OPTIMIZING COGNITIVE FUNCTIONING AFTER TBI

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Traumatic injury to the brain can affect the core of what makes us human—our cognition and emotion. Although the injuries are acute, functional deficits that result from TBI may produce tremendous *chronic* burden on individuals, families, and health care systems. Long-term consequences of TBI frequently include impaired cognitive functions involving attention, executive abilities, and learning and memory as well as emotional volatility and increased incidences of psychiatric comorbidities. Effective approaches to improving functioning are needed, and the benefits may be far-reaching. We discuss some basic principles to guide current practice, and provide some pearls for application. Interventions are more likely to be effective when we take into account multiple levels of brain functioning, from neurons to pharmacological systems to social networks. The potential to improve cognitive functioning via training is of special importance, and benefits may synergize with pharmacologic and other approaches. Significant benefits can be gained by addressing important modulators of functioning such as sleep and fatigue.

Patients with so-called 'mild-moderate' TBI may have symptoms that are not readily recognized by health care providers, but which are personally significant. With the increase in military injuries and the combination of physical and experiential trauma (TBI and PTSD), cognitive-emotional targets of therapy deserve special consideration. Ironically, cognitive problems that have become chronic tend to receive less medical attention. The far-reaching impact of these seemingly "invisible" deficits is often not recognized. A long-term view is needed and major long-term issues need to be taken into account in clinical care (Chen and D'Esposito 2010). For example, individuals who cannot pay attention, hold information in mind, and actively participate in learning activities will have reduced benefit from rehabilitation, school or other treatments requiring active participation. Furthermore, individuals who have suffered a TBI may also be at increased risk for developing cognitive changes later in life.

This syllabus provides a preview of the AAN course. Key References are suggested for more detailed review.

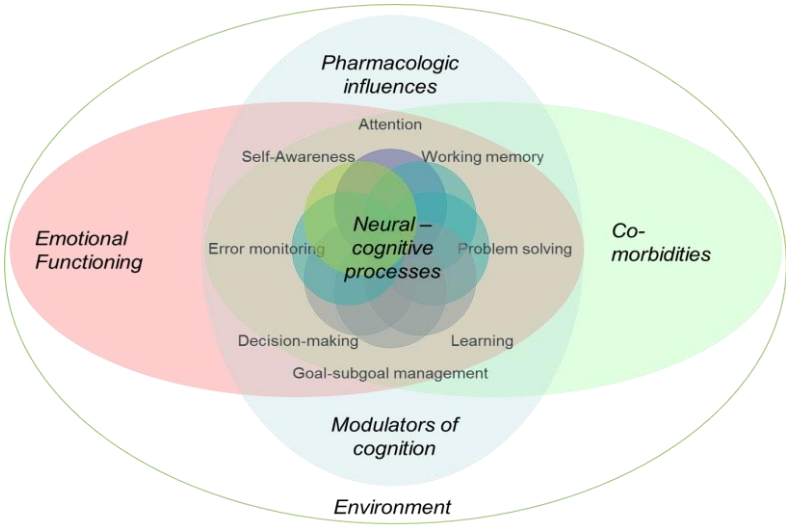
Injuries and Cognitive Symptoms: The most common difficulties after TBI involve complex attention, learning, memory, organization, behavioral and emotional self-regulation and other processes important for goal-directed behavior. Among cortical regions, prefrontal and mesial temporal structures are vulnerable to contusions and hemorrhages. Deficits in goal-directed or executive control functions are generally attributable to damage to prefrontal systems, which include not only PFC per se but also extensive interconnections with subcortical and posterior cortical structures (D'Esposito and Chen 2006). The importance of axonal injuries in TBI highlights the need to understand brain functioning in terms of distributed but coordinated network processes (Chen et al. 2006). Diffuse or multifocal axonal injury may affect commissural, callosal, association as well as particularly vulnerable long fibers, including those carrying neuromodulators in projections from the brainstem to cerebral end targets and those that connect the prefrontal cortex (PFC) with other brain regions. Some of the most common deficits with distributed axonal injury, even in the absence of cortical lesions, are in speed of processing, frontal executive functions, and memory (Scheid et al. 2006; Levine et al. 2008). Thus, understanding the importance of network interactions is an important foundation for understanding the functional consequences of TBI, which might otherwise be labeled "non-focal."

Education regarding typical aspects of recovery can be reassuring, and, fortunately, the recovery trajectory for most individuals who survive TBI is positive over time. However, there is significant variability in the rate and end point of recovery. Multiple factors may contribute to or 'modulate' symptoms. These factors may be important in formulating interventions to improve functioning.

Numerous individuals returning from combat activities suffer from both TBI and varying degrees of post-traumatic stress symptoms or PTSD – a Combined Combat Neurotrauma Syndrome (Chen et al. 2012). Experience suggests that the combination of TBI with PTSD may result in more prolonged or more complicated courses of recovery. Both physical and experiential trauma may have immediate as well as long-term effects on brain functioning. This combination further challenges us to consider multi-faceted approaches for optimizing functioning.

Approaches to Intervention: The following are key points to consider in determining interventions for improving cognitive functioning after brain injury. Sources of dysfunction may be multifactorial, and each factor or interaction of factors represents a potential target for intervention. Core targets of intervention include specific neural-cognitive processes important for healthy, goal-directed functioning after brain injuries. However, these processes may also be affected by factors that modulate physiologic brain states and cognitive performance (e.g., sleep, fatigue), pharmacologic influences (e.g., medications, other drugs), emotional functioning (e.g., irritability, anger, depression), and other comorbidities (e.g., chronic pain). The interactive nature of these factors is illustrated in the overlapping layers in the Figure. Any or all of the above may have to be taken into account for a therapeutic intervention to be effective. Often, it is ideal to take an integrated approach that addresses multiple targets based on a particular therapeutic goal.

Figure. Multiple sources of dysfunction lead to multiple tiers of intervention.



Core '*gateway' processes*: Some processes may be worth targeting even if "deficits" are not detectable. This especially includes domain-general processes that are "gateways" to learning and change. These include "meta-cognitive" processes such as self-awareness (awareness of one's abilities, strengths, weaknesses, and goals, with the ability to monitor and review one's actions in these contexts), and functions for regulating attention, learning, and memory in an organized, goal-directed manner. These processes will also be crucial for continued learning, adaption and problem-solving outside of clinician-guided settings.

Approaches for modifying behavior include *training*, i.e., the guidance of learning through activities with specific learning goals. Training forms the most fundamental core of post-injury rehabilitation, but may be combined with approaches that optimize biology and other modulators to maximize benefit. Addressing the fundamental ability to regulate one's *cognitive-emotional (brain) state* may have a far-reaching impact on goal-directed functioning. Engagement of *active participation* for each individual in treatment is a major factor in treatment outcome. Elements of enhancing engagement include raising awareness of one's abilities and difficulties, opportunities for self-direction during treatment, and active attempts at applying and transferring learned skills to personally relevant situations and goals. These considerations become all the more important when deficits affect awareness, motivation, attention, and other aspects of self-regulation. Issues of active avoidance or negative reactions to intervention may be further heightened when TBI is combined with PTSD or other psychological health conditions. *Transfer* of gains to new contexts, and *generalization* to each individual's personal life must be taken into account when considering intervention approaches as well as measurement of outcomes.

Training to Improve Cognitive Functioning: Training forms the most fundamental core of post-injury rehabilitation. Training involves specific activities that guide changes in brain functioning based on specific learning goals. Within the training approaches, different learning goals may be defined.

Training may emphasize the learning and application of cognitive skills and/or strategies. Strategies help to organize behavior and may be helpful in improving the efficiency or effectiveness of accomplishing particular tasks. Strategies, once internalized, may be thought of as providing intrinsic "tools" available to an individual to

help accomplish particular tasks. Factors to consider include to what extent the strategies are context-specific or transferable to other contexts, to what extent the individual can learn and remember the strategy, and to what extent the individual will be able to prospectively initiate use of the strategy in the appropriate situations. For example, it is not uncommon for an individual to be able to learn a strategy during therapy (e.g., a method for breaking problems into manageable steps), but then fail to apply this strategy when faced with a real-world problem. Such failures of transfer may be directly related to an individual's cognitive deficits. Useful strategies have included day planner usage, time management, goal setting, self-monitoring, as well as using external cues for reminders (e.g. Manley, Huckans et al. 2010; Storzbach 2016).

A *skills-based* approach is emphasized here. Skills may generally be considered as the integrated use of particular neurologic functions or processes for the accomplishment of functional tasks. Skill training may emphasize either practice on specific functional tasks (e.g. making a sandwich) or specific processes (e.g. working memory, across specific tasks). The choice of approach may depend on the nature and severity of cognitive deficits. It has been argued that functional approaches (training on specific tasks) may be more effective for patients with severe deficits (Giles 2010). Approaches for process-targeted skill training are elaborated on in this paper.

It is conceptually simple to understand how one might train motor strength by training particular muscles, but how would one prescribe training for "executive control" functions? Control over neurologic functions to accomplish goals may involve control over perception and information processing, motor actions, emotional functioning, as well as other aspects of behavior. At the simplest level, neural aspects of control involve modulation of neural activity from the "top-down" based on goals, as well as coordination and monitoring of distributed neural networks in the brain. Without such control, activity would be either driven by low-level processes, such as by "stimulus-response" principles, or generally disorganized, with poorly coordinated activity that lacks guidance by a higher level goal structure.

Functions of *learning and memory* are integrally intertwined with all of the above process of goal-direction. Indeed, one of the most common subjective complaints after TBI is of problems with "memory." Problems with memory encoding and retrieval may also be related to attention and "frontal executive" functions that influence the selectivity and depth of information processing, as well as the ability to organize information to be encoded and strategically retrieve information to be recalled.

Principles for Improving Functions of Goal-Directed Control (aka Frontal Lobe Functions)
Given the difficulty in understanding and designing interventions to improve goal-directed cognitive functioning, we share some basic principles of training that could be incorporated into interventions to target and maximize improvements in these functions (see Key References for more details). These principles may not only bolster therapies where goal-directed cognition is the primary target of therapy but may also be incorporated into cognitive, motor, speech, or other therapies in order to maximize the targeting of frontal systems functions in any of these contexts. Strategic synergies with pharmacotherapy can be valuable, and principles to guide pharmacotherapy are discussed in a later section.

1. *Goal-based training of process, not content*: Cognitive training tasks should challenge patients to engage "top-down" control processes mediated by PFC networks (D'Esposito and Chen 2006). Cognitive training should explicitly include a goal-based approach. The role of goal-based executive processes may be to functionally organize the multiple neural processes necessary for accomplishing the goal, including selecting the relevant pathways or processes (while excluding others), coordinating them at any given moment in time, and dynamically adjusting this coordination while maintaining the central goal across time to eventually accomplish the goal.

The regulation of information processing in the brain deserves special emphasis. Selective processing of goal-relevant information, a central component of executive control, is a crucial gateway that filters what information gains access to more in-depth processing. The integrity of information processing, whether from perception or through other steps to action, requires mechanisms of selection, maintenance, and protection from disruption during working memory, learning, decision-making, and/or problem-solving. The protection of information processing from distractions anywhere along this pathway is crucial to efficient and effective goal attainment, especially when extended time or multiple steps are required. Increasing evidence supports the proposition that training-based therapies have utility for rehabilitation in the chronic phase of TBI, including training for attention and working memory (Cicerone et al. 2000, 2005; Kennedy et al. 2008; Levine et al. 2008; Rohling et al. 2009;

Klingberg 2010; Westerberg et al. 2007; Chen et al. 2011). To what extent process-targeted, computer-based approaches may be helpful for individuals with brain injury, with improvements that generalize to real-world functioning will be worth further investigation. Supportive pharmacotherapy may be considered.

2. Cognitive training tasks should *progressively challenge* the patient. The importance of progressive increases in challenge is underscored by the ability of the brain to adapt to tasks – thus, tasks become less effective at encouraging learning in the targeted domain unless challenges are increased.

3. Training should explicitly address pathways for the *transfer and generalization* of training effects to new and real-world contexts. Training across *multiple modalities* may maximize engagement of core networks leading to improved functioning across contexts. Linking skill use to a goal-based framework – with clear delineation of goals, increased awareness of goal-relevance and derailments, and the use of implementation intentions (e.g. if…then…I will apply the skill) - can maximize the likelihood of beneficial skill use.

4. *Meta-cognitive strategy training*, such as those targeting problem-solving, may improve functioning in individuals with brain injury and have been recommended in practice guidelines (Cicerone et al. 2005; Kennedy et al. 2008)(D'Zurilla and Goldfried 1971; Kabat-Zinn 1990; VonCramon et al. 1991; Cicerone 2002; Rath et al. 2003; Robertson et al. 2005; Nezu et al. 2007; Vas et al. 2011). For example, in goal management training (Levine et al. 2000), patients are trained to clearly define a goal, learn the steps required to achieve it, and then regularly check their progress.

5. Training goal-directed control of *brain states*. Perhaps one of the most fundamental targets of training is the regulation of one's brain state. All cognition and behavior occurs from the foundation of an underlying brain state. The effectiveness and efficiency of functioning depends on the regulation of these states as appropriate to a current goal. At a neural level, modulation of brain states alters signal and noise properties of information processing systems in the brain that support abilities such as goal-directed control functions (Arnsten and Goldman-Rakic 1998; Gold and Shadlen 2001; Jazayeri 2008). At a behavioral level, axes of cognition, emotion, and alertness/arousal state translate from brain network states, and these axes must be regulated in an integrated manner to achieve an optimal state for any current situation or goal.

One behavioral axis of brain state is *alertness/arousal regulation.* Optimal arousal state may be considered a pre-requisite for effectively activating and engaging other cognitive functions such as selective attention, working memory, and executive control (Sturm et al. 1999; Posner 2008). Regulation of arousal state needs to be considered in terms of optimizing balance for any given current goal and context. A state of hyper-arousal may lead to rapid shifts of attention (distractibility) while low arousal may lead to poor activation and maintenance of attention. Patients with TBI–PTSD may show severe hyper-arousal, while patients with more severe TBI may exhibit marked deficits in alertness (Manly et al. 1999; Sturm et al. 1999; Posner 2008). Noradrenergic systems involving inter-connected regions of brainstem and frontal cortex, in particular, have been proposed to be particularly important mediators of alertness state (Aston-Jones and Cohen 2005). Approaches to regulating arousal state may involve behavioral regulation training, and pharmacotherapy can be particularly helpful in this area.

Interactions of emotion and cognition are particularly important to address after TBI and especially with the combination of TBI and PTSD, perhaps the "hallmark" syndrome of recent combat activities. The issues from TBI–PTSD include disruption of core cognitive and emotional regulation mechanisms that are essential for goal-directed functioning in life. Emotional and cognitive control are directly tied together in that the underlying neural systems interact significantly in achieving self-regulatory control necessary for goal-directed behavior. Dorsolateral PFC and ventromedical PFC interact in the regulation of emotions, with modulation of amygdala (Phelps et al. 2004). The addition of PTSD to TBI may contribute to not only emotional but also cognitive difficulties. The most common cognitive deficits associated with PTSD involve sustained and selective attention, executive functions, and memory (Vasterling and Brewin 2005; Brandes et al. 2002; Gilbertson et al. 2001), e.g. impaired ability to gate, monitor, and regulate the flow of incoming information and environmental stimuli (Vasterling et al. 1998). Also, given the known limitations of neural processing resources, it seems logical that an increase in "load," whether from cognitive or emotional sources, would lead to less efficient overall functioning.

Current experience suggests that PTSD in individuals who also sustain a TBI may be a more complicated, and the chronicity of symptoms may be extended. Patients with TBI–PTSD may respond differently to standard treatments compared to those with only TBI or PTSD. Cognitive limitations may make it necessary to modify cognitive-behavioral psychotherapies. Conversely, the emotional dysregulation, avoidance, and potential for triggering may impede engagement in cognitive rehabilitation therapies. Interventions that improve attentional self-regulation may also improve emotional self-regulation, and vice versa. Thus, in order to improve an individual's ability to learn, change, and adapt in the process of goal attainment, it will often be necessary to address both cognitive and emotional self-regulation.

Training may help to improve state regulation. For example, self-regulation and mindfulness-based training approaches may reduce the load of non-relevant cognitive or emotional processing on limited neuro-cognitive resources, and improve attention, working memory and goal-directed functioning for individuals with brain injury (Posner et al. 2006; Jha et al. 2007; Slagter et al. 2007; Novakovic-Agopian et al. 2011; Jha et al 2010; Novakovic-Agopian et al. 2011; Cole et al., 2015; Janak et al., 2015).

6. *Integrated training*. Given the inter-related nature of core processes of cognitive functioning, emotional functioning and other modulators, it is rational to systematically integrate therapies targeting these overlapping processes. Indeed, these processes evolved to function in an integrated, not isolated manner. In particular, certain gateway functions (e.g. brain state regulation and selective information processing) are necessary foundations for higher level functioning. Furthermore, the engagement of these foundational processes is increased and motivated by the higher level complex goals and challenging situations.

In one example approach, training in brain state regulation can be strengthened and applied to the pursuit of higher level goals. Improving the goal-directed regulation of *brain states* is hypothesized to help individuals better achieve their goals by strengthening their abilities to direct and sustain attention toward goal-relevant information, selectively maintain this information over time, manage non-relevant distractions, and re-direct attention. We argue that for *state regulation skills* (SRS) to be effectively learned, training should include at least four key elements (Chen, Loya, & Binder, in press). First, training should facilitate each trainee's conceptual understanding of trained skills, including the underlying rationale and intended benefits of skill use. Second, training should include opportunities where skill use can be *extensively practiced* across a wide range of goal contexts and challenges. This may help with skill development and promote *automaticity* in skill use, increasing the likelihood that a *state regulation response* will be triggered *in-the-moment* during any challenge context. Third, training should increase trainees' awareness of situations where their goal-direction is vulnerable to disruption, and foster their intentions to apply skills in instances when they are most likely to be derailed. Finally, these elements need to be tied together in a goal framework, explicitly supporting the *strategic application* of SRS to bolster goal attainment efforts. Together, these elements may maximize application of SRS in situations when and where they are needed most.

These principals of been incorporated into a series of training interventions that support *guided learning* of SRS via stepwise experiences that integrate skill instruction, interactive coaching, and intensive skill practice across multiple contexts and settings, bridging from digital game-based scenarios to personal life. This contrasts with training then relies on practice on isolated tests or training in abstraction, such as in a quiet room. Neural and behavioral changes have been found with SRS training (e.g. Novakovic-Agopian et al. 2011; Novakovic-Agopian et al 2014; Loya et al. 2014; Chen, Loya et al. in press). Another intervention that combines attention and problem-solving as targets of therapy in a group-based training protocol has also been described and tested (Evans et al. 2001, 2005; Miotto et al. 2009). Cooper et al (2017) found that cognitive rehabilitation combined with cognitive-behavioral psychotherapy reduced functional cognitive symptoms in military service members with mTBI compared with psychoeducation or medication management alone.

Pharmacotherapy: Principles of integrated pharmacotherapy and rehabilitation

Careful application of pharmacotherapy can play an important role in improving cognitive functioning after brain injury. Tailored *pharmachotherapy* should take into account factors for synergistically optimizing functioning (Chen et al. 2012; Chen and Loya 2014). Clinical evidence to support particular medications post-TBI is sparse but slowly accumulating (reviewed in Warden et al. 2006; Jorge and Arciniegas 2014; Bhatnagar et al. 2016). A

clinician's prescription for any given individual still relies on theory and/or empiric practice, informed by limited direct evidence or extrapolation from other populations. It is valuable to consider not only the immediate effects of pharmacologic agents but also the potential influences on processes of learning. Different drugs, as well as different doses of the same drug, may have differential effects for specific neural subsystems and the behaviors they subserve. Systematic individual trials involving step-wise dose adjustments of medications may be helpful.

There are a number of reasons to consider neuromodulator systems of the brain as therapeutic targets. These include findings that TBI tends to affect cognitive functions dependent on these neuromodulators, such as dopamine, norepinephrine, acetylcholine, and serotonin, and the predilection for TBI to affect the cortical termination zones as well as the long projection fibers that carry these neuromodulators.

Helpful and hurtful effects of drugs must be considered, and these may occur simultaneously. For example, more detailed examination may reveal domain-specific effects (as described in McDowell et al. 1998) or simultaneous helpful vs. detrimental effects on separable brain systems (i.e., "double-edged sword" effects) (Cools et al. 2001).

It is also valuable to consider immediate vs. longer-term effects of pharmacologic modulation. Drug effects may be supportive for current issues, but may also be detrimental for longer-term goals. For example, anti-dopaminergic medications have long been used to address problematic behavior post-injury. The immediate effects may seem helpful (e.g., reducing behavioral instability), but the same medication may adversely affect functioning in a cumulative manner (e.g., by altering attention and learning during training). It is important to manage the goals, timing and duration of therapy.

Polypharmacy is a common problem, likely due to factors such as multiple comorbidities with TBI (e.g., anxiety, PTSD, insomnia, pain) and attempts to treat some post-TBI sequelae (e.g., behavioral dysregulation, seizures, headaches). A valuable first-step in clinical decision-making is a review of medications that may contribute to poor cognitive functioning. Unfortunately, numerous medications commonly used for patients with TBI have adverse effects on cognition or learning/plasticity.

Post-traumatic epilepsy, especially with complex partial seizures, is a treatable potential contributor to cognitive dysfunction. However, medications may need to be managed with attention to cognitive side effects. Phenytoin has been shown to impair cognitive function in patients with severe TBI (Dikmen et al. 1991, 2000). Carbemazepine may also have cognitive side effects (Smith et al. 1994). Among older anti-epileptic agents, valproate may be preferable. Among newer agents, topiramate may be particularly concerning for cognitive side effects. Levetiracetam has fewer drug interactions, though may contribute to mood/though disturbances.

Benzodiazepines and baclofen are GABA agonists, and these may reduce the rate of recovery from TBI (Zafonte et al. 2004). The use of these medications should be minimized in the context of cognitive dysfunction after TBI. In certain circumstances, spasticity may be treated by more localized means (e.g., intrathecal baclofen or targeted botulinum toxin). On the other hand, strategic and judicious use of beta blockers or benzodiazepines may improve cognitive functioning clouded by severe anger or anxiety.

Dopamine antagonists, such as haloperidol, have been shown to impede learning and recovery (Stanislav 1997; Wilson et al. 2003; Meintzschel and Ziemann 2006; Hoffman et al. 2008; Kline et al. 2008). These agents are commonly used for managing behavioral dysregulation, but should be used sparingly, and continual use should be avoided as much as possible. On the other hand, limited strategic use at night may improve sleep and daytime functioning, especially for some individuals with nightmares and anxiety related to PTSD.

Selective serotonin and/or norepinephrine reuptake inhibitors (SSRIs) may help reduce emotional lability and improve functioning, and although evidence is limited for TBI, this may be especially useful in the contexts of depressive or anxious symptoms. There are also theoretical reasons to consider SNRIs for improving attention and related adrenergic functions.

In sum, it is important to repeatedly review the rationale, necessity, and dosage of each medication at each clinical juncture, with a concern for potential adverse effects on cognition and recovery. It is best to initiate pharmacotherapy in the context of a plan for non-pharmacologic treatment, and to have clear rationale for how

the pharmacotherapy will support the long-term goals of treatment along with plans to eventually taper or more selectively use pharmacotherapy. Discontinuing certain medications can be as valuable as starting any medications in the rehabilitation course.

Pharmacotherapy and goal-directed control (attention, memory and executive functioning):
A number of options for pharmacotherapy currently exist; however, there is relatively little data to guide the optimal choice of agent for any given individual. Pharmacotherapy is primarily empiric, but some guidance might come from some definition of the treatment target (e.g. speed of processing vs. memory), theoretical considerations (e.g. likelihood of cholinergic vs. dopaminergic vs. noradrenergic dysfunction), as well as management of other co-morbidities (e.g. depression, fatigue, insomnia, anxiety, headaches). One of the important general principles, or aspirations, is that the use of these agents may increase the rate of learning and recovery.

Commonly used pharmacologic agents to increase alertness/arousal affect neuromodulator function and include methylphenidate and amphetamines as well as newer stimulants. Modafinil and related drugs may promote alertness. “Antidepressants” with noradrenergic targets and possible “activating” effects, such as venlafaxine or duloxetine, may be helpful for some individuals. These agents could be considered for use as agents satisfying multiple therapeutic goals. As always, the effects of medications prescribed for other reasons must be evaluated.

Dopaminergic and mixed catecholamine agents may be useful for improving aspects of cognitive functioning in patients with TBI. Methylphenidate probably has the greatest amount of supportive evidence for use after TBI (Warden, 2006;Writer, 2009). Trials have documented improvements in aspects of attention and speed of information processing following TBI (J. Whyte et al., 2004) Methylphenidate may also improve learning and memory functioning after TBI by improving attention to information. Dextroamphetamine may also help to improve aspects of attention and speed of processing, but there is little data fully testing its effects in chronic TBI (Hornstein, 1996). Bromocriptine may enhance aspects of executive functioning in patients with severe TBI (McDowell, Whyte, & D'Esposito, 1998) but again data are mixed (E. M. Whyte et al., 2008). Amantadine may improve executive function, in addition to alertness (Sawyer, 2008). Atomoxetine has shown promise in other settings, but when tested in a relatively large randomized, controlled trial for TBI, no effects on testing and subjective measures of attention could be detected relative to a control group (Ripley, 2014). As a general guideline, dosing of agents that modulate catecholaminergic function should be based on individual response, noting that neuromodulatory effects tend to follow a U-shaped curve that may vary in dose-relationship for each individual.

Acetylcholine systems may be particularly important to address given the predilection for TBI to damage medial temporal structures, the basal forebrain and long tracts that connect structures important for memory processing. The cholinesterase inhibitor donepezil has been recommended to enhance aspects of memory function for patients with moderate to severe TBI in subacute and chronic periods of recovery based on trial data (Warden, 2006;Whelan, 2000;Wortzel, 2012; Zhang, 2004). Some data supports the use of rivastigmine for improving memory deficits as well in patients with moderate to severe memory impairment at baseline (Silver et al., 2006; Tenovuo, 2005). In general, these cholinesterase inhibitors appear to be safe and well-tolerated in patients with TBI. Problems with memory encoding and retrieval may also be related to frontally mediated functions such as selectivity and depth of information processing, ability to organize information to be encoded and ability to strategically retrieve information to be recalled. Methylphenidate, amphetamines, and other agents that enhance attention or executive control may also improve learning and memory functioning after TBI. To what extent these medications are indicated for mild TBI, such as from blasts, needs to be further tested, and additional considerations of the interaction with anxiety and PTSD need to be considered.

Maximizing synergies between pharmacotherapy and training therapies is an important frontier where strategic transitional use of medications could enhance response to behavioral therapies. This approach could contribute to a long-term goal of improving an individual’s intrinsic functioning and allowing pharmacotherapy to be reduced over time.

Domain-general symptoms as targets of therapy: fatigue and sleep.
Energy and Central Fatigue: Adequate energy is required to drive cognition and behavior, particularly for the effortful pursuit of higher order goals, learning, adapting and problem-solving in the context of challenges after brain injury. However, fatigue is reported to be one of the most common and debilitating symptoms after TBI

(Hillier, Sharpe, & Metzer, 1997; Olver, Ponsford, & Curran, 1996). There is no standard definition of fatigue, but key elements include a requirement for increased effort to maintain mental activities and difficulty sustaining goal-directed efforts (Fellus & Elovic, 2007). Central fatigue, related to disturbance in the CNS, is itself a major cause of poor functioning (Bushnik, Englander, & Wright, 2008). Helping an injured individual to manage available energy, including increasing available energy for key goals, would be of great benefit for optimizing current functioning and encouraging learning for longer-term improvements.

When assessing fatigue, a key goal is determining potential contributing factors that may serve as direct targets for clinical management, including through assessing associated factors, such as sleep, depression and pain.(Englander, Bushnik, Oggins, & Katznelson, 2010; Ponsford et al., 2012) From a clinical best practice perspective, regular physical exercise, which has shown to reduce fatigue in other clinical populations(Fulcher & White, 1997)(Mock et al., 2005), is a front-line treatment option.

Compensatory strategies to manage energy use, such as setting restrictions on the length of time to engage in certain activities, may also be helpful. This behavioral approach involves identifying personal and/or situational factors associated with fatigue, and then developing strategies for managing or modifying these factors in order to minimize energy loss.

Reducing distractions and thereby minimizing the amount of cognitive effort required to accomplish tasks may also be beneficial. Improved self-regulation of attention and other aspects of cognitive processing may help improve cognitive efficiency. Similarly, improving regulation of emotions, such as anger, may also be helpful.

Understanding the neural bases of fatigue may help inform treatments, and one theory relates to increased recruitment of neural resources not required for uninjured persons (DeLuca, Genova, Hillary, & Wylie, 2008; McAllister et al., 1999)(Van Zomeren, 1984).

A review of medications is important, as beta-blockers, anti-dopaminergics and anti-epileptics may all contribute to feelings of tiredness. Pharmacotherapy with agents that improve alertness, attention and concentration, such as methylphenidate, amantadine, dextroamphetamine, atomoxetine or modafinil, as well as activating antidepressants may also be helpful, though evidence mostly comes from other disease conditions (Krupp et al., 1995; Mendonca, Menezes, & Jog, 2007; Minton, Richardson, Sharpe, Hotopf, & Stone, 2008; Rammohan et al., 2002). Preliminary findings of medication trials to treat fatigue within the context of TBI have been mixed[19,20,] (Johansson et al., 2014) and more research is clearly needed to ascertain specific medication effects. Timing pharmacotherapy to augment participation in non-pharmacologic therapies can be valuable.

***Sleep*:** Sleep disturbance is one of the most common yet least studied sequelae of TBI (R. J. Castriotta et al., 2007; Mahmood, Rapport, Hanks, & Fichtenberg, 2004; Watson, Dikmen, Machamer, Doherty, & Temkin, 2007; Zeitzer, Friedman, & O'Hara, 2009). Up to 84% of persons with a TBI experience some form of sleep disturbance (Lew et al., 2007), with symptoms of insomnia being the most frequent complaint [4](Richard J. Castriotta & Murthy, 2011). The neurocognitive, behavioral, and physiological effects of poor sleep within the general population have been well documented (Durmer & Dinges, 2005; Walker & van der Helm, 2009). Importantly, several studies (Fichtenberg, Millis, Mann, Zafonte, & Millard, 2000; Kempf, Werth, Kaiser, Bassetti, & Baumann, 2010; Orff, Ayalon, & Drummond, 2009; Ponsford et al., 2013) have documented that sleep disturbance persists for many persons with mild to moderate TBI several years post-injury, underscoring the importance of addressing this potential chronic sequel of brain injury.

More broadly, sleep regulation and adequate sleep may be of fundamental importance for learning and recovery after brain injury. Sleep deprivation may adversely affect functions crucial for learning, such as alertness, sustained attention,(I. L. Bloomfield, Espie, & Evans, 2009) and other forms of attention and memory, with particular adverse effects on frontal systems functions.(Mahmood et al., 2004; Muzur, Pace-Schott, & Hobson, 2002; Yoo, Hu, Gujar, Jolesz, & Walker, 2007) Chronic lack of sleep may also be associated with anxiety and depression. (Neckelmann, Mykletun, & Dahl, 2007). From another perspective, sleep, including in the form of brief naps, has been shown to benefit learning of information or skills learned prior to sleeping (Mednick, Nakayama, & Stickgold, 2003; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002), even in the absence of REM-sleep (Tucker et al., 2006). Thus, promoting sleep as a prospective intervention (i.e., encouraging sleep after learning) may be a valuable component of rehabilitation.

Despite the importance of sleep for optimizing functioning and enhancing learning after TBI, no strong evidence base exists to guide clinical best practice (Orff et al., 2009; Weber, Webb, & Killgore, 2013). However, there are a number of clinically useful options available. For many individuals, there may be opportunities for improving functioning in just addressing basic aspects of sleep hygiene. Identifying and treating *sleep apnea* is another major priority for persons with TBI. Caution should be exercised regarding prescription of sleep-inducing medications such as benzodiazepines within this context, as they may actually exacerbate apnea. Treatment via a CPAP machine has been shown to be helpful for obstructive sleep apnea following TBI (R. J. Castriotta et al., 2009).

Pharmacologic agents for inducing or prolonging sleep all have potential side effects, and balancing effects become more complex when cognitive dysfunction and other medications, amongst other factors, inter-mix. Benzodiazepines and atypical GABA-agonists, some of the most commonly used sleep agents, may have adverse effects on cognition as well as neuroplasticity following injury (Larson & Zollman, 2010) as well as rebound effects. Judicious short-term use can be beneficial in limited situations (e.g. when overwhelming anxiety contributes to insomnia), but rapid tolerance and dependence can make management difficult. Other agents, such as trazodone, or newer anti-depressants such as mirtazapine, may have clinical utility, though there is little data to guide their use after TBI. Assistance with impediments to sleep, such as nightmares, can have a significant positive impact, and thus agents such as prazosin can be helpful. Individuals with TBI may have increased sensitivity to adverse effects, such as prolonged cognitive effects the next day, so, in general, low doses or slow titrations may be particularly important. Sleep-supportive agents may play an important short-term role during rehabilitation. Use of such drugs would ideally be limited in time, matched with non-pharmacologic therapies with the goal of eventually improving sleep management and tapering off medications.

Non-pharmacological therapies aimed at addressing psychological factors thought to perpetuate sleep disturbance have shown great potential. One particularly promising treatment, Cognitive Behavioral Therapy for Insomnia (CBT-I), incorporates both cognitive (e.g., addressing maladaptive sleep-related beliefs) and behavioral (e.g., stimulus control) approaches to combat insomnia (Morin et al., 2006; Murtagh & Greenwood, 1995)(Ouellet & Morin, 2004)(Ouellet & Morin, 2007).

There is also some suggestive evidence that treatments targeting the regulation of the circadian rhythm and sleep-wake cycle are effective in the context of TBI-related sleep disturbance – this may include using exogenous melatonin therapies (Kemp, Biswas, Neumann, & Coughlan, 2004), light therapy (Ponsford et al., 2012). Intensive schedule regularization in combination with efforts to augment sleep or wake signaling (e.g. melatonin supplementation at night; sunlight, exercise, possibly stimulants in the morning) may be valuable.

Management of sleep as a direct, explicit target of therapy is an important frontier for further development.

Conclusions and Directions for Future Work

The effects of TBI on cognition are complex and have challenged clinicians throughout history, as well as deterred neuroscientists from pursuing studies in this “messy” area of inquiry. The complexity is compounded by combinations of physical and experiential injury, as well as other comorbidities. Much work will need to be done to better define effective therapies for cognitive dysfunction caused by brain injuries. Research and development along several key directions will be crucial. Approaches that bridge the basic neuroscience of neural-cognitive functioning with the practical realities of clinical rehabilitation will be valuable in intervention development. It will be particularly important to consider the relationships between levels of functioning in order to maximize transfer and generalization of benefits.

Key References for Additional Reading

- Chen, A.J.-W. and Novakovic-Agopian, T. Interventions to improve cognitive functioning after traumatic brain injury. In *Traumatic Brain Injury: Approach to Diagnosis, Management, and Rehabilitation*, Ed. J. Tsao. Springer-Verlag, 2012.
- Chen AJ-W, Loya F. Mild-moderate TBI: clinical recommendations to optimize neurobehavioral functioning, learning, and adaptation. Seminars in Neurology. 2014 Nov;34(5):557-71
- Jorge RE, Arciniegas DB. Mood disorders after TBI. Psychiatr Clin North Am 2014;37(1):13–29
- Bhatnagar, S., Iaccarino, M. A., & Zafonte, R. Pharmacotherapy in rehabilitation of post-acute traumatic brain injury. Brain research. 2016; 1640, 164-179.

Citations

Ackerman, R., DiRamio, D., & Garza , R. L. Transitions: Combat veterans as college students. New Directions for Student Services. 2009; 126: 5-14.

Arnsten AF, Goldman-Rakic PS. Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism. Arch Gen Psychiatry. 1998;55(4):362–8.

Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci. 2005;28:403–50.

Awh E, Vogel EK. The bouncer in the brain. Nat Neurosci. 2008;11(1):5–6.

Ayalon L, Borodkin K, et al. Circadian rhythm sleep disorders following mild traumatic brain injury. Neurology. 2007;68(14):1136–40.

Baddeley AD. Is working memory still working? Am Psychol. 2001;56(11):851–64.

Badre D, D'Esposito M. Is the rostro-caudal axis of the frontal lobe hierarchical? Nat Rev Neurosci. 2009;10(9):659–69.

Baldo JV, Delis DC, et al. Is it bigger than a breadbox? Performance of patients with prefrontal lesions on a new executive function test. Arch Clin Neuropsychol. 2004;19(3):407–19.

Baldo JV, Schwartz S, et al. Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. J Int Neuropsychol Soc. 2006;12(6):896–900.

Baldo JV, Shimamura AP, et al. Verbal and design fluency in patients with frontal lobe lesions. J Int Neuropsychol Soc. 2001;7(5):586–96.

Baldo JV, Shimamura AP. Letter and category fluency in patients with frontal lobe lesions. Neuropsychology. 1998;12(2):259–67.

Banich MT, Milham MP, et al. fMri studies of Stroop tasks reveal unique roles of anterior and posterior brain systems in attentional selection. J Cogn Neurosci. 2000a;12(6):988–1000.

Banich MT, Milham MP, et al. Prefrontal regions play a predominant role in imposing an attentional 'set': evidence from fMRI. Brain Res Cogn Brain Res. 2000b;10(1–2):1–9.

Barnett SM, Ceci SJ. When and where do we apply what we learn? A taxonomy for far transfer. Psychological Bull. 2002;128(4):612-37.

Baumann, C. R., Stocker, R., Imhof, H. G., Trentz, O., Hersberger, M., Mignot, E., & Bassetti, C. L. (2005). Hypocretin-1 (orexin A) deficiency in acute traumatic brain injury. Neurology, 65(16009905), 147-149.

Baumann, C. R., Werth, E., Stocker, R., Ludwig, S., & Bassetti, C. L. (2007). Sleep-wake disturbances 6 months after traumatic brain injury: a prospective study. Brain, 130(Pt 7), 1873-1883. doi:10.1093/brain/awm109

Bavelier, D., Green, C. S., Pouget, A., & Schrater, P. Brain plasticity through the life span: learning to learn and action video games. Annu Rev Neurosci. 2012; 35: 391-416.

Bedard, M., Felteau, M., Gibbons, C., Rupert, K., Mazmanian, D., Fedyk, K., & Mack, G. (2005). A Mindfulness-Based Intervention to Improve Quality of Life Among Individuals Who Sustained Traumatic Brain Injuries: One-Year Follow-Up. The Journal of Cognitive Rehabilitation(23), 8-13.

Belanger HG, Curtiss G, Demery JA, Lebowitz BK, Vanderploeg RD. Factors moderating neuropsychological outcomes following mild traumatic brain injury: A metaanalysis. J Int Neuropsychol Soc. 2005;11(3):215–27

Belanger HG, Curtiss G, et al. Factors moderating neuropsychological outcomes following mild traumatic brain injury: a meta-analysis. J Int Neuropsychol Soc. 2005;11(3):215–27.

Belanger HG, Kretzmer T, et al. Cognitive sequelae of blast-related versus other mechanisms of brain trauma. J Int Neuropsychol Soc. 2009;15(1):1–8.

Bhatnagar, S., Iaccarino, M. A., & Zafonte, R. Pharmacotherapy in rehabilitation of post-acute traumatic brain injury. Brain research. 2016; 1640, 164-179.

Binder LM, Rohling ML, et al. A review of mild head trauma. Part I: meta-analytic review of neuropsychological studies. J Clin Exp Neuropsychol. 1997;19(3):421–31.

Bloomfield IL, Espie CA, et al. Do sleep difficulties exacerbate deficits in sustained attention following traumatic brain injury? J Int Neuropsychol Soc. 2009;16(1):17–25.

Bloomfield, I. L. M., Espie, C. A., & Evans, J. J. (2010). Do sleep difficulties exacerbate deficits in sustained attention following traumatic brain injury? J Int Neuropsychol Soc, 16(19796442), 17-25.

Bloomfield, I. L., Espie, C. A., & Evans, J. J. (2009). Do sleep difficulties exacerbate deficits in sustained attention following traumatic brain injury? Journal of the International Neuropsychological Society, 16(1), 17-25. doi:S1355617709990798 [pii] 10.1017/S1355617709990798

Blumenfeld RS, Ranganath C. Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. Neuroscientist. 2007;13(3):280–91.

Borgaro SR, Gierok S, et al. Fatigue after brain injury: initial reliability study of the BNI Fatigue Scale. Brain Inj. 2004;18(7):685–90.

Brandes D, Ben-Schachar G, et al. PTSD symptoms and cognitive performance in recent trauma survivors. Psychiatry Res. 2002;110(3):231–8.
Brewin CR, Kleiner JS, et al. Memory for emotionally neutral information in posttraumatic stress disorder: a meta-analytic investigation. J Abnorm Psychol. 2007;116(3):448–63.
Bryant R, Hopwood S. Commentary on “Trauma to the Psyche and Soma”. Cogn Behav Pract. 2006;13(1):17–23.
Bryant RA, Marosszeky JE, et al. Coping style and post-traumatic stress disorder following severe traumatic brain injury. Brain Inj. 2000;14(2):175–80.
Bryant, R. A., O'Donnell, M. L., Creamer, M., McFarlane, A. C., Clark, C. R., & Silove, D. The psychiatric sequelae of traumatic injury. Am J Psychiatry. 2010; 167(3): 312-320
Brzezinski, A., Vangel, M. G., Wurtman, R. J., Norrie, G., Zhdanova, I., Ben-Shushan, A., & Ford, I. (2005). Effects of exogenous melatonin on sleep: a meta-analysis. Sleep Med Rev, 9(15649737), 41-50.
Bunge SA, Dudukovic NM, et al. Immature frontal lobe contributions to cognitive control in children: evidence from fMRI. Neuron. 2002a;33(2):301–11.
Bunge SA, Hazeltine E, et al. Dissociable contributions of prefrontal and parietal cortices to response selection. Neuroimage. 2002b;17(3):1562–71.
Bunge SA, Kahn I, et al. Neural circuits subserving the retrieval and maintenance of abstract rules. J Neurophysiol. 2003;90(5):3419–28.
Bunge SA, Ochsner KN, et al. Prefrontal regions involved in keeping information in and out of mind. Brain. 2001;124(Pt 10):2074–86.
Bunge SA, Wendelken C, et al. Analogical reasoning and prefrontal cortex: evidence for separable retrieval and integration mechanisms. Cereb Cortex. 2005;15(3):239–49.
Bunge SA, Zelazo PD. A brain-based account of the development of rule use in childhood. Curr Dir Psychol Sci. 2006;15(3):118–21.
Burgess PW, Gonen-Yaacovi G, et al. Functional neuroimaging studies of prospective memory: what have we learnt so far? Neuropsychologia. 2011;49(8):2246–57.
Burke LA, Hutchins HM. Training transfer: An integrative literature review. Human resource development review. 2007;6(3):263-96.
Burton, T. Why some patients get no help after brain injury. Wall St j. January 8, 2007. http://online.wsj.com/article/SB116822903868669978.html.
Bushnik T, Englander J, et al. Patterns of fatigue and its correlates over the first 2 years after traumatic brain injury. J Head Trauma Rehabil. 2008b;23(1):25–32.
Bushnik T, Englander J, et al. The experience of fatigue in the first 2 years after moderate-to-severe traumatic brain injury: a preliminary report. J Head Trauma Rehabil. 2008a;23(1):17–24.
Bushnik, T., Englander, J., & Wright, J. (2008). Patterns of fatigue and its correlates over the first 2 years after traumatic brain injury. Journal of Head Trauma Rehabilitation, 23(1), 25-32. doi:10.1097/01.HTR.0000308718.88214.bb 00001199-200801000-00006 [pii]
Cahill S, Rothbaum B, et al. Cognitive-behavioral therapy for adults. In: Foa EB, Keane TM, Friedman MJ, Cohen JA, editors. Effective treatments for PTSD: practice guidelines for the international society for traumatic stress studies. New York: Guilford Press; 2009. p. 139–222.
Caltagirone C. Telecommunications technology in cognitive rehabilitation. Funct Neurol. 2008;23(4):195.
Canessa N, Ferini-Strambi L. Sleep-disordered breathing and cognitive decline in older adults. JAMA. 2011;306(6):654–5.
Canessa, N., & Ferini-Strambi, L. (2011). Sleep-disordered breathing and cognitive decline in older adults. JAMA, 306(6), 654-655. doi:306/6/654 [pii] 10.1001/jama.2011.1124
Cantor, J. B., Ashman, T., Gordon, W., Ginsberg, A., Engmann, C., Egan, M., Flanagan, S. (2008). Fatigue after traumatic brain injury and its impact on participation and quality of life. J Head Trauma Rehabil, 23(18219234), 41-51.
Carlson, K. F., Kehle, S. M., Meis, L. A., Greer, N., MacDonald, R., Rutks, I., et al. Prevalence, assessment, and treatment of mild traumatic brain injury and posttraumatic stress disorder: a systematic review of the evidence. J Head Trauma Rehabil. 2011, 26(2): 103-115.
Castriotta RJ, Wilde MC, et al. Prevalence and consequences of sleep disorders in traumatic brain injury. J Clin Sleep Med. 2007;3(4):349–56.
Castriotta, R. J., & Murthy, J. N. (2011). Sleep disorders in patients with traumatic brain injury: a review. CNS Drugs, 25(21062105), 175-185.
Castriotta, R. J., Atanasov, S., Wilde, M. C., Masel, B. E., Lai, J. M., & Kuna, S. T. (2009). Treatment of sleep disorders after traumatic brain injury. J Clin Sleep Med, 5(2), 137-144.

Castriotta, R. J., Wilde, M. C., Lai, J. M., Atanasov, S., Masel, B. E., & Kuna, S. T. (2007). Prevalence and consequences of sleep disorders in traumatic brain injury. Journal of Clinical Sleep Medicine, 3(4), 349-356.
Cate, C.A. Million Records Project: Research from Student Veterans of America. Student Veterans of America, Washington, DC. 2014.
Chen AJ-W, Abrams GM, et al. Functional re-integration of prefrontal neural networks for enhancing recovery after brain injury. J Head Trauma Rehabil. 2006;21(2):107–18.
Chen AJ-W, Britton M, et al. Sharpening of neural representations: a mechanism of top-down control over information processing by selective attention. New York City: Cognitive Neuroscience Society; 2007.
Chen AJ-W, D'Esposito M. Traumatic brain injury: from bench to beside to society. Neuron. 2010;66(1):11–4.
Chen AJW, Loya F, Binder D. Technological Innovations to Enhance Neurocognitive Rehabilitation. In: Kane RL, Parsons TD, editors. The Role of Technology in Clinical Neuropsychology. Oxford, UK: Oxford University Press; in press.
Chen AJ-W, Loya F. Mild-moderate TBI: clinical recommendations to optimize neurobehavioral functioning, learning, and adaptation. Semin Neurol. 2014 Nov;34(5):557-71.
Chen AJW, Novakovic-Agopian T, et al. Training of goal-directed attention regulation enhances control over neural processing for individuals with brain injury. Brain. 2011.
Chen JK, Johnston KM, et al. Recovery from mild head injury in sports: evidence from serial functional magnetic resonance imaging studies in male athletes. Clin J Sport Med. 2008;18(3):241–7.
Chesson, A. L., Anderson, W. M., Littner, M., Davila, D., Hartse, K., Johnson, S., Rafecas, J. (1999). Practice parameters for the nonpharmacologic treatment of chronic insomnia. An American Academy of Sleep Medicine report. Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep, 22(10617175), 1128-1133.
Cicerone KD, Azulay J. Diagnostic utility of attention measures in postconcussion syndrome. Clin Neuropsychol. 2002;16(3):280–9.
Cicerone KD, Dahlberg C, et al. Evidence-based cognitive rehabilitation: recommendations for clinical practice. Arch Phys Med Rehabil. 2000;81(12):1596–615.
Cicerone KD, Dahlberg C, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. Arch Phys Med Rehabil. 2005;86(8):1681–92.
Cicerone KD, Langenbahn DM, Braden C, Malec JF, Kalmar K, Fraas M, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. Arch Phys Med Rehabil. 2011;92(4):519-30.
Cicerone KD. Remediation of "working attention" in mild traumatic brain injury. Brain Inj. 2002;16(3):185–95.
Cole, M. A., Muir, J. J., Gans, J. J., Shin, L. M., D'Esposito, M., Harel, B. T., & Schembri, A. Simultaneous Treatment of Neurocognitive and Psychiatric Symptoms in Veterans with Post-Traumatic Stress Disorder and History of Mild Traumatic Brain Injury: A Pilot Study of Mindfulness-Based Stress Reduction. Mil Med. 2015; 180(9): 956-963.
Collette F, Van der Linden M, et al. Exploring the unity and diversity of the neural substrates of executive functioning. Hum Brain Mapp. 2005;25(4):409–23.
Cools R, Barker RA, et al. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. Cereb Cortex. 2001;11(12):1136–43.
Cools R, Barker RA, et al. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. Neuropsychologia. 2003;41(11):1431–41.
Cools R, Gibbs SE, et al. Working memory capacity predicts dopamine synthesis capacity in the human striatum. J Neurosci. 2008;28(5):1208–12.
Cooper, D. B., Bowles, A. O., Kennedy, J. E., Curtiss, G., French, L. M., Tate, D. F., & Vanderploeg, R. D. Cognitive Rehabilitation for Military Service Members With Mild Traumatic Brain Injury: A Randomized Clinical Trial. J Head Trauma Rehabil; in press.
Corbetta M, Kincade MJ, et al. Neural basis and recovery of spatial attention deficits in spatial neglect. Nat Neurosci. 2005;8(11):1603–10.
Cowan N, Morey CC. Visual working memory depends on attentional filtering. Trends Cogn Sci. 2006;10(4):139–41.
Crone EA, Donohue SE, et al. Brain regions mediating flexible rule use during development. J Neurosci. 2006;26(43):11239–47.
Curtis CE, D'Esposito M. Persistent activity in the prefrontal cortex during working memory. Trends Cogn Sci. 2003;7(9):415–23.
Curtis CE, Rao VY, et al. Maintenance of spatial and motor codes during oculomotor delayed response tasks. J Neurosci. 2004;24(16):3944–52.

D'Esposito M, Aguirre GK, et al. Functional MRI studies of spatial and non-spatial working memory. Cogn Brain Res. 1998;7:1–13.
D'Esposito M, Chen AJW. Neural mechanisms of prefrontal cortical function: implications for cognitive rehabilitation. In: Moller A, Chapman SB, Lomber SG, editors. Reprogramming the human brain: progress in brain research. Elsevier; 2006. 157.
D'Esposito M, Detre JA, et al. The neural basis of the central executive system of working memory. Nature. 1995;378(6554):279–81.
D'Esposito M, Gazzaley A. Neurorehabilitation and executive function. In: Selzer ME, Cohen L, Gage FH, Clarke S, Duncan PW, editors. Neural rehabilitation and repair. Cambridge, UK: Cambridge University Press; 2006 p. 475–87.
D'Esposito M, Postle BR, et al. Maintenance versus manipulation of information held in working memory: an event-related fMRI study. Brain Cogn. 1999;41(1):66–86.
D'Esposito M, Postle BR. The dependence of span and delayed-response performance on prefrontal cortex. Neuropsychologia. 1999;37(11):1303–15.
D'Zurilla TJ, Goldfried M. Problem solving and behavior modification. J Abnorm Psychol. 1971;78:107–26.
Dahlin E, Neely AS, et al. Transfer of learning after updating training mediated by the striatum. Science. 2008;320(5882):1510–2.
Davis, J. J., Walter, K. H., Chard, K. M., Parkinson, R. B., & Houston, W. S. Treatment adherence in cognitive processing therapy for combat-related PTSD with history of mild TBI. Rehabil Psychol. 2013; 58(1): 36-42.
De Groot MH, Phillips SJ, et al. Fatigue associated with stroke and other neurologic conditions: implications for stroke rehabilitation. Arch Phys Med Rehabil. 2003;84(11):1714–20.
De La Rue-Evans, L., Nesbitt, K., & Oka, R. K. (2013). Sleep hygiene program implementation in patients with traumatic brain injury. Rehabil Nurs, 38(1), 2-10. doi:10.1002/rnj.66
Degutis JM, Van Vleet TM. Tonic and phasic alertness training: a novel behavioral therapy to improve spatial and non-spatial attention in patients with hemispatial neglect. Front Hum Neurosci. 2010;4:60.
DeLuca, J., Genova, H. M., Hillary, F. G., & Wylie, G. (2008). Neural correlates of cognitive fatigue in multiple sclerosis using functional MRI. J Neurol Sci, 270(18336838), 28-39.
Department of Defense. 2016 Q3 DoD worldwide numbers. Washington, D.C.: Author. 2016. Retrieved from http://dvbic.dcoe.mil/files/tbi-numbers/DoD-TBI-Worldwide-Totals_2016_Q3_Nov-10-2016_v1.0_508_2016-12-27.pdf.
Departments of Veterans Affairs. Veterans Benefit Administration Annual Benefits Report
Desimone R. Visual attention mediated by biased competition in extrastriate visual cortex. Philos Trans R Soc Lond B Biol Sci. 1998;353(1373):1245–55.
Dikmen SS, Machamer JE, et al. Neuropsychological effects of valproate in traumatic brain injury: a randomized trial. Neurology. 2000;54(4):895–902.
Dikmen SS, Temkin NR, et al. Neurobehavioral effects of phenytoin prophylaxis of posttraumatic seizures. JAMA. 1991;265(10):1271–7.
Doctor JN, Castro J, et al. Workers' risk of unemployment after traumatic brain injury: a normed comparison. J Int Neuropsychol Soc. 2005;11(6):747–52.
Donohue SE, Wendelken C, et al. Retrieving rules for behavior from long-term memory. Neuroimage. 2005;26(4):1140–9.
Drake AI, Gray N, et al. Factors predicting return to work following mild traumatic brain injury: a discriminant analysis. J Head Trauma Rehabil. 2000;15(5):1103–12.
Duncan J, Burgess P, et al. Fluid intelligence after frontal lobe lesions. Neuropsychologia. 1995;33(3):261–8.
Duncan J, Emslie H, et al. Intelligence and the frontal lobe: the organization of goal-directed behavior. Cognit Psychol. 1996;30(3):257–303.
Durmer, J. S., & Dinges, D. F. (2005). Neurocognitive consequences of sleep deprivation. Seminars in Neurology, 25(1), 117-129. doi:10.1055/s-2005-867080
Englander, J., Bushnik, T., Oggins, J., & Katznelson, L. (2010). Fatigue after traumatic brain injury: Association with neuroendocrine, sleep, depression and other factors. Brain Inj, 24(20961172), 1379-1388.
Erickson KI, Colcombe SJ, et al. Training-induced functional activation changes in dual-task processing: an FMRI study. Cereb Cortex. 2007;17(1):192–204.
Eskridge, S. L., Macera, C. A., Galarneau, M. R., Holbrook, T. L., Woodruff, S. I., MacGregor, A. J et al. Influence of combat blast-related mild traumatic brain injury acute symptoms on mental health and service discharge outcomes. J Neurotrauma. 2013; 30(16): 1391-1397.
Evans J. Can executive impairments be effectively treated? In: Effectiveness of rehabilitation for cognitive deficits. New York, Oxford University Press; 2005. p. 247–57.

Evans J. Rehabilitation of the dysexecutive syndrome. In: Wood R, McMillan T, editors. Neurobehavioural disability and social handicap. London: Psychology Press; 2001. p. 209–27.
Fellus JL, Elovic EP. Fatigue: assessment and treatment. In: Zasler ND, Katz DI, Zafonte R, editors. Brain injury medicine. New York: Demos Medical Publishing; 2007.
Fellus, J. L., & Elovic, E. P. (2007). Fatigue: Assessment and Treatment. In N. D. Zasler, D. I. Katz, & R. Zafonte (Eds.). New York: Demos Medical Publishing.
Ferracioli-Oda, E., Qawasmi, A., & Bloch, M. H. (2013). Meta-analysis: melatonin for the treatment of primary sleep disorders. PLoS One, 8(5), e63773. doi:10.1371/journal.pone.0063773
Fichtenberg, N. L., Millis, S. R., Mann, N. R., Zafonte, R. D., & Millard, A. E. (2000). Factors associated with insomnia among post-acute traumatic brain injury survivors. Brain Inj, 14(10914647), 659-667.
Fiscal Year 2014. Washington, D.C.: Author. 2014. Retrieved from http://benefits.va.gov/REPORTS/abr/ABRCombined-FY14-11052015.pdf.
Fischer S, Gauggel S, et al. Awareness of activity limitations, goal setting and rehabilitation outcome in patients with brain injuries. Brain Inj. 2004;18(6):547–62.
Fish J, Manly T, et al. Compensatory strategies for acquired disorders of memory and planning: differential effects of a paging system for patients with brain injury of traumatic versus cerebrovascular aetiology. J Neurol Neurosurg Psychiatry. 2008a;79(8):930–5.
Fish J, Manly T, et al. Long-term compensatory treatment of organizational deficits in a patient with bilateral frontal lobe damage. J Int Neuropsychol Soc. 2008b;14(1):154–63.
Frencham KA, Fox AM, et al. Neuropsychological studies of mild traumatic brain injury: a meta-analytic review of research since 1995. J Clin Exp Neuropsychol. 2005;27(3):334–51.
Fulcher, K. Y., & White, P. D. (1997). Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. BMJ, 314(9180065), 1647-1652.
Fuster JM. Executive frontal functions. Exp Brain Res. 2000;133(1):66–70.
Gardner, R. C., Burke, J. F., Nettiksimmons, J., Goldman, S., Tanner, C. M., & Yaffe, K. Traumatic brain injury in later life increases risk for Parkinson disease. Ann Neurol. 2015; 77(6): 987-995.
Gardner, R. C., Burke, J. F., Nettiksimmons, J., Kaup, A., Barnes, D. E., & Yaffe, K. Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity. JAMA Neurol. 2014; 71(12): 1490-1497.
Gazzaley A, Cooney JW, et al. Top-down enhancement and suppression of the magnitude and speed of neural activity. J Cogn Neurosci. 2005;17(3):507–17.
Gilbert SJ, Spengler S, et al. Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. J Cogn Neurosci. 2006;18(6):932–48.
Gilbertson MW, Gurvits TV, et al. Multivariate assessment of explicit memory function in combat veterans with posttraumatic stress disorder. J Trauma Stress. 2001;14(2):413–32.
Giles GM. Cognitive versus functional approaches to rehabilitation after traumatic brain injury: commentary on a randomized controlled trial. Am J Occup Ther. 2010;64(1):182–5.
Girard, P. Military and VA telemedicine systems for patients with traumatic brain injury. J Rehabil Res Dev. 2007; 44(7): 1017–1026.
Gold JI, Shadlen MN. Neural computations that underlie decisions about sensory stimuli. Trends Cogn Sci. 2001;5(1):10–6.
Goldman-Rakic PS, Friedman HR. The circuitry of working memory revealed by anatomy and metabolic imaging. In: Levin H, Eisenberg H, Benton A, editors. Frontal lobe function and dysfunction. New York: Oxford University Press; 1991. p. 72–91.
Gouveia PA, Brucki SM, et al. Disorders in planning and strategy application in frontal lobe lesion patients. Brain Cogn. 2007;63(3):240–6.
Gualtieri CT, Evans RW. Stimulant treatment for the neurobehavioural sequelae of traumatic brain injury. Brain Inj. 1988;2(4):273–90.
Hailey, D., Roine, R., Ohinmaa, A., & Dennett, L. The status of telerehabilitation in neurological applications. J Telemed Telecare. 2013; 19(6): 307–310.
Hallock, H., Collins, D., Lampit, A., Deol, K., Fleming, J., & Valenzuela, M. Cognitive training for post-acute traumatic brain injury: a systematic review and meta-analysis. Front Hum Neurosci. 2016; 10.
Haskins EC, Cicerone KD, Trexler LE. Cognitive rehabilitation manual: Translating evidence-based recommendations into practice. Reston, Virginia, USA: American Congress of Rehabilitation Medicine; 2012.
Haxby JV, Gobbini MI, et al. Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science. 2001;293(5539):2425–30.
Hecaen H, Albert ML. Human neuropsychology. New York: Wiley; 1978.

Hillary FG. Neuroimaging of working memory dysfunction and the dilemma with brain reorganization hypotheses. J Int Neuropsychol Soc. 2008;14(4):526–34.
Hillier SL, Sharpe MH, et al. Outcomes 5 years post-traumatic brain injury (with further reference to neurophysical impairment and disability). Brain Inj. 1997;11(9):661–75.
Hillier, S. L., Sharpe, M. H., & Metzer, J. (1997). Outcomes 5 years post-traumatic brain injury (with further reference to neurophysical impairment and disability). Brain Injury, 11(9), 661-675.
Hoffman AN, Cheng JP, et al. Administration of haloperidol and risperidone after neurobehavioral testing hinders the recovery of traumatic brain injury-induced deficits. Life Sci. 2008;83(17–18):602–7.
Hoge CW, McGurk D, et al. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. N Engl J Med. 2008;358(5):453–63.
Hoge, Charles W., et al. Mild traumatic brain injury in US soldiers returning from Iraq. N Engl J Med. 2008; 453-463.
Huckans M, Pavawalla S, et al. A pilot study examining effects of group-based Cognitive Strategy Training treatment on self-reported cognitive problems, psychiatric symptoms, functioning, and compensatory strategy use in OIF/OEF combat veterans with persistent mild cognitive disorder and history of traumatic brain injury. J Rehabil Res Dev. 2010;47(1):43–60.
Huckans, M., Pavawalla, S., Demadura, T., Kolessar, M., Seelye, A., Roost, N., et al. A pilot study examining effects of group-based Cognitive Strategy Training treatment on self-reported cognitive problems, psychiatric symptoms, functioning, and compensatory strategy use in OIF/OEF combat veterans with persistent mild cognitive disorder and history of traumatic brain injury. J Rehabil Res Dev. 2010; 47(1): 43.
Hux K, Schneider T, et al. Screening for traumatic brain injury. Brain Inj. 2009;23(1):8–14.
Hyndman D, Ashburn A. People with stroke living in the community: attention deficits, balance, ADL ability and falls. Disabil Rehabil. 2003;25(15):817–22.
Ilinisky IA, Jouandet ML, et al. Organization of the nigrothalamocortical system in the rhesus monkey. J Comp Neurol. 1985;236:315–30.
Ivins BJ. Hospitalization associated with traumatic brain injury in the active duty US Army: 2000-2006. NeuroRehabilitation. 2010; 26(3):199-212.
Jacoby N, Ahissar M. What does It take to Show that a Cognitive Training Procedure is Useful? A critical evaluation. Prog Brain Res. 2013;207:121-40.
Jaeggi SM, Buschkuehl M, et al. Improving fluid intelligence with training on working memory. Proc Natl Acad Sci USA. 2008;105(19):6829–33.
Janak, J. C., Cooper, D. B., Bowles, A. O., Alamgir, A. H., Cooper, S. P., Gabriel, K. P., Orman, J. A. Completion of Multidisciplinary Treatment for Persistent Postconcussive Symptoms Is Associated With Reduced Symptom Burden. J Head Trauma Rehabil. 2015; 32(1): 1-15.
Jazayeri M. Probabilistic sensory recoding. Curr Opin Neurobiol. 2008;18(4):431–7.
Jha AP, Krompinger J, et al. Mindfulness training modifies subsystems of attention. Cogn Affect Behav Neurosci. 2007;7(2):109–19.
Jha, A.P., Stanley, E. A., Kiyonaga, A., et.al., Examining the protective effects of mindfulness training on working memory capacity and affective experience. Emotion, 2010. 10: p. 54-64
Johansson, B., Bjuhr, H., & Ronnback, L. (2012). Mindfulness-based stress reduction (MBSR) improves long-term mental fatigue after stroke or traumatic brain injury. Brain Inj, 26(22794665), 1621-1628.
Johansson, B., Wentzel, A. P., Andrell, P., Odenstedt, J., Mannheimer, C., & Ronnback, L. (2014). Evaluation of dosage, safety and effects of methylphenidate on post-traumatic brain injury symptoms with a focus on mental fatigue and pain. Brain Inj, 28(24377326), 304-310.
Kabat-Zinn J. Full catastrophe living. New York, NY: Delacorte Press; 1990.
Kane MJ, Engle RW. The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: an individual-differences perspective. Psychon Bull Rev. 2002;9(4):637–71.
Kelly AM, Garavan H. Human functional neuroimaging of brain changes associated with practice. Cereb Cortex. 2005;15(8):1089–102.
Kelly C, Foxe JJ, et al. Patterns of normal human brain plasticity after practice and their implications for neurorehabilitation. Arch Phys Med Rehabil. 2006;87(12 Suppl 2):S20–9.
Kemp, S., Biswas, R., Neumann, V., & Coughlan, A. (2004). The value of melatonin for sleep disorders occurring post-head injury: a pilot RCT. Brain Inj, 18(15223743), 911-919.
Kempf, J., Werth, E., Kaiser, P. R., Bassetti, C. L., & Baumann, C. R. (2010). Sleep-wake disturbances 3 years after traumatic brain injury. J Neurol Neurosurg Psychiatry, 81(20884672), 1402-1405.
Kennedy MR, Coelho C, et al. Intervention for executive functions after traumatic brain injury: a systematic review, meta-analysis and clinical recommendations. Neuropsychol Rehabil. 2008;18(3):257–99.

Kennedy, M. R., Krause, M. O., & Turkstra, L. S. An electronic survey about college experiences after traumatic brain injury. NeuroRehabilitation. 2008; 23(6): 511-520.
Kesler SR, Adams HF, et al. Premorbid intellectual functioning, education, and brain size in traumatic brain injury: an investigation of the cognitive reserve hypothesis. Appl Neuropsychol. 2003;10(3):153–62.
Kim YH, Yoo WK, et al. Plasticity of the attentional network after brain injury and cognitive rehabilitation. Neurorehabil Neural Repair. 2009;23(5):468–77.
Kimberg DY, D'Esposito M, et al. Effects of bromocriptine on human subjects depend on working memory capacity. Neuroreport. 1997;8(16):3581–5.
Kline AE, Hoffman AN, et al. Chronic administration of antipsychotics impede behavioral recovery after experimental traumatic brain injury. Neurosci Lett. 2008;448(3):263–7.
Klingberg T. Training and plasticity of working memory. Trends Cogn Sci. 2010;14(7):317–24.
Kolb DA. Experiential learning: Experience as the source of learning and development. Saddle River, NJ: Pearson Education, Inc.; 2014.
Konrad, C., Geburek, A. J., Rist, F., Blumenroth, H., Fischer, B., Husstedt, I., et al. Long-term cognitive and emotional consequences of mild traumatic brain injury. Psychol Med. 2011; 41(06): 1197-1211.
Krupp, L. B., Coyle, P. K., Doscher, C., Miller, A., Cross, A. H., Jandorf, L., .Grimson, R. (1995). Fatigue therapy in multiple sclerosis: results of a double-blind, randomized, parallel trial of amantadine, pemoline, and placebo. Neurology, 45(7501140), 1956-1961.
Laatsch LK, Thulborn KR, et al. Investigating the neurobiological basis of cognitive rehabilitation therapy with fMRI. Brain Inj. 2004;18(10):957–74.
Langlois JA, Kegler SR, et al. Traumatic brain injury-related hospital discharges. Results from a 14-state surveillance system, 1997. MMWR Surveill Summ. 2003;52(4):1–20.
Larson, E. B., & Zollman, F. S. (2010). The effect of sleep medications on cognitive recovery from traumatic brain injury. J Head Trauma Rehabil, 25(20051895), 61-67.
Leskin LP, White PM. Attentional networks reveal executive function deficits in posttraumatic stress disorder. Neuropsychology. 2007;21(3):275–84.
Levine B, Robertson IH, et al. Rehabilitation of executive functioning: an experimental-clinical validation of goal management training. J Int Neuropsychol Soc. 2000;6(3):299–312.
Levine B, Stuss DT, et al. Cognitive rehabilitation in the elderly: effects on strategic behavior in relation to goal management. J Int Neuropsychol Soc. 2007;13(1):143–52.
Levine B, Turner G, et al. (2008). Cognitive rehabilitation of executive dysfunction In : Cognitive Neurorehabilitation: Evidence & Applications (2nd Edition). D. T. Stuss, G. Winocur and I. H. Robertson Editors. Cambridge Unuversity Press; pp 464–87.
Lew, H. L., Poole, J. H., Vanderploeg, R. D., Goodrich, G. L., Dekelboum, S., Guillory, S. B., Cifu, D. X. (2007). Program development and defining characteristics of returning military in a VA Polytrauma Network Site. J Rehabil Res Dev, 44(18075959), 1027-1034.
Lew, H. L., Tun, C., & Cifu, D. X. Prevalence of chronic pain, posttraumatic stress disorder, and persistent postconcussive symptoms in OIF/OEF veterans: polytrauma clinical triad. 2009. J Rehabil Res Dev, 46(6), 697.
Lewis V, Creamer M, et al. Is poor sleep in veterans a function of post-traumatic stress disorder? Mil Med. 2009;174(9):948–51.
Lezak MD. Neuropsychological assessment. New York: Oxford University Press; 1995.
Loya, F., Binder, D., Rodriguez, N., Buchanan, B., Novakovic-Agopian,T& Chen, AJW. Guided experiential training of self-regulation skills: A controlled pilot study of brain injury tele-rehabilitation. Manuscript under review.
Loya, F., Novakovic-Agopian, T., Binder, D., Rossi, A., Rome, S., Murphy, M., et al. Long-term use and perceived benefits of Goal-Oriented Attentional Self-regulation (GOALS) training in chronic brain injury. Rehabil Res Pract. In press.
Loya, F., Rodriguez, N., Binder, D., Buchanan, B., Novakovic-Agopian, T., & Chen, A. J. W. (2014, March). 'From start-up to CEO': Development of game-assisted training for persons with brain injury to improve higher order functional cognition. Poster presented at the Tenth World Congress on Brain Injury, San Francisco, CA.
Luks TL, Simpson GV, et al. Evidence for anterior cingulate cortex involvement in monitoring preparatory attentional set. Neuroimage. 2002;17(2):792–802.
Machamer J, Temkin N, et al. Stability of employment after traumatic brain injury. J Int Neuropsychol Soc. 2005;11(7):807–16.
MacLeod CM, Dunbar K. Training and Stroop-like interference: evidence for a continuum of automaticity. J Exp Psychol Learn Mem Cogn. 1988;14(1):126–35.
MacLeod CM. Half a century of research on the Stroop effect: an integrative review. Psychol Bull. 1991;109(2):163–203.

Mahmood O, Rapport LJ, et al. Neuropsychological performance and sleep disturbance following traumatic brain injury. J Head Trauma Rehabil. 2004;19(5):378–90.
Mahmood, O., Rapport, L. J., Hanks, R. A., & Fichtenberg, N. L. (2004). Neuropsychological performance and sleep disturbance following traumatic brain injury. Journal of Head Trauma Rehabilitation, 19(5), 378-390. doi:00001199-200409000-00003 [pii]
Manly T, Hawkins K, et al. Rehabilitation of executive function: facilitation of effective goal management on complex tasks using periodic auditory alerts. Neuropsychologia. 2002;40:271–81.
Manly T, Robertson IH, et al. The absent mind: further investigations of sustained attention to response. Neuropsychologia. 1999;37(6):661–70.
Mathias JL, Beall JA, et al. Neuropsychological and information processing deficits following mild traumatic brain injury. J Int Neuropsychol Soc. 2004;10(2):286–97.
Mathias JL, Coats JL. Emotional and cognitive sequelae to mild traumatic brain injury. J Clin Exp Neuropsychol. 1999;21(2):200–15.
Mauri M, Sinforiani E, et al. Interaction between Apolipoprotein epsilon 4 and traumatic brain injury in patients with Alzheimer's disease and Mild Cognitive Impairment. Funct Neurol. 2006;21(4):223–8.
McAllister, T. W., Saykin, A. J., Flashman, L. A., Sparling, M. B., Johnson, S. C., Guerin, S. J., Yanofsky, N. (1999). Brain activation during working memory 1 month after mild traumatic brain injury: a functional MRI study. Neurology, 53(10522888), 1300-1308.
McDowell S, Whyte J, et al. Differential effect of a dopaminergic agonist on prefrontal function in traumatic brain injury patients. Brain. 1998;121(Pt 6):1155–64.
McDowell, S., Whyte, J., & D'Esposito, M. (1998). Differential effect of a dopaminergic agonist on prefrontal function in traumatic brain injury patients. Brain, 121 (Pt 6, 1155-1164.
McNab F, Varrone A, et al. Changes in cortical dopamine D1 receptor binding associated with cognitive training. Science. 2009;323(5915):800–2.
Mednick S, Nakayama K, et al. Sleep-dependent learning: a nap is as good as a night. Nat Neurosci. 2003;6(7):697–8.
Mednick, S., Nakayama, K., & Stickgold, R. (2003). Sleep-dependent learning: a nap is as good as a night. Nature Neuroscience, 6(7), 697-698. doi:10.1038/nn1078 nn1078 [pii]
Meintzschel F, Ziemann U. Modification of practice-dependent plasticity in human motor cortex by neuromodulators. Cereb Cortex. 2006;16(8):1106–15.
Melby-Lervag M, Hulme C. Is working memory training effective? A meta-analytic review. Dev Psychol. 2013;49(2):270-91.
Mendonca, D. A., Menezes, K., & Jog, M. S. (2007). Methylphenidate improves fatigue scores in Parkinson disease: a randomized controlled trial. Mov Disord, 22(14), 2070-2076. doi:10.1002/mds.21656
Miller BT, D'Esposito M. Searching for "the top" in top-down control. Neuron. 2005;48(4):535–8.
Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci. 2001;24:167–202.
Miller, S. C., Whitehead, C. R., Otte, C. N., Wells, T. S., Webb, T. S., Gore, R. K., & Maynard, C. Risk for broad-spectrum neuropsychiatric disorders after mild traumatic brain injury in a cohort of US Air Force personnel. Occup Environ Med. 2015;72(8): 560-566.
Milliken CS, Auchterlonie JL, et al. Longitudinal assessment of mental health problems among active and reserve component soldiers returning from the Iraq war. JAMA. 2007;298(18):2141–8.
Minton, O., Richardson, A., Sharpe, M., Hotopf, M., & Stone, P. (2008). A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue. J Natl Cancer Inst, 100(18695134), 1155-1166.
Miotto E, Evans J, et al. Rehabilitation of executive dysfunction: a controlled trial of an attention and problem solving treatment group. Neuropsychol Rehabil. 2009;19:517–40.
Miotto EC, Savage CR, et al. Bilateral activation of the prefrontal cortex after strategic semantic cognitive training. Hum Brain Mapp. 2006;27(4):288–95.
Mock, V., Frangakis, C., Davidson, N. E., Ropka, M. E., Pickett, M., Poniatowski, B., McCorkle, R. (2005). Exercise manages fatigue during breast cancer treatment: a randomized controlled trial. Psychooncology, 14(15484202), 464-477.
Monson C, Schnurr P, et al. Cognitive processing therapy for veterans with military-related posttraumatic stress disorder. J Consult Clin Psychol. 2006;74(5):898–907.
Morin, C. M., Bootzin, R. R., Buysse, D. J., Edinger, J. D., Espie, C. A., & Lichstein, K. L. (2006). Psychological and behavioral treatment of insomnia:update of the recent evidence (1998-2004). Sleep, 29(17162986), 1398-1414.
Murtagh, D. R., & Greenwood, K. M. (1995). Identifying effective psychological treatments for insomnia: a meta-analysis. J Consult Clin Psychol, 63(7896994), 79-89.

Muzur A, Pace-Schott EF, et al. The prefrontal cortex in sleep. Trends Cogn Sci. 2002;6(11):475–81.
Muzur, A., Pace-Schott, E. F., & Hobson, J. A. (2002). The prefrontal cortex in sleep. Trends in Cognitive Sciences, 6(11), 475-481. doi:S1364661302019927 [pii]
Nampiaparampil D. Prevalence of chronic pain after traumatic brain injury: a systematic review. JAMA. 2008;300(6):711–9.
Neckelmann D, Mykletun A, et al. Chronic insomnia as a risk factor for developing anxiety and depression. Sleep. 2007;30(7):873–80.
Neckelmann, D., Mykletun, A., & Dahl, A. A. (2007). Chronic insomnia as a risk factor for developing anxiety and depression. Sleep, 30(7), 873-880.
Newman SD, Carpenter PA, et al. Frontal and parietal participation in problem solving in the Tower of London: fMRI and computational modeling of planning and high-level perception. Neuropsychologia. 2003;41(12):1668–82.
Nezu AM, Nezu CM, et al. Solving life's problems. New York: Springer Publishing Company; 2007.
Ng EMW, Polatajko HJ, Marziali E, Hunt A, Dawson DR. Telerehabilitation for addressing executive dysfunction after traumatic brain injury. Brain Inj. 2013;27(5):548-64
Nithianantharajah J, Hannan AJ. The neurobiology of brain and cognitive reserve: mental and physical activity as modulators of brain disorders. Prog Neurobiol. 2009;89(4):369–82.
Norris, J. N., Sams, R., Lundblad, P., Frantz, E., & Harris, E. Blast-related mild traumatic brain injury in the acute phase: acute stress reactions partially mediate the relationship between loss of consciousness and symptoms. Brain Inj. 2014; 28(8): 1052-1062.
Novakovic-Agopian T, Chen A, et al. Rehabilitation of executive functioning with training in attention regulation applied to individually defined goals: a pilot study bridging theory, assessment and treatment. J Head Trauma Rehabil. 2011;26(5):325–38.
Novakovic-Agopian, Abrams G. Chen, A, et.al. Short and Long Term Outcomes of Executive Function Training in Veterans with Chronic TBI. Presentation at the 9 World Congress on Neurorehabilitation, Philadelphia, PA, May 2016
Novakovic-Agopian, T., Abrams G., Chen, A., et.al.(2015). Executive Function Training in Veterans with Chronic TBI: Short and Longer Term Outcomes. Presentation at the ACRM Conference, Dallas, TX,
Novakovic-Agopian, T., Chen, A., Abrams G., et.al.(2014a) , Goal-Oriented Executive Function Training in Veterans with Chronic TBI: Short and Longer Term Outcomes, in 10th World Congress on Brain Injury. San Francisco
Novakovic-Agopian, T., Chen, A., Rome, S., Rossi, A., Abrams, A. et.al., Assessment of Sub-Components of Executive Functioning in Ecologically Valid Settings: The Goal Processing Scale. Journal of Head Trauma Rehabilitation, 2014b. 29: p. 136-146.
Okie S. Traumatic brain injury in the war zone. N Engl J Med. 2005;352(20):2043–7.
Olesen PJ, Westerberg H, et al. Increased prefrontal and parietal activity after training of working memory. Nat Neurosci. 2004;7(1):75–9.
Olver JH, Ponsford JL, et al. Outcome following traumatic brain injury: a comparison between 2 and 5 years after injury. Brain Inj. 1996;10(11):841–8.
Olver, J. H., Ponsford, J. L., & Curran, C. A. (1996). Outcome following traumatic brain injury: a comparison between 2 and 5 years after injury. Brain Injury, 10(11), 841-848.
Orff, H. J., Ayalon, L., & Drummond, S. P. A. (2009). Traumatic brain injury and sleep disturbance: a review of current research. J Head Trauma Rehabil, 24(19461363), 155-165.
Ouellet, M.-C., & Morin, C. M. (2004). Cognitive behavioral therapy for insomnia associated with traumatic brain injury: a single-case study. Arch Phys Med Rehabil, 85(15295756), 1298-1302.
Ouellet, M.-C., & Morin, C. M. (2007). Efficacy of cognitive-behavioral therapy for insomnia associated with traumatic brain injury: a single-case experimental design. Arch Phys Med Rehabil, 88(18047872), 1581-1592.
Ouellet, M.-C., Beaulieu-Bonneau, S., & Morin, C. M. (2006). Insomnia in patients with traumatic brain injury: frequency, characteristics, and risk factors. J Head Trauma Rehabil, 21(16717498), 199-212.
Owen AM, Hampshire A, Grahn JA, Stenton R, Dajani S, Burns AS, et al. Putting brain training to the test. Nature. 2010;465(7299):775-8.
Ownsworth T, McKenna K. Investigation of factors related to employment outcome following traumatic brain injury: a critical review and conceptual model. Disabil Rehabil. 2004;26(13):765–83.
Ozdemir F, Birtane M, et al. Cognitive evaluation and functional outcome after stroke. Am J Phys Med Rehabil. 2001;80(6):410–5.
Park DC, Polk TA, et al. Aging reduces neural specialization in ventral visual cortex. Proc Natl Acad Sci USA. 2004;101(35):13091–5.

Paulus MP, Potterat EG, et al. A neuroscience approach to optimizing brain resources for human performance in extreme environments. Neurosci Biobehav Rev. 2009;33(7):1080–8.
Persson J, Reuter-Lorenz PA. Gaining control: training executive function and far transfer of the ability to resolve interference. Psychol Sci. 2008;19(9):881–8.
Petersen SE, van Mier H, et al. The effects of practice on the functional anatomy of task performance. Proc Natl Acad Sci USA. 1998;95(3):853–60.
Phelps EA, Delgado MR, et al. Extinction learning in humans: role of the amygdala and vmPFC. Neuron. 2004;43(6):897–905.
Pietrzak, R. H., Johnson, D. C., Goldstein, M. B., Malley, J. C., & Southwick, S. M. Perceived stigma and barriers to mental health care utilization among OEF-OIF veterans. Psychiatr Serv. 2009; 60(8): 1118-1122.
Plassman BL, Havlik RJ, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology. 2000;55(8):1158–66.
Polusny MA, Kehle SM, et al. Longitudinal effects of mild traumatic brain injury and posttraumatic stress disorder comorbidity on postdeployment outcomes in national guard soldiers deployed to Iraq. Arch Gen Psychiatry. 2011;68(1):79–89.
Ponsford, J. L., Downing, M. G., Olver, J., Ponsford, M., Acher, R., Carty, M., & Spitz, G. Longitudinal follow-up of patients with traumatic brain injury: Outcome at two, five, and ten years post-injury. J Neurotrauma; 2014, 31(1), 64-77.
Ponsford, J. L., Parcell, D. L., Sinclair, K. L., Roper, M., & Rajaratnam, S. M. W. (2013). Changes in sleep patterns following traumatic brain injury: a controlled study. Neurorehabil Neural Repair, 27(23549523), 613-621.
Ponsford, J. L., Ziino, C., Parcell, D. L., Shekleton, J. A., Roper, M., Redman, J. R., .Rajaratnam, S. M. W. (2012). Fatigue and sleep disturbance following traumatic brain injury--their nature, causes, and potential treatments. J Head Trauma Rehabil, 27(22573041), 224-233.
Posner MI, Sheese BE, et al. Analyzing and shaping human attentional networks. Neural Netw. 2006;19(9):1422–9.
Posner MI. Measuring alertness. Ann N Y Acad Sci. 2008;1129:193–9.
Postle BR. Working memory as an emergent property of the mind and brain. Neurosci. 2006;139:23–38.
Prigatano GP, Wong JL. Cognitive and affective improvement in brain dysfunctional patients who achieve inpatient rehabilitation goals. Arch Phys Med Rehabil. 1999;80(1):77–84.
Rammohan, K. W., Rosenberg, J. H., Lynn, D. J., Blumenfeld, A. M., Pollak, C. P., & Nagaraja, H. N. (2002). Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. J Neurol Neurosurg Psychiatry, 72(2), 179-183.
Ranganath C, Heller AS, et al. Dissociable correlates of two classes of retrieval processing in prefrontal cortex. Neuroimage. 2007;35(4):1663–73.
Ranganath C, Johnson MK, et al. Prefrontal activity associated with working memory and episodic long-term memory. Neuropsychologia. 2003;41(3):378–89.
Ranganath C. Working memory for visual objects: complementary roles of inferior temporal, medial temporal, and prefrontal cortex. Neuroscience. 2006;139(1):277–89.
Raskin SA. Memory. In: Raskin SA, Mateer C, editors. Neuropsychological management of mild traumatic brain injury. Oxford: Oxford University Press; 2000.
Rath J, Simon D, et al. Group treatment of problem-solving deficits in outpatients with traumatic brain injury: a randomised outcome study. Neuropsychol Rehabil. 2003;13(4):461–88.
Rauch S, Defever E, et al. Prolonged exposurefor PTSD in a Veterans Health Administration PTSD clinic. J Trauma Stress. 2009;22(1):60–4.
Repovs G, Baddeley A. The multi-component model of working memory: explorations in experimental cognitive psychology. Neuroscience. 2006;139(1):5–21.
Robertson IH. Goal management training: a clinical manual. Cambridge: PsyConsult. 1996.
Rohling ML, Faust ME, et al. Effectiveness of cognitive rehabilitation following acquired brain injury: a meta-analytic re-examination of Cicerone et al'.s (2000, 2005) systematic reviews. Neuropsychology. 2009;23(1):20–39.
Rosen HJ, Petersen SE, et al. Neural correlates of recovery from aphasia after damage to left inferior frontal cortex. Neurology. 2000;55(12):1883–94.
Ruff R. Two decades of advances in understanding of mild traumatic brain injury. J Head Trauma Rehabil. 2005;20(1):5–18.
Saatman KE, Duhaime AC, et al. Classification of traumatic brain injury for targeted therapies. J Neurotrauma. 2008;25(7):719–38.

Salmond CH, Chatfield DA, et al. Cognitive sequelae of head injury: involvement of basal forebrain and associated structures. Brain. 2005;128(Pt 1):189–200.
Sanchez-Carrion R, Fernandez-Espejo D, et al. A longitudinal fMRI study of working memory in severe TBI patients with diffuse axonal injury. Neuroimage. 2008;43(3):421–9.
Sayer, N. A., Rettmann, N. A., Carlson, K. F., Bernardy, N., Sigford, B. J., Hamblen, J. L., & Friedman, M. J. Veterans with history of mild traumatic brain injury and posttraumatic stress disorder: challenges from provider perspective. J Rehabil Res Dev. 2009; 46(6): 703-716
Scheid R, Walther K, et al. Cognitive sequelae of diffuse axonal injury. Arch Neurol. 2006;63(3):418–24.
Schneiderman AI, Braver ER, et al. Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: persistent postconcussive symptoms and posttraumatic stress disorder. Am J Epidemiol. 2008;167(12):1446–52.
Schnurr P, Friedman M, et al. Cognitive behavioral therapy for posttraumatic stress disorder in women: a randomized controlled trial. JAMA. 2007;297(8):820–30.
Schumacher EH, Lauber E, et al. PET evidence for an amodal verbal working memory system. Neuroimage. 1996;3:79–88.
Schwartz A. New sign of brain damage in N.F.L. New York: New York Times; 2009.
Selemon RD, Goldman-Rakic PS. Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network serving spatially guided behavior. J Neurosci. 1988;8:4049–68.
Shallice T, Burgess PW. Deficits in strategy application following frontal lobe damage in man. Brain. 1991;114:727–41.
Shekleton, J. A., Parcell, D. L., Redman, J. R., Phipps-Nelson, J., Ponsford, J. L., & Rajaratnam, S. M. W. (2010). Sleep disturbance and melatonin levels following traumatic brain injury. Neurology, 74(20498441), 1732-1738.
Shipstead Z, Redick TS, Engle RW. Is working memory training effective? Psych bull. 2012;138(4):628-54.
Silver JM, Koumaras B, et al. Effects of rivastigmine on cognitive function in patients with traumatic brain injury. Neurology. 2006;67(5):748–55.
Silver, J. M., Koumaras, B., Chen, M., Mirski, D., Potkin, S. G., Reyes, P., Gunay, I. (2006). Effects of rivastigmine on cognitive function in patients with traumatic brain injury. Neurology, 67(5), 748-755. doi:01.wnl.0000234062.98062.e9 [pii] 10.1212/01.wnl.0000234062.98062.e9
Simons, D.J., Boot, W.R., Charness, N., Gathercole, S.E., Chabris, C.F., Hambrick, D.Z., et al. Do “Brain Training” programs work? Psychol Sci Public Interest, 17(3), 103-186.
Slagter HA, Lutz A, et al. Mental training affects distribution of limited brain resources. PLoS Biol. 2007;5(6):e138.
Smith Jr KR, Goulding PM, et al. Neurobehavioral effects of phenytoin and carbamazepine in patients recovering from brain trauma: a comparative study. Arch Neurol. 1994;51(7):653–60.
Sohlberg MM, Mateer CA. Effectiveness of an attention-training program. J Clin Exp Neuropsychol. 1987;9(2):117–30.
Sohlberg MM, McLaughlin KA, et al. Evaluation of attention process training and brain injury education in persons with acquired brain injury. J Clin Exp Neuropsychol. 2000;22(5):656–76.
Soo C, Tate R. Psychological treatment for anxiety in people with traumatic brain injury. Cochrane Database Syst Rev. 2007(3): CD005239.
Spitzer H, Desimone R, et al. Increased attention enhances both behavioral and neuronal performance. Science. 1988;240(4850):338–40.
Stanislav SW. Cognitive effects of antipsychotic agents in persons with traumatic brain injury. Brain Inj. 1997;11(5):335–41.
Staub F, Bogousslavsky J. Fatigue after stroke: a major but neglected issue. Cerebrovasc Dis. 2001;12(2):75–81.
Stein, M. B., Kessler, R. C., Heeringa, S. G., Jain, S., Campbell-Sills, L., Colpe, L. J., Army Starrs collaborators. Prospective Longitudinal Evaluation of the Effect of Deployment-Acquired Traumatic Brain Injury on Posttraumatic Stress and Related Disorders: Results From the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS). Am J Psychiatry. 2015; 172(11): 1101-1111.
Storzbach, D., Twamley, E. W., Roost, M. S., Golshan, S., Williams, R. M., O'Neil, M., et al. Compensatory Cognitive Training for Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn Veterans With Mild Traumatic Brain Injury. J Head Trauma Rehabil. 2017; 32(1): 16-24.
Strangman GE, Goldstein R, et al. Neurophysiological alterations during strategy-based verbal learning in traumatic brain injury. Neurorehabil Neural Repair. 2009;226–236.
Sturm W, de Simone A, et al. Functional anatomy of intrinsic alertness: evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere. Neuropsychologia. 1999;37(7):797–805.

Stuss DT, Alexander MP. Is there a dysexecutive syndrome? Philos Trans R Soc Lond B Biol Sci. 2007;362(1481):901–15.
Taber KH, Hurley RA. PTSD and combat-related injuries: functional neuroanatomy. J Neuropsychiatry Clin Neurosci. 2009;21(1):1p. preceding 1, 1–4.
Tatemichi TK, Paik M, et al. Dementia after stroke is a predictor of long-term survival. Stroke. 1994;25(10):1915–9.
Tenovuo, O. (2005). Central acetylcholinesterase inhibitors in the treatment of chronic traumatic brain injury-clinical experience in 111 patients. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 29(1), 61-67.
Thompson-Schill SL, Jonides J, et al. Effects of frontal lobe damage on interference effects in working memory. Cogn Affect Behav Neurosci. 2002;2(2):109–20.
Thurman D, Alverson C, et al. Traumatic brain injury in the United States: a public health perspective. J Head Trauma Rehabil. 1999;14(6):602–15.
Toglia J, Kirk U. Understanding awareness deficits following brain injury. NeuroRehabilitation. 2000;15(1):57-70.
Tucker MA, Hirota Y, et al. A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. Neurobiol Learn Mem. 2006;86(2):241–7.
Tucker, M. A., Hirota, Y., Wamsley, E. J., Lau, H., Chaklader, A., & Fishbein, W. (2006). A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. Neurobiology of Learning and Memory, 86(2), 241-247. doi:S1074-7427(06)00034-7 [pii] 10.1016/j.nlm.2006.03.005
van Baalen B, Odding E, et al. Cognitive status at discharge from the hospital determines discharge destination in traumatic brain injury patients. Brain Inj. 2008;22(1):25–32.
Van Den Heuvel C, Thornton E, et al. Traumatic brain injury and Alzheimer's disease: a review. Prog Brain Res. 2007;161:303–16.
van Reekum R, Cohen T, et al. Can traumatic brain injury cause psychiatric disorders? J Neuropsychiatry Clin Neurosci. 2000;12(3):316–27.
Van Velzen, J. M., Van Bennekom, C. A. M., Edelaar, M. J. A., Sluiter, J. K., & Frings-Dresen, M. H. W. How many people return to work after acquired brain injury?: a systematic review. Brain Inj. 2009; 23(6): 473-488.
Van Vleet TM, Hoang-Duc AK, et al. Modulation of non-spatial attention and the global/local processing bias. Neuropsychologia. 2011;49(3):352–9.
Van Zomeren, A. H., Brouwer, W. H., & Deelman, B. G. (1984). Attentional deficits: The riddles of selectivity, speed and alertness Closed head injury: Psychological, social and family consequences. Oxford: Oxford University Press.
Vanderploeg RD, Belanger HG, et al. Mild traumatic brain injury and posttraumatic stress disorder and their associations with health symptoms. Arch Phys MedRehabil. 2009;90:1084–93.
Vanderploeg RD, Curtiss G, et al. Long-term neuropsychological outcomes following mild traumatic brain injury. J Int Neuropsychol Soc. 2005;11(3):228–36.
Vanderploeg, R. D., Belanger, H. G., Horner, R. D., Spehar, A. M., Powell-Cope, G., Luther, S. L., & Scott, S. G. Health outcomes associated with military deployment: mild traumatic brain injury, blast, trauma, and combat associations in the Florida National Guard. Arch Phys Med Rehabil. 2012; 93(11): 1887-1895
Vanderploeg, R. D., Curtiss, G., & Belanger, H. G. Long-term neuropsychological outcomes following mild traumatic brain injury. J Int Neuropsychol Soc. 2005;11(03): 228-236.
Vas A, Chapman S, et al. Higher-order reasoning training years after traumatic brain injury in adults. J Head Trauma Rehabil. 2011;26(3):224–39.
Vasterling JJ, Brailey K, et al. Attention and memory dysfunction in posttraumatic stress disorder. Neuropsychology. 1998;12(1):125–33.
Vasterling JJ, Brewin CR. Neuropsychology of PTSD. New York: The Guilford Press; 2005.
Vasterling JJ, Duke LM, et al. Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. Neuropsychology. 2002;16(1):5–14.
Verfaellie M, Vasterling JJ. Memory in PTSD: a neurocognitive approach. In: Shiromani P, Keane TM, LeDoux J, editors. Neurobiology of PTSD. Totowa, NJ: Humana Press; 2009. p. 105–32.
Veterans Health Administration Office of Rural Health. Fact sheet: Information about the Office of Rural Health and Rural Veterans. 2015. Retrieved from http://www.ruralhealth.va.gov/docs/factsheets/ORH_General_FactSheet_2014.pdf.
Vogel EK, McCollough AW, et al. Neural measures reveal individual differences in controlling access to working memory. Nature. 2005;438(7067):500–3.
Volkow ND, Wang GJ, et al. Sleep deprivation decreases binding of [11C]raclopride to dopamine D2/D3 receptors in the human brain. J Neurosci. 2008;28(34):8454–61.

VonCramon D, Matthes-Von Cramon G, et al. Problem-solving deficits in brain-injured patients: a therapeutic approach. Neuropsychol Rehabil. 1991;1:45–64.
Walker, M. P., & van der Helm, E. (2009). Overnight therapy? The role of sleep in emotional brain processing. Psychol Bull, 135(19702380), 731-748.
Walker, M. P., Brakefield, T., Morgan, A., Hobson, J. A., & Stickgold, R. (2002). Practice with sleep makes perfect: sleep-dependent motor skill learning. Neuron, 35(12123620), 205-211.
Warden DL, Gordon B, et al. Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. J Neurotrauma. 2006;23(10):1468–501.
Watson NF, Dikmen S, et al. Hypersomnia following traumatic brain injury. J Clin Sleep Med. 2007;3(4):363–8.
Watson, N. F., Dikmen, S., Machamer, J., Doherty, M., & Temkin, N. (2007). Hypersomnia following traumatic brain injury. Journal of Clinical Sleep Medicine, 3(4), 363-368.
Weber, M., Webb, C. A., & Killgore, W. D. S. (2013). A Brief and Selective Review of Treatment Approaches for Sleep Disturbance following Traumatic Brain Injury. Journal of Sleep Disorders and Therapy, 2(2).
Westerberg H, Jacobaeus H, et al. Computerized working memory training after stroke – a pilot study. Brain Inj. 2007;21(1):21–9.
Whelan-Goodinson, R., Ponsford, J., Johnston, L., & Grant, F. Psychiatric disorders following traumatic brain injury: their nature and frequency. J Head Trauma Rehabil. 2009; 24(5): 324-332
Whyte J, Hart T, et al. Effects of methylphenidate on attention deficits after traumatic brain injury: a multidimensional, randomized, controlled trial. Am J Phys Med Rehabil. 2004;83(6):401–20.
Whyte J, Hart T, et al. Effects of methylphenidate on attentional function after traumatic brain injury. A randomized, placebo-controlled trial. Am J Phys Med Rehabil. 1997;76(6):440–50.
Whyte J, Polansky M, et al. Sustained arousal and attention after traumatic brain injury. Neuropsychologia. 1995;33(7):797–813.
Whyte, E. M., Lenze, E. J., Butters, M., Skidmore, E., Koenig, K., Dew, M. A., Munin, M. C. (2008). An open-label pilot study of acetylcholinesterase inhibitors to promote functional recovery in elderly cognitively impaired stroke patients. Cerebrovascular Diseases, 26(3), 317-321. doi:000149580 [pii] 10.1159/000149580
Whyte, J., Hart, T., Vaccaro, M., Grieb-Neff, P., Risser, A., Polansky, M., & Coslett, H. B. (2004). Effects of methylphenidate on attention deficits after traumatic brain injury: a multidimensional, randomized, controlled trial. American Journal of Physical Medicine and Rehabilitation, 83(6), 401-420.
Wilson MS, Gibson CJ, et al. Haloperidol, but not olanzapine, impairs cognitive performance after traumatic brain injury in rats. Am J Phys Med Rehabil. 2003;82(11):871–9.
Worthington, A. D., Matthews, S., Melia, Y., & Oddy, M. (2006). Cost-benefits associated with social outcome from neurobehavioural rehabilitation. Brain Inj, 20(17062426), 947-957.
Yaffe K, Laffan AM, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA. 2011;306(6):613–9.
Yaffe, K., Laffan, A. M., Harrison, S. L., Redline, S., Spira, A. P., Ensrud, K. E., Stone, K. L. (2011). Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA, 306(6), 613-619. doi:306/6/613 [pii] 10.1001/jama.2011.1115
Yochim B, Baldo J, et al. D-KEFS Trail Making Test performance in patients with lateral prefrontal cortex lesions. J Int Neuropsychol Soc. 2007;13(4):704–9.
Yochim BP, Baldo JV, et al. D-KEFS Tower Test performance in patients with lateral prefrontal cortex lesions: the importance of error monitoring. J Clin Exp Neuropsychol. 2009;31(6):658–63.
Yoo SS, Hu PT, et al. A deficit in the ability to form new human memories without sleep. Nat Neurosci. 2007;10(3):385–92.
Yoo, S. S., Hu, P. T., Gujar, N., Jolesz, F. A., & Walker, M. P. (2007). A deficit in the ability to form new human memories without sleep. Nature Neuroscience, 10(3), 385-392. doi:nn1851 [pii] 10.1038/nn1851
Yu W, Ravelo A, et al. Prevalence and costs of chronic conditions in the VA health care system. Med Care Res Rev. 2003;60(3 Suppl):146S–67.
Yurgil, K. A., Barkauskas, D. A., Vasterling, J. J., Nievergelt, C. M., Larson, G. E., Schork, N. J., Marine Resiliency Study, T. Association between traumatic brain injury and risk of posttraumatic stress disorder in active-duty Marines. JAMA Psych. 2014; 71(2): 149-157.
Zafonte R, Lombard L, et al. Antispasticity medications: uses and limitations of enteral therapy. Am J Phys Med Rehabil. 2004;83(10 Suppl):S50–8.
Zeitzer JM, Friedman L, et al. Insomnia in the context of traumatic brain injury. J Rehabil Res Dev. 2009;46(6):827–36.
Zeitzer, J. M., Friedman, L., & O'Hara, R. (2009). Insomnia in the context of traumatic brain injury. Journal of Rehabilitation Research and Development, 46(6), 827-836.

Zelano C, Bensafi M, et al. Attentional modulation in human primary olfactory cortex. Nat Neurosci. 2005;8(1):114–20.
Zhang L, Plotkin RC, et al. Cholinergic augmentation with donepezil enhances recovery in short-term memory and sustained attention after traumatic brain injury. Arch Phys Med Rehabil. 2004;85(7):1050–5.
Zhang ZG, Chopp M. Neurorestorative therapies for stroke: underlying mechanisms and translation to the clinic. Lancet Neurol. 2009;8(5):491–500.
Zumstein, M. A., Moser, M., Mottini, M., Ott, S. R., Sadowski-Cron, C., Radanov, B. P., & Exadaktylos, A. Long-term outcome in patients with mild traumatic brain injury: a prospective observational study. J Trauma Acute Care Surg. 2011; 71(1): 120-127