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**Review**

# The Role of Thalamic Damage in Mild Traumatic Brain Injury

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## Abstract

There is growing alarm in the United States about an epidemiologically large occurrence of mild traumatic brain injury with serious long lasting consequences. Although conventional imaging has been unable to identify damage capable of explaining its organic origin or discerning patients at risk of developing long-term or permanently disabling neurological impairment, most disease models assume that diffuse axonal injury in white matter must be present but is difficult to resolve. The few histopathological investigations conducted, however, show only limited evidence of such damage, which cannot account for the stereotypical globalized nature of symptoms generally reported in patients. This review examines recent proposals that in addition to white matter, the thalamus may be another important further site of injury. Although its possible role still remains largely under-investigated, evidence from experimental human and animal models, as well as simulational and analytical representations of mild head injury and other related conditions, suggest that this strategically vital region of the brain, which has reciprocal projections to the entire cerebral cortex, could feasibly play an important role in understanding pathology and predicting outcome.


**Key words:** concussion; experimental disease models; mild traumatic brain injury; pathophysiology; thalamus

## Introduction

Mild traumatic brain injury (mTBI) represents one of the most serious public health threats facing the United States in the 21st century.[1] It is estimated to account for about 75% of the 1.5 million head trauma cases reported annually by hospital emergency departments, and costs more than $17 billion per year in health care utilization and lost productivity.[2] The constellation of symptoms arising from a bump, blow, or jolt to the head in the absence of any skull fractures can include many persistent and disabling somatic (e.g., headaches, dizziness, insomnia, fatigue, blurred vision, sound and light sensitivity, and seizures), cognitive (e.g., attention, concentration, memory, and executive functioning deficits), and affective (e.g., irritability, depression, anxiety, sleep disturbances, problems with emotional control, and loss of initiative) sequelae.[1–4] Unfortunately, conventional magnetic resonance imaging (MRI) and computerized tomography (CT) fail to detect any evidence of brain damage that can account for the organic origin of these impairments or identify patients at risk of developing a long-term or permanently debilitating neurological condition.[5]

Nevertheless, most pathological models of mTBI currently assume diffuse axonal injury (DAI) must be present, which cannot be resolved using standard clinical imaging[5] since it is a key feature in more severe forms of brain trauma[5,6] DAI is the widespread presence of lesions throughout white matter tracts that are induced by rotational forces, which cause stress shearing in places where tissues of differing density interface.[6] Although very few histopathological investigations of mTBI have been conducted, there is some clinical evidence to suggest it does cause structural damage to axons.[7–11] These injuries, however, are strongly focalized and tend to cluster in regions such as the gray-white junction, the splenium of the corpus callosum, and the brain stem, and cannot account for the stereotypical globalized nature of symptoms commonly experienced by patients.[5]

One possible explanation for this discrepancy is that, in addition to white matter, the thalamus could perhaps be another important site of injury in mTBI.[5,7–17] This deep gray matter structure is often described as the central relay station of the brain because it has reciprocal projections to the entire cerebral cortex, and plays a principal role in the processing and transmission of information between sensory, motor, and associative regions.[18] These multiple functional pathways influence many global activities and therefore could potentially account for a great deal of the morbidity associated with mTBI. While the role that thalamic damage might play in mTBI has remained largely under-investigated, there is evidence to support the feasibility of its involvement.

## Neuropathological Evidence

Ross and colleagues[19] identified selective neuronal loss in the thalamic reticular nucleus of postmortem patients with severe brain trauma and noted that since this is a $\gamma$-aminobutyric acid population of cells which project only to other thalamic nuclei, the damage must have resulted from a mechanism not related to DAI, contusion,

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or vascular compromise. Interestingly, Gronwall[20] previously suggested that the loss of reticular nucleus neurons may be associated with sustained attention deficits in mTBI. Anderson and colleagues[7] reported that MRI volumetric analysis demonstrated that patients with moderate-to-severe brain trauma exhibited smaller thalamic volumes than patients with mild to moderate brain trauma, and patients with visible nonthalamic lesions were associated with smaller thalamic volumes than patients without visible lesions. These results were interpreted to imply that in the presence of cortical lesions, the thalamus may become susceptible to transneuronal degeneration. This understanding also is supported by Adams and colleagues,[21] who observed that 80% of 35 patients in the vegetative state had thalamic irregularities attributed to DAI or ischemia, and Natale and colleagues,[22] who presented an experimental mouse model of brain trauma that showed cortical damage could result in delayed remote thalamic neuronal apoptosis. Maxwell and colleagues[23] used stereological techniques to investigate thalamic damage in patients with moderate and severe brain trauma who survived between 6 h and three years and found evidence of neuronal loss in the dorsal medial nucleus and ventral posterior nucleus. It was concluded that dorsal medial nucleus neuronal loss may form the basis for predicting the outcome of patients with moderate or severe brain trauma or patients in vegetative state. Evidence also was found to suggest an ongoing response to injury by thalamic neurons when post-traumatic survival was greater than four months.

## Symptomatological Evidence

### *General*

Abdel-Dayam and colleagues[12] conducted a single photon emission CT study in which 77% of 228 patients with mild or moderate brain trauma were found to exhibit focal areas of hemodynamic impairment that included the thalamus and the basal ganglia (55.2%), the frontal lobes (23.8%), the temporal lobes (13%), the parietal lobes (3.7%), and the insular region and the occipital lobes (4.6%). The most common clinical complaints of patients (headaches, dizziness, and memory problems) were associated with greater numbers of focal areas in the thalamus and basal ganglia.

### *Headache*

There is ample evidence to show that pain, such as the type associated with headaches experienced by patients with mTBI, is gated in the thalamus.[24] More commonly, however, patient complaints closely resemble the prodromic symptoms in migraine which, by analogy, despite etiological and pathogenic differences, still suggest the potential involvement of the thalamus and thalamocortical circuits. Kobari and colleagues[25] examined patients during spontaneously-occurring migraine using xenon enhanced CT and reported hemodynamic changes in the thalamus, the basal ganglia, and the cerebral cortex. Coppola and colleagues[26] suggested, after studying high frequency oscillations of sensory evoked potentials in patients with migraine, that activity in thalamocortical projections is interictally decreased in migraine and could possibly explain the reduced pre-activation level of sensory cortices. Studies directed at understanding the relationship between migraine and vestibular symptoms (vertigo and sensitivity to sound and light) also have suggested that links between the thalamocortical processing centers, the vestibular nuclei, and the trigeminal system could provide the basis for a pathophysiological model of migraine-related vertigo.[27]

### *Insomnia*

Loss of consciousness associated with mTBI can result in alterations of the sleep–wake cycle, especially insomnia. The cycle is controlled by neuronal systems contained in the thalamus, the hypothalamus, the brain stem, and the basal forebrain.[28] The thalamus is the first relay station in which afferent information is blocked at sleep onset to prevent the cerebral cortex from receiving incoming peripheral stimuli. It also has been shown to play a primary role in the organization of the sleep–wake rhythm. This has been confirmed by experimental findings that athalamic cats display severe and persistent insomnia and clinical observations that thalamic degeneration with selective or prevalent involvement of the anterior nucleus or the dorsal medial nucleus results in virtually abolishing the ability of patients to generate an electroencephalographic sleep pattern. The thalamic midline and intralaminar nuclei receive impulses from the brain stem reticular formation and relay them to the ventral anterior nucleus from which projections ascend to the cortex. Since the reticular nucleus is traversed by fibers that connect the thalamus with the cerebral cortex, it is hypothesized to be the pacemaker responsible for synchronizing the activity of thalamic neurons and generating spindle rhythms during sleep.[29]

### *Fatigue*

Central fatigue is a symptom common to several neurological diseases including mTBI. It represents a disorder in the performance of physical and mental tasks requiring self motivation and internal cueing and is attributed to a failure of the nonmotor output channels in the basal ganglia. The neurons of the basal ganglia are involved in higher order cognitive aspects of motor control and also influence many other functions through extensive connections with the association cortex and limbic structures. Interruption of the striatocortical fibers or a net change in the thalamic activity suppressing cortical activation via the striato-thalamo-cortical loop will predispose to fatigue. Since the thalamus is the final common pathway of the corticofugal projections from the basal ganglia, an increase in net thalamic inhibition or a shift in the reciprocal state of activation between the thalamus and the subthalamic nucleus will modify the cortical response to the basal ganglia input. Recent evidence supports this model since dysrhythmias in the thalamocortical loop are associated with disorders in which fatigue is common.[30]

### *Cognition*

The relationship between the thalamus and cognitive function has been described with respect to several neurological conditions as well as, preliminarily, mTBI. Van der Werf and colleagues[31] used experimental and established neuropsychological tests to study patients with thalamic infarction and demonstrated that the thalamus plays a crucial role in memory, executive functioning, and attention. Damage to several distinct thalamic areas, including the anterior nucleus, the dorsal medial nucleus, and the midline and intralaminar structures, were found to contribute to amnesia. Conversely, posterior and lateral lesions developed without memory impairment, showing a degree of functional specificity in the thalamus. Executive functioning deficits did not exhibit a strong association with restricted thalamic structures except for the ventral internal medullary lamina and the ventral dorsal medial nucleus. Attention and processing speed deficits were not associated with specific structures in the thalamus, suggesting that inattention is a general feature of thalamic diseases irrespective of where damage

occurs. Salmond and colleagues[32] reported that in patients with moderate-to-severe brain trauma MRI voxel based morphometry revealed reduced gray matter density in the thalamus, the hippocampal formation, the basal forebrain, and regions of the neocortex, which was consistent with deficits in sustained attention, associative learning, and reaction time. These results suggest that changes in the integrity of the central cholinergic system could account for the cognitive sequelae, which may be possible to ameliorate through pharmaceutical intervention. Wood and Bigler[16] measured reduced thalamic volume in patients with mild, moderate, and severe brain trauma using MRI that correlated with sensory–perceptual errors. In line with these results, Fernández-Espejo and colleagues[33] similarly detected lower thalamic volume in patients with severe brain trauma using MRI that, along with significant bilateral regional atrophy in the dorsal medial nucleus and the internal medullar lamina, was correlated with worse Disability Rating Scale scores. Ge and colleagues[13] found that MRI perfusion imaging showed evidence of reduced cerebral blood flow in the thalamus of patients with mTBI almost two years after injury, which correlated with neurocognitive measures of impairment in executive functioning, memory, learning, processing speed, and response speed. Little and colleagues[10] examined patients with mild and moderate-to-severe brain trauma using diffusion tensor imaging (DTI) and concluded that DAI had resulted in damage to thalamic projection fibers, as indicated by decreased fractional anisotropy (FA), a measure of uniformity in water molecule movement, which was correlated with neurocognitive measures for impairment in attention, executive functioning, and memory (Table 1). Messé and colleagues[11] also investigated patients with mTBI using DTI at a mean of 17.2 d after injury and observed that damage to the anterior thalamic radiations, as indicated by decreased FA, was correlated with persistent post-concussion symptoms determined by a behavioral and cognitive assessment given three and four months later (Table 1). Grossman and colleagues applied DTI and diffusional kurtosis imaging (DKI) to patients with mTBI in both cross-sectional[8] and longitudinal[9] studies and detected evidence of thalamic damage within one month following injury and more than nine months following baseline, as indicated by decreased mean kurtosis, a measure of the diffusional complexity of water molecule movement, that was correlated with poor performance on neurocognitive measures for attention, concentration, and processing speed, as well as cognitive impairment (Table 1). While there is still no precise understanding of DKI in relationship to the underlying cellular environment, recent analytical and animal modeling investigations suggest these results reflect subtle precursory changes in axonal and myelin density[34] or the presence of inflammation marked by reactive astrogliosis.[35] This is consistent with what Ramlackhansingh and colleagues[36] reported for patients with moderate-to-severe brain trauma who underwent positron emission tomography in which microglial-related inflammatory processes found in the thalamus were correlated with increased cognitive impairment even 17 years after injury. Squarcina and colleagues[37] applied a novel method for assessing specific thalamocortical white matter connections in DTI and determined that in patients with mild, moderate-to-severe, and severe brain trauma, it yielded even greater evidence of damage than was recognized with standard probabilistic tractography used in previous investigations. Tang and colleagues[14] identified a disrupted pattern of resting-state neuronal networks in patients with mTBI using functional MRI (fMRI) that indicated thalamocortical connectivity abnormalities, which were correlated with diminished neurocognitive functioning and clinical symptoms. Zhou and colleagues[17] also found that patients with mTBI examined using fMRI exhibited a reduction in both the fractional amplitude of low frequency fluctuations for the thalamus and connectivity between thalamo-thalamo, thalamo-frontal, and thalamo-temporal regions during resting-state and task-related activities. Another related study, conducted by Tarapore and colleagues[15] investigating patients with mild, moderate, and severe brain trauma using magnetic encephalography showed a reduction in connectivity for the right thalamus and bilateral frontal and parieto-temporo-occipital regions during resting state. In an interesting final study worth noting, Schiff and colleagues[38] showed that deep-brain stimulation of the unspecific thalamocortical system through certain midline thalamic nuclei can produce an alerting effect in a minimally-conscious state patient with severe brain trauma. They interpreted these results as evidence that it is possible to compensate for loss of arousal regulation caused by chronic under activation of potentially recruitable large-scale networks normally controlled by the corticostriatopallidal-thalamocortical system. This raises the possibility that similar approaches might be useful in the treatment of patients with mTBI.

### Simulational and Analytical Evidence

King and colleagues[39] examined brain displacement and deformation in mTBI under experimentally-controlled impact conditions using human cadaveric head and neck specimens, and reported that the strain rate and the product of strain and strain rate in the midbrain region at the vicinity of the thalamus were particularly good predictors for where significant tissue damage was likely to be observed. Both Zhang and colleagues[40] and Vivano and colleagues[41] investigated the susceptibility of different cerebral tissues to injury in mTBI using a finite element model of the human head and similarly concluded that the highest shear stress levels are localized to the midbrain region. Vivano and colleagues also noted that their findings were correlated with memory and cognitive dysfunction. Bayly and colleagues[42] measured in vivo brain deformation in human volunteers undergoing mild posterior-anterior

Table 1. Positive Correlations between MRI Diffusion Measures in Thalamus and Cognitive Outcome for Patients with mTBI[a]

| *MRI diffusion measure* | *Attention (4)*[b] | *Concentration (2)*[b] | *Executive functioning (4)*[b] | *Memory (4)*[b] | *Psychomotor ability (2)*[b] | *Information processing (1)*[b] | *Cognitive impairment (2)*[b] | *Persistent PCS (1)*[b] |
|---|---|---|---|---|---|---|---|---|
| FA (4)[c] | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 |
| MK (2)[c] | 2 | 2 | 0 | 0 | 1 | 1 | 1 | 0 |

[a]Total number of papers assessing correlations ($n=4$; Grossman and colleagues,[8,9] Little and colleagues,[10] and Messe and colleagues[11]).
[b]Total number of papers assessing correlations using indicated cognitive domain.
[c]Total number of papers assessing correlations using indicated MRI diffusion measure.
MRI, magnetic resonance imaging; mTBI, mild traumatic brain injury; PCS, post-concussion symptoms; FA, fractional anisotropy; MK, mean kurtosis.

head deceleration while a series of MRI images with tissue tracking tag lines were obtained to estimate the strain tensor field during impact. It was observed that the brain continued to move when the skull decelerated but was constrained at the basal tethering region, which caused high shear strain fields on certain inner structures that included the thalamus. When the experiment was repeated using an angular acceleration for the head, shear strain fields were found to be mediated by similar factors and analogously increased in the region of the thalamus.[43]

## Conclusions

In addition to anatomical and physiological considerations, there is evidence from forensic histology, advanced quantitative imaging, experimental animal modeling, as well as simulational and analytical methods to suggest that the thalamus might play a significant role in impairment caused by mTBI. Even so, few studies have presently been conducted to explore the susceptibility of this structure to damage and the degree to which it could potentially influence outcome.

To address these matters, it is necessary to determine whether in mTBI the thalamus is subject to primary injury caused by immediate direct traumatic insult or secondary injury caused by long-term indirect degenerative processes related to white matter. On the one hand, the findings reported by Bayly and colleagues,[42,43] King and colleagues,[39] Ross and colleagues,[19] Vivano and colleagues,[41] and Zhang and colleagues[40] seem to support a primary injury model. On the other hand, the results described by Adams and colleagues,[21] Anderson and colleagues,[7] and Natale and colleagues[22] appear to corroborate a secondary injury model. Perhaps, therefore, some combination of primary and secondary injury is at work since both these mechanisms do not necessarily have to be mutually exclusive. This is indeed what the diffusion imaging investigations carried out by Grossman and colleagues[8,9] suggest, in which patients with mTBI demonstrated moderate correlations between measures for the thalamus, indicating primary injury, and between measures for the thalamus and total white matter, indicating secondary injury.

An understanding of the role played by thalamic damage in mTBI would be greatly improved if certain key experimental predictions could be tested. This, however, is made complicated by the fact that histopathology, considered the gold standard, is difficult to obtain since most patients do not die from such injury. One approach to addressing the matter, for example, might be to perform studies on non-human primates sacrificed to examine tissue samples from specific thalamic nuclei following various simulations of mild head injury accompanied by behavioral and psychophysics analysis.

Considering the strategically vital position of the thalamus to brain functioning and evidence pointing to its probable involvement in the pathophysiology of mTBI, there seems every reason to continue investigating these questions further and determine whether it can yield biomarkers helpful for early prediction of long-term or permanent brain damage and cognitive outcome.

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