Network topology and dynamics in traumatic brain injury
Aron K Babey1,2,3,4,5,6,7, Antonio Bell8, Ann Logan8, Rachael Rubin1,2,9, Marta Zamroziewicz1,2 and Joachim T Operskalski1,2

We propose a network approach to clinical translation that defines core behavioral phenotypes of traumatic brain injury (TBI) with respect to damage to specific intrinsic connectivity networks (ICNs). We survey recent approaches to clinical translation from cognitive neuroscience that enhance network function and recovery from brain injury through interventions that deliver targeted (network specific) and global (systemic) effects. A network approach provides insight into the mechanisms of brain injury, linking ICN characteristics to specific profiles of cognitive impairment, providing key neurobiological targets for therapeutic intervention, and motivating new perspectives about the nature of cognitive recovery and rehabilitation in TBI.

Addresses
1 Decision Neuroscience Laboratory, University of Illinois, Urbana, IL, USA
2 Beckman Institute for Advanced Science and Technology, University of Illinois, Urbana, IL, USA
3 Department of Internal Medicine, University of Illinois, Champaign, IL, USA
4 Department of Psychology, University of Illinois, Champaign, IL, USA
5 Department of Speech and Hearing Science, University of Illinois, Champaign, IL, USA
6 Neuroscience Program, University of Illinois, Champaign, IL, USA
7 Institute for Genomic Biology, University of Illinois, Champaign, IL, USA
8 College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, UK
9 Carle Neuroscience Institute, Carle Foundation Hospital, Urbana, IL, USA

Corresponding author: Babey, Aron K (babey@illinois.edu)
URL: http://DecisionNeuroscienceLab.org/

Pathophysiology of TBI
The pathophysiology of TBI encompasses a cascade of events that produce focal and diffuse neuronal injury [3–5]. The primary effects of injury in non-penetrating TBI are caused by mechanical forces imparting linear or rotational acceleration to the brain that result in a combination of pathoanatomical abnormalities [6]. These abnormalities include localized contusions, stretching and shearing of axons in the white matter and deep cerebral structures, tissue lacerations, and tearing of intracranial vessels [3]. The primary injury, which occurs at the time of the initial impact and is not amenable to treatment, is followed by the activation of a complex interplay of pathophysiological mechanisms and compensatory responses that evolve over several hours, days or weeks. These responses will ultimately result in either further neuronal damage, known as secondary injury, or cellular repair and reorganization of neural connections that are potentially amenable to treatment. Known mechanisms of secondary injury include ischemia, neuroinflammation, excitotoxicity, and oxidative stress [3–5].

TBI produces a range of cognitive, affective, social, and behavioral sequelae that affect neurological function,
quality of life, independence, and social interaction [7]. Neurobehavioral impairments correlate with the severity of head trauma as defined by the Glasgow Coma Scale (GCS), which provides a broad classification of mild (GCS of 13–15), moderate (GCS of 9–12), and severe injury (GCS of 3–8). TBI severity reflects the presence of key neurobehavioral features of post-traumatic encephalopathy [8], which include impairments in arousal, awareness, episodic memory, and executive functions (Table 1). Severe TBI is typically characterized by protracted impairment across all levels, including processes for: (1) general alertness and readiness to respond to the environment (arousal); (2) the ability to detect behaviorally salient events (awareness); (3) the internal focus of attention during self-referential cognitive activity (episodic memory); and (4) the external focus of attention during goal-directed, cognitively demanding tasks (executive functions). By contrast, moderate and mild TBI are typically expressed by primary impairments in episodic memory and executive functions.

Whereas standard neuroimaging techniques (MRI or CT) are able to detect severe brain damage, mild and often moderate TBI, which typically reflect traumatic axonal injury, may not show meaningful structural abnormalities using conventional approaches. Recent progress in neuroimaging methods supports a more fine-grained classification of brain injury, providing evidence that traumatic axonal injury is a key determinant of persistent cognitive impairment [9] and suggesting that the neurobehavioral features of post-traumatic encephalopathy can be derived from an examination of the structural and functional integrity of large-scale ICNs [10].

### Table 1

<table>
<thead>
<tr>
<th>PTE stage</th>
<th>Primary impairment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Coma</td>
<td>Arousal</td>
<td>Impaired arousal with no response to sensory stimulation and no spontaneous behavior</td>
</tr>
<tr>
<td>2. Delirium</td>
<td>Awareness</td>
<td>Reduced awareness of the environment with impairments in the ability to focus, sustain, and/or shift attention</td>
</tr>
<tr>
<td>3. Amnesia</td>
<td>Episodic memory</td>
<td>Impaired episodic memory, including orientation to time, place, and context, as well as autobiographical memory for the immediate post-injury period</td>
</tr>
<tr>
<td>4. Dysexecutive syndrome</td>
<td>Executive functions</td>
<td>Impaired executive functions for goal-directed behavior, including working memory, reasoning, judgment, and decision making</td>
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A network approach to clinical translation

A fundamental challenge for TBI research is to characterize the neurological impairment produced by the injury and to link these factors to specific cognitive, affective, social, and behavioral deficits. Clinical diagnosis and treatment of TBI is further complicated by secondary, downstream effects of brain injury, which may include post-traumatic stress disorder, dementia, psychosocial health problems, epilepsy, pain, and other alterations in personality and behavior [3]. Repeated exposure to head trauma may produce additional complications and result in chronic traumatic encephalopathy, a progressive neurodegenerative disease known to affect boxers and retired professional football players [11]. Thus, when examined in the context of broad classification methods (e.g., the GCS), the complex pathophysiology and prognosis of TBI can be extremely difficult to characterize.

These concerns highlight the need for accurate and precise TBI assessment standards [10] and have motivated recent efforts in cognitive neuroscience to move beyond broad classifications of behavior — reflected in the standard diagnosis of ‘mild’, ‘moderate’, or ‘severe’ TBI — and instead to characterize the structural and functional integrity of specific ICNs following TBI [10,12,13]. This approach has the potential to advance our understanding of the mechanisms of brain injury, linking ICN characteristics to specific profiles of cognitive impairment. A network approach to clinical translation would also provide critical information to guide therapy — identifying specific neurobiological targets for intervention and motivating a tailored approach based on the patients’ profile of network impairment, cognitive deficits, and functional goals.

Behavioral phenotypes of TBI

TBI is fundamentally characterized by impairments in cognitive control — a set of capacities that enable the regulation and control of attention, memory, and thought. Cognitive control enables an individual to override automatic responses to the immediate environment and to flexibly allocate cognitive resources to support goal-directed, purposeful behavior [14**,15]. Cognitive control functions provide the basis for planning, problem solving, and enable adaptive behavior in response to functional loss [16].

Accumulating neuroscience evidence indicates that cognitive control functions are implemented within a distributed network of highly interconnected brain regions that are susceptible to focal cortical contusions and traumatic axonal injury in TBI [17**,18–22]. These networks enable communication across long distance cortical sites and reflect structural and functional
interactions among brain regions. Three ICNs have been the focus of research on cognitive control (Figure 1): (1) the salience network [23**]; (2) the default mode network [24**]; and (3) the central executive network [25**]. The salience network comprises nodes within the anterior insula and dorsal anterior cingulate cortex, and directs attention to behaviorally salient events in the internal and/or external environment, such as emotions and interoceptive states (the sense of the physiological condition of the body) [23**]. The default mode network comprises regions within the ventromedial prefrontal cortex, posterior cingulate cortex, angular gyrus and medial temporal lobe, and enables the internal focus of attention during self-referential cognitive activity, autobiographical memory and social cognition [24**]. The central executive network is comprised primarily of the dorsolateral prefrontal cortex and the posterior parietal cortex, and supports the external focus of attention during goal-directed, cognitively demanding tasks [25**].

We propose that the neurobehavioral features of post-traumatic encephalopathy [8] and classic behavioral phenotypes of TBI [27] emerge from selective damage to each cognitive control network. Damage to the salience

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network produces deficits in awareness, as evidenced by impairments in the ability to focus, sustain, and/or shift attention. Damage within the default mode network produces impairments in internally oriented tasks, including autobiographical memory, mental representations of situational knowledge (e.g., time and place) and social behavior (e.g., imagining the perspective of others). Central executive network dysfunction results in the classic dysexecutive syndrome marked by impairments in externally oriented tasks that engage, for example, general intelligence [17**,28], fluid intelligence [18], cognitive flexibility [22], working memory [29,30], and problem solving [31].

We advocate a systems-level approach to characterizing behavioral phenotypes of TBI and propose that each ICN supports specific facets of cognitive control (Table 2). These networks together comprise a dynamic system that mediates goal-directed behavior across multiple tasks and cognitive demands. According to this framework, the relative engagement of each network reflects the recruitment of specific control operations. Internally oriented tasks selectively activate the default mode network, whereas externally oriented tasks preferentially engage the central executive network [32–35]. The salience network is known to modulate recruitment of the default mode and central executive networks and therefore supports interactions between the processing of internally versus externally oriented tasks [36,37].

Research on the basic properties of the cognitive control system motivates hypotheses about the nature of network dysfunction in TBI. The cognitive control system consists of association areas that use feedback control to regulate processes in a variety of brain systems [15,38,39]. Computational models indicate that cognitive control is implemented in two primary steps [40**]: first, a goal is selected via reward prediction by the basal ganglia (‘goal setting’ process); and second, a sequence of actions (or subgoals) that can be performed to achieve the goal are selected by matching the current state to the maintained goal state (‘goal searching’ process). Feedback control mechanisms support the maintenance of homeostatic balance across ICNs, enabling adaptive behavior and coordination. The control system’s ability to regulate other networks lead it to reduce goal-disrupting processes that manifest overtly as symptoms of TBI (Table 1). Thus, TBI is a disorder in which network disruption produces impairments in cognitive control and in the capacity to regulate harmful symptoms.

### Network diagnostics in TBI

Methods from network science [41] have sharpened our understanding of network dysfunction in TBI, providing diagnostic tools [42,43,44**] to measure the structural and functional integrity of ICNs following brain injury. Network diagnostics support a detailed characterization of the respects in which ICNs are damaged and enable a more precise understanding of how behavioral phenotypes of TBI emerge from specific types of network dysfunction (Table 2).

Network diagnostics provide information about network segregation, integration, and influence [45] (Figure 2). Network segregation refers to the degree to which a network’s elements form separate clusters (measured by the clustering coefficient; Figure 2a). Network integration refers to the capacity of the network to become interconnected and communicate information (measured by path length and distance; Figure 2b). Finally, network influence indicates how individual regions or connections are embedded in the network and the extent to which they contribute to the networks structural integrity and functional organization (measured by node degree and centrality; Figure 2c,d, respectively).

By mapping the topology of ICNs along with the patient’s profile of brain damage, network diagnostics can be applied to characterize the influence of brain damage on network function and therefore to understand the nature of cognitive control deficits resulting from brain injury. From this perspective, damage to regions or connections that have high values of network influence will produce more severe impairments to ICN function. This hypothesis has recently been applied to account for the observed variability in the effects of focal brain injury on cognition [46–50], explaining why in some cases focal injury produces widespread cognitive impairment (high network influence), whereas in other cases only limited deficits are observed (low network influence). Indeed, recent studies have examined network metrics in the context of brain injury and demonstrated that damage to regions with high network centrality (i.e., hub regions

<table>
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<th>PTE stage</th>
<th>Primary impairment</th>
<th>Cognitive control process</th>
<th>Network dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Coma</td>
<td>Arousal</td>
<td>System-wide dysfunction</td>
<td>Global</td>
</tr>
<tr>
<td>2. Delirium</td>
<td>Awareness</td>
<td>Attention to behaviorally salient events</td>
<td>Salience network</td>
</tr>
<tr>
<td>3. Amnesia</td>
<td>Autobiographical memory</td>
<td>Internal focus of attention</td>
<td>Default mode network</td>
</tr>
<tr>
<td>4. Dysexecutive Syndrome</td>
<td>Executive functions</td>
<td>External focus of attention</td>
<td>Central executive network</td>
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Table 2: Network dysfunction associated with each stage of post-traumatic encephalopathy (PTE).
Figure 2

Network diagnostics, (a) The clustering coefficient represents the extent to which a node’s neighbors are connected among themselves. The ‘high clustering’ node (highlighted in red) has a total of six neighbors. These neighbors maintain 8 out of 15 possible connections (with a clustering coefficient of 0.53). By contrast, the ‘low clustering’ node (highlighted in red) has five neighbors with only one mutual connection. (b) The length of the shortest path corresponds to the distance between two nodes. The two nodes (highlighted in black) connect to each other in three steps, with a shortest path that travels through two intermediate nodes (shown in gray). (c) Node degree is the number of links attached to a given node. (d) The example network shown here can be decomposed into two ICNs that are interconnected by a single hub node (highlighted in red). Figure modified with permission from [45].

that connect multiple ICNs; Figure 2d), result in severe and widespread cognitive impairment [46–50].

An emerging area of research investigates dynamic aspects of ICN function [36,37] and motivates hypotheses about the effects of TBI on global network dynamics [51**,52–58]. Recent findings indicate that the salience network modulates recruitment of the default mode and central executive networks [36,37]. According to this view, the salience network supports interactions between the processing and maintenance of internally versus externally oriented tasks. In particular, the anterior insula is involved in evaluating the salience of incoming stimuli and initiating a behavioral response via engagement of appropriate ICNs [59,60]. Anterior insula dysfunction within the salience network might induce deviant salience mapping and cause aberrant engagement and disengagement of ICNs [61], giving rise to attentional impairments and inadequate regulation and control of behavior. Such impairments are a hallmark of TBI and are often expressed in the form of disinhibition, childishness, aggressive and abusive behavior, selfishness, and impulsivity [27]. Indeed, aberrant interactions between default mode, salience, and central executive networks, due to insular dysfunction within the salience network, may represent a fundamental characteristic of cognitive control deficits in TBI.

A growing body of evidence supports the efficacy of network diagnostics for TBI, demonstrating abnormalities in functional connectivity within ICNs following mild TBI [51**,52], in addition to altered global network dynamics [53]. The application of multivariate statistics to predict outcome using neuroimaging metrics provides a powerful approach for the discovery of neural biomarkers of TBI [62]. Furthermore, recent developments in the assessment of dynamic intrinsic connectivity across short temporal epochs [63,64] may provide further precision in characterizing the temporal dynamics of ICNs following TBI. Thus, this burgeoning area of research applies network diagnostics to establish more accurate and precise TBI assessment standards and motivates new
research to investigate how network topology and dynamics are shaped by therapeutically effective interventions for TBI.

**Interventions for network dysfunction in TBI**

The brain’s natural response to injury is characterized by: (1) the activation of cell repair mechanisms to reduce edema and inflammation [65]; (2) functional cell plasticity and modification of previously existing ICNs; and (3) anatomical plasticity to support the formation of new connections [66]. Thus, functional and structural plasticity enable the reorganization and repair of ICNs to support cognitive recovery in TBI [67–70].

Accumulating neuroscience evidence indicates that the brain’s capacity to recover from injury depends on cognitive reserve [71–73]. The cognitive reserve hypothesis explains variability in symptom expression following TBI on the basis of individual differences in vulnerability to the effects of brain injury and the capacity to adapt or compensate for functional loss [73,74]. The cognitive reserve hypothesis is supported by evidence demonstrating that lifestyle, neuroanatomical, and functional brain characteristics are linked to TBI symptom expression [71–73]. Poor diet, physical fitness, alcoholism, drug abuse, psychiatric history, and other neurological insults can make individuals with TBI more susceptible to cognitive decline [73,74]. Treatment of these factors can therefore help to prevent cognitive symptoms and decline (for novel nutritional interventions for TBI, see [75]).

We review emerging approaches to clinical translation from cognitive neuroscience that enhance ICN function in TBI through: first, targeted interventions that influence network topology and dynamics; and second, novel approaches that deliver global effects to promote cognitive reserve and resilience to brain injury.

**Enhancing network function through neuromodulation**

Recent evidence from cognitive neuroscience supports the application of non-invasive brain stimulation techniques to promote the recovery of network function following TBI [76–81]. Transcranial direct-current brain stimulation (tDCS) involves the administration of a weak DC current to the scalp to modulate the excitability of ICNs [82], which is thought to ‘prime’ network regions to respond optimally to cognitive rehabilitation. Relatively brief periods of tDCS (30 min) have been found to enhance learning in a variety of perceptual, cognitive, and motor tasks [76–81].

Surface-based anodal tDCS increases excitability in the cortex near the positive electrode, through weak but coherent polarization of the membrane potential of radially oriented axons [83–85]. Long-term potentiation has been proposed as a possible mechanism for the longer-term and behavior-enhancing effects of tDCS [86]. It has been suggested that tDCS engenders learning by enhancing attention to critical stimuli and events within new tasks [78,79]. In addition to improving task performance during practice, tDCS is known to facilitate transfer, improving performance on entirely new tasks [87].

The low intensity currents in tDCS are well tolerated by patients and can be applied transcranially without interruption in cognitive rehabilitation. However, the main limitation of conventional tDCS is poor control over brain stimulation location and focality. New high definition-tDCS (HD-tDCS) is able to overcome this limitation with the use of specialized HD electrode arrays. Modeling studies have shown that HD electrodes can generate the highest intensity on cortical targets [88–92] as compared to the conventional sponge electrodes. Once the precise target is established one can use computational models to optimize placement of such HD electrodes to maximize intensity on target and thus maximize the expected effect sizes [93].

HD-tDCS may be guided by network diagnostics to selectively target specific ICNs and to shape network organization based on measures of network segregation, integration, and influence. Although HD-tDCS has not been applied to the context of TBI, early evidence indicates that anodal tDCS may support improved attentional processing in TBI [94] and in related clinical populations [95,96]. The focus of current research is to characterize the ICNs that are altered by TBI (Figure 1) and to more precisely measure the functional and structural characteristics of these networks (Figure 2) as they adapt in response to therapeutically effective applications of HD-tDCS. An important motivation of this research is to develop a personalized treatment approach for TBI that examines network diagnostics along with biomarkers of the traits (e.g., health status, nutrition, genetics, etc.) and states of the patient (e.g., sleep quality, energy level, mood, etc.) in an effort to optimize clinical therapy.

**Enhancing global characteristics of network function through physical activity**

In addition to investigating the benefits of a targeted approach to therapy, interventions that promote cognitive reserve and deliver global effects should also be examined. Indeed, the application of these complementary approaches in a multimodal intervention may deliver synergistic effects that enhance ICN function and promote cognitive reserve and resilience to brain injury.

An extensive neuroscience literature supports the efficacy of physical activity interventions for improved cognitive performance and brain health [97]. A rapidly expanding animal literature suggests that increased exercise leads to global, systemic effects, including: (1) the birth of new neurons in the hippocampus; (2) increased connections among neurons throughout the
brain; (3) the development of new vasculature structure; (4) increased production of neurotrophic proteins, such as brain derived neurotrophic factor (BDNF); (5) reduction of proteins associated with neurodegeneration in mouse models of Alzheimer’s disease; and (6) enhanced learning and memory [97]. These findings have been observed across the lifespan and in a multitude of species, including rodents, dogs, and monkeys [98].

The increasing molecular and cellular knowledge of exercise effects in animals provides the basis for human studies of physical activity, fitness, and exercise. In a meta-analysis of eighteen human randomized controlled trials published in 2003 by Colcombe and Kramer, a moderate effect size between exercise and cognition was reported [100**]. Specifically, the meta-analysis revealed a clear and significant positive effect of aerobic exercise training on cognitive function. Furthermore, exercise training had both general and selective effects on cognitive function. Although exercise effects were observed across a variety of cognitive tasks, the effects were largest for tasks that engage the central executive network, including planning, problem solving, cognitive flexibility, and working memory (Figure 3). Lastly, the meta-analysis revealed that aerobic exercise training combined with strength and flexibility training had a greater positive effect on cognition compared to exercise training programs that included only aerobic components.

More recently, human studies have begun to include measures of brain function and structure along with behavioral measures of cognition. These studies have reported that relatively brief fitness programs result in increased brain volume in the hippocampus [101,102], benefits in the striatum [91], and increases in the integrity of white matter tracts [103]. Additionally, these fitness programs enhance patterns of brain activation [104,105], including measures of functional connectivity of frontal and parietal brain regions, suggesting more efficient activity within the central executive network [99,106].

While the majority of experiments have focused on older adults, more recent studies have reported similar cognitive and brain benefits of exercise and physical activity in children [107,108] and young adults [109–111]. Collectively, these studies have demonstrated that physical activity and aerobic fitness benefit brain function and cognitive performance across a variety of aspects of cognitive control, including attention and inhibition [112], working memory [113], mental flexibility [109], and action monitoring/error detection [110,114], as well as hippocampal-dependent memory [101,115,116].

Despite the global benefits of physical activity and the potential to improve cognitive performance and brain health, remarkably little research has evaluated the effects of physical activity on cognition following TBI (for a review of the literature on physical activity intervention for neurological disorders, see [117]). Consistent with the literature in healthy adults, evidence indicates that physical activity in a 4-week aerobic fitness intervention (using a cycle ergometer) produced improvement in executive functions following TBI [118]. We note that the application of physical fitness interventions for TBI can be personalized for the patient, selecting from a variety of fitness activities (e.g., aerobic, strength, and flexibility training) that accommodate the patient’s abilities and functional goals.

Figure 3

Cognitive benefits of exercise.
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Conclusion
Recent neuroscience research provides insight into the mechanisms of TBI, at the molecular, cellular and circuit levels, but translating these discoveries into clinical applications remains a critical challenge. We have examined how we can translate research on the mechanisms of TBI into effective therapeutic interventions and proposed a framework for understanding the neurobehavioral features of post-traumatic encephalopathy in terms of network dysfunction within specific large-scale ICNs. Guided by this framework, we surveyed recent approaches to clinical translation from cognitive neuroscience that enhance network function and recovery from brain injury through interventions that deliver targeted (network specific) and global (systemic) effects. A network approach to the classification of the neurobehavioral features of TBI provides insight into the mechanisms of brain injury, linking ICN characteristics to specific profiles of cognitive impairment, providing key neurobiological targets for therapeutic intervention, and motivating new perspectives about the nature of cognitive recovery and rehabilitation in TBI.

Conflict of interest
Nothing declared.

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40. Braver TS, Cohen JD: Dopamine, cognitive control, and schizophrenia: the gating model. Prog Brain Res 1999, 121:327-349. This article established a seminal computational model of cognitive control.


This meta-analysis presented evidence to establish the beneficial effects of physical fitness intervention on cognitive performance and brain health.

Cognitive enhancement


