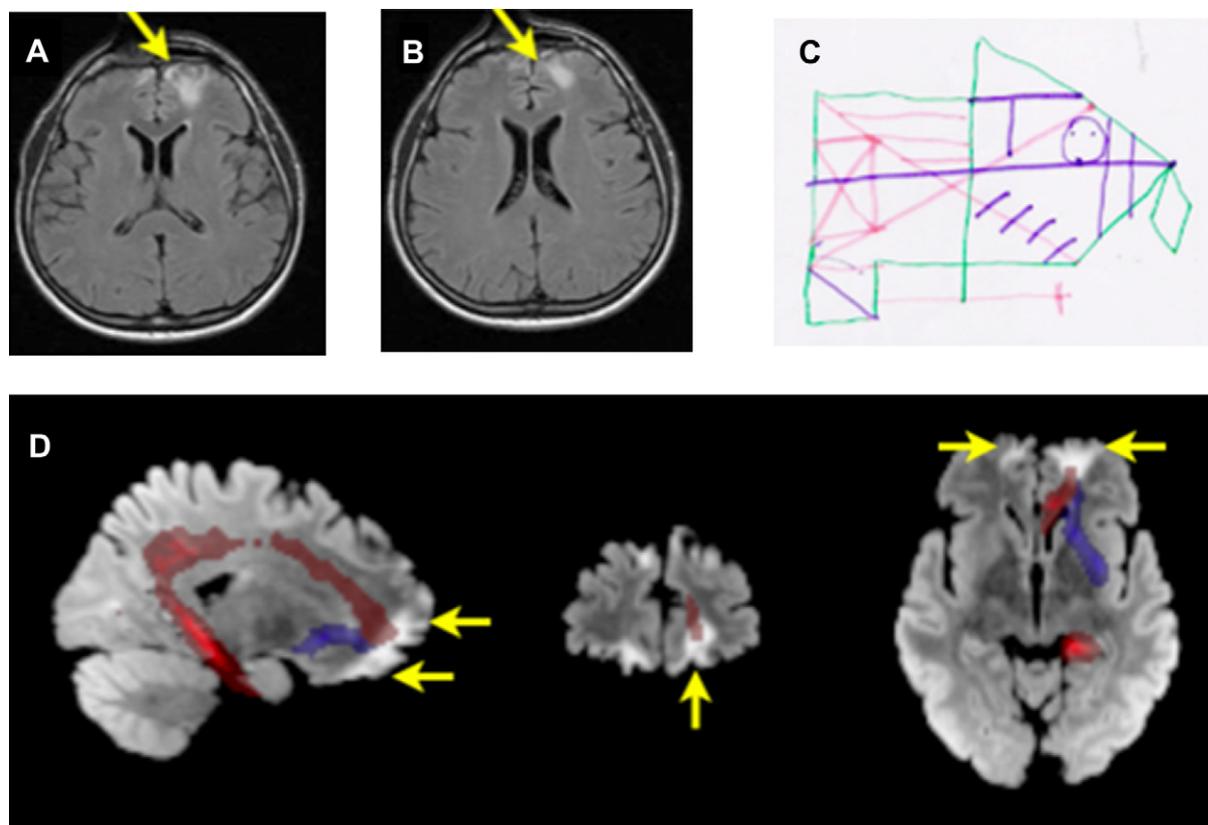


Fig. 2 – A case of moderate TBI victim with an abulic syndrome. MRI scans illustrating the identifiable damages (yellow arrows) using T1 (A and B) contrast. Copy of Rey's Complex Figure (C). The overlap of the MRI scan with a probabilistic atlas of the white matter pathway (Thiebaut de Schotten et al., 2011) suggests an impairment of left anterior cingulate cortex (red) and left uncinate fasciculus (blue) (D).

coefficient – ADC, fractional anisotropy – FA etc.) regarding the degree of water diffusion in the brain and from which it is possible to reconstruct white matter connections (Basser et al., 1994). In the absence of resistance in the brain, water will diffuse randomly (isotropic diffusion) and is associated with a high ADC and low FA. In the tight organisation of the axons in the brain, white matter coerces the water to diffuse in a more uniform direction parallel to the axons (for a review see Jones, 2008). This phenomenon is referred to as FA and is associated with a low ADC and a high FA.

In the acute stage of a traumatic lesion, the cellular swelling will increase the FA and decrease the ADC as the water diffusion is more constrained to one direction. In the chronic stage, this effect will be reversed as the membrane degradation and the cellular lysis will give more space for water to diffuse and then increase the ADC and decrease the FA. Jones et al. were the first to report a narrow band of tissue showing a reduction of diffusion without any associated differences on classical head injury scans. This study demonstrated the advantage of using information contained within the DTI, in addition to more conventional imaging sequences. Based on these observations, we briefly review DTI analysis of TBI that utilized three different approaches:

- (a) Whole brain voxel-based analysis;
- (b) Region of interest (ROI) analysis; and
- (c) In vivo tractography.

(a) Whole brain voxel-based DTI analysis is an operator-independent approach that allows the analysis of the entire brain volume without a-priori hypotheses regarding the anatomical location of between group differences or correlations. Using this approach it is difficult to attribute a significant cluster to a single tract (Catani, 2006). Despite this limitation, patients with a minor TBI showed axonal deterioration in comparison to controls (Bazarian et al., 2007; Lipton et al., 2009). Reduced FA values for the TBI subjects were detected in the genu of corpus callosum, posterior limb of internal capsule, superior longitudinal fasciculus, superior fronto-occipital fasciculus, and centrum semiovale (Yuan et al., 2007). Within the TBI group, the whole DTI voxel based was also correlated with the gradient of TBI severity and revealed GCS scores positively correlated with FA in several WM areas including the corpus callosum, the posterior limb of the internal capsule, the superior longitudinal fasciculus, the cortico-spinal tract, the superior occipito frontal fasciculus and the inferior occipito frontal fasciculus (Yuan et al., 2007). These observations revealed that after a TBI, DTI measure of the white matter damage could be a good predictor of the initial severity of the trauma. However, the evolution of this damage in time is not correlated with the success in the rehabilitation of the patient, as neural reorganisation occurs, that may be better detected by functional MRI analysis.

(b) Another approach consists of defining a ROI to identify between group differences or correlations in a specific brain

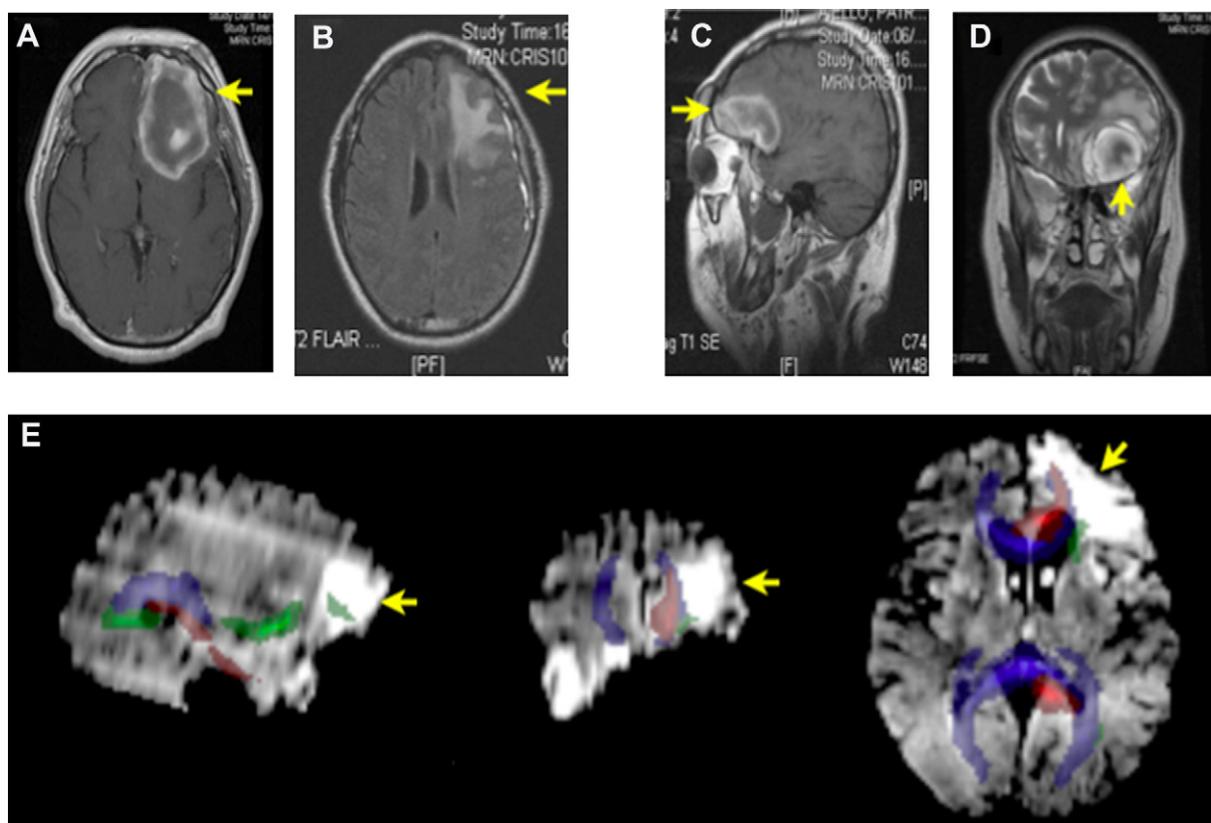


Fig. 3 – A case of severe TBI victim with a dysexecutive syndrome. MRI scans illustrating the identifiable damages (yellow arrows) using T1 (A, B and C) and T2 (D) contrasts. The overlap of the MRI scan with a probabilistic atlas of the white matter pathway (Thiebaut de Schotten et al., 2011) suggests an impairment of left anterior cingulate cortex (red), anterior corpus callosum (blue) and inferior fronto-occipital fasciculus- IFOF (green) (E).

region. This approach may lack sufficient statistical power due to the high degree of intra and inter-subject variation of the anatomy and the FA values, even within a highly homogenous tract (Catani, 2006). Despite these limitations, group comparisons reported lower ADC and higher FA values in TBI subjects when compared to controls (Hou et al., 2007; Newcombe and Russell, 1969). Analysis of ROIs also showed that FA values of the genu, stem, and splenium of the corpus callosum, and the columns of the fornix were lower in patients with TBI than in the healthy controls (Nakayama et al., 2006). Bazarian et al. (2007) identified a significantly lower ADC in the left anterior internal capsule and higher maximum ROI-specific median FA values in the posterior corpus callosum in minor TBI. These FA values correlated with control and motor neurobehavioral tests and were predictive of the duration of a coma. Niogi et al. also observed a correlation between specific neuropsychological assessment and ROI measurement. In particular, attentional control correlated with FA in the anterior part of the left corona radiata, and memory performance correlated with FA in the uncinate fasciculus (Niogi et al., 2008).

(c) DTI also provides the opportunity to perform *in vivo* tractography or ‘virtual dissections’ of the major white matter pathways (Catani et al., 2002; Catani and Thiebaut de Schotten, 2008; Lawes et al., 2008; Mori et al., 2005, 2002; Wanaka et al., 2004). These reconstructions of white matter trajectories are loyal to classical anatomical descriptions

derived from post-mortem studies in humans (Dejerine, 1895) and experimental neuronography in monkeys (Schmahmann et al., 2007; Thiebaut de Schotten et al., this issue; Yeterian et al., this issue). Thus far, DTI has been extensively exercised in recent literature and it has been of paramount importance in understanding functions such as, language (Catani et al., 2007; Catani and Ffytche, 2005; Vernooij et al., 2007; Powell et al., 2008), reading (Epelbaum et al., 2008) and spatial processing (Thiebaut de Schotten et al., 2005; Urbanski et al., 2008, 2011). Measurement, such as diffusivity and FA, can be extracted from these specific reconstructions and provide an estimate of the microstructural integrity of axons (Jones, 2008; Beaulieu, 2009). Therefore, DTI presents a promising approach to the characterisation of microscopic damage to specific white matter pathways following TBI. It provides a valuable marker for the severity of traumatic injury and perhaps a prognostic indicator of the recovery pattern of non-motor functions such as cognitive-behavioural sequelae (Huisman et al., 2004; Inglese et al., 2005). This approach overcomes some of the limitations that whole voxel-based DTI and the ROI analysis presents (Catani, 2006). In particular, it gives results attributable to single tracts, whilst taking into account inter-individual anatomical variability (Thiebaut de Schotten et al., 2011).

Lee et al. revealed for the first time using tractography, an acute axonal shearing injury of the corpus callosum (Lee and

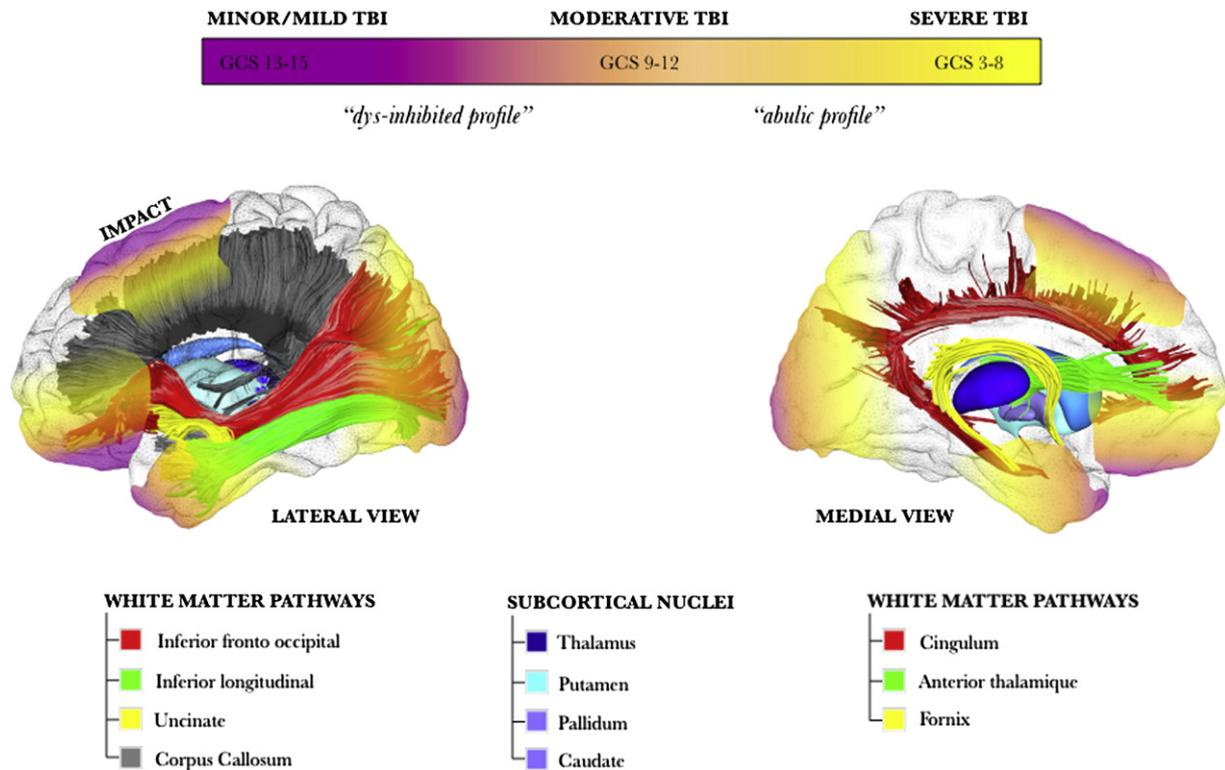


Fig. 4 – Lateral and medial view of the visible brain damage according to the severity of the TBI and representation of the subjacent white matter tract with invisible injury.

Newberg, 2005). DTI tractography showed a specific axonal injury of the splenium that correlated with the patient's left hemialexia, a functional deficit caused by disconnection of the right visual cortex from the language centres of the dominant left hemisphere. One year later Nakayama et al. reported damage to the architecture of the corpus callosum and the fornix tractography in a group of twenty-three TBI patients as compared to controls (Nakayama et al., 2006). In 2008, Wilde et al. reconstructed corpus callosum of ten TBI victims with tractography and showed a significant correlation between the cognitive (poor memory and concentration), affective (depression, irritability), and somatic (headache, dizziness) post-concussion symptoms, and the FA measurement specific to this tract (Wilde et al., 2008). Meanwhile, Wang et al. (2008) demonstrated that the DTI measure of the diffuse axonal injury of the anterior body and the splenium of the corpus callosum was a valuable biomarker that predicts the long-term outcome of TBI. Finally, Jang and co-authors showed that DTI tractography of the cortico-spinal tract reveals an FA decrease or diffuse axonal injury associated with TBI victims with motor weaknesses (Jang et al., 2009).

6. Discussion

TBI, although the most frequent of all neurological illnesses in the Western societies, still has not gained relevance in the "eyes" of most neurologists because its consequences are not commonly defined within traditional "organic" templates and definitions of structure–function correlations associated with

focal cortical lesions. The field of neurology is generally more attracted by deficits and syndromes, whose main basis remains "physical and objective", or at least easily documentable with the few tools still representing the clinician's armamentarium. As soon as symptoms become less "visible" with neuroradiological or electrophysiological investigations, and not easily circumscribed within vascular boundaries, our competence diminishes and interpretation of disturbed behaviour is left to "functional" domains and more prone to "psychological" investigation. TBI is not a "focal" injury; it is not "vascular" nor "degenerative" or "inflammatory". It escapes most of the well known pathophysiological interpretations, rendering it difficult to understand and accept.

We have recently witnessed a growing interest in the field of structural and functional neuroimaging that may significantly impact our understanding of the "anatomy" and the pathogenesis of neurological illnesses (Catani and Ffytche, 2010), including cerebral trauma. Today, brain lesions can be mapped onto both cytoarchitectonic templates (Amunts et al., 2005, 2000, 1999) and more recent white matter atlases (Lawes et al., 2008; Oishi et al., 2010; Catani and Thiebaut de Schotten, in press), allowing us to correlate dysfunctions not only with discrete cerebral areas but also with parallel-distributed networks of complex cognitive–behavioural circuits (Catani and Thiebaut de Schotten, in press). These atlases might be useful in severe injury where physical and "visible" disturbances somehow need an official neurological intervention. In that case, standard MRI certainly offers information for the quantification of the neuropathology spectrum including damage to the brainstem and mid brain structures (Hughes

et al., 2004). However, most of the TBI victims suffer minor to moderate damage of the white matter, inducing severe cognitive damages, not “visible” to the standard neurological examination, and not limited to the corpus callosum and the internal capsule. Consequently, most TBI victims may encounter a variability of neurological and neuropsychological opinions once they have recovered from most of their injuries, although they are not yet fully restored to their baseline functioning. These residual symptoms can be difficult to demonstrate convincingly to legal and insurance experts, due to the complexities involved in linking these symptoms to their true traumatic and “organic” origin. While the neuropsychological investigation and traditional neuroimaging results can be of assistance, they are not part of the classical neurological tools, nor do they explicitly demonstrate that the traumatic damage is “cerebral”. Considering minor TBI, where traditional neuroimaging provides negative results, DTI potentially offers visible information about microstructural damage following diffuse axonal injury and its consequences (Sidaros et al., 2008). Such white matter damage, as well as the interruption of white matter tracts, has been frequently shown to be directly associated with cognitive-behavioural sequelae in TBI victims. DTI tractography sensitivity to changes in the microstructure of white matter represents a very promising methodology for studying TBI. Using this approach, recent reports have more credibly advanced a better understanding of TBI brain pathophysiology, expanding from a perspective of mainly localised cortical damage, to a broader view of gray and white matter damage that encompasses the visible and subtle aspects of TBI.

DTI is sensitive to white matter changes following TBI. Reductions in FA and axial diffusivity emerge in the first few hours following cortical contusions and/or brain microbleeds that result secondary to TBI. Patients without microbleeds also show significant white matter abnormalities, demonstrating that considerable white matter damage may be present following TBI even when conventional MRI is normal (Kinnunen et al., 2011). The relationship between DTI measures of frontal white matter damage and cognitive dysfunction appears more complex. TBI produces a disconnection of various frontal white matter tracts, but its entity and its correlation with residual clinical profiles remains unclear. An atlas approach offers the opportunity to overlap fibre tracts onto conventional CT or MRI images allowing to infer a direct correlation between functional impairment and disconnection of white matter structures. The Atlas approach is however limited by the availability of current knowledge on fibre tract anatomy. Most of the U-shaped connections of the human frontal lobe have in fact not been described using classical post-mortem dissections. We predict that in the future a comprehensive description of these fibres and their representation in standardised digital atlases could fill the gap between complex clinical manifestations and current broadly defined frontal lobe networks (Eslinger et al., 2007).

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REFERENCES

- Amunts K, Kedo O, Kindler M, Pieperhoff P, Mohlberg H, Shah NJ, et al. Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: Intersubject variability and probability maps. *Anatomy and Embryology*, 210(5–6): 343–352, 2005.
- Amunts K, Malikovic A, Mohlberg H, Schormann T, and Zilles K. Brodmann’s areas 17 and 18 brought into stereotaxic space – where and how variable? *NeuroImage*, 11(1): 66–84, 2000.
- Amunts K, Schleicher A, Burgel U, Mohlberg H, Uylings HB, and Zilles K. Broca’s region revisited: Cytoarchitecture and intersubject variability. *Journal of Comparative Neurology*, 412(2): 319–341, 1999.
- Arfanakis K, Houghton VM, Carew JD, Rogers BP, Dempsey RJ, and Meyerand ME. Diffusion tensor MR imaging in diffuse axonal injury. *American Journal of Neuroradiology*, 23(5): 794–802, 2002.
- Assaf Y and Pasternak O. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: A review. *Journal of Molecular Neuroscience*, 26(8): 1133–1144, 2008.
- Basser PJ, Mattiello J, and LeBihan D. MR diffusion tensor spectroscopy and imaging. *Biophysics Journal*, 66(1): 259–267, 1994.
- Bazarian JJ, Zhong J, Blyth B, Zhu T, Kavcic V, and Peterson D. Diffusion tensor imaging detects clinically important axonal damage after mild traumatic brain injury: A pilot study. *Journal of Neurotrauma*, 24(9): 1447–1459, 2007.
- Beaulieu C. The biological basis of diffusion anisotropy. In Johansen-Berg H and Behrens TE (Eds), *Diffusion MRI: From Quantitative Measurement to In vivo Neuroanatomy*. London: Elsevier, 2009: 105–126.
- Bhullar I, Roberts E, Brown L, and Lipei H. The effect of age on blunt traumatic brain-injured patients. *American Surgery*, 76(9): 966–968, 2010.
- Catani M. Diffusion tensor magnetic resonance imaging tractography in cognitive disorders. *Current Opinion in Neurology*, 19(6): 599–606, 2006.
- Catani M, Allin MP, Husain M, Pugliese L, Mesulam MM, Murray RM, et al. Symmetries in human brain language pathways correlate with verbal recall. *Proceedings of National Academy of Sciences of the United States of America*, 104(43): 17163–17168, 2007.
- Catani M and Ffytche DH. The rises and falls of disconnection syndromes. *Brain*, 128(10): 2224–2239, 2005.
- Catani M and Ffytche DH. New section: Cortex clinical neuroanatomy. *Cortex*, 46(1): 1, 2010.
- Catani M, Howard RJ, Pajevic S, and Jones DK. Virtual in vivo interactive dissection of white matter fasciculi in the human brain. *NeuroImage*, 17(1): 77–94, 2002.
- Catani M and Thiebaut de Schotten M. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex*, 44(8): 1105–1132, 2008.
- Catani M and Thiebaut de Schotten M. *Atlas of Human Brain Connections*. Oxford: Oxford University Press, in press.
- Charlton R, Barrick TR, Lawes INC, Markus HS, and Morris R. White matter pathways associated with working memory in normal aging. *Cortex*, 46(4): 474–489, 2010.
- Dejerine J. *Anatomie des centres nerveux*. Paris: Rueff et Cie, 1895.

- El-Sayed T, Mota A, Fraternali F, and Ortiz M. Biomechanics of traumatic brain injury. *Computer Methods in Applied Mechanics and Engineering*, 197: 4692–4701, 2008.
- Epelbaum S, Pinel P, Gaillard R, Delmaire C, Perrin M, Dupont S, et al. Pure alexia as a disconnection syndrome: New diffusion imaging evidence for an old concept. *Cortex*, 44(8): 962–974, 2008.
- Eslinger P, Grattan L, and Geder L. Impact of frontal lobe lesions on rehabilitation and recovery from acute brain injury. *Neurorehabilitation*, 5(2): 161–182, 1995.
- Eslinger PJ, Zappalà G, Chakara F, and Barrett AM. Cognitive impairments after traumatic brain injury. In: *Brain Injury Medicine*. New York: Demos, 2007: 45–56.
- Gaetz M. The neurophysiology of brain injury. *Clinical Neurophysiology*, 115(1): 4–18, 2004.
- Gennarelli TA, Thibault LE, Adams JH, Graham DI, Thompson CJ, and Marcincin RP. Diffuse axonal injury and traumatic coma in the primate. *Annals of Neurology*, 12(6): 564–574, 1982.
- Gouick J and Gentleman D. The emotional and behavioural consequences of traumatic brain injury. *Trauma*, 6(4): 285–292, 2004.
- Gualtieri T. The problem of mild head injury. *Neuropsychiatry, Neuropsychology and Behavioral Neurology*, 8: 127–136, 1995.
- Hashimoto K, Okumura A, Shinoda J, Abo M, and Nakamura T. Tensor magnetic resonance imaging in a case of mild traumatic brain injury with lowered verbal intelligence quotient. *Journal of Rehabilitation Medicine*, 39(5): 418–420, 2007.
- Henry JD, Philips LH, Crawford JR, Ietswaart M, and Summers F. Theory of mind following traumatic brain injury: The role of emotion recognition and executive dysfunction. *Neuropsychologia*, 44(10): 1623–1628, 2006.
- Hou DJ, Tong KA, Ashwal S, Oyoyo U, Joo E, Shutter L, et al. Diffusion-weighted magnetic resonance imaging improves outcome prediction in adult traumatic brain injury. *Journal of Neurotrauma*, 24(10): 1558–1569, 2007.
- Hughes DG, Jackson A, Mason DL, Berry E, Hollis S, and Yates DW. Abnormalities on magnetic resonance imaging seen acutely following mild traumatic brain injury: Correlation with neuropsychological tests and delayed recovery. *Neuroradiology*, 46(7): 550–558, 2004.
- Huisman TA, Schwamm LH, Schaefer PW, Koroshetz WJ, Scetty-Alva N, Ozsunar Y, et al. Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. *American Journal of Neuroradiology*, 25(3): 370–376, 2004.
- Inglese M, Makani S, Johnson G, Cohen BA, Silver JA, Gonen O, et al. Diffuse axonal injury in mild traumatic brain injury: A diffusion tensor imaging study. *Journal of Neurosurgery*, 103(2): 298–303, 2005.
- Jang SH, Kim DS, Son SM, Cho YW, Kim SH, Kim OL, et al. Clinical application of tensor tractography for elucidation of the causes of motor weakness in patients with traumatic brain injury. *Neurorehabilitation*, 24(3): 273–278, 2009.
- Jennett B. The problem of mild head injury. *Practitioner*, 221(1321): 77–82, 1978.
- Jones DK. Studying connections in the living human brain with diffusion MRI. *Cortex*, 44(8): 936–952, 2008.
- Kinnunen KM, Greenwood R, Powell JH, Leech R, Hawkins PC, Bonnelle V, et al. White matter damage and cognitive impairment after traumatic brain injury. *Brain*, 134(2): 449–463, 2011.
- Kolb B and Wishaw IQ. *Fundamentals of Human Neuropsychology*. New York: Freeman & Co, 1990.
- Kraus MF, Susmaras T, Caughlin BP, Walker CJ, Sweeney JA, and Little DM. White matter integrity and cognition in chronic traumatic brain injury: A diffusion tensor imaging study. *Brain*, 130(10): 2508–2519, 2007.
- Lawes INC, Barrick TR, Murugam V, Spierings N, Evans DR, Song M, et al. Atlas-based segmentation of white matter tracts of the human brain using diffusion tensor tractography and comparison with classical dissection. *NeuroImage*, 39(1): 62–79, 2008.
- Lee B and Newberg A. Neuroimaging in traumatic brain injury. *Journal of the American Society of Experimental Neurotherapeutics*, 2(2): 372–383, 2005.
- Levine B, Fujiwara E, O'Connor C, Richard N, Kovacevic N, and Mandic M. In vivo characterization of traumatic brain injury neuropathology with structural and functional imaging. *Journal of Neurotrauma*, 23(10): 1396–1411, 2006.
- Li XY and Feng DF. Diffuse axonal injury: Novel insights into detection and treatment. *Journal of Clinical Neuroscience*, 16(5): 614–619, 2009.
- Lipton ML, Gulko E, Zimmermann ME, Friedman BW, Kim M, Gellella E, et al. Diffusion-tensor imaging implicates prefrontal axonal injury in executive function impairment following very mild traumatic brain injury. *Radiology*, 252(3): 816–824, 2009.
- Lucas J. Traumatic brain injury and post-concussive syndrome. In Snyder PJ and Nussbaum PD (Eds), *Clinical Neuropsychology*. Washington DC: APA, 1999: 243–265.
- Marquez de La Plata CD, Garces J, Shokri Kojori E, Grinnan J, Krishnan K, Pidikiti R, et al. Deficits in functional connectivity of hippocampal and frontal lobe circuits after traumatic axonal injury. *Archives of Neurology*, 68(1): 74–84, 2011.
- Mateer C and Sira C. Cognitive and emotional consequences of TBI: Intervention strategies for vocational rehabilitation. *Neurorehabilitation*, 21(4): 315–326, 2006.
- McDonald S and Flanagan S. Social perception deficits after traumatic brain injury: Interaction between emotion recognition, mentalizing ability, and social communication. *Neuropsychology*, 18(3): 572–579, 2004.
- Mesulam MM. From sensation to cognition. *Brain*, 121(6): 1013–1052, 1998.
- Mori S, Wanaka S, Nagae-Poetscher LM, and van Zijl PCM. *MRI Atlas of Human White Matter*. Amsterdam: Elsevier, 2005.
- Mori S, Kaufmann WE, Davatzikos C, Stieltjes B, Amodei L, Fredericksen K, et al. Imaging cortical association tracts in the human brain using diffusion-tensor-based axonal tracking. *Magnetic Resonance in Medicine*, 47(2): 215–223, 2002.
- Nakayama N, Okumura A, Shinoda J, Yasokawa YT, Miwa K, Yoshimura SI, et al. Evidence for white matter disruption in traumatic brain injury without macroscopic lesions. *Journal of Neurology, Neurosurgery and Psychiatry*, 77(7): 850–855, 2006.
- Newcombe F and Russell WR. Dissociated visual perceptual and spatial deficits in focal lesions of the right hemisphere. *Journal of Neurology*, 32(2): 73–78, 1969.
- Niogi SN, Mukherjee P, Ghajar J, Johnson C, Kolster RA, Sarkar R, et al. Structural dissociation of attentional control and memory in adults with and without mild traumatic brain injury. *Brain*, 131(12): 3209–3221, 2008.
- Oishi K, Faria AV, Van Zijl PCM, and Mori S. *MRI Atlas of Human White Matter*. Elsevier, 2010.
- Pontifex MB, O'Connor PM, Broglio SP, and Hillman CH. The association between mild traumatic brain injury history and cognitive control. *Neuropsychologia*, 47(14): 3210–3216, 2009.
- Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, et al. Imaging language pathways predicts postoperative naming deficits. *Journal of Neurology, Neurosurgery and Psychiatry*, 79(3): 327–330, 2008.
- Rimrodt SL, Peterson DJ, Denckla MB, Kaufmann WE, and Cutting LE. White matter microstructural differences linked to left perisylvian language network in children with dyslexia. *Cortex*, 46(6): 739–749, 2010.
- Schmahmann JD, Pandya DN, Wang RP, Dai G, D'Arceuil HE, De Crespigny AJ, et al. Association fibre pathways of the brain: Parallel observations from diffusion spectrum imaging and autoradiography. *Brain*, 130(3): 630–653, 2007.

- Senathi-Raja D, Ponsford J, and Schoenberger M. Impact of age on long-term cognitive function after traumatic brain injury. *Neuropsychology*, 24(3): 336–344, 2010.
- Sidaros A, Engberg AW, Sidaros K, Liptrot MG, Herning M, Petersen P, et al. Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: A longitudinal study. *Brain*, 131(1): 559–572, 2008.
- Sidaros A, Skimminge A, Liptrot MG, Sidaros K, Engberg AW, Herning M, et al. Long-term global and regional brain volume changes following severe traumatic brain injury: A longitudinal study with clinical correlates. *NeuroImage*, 44(1): 1–8, 2009.
- Sugiyama K, Kondo T, Higano S, Minoru E, Watanabe H, Shindo K, et al. Diffusion tensor imaging fiber tractography for evaluating diffuse axonal injury. *Brain Injury*, 21(4): 413–419, 2007.
- Tagliaferri F, Compagnone C, Korsic, Servadei, and Kraus J. A systematic review of brain injury epidemiology in Europe. *Acta Neurochirurgica (Wien)*, 148(3): 255–268, 2006.
- Thiebaut de Schotten M, Dell'Acqua F, Valabregue R, and Catani M. The monkey to human comparative anatomy of the frontal lobe association tracts. *Cortex*, this issue.
- Thiebaut de Schotten M, ffytche DH, Bizzi A, Dell'Acqua F, Allin M, Walshe M, et al. Atlasing location, asymmetry and intersubject variability of white matter tracts in the human brain with MR diffusion tractography. *NeuroImage*, 54(1): 49–59, 2011.
- Thiebaut de Schotten M, Kinkingnehun S, Delmaire C, Lehericy S, Duffau H, Thivard L, et al. Visualization of disconnection syndromes in humans. *Cortex*, 44(8): 1097–1103, 2008.
- Thiebaut de Schotten M, Urbanski M, Duffau H, Volle E, Levy R, Dubois B, et al. Direct evidence for a parietal–frontal pathway subserving spatial awareness in humans. *Science*, 309(5744): 2226–2228, 2005.
- Thomas C, Avidan G, Humphreys K, Jung KJ, Gao F, and Behrmann M. Reduced structural connectivity in ventral visual cortex in congenital prosopagnosia. *Nature Neuroscience*, 12(1): 29–31, 2009.
- Thomas C, Humphreys K, Jung KJ, Minshew N, and Behrmann M. The anatomy of the callosal and visual-association pathways in high-functioning autism: A DTI tractography study. *Cortex*, 47(7): 863–873, 2011.
- Thurman DJ, Coronado V, and Selassie A. The epidemiology of TBI: Implications for public health. In: *Brain Injury Medicine*. New York: Demos, 2007: 45–56.
- Trexler LE and Zappalà G. Re-examining the determinants of recovery and rehabilitation of memory defects following traumatic brain injury. *Brain Injury*, 2(3): 187–203, 1988.
- Urbanski M, Thiebaut de Schotten M, Rodrigo S, Catani M, Oppenheim C, Touzè E, et al. Brain networks of spatial awareness: Evidence from diffusion tensor imaging tractography. *Journal of Neurology, Neurosurgery and Psychiatry*, 79(5): 598–601, 2008.
- Urbanski M, Thiebaut de Schotten M, Rodrigo S, Catani M, Oppenheim C, Touzè E, et al. DTI-MR tractography of white matter damage in stroke patients with neglect. *Experimental Brain Research*, 208(4): 491–505, 2011.
- Vernooij MW, Smits M, Wielopolski PA, Houston GC, Krestin GP, and van der Lugt A. Fiber density asymmetry of the arcuate fasciculus in relation to functional hemispheric language lateralization in both right- and left-handed healthy subjects: A combined FMRI and DTI study. *NeuroImage*, 35(3): 1064–1076, 2007.
- Wanaka S, Jiang H, Nagae-Poetscher LM, van Zijl PC, and Mori S. Fiber tract-based atlas of human white matter anatomy. *Radiology*, 230(1): 77–87, 2004.
- Wang JY, Bakhadirov K, Devous Sr MD, Abdi H, McColl R, Moore C, et al. Diffusion tensor tractography of traumatic diffuse axonal injury. *Archives of Neurology*, 65(5): 619–626, 2008.
- Wilde EA, McCauley SR, Hunter JV, Bigler ED, Chu Z, Wang ZJ, et al. Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. *Neurology*, 70(12): 948–955, 2008.
- Yeterian EH, Pandya DN, Tomaiuolo F, and Petrides M. The cortical connectivity of the prefrontal cortex in the monkey brain. *Cortex*, this issue.
- Yuan W, Holland SK, Schmithorst VJ, Waltz NC, Cecil KM, Jones BV, et al. Diffusion tensor MR imaging reveals persistent white matter alteration after traumatic brain injury experienced during early childhood. *American Journal of Neuroradiology*, 28(10): 1919–1925, 2007.
- Zald DH and Andreotti C. Neuropsychological assessment of the orbital and ventromedial prefrontal cortex. *Neuropsychologia*, 48(12): 3377–3391, 2010.
- Zappalà G. The frontal lobes: Executive and behavioural control of human reasoning. Implications for understanding brain injury. *Rivista Italiana di Neurobiologia*, 54(4): 195–202, 2008.
- Zappalà G and Trexler LE. Quantitative and qualitative aspects of memory performance after minor head-injury. *Archives of Clinical Neuropsychology*, 7(2): 145–154, 1992.