Interventions to Improve Cognitive Functioning After Traumatic Brain Injury (TBI)

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Introduction and Overview

Case

A service member returning from active duty deployment to the Middle East states that he was exposed to multiple blasts in combat. In one incident, while he was riding in a convoy, his truck was struck by a blast from a roadside improvised explosive device. A wheel was caught in the crater and the vehicle dove into a ditch. "I think my head struck the side of the truck, and I may have blacked out—I'm not sure how long." He admits to feeling dazed and somewhat confused. This seemed to resolve within a day, and the soldier returned to full duty. However, he was exposed to several more blasts during his deployment. While he cannot recall the details of each incident clearly, he endorses feeling dazed with each episode. He complains that he has had many difficulties since returning home. He has had trouble getting organized for job applications and other tasks—"I would get started, but then I always ended up doing something else." He complains of feeling highly distractible and easily overwhelmed and states that his memory is like "swiss cheese." Others describe him as irritable and easily angered. He has difficulty in sleeping, feels depressed, and avoids leaving his home.

Cognitive Dysfunction from Traumatic Brain Injury

This individual's experience is quite common among veterans who have served on active duty. Recent combat-related activities in the Middle East have resulted in an increased incidence of TBI among military personnel. The rate of TBI-related military hospitalizations increased by 105% between 2000 and 2006 [1], and over 350,000 servicemen and women have been diagnosed with a TBI since 2000 [2]. Moreover, it is estimated that one in five service members of the conflicts in Iraq and Afghanistan sustained a TBI during combat operations [3] and that nearly 60% of those exposed to blasts incurred some form of closed head injury [4]. Although the majority of these military-related injuries can be classified as "mild," their long-term consequences are often far-reaching and multiple. One study of medical records at a United States Department of Veterans Affairs (VA) Medical

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Center Polytrauma clinic found that nearly 70% of veterans reported persistent post-concussive symptoms [5], defined as symptoms lasting 3 months or longer, following their initial injury. Of note, this symptom profile differs considerably from the typical recovery trajectory [6]. For these reasons, TBI is considered the "signature injury" of the conflicts in Iraq and Afghanistan [7].

From Acute to Chronic Cognitive Dysfunction

In an instant, an injury to the brain can cause changes that affect a person for a lifetime. Although the injuries are acute, functional deficits that result from TBI may produce tremendous *chronic* burden on individuals, families, and health-care systems. This discussion will focus on problems that persist to become debilitating on a chronic basis. This is an important area to address for several reasons. The intrinsic importance of problems that are persistent (not resolving spontaneously or not responsive to therapies) is obvious. Acquired brain injuries have been a leading cause of long-term disability in the USA even before the current conflicts [8] and a leading contributor to increasing health-care costs in the VA health-care system [9]. Individuals with TBI are at risk for being unable to live independently. Surveillance for TBI across 14 states showed that approximately one-third of patients continue to require assistance with daily activities 1 year after injury [10]. For patients hospitalized for TBI, cognitive status is a major factor in determining whether individuals are to be discharged from institutions [11]. 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 [12–14]. A more dire but difficult to quantify consequence is the cascade that may lead to poor community outcomes, including joblessness, homelessness, additional poor health outcomes, and even suicide [15–17].

For less severe dysfunction, patients may have symptoms that are not readily recognized by health-care providers but which are significant and need to be addressed [18]. One specific challenge for combat-related injury is that some of the "milder" effects of brain injury may not be immediately detected. Detection may be particularly complicated as some individuals experience problems that only become apparent with a change in setting, new cognitive demands, loss of supportive social structure, and demands to learn new skills or knowledge. For example, cognitive dysfunction may become particularly debilitating during transitions from the familiar structure of military life to civilian life, including adjustments to school or new occupations.

TBI, if recognized at all, is predominantly addressed during acute stages. Ironically, *chronic* cognitive problems tend to receive relatively little medical attention. The issue of insurance coverage in the private sector has been raised as one barrier to care that has even been recognized by the public press [19]. However, another fundamental factor is the need for improved guidance for treating chronic cognitive dysfunction. Treatment needs tend to be complex and individualized, and few general guidelines have been available to guide treatment. However, an evidence base for cognitive rehabilitation interventions is being progressively strengthened. For military veterans, access to care has improved significantly in the past decade.

A long-term view is needed and major long-term issues need to be taken into account in clinical programs [20]. The far-reaching impact of these seemingly "invisible" deficits is often not recognized. For example, individuals who cannot pay attention, hold information in mind, and actively participate in learning activities will have reduced benefit from other rehabilitation efforts, such as those directed toward motor or speech functions [21]. Individuals who have suffered a TBI may also be at increased risk for developing cognitive changes later in life [22–26].

Injuries and Cognitive Symptoms

Although it is commonly understood that TBI can result in almost any neurologic deficit, the most

common and persistent deficits tend to be in cognitive functions. Among cortical regions, prefrontal and mesial temporal structures are vulnerable to contusions and hemorrhages. These correspond to deficits in frontal executive functions and declarative memory, as well as other aspects of behavioral and emotional self-regulation. Diffuse or multifocal axonal injury may affect commissural, callosal, and 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 [27]. The nature of cognitive dysfunction with TBI and intervention approaches for these symptoms are discussed in greater detail in this chapter.

Are cognitive deficits important in mild TBI (mTBI)? The occurrence of cognitive deficits in moderate and severe TBI is well-recognized, but cognitive deficits may also be a significant problem after so-called "mild" TBI [6, 13, 28–32]. Delineation of cognitive dysfunction has been more problematic, however. The controversies and debates have been extensive. Recent data from systematic tracking of individuals with mild TBI in both civilian and military settings are consistent with clinical observations that a significant number of individuals continue to have symptoms months to years after injury [33, 34]. We argue that it is particularly important to define the severity of dysfunction, rather than relying on a gross grading of initial injury severity. It is clear that traditional labels of "mild, moderate, or severe" are poor characterizations of individuals with TBI [35]. Furthermore, injury history is often not clear for many veterans who suffered injury(ies) in the field, making these labels even more imprecise. Current functional status is measurable. For the current discussion, an emphasis is placed on considering persistent "mild" cognitive dysfunction. Although self-reported symptoms and outcomes from cognitive testing vary greatly, deficits in control processes, including attention and working memory, and speed of information processing are commonly reported and may be the most affected domains in mTBI [6, 13, 28–32]. Aspects of executive control may be important factors in determining successful return to work after mTBI [36].

Spontaneous recovery? Despite their importance, chronic deficits in cognitive functions are often poorly addressed. Advice that recovery will occur with time can be reassuring, and, fortunately, the recovery trajectory for most patients who survive TBI is positive over time. However, there is significant variability in the rate and end point of recovery. A significant minority (10–20% of those with "mild" TBI, in nonmilitary settings) report persistent deficits that can last months and years post-injury, leaving chronic, residual disabilities that have a wide-ranging impact on an individual's life [28, 37]. Persistence of symptoms after combat neurotrauma is worth special consideration. As will be discussed in this chapter, there may be a number of contributors to poor cognitive functioning, aside from the physical brain injury per se.

Approaching treatment of post-TBI cognitive dysfunction is complicated by the frequent occurrence of multiple and varied symptoms. For example, the existence of a "post-concussive syndrome" (PCS) is now widely accepted, though this remains a somewhat difficult to define entity or entities, with variable presentations, sources, and possible courses. The syndrome may be characterized by headaches, dizziness, general malaise, excessive fatigue, and/or noise intolerance; irritability, emotional lability, depression, and/or anxiety; subjective complaints of concentration and/or memory difficulties; insomnia; reduced tolerance to alcohol; preoccupation with these symptoms; and fear of permanent brain damage. Documentation of cognitive dysfunction on "objective" testing is not required for diagnosis even though cognitive symptoms are common.

Although these symptoms, by definition, occur after a concussion, this does not necessarily mean that brain injury directly causes these symptoms. Multiple factors may contribute to or "modulate" symptoms. This is a particularly important consideration given the contexts in which physical trauma and recovery periods

occur, including the associated traumatic experiences in combat or even in medical settings. These factors may be important in formulating interventions to improve functioning.

A Combined Combat Neurotrauma Syndrome

It is increasingly recognized that a large portion of individuals returning from combat activities suffer from both TBI and post-traumatic stress (PTS) symptoms or even the full disorder (PTSD). A 2005 survey of Iraq/Afghanistan veterans found that for the 12% of 2235 respondents with a history of mTBI, the strongest factor associated with persistent post-concussive symptoms was PTSD, even after removing overlapping symptoms from the PTSD score [38]. A cross-sectional survey of Army veterans, 3–4 months after return from Iraq in 2006, revealed the highest prevalence of PTSD among those with a history of loss of consciousness (LOC) [7]. LOC was also associated with major depression. mTBI (defined by a history of traumatically induced disruption of brain function accompanied by LOC or alteration of mental status) was associated with post-concussive symptoms—but not after controlling for PTSD and depression. In examining the incidence of PTSD, rates increase in relationship to the occurrence of TBI, with increased incidence of PTSD along the gradient of no TBI to altered mental status to LOC [39]. Veterans with history of mTBI are two to three times more likely to demonstrate significant PTSD symptoms than those with no brain injury [38, 40]. A 1.5- to 2.7-fold magnitude increase in PTSD risk associated with history of mTBI has been observed in active duty service members [41–44]. PTSD diagnosis and symptoms and persistent post-concussive symptoms are more common among those reporting mTBI with LOC as compared to those with mTBI without LOC [7, 45, 46]. A study examining TBI and PTSD service utilization of OIF veterans found that 1-year post-deployment, 65% of those with mTBI–PTSD reported seeking treatment for concerns related to re-integration [47]. Observation suggests that the combination of TBI with PTSD may result in more prolonged or more complicated courses of recovery. All of these epidemiological findings raise questions about the interactions between TBI and PTSD.

The interactions between TBI and PTSD are undoubtedly complex and multilayered. Trauma may alter an individual's brain functioning via many routes. Direct physical injury may certainly be caused by traumatic forces, leading not only to contusions, hemorrhages, and even strokes but also injuries to the white matter fibers that connect brain regions. However, severe distress from the traumatic experience may also have immediate as well as long-term effects on brain functioning. Post-traumatic stress effects are increasingly recognized as being mediated by altered brain functions and possibly structure. Both physical and experiential trauma may contribute to acute disruption of function as well as ongoing cascades of sequelae that layer upon the initial injury. Understanding that these mechanisms of injury interact at multiple levels is of great importance for understanding, diagnosing, and managing the effects of these injuries. This may have particularly important ramifications for the formulation of interventions, and this is discussed in detail in this chapter.

The story told by the veteran above is likely to raise a number of important questions in a clinician's mind, including questions of etiology, diagnosis, and diagnostics, but perhaps the most important question is this: What can be done to improve this person's functioning?

Approaches to Intervention

Synopsis of Intervening to Improve Cognitive Functioning

The following are key points to consider in determining interventions for improving cognitive functioning after brain injury:

- The most common difficulties after TBI involve complex attention, learning, memory, organization, and other processes important for goal-directed behavior.

- Sources of dysfunction may be multifactorial, and each factor or interaction of factors represents a potential target for intervention. Sources include not only deficits in specific neural processes but also functional difficulties in engaging cognitive processes for goal-relevant activities, factors that modulate physiologic brain states, emotional factors that interact with cognitive functioning, pharmacologic and other biological modifiers, and interactions of cognition with specific environments. The interactive nature of these factors is illustrated in the overlapping layers in Fig. 1. Any or all of the above may have to be taken into account for a therapeutic intervention to be effective. Each of these layers is discussed in this chapter.
- Interventions may be targeted to specific cognitive processes, specific sources of dysfunction, supportive processes, specific modulating or exacerbating factors, and/or an integrated approach that addresses multiple targets concurrently based on a particular therapeutic goal.
- Some processes may be worth targeting even if "deficits" are not detectable. This includes, especially, domain-general processes that are "gateways" to learning and change. A core set of cognitive processes may be considered central to enhancing the rehabilitation process itself. 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

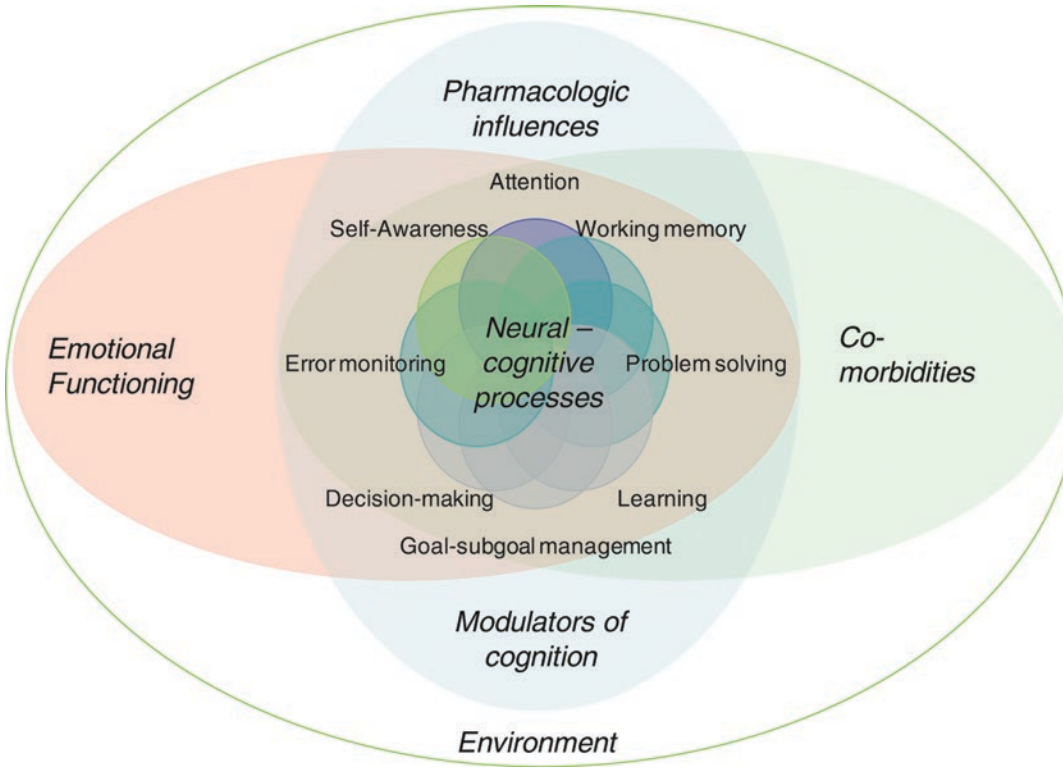

Fig. 1 Multiple sources of dysfunction lead to multiple tiers of intervention. Core targets of intervention include specific neural–cognitive processes important for healthy, goal-directed functioning after brain injuries. However, these processes may also be affected by modulators that alter cognitive state or 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). All of these are potential targets for interventions to improve cognitive functioning

for regulating attention, learning, and memory in an organized, goal-directed manner. These processes will also be crucial for continued learning and adaption outside of clinician-guided settings.

- Underlying cognitive and emotional functioning are aspects of brain state, so addressing the fundamental ability to regulate one's state may have a far-reaching impact.
- 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.
- A number of factors may need to be accounted for in synergizing therapies to optimize improvements in functioning. These include understanding not only the immediate effects of pharmacologic agents but also the potential influences on processes of learning and change and relationships between the underlying neural systems modified by these agents vs. training. Different drugs, as well as different doses of the same drug, may have differential effects for specific neural subsystems and the behaviors they subserve.
- 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.

Overarching Considerations in Intervening to Improve Cognitive Functioning After Brain Injury

Interventions may be considered along a number of major axes. Each of these axes briefly highlights particular considerations in determining optimal interventions, discussed briefly in this overview and in more detail in subsequent sections. Considering the spectrum along each axis may be helpful in determining the best approach for each patient.

Targeting the Environment vs. the Patient Managing an individual's environment (organization of the physical environment, work, time demands, etc.) is a common approach to post-injury care. This may be particularly valuable during acute phases of injury or with more severe deficits in self-management. This approach may sometimes be taken alone for at least two reasons. First, there may be an interest in maximizing function in a specific environment, given the least amount of time and effort. Second, there may be an assumption that the patient's functioning is "static." However, there may be significant functional plasticity over long periods of time, even if the time course is not always in line with standard practice parameters. This chapter focuses more on patient-targeted approaches, where one of the ultimate goals is to alter the abilities of an individual to adapt to or manage their own environment.

Targeting of Ancillary Health Factors vs. Directly Targeting Central Neural–Cognitive Processes A number of ancillary factors may be addressed that may have dramatic effects on cognitive functioning. Addressing these contributing factors may reveal a clearer picture of the underlying status of an individual's cognitive functioning and may complement approaches targeted at improving core functioning.

Application of External Tools vs. Internalized Skills and Strategies Within an individual's "personal environment," one may consider external tools vs. internal tools available for a patient's use. The use of external tools is clearly a valuable

aspect of human functioning and has an important role in improving functioning post-injury. Strong evidence supports the use of external tools for improving an individual's ability to accomplish intended actions. Tools may provide immediate benefits as external "signals" or orthotics (e.g., paging systems for alerts or reminders [48, 49]), but they may also include training to leverage external tools to compensate for one's deficits or augment one's abilities (e.g., using a planner to improve organizational skills). An important question for continued investigation is the extent to which any tools may improve an individual's intrinsic abilities. In this chapter, we focus on approaches that may alter an individual's functioning via internalized skills and strategies.

Behavioral Modification vs. Biological Modulation Methods for modifying biological underpinnings of behavior may be applied separately or in combination with behavioral modification. Biological modification approaches may include not only pharmacotherapy but also identification and targeting of factors that influence the neural systems that support cognition. These may include factors, such as sleep, pain, physical activity, circadian systems, nutrition, and more. It is valuable to keep in mind that biological approaches will more likely aid in accomplishing therapeutic goals when applied in the context of a behavioral modification plan (e.g., goal-driven rehabilitation training), rather than in isolation. Behavioral therapies may be more successful with strategic biological modulation—for example, learning capacity may improve with coordinated efforts to improve sleep, attention, and memory.

Factors That Modulate Cognitive Functioning and "Brain State" on a Dynamic Basis: Important Targets of Therapy

Medications

Integrating Pharmacotherapy with Rehabilitation Careful application of pharmacotherapy can play an important role in improving cognitive functioning after brain injury. Clinical evidence to support particular medications post-TBI is sparse but slowly accumulating (reviewed in [50]). 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. Systematic individual trials involving stepwise 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. Almost all of the major neuromodulators of the brain are produced in small nuclei at the base of the brain or in the brain stem and project to distributed cerebral structures. Acetylcholine from the basal forebrain is projected to cortex throughout the brain. Dopamine from the ventral tegmental area is projected primarily to PFC. Norepinephrine from the locus coeruleus is projected to cortex throughout the brain, as well as thalamus, cerebellum, and spinal cord. Serotonin (5-HT) is also predominantly produced in brainstem and rostral nuclei (in the pons and midbrain) projections throughout the brain, with prominent targets including frontal lobes and hippocampus. On the other hand, GABA neurons are distributed throughout the brain, in particular as inhibitory inter-neurons. Disruption in one or more of these systems presumably contributes to neurologic symptoms seen in TBI.

A number of drugs that affect neuromodulator systems have been used in clinical practice for years. Each pharmacotherapeutic agent is, in theory, targeted to particular neural systems, whether defined by particular receptor types, synthesis of or metabolism of particular neurotransmitters, or other drug-specific mechanisms. The delineation of the targets of a particular drug in relation to cognitive functioning is an area in need of further investigation.

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 and coauthors [51]) or simultaneous helpful vs. detrimental effects on separable brain systems (i.e., "double-edged sword" effects) [52]. An important frontier will be to determine the pharmacology of each patient, potentially providing guidance for therapy.

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.

Patients may have prescriptions for issues that arise during the many phases from acute injury to chronic recovery. 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 [53, 54]. Carbamazepine may also have cognitive side effects [55]. 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 it may contribute to mood/thought disturbances.

Benzodiazepines and baclofen are GABA agonists, and these may reduce the rate of recovery from TBI [56]. 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 anxiety.

Dopamine antagonists, such as haloperidol, have been shown to impede learning and recovery [57–61]. 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 (SNRIs) 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.

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. In general, when medications are deemed necessary, cognitive functioning should be monitored while dosing is adjusted. 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.

Alertness and Arousal State

Optimal arousal state may be considered a prerequisite for effectively activating and engaging

other cognitive functions. The concept of alertness is integrally tied to the sustainment of attention. The translation of alertness or arousal to task-related attention may lead to greater neural–cognitive processing [62]. Tonic alertness refers to the ongoing state of intrinsic arousal that is intimately involved in sustaining engagement during higher-order functions, such as selective attention, working memory, and executive control [63, 64]. Although the term "attention" is commonly used in this context, it should be distinguished from the many other meanings of attention, as separable neural systems appear to subserve alertness vs. other "attention" functions [63, 64]. Alertness may influence performance in almost all cognitive domains, including during rehabilitation [62–64]. Improving regulation of this "gateway" function may improve an individual's "readiness" to participate in rehabilitation.

Regulation of arousal state needs to be considered in terms of optimizing balance for any given goal or context. Patients with more severe TBI may exhibit marked deficits in alertness [65, 66]. Noradrenergic systems involving inter-connected regions of brainstem and frontal cortex, in particular, have been proposed to be particularly important mediators of alertness state [67]. The importance of long distance connections, both for delivering noradrenergic signals from brainstem to cortex as well as regulation of brainstem nuclei, may help to explain why alertness is so often dysregulated after TBI. High levels of arousal may also be maladaptive. This is a significant problem with TBI–PTSD, for example. Thus, therapies may need to focus on the concept of optimizing the *regulation* of alertness, rather than simply increasing or decreasing arousal per se.

Approaches to regulating arousal state may involve behavioral regulation, training, and pharmacologic treatments. Recent training approaches may provide methods for improving regulation of arousal and are discussed in more detail with other training approaches. A number of pharmacologic agents that affect alertness and arousal are already in common use. However, the effects of each agent can be quite individual, especially given underlying issues with variability in alertness state, i.e., lability, rather than a simple unidirectional deficit. Thus, each agent needs to be considered carefully based on patient goals and treatment contexts. Multifactorial considerations become particularly challenging when TBI is combined with post-traumatic stress symptoms, behavioral lability, anxiety, or depression.

Commonly used pharmacologic agents that affect neuromodulator function include methylphenidate and amphetamines as well as newer stimulants. For example, methylphenidate has been shown to alter sustained attention in patients with TBI [68]. Modafinil is a newer agent that promotes alertness. Atomoxetine works selectively on noradrenergic systems. "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, minimizing the total number of different medications. Reuptake inhibitors for serotonin as well as norepinephrine are perhaps among the few agents that may improve stability of arousal state.

As always, the effects of medications prescribed for other reasons must be evaluated. Other factors that modulate cognitive state that are related to alertness are fatigue and sleep. These are discussed separately, given some distinct considerations.

Energy and Post-Injury 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 [69, 70]. 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 [71]. Central fatigue, related to disturbance in the CNS, is itself a major cause of poor functioning and can adversely impact recovery efforts, emotional well-being,

cognitive functioning, quality of life, and one's ability to perform daily activities [72, 73]. Fatigue can manifest as difficulties with concentration, feelings of being overwhelmed, and/or lack of perseverance with tasks that feel too effortful. 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, it is critical to take into account its dynamic nature, noting how it fluctuates over time and in the various contexts in which an individual functions. 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 [74, 75]. From a clinical best practice perspective, regular physical exercise, which has shown to reduce fatigue in other clinical populations [71, 76], is a front-line treatment option. Factors such as poor motivation, chronic pain, and other physical limitations may need to be addressed to help patients fully engage in this form of treatment. Overcoming these problems may require creative problem-solving, with guidance in individualizing exercise activities.

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. One potential complication of this approach may stem from the decreased awareness of persons with brain injury to accurately identify and observe these factors. Patients may require repeated assistance and scaffolding to identify potentially modifiable situations or behaviors that contribute to fatigue, as well as support in implementing strategies in personal life.

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 required. There is some preliminary support for the use of mindfulness-based stress reduction (MBSR) to reduce fatigue. Studies incorporating MBSR principles have found reductions in mental fatigue for persons with TBI or stroke [77] and increased self-reported energy at 1-year follow-up [78]. Such findings are cause for optimism, as they suggest that non-pharmacological, state-based approaches have great clinical potential. A review of medications is important, as beta blockers, anti-dopaminergic agents, and anti-epileptic drugs 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. Research has shown that these agents confer benefit for persons experiencing illnesses where fatigue is a common feature [79–82]. Preliminary findings of medication trials to treat fatigue within the context of TBI have been mixed [83], and more research is clearly needed to ascertain specific medication effects. The use of pharmacotherapy timed to augment participation in other therapies remains a major frontier for development with potentially wide-reaching benefits for individuals with brain injury. The development of objective measures of fatigue may be particularly helpful for identifying underlying causes of fatigue. Potential neural correlates of fatigue in persons with TBI and other forms of brain injury have been explored using functional MRI (fMRI) [84, 85], with findings of increased activity in multiple brain areas suggesting compensatory recruitment of neural resources not required of uninjured persons [86]. Elucidating the underlying biology of fatigue may have important implications for further management approaches.

Sleep

Sleep disturbance is one of the most common, yet least studied, sequela of TBI [87–90]. Recent research estimates that up to 84% of persons with a TBI experience some form of sleep disturbance

[5], with symptoms of insomnia being the most frequent complaint [91]. Sleep difficulties may arise from multiple sources, including the direct effects of alterations to brain chemistry [92, 93] or secondarily to comorbidities, such as anxiety and depression or chronic pain [94, 95] that frequently occur within the context of mild to moderate TBI. Consequently, clarifying the complex web of potential factors contributing to sleep disturbance represents an important clinical goal, with direct implications for the development of therapeutic interventions targeting multiple potential levels. The neurocognitive, behavioral, and physiological effects of poor sleep within the general population have been well documented [96, 97]. Within TBI populations, specifically, sleep disturbance has been shown to exacerbate deficits in sustained attention [98] and may also contribute to worse rehabilitative outcomes [99] and quality of life [100]. Importantly, several studies [95, 101–103] have documented that sleep disturbance persists in many persons with mild to moderate TBI for several years post-injury, underscoring the importance of addressing this potential chronic sequela 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 [98], and other forms of attention and memory, with particular adverse effects on frontal system functions [88, 104, 105]. Chronic lack of sleep may also be associated with anxiety and depression [106].

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 [107, 108], even in the absence of REM sleep [109]. 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 [103, 110]. However, there are a number of clinically useful options available. The most basic considerations include recommendations for sleep hygiene, including limiting the use of substances (e.g., caffeine, alcohol, or other drugs) known to adversely affect sleep, stimulus control, sleep restriction, and relaxation techniques. One recent study found that educating nursing staff was critical in helping to change behaviors supportive of proper sleep in a hospital setting [111]. For many individuals, there may be opportunities for improving functioning in just addressing basic aspects of sleep hygiene.

Pharmacologic agents for inducing or prolonging sleep all have potential side effects, and balancing effects become more complex when cognitive dysfunction and other medications, among other factors, inter-mix. Furthermore, medication-induced sleep does not replace normal physiologic sleep. Benzodiazepines and atypical GABA agonists, some of the most commonly used sleep agents, may have adverse effects on cognition and neuroplasticity following injury as well as rebound effects [112]. 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 antidepressants, such as mirtazapine, may have clinical utility, although there are few data to guide their use after TBI. 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. For example, such drugs may be used during initial phases of therapy, to temporarily address extreme sleep deprivation and associated complications of cognitive and emotional dysfunction that may impede initiation of other therapies with longer-term benefits. 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 is Cognitive Behavioral Therapy for Insomnia (CBT-I). In general, cognitive–behavioral therapy is based upon the premise that feelings and behaviors are driven by underlying thoughts. Thus, in therapy, a primary task is changing unhelpful patterns of thinking as a means of bringing about behavioral change and improving one's overall well-being. CBT-I both addresses unhelpful cognitions associated with insomnia (e.g., addressing maladaptive sleep-related beliefs) and utilizes behavioral techniques (e.g., stimulus control). Meta-analytic findings [113, 114] indicate this approach is as efficacious as pharmacotherapy in the short term and potentially more effective in the long run. There is some suggestive evidence that this treatment approach may be beneficial for persons with TBI. Ouellet and Morin [115, 116] reported positive results, including polysomnographic changes, following CBT-I in persons with TBI of varying severity, providing some preliminary indication that this may be a helpful treatment.

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. Disruption to the production or synthesis of melatonin, a hormone involved in the regulation of the sleep-wake cycle, following brain injury has been posited to be one mechanism through which sleep disturbance occurs following TBI [117]. Exogenous melatonin therapies have been shown to result in modest benefits in sleep-related outcomes in non-TBI populations [118, 119], and preliminary findings suggest it may be helpful in the context of TBI [120]. Others [75] have also suggested that light therapy may be a beneficial treatment approach given its effectiveness in treating a broad range of sleep pathologies [121]. Intensive schedule regularization in combination with efforts to augment sleep or wake signaling (e.g., melatonin supplementation at night, sunlight, exercise, and possibly stimulants in the morning) may also be valuable.

Identifying and treating sleep apnea is another major priority for persons with TBI. Sleep apnea has been shown to contribute to cognitive dysfunction via both disruptions of the regular sleep cycle and potentially from hypoxia itself [122, 123]. Caution should be exercised regarding prescription of sleep-inducing medications, such as benzodiazepines, within this context as they may actually exacerbate apnea. Traditional treatment via a CPAP machine has been shown to be helpful for obstructive sleep apnea following TBI [124].

Management of sleep as a direct, explicit target of therapy is an important frontier for further development. There remains a major need for defining optimal approaches for improving sleep duration and quality after TBI, as well as determining how best to integrate sleep into rehabilitation treatment regimens. Successful improvement of sleep will have far-reaching benefits for individuals with TBI and neuro-behavioral dysfunction, especially as they work through other modalities to improve functioning.

Pain

Pain is a common accompaniment of TBI. Chronic pain, in particular, may have wide-ranging effects on well-being, emotional and social functioning as well as cognitive functioning. Although detailed consideration is beyond the scope of this chapter, there are some general principles worth considering in the context of optimizing functioning. Some of the effects of pain on cognition may be mediated by influences on sleep, mood, and energy levels. For example, chronic pain may lead to irritability and poor frustration tolerance, reducing cognitive effort for cognitive tasks that are challenging. Pain may also modulate cognitive functioning via increased fatigue or poor sleep. On the other hand, treatments for chronic pain, such as with opioid analgesics, may contribute to poor cognitive functioning. Although opioid medications may play an important role in pain management, especially in settings of acute injury, other approaches may be particularly valuable in the long term.

Multidisciplinary collaboration in an intensive program may be necessary, especially given the multifactorial nature of chronic pain. Approaches to pain management that include strengthening of self-regulation and coping

(e.g., with mindfulness-based training or biofeedback), as well as localized interventions (e.g., transcutaneous electrical stimulation, injections), with a goal of minimizing systemic opiates, may be particularly valuable.

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 that help to organize behavior 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. Effective application of a strategy typically results in an immediate beneficial effect; however, the long-term benefits depend on a number of factors. 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.

Available literature on treatment of combat-related "mTBI" is sparse. A recent pilot study examined strategy training in combat veterans with mild cognitive dysfunction and a history of TBI [125]. Training involved a variety of compensatory internal and external cognitive strategies, including day planner usage in a structured group-based format. Following training, participants reported increased use of compensatory cognitive strategies and day planners, increased perception that these strategies were useful to them, increased life satisfaction, and decreased depressive, memory, and cognitive symptom severity. Storzbach and colleagues [126] also recently reported success with training veterans with mTBI compensatory cognitive strategies, which included a range of targets such as time management, goal setting, organization, self-monitoring, sleep hygiene, and internal and external memory strategies. Relative to veterans undergoing usual care, veterans receiving compensatory cognitive training reported fewer cognitive and memory issues and greater strategy use at 5-week follow-up. They also evidenced greater improvements on neurocognitive tests of attention, learning, and executive functions. Cooper and colleagues [127] found that therapist-directed cognitive rehabilitation either alone or combined with cognitive–behavioral psychotherapy reduced functional cognitive symptoms in military service members with mTBI compared with psychoeducation or medication management. These preliminary investigations are encouraging and suggest that cognitive training that includes compensatory strategies may confer functional and/or neurocognitive benefits to post-acute TBI patients [128].

A skills-based approach may also be taken. Though the distinctions between strategies and skills may blur, skills may generally be considered as the integrated use of particular neurologic functions or processes for the accomplishment of functional tasks. Skill training is generally considered a more gradual process, with improvements accumulating over repetitive practice. Skills may be further divided into the concepts of "neurologic skills" (based on definable neurocognitive processes which are applicable to multiple tasks or situations) or "functional skills" (procedures for accomplishing a task, such as making a sandwich). The latter may blur the borders between potentially separable cognitive processes, but this is ecologically relevant as real-life tasks typically require the integration of multiple neurologic processes.

These differing approaches may help to achieve different goals in rehabilitation. For example, it is theorized that if fundamental neural–cognitive processes are improved, then the benefits will more likely carry over to tasks and contexts outside the training. On the other hand, training on specific actions (functional tasks) may be thought of as consolidating a particular task-specific skill or procedure. As such, the behavioral improvements may be more immediately apparent as patients improve in task performance, but the improvements may be task- or context-specific. The choice of approach may depend on the nature and severity of cognitive deficits. It has been argued that functional approaches may be more effective for patients with severe deficits [129].

The utility of training that targets specific neurologic processes remains controversial, and this is an active area of research and development. Process-targeted methods have typically involved practice on tasks "isolated" from complex real-world situations. The development of training programs that target neurologic processes and result in effective and ecologically relevant gains remains an important frontier for further advancement in intervention development. Optimization of methods for higher level cognitive functions continues to be a challenge. Advances in neuroscience, informed by clinical concerns, provide a foundation for defining, targeting, and training cognitive functions. In the next section, we outline the foundations for process-targeted, neuroscience-driven interventions that address important functional goals.

Cognitive Neuroscience Foundations for Rehabilitation Training

Although a wide range and variety of deficits can result from TBI, symptoms in two general areas stand out as some of the most common and disruptive to patients—"executive control" and memory. The abilities of paying attention, holding information in mind, organizing, and developing efficient strategies for completing activities seem to be particularly vulnerable to TBI. These processes come together in the regulation and control of other, more basic neurologic processes based on goals and are often referred to as "executive control" functions [130, 131]. Although problems with memory are some of the most commonly reported complaints after TBI, the actual deficits may be quite varied. Processes important for goal-directed behavior, learning, and memory will receive special focus in this section.

Functional Impacts of Cognitive Dysfunction and the Impetus to Address Them

Processes important for goal-directed behavior, learning, and memory are fundamental for successful independent living, and deficits may directly contribute to poor outcomes. At the broadest level, poor executive control leads to disorganized behavior that affects numerous aspects of personal functioning. Executive control functions are crucial for the pursuit of educational and occupational goals [36, 132–134], with TBI resulting in an increased rate of job turnover and reduced job status [134]. However, the effects may be even more fundamental in the process of recovery from brain injury.

As empirically observed by rehabilitation clinicians, if certain cognitive functions are not intact, other attempts at rehabilitation are made much more difficult. Who, after all, are the most difficult individuals to teach? Which patients are most likely to be labeled as "not ready" for intensive rehabilitation efforts? Individuals who cannot pay attention, hold information in mind, and actively participate in learning activities may have reduced benefit from rehabilitation training efforts for other neurologic domains [21, 135–138]. As a frontier reaching beyond simply triaging patients, the remediation of these functions may be valuable for influencing learning and recovery in other neurologic domains. For example, improved goal-directed functioning may enhance an individual's ability to actively participate in attempts to rehabilitate motor functions, allowing an individual to hold learning goals in mind, selectively focus attention on learning activities, and solve problems in the numerous intervening steps between a current state and achieving a learning goal. Finally, individuals with brain injury spend a

much larger amount of time on their own than with a therapist; thus, the importance of executive control and memory functions translates to an individual's ability to self-teach skills, remember strategies, and self-adjust to residual deficits in any domain.

Foundations for Training: Neural Bases of Cognitive Functions Important After TBI

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? Reviews of interventions have noted a gap between theories about subsystems of executive functions and intervention design and practice [139–141]. A better understanding of the nature of the specific underlying neural processes as well as mechanisms of learning and recovery specific to these functions may help advance treatment development [142–144].

Neurologic deficits caused by TBI are not unique to trauma per se, but certain patterns of dysfunction are more common with TBI than other causes of injury. While these patterns are partially explained by traditional neurologic localization with focal cerebral lesions, the localization approach has left many TBI sequelae poorly explained. Basic abilities, such as ambulation and speech, may be spared, and the impact of deficits may only become clear when individuals are challenged by the complexities of real life. Deficits in 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 [143]. The importance of axonal injuries in TBI highlights the need to understand brain functioning in terms of distributed but coordinated network processes [142]. "Diffuse axonal injury" without focal cortical lesions has been shown to lead to changes in executive working memory processing activity [141].

PFC is involved in multiple major networks [145]. One major network involves connections with posterior parietal cortex as well as anterior and posterior cingulate and medial temporal lobe regions [146]. Another major network involves cortical–subcortical connections between the PFC and the striatum, globus pallidus, substantia nigra, and mediodorsal nucleus of the thalamus [147]. Additional interactions with other more posterior brain regions such as sensory or motor cortex are likely important for the domain specificity of control processes [148, 149]. Deficits may also be related to damage to neuromodulatory pathways from the base of the brain to the cortex. These interactions are crucial for the modulatory control of distributed neuronal activity in order to facilitate processes that are relevant to internal goals while suppressing non-relevant processes [150–152].

How is goal-directed control implemented in neural systems? 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. The modulation of neurologic processes from the "top-down" is accomplished by at least two important general mechanisms: *selection* (enhancement and suppression) of neural activity based on goal direction and active *maintenance* of goal-relevant neural activity for the accomplishment of tasks. The functional integration of neurons within local networks is also important. The neural representations of information appear to be coded not in single neurons, but rather in networks of neurons. For example, representations of the myriad possible visual objects, including household objects, faces, etc., have been shown to be encoded in a distributed architecture [153]. This organizational architecture allows for a much wider range of information to be encoded with a limited number of neurons. Otherwise, if a separate neuron were needed for every item or variation of information stored, the number of neurons needed would far exceed what exists in the human brain. Distributed injury, atrophy, or degeneration could disrupt neural processing even in the absence

of obvious cortical lesions. Examples of this may occur in age-related degeneration [154] and are likely to occur in TBI as well.

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." This also has implications for the measurement methodologies to be used to understand neural mechanisms of injury, learning, and recovery in rehabilitation studies. Examples of this frontier are discussed at the end of this chapter.

Cognitive Functions as Potential Targets of Therapy

Functions for Goal-Directed Control: Attention and Other Component Processes of "Executive Control"

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. One way to organize our conceptualization of control functions is to consider the components required for successful goal attainment. (For additional discussion, anatomically based schema for subdividing frontal functions [141, 155] and goal management steps have been reviewed by others [156, 157].) Deficits in any component may disrupt efficient and effective goal attainment:

- At the outset, a *goal* needs to be generated and/or selected. Whether the goal is simple or complex (e.g., make a cup of coffee vs. apply for college), inability to generate clear goals, or deficiencies in evaluating and selecting a manageable goal, will obviously result in poor goal attainment.
- This goal will then be important for guiding all subsequent processes. An *attentional set* based on the selected goal needs to be established, framing all upcoming information or actions [158–160]. Poor establishment of the appropriate set will make it more likely that the individual will be distracted or take the wrong path.
- Goal attainment activities need to be *initiated*, and this depends on motivation and an appropriate level of alertness or arousal. Apathy, depression, and low arousal (such as from fatigue) may lead to poor initiation.
- Goal attainment activities including determining the optimal *plans* to accomplish the main goal. Planning includes more in-depth analysis of the goal and breakdown of the goal into an appropriately sequenced series of subgoals (steps), including re-organization of potential actions in relation to the main goal. These processes may require interactions across a hierarchy of prefrontal networks [161].
- *Strategy* determination and related processes of planning are crucial for efficient goal attainment, especially with more complex tasks. This higher level function is relevant for learning, memory, and problem-solving. Patients with frontal injuries show impairments in strategic planning and organization of information [162, 163].
- Some goals may require more complex levels of planning, and *maintenance of the goal* during this process can be important. The planning process can be thrown off track with forgetting of the main goal or disconnection of planning from the goal (one form of "goal neglect") [164].
- Translation of the imagined cognitive sequences (plans) into action requires a step of *initiation of action* that is separable from the initiation of planning and decision-making and is another point at which an individual may stall.
- Once actions are initiated, goals and plans need to be maintained to accomplish each subgoal and the sequence of subgoals that build toward the main goal. *Goal maintenance* becomes increasingly important with goals that require multiple steps over extended periods of time, as the risk of going "off track" increases [165, 166]. This may be another form of "goal neglect" [164].
- Throughout the goal attainment process, the individual will likely be exposed to vast amounts of information (from perception or memory)—some of this will be relevant and

some non-relevant to the goal. Positive selection of goal-relevant information for deeper processing (with the complementary negative selection of non-relevant information) at the outset and at every stage of the goal attainment process will be necessary to reach the goal, or else the individual may be distracted or even overwhelmed. Selected information needs to be maintained, at the exclusion of other competing information, to accomplish each step toward the goal. The *selection and maintenance of goal-relevant information* involves processes often referred to as selective attention and working memory, functions that are integrally related [167–174].

- Similarly, a plethora of actions is possible at any moment in time, but only a selected few will be goal-relevant. *Response selection and inhibition* refers to the ability to select between competing alternatives and to inhibit inappropriate response tendencies [175, 176].
- In determining appropriate actions, multiple considerations may need to be integrated. Relational integration requires the ability to integrate multiple relationships and is crucial in problem-solving and reasoning [177, 178].
- There may be a need to transition between tasks, such as to move to the next subgoal or to deal with an interruption and yet return back to the goal-relevant path. *Direction and redirection* of attention, information processing, and actions is necessary for successfully making these transitions. Patients with frontal lesions are relatively impaired on tests that require switching between tasks or attentional sets [179].
- Once actions are taken, the results that follow may or may not be relevant to goal attainment. Comparison of results with the original goals and detection of disparities or errors is necessary for correction of the above series of processes to ultimately achieve the goal. However, neglect of the goal, deficits in awareness of errors, as well as failure to take corrective actions are major impediments to successful goal attainment.
- Independence in the above processes, and cognitive functioning in general, requires some ability to *generate* ideas and information with minimal cuing, especially for processes that require creativity and/or problem-solving. Aspects of generative ability may be impaired with brain injuries [180–182]. Overall, frontal systems appear to be broadly important for core abilities that allow a person to flexibly and adaptively solve problems across multiple contexts [183, 184].

Functions of *learning and memory* are integrally intertwined with all of the above processes of goal direction. Thus, this discussion treats these processes as part of the ensemble of functions needed for goal attainment. For example, information, strategies, and skills need to be learned and remembered so that they may be applied to problem-solving and goal attainment. Conversely, learning and memory are also dependent on many of the control processes discussed. Indeed, one of the most common subjective complaints after TBI is problems with "memory."

The underlying sources of these complaints may vary. Deficits related to declarative or episodic memory may be related to damage to medial temporal structures. The basal forebrain and long tracts that connect the forebrain to other structures are also important for memory processing. The basal forebrain, a major source of cholinergic projections throughout the brain, is particularly vulnerable to injury, and, furthermore, long projections may be vulnerable to shearing injury [185]. However, complaints of problems with "memory" do not necessarily equate to problems with these structures.

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 [186]. Encoding and retrieval of information from memory may be impaired in individuals with frontal system dysfunction. Important aspects of encoding and retrieval of information from memory appear to be mediated

by the role of PFC in activating, maintaining, and organizing information in working memory, as well as in re-activating and retrieving stored information [187, 188]. A common deficit seen is that a patient has difficulty on free delayed recall, but when provided with a retrieval strategy (cue), his or her performance improves. An additional set of functions is important for the "prospective" memory of upcoming events or actions [189].

Behavioral approaches to compensating for or training memory have been reviewed elsewhere (e.g., [190]). For patients with severe deficits in declarative memory related to mesial temporal injury, external aids are particularly valuable. Evidence to date argues against significant potential for remediation of such memory deficits, though this has mainly been examined in the context of hypoxic injury. However, memory problems related to deficits in controlled aspects of encoding and retrieval (related to executive control functions) may respond well to training, such as with strategies for selecting or organizing information for memory. Thus, distinguishing the underlying etiologies of memory complaints may be highly valuable in therapeutic decision-making.

Pharmacotherapy

A number of options for pharmacotherapy currently exist; however, there are relatively few data to guide the optimal choice of agent for any given individual. Pharmacotherapy is primarily empiric, but 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 comorbidities (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.

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 [50, 191]. Trials have documented improvements in aspects of attention and speed of information processing following TBI [192]. 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 are few data fully testing its effects in chronic TBI [193]. Bromocriptine may enhance aspects of executive functioning in patients with severe TBI [51], but again data are mixed [194]. Amantadine may improve executive function, in addition to alertness [195]. 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 [196]. 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 [50, 197–199]. Some data support the use of rivastigmine for improving memory deficits as well in patients with moderate to severe memory impairment at baseline [200, 201]. 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 mTBI, 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, thus allowing pharmacotherapy to be reduced over time.

Targeting Cognitive Functions: Integration of Component Processes

In sum, each component process provides a potential target for intervention. This is summarized in a schematic (Fig. 2).

Discussed as separate processes, the above may seem like a confusing and complex array of functions that are difficult to understand or target. However, an important principle is that the component processes need to be *coordinated* or *functionally integrated* in the accomplishment of any particular goal. Goals may be conceptualized as serving 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. Thus, not only the components but also their functional coordination may be important targets for intervention. Process-based approaches may be analogous to isolating and working out the biceps muscle, while functional approaches may be analogous to training the coordination of multiple muscles to accomplish basketball 3-point shots. A more advanced question is whether training that involves functionally integrated approaches may actually serve as an effective, more motivating way to improve underlying component processes.

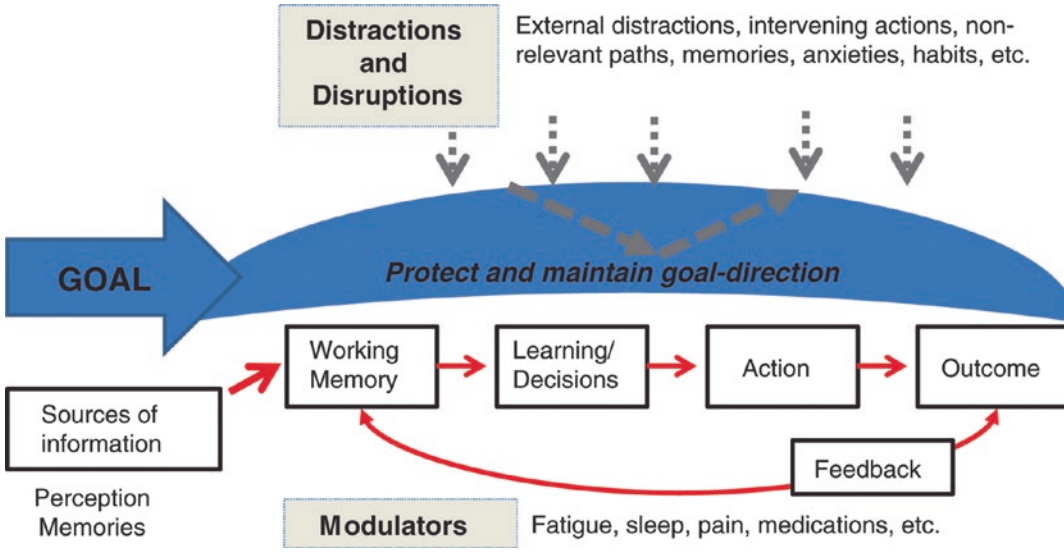

Fig. 2 Component processes in pathways to goal attainment: targets for intervention. All the main processes, *connected in red*, work together for goal attainment and are potential targets for interventions. An overarching target for strengthening involves abilities to protect and maintain goal-directed processes from distractions and disruptions, which may otherwise affect any component in the pathway. As discussed separately, other potential modulators may influence the central processes and are also potential targets for other forms of intervention

Principles for Training and Improving Functions of Goal-Directed Control

Functions that subserve goal-directed behavior are a particularly important training target for individuals with TBI. This encompasses functions that have far-reaching influence on neural processes in almost any neurologic domain, crucial to navigating the challenges of learning and adaptation after injury. Given the difficulty in understanding and designing interventions to improve goal-directed cognitive functioning, we have proposed some basic principles of training could be incorporated into interventions to target and maximize improvements in these functions [143].

Many of the methods applied in clinical rehabilitation are designed for the learning of strategies that compensate for deficits. We focus here on possible approaches for improving goal-directed control deficits, a challenging but worthwhile goal that remains at the frontiers of clinical rehabilitation. 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 system functions in any of these contexts. Furthermore, increasing the engagement of goal-directed control in these settings may maximize improvements across domains:

1. Training of process, not content: cognitive training tasks should challenge patients to engage "top-down" modulatory processes mediated by PFC networks.

   Tasks that require selective processing of competing information based on task relevance (selective attention), working memory (e.g., the maintenance of information over a short period of time and especially manipulation of that information), performance of dual tasks, as well as goal–subgoal management have all been shown to engage the PFC networks [143, 158, 159, 167, 202]. During the performance of these tasks, it is the processing demands, and not the specific contents of stimuli per se, that engage PFC networks. For example, PFC networks are engaged during working memory tasks regardless of the type of information (e.g., words or objects) that must be remembered [203, 204]. Thus, training needs to target specific top-down control *processes* and not *specific task content*. This contrasts with training that emphasizes repetition of task content, which promotes a shift toward automatic processing and disengagement of PFC-mediated control [205], as well as knowledge-based education approaches. Importantly, examination of the neural substrates of these functions emphasizes the engagement of *networks across multiple brain regions*, not just the PFC. This is particularly relevant to patients with "disconnection" injuries. Therapies that target control processes may be a way of promoting the "re-integration" of damaged brain into functional networks [142]. Targeting core PFC functions in process-oriented training should increase the likelihood of generalization of gains to new contexts, although this may not be sufficient without additional considerations.
2. 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 it. In the development of a training protocol, it is important to consider the processes required for accomplishment of any specific goals during training. These processes will differ depending on the nature of the goals. For example, if the goal is to make a quick decision regarding a left vs. right button press based on an image on a computer screen in an isolated setting, then the engaged processes and the level of integration necessary will be very different than what is engaged by a more complex task, such as paying attention to one's supervisor in a noisy office in order to

accomplish an extended project. Thus, the opportunity for the greatest engagement of goal-direction processes will be provided with complex goals.

A goal-based approach will allow training of multiple goal-direction processes. Who sets the goals? *Goal generation* involves the highest levels of goal-directed control, requiring generation de novo or retrieval and appraisal of potential goals that will guide behavior. Training that involves an active role for the trainee in defining the goals and subgoals of the tasks being learned may differ in effect from when goals are "assigned." Coordination of the many steps required for goal attainment may critically rely on the protection and maintenance of the goal. Thus, goals which require greater lengths of time and multiple tasks to accomplish will provide greater challenge to *maintenance* of goal information. What is the *personal relevance* of the goals to the individual? It is important for several reasons that the goals of training are of significance to the patient: this will increase motivation, encourage application of skills to ("real-life") goals that are often more complex than "artificial" goals, and allow for increased practice of goal processing in daily life. There is also the potential for increased positive feedback from accomplishment of goals that are important to the trainee. Incorporation of some or all of these features would significantly affect the nature of the intervention and likely benefits.

3. Cognitive training tasks should progressively challenge the patient.

The importance of progressive increases in challenge difficulty and complexity level is underscored by the ability of the brain to adapt to tasks. Even tasks that engage goal-directed control processes may become less challenging with practice and, thus, less effective at encouraging learning in the targeted domain. As a patient's level of function improves for a specific process, tasks may need to be adjusted such that demands for that process are increased. This is more specific than simply increasing the general "difficulty" of the task, as parameters that are adjusted should quantitatively vary the level of engagement of specific processes, such as working memory, multitasking [206], updating [207], or interference control [208]. Extensive studies on the effects of practice of well-known cognitive control tasks have documented context-specific improvements [209, 210]. Thus, simply practicing isolated, purportedly process-targeted tasks may not be sufficient to improve functioning in a significant way, even if the trainee is challenged progressively.

4. Training should explicitly address pathways for the transfer and generalization of training effects to new and real-world contexts.

A major gauge of the success of any training-based therapy is the extent to which benefits actually extend beyond the training tasks and context. As mentioned above, if functions of the core PFC networks for goal-directed control are effectively improved, then generalization of benefits should be more likely. How would this be accomplished? There are two complementary principles of use here: (1) strengthen the underlying ability and develop automaticity in the use of the ability and (2) maximize the likelihood of goal-relevant application of the skill when and where needed.

In order to effectively target and strengthen core PFC functions, and not simply context-specific abilities, it is arguably important to train the target processes in multiple modalities and multiple settings. PFC is multimodal association cortex, and PFC networks serve to integrate information from multiple modalities [148, 204, 211, 212]. Training across *multiple modalities* may maximize engagement of core PFC networks, leading to improved functioning across contexts.

Linking skill use to a goal-based framework can maximize the likelihood of beneficial skill use. The above simplified process-oriented view of PFC involvement in goal-directed control raises a question regarding the importance of the *context(s)* in which these functions are engaged. Any training context carries with it important cues and inherent structure, which may provide scaffolding for

an injured individual. Most deficits in goal-directed control are only apparent in contexts that lack strong external cues for action, requiring hierarchical organization that allows top-down goal-directed signals to out-compete bottom-up signals encouraging engagement with the environment [164, 183]. Thus, the opportunity for the greatest engagement of goal-direction processes will be provided in *unstructured* settings. Strengthening of an internal goal-based framework is vital to engaging goal-directed control abilities in these settings.

5. Meta-cognitive strategy training may provide a form of goal-directed control function remediation.

   Meta-cognitive strategies are proposed to play an important role in achieving generalizable improvements in goal-directed functioning. One hallmark of prefrontal network dysfunction is difficulty in structuring cognition and behavior by employing strategies to efficiently and effectively accomplish goals. Training to strengthen goal definition and goal awareness can help in activating goal-directed control when and where relevant to accomplishing a goal.

   Increasing clinical evidence supports the proposition that training-based therapies targeting problem-solving, involving the use of meta-cognitive strategies, may improve functioning in individuals with brain injury [139, 140, 213]. Several interventions have been developed and implemented with such an approach [157, 214–219]. For example, in goal management training [156], patients are trained to clearly define a goal, learn the steps required to achieve it, and then regularly check their progress. Engagement of PFC appears to play an important role in the successful application of strategies [220, 221]. Thus, meta-cognitive strategy training may enhance PFC-mediated control processes, rather than simply being compensatory. The neural mechanisms underlying successful improvement with meta-cognitive strategy training will be worth further investigation.

6. Training of goal-directed control of brain states.

   All cognition and behavior occur from the foundation of an underlying brain state. The effectiveness and efficiency of functioning depend on the regulation of these states as appropriate to a current goal. This leads to perhaps the most fundamental of all the training principles. Goal-directed control may be improved via improved regulation of brain states. 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 [222–224]. Thus, training that improves regulation of brain states may also improve cognitive function following brain injury. A full understanding of the regulation of brain states that is translatable to treatment considerations still needs to be developed; however, certain aspects of state regulation are understood to be important for cognitive functioning.

   It is clear that brain states established by alertness and arousal, attentional sets, emotional states, and motivation can affect cognitive functioning. For example, 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 [63, 64, 66]. Interventions that improve the regulation of arousal state may improve goal-directed functioning. External cues may help [48, 49, 225], but training to improve self-regulation, from mindfulness exercises to more recent developments with computer-assisted techniques, may also be helpful [226, 227]. Mindfulness-based training approaches may train regulation of arousal state, reduce the load of non-relevant cognitive or emotional processing on limited neuro-cognitive resources, and improve an individual's ability to redirect attention to goal-relevant processes [228–231]. A recent study illustrated that a modified

MBSR training program, Mindfulness-Based Mind Fitness Training, may help healthy military personnel preparing for deployment to regulate their emotions [232]. It is often presumed that individuals with goal-directed control function deficits due to brain injuries would not be good candidates for such training, given difficulty with attention regulation. We have found, however, that cognitive training that incorporates principles of mindfulness can improve attention, working memory, and goal-directed functioning for individuals with brain injury [231].

It is worth noting that improvements in state regulation may improve implicitly during any training intervention. For example, it is likely that trainees develop self-regulatory skills during intensive training when tasks are challenging (cognitively or physically), requiring the ability to regulate one's cognitive and emotional states [233]. Thus, even tasks that are described as task-based (e.g., computer games) may result in improvements in functioning that are due to improvements in state regulation and/or an enhanced capacity to learn. This has more recently been recognized in basic studies of the effects of video game training (e.g., [234])

7. Interactions of emotion and cognition.

Special consideration needs to be made for the importance of emotion regulation for optimal cognitive functioning. Poor emotional control can significantly affect cognition and goal attainment. 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.

Dysregulation of emotion can occur at multiple levels. An individual experiencing feelings of anxiety, irritability, and/or distress will be less able to effectively complete tasks that require overcoming challenges and solving problems, especially unexpected ones. Even further, he or she may negatively "overreact" to challenging situations, and the emotional reaction may impede the clear cognition needed for effective goal attainment. It is also likely that reduced cognitive control would contribute to poorer emotional control. Individuals with TBI, with reduced self-regulatory control, may have more difficulty in managing and altering negative and/or traumatic associations and the "triggered" emotions. For example, an inability to filter out information and demands that are not directly related to a current goal (additional "cognitive noise") may lead to increased feelings of being overwhelmed. Indeed, 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. 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. These issues are discussed in more detail in the next section, with a focus on the combination of TBI and PTSD, perhaps the "hallmark" syndrome of recent combat activities.

Cognition, Emotion, and Combined TBI–PTSD: Frontiers for Treatment

Interactions of TBI–PTSD

Either TBI or PTSD alone may alter cognitive, emotional, and behavioral functioning. The co-occurrence of TBI and PTSD raises the question of how the two entities interact, and whether the combination of physical and experiential trauma results in consequences not simply explained by additive effects of TBI or PTSD alone.

PTSD and mTBI may have independent and additive roles [235], but may also interact at multiple levels, including at the genesis of injury, the maintenance of symptoms, various aspects of cognitive–emotional functioning, and at the level of neural mechanisms. Features of each may interact to worsen functioning and/or

make treatment more difficult. Approaching TBI–PTSD will require a multifactorial approach that addresses multiple, interacting layers of functioning. Furthermore, potential special features of the combination may need to be addressed. Defining certain core targets of intervention, such as processes of self-regulatory control important for both TBI and PTSD, may provide a gateway to enhance the success of other aspects of therapy. Special considerations are discussed in more depth in each section below.

Interactions Between Cognitive and Emotional Functioning with TBI–PTSD

Although TBI can result in dysfunction in almost any neurologic domain, the most common and persistent deficits tend to be in the *control* of cognitive–emotional functions. Indeed, injured individuals may be able to engage basic functions, but the disrupted regulation of these functions leads to variability, lability, and inconsistency. As a classic example, some individuals with TBI display emotional lability, in one instant cooperative and friendly, in the next instant irritable and angry. This may be due to cognitive factors, such as misinterpreting or overreacting to environmental stimuli, as well as issues in the control of emotions or behavioral expression. This characterization overlaps greatly with PTSD. Effective regulation of emotion is crucial for optimal cognitive functioning. Dysfunction in emotional control, leading to frustration, irritability, anger, or even apathy, may significantly alter cognitive performance.

In another example, individuals may commonly complain of reduced ability to pay attention and hold information in mind, affecting many aspects of life functioning. However, attentional processes may be disrupted by "noise" from both "external" and "internal" sources. For example, it may be difficult to concentrate on a single conversation when other conversations are being heard in a crowded room, or it may be difficult to focus on a lecture during class when emotion-laden thoughts are also distracting from processing that goal-relevant stream of information. Should these symptoms be attributed to TBI or PTSD? Or is that the wrong question?

The Occurrence of PTSD May Add to the Cognitive Dysfunction Associated with TBI

The addition of PTSD to TBI may contribute to cognitive difficulties. The most common cognitive deficits associated with PTSD involve attention, executive functions, and memory [236]. Attention and executive function deficits commonly found in PTSD include working memory difficulties [237, 238], problems in sustaining attention over time [239], response inhibition [240, 241], and impaired ability to gate, monitor, and regulate the flow of incoming information and environmental stimuli [241].

A number of studies have documented impairment in learning and remembering new information in PTSD patients. With respect to learning new information, impairments in PTSD have been noted on both verbal and visual memory tasks but are more pronounced on verbal memory tasks [242]. PTSD-related deficits have been observed at different stages of memory processing, including the initial registration of new information and, somewhat less commonly, in retaining the newly learned information over time [236, 243].

Could TBI Contribute to the Development and Sustainment of PTSD Symptoms?

There are clearly commonalities in terms of the external events that generate physical and experiential trauma. Could TBI contribute to the development and sustainment of PTSD symptoms? The occurrence of TBI could actually increase the risk of development of PTSD. Repeated exposure to experiences involving fear, horror, or helplessness in situations of threat to life or well-being is common in combat.

In the post-deployment health assessment and re-assessment of 88,000 soldiers, 53% witnessed someone wounded or killed, 49% felt in danger of being killed, and up to 42% required mental health treatment, with PTSD reported in up to 25% [244]. There is an increased risk of PTSD with personal physical injury. In particular, there is an increased rate of PTSD for those with TBI (RR 1.8) [245]. In examining the incidence of PTSD, rates increase in relationship to the occurrence of mTBI, with increased incidence of PTSD along the gradient of no TBI to altered mental status to LOC [39]. All of these numbers argue that some aspect of TBI contributes to the development or sustainment of PTSD symptoms. From the initial instant of injury mechanism, physical and experiential injuries are intertwined. However, there are likely additional interactions that contribute to symptom maintenance across time.

Cognitive Dysfunction May Impede Treatment for Emotional Problems, and Emotional Dysregulation May Impede Treatment of Cognitive Dysfunction

Severe emotional control dysfunction, including anxiety, hyper-vigilance, and avoidance, may become significant barriers to treatment of cognitive issues. On the other hand, cognitive deficits, especially those affecting aspects of attention, learning, and memory, may become barriers to effective treatment of emotional issues. Existing interventions designed for TBI rehabilitation or PTSD alone may need to be modified in order to maximize effectiveness. The modifications may require crossing the boundaries between traditional disciplines, creating a significant challenge in care systems designed to address single diagnoses.

Modifications to Existing Treatments

In current practice, most interventions are directed toward a diagnosis of PTSD or TBI, but not both. Treating PTSD, in the context of TBI, may differ from treating PTSD alone. For individuals in the chronic phase of the disorder, the PTSD treatments with the strongest evidence are cognitive–behavioral psychotherapies [246] such as cognitive processing therapy as well as prolonged exposure [247, 248]. Preliminary data also suggest that these therapies will be helpful for Operational Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans. A small ongoing trial of prolonged exposure among OEF/OIF veterans has shown a 50% reduction in PTSD symptoms following treatment [249]. There is some evidence supporting the effectiveness of CBT for the treatment of acute stress disorder following mTBI and CBT combined with neurorehabilitation for targeting general anxiety symptomatology in people with mild-to-moderate TBI [250]. One type of trauma-focused therapy that has received widespread empirical support is cognitive processing therapy (CPT). As in other CBT variants, CPT primarily focuses on challenging maladaptive beliefs as a means of improving well-being. CPT specifically focuses on developing strategies for evaluating and changing unhelpful thoughts about oneself and the larger environment and/or world that develop in response to a traumatic event and which contribute to dysfunction and poor adaptation. A recent retrospective analysis by Davis and coauthors of CPT for 136 veterans with PTSD showed no difference in treatment completion rates between veterans with or without a history of mTBI [251].

Modification of these approaches for individuals with cognitive dysfunction remains an important frontier for intervention development. Current experience suggests that PTSD in individuals who also sustain a TBI may be 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 therapies, and emotion regulation and impulse control problems may complicate the use of exposure techniques. Physical pain, which frequently occurs after TBI, may

limit the extent to which patients can engage in PTSD treatments that involve in-person exposure to anxiety-producing situations [252, 253]. Conversely, the emotional dysregulation, avoidance, and potential for triggering may impede engagement in cognitive rehabilitation therapies. Reduction of PTSD and management of severe TBI may be facilitated by teaching patients more adaptive coping strategies [254].

Interventions for TBI–PTSD

Recognizing complexities with regard to TBI diagnosis and attribution of symptoms, a recent VA directive stated the following: "The assessment of an individual with persistent concussion/mTBI-related symptoms should be directed to the *specific nature of the symptoms regardless of their etiology*. The *management* of an individual who has sustained a documented concussion/mTBI and has *persistent* cognitive and behavioral symptoms after 1 month should not differ *based on the specific underlying etiology of their symptoms* (i.e., concussion vs. pain, concussion vs. stress disorder)."

Combined approaches for co-treating the variety of emotional/behavioral and cognitive sequelae may need to involve mental health/PTSD specialists and TBI rehabilitation specialists [235]. Therapeutic formulations may also need to address associated issues with substance use disorders, pain, and the other issues discussed in this chapter.

Vanderploeg and coauthors discuss the need to intervene early after military post-deployment with social and emotional adjustment interventions, including the development of mindfulness-based relaxation and stress management skills, improved sleep hygiene, and education regarding substance use/abuse and alternative coping supports [235]. They further suggest that early symptom-based adjustment and stress management interventions may minimize the development or prolongation of PTSD and additionally may serve to reduce residual symptoms associated with TBI. Current findings also suggest that PTSD treatment likely should be prioritized after combat or other types of injury, regardless of TBI status, to decrease symptom complaints and enhance outcomes. Similarly, in a recent study, 40 VA rehabilitation providers interviewed [255] indicated that patients with PTSD and history of mTBI require more repetition, attention, and time to complete assignments related to their PTSD treatment.

In a recent pilot study by Cole and coauthors, nine veterans with PTSD and mTBI history participated in an 8-week mindfulness group class and reported high levels of satisfaction with the intervention. PTSD symptoms measured by the PTSD Checklist-Military version (PCL-M) were significantly improved after treatment, and gains were maintained at the 3-month follow-up [256]. Janak and coauthors conducted a multidisciplinary treatment program (which included cognitive rehabilitation, behavioral health interventions, occupational therapy, vestibular rehabilitation, and medical management) in a group of 257 active duty service members with persistent post-concussive symptoms. Participants had a history of mTBI (median 5 months post-injury), and at baseline, 34% met criteria for PTSD. After treatment, both post-concussive symptoms (measured by the Neurobehavioral Symptom Inventory, NSI) and PTSD symptoms (measured by the PCL-M) declined. Of note is that the subset of participants with PTSD diagnoses had a higher number of post-concussive symptoms both before and after treatment, as well as smaller treatment effect [257].

Targeting Core Self-Regulatory Control Functions Involved in TBI–PTSD

These considerations argue strongly that treatments that effectively improve cognitive and emotional self-regulatory functions may be particularly valuable in treating the combined neurotrauma syndrome. The issues from TBI–PTSD include disruption of core cognitive and emotional regulation mechanisms that are essential for goal-directed functioning in life. Interventions that strengthen the goal-directed

control functions, such as the selection of relevant information along with inhibition of distracting information, may be particularly helpful. Dorsolateral PFC and ventromedial PFC interact in the regulation of emotions, with modulation of amygdala [258]. These interacting circuits are likely to be important for cognitive and emotional self-regulation training such as mindfulness-based attention regulation. This forms an important foundation for further development of interventions for TBI–PTSD.

Neural Bases of TBI–PTSD and Frontiers in Intervention Development

Treating individuals with TBI–PTSD symptomatically, regardless of diagnosis, is an important initial approach. However, it is possible that intervention approaches may be refined as more is learned about the underlying biology of the disorders. Consideration of potential interrelationships between traumatic and experiential injury at neural levels generates important hypotheses for guiding research and intervention development. Direct interactions may be understood based on structural neuroanatomy, functional neural network circuitry, and neuropharmacology. Neurologic abnormalities associated with TBI may complicate abnormalities associated with PTSD. Limbic structures, including the amygdala, are thought to be integral to emotions (e.g., anxiety) involved in the fear response. As a "modulator" of the limbic system, the medial PFC is thought to play a significant inhibitory role, allowing higher-order cognitive functions to moderate less volitional limbic-based fear responses. Because TBI may involve damage to prefrontal circuits, the additional loss of inhibitory control of the limbic system related to the TBI may play a role in exacerbating and maintaining PTSD symptoms.

Investigations that focus on neural mechanisms of learning and plasticity in particular will be valuable for better understanding the pathogenesis of symptoms and dysfunction as well as providing foundations for treatment approaches. Neural level considerations suggest that certain treatment approaches used for TBI or PTSD may need to be modified in order to maximize beneficial effects and reduce potential for unexpected harm in individuals with the combined syndrome. This applies to pharmacologic and other biological approaches, as well as behavioral approaches.

On a broader level, all of the above interactions argue for a reconsideration of a combined combat neurotrauma syndrome as an entity distinct from TBI or PTSD, with features that are not simply the addition of the two. Definition of this syndrome has implications for guiding future research, defining new research questions as well as requiring new approaches and methodologies. Regardless of whether we can define a definitive syndrome and its etiology, it is clear that the combinations of symptoms that veterans experience after combat do need to be addressed with available tools immediately. Addressing these symptoms will require a multifactorial approach that takes into account contributory environmental, personal, social, emotional, and cognitive factors as well as changes in underlying neural systems. In particular, a much greater emphasis on cognitive, emotional, and behavioral self-regulation may be needed, even in individuals with so-called "mild" TBI.

Tested Theory-Driven Cognitive Interventions for Attention, Working Memory, and Other Control Processes

A variety of innovations have been developed for targeting aspects of cognitive functioning. Individualization is a key tenet for optimizing rehabilitation. Thus, each therapist may provide a different intervention for each patient, and systematically studying such interventions is challenging. A small number of structured intervention protocols have been directly studied. Increasing evidence supports the proposition that training-based therapies have utility for rehabilitation in the chronic phase of TBI, including training for attention, working memory, problem-solving, and other strategic aspects of goal management.

Even within the domain of attention, there may be many varieties of approaches to training. A selected handful of theory-driven interventions are highlighted here. A new paradigmatic example is attention process training (APT), originally formulated by Sohlberg and Mateer [259, 260]. Versions of APT train a hierarchy of attention processes using guided exercises. This method, along with other clinically based approaches, has been reviewed in multiple reviews and meta-analyses [139–141, 261, 262], and there is significant evidence to support their use for patients with brain injury. This and other approaches that target specific processes, including a number using computer-based tasks, have been demonstrated to improve functioning on targeted measures. However, the transfer and generalization of gains from task practice have turned out to be an important barrier [144]. This raises important questions regarding the nature of transfer beyond practiced tasks, and the development of approaches to enhance generalization remains an important goal.

Some recent approaches have shown promise in not only improving the targeted processes but also showing transfer of benefits to other tasks that were not included in training. In a series of studies utilizing computer-based practice of tasks that progressively engage spatial working memory, Klingberg and colleagues have shown improvements in working memory functioning as well as transfer to higher level cognitive functions that presumably rely on working memory [263, 264]. In healthy subjects, improvements correlated with increases in activation in PFC and parietal regions, as well as changes in dopamine receptor binding [265, 266]. Other recent studies testing computer-based tasks with healthy individuals have generated excitement by demonstrating improvements in aspects of goal-directed control and even general fluid intelligence [206–208, 267]. 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.

Approaches that train the use of meta-cognitive strategies have demonstrated utility for individuals with brain injury. Noting that many individuals with brain injury have difficulties with specific aspects of goal management, including making absent-minded slips, going off track, and having difficulty completing multi-step tasks, goal management training emphasizes the cessation of ongoing activity and a meta-cognitive strategy for breaking down goals into manageable substeps. This approach attempts to ameliorate deficits related to goal neglect, and studies testing training protocols have shown that learning of these strategies may improve goal management for individuals with brain injury as well as healthy older adults [156, 268].

Another intervention that combines attention and problem-solving as targets of therapy in a group-based training protocol was recently described by Evans [269, 270]. Initial group sessions address attentional difficulties, and later sessions introduce and practice the use of problem-solving strategies. Participants are encouraged to adopt a systematic approach to solving problems and to manage and monitor goal achievement through periodic mental checking. In a study by Miotto and coauthors [271], participants with chronic frontal lesions showed improvement on a measure of functional performance with multiple tasks and on caregiver ratings of executive functioning, although not on neuropsychological tests, after the implementation of training relative to control conditions.

We are all constantly faced with sources of information that either contain too much information or are ambiguous with respect to one's goals. The ability to synthesize core meaning from incoming information (i.e., "get the gist") is important for goal-directed behavior in everyday life and relies on the integration of a number of cognitive processes. Chapman and colleagues have developed protocols to train gist-based strategic reasoning, guiding individuals through steps that engage attention (repeating and filtering the information), working memory (integration of information), and higher level elaborative reasoning (expanding, extracting). Training has been shown to improve the ability to extract gist, as well as other aspects of learning and reasoning, for both children and adults with brain injury

[272]. Performance on tests of attention and working memory also improved. This raises the interesting possibility that training in higher level integrative abilities may improve more basic functions.

Targeting the Gateways to Goal Achievement

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 [273–277]. 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.

The general principles proposed earlier in this chapter for optimally training control functions would ideally be applied with this specific "selection" gateway as a target. In one example of a rehabilitation neuroscience study, our particular interest was in examining neural–behavioral changes with an intervention that targets goal-oriented attention regulation [231]. Participants with chronic brain injury and executive dysfunction completed a training intervention for goal-oriented attentional self-regulation (GOALS) that takes into account the links connecting attention, working memory, and goal-based direction of behavior in daily life. In contrast to training via practice on isolated tasks, this training protocol involved application of attention regulation skills and strategies to participant-defined goals in real-life, ecologically valid settings.

Two conceptual lines converged to delineate target processes for intervention. First, pathways from perception to action require mechanisms for the selection of information for in-depth processing, as well as the maintenance and protection of this information from disruption during working memory and subsequent learning, decision-making, and/or problem-solving. Second, many patients with brain injuries show an overall "life disorganization," with poor ability to manage and attain goals, even when they may be able to describe their intentions at the outset. Duncan and others have described this phenomenon as "goal neglect" [164, 183]. We reasoned that selective maintenance of goal-related information is important for guiding sequences of steps (subgoals) required to accomplish the goal. Therefore, intervening on these processes may help to ameliorate symptoms of goal neglect. The experimental training protocol was based on training interventions that have been applied to patients with brain injury as well as other populations [156, 157, 214, 216, 219, 268], with special emphasis on mindfulness-based attention regulation strategies applied to daily life situations and complex, project-based functional tasks. An overarching hypothesis was that training that improves goal-directed control over neural processing would benefit all subsequent stages of goal-based processing, helping by making damaged, poorly integrated collections of neurons into more efficient, better integrated functional networks for the performance of relevant tasks and, ultimately, goal attainment in real-life contexts.

It may be argued that the ecologically valid measurement of executive control functioning requires observation and quantification of performance with real-life, functional tasks in a low-structure environment. We, therefore, assessed training-related changes in participant functioning on measures of performance in "real-life" low-structure settings. Following training, participants showed improvements in accomplishing tasks, confirming generalization of training effects to complex, real-life settings. In testing whether functional improvements might be related to improvements in the targeted cognitive functions, we also assessed domain-specific changes utilizing neuropsychological testing. Participants who completed a course of GOALS training improved on neuropsychological measures of complex

attention and executive functions, including working memory, mental flexibility, inhibition, and sustained attention:

- A recent randomized control study of 33 veterans with a history of chronic mild to severe TBI and executive dysfunction [278] indicates similar results to the initial predominantly civilian study [231] described above, showing improvements after GOALS, but not after control educational intervention (EDU), on a neuropsychological composite measures of attention and executive function ($p < 0.001$) and working memory ($p < 0.02$) [279, 280]. Participants also improved after GOALS, but not after control EDU intervention, on complex "real-life tasks" performance—Goal Processing Scale (GPS [280, 281] (GPS Overall Performance $p < 0.01$ and Sequencing and Switching of Attention subdomain $p < 0.5$). Similarly, after GOALS, but not after matched control EDU intervention, participants indicated improvement on self-report measures of emotional regulation and functioning, including Profile of Mood States (POMS) Confusion at $p < 0.02$).
- These results suggest that improving cognitive control (attentional self-regulation in particular) may also improve functioning in other domains, including emotional regulation and complex daily tasks, and are supported by preliminary findings from a recently completed randomized control study with 40 veterans with current diagnosis of PTSD and history of chronic mTBI [278, 279]. Preliminary results of this study indicate that post GOALS, but not control EDU training, participants significantly improved from baseline on overall neuropsychological attention and executive function composite score ($p < 0.001$) and following subdomain scores: working memory ($p < 0.05$), sustained attention ($p < 0.001$), and inhibition ($p < 0.001$). Post-GOALS participants also improved on complex functional Goal Processing Scale Learning and Memory subdomain ($p < 0.05$). Participants also reported significant improvement in daily functioning on MPAI Ability Scale ($p < 0.05$), and on emotional regulation self-report measures: PTSD symptoms on PCL-M Total Score, and Re-Experiencing subscore ($p < 0.05$) and on POMS Overall Mood Disturbance and Depression ($p < 0.05$).

Long-term follow-up is particularly helpful to determine what aspects of an intervention have enduring benefits. In a follow-up conducted 6 months to 2 years post-training, 94% of participants with chronic ABI indicated continuing use of at least one trained strategy in their daily life [282]. Similarly, in a recently completed study, 21 out of 23 veterans with a history of TBI reported retaining and incorporating some of the trained strategies in their lives 6 months to 2 years following completion of GOALS training [283]. Importantly twice as many (10 out of 23) reported returning to competitive employment (compared to 5 *out of 23 prior to training*). Preliminary results from 20 veterans who also completed in-person behavioral assessments indicate that they have maintained significant improvements up to 2 years post-GOALS training relative to their pre-training performance on neuropsychological measures (attention and executive function, auditory working memory, and mental flexibility), complex functional task performance (GPS Overall Performance, Planning, Self-Monitoring, and Learning/Memory), and self-report measures of emotional regulation (POMS Total Mood Disturbance, Depression, Tension and Confusion; Beck Depression Inventory). These findings suggest that training self-regulatory cognitive and emotional control strategies applied to personally relevant situations and goals may provide meaningful and lasting improvements in cognitive, emotional, and occupational functioning and may have directly relevant applications toward helping veterans with history of TBI return to work and/or school.

Understanding the neural bases of cognition, including the mechanisms by which improvements occur, may provide guidance for the development of treatments to enhance functioning [139–143]. Intervening via rehabilitation provides an opportunity to probe such mechanisms. Functional neuroimaging studies examining

changes associated with various forms of training in neurologically intact individuals have shown different patterns of results, primarily in terms of increases or decreases in regional brain activation, and the significance of these results remains unclear [284–286]. It is also unclear from functional neuroimaging studies of patients with acquired brain injuries as to what neural changes support improved recovery of cognitive function [287–290]. Information regarding neural mechanisms of improvement in executive control functions is particularly sparse. Even the extent to which the neural systems that underlie executive control are plastic, if at all, has remained an open question. Only a handful of fMRI studies to date have examined cognitive rehabilitation following brain injury [291, 292], and even fewer have examined the effects of rehabilitation interventions on executive control functions [293]. We attempted to identify neural mechanisms that underlie improvements in attention and executive control with the above described rehabilitation training.

We hypothesized that training in attention regulation improves cognitive performance by enhancing goal-based modulatory control of neural processing. fMRI methods adapted for testing the effects of intervention for patients with varied injury pathology were used to index modulatory control of neural processing [294]. Another important paradigm shift is supported by measurements that "read the *information*" coded in brain networks, rather than simply quantifying activity levels. Information is represented in the brain through the coordinated activity of distributed networks. Methods for decoding neural information representations may provide valuable tools for gauging the functional integration of these networks, particularly important in individuals who have suffered brain injury and potentially a "disintegration" of brain networks. We hypothesized that attention regulation training would lead to changes in tuning of neural representations, such that the balance of representation would favor goal-relevant information. Our findings with training were consistent with this prediction. Modulation of neural processing in extrastriate cortex was significantly enhanced by attention regulation training.

As discussed above, the lateral PFC has been strongly implicated as a source of attentional control signals that could bias neural processing in extrastriate cortex [151, 295, 296]. The pattern of findings within lateral PFC showed that changes in function depended on the baseline state of any given individual. One particularly important but challenging question for further investigation is to understand the individual variability in mechanisms by which different individuals may achieve improvement in functioning after brain injury.

Harnessing Technology to Enhance Neurocognitive Skills Training

A central goal of any program of cognitive rehabilitation is to promote functional improvements in the everyday lives of patients with brain injury, particularly related to navigating the complexities and ambiguities that characterize most low-structured settings in the real world. We argue that for rehabilitation to effectively achieve this functional goal, training must include a range of activities that allow for generalizable neurocognitive skills to be sufficiently learned, practiced, and developed [231, 297, 298]. It is particularly important that these experiences include practice with managing the types of cognitive–emotional challenges that commonly interfere with goal-directed functioning for persons with brain injury, such as being overwhelmed by too much information, tolerating frustrations, managing distractions, and coordinating and following through with multi-step plans, especially when steps are distributed over time and space.

In our previous work [231, 294], we emphasized training skill use directly within the context of participants' individually defined goals as one especially valued training experience. An aspiration of this approach is to facilitate supported skill practice (via individualized coaching) in naturalistic settings and on the types of everyday activities that many with brain injury report experiencing difficulty performing. However, there

are both theoretical and practical limitations to the degree of "hands-on" coaching and guidance practitioners can provide to their patients in the community. Outside of the observable clinical setting, it is often unclear to what extent patients follow through with agreed upon treatment plans; opportunities to practice skill use may be missed altogether, or skills may be implemented inadequately (or even incorrectly) in identified situations. A clinician's primary source of information in such instances is patient self-report, yet these accounts may be incomplete or inaccurate due to common sequelae of brain injury, such as poor memory, limited self-awareness, or lack of insight [183, 299]. This can result in missed opportunities to guide and influence ongoing skill development. Incorporating more active learning opportunities directly into clinical rehabilitation, including those that readily allow for skills to be modeled and directly observed so coaching and feedback can be provided, may enhance the overall effectiveness and long-term benefit of neurocognitive skills training.

In addition, there are many intermediate steps between initial skill learning and the ultimate successful application of skills in community settings that need to be explicitly addressed for clinical rehabilitation to best promote robust functional gains [300]. First, and as noted previously, skills training would ideally involve tasks of increasing challenge; many patients with brain injury would benefit from achieving a degree of skill mastery on relatively easier tasks before progressing to more complex ones. Once these more complex tasks have been introduced, patients may then benefit from practicing skills in additional contexts involving higher-order challenges, such as with managing distractions and disruptions to primary task activities. It is difficult if not impossible to achieve this degree of environmental control in most real-world settings. Second, it is imperative during early stages of skill learning that the consequences of skill practice are benign. Failures with skill use are an expected and important component of the learning process [301]. If skills are prematurely applied in real-world settings to ill effect, it may undermine the perceived utility of skill use as well as discourage skill experimentation–factors known to play a critical role with promoting skill use over the long-term [302, 303]. Thus, patients may benefit from training activities that allow for skills to be practiced but which do not carry overly harmful inherent risk.

To address the needs identified above, we recently developed a training system to better support the stepwise learning of self-regulation skills for patients with brain injury [300, 304, 305]. This approach integrates skill instruction, interactive coaching, and intensive skill practice across multiple contexts and settings, including in digital game-based scenarios. Contrary to many training programs that utilize gaming technologies (see [306] for a comprehensive review), we integrated digital scenarios directly into training for the explicit purpose of providing a platform where trained self-regulation skills can be practiced and developed. Thus, the overarching purpose of gameplay is to provide varied and multiple contexts to practice self-regulation skills. The lack of explicit and generalizable skills training involved with many computerized brain training programs that adopt drill-and-practice methodologies may be one reason why that approach has limited evidence of transfer [307–310].

We designed digital scenarios in consultation with individuals with brain injury to reflect difficulties that they commonly experience, such as holding information in working memory, managing distractions, multitasking, and making goal-based decisions. Cognitive challenges within game scenarios were parameterized across multiple indices and are continually adjusted based upon performance to engage patients at the upper bound of their demonstrated capacity. One gameplay revolves around the establishment of a food truck business, and trainees are tasked with fulfilling orders following a brief on-screen presentation. While completing this central task, trainees are exposed to distractions in the form of passersby who make varying requests requiring immediate action. These occur at different phases of goal pursuit (e.g., encoding vs. action) and differ in their intensity. Gameplay increases in complexity over the course of training to involve

different scenarios requiring goal prioritization, multitasking, and self-monitoring.

Gameplay is incorporated into an overall training framework in order to facilitate skill learning and skill transfer. Self-regulation skills taught during training sessions are first modeled by trainers in the context of gameplay before trainees practice and experiment with skill use on their own. Objective feedback is provided to trainees both immediately during gameplay as well as in summary form during each training session. This helps to establish clear links between gameplay, skill use, and game performance. Trainers work closely with patients to help identify game junctures where skill use might be helpful, establish plans for utilizing skills in those instances, and develop and refine their application. Gameplay experiences are further utilized to facilitate discussions on how trained skills can be applied in trainees' individual lives. For instance, a trainee may be asked to articulate the nature of challenges within the game world and then will be guided through similar discussions using hypothetical and real-world examples. Game experiences serve multiple roles in this training system, including to help establish conceptual understanding for the relevance of targeted skills, raise awareness of situations and different phases of goal pursuit (e.g., encoding information versus redirecting attention following a distraction) where skill use may be beneficial, repeatedly and intensively practice skill use during these various phases, receive immediate and personalized feedback on skill use at such times, and support intentions and establish plans for utilizing skills in everyday life.

As in our previous intervention work, the primary training target in this system involves strengthening individuals' abilities to strategically apply self-regulation skills across settings and contexts. This is hypothesized to directly effect neural functioning, including neural networks involved with cognitive functions commonly impacted by brain injury, such as working memory and information processing [311]. To facilitate skill practice, the overall training is situated within a goal framework. Goals help guide skill application by providing a necessary point of reference for when individuals are dysregulated (i.e., when neurocognitive functioning poorly aligns with one's goal), and, thus, skill use is appropriate and may be beneficial. Training includes didactics and discussions on goal setting, self-regulation theory, and how to consider current states and behaviors in the context of one's goals. Trainers provide ongoing support and guidance to help increase trainees' *goal mindedness* and apply skills in game and personal life contexts.

Translation to Intervention Implementation and Delivery in Systems of Care

The considerations discussed in this chapter suggest important changes in the organization of existing systems of care. How integrated is the overall approach to the patient? The organization of care needs to be considered given the complex nature of cognitive dysfunction after brain injury and the approaches that are needed to improve functioning. The effective integration of any or all of the neural–cognitive processes and modulators illustrated in Fig. 1 is a particularly important determinant of overall cognitive functioning. Intervention approaches may need to foster the effective integration of these processes, and this may require integrating expertise across disciplines.

This may involve team members addressing and reinforcing common themes and issues that cross domains. Taking into account interactions between emotions and cognition is particularly relevant given the frequent co-occurrence of TBI and post-traumatic stress symptoms. Specific themes may be emphasized by multiple team members in different contexts and modalities, increasing the chances of accomplishing a therapeutic goal. For example, self-regulation skills may be learned best if applied in a range of situations. Individual practitioners may need to expand their range of expertise, for example, incorporating strategies that bridge cognitive rehabilitation with mental health, pain management, and substance abuse. Thus,

effective integration can require not only multidisciplinary but interdisciplinary and even transdisciplinary care.

Delivery of Care

Certain issues in the implementation and delivery for military veterans deserve special consideration. Treatment implementation and delivery methods need to be adapted to take into account issues related to geographic distribution of veterans, the "culture" of the military as well as community settings for post-military life, a high level of comorbidity with PTSD and other mental health conditions, individual goals after military service (e.g., educational or occupational), and more.

The wide geographic distribution of veterans creates challenges for treatment delivery and implementation. For example, one of the largest catchment areas for veterans returning from the combat in the Middle East spans thousands of square miles of Northern California, Nevada, and Hawaii, from oceans to mountains and desert as well as cities. The majority of veterans are not within easy travel distance to specialty medical centers. This limits the applicability of intensive on-site therapies and raises challenges to achieving integrated, interdisciplinary care.

Many of the cognitive, emotional, or behavioral problems that occur with TBI, even without deficits in other physical functions, have not been standard indications for inpatient or residential treatment. Expansion of inpatient or *residential* care programs may be necessary to provide access to integrated care in the *chronic* phases after injury.

Tele-rehabilitation

The use of tele-video technologies to extend the reach of neurocognitive interventions to those lacking direct access to rehabilitation holds tremendous promise. This is particularly relevant for the Veterans Health Administration given projections that over one million servicemen and women will transition to veteran status by 2020, many of whom will be returning to their rural communities with brain injury and related ailments [312]. Unfortunately, the majority of research and development on tele-rehabilitation has not focused on neurocognitive skills training but instead has emphasized assessment and diagnosis [313, 314]. Several aspects of tele-video communications, if not properly addressed as part of intervention development and design, can potentially undermine skills training (see Ng and colleagues [315] for an example). Of central importance is the difficulty with providing individualized guidance and support during training exercises over tele-video, potentially limiting how well skills can be developed and ultimately transferred to everyday goal pursuit. Thus, a critical goal for tele-rehabilitation research is addressing difficulties with effectively delivering training given limitations of remote interactions [316].

One potential means of providing remote training experiences of sufficient intensity and that allow for direct coaching on skill use is through using computer-assisted therapy tools, as in the training system we developed and previously described. In an initial pilot study, we adapted this training system for tele-video and assessed the feasibility of remote implementation as well potential training effects. In this adaptation, gameplay and modeling and observations of skill use are relayed in real time through use of an additional document viewer camera.

Preliminary findings from this pilot investigation were very encouraging [304]. Eighteen participants (15 veterans) with history of mild–moderate TBI and concurrent symptoms of PTS were assigned to remote training ($n = 8$) or treatment as usual (TAU) ($n = 10$) conditions. Groups were well matched across most demographic and injury characteristics, with the only notable exceptions being that TAU controls reported more symptoms of PTS and were slightly older than those undergoing remote training.

All aspects of the training protocol were successfully administered for all participants, with minimal technical difficulties. Participants were highly engaged with training, amassed signifi-

cant practice with skill application in game scenarios (participants practiced applying skills within game scenarios a median of 722 times and spent approximately 1/3 of total gameplay time engaging in self-regulation practices), and were able to benefit from remote coaching efforts to improve their ability to apply skills in their daily lives. As one illustration, a veteran who had difficulty understanding training concepts and identifying situations where skill use might be helpful was aided by the combination of coaching and gameplay experiences. His trainer utilized observations and experiences within the game world to increase the veteran's conceptual understanding of skills and as the basis for discussing how they could be extended to his personal life. For example, experiences with using self-regulation skills to manage reactions to customers' changing expressions within the game world were utilized to frame discussions about employing the same skills to better manage his frustrations with interacting with others at work. In addition, he was able to observe how his performance improved when he practiced self-regulation prior to starting a task, and these observations were utilized to discuss how this practice could be used before starting his workday or prior to beginning his daily commute. By the end of training, this veteran was able to identify a much broader array of game scenarios and personal contexts where skill use might be relevant.

Regarding objective benefits of the intervention, participants receiving remote training improved on a composite measure of complex attention, working memory, and executive functions (d = 0.64), whereas participants receiving TAU showed relatively minimal change (d = −0.07). Remote training participants also demonstrated improvements of a medium effect size on a functional real-world task (d = 0.42). On self-report measures, participants in remote training reported improvements of medium effect size on tasks requiring working memory (d = −0.55) and planning and organization (d = −0.56), whereas TAU showed minimal changes in these domains (d = −0.09 and −0.04, respectively). Self-perceived changes following training were also observed across a wide range of cognitive processes, notably with respect to attention and working memory and planning. Effect sizes for these changes were extremely large. As a preliminary test of the remote application of this training system, the objective and self-reported improvements together suggest that it is plausible that this training system may confer neurocognitive benefits. Furthermore, a training system that integrates coaching with intensive practice applying self-regulation skills in digital game scenarios and personal life is feasible to deploy for tele-rehabilitation.

Reaching Students "Where They Are"

Another important barrier is the divide between "medical care" and community. It is an unfortunate but well-recognized fact that many persons in need of services, in particular the community of younger veterans, are reluctant to seek medical help due to issues such as stigma [317]. Without adequate help, many of these veterans are unsuccessful in their efforts to re-integrate into the community, which frequently includes lack of success in post-secondary educational settings. Veterans are utilizing the GI bill at the highest rates since its inception, with over one million beneficiaries receiving an excess of $12 billion in payments in 2013 alone [318]. Yet, many student–veterans struggle in the academic setting, with the non-completion rate nearing 50% [319].

Students with TBI endorse a range of physical, cognitive, and emotional difficulties, including problems with attention, memory, and organization [139]. For military veterans, combat-related injuries are also associated with poorer and/or more inconsistent classroom attendance [320]—a factor critical for overall scholastic success. Students with TBI report having to work harder than prior to their injuries, but often lack appropriate tools and/or services to address their needs. This is particularly true for student–veterans who also often experience associated symptoms of PTS and chronic pain [319]. Innovative approaches to provide rehabilitation to support the long-term success of students with TBI are needed.

One potential means to increase access to rehabilitation for students is to integrate clinically informed skills training directly into the classroom setting. We recently adapted our experiential learning training system, which combined coaching and intensive skill practice across multiple contexts including digital game scenarios, for the college classroom setting. A major impetus for this adaptation was to provide students with TBI direct support with skill application on their academic goals and to overcome academic obstacles, including procrastination, environmental distractions, competing priorities, and academic anxieties, among others.

We completed a pilot investigation of this approach at a 4-year university, where we offered the intervention as a for-credit class in an attempt to increase access to training for college students. Participants included students with and without a history of TBI. Among the cohort of students with TBI ($n = 22$), we observed positive pre-post changes to performance on a computerized measure of working memory in the context of distractions ($d = 1.59$). Further, a subset of student–veterans with TBI who participated in neurocognitive assessments ($n = 9$) showed training-associated improvements on a composite measure of attention, working memory, and executive functions ($d = 0.42$). The magnitude of this latter change parallels results of our telerehabilitation pilot. Of note, changes observed following classroom training were selective to the training condition and were not seen in control conditions.

End of the semester feedback indicated that the training was acceptable and engaging and perceived to beneficial. Students reported success with applying skills to a range of academic tasks and challenges: 85% of students reported skills to redirect attention when distracted; 87% while working on homework/projects; 87% while studying; and 69% while attending lecture/class. Taken together, these data and experiences highlight that it is feasible to offer self-regulation training in a group format and that it is capable of engaging college-level students with TBI. Increasing access to neurorehabilitation by instituting a training-for-course-credit model may help combat issues related to stigma and, thus, get students the help they need and deserve.

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.

Building a strong theoretical and scientific foundation will be valuable for guiding the development of new therapies. Understanding the brain systems that underlie the cognitive changes associated with brain injury should help in the delineation of targets in the rehabilitation of an individual with TBI. In particular, this knowledge will open the way for therapies that target biological systems and synergistically augment the beneficial specific effects of training.

Mechanisms of plasticity at multiple levels of neural functioning may be harnessed, but any neural changes will need to be sculpted to beneficially affect neurological functioning. Training provides a crucial set of methods to guide plasticity to achieve functionally integrated networks and improvements in behavioral functioning. For example, pharmacotherapy and other biological modification therapies may be integrated into rehabilitation to help augment learning, but much work needs to be done to define the specific effects of drugs at multiple levels of nervous system function, in order to best define combined behavioral-pharmacotherapeutic prescriptions.

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 rela-

tionships between levels of functioning in order to maximize transfer and generalization of benefits.

Improved measures of the effects and mechanisms of interventions are sorely needed. Lack of adequate measurements limits intervention development. Measurement development needs to progress in at least two directions. First, biomarkers of the neural processes that mediate cognitive functions affected by brain injuries would be valuable for determining mechanisms. Cognitive neuroscience can serve as a foundation for development of these biomarkers, and new biomarkers of higher-order cognitive functioning are especially needed. These measurements will be crucial for elucidating mechanisms of the benefits (or lack thereof) for any intervention. Just as importantly, measurements that reflect functioning in ecologically relevant, real-life contexts are needed. Most tests of cognitive functioning, including neuropsychological tests and most cognitive neuroscience measures, are designed to isolate the processes of interest. On the other hand, the few functional assessment measures available are not linked in any clear way to the underlying neural–cognitive component processes affected by TBI. The development of ecologically relevant, neuroscience-driven interventions will benefit greatly from measurements that bridge neural–cognitive processes to real-world behavior.

Taking a long-term view on TBI in the context of the lifespan may lead to a major paradigm shift for the field. We will need to consider the enhancement of ongoing learning, recovery, and/or maintenance as a long-term goal of post-injury "brain health." Keeping in mind the benefits of bridging across levels of human functioning, across disciplines, and across the lifespan will significantly alter the emphasis of research and intervention development, expanding the horizons for improving cognitive functioning for individuals who have suffered brain injury.

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