A. **TITLE**

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B. **Neurocase.** 2007 Aug;13(4):226-8 Disruption of limbic pathways in a case of profound amnesia

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ABSTRACT:
We report a case of episodic amnesia in which the anatomical basis of injury was investigated by diffusion tensor imaging (DTI). Two months after an adult male suffered severe closed head injury, conventional magnetic resonance imaging (cMRI) revealed only a right superior frontal lesion. However, 14 years later, DTI revealed structural anomalies not visible on cMRI involving limbic white matter tracts, notably the fornix, which could explain the amnesia.
INTRODUCTION/ PATIENT HISTORY

Severe anterograde episodic amnesia, commonly referred to as the “amnesic syndrome,” is caused by lesions in the limbic system [1]. In its pure form, as a pronounced yet selective difficulty in remembering recent episodes, it is infrequently encountered in closed head injury which usually involves diffuse or multi-focal lesions and is, consequently, associated with a variety of general cognitive or specific mnemonic deficits, in addition to possible anterograde episodic amnesia. The patient described here represents an exceptional case in that his major deficit was (and remains) episodic amnesia. Our rationale for commenting on this case is not the rarity of its presenting symptom but the usefulness of diffusion tensor imaging (DTI) as a noninvasive neuroimaging technique in disclosing its underlying pathophysiology. The condition described in this case report could not be clearly explained by traditional computed tomography (CT) or conventional magnetic resonance imaging (cMRI).

The patient is an African-American 41 year old male who sustained a closed head injury in a motor vehicle accident 14 years before this study, at 27 years of age. Upon arrival to hospital his Glasgow Coma Scale [2] score was 9. CT scan of the brain on the day of injury showed diffuse axonal injury and left orbital blowout fracture. He was sedated and underwent monitoring of intracranial pressure which remained stable. After 20 days he began to follow commands. He had no history of relevant injuries or illnesses, including substance abuse or behavioral problems. School records showed normal achievement. At the time of injury he lived independently and worked as a truck driver. At one month after injury, neurologic evaluation showed hyperactive deep tendon reflexes bilaterally, decreased left nasolabial fold, and 4/5 muscle strength except for bilateral shoulder weakness. He was oriented to person and did not recall the event of injury. The patient also exhibited profound amnesia for recent events that led to his hospitalization.
Behavior was grossly passive with minimal initiation even in response to unpleasant physical stimuli.

CT scan of the brain at 6 weeks after injury showed only mild atrophy. cMRI scan at 8 weeks after injury showed non-specific signal abnormalities in the right frontal convexity and scattered through the frontal and periventricular white matter. During the first 9 years after injury, the patient underwent 5 comprehensive neuropsychological evaluations that documented the persistence of his memory deficit. At the final assessment, he was oriented to place but not consistently to date. On formal memory testing, he failed with few exceptions to recall any items of either verbal or visual information after a 30-minute delay. Because neither of the above-mentioned CT or MRI scans provided a satisfactory anatomical explanation of the symptomatology, we asked the patient to volunteer for another MR scan during which structural and Diffusion Tensor Imaging (DTI) data were collected. DTI has been shown to be more sensitive and specific to pathological and microstructural changes in the living gray and white matter tissue. DTI provides quantitative scores to assess the integrity of white matter connectivity and myelin integrity in health and disease [4]

METHODS

cMRI and DTI data from the entire brain were acquired with a Philips 3.0 T Intera system using a SENSE receive head coil. The MRI protocol included cMRI sequences (spoiled 3d gradient echo, FSE, FLAIR) and phase-sensitive MRI, in addition to a matching prescription of DTI data. The DTI data were acquired using a single-shot spin echo diffusion sensitized EPI sequence with the balanced Icosa21 encoding scheme [3], b=1000 s.mm\(^2\), TR=6.1 s, TE= 84 ms. Diffusion-weighted data were distortion-corrected using the mutual information maximization approach [5] and processed as described in [7]. Three-dimensional fiber reconstruction of the fornix was
conducted using the Fiber Assignment by Continuous Tracking algorithm [6, 8]. The fornix was reconstructed by including tracts that intersected regions of interest placed on the fimbria, fornix body and columns, and by excluding extraneous tracts. Tractography thresholds were minimum fractional anisotropy (FA) of 0.12 and maximum angle transition of 60º. Imaging was also performed on a healthy male subject of the same age (FA threshold 0.15).

RESULTS
cMRI revealed a region of encephalomalacia in the right frontal lobe, bilateral white matter abnormalities in the periventricular white matter and evidence of the ventriculostomy track through the anterior body of the corpus callosum. In addition, as shown in Figure 1, cMR showed cerebral atrophy and deep white matter volume loss including severe thinning of the corpus callosum. Evidence of left sided hippocampal sclerosis and atrophy was also noted. Much more revealing, however, is the DTI tract reconstruction (see Figure 2) demonstrating evidence of substantial decrease in fiber bundle connectivity in the fornix crura and columns. The decreased connectivity, which prevented full reconstruction of the fornix even at the reduced FA threshold of 0.12, is possibly indicative of loss of myelination or axonal impairment [9].

DISCUSSION
Loss of connectivity in the fornix as revealed by DTI is the most plausible explanation of the profound amnesia in this patient. cMRI of closed head injury generally reveals cerebral volume loss and thinning of the corpus callosum and fornix [10-11], as in the patient reported here. Along with the right frontal lesion, these findings may help explain the patient’s lack of initiative but they do not, however, account for the severe memory deficit. Transection of the fornix columns has been shown to produce anterograde episodic amnesia of severity comparable to this patient’s impairment [1]. Since the fornix includes fibers originating in the hippocampus and
terminating in the mammillary bodies, a role for the fornix in memory function would be predicted. However, measurements of fornix anatomy obtained by structural imaging after severe head injury have not been shown to correlate strongly with memory test results [10-11]. The reason for that may be that conventional MRI does not provide quantitative measures to assess white matter connectivity in three dimensional space, thus its specificity is limited while DTI is more specific to microstructural changes in myelination and axonal packing. The evidence of hippocampal injury revealed by cMRI in this patient does not account for the symptomatology because the hippocampal damage was unilateral. Previous cases of amnesia associated with unilateral hippocampal injury generally had memory impairment in one modality [1], such as impaired verbal memory after left-sided damage, unlike the present patient who had global memory impairment involving both verbal and visual material. This case report demonstrates how DTI may provide clear accounts of symptoms in terms of underlying neuropathology that conventional structural imaging may fail to detect.
REFERENCES


FIGURE LEGENDS

Figure 1. (a) Conventional MR images at the sagittal midline obtained at 14 years after injury reveal wasting of the corpus callosum and fornix, in comparison with a same-age healthy male subject (b). In these phase-sensitive images, pixel intensity is highest in white matter structures.

Figure 2. (a) Three-dimensional tract reconstruction of the fornix reveals severely reduced connectivity in the fornix in comparison with the same-age healthy control subject (b). In these tractography images, reconstructed fornix fibers (FA threshold 0.12 for patient, 0.15 for control) are labeled in red. Unweighted (b0) DT images are shown in the background for reference.
Figure 1