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The Predictive Brain State: Timing Deficiency in Traumatic Brain Injury?

Jamshid Ghajar, MD, PhD, Richard B. Ivry, PhD, and the Cognitive and Neurobiological Research Consortium

Attention and memory deficits observed in traumatic brain injury (TBI) are postulated to result from the shearing of white matter connections between the prefrontal cortex, parietal lobe, and cerebellum that are critical in the generation, maintenance, and precise timing of anticipatory neural activity. These fiber tracts are part of a neural network that generates predictions of future states and events, processes that are required for optimal performance on attention and working memory tasks. The authors discuss the role of this anticipatory neural system for understanding the varied symptoms and potential rehabilitation interventions for TBI.

Preparatory neural activity normally allows the efficient integration of sensory information with goal-based representations. It is postulated that an impairment in the generation of this activity in traumatic brain injury (TBI) leads to performance variability as the brain shifts from a predictive to reactive mode. This dysfunction may constitute a fundamental defect in TBI as well as other attention disorders, causing working memory deficits, distractibility, a loss of goal-oriented behavior, and decreased awareness.

“'The future is not what is coming to meet us, but what we are moving forward to meet.”

—Jean-Marie Guyau


TBI is a global health problem in terms of incidence, cost, and impact on daily living. Worldwide, an estimated 57 million individuals have been hospitalized with TBI. The Glasgow Coma Scale (GCS) has come to serve as a standardized assessment instrument to classify the severity of TBI, with scores ranging from a low of 3 (comatose) to 15 (awake and following commands). The GCS score is a reliable measure of the level of consciousness, but it is of questionable utility for assessing current cognitive status and predicting longer-term cognitive sequelae. Additional assessments are especially critical given that more than 80% of individuals classified as mild TBI or concussion have GCS scores between 13 and 15. In the United States, medical center emergency rooms report approximately 1.74 million cases of mild TBI. These estimates fail to include unrecognized or unreported TBI cases that may number up to 3 million for sports-related injuries and up to 40% for personnel participating in current military engagements.

Mild TBI or concussion with a normal GCS score implies little or no brain injury; indeed, CT imaging studies reveal traumatic lesions in less than 15% of patients. Cognitive sequelae, which are difficult to measure, are often ascribed to the traumatic event or pre-morbid factors. However, we postulate that subtle brain white matter tract lesions that are not detected by standard forms of neuroimaging may lead to chronic difficulties in complex cognitive tasks. These white matter tract lesions are located predominantly in anterior cerebral areas, which are selectively vulnerable to rotational shearing injury. Furthermore, these fiber tracts are part of a neural network that generates predictions of future states and events, processes that are required for optimal performance on attention and working memory tasks. We hypothesize that impairments in this anticipatory process likely contribute to the fact that approximately 20% of individuals with TBI end up being classified as chronically disabled.

Unless otherwise specified, we use the term “TBI” to denote mild TBI patients and survivors of more severe TBI who are awake and responsive. Although we expect the general ideas advanced here are relevant for understanding the cognitive deficits in all forms of TBI, much of the discussion in the literature has centered on accounting for the cognitive deficits that persist even in individuals with relatively mild overt symptoms.
THE PREDICTIVE BRAIN STATE

Currently, there is no causative explanation for the attention deficits and persistence of symptoms in TBI patients. An extensive review of TBI by Alexander finds no single psychological, physiologic, somatic, or demographic factor that can account for persistent postconcussive symptoms (PCS). Many PCS symptoms are equally compatible with diagnoses of depression, anxiety, and chronic pain as they are with disorders of cognition. The lack of a clear understanding of the mechanisms underlying concussive symptoms has important consequences for the treatment of these individuals. For example, clear assessment guidelines are lacking to help determine when it is appropriate for athletes with concussive symptoms to resume sports, in large part because there is no consensus on objective measures to assess the level of cognitive function at which there remains a high vulnerability for reinjury.

A widely accepted view is that frontal lobe damage underlies the cognitive deficits associated with TBI. This view is consistent, to some degree, with the central role attributed to this brain region in functions related to attention and working memory. However, frontal lobe lesion volumes in TBI patients do not correlate with neuropsychological deficits. This observation, coupled with more sophisticated models of cognition, suggests that these complex processes involve distributed neural networks and that the effects of TBI reflect disruption of these networks. While TBI certainly results in frontal-like symptoms, one goal in this review is to encourage a broader conceptualization of how TBI might disrupt control processes. In particular, we outline a network-based hypothesis that emphasizes an impairment in anticipatory control, a form of prediction. Rather than attribute this process to a single neural region such as the frontal lobe, we consider how this predictive aspect of brain function emerges through the interactions of frontal and parietal regions, as well as the cerebellum.

A core premise we develop in this article is that one aspect of attention emerges from the generation of moment-to-moment expectancies about the immediate future. To be clear, we argue that the causal link here is not that sensory expectancy requires attention; rather, we propose that attention is the consequence of, or rather, is manifest as expectancies of the future. These expectancies are a core feature of goal-oriented behavior, providing predictions to be compared with sensory feedback. These expectancies, based on prior experience, are essential for ensuring the fluid operation of cognitive functions, allowing them to be anticipatory rather than reactive. One consequence of successful anticipation is that performance becomes less variable. By accurately anticipating the future, the performer is less likely to miss task-relevant information or be distracted by irrelevant information, 2 prominent sources of errors. By anticipation, the individual is “paying attention,” creating a future-oriented brain state.

Anticipatory Neural Network

Prediction is a general feature of cognition, operating over multiple time scales. When driving, we may anticipate the actions of an oncoming car as well as think about the location of a lunch-stop, 100 miles down the highway. Within the framework of our model of TBI-related cognitive deficits, we limit our discussion to the saliency of short-range predictions that require the comparison of expectancies and feedback with real-time properties. We hypothesize that these temporal predictions emerge from the interactions of a network involving frontal, parietal, and cerebellar areas (Table 1). Could one prominent source of performance variability in TBI be related to an impaired ability to generate and/or maintain predictive states? Our premise is that disruption of the connectivity between these areas affects this predictive capability and, as such, results in deficits in goal-oriented behavior arising from problems with attention and working memory.

One way to examine the neural underpinnings of prediction is to study the activation and coherence of activation in and between cortical areas that are required for anticipatory activity in attention and working memory. Studies of spatial attention frequently use tasks in which a cue, indicating either the probable location of a stimulus or serving solely as an alerting signal, is followed after a short delay by an imperative stimulus. Neuroimaging studies consistently reveal that, following the cue, a network encompassing the dorsolateral prefrontal cortex (PFC) and parietal lobe is engaged, most prominently in the right hemisphere. In addition to this cerebral cortical network, anticipation also engages the cerebellum; functional magnetic resonance imaging (fMRI) studies consistently show activation of the cerebellum during the interval following attentional cues (Figure 1). This activation is not dependent on the presence of movement, although it may require the preparation of a potential response.

Electrophysiological markers of anticipation associated with the PFC include the readiness potential (RP) on tasks in which the movement is self-initiated and contingent negative variation (CNV) when the response is initiated following an imperative stimulus. In TBI patients, the CNV amplitude is decreased. Reaction times become more variable, and errors in performance correlate with the amplitude of the CNV. There are also reported reductions or absence of the RP in TBI patients in self-initiated movements (Figure 2), similar to that
observed in patients with lesions of the cerebellar dentate nucleus. The cerebellum (and basal ganglia) are assumed to contribute to the RP and CNV through thalamic relays. Similar findings of decreased frontal preparatory electroencephalography have been reported to predict deficits in attention in normal volunteers. The relationship between parietal and PFC anticipatory activity has been examined in various ways. Within the parietal lobes, anticipatory markers are observed in inferior parietal lobule (IPL), intraparietal sulcus, and the posterior parietal area. A recent functional connectivity study identified 2 distinct networks. A fronto-parietal-cerebellar network was consistently engaged following cues indicating the onset of experimental tasks; in contrast, a cingulo-opercular network was selectively associated with the maintenance of internal goals. The former was most active in predictable situations, when the conditions allow the participants to know when a stimulus will appear rather than when the stimuli occur at random points in time. This observation underscores the temporal property of this attentional network. Goal maintenance or intention is generally independent of this temporal constraint.

The frontal-parietal network is also activated in working memory tasks. Variability in antecedent activity in IPL can predict on a trial-to-trial basis performance on a working memory task. Interestingly, initial encoding in a working memory task does not correlate with performance unless there is a high level of sustained activity in PFC and IPL during the maintenance period before retrieval.

Polysynaptic tracers have been used to identify cerebral cortical targets of the deep cerebellar nuclei in the monkey. This work has shown that, in addition to
projections to primary and secondary motor areas, there are significant cerebello-thalamo-cortical projections to the prefrontal and parietal cortex. These anatomical connections could be essential for refining anticipatory neural activity in the cortex. Within the domain of sensorimotor control, it has been hypothesized that the cerebellum generates forward models related to the consequences of planned actions and the resultant changes in sensory feedback. Extending this idea to a more general role in anticipation that includes the prefrontal and parietal cortex, the specialized role of the cerebellum may be to provide the precise timing for these predictions. As such, increases in performance variability could be a consequence of poorly formed predictions. We recognize that a lack of preparation can arise from many causes. For example, performance will be variable if an alert person is unable to maintain the current goal. Less consideration has been given to preparatory problems that may result from failures of anticipation, or predictions that are mistimed.

These findings suggest that the PFC, IPL, and cerebellum interact to maintain information during delay periods associated with anticipatory activity, either related to the expectation of an imperative stimulus or the retrieval of information from working memory. Models of these interactions suggest a synchronization process that enables an expectancy to be maintained and compared with incoming sensory information (Figure 3).

Performance Variability, Predictive Timing, and Self-Agency

In most studies, performance variability is considered at the group level. Individual variability tends to be ignored, with the various observations in each condition collapsed into a single mean. However, in terms of the study of attention and anticipation, intra-individual variability (IIV) is likely to prove quite informative. Interestingly, variability has frequently been the primary dependent variable in studies of temporal processing. A recent review finds that high IIV is a prominent feature of TBI. In addition to an increase in IIV and their resultant errors, TBI patients have longer reaction times, are more distractible, and experience difficulty in sustaining attention. Similarly, the IIV that occurs in TBI is associated with decreased awareness and, in high variability states, a lack of awareness and self-agency.

Accurate predictive timing, the ability to synchronize what is expected with what is observed, produces low variability and a heightened focus of attention and self-agency. This ability is a prerequisite for performance that will be less prone to interference or distraction. The better one attends, the more aware one can be of the object of attention.

ANTERIOR AXONAL SHEARING AND SYMPTOMS

The preceding discussion outlines a general model in which well-timed predictions can yield attentional control that results in decreased IIV and reduced distractibility, and consequently, improved performance and awareness. This predictive process may be selectively disrupted in TBI due to the rotational shearing vulnerability of white matter tracts that support this preparatory activity. In addition, compensation for variable predictive timing by increased prefrontal cortical recruitment may explain many of the “secondary” post-concussive symptoms of TBI.

Diffuse Axonal Injury

Diffuse axonal injury (DAI), also known as traumatic axonal injury when lesions are more focal, resulting
from rotational shear forces\textsuperscript{65-67} is common in TBI\textsuperscript{68} and may account for persistent cognitive deficits and symptoms.\textsuperscript{69,70} This pattern of injury, distinguished from focal contusion without shearing, is characterized by damage to anterior axons at the gray/white matter junction of the cerebral hemispheres, corpus callosum, and in severe cases, dorsolateral midbrain. These patterns of shearing are often accompanied by similar damage in the superior cerebellar peduncles.\textsuperscript{71,72} Deep white matter abnormalities on magnetic resonance imaging (MRI) are associated with poorer neuropsychological test performances and poor long-term outcome.\textsuperscript{73} The severity of deep white matter tract injury may explain many TBI-induced cognitive deficits, ranging from mild concussion to the vegetative state.\textsuperscript{74,75}

The normal CT or MRI scans observed in the majority of cases of mild TBI may belie microscopic axonal pathology. The sensitivity of most MRI structural studies is insufficient to detect white matter tract disruption or small areas of edema. Postmortem analysis, when conducted within a few hours of severe TBI, shows extensive microscopic hemorrhages and severing of nerve fibers in pons, midbrain, and corpus callosum, consistent with shearing forces.\textsuperscript{76} Even in TBI cases classified as mild (in which the patients died of other causes), white matter microhemorrhages in the brain stem, cerebral hemispheres, and corpus callosum are evident.\textsuperscript{77}

**DAI and Deficits in Attention and Working Memory**

MRI diffusion tensor imaging (DTI) uses the characteristics of water diffusion to assess the integrity of white matter pathways.\textsuperscript{78} This method has been used to better quantify the extent of DAI damage\textsuperscript{79-82} and clinical outcome\textsuperscript{11} following TBI. Deficits in processing speed, working memory, and attention have been attributed to DAI.\textsuperscript{83,84} In addition, DAI patients have broader cortical activation in working memory tasks.\textsuperscript{85} More recent studies suggest that DAI can cause chronic postconcussive symptoms in executive function and memory dysfunction.\textsuperscript{69,81,86-88} Compared to conventional structural studies, DTI appears to be more sensitive and accurate\textsuperscript{89} in correlating pathology with attention and memory deficits (Figure 4).\textsuperscript{90,111} These observations suggest that white matter shear injury in TBI plays a prominent causal role in the observed cognitive deficits.

As revealed by DTI, the predominant sites for mild TBI axonal shearing are located in anterior white matter tracts connecting PFC with posterior cortical regions and subcortical structures.\textsuperscript{91,111} Even in normal patients, DTI imaging shows a significant correlation between working memory function and maturation of white matter tract connectivity between the PFC and the parietal lobe.\textsuperscript{92} PFC and IPL have reciprocal connections with the cerebellum with input passing through the internal capsule and pons and output through the superior cerebellar peduncle and thalamus. Shearing anywhere along this pathway could disrupt preparatory neural processes, as well as comparison processes in which these predictive representations are compared to sensory input.

The diffuse character of TBI has traditionally discouraged rigorous studies of structure-function relationships. However, recent results from our research group report a significant dissociation between cognitive impairments in TBI individuals with predominant pathology in the anterior corona radiata or uncinate fasciculus. The former connects the lateral PFC with other cortical areas, thalamus, and cerebellum; the latter serves as a primary pathway between the lateral PFC and parahippocampal cortex. Patients with prominent shearing in the uncinate fasciculus exhibited deficits in working memory tasks. In contrast, patients with prominent shearing in the anterior corona radiata exhibited deficits in tasks of executive attention.\textsuperscript{111} Others have reported significant DTI changes in tracts that support working memory in TBI patients.\textsuperscript{90} The direction of rotational shear forces at the time of TBI may lead to shearing in certain pathways due to differences in tract orientation.

**TBI Symptoms: Predictive Timing Deficits and Compensation?**

The most common postconcussive symptoms encountered after TBI\textsuperscript{10,13,93} are traditionally grouped into 3 categories: cognitive, somatic complaints, and affective

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**Figure 4.** Magnetic resonance imaging–diffusion tensor imaging images in a normal control individual and a mild traumatic brain injury (TBI) patient. The patient shows reduced white matter integrity in the right anterior corona radiata (ACR) shown by the circled region, compared to the normal individual’s circled left and right ACR. Courtesy of Niogi S, Weill Medical College of Cornell University.
complaints (Table 2). Cognitive function is a major predictor of poor outcome in TBI patients. In particular, working memory is vulnerable and likely underlies many of the prominent problems associated with daily life activities that require planning and problem solving. Similar neuropsychological deficiencies are seen in children with TBI. Some symptoms of TBI may result from damage to core cognitive processes, whereas others may be due to compensatory mechanisms recruited to minimize the ensuing performance variability.

The performance of individuals with TBI is especially vulnerable to tasks that tax attention, such as when task-relevant and task-irrelevant stimuli are intermixed, or if there is an increase in task difficulty. Activation patterns in chronic patients with TBI tend to be abnormal on tasks of executive function. These abnormalities may be manifest as more diffuse patterns of cortical recruitment or as greater increases in prefrontal activity despite performance levels that are below that observed in controls. Even when performance is matched to controls, TBI patients with diffuse axonal injury exhibit elevated prefrontal activation on working memory tasks (Figure 5).

These findings of increased cortical activation during cognitive tasks in TBI patients is similar to those reported for aging, stroke, and Alzheimer’s disease. These effects have been related to increased variability in reaction time and inconsistency in performance.

Could the increase in cortical recruitment in TBI reflect a compensatory mechanism arising because anticipatory neural activity is disrupted? Consider an analogy to cerebellar dysmetria. This disorder results in increased cortical control to correct trajectory deviations, a compensatory process that can correct for impairments in the feed-forward processes dependent on the cerebellum. An increase in prefrontal activity may be a response to the disruption of predictive mechanisms for cognition, perhaps triggered by an increase in performance variability and errors in performance. Evidence in support of this hypothesis comes from a developmental fMRI study of working memory. Compared to adults, children exhibited weaker PFC-IPL coherence and greater activation of PFC during the delay period. These neural changes were accompanied by higher performance variability and distractability. Similar studies need to be done in TBI patients to investigate if a similar dissociation is observed between measures of PFC-IPL-cerebellar coherence and local activation levels.

<table>
<thead>
<tr>
<th>Cognitive</th>
<th>Somatic</th>
<th>Affective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory difficulty*</td>
<td>Headache*</td>
<td>Depression</td>
</tr>
<tr>
<td>Attention deficit</td>
<td>Fatigue*</td>
<td>Irritability*</td>
</tr>
<tr>
<td>Decreased concentration*</td>
<td>Insomnia</td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td>Balance and coordination problem</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tinnitus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep disturbances*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sensitivity to noise or light*</td>
<td></td>
</tr>
</tbody>
</table>

Classifying symptoms based on the framework outlined in this article would posit that postconcussive symptoms encountered after a TBI could be grouped into primary and secondary causes (Table 3). Primary symptoms arise from TBI axonal shearing in white matter tracts connecting the PFC-IPL-cerebellar network leading to decreased PFC-IPL coherence (Figure 6). The resulting increase in variability would be manifest as increased distractibility, working memory deficits, and problems with balance and coordination. An inability to anticipate sensory events, resulting in a temporal mismatch of sensory expectation to actual sensory input, could lead to dizziness, tinnitus, and sensory hypersensitivity. Self-agency would be abnormal due to the desynchronization between actions and their resulting consequences.

Secondary symptoms might be a consequence of heightened activation of the PFC. This might arise from an increase in error signals and performance variability. PFC recruitment, serving as a compensatory mechanism, could help bridge the moment-to-moment temporal discrepancies. The expended effort might underlie fatigue, headache, irritability, anxiety, and when prolonged, depression.

### Variability As a Metric of Prediction

If a consequence of accurate anticipation is a reduction in performance variability, then variability can be used as a metric to assess this aspect of attention. By definition, attention varies over time. Relatively continuous and extended measures of performance should be used to gauge moment-to-moment fluctuations in performance within individuals. Tasks used to assess IIV have typically involved relatively discrete measures such as reaction time, allowing measurements, at best, every few seconds. Such measures may be relatively insensitive to lapses in attention.

We have employed a task in which we measure circular smooth pursuit eye movements during a predictive tracking task, lasting 2.5 seconds using a high-resolution camera sampling performance at 500 Hz over blocks of 20 trials. The predictive nature of this task engages the PFC-parietal-cerebellar network, similar to that observed in studies of spatial attention. The variability in the difference between eye and target position, as well as velocity error (the difference between target velocity and eye velocity), both correlate with performance on a working memory task. TBI patients with chronic cognitive symptoms had higher variability and a persistent lag in eye position compared to control individuals. Further studies have demonstrated that adding a concurrent secondary task (short-term verbal memory) during the smooth pursuit tracking task produces different effects on velocity error variability in control and TBI patients. In TBI patients, there is a significant increase in variability as the difficulty of the secondary task increases. In contrast, control individuals showed a decrease in velocity error variability when the length of the word list was increased, a counterintuitive finding, yet one that is also observed in other attention-loading situations.

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**Table 3. Post-Concussive Symptoms**

<table>
<thead>
<tr>
<th>Primary Symptoms – Related to Predictive Timing Deficit</th>
<th>Secondary Symptoms – Related To PFC Compensation and Error Signaling</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreased attention</td>
<td>• Fatigue</td>
</tr>
<tr>
<td>• Decreased memory</td>
<td>• Headache</td>
</tr>
<tr>
<td>• Decreased concentration</td>
<td>• Insomnia</td>
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<tr>
<td>• Balance and coordination problem</td>
<td>• Irritability</td>
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<tr>
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<td>• Dizziness</td>
<td>• Depression</td>
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<tr>
<td>• Tinnitus</td>
<td></td>
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<tr>
<td>• Sensory sensitivity</td>
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</table>

**Figure 6.** Figure showing predominant focal areas of diffuse axonal injury (DAI).
studies with normal individuals (Ghajar J, Suh M, Kolster RA, et al. Smooth pursuit eye movement variability under dual-task load predicts white matter shear injury in mild TBI patients. Society for Neuroscience 37th Annual Meeting. San Diego 2007) (Figure 7). We suggest that the secondary task results in increased recruitment of the PFC, with the consequence of greater coherence across the prefrontal-parietal-cerebellar network required for tracking. In TBI, a similar increase in PFC activity can support secondary task performance but fails to result in benefits on the tracking task. Indeed, by diverting resources from the tracking task, performance becomes more variable.

SUMMARY

The inability to efficiently and consistently use predictive mechanisms, even with increased prefrontal cortical activation, is posited to be a major cause of disability in TBI, and possibly other disorders of attention. Damage to a prefrontal-parietal-cerebellum network, both from direct neural insult and shearing of the white matter tracts linking these areas, impinges on this predictive capability. The cerebellum is posited to be involved in producing the requisite timing required to match predictions and the consequences of actions. In the absence of this timing, the PFC must be reactive in integrating expectancies and input. A breakdown in anticipatory behavior will result in an increase in performance variability and a host of profound disturbances of cognition, some of which are the direct result of the pathology and some of which arise as part of compensatory processes.

Current accounts of TBI that emphasize a loss of top-down control of attention dependent on the prefrontal cortex are insufficient to explain the deficits in TBI. A perspective that focuses on how the brain generates predictive states through the interaction of the prefrontal and parietal cortex, coupled with feed-forward timing from the cerebellum, may offer a more complete account. Presently, there are not strong data to support either model. However, the predictive brain state model offers a testable scientific construct, as well as a framework that can be useful in diagnostic and therapeutic interventions that emphasize individual variability in performance.

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