Investigating Connectivity of Orbitomedial Prefrontal Region in a Patient with Traumatic Brain Injury

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SUMMARY

The majority of the research studying the prefrontal region has focused on gray matter injury. However, recent studies show that damage to white matter also contributes to the development of cognitive impairment after traumatic brain injury (TBI). Through the use of diffusion tensor imaging (DTI), it is now possible to assess the white matter fiber pathways between brain regions. With Diffusion Tensor Tractography (DTT), fibers of interest can be three dimensionally reconstructed and associated measurements can be performed. In this paper, we present the case of an individual that suffered from panic attacks, behavioral changes, auditory hallucinations and disturbing bodily sensations after traumatic brain injury. The patient was evaluated with a detailed clinical and neuropsychological assessment, magnetic resonance imaging (MRI) and DTI. MRI revealed cystic encephalomalasia with a diameter of 3.4 cm in the left orbitomedial frontal region. With DTT, major white matter tracts of the traumatized area were compared with symmetrical tracts in the contralateral side. Streamline count for the right inferior fronto-occipital fasciculus (iFOF) was 54 while no streamlines could be found for the left iFOF. For the left uncinate fasciculus and the left cingulum, streamline counts were significantly lower compared with the right side (62% and 34% lower; respectively). White matter damage in TBI can cause dysfunction of different brain regions through disruption of connections with the traumatized area. In this case report, we emphasized that symptoms were not limited with dysfunction of the traumatized region and the regular functions of other brain regions were also affected via the disturbance of connection pathways.

Keywords: Traumatic brain injury, Diffusion tensor imaging, Prefrontal cortex, Diffusion tractography

INTRODUCTION

The prefrontal region plays an important role in executive functions including the ability to recognize future consequences resulting from current actions, suppress unacceptable social responses and determine similarities and differences between things or circumstances (Pal et al. 2012).

The vast majority of the research studying the prefrontal region has focused on gray matter injury so far. But recent studies show that the damage to brain connections also contributes to cognitive impairment after traumatic brain injury (Zappalà et al. 2012). Through the use of diffusion tensor imaging (DTI), it is now possible to assess the white matter (WM) fiber pathways between brain regions. In this method, the structural integrity of white matter is evaluated based on water diffusion and the term "fractional anisotropy" (FA) is used to define the structural integrity of axon fibers (Kitis et al. 2012). Furthermore, with Diffusion Tensor Tractography (DTT), the fibers of interest can be three dimensionally reconstructed and associated measurements can be performed.

In this article, we focused on the connectivity damage of a single traumatic brain injury patient and tried to determine the contribution of the white matter injury to symptoms. We attempted to show that different brain regions work together as a network and a defect in one region may affect the regular functions of other brain regions via the disturbance of connected pathways.

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CASE REPORT

VS, a 38-year-old male (8 years of education), presented with irritability, aggressive behavior, excessive alcohol use, gambling and auditory hallucinations in the form of a human voice speaking to him. The patient and his family stated that his complaints started after falling from a 7 meter high building when he was 16. According to the patient's history and medical records that could be accessed, he lost consciousness for approximately one hour after the fall. Periorbital ecchymosis and cerebrospinal fluid rhinorrhea were detected. Neuroradiological examination with computerized tomography demonstrated a 7 millimeter thick epidural hemorrhage and a hypodense contusional lesion in the left frontal region. The patient was hospitalized for four weeks and discharged after the rhinorrhea stopped without any surgical intervention.

The patient stated that he became an aggressive and reckless person after the accident. He could hardly stop himself from swearing or attacking people around him and he argued with his employers and co-workers frequently. Therefore, he was not able to maintain employment. During this time he started betting on horse races. He stated that he couldn't stop himself from betting all his money even though he knew that he couldn't win. Furthermore, panic attacks with paresthesias on the right side of his body led the patient to the emergency department three or four times per week. He gradually increased his amount of alcohol consumption to get rid of these paresthesias. A few years after the accident he started to hear a stranger's voice ordering him to do good or bad things. The patient often argued with that voice if it ordered him to do harmful things. At the time of psychiatric admission, he was drinking up to 8 standard drinks three or four days per week and smoking about 1 package of cigarettes per day. No other substance use was reported. His family history was significant for an aunt diagnosed with schizophrenia.

Psychiatric Examination

During the psychiatric examination the patient was conscious and fully oriented to time and place. He was dressed appropriately according to his age and sociocultural status. He had a depressed mood and mournful affect. His speech and gestures were normal. He had insomnia at the initial and middle level. As for perceptual disturbances, he had auditory hallucinations in the form of strangers speaking to him. No positive psychotic symptom or suicidal thoughts were detected in his thought content. Negative symptoms of schizophrenia like affective blunting or poverty of speech were also not observed.

Clinical and Neuropsychological Assessment

The patient was evaluated with Beck's Depression Inventory (BDI), Mini Mental State Examination (MMSE) and a detailed neuropsychological test battery as shown in Table 1.

Table 1. Neuropsychological and Clinical Assessment

TESTS	SCORES
MMSE	29/30
BDI	44/63
Verbal Memory	
Immediate Recall	7/15*
Max Span	14/15
Total Score	113/150*
Free Delayed Recall	13/15
Logical Memory	
Total Immediate Recall	38/75*
Total Delayed Recall	15/50*
Total Recognition	29/30
Percent Retention	60%
Mental Control	31/40
Attention &Working Memory	
Forward Digit Span	8/8
Backward Digit Span	7/7
Letter-Number Sequencing	13/21(span: 7)
Cognitive Shifting Interference	
Stroop (time)	58" (normal)
Trail Making (time)	87" *
Wisconsin Card Sorting Test	
Total Errors	48/128*
Perseverative Error	22/48 (17%)*
Completed Category	4/6*
Language	
Naming (Short form)	15/15
Verbal Fluency	Normal
Visuospatial Abilities	
Rey-Osterreich Complex Figure Test	
Copying	Normal
Immediate Recall	14/36
Delayed Recall	11/36
Percent Retention	67% (Information loss)*
Clock Drawing	10/13
Copy of Figure	4/4
Motor Speed	
Left Finger Tapping (in 10 sec)	41
Right Finger Tapping (in 10 sec)	45
Risk-Taking Decisions	
Iowa Gambling Test	-24 (Net score)

Scores: The number of correct responses out of the maximal score. *indicates scores under the normative data.
MMSE: Mini Mental State Examination; **BDI:** Beck's Depression Inventory;

Verbal abilities such as language and verbal fluency were preserved. He had moderately low scores in verbal memory and logical memory (Wechsler Memory Scale) tests. Visuospatial abilities were assessed with the clock drawing test, Rey-Osterreich Complex Figure Test and Wechsler Memory Scale's visual reproduction subtests. These tests revealed normal visuospatial functioning.

Frontal functioning was assessed by cognitive shifting, inhibition, interference and decision-making abilities. His difficulty in shifting categories in the trail making test resulted in a prolonged response time. Consistently, perseverative errors during the category changes in the Wisconsin Card Sorting

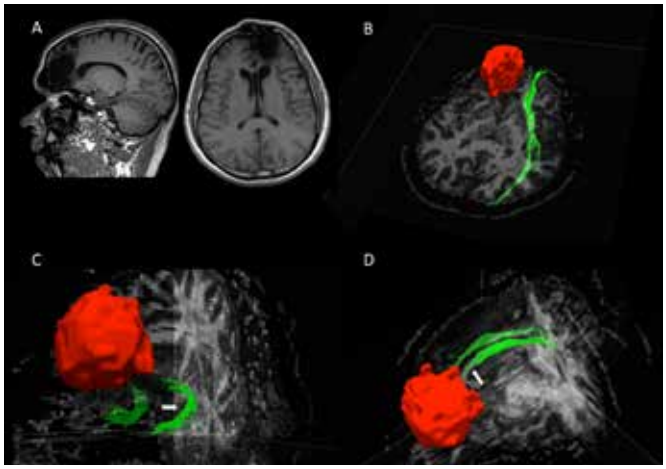

Figure 1. MRI and tractography images - The red structure with irregular margins represents the lesion in the left orbitofrontal area. See Table 2 for the streamline counts and FA values. A. T1 weighted images in sagittal and axial plane. Cystic encephalomalasia with a diameter of 3.4 cm in the left orbitomedial frontal region is shown. B. The right inferior fronto-occipital fasciculus (İFOF). No streamlines belonging to the left İFOF could be found. C. The left uncinate fasciculus (arrow) is thinner compared to the right. D. Anterior part of the left cingulum bundle (arrow) is thinner compared to the right.

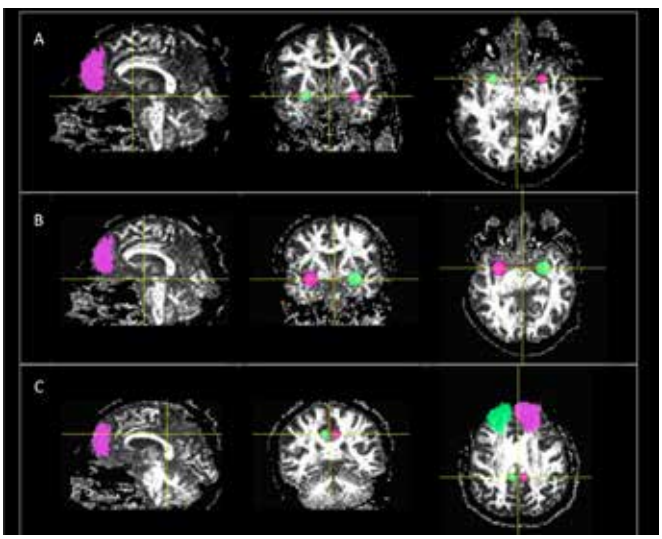

Figure 2. Regions of Interest (ROI)- The purple area with irregular margins in the left frontal lobe represents the lesion. A symmetrical ROI (green) is created in the undamaged right frontal lobe. Purple and grean circles are the ROI's in which measurements were performed for each tract. A. Inferior fronto-occipital fasciculus B. Uncinate fasciculus C. Cingulum bundle.

Test (WCST) were observed, and the test was not completed. Stroop Test performance was within the normal limits. In the Iowa Gambling Test, the patient selected more cards from disadvantageous decks and ended up with a negative score, which means that although he knew and understood the risks well, he intentionally performed more risky behaviors.

Anatomical MRI Study

MR imaging was performed on a 3.0 Tesla scanner (Siemens Magnetom Verio, Erlangen, Germany) with a 12-channel head matrix coil. In addition to conventional MRI sequences, T1-weighted (T1W) sagittal 3D MP-RAGE sequence and diffusion tensor imaging sequence were acquired to perform fiber tracking.

In order to detect the tracts affected by trauma, three dimensional regions of interest (ROI) in the lesion area and symmetrical area were created (Figure 1). We planned to compare the undamaged tracts passing through the symmetrical area of the lesion with the contralateral side in terms of streamline counts.

We used ITK-SNAP (Yushkevich et al. 2006) software on 3D-T1W MR images to make a three dimensional region of interest in the lesion. With optimum parameters for our case, we delineated the lesion area and the symmetrical area. Fiber tracking was performed using Diffusion Toolkit from TrackVis software (Wedeen et al. 2008). The fiber tracking software allows the identification of the tracts, 3D visualization, and quantitative analyses on the delineated tracts. Using lesion and symmetrical ROIs as seed points, we traced fiber tracts. To isolate specific tracts, we placed other ROI's on the route of the tracts (Figure 2).

Standard T1W MRI scan revealed cystic encephalomalasia and gliosis with a maximum diameter of 3.4 cm in the left orbitomedial frontal cortex (Figure 1). In the detailed investigation with DTI tractography, we found 3 major tracts that were affected compared to symmetrical ROI. Streamline count for the right inferior fronto-occipital fasciculus (iFOF) was 54 while no streamlines belonging to the left iFOF could be found. For the left Uncinate Fasciculus (UF) and the left Cingulum Bundle, streamline counts were also significantly lower compared to the right (62% and 34% respectively). Tractography images of the affected tracts are shown in Figure 1. Streamline counts and fractional anisotropy values are listed in Table 2.

Table 2. Tractography results for the affected tracts

	LEFT	RIGHT
IFOF*		
Streamline Count	0	54
Mean FA	N/A	0,548 0.142
Uncinate Fasciculus		
Streamline Count	25	66
Mean FA	0,44 0.168	0,405 0.114
Cingulum Bundle		
Streamline Count	48	73
Mean FA	0,474 0.122	0,582 0.111

IFOF = Inferior fronto-occipital fasciculus **FA** =Fractional Anisotropy

DISCUSSION

Our patient had a head trauma resulting in a large gray matter deficit in the left orbitomedial prefrontal cortex when he was 16 years old. Since then, he has suffered from behavioral disturbances, panic attacks, paresthesias and auditory hallucinations. The neuropsychological evaluation showed disrupted memory and decreased performance on complex cognitive and emotional / behavioral tasks. MRI scans with diffusion tensor imaging showed that in addition to the 19 cm^3 lesion in the left orbitofrontal region, the inferior fronto-occipital fasciculus, the uncinate fasciculus and the cingulum on the ipsilateral side were affected.

The current literature considering patients with ventromedial – prefrontal cortex (VM-PFC) damage has generally reported emotional and behavioral changes including disinhibition, poor decision making and decreased social and occupational functioning (Cato et al. 2004, Levens et al. 2014). In the present case, significant behavioral disturbances, low scores on the Iowa Gambling Test and standard T1W MRI scan findings were consistent with the current literature on VM-PFC damage. Furthermore, DTI evaluation revealed damage in multiple white matter tracts that could not be properly evaluated in the standard MRI sequences.

Axons in the white matter are especially vulnerable to mechanical loading caused by rotational forces. During most traumatic brain injuries by motor vehicle collisions and falls, diffuse axonal injury occurs due to shearing forces (Zappalà et al. 2012). Due to compliance and ductility of axons, disconnection at the moment of injury, called "primary axotomy", is considered a relatively rare occurrence. Instead, in the majority of TBI cases, the swelling that follows cytoskeletal disruption induces "secondary axotomy" and recent evidence suggests that axonal degeneration continues even years after injury (Johnson et al. 2013). In the present case, three major tracts associated with the prefrontal cortex were found to be damaged. We determined that the damaged tracts and regions that connect to the traumatized area may be important, as the white matter damage might contribute to the clinical manifestations.

The left inferior fronto-occipital fasciculus of our patient was considered to be totally destroyed because no fibers of this tract could be visualized. iFOF is the major connection pathway between the occipital lobe and the orbitofrontal cortex in humans and currently is accepted as a unique tract to human brain (Thiebaut de Schotten et al. 2012, Catani & Thiebaut de Schotten 2008, Catani et al. 2012). It originates from the occipital lobe and runs parallel to the inferior longitudinal fasciculus in its course to the temporal lobe. After reaching the temporal lobe, fibers of the iFOF gather together and enter the external capsule to terminate in the orbitofrontal cortex (Catani & Thiebaut de Schotten 2008, Thiebaud de Schotten et al. 2011). In addition to the orbitofrontal cortex and the occipital lobe, iFOF also has connections with the basal temporal lobe and superior parietal lobe (Martino et al. 2010).

In the present case, considering the connections of iFOF with the temporal lobe, it is possible that the total destruction of the left iFOF might be contributing to the auditory hallucinations that started a few years following this patient's injury. Recently, abnormalities of iFOF fractional anisotropy values were shown in patients with auditory hallucinations and schizophrenia (Mitelman et al. 2007, Koch et al. 2010, Amad et al. 2014, Liu et al. 2014, Yao et al. 2013, Zanetti et al. 2013). Curčić-Blake et al. (2015) found that the severity of hallucinations correlated negatively with white matter integrity in iFOF. In our case, secondary axotomy caused by cytoskeletal disruption may have caused progressive iFOF degeneration and auditory hallucinations in the subsequent years after the trauma. However, the role of the inferior fronto-occipital fasciculus in auditory hallucinations and schizophrenia is controversial and remains to be clarified.

It has been suggested that iFOF could play a role in reading (Catani & Mesulam 2008), visual attention (Doricchi et al. 2008, Urbanski et al. 2011, Urbanksi et al. 2008) and the semantic system (Duffau et al. 2005). However, the neuropsychological test results regarding visuospatial functioning and semantic skills of our patient were within normal limits. This might be due to compensation by the unaffected iFOF tract on the contralateral side.

The left uncinate fasciculus of our patient was significantly damaged as reflected by lower streamline counts in the left uncinate fasciculus compared to the right (L:25, R:66). UF is a hook shaped association tract that connects the temporal lobe and limbic structures with the medial and lateral orbitofrontal cortex (Catani & Thiebaut de Schotten 2008). It is possible that the damage in the left UF may be contributing to psychopathic behavior, anxiety symptoms and memory deficits via the disconnection of the frontal lobe with the temporal lobe and limbic structures. In a recent review about UF, Von Der Heide et al. (2013) indicated that the UF has a role in episodic memory, language and social-emotional processing. It was also mentioned that UF facilitates modifying behaviors by allowing the interaction between the temporal lobe-based stimulus and orbitofrontal cortex.

The defect in the UF might also contribute to the existence of auditory hallucinations. Lower FA values of UF in the patients with auditory hallucinations have been reported (Hubl et al. 2004, Curčić-Blake et al. 2013). However, there are studies reporting reduced, increased or no change in fractional anisotropy values of UF in schizophrenic patients relative to healthy subjects (Von Der Heide et al. 2013). Thus, the

role of UF in schizophrenia and auditory hallucinations is still controversial.

The left cingulum bundle of our patient was also partially damaged (Streamline counts L:48 R:73). The cingulum is a sickle-shaped tract consisting of fibers of different length running within the cingulate cortex. Its longest fibers connect the anterior temporal region to the orbitofrontal cortex. It is involved in memory and emotions, considered to be a part of the limbic system and regarded as an interface between emotion and cognition (Allman et al. 2001, Hubl et al. 2004, Catani & Thiebaut de Schotten 2008). In the present case, the partial damage in the cingulum bundle may be contributing to anxiety symptoms and treatment-resistant depression.

Clinical manifestations of traumatic brain injury patients develop through the interaction of different interrelated factors. For example, major depression is reported up to 77% after TBI. Diffuse axonal injury and effects on prefronal-limbic structures are thought to play a role in its emergence. In our patient, treatment – resistant depression reflected by a high Beck's Depression Inventory score might be contributing to clinical findings and decreased performance in neuropsychological tests. However it is difficult to distinguish the contributions of interrelated factors to the clinical picture. In this paper, we tried to emphasize the potential contribution of white matter injury to clinical findings.

CONCLUSION

In conclusion, the cortical defect in the left orbitofrontal region alone was not enough to explain all of the clinical manifestations of our traumatic brain injury case. The tractography study showed that major white matter tracts connecting the traumatized area to the temporal lobe were also damaged and this may be helpful in explaining the clinical findings, such as auditory hallucinations. Therefore, we tried to emphasize that clinical findings were not restricted to dysfunction of the traumatized area. Instead, functions of other cortical areas may be disrupted due to damaged pathways passing through the region.

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