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Executive (dys)function after traumatic brain injury: special considerations for behavioral pharmacology

Jenny E. Ozga^a, Jessica M. Povroznik^b, Elizabeth B. Engler-Chiurazzi^b and Cole Vonder Haar^a

Executive function is an umbrella term that includes cognitive processes such as decision-making, impulse control, attention, behavioral flexibility, and working memory. Each of these processes depends largely upon monoaminergic (dopaminergic, serotonergic, and noradrenergic) neurotransmission in the frontal cortex, striatum, and hippocampus, among other brain areas. Traumatic brain injury (TBI) induces disruptions in monoaminergic signaling along several steps in the neurotransmission process – synthesis, distribution, and breakdown – and in turn, produces long-lasting deficits in several executive function domains. Understanding how TBI alters monoaminergic neurotransmission and executive function will advance basic knowledge of the underlying principles that govern executive function and potentially further treatment of cognitive deficits following such injury. In this review, we examine the influence of TBI on the following measures of executive function – impulsivity, behavioral flexibility, and working memory. We also describe

monoaminergic-systems changes following TBI. Given that TBI patients experience alterations in monoaminergic signaling following injury, they may represent a unique population with regard to pharmacotherapy. We conclude this review by discussing some considerations for pharmacotherapy in the field of TBI. *Behavioural Pharmacology* 29:617–637 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Traumatic brain injury (TBI) occurs when an external force (e.g. mechanical deformation, rapid deceleration, blast wave) is applied to the brain and affects more than 200 per 100 000 people each year globally (Bryan-Hancock and Harrison, 2010). While many people recover with minimal complications, a significant portion goes on to develop chronic behavioral and cognitive deficits, resulting in an estimated 1–2% of people with TBI-related disabilities (Thurman *et al.*, 1999; Zgaljardic *et al.*, 2015), and accounting for a staggering \$76.5 billion USD economic burden as of 2010, with 10-year costs averaging \$270 000 per patient (Corso *et al.*, 2006; Coronado *et al.*, 2012; Ponsford *et al.*, 2013). Brain injury is considered to be a major risk factor in the development of neurodegenerative disorders, including Parkinson's and Alzheimer's diseases (Semchuk *et al.*, 1993; Plassman *et al.*, 2000), and is associated with increased rates of depression, anxiety, attention-deficit disorders, suicidality, and substance abuse following such central nervous system damage (Moor *et al.*, 2006; Vaishnavi *et al.*, 2009; Rao *et al.*, 2010; Konrad *et al.*, 2011; Reeves and Panguluri, 2011;

Zgaljardic *et al.*, 2015). Notably, these disorders impair a wide variety of behaviors commonly considered under the umbrella of 'executive function,' including memory, behavioral flexibility, impulsivity, and decision-making (Alves *et al.*, 2014; Bredemeier and Miller, 2015; Day *et al.*, 2015; Sharp *et al.*, 2015; Kingdon *et al.*, 2016).

Given the considerable difficulty of determining the causes of executive function deficits in clinical TBI patients, several injury models have been developed for inducing experimental TBIs in nonhuman animals, that map on to clinical injuries and severities (Morganti-Kossmann *et al.*, 2010). These injury types may be induced using various methods (e.g. controlled-cortical impact, fluid percussion, weight drop, blast) and at a spectrum of severities, each with unique pathological characteristics. Focal injuries result largely in localized contusion and cell death while being highly reproducible in the animal laboratory. In contrast, concussive and blast injuries generate a diffuse pattern of injury with axonal shearing that are less reproducible than focal injuries. In animal models, severity of injury is directly related to the amount of force applied to the animal's brain and strongly tied to neurological outcome (Xiong *et al.*, 2013), while clinical measurements rely on neurological outcomes such as the Glasgow Coma Scale to assess severity (Teasdale and Jennett, 1974). Regardless of primary injury type, cascades of secondary damage are initiated, which may include

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neurochemical and ionic disequilibrium in neurons, depletion of cellular energy reserves, mitochondrial dysfunction, lipid peroxidation and DNA damage, upregulated neuroinflammation, and compromised glial and endothelial support networks, that coalesce to contribute to enduring dysfunction after TBI (Prins *et al.*, 2013).

While various animal models have been used for several decades to study the pathology of brain injury, only recently has more attention been given to behavioral assessment of higher-order function. For many decades, the primary assessment of cognitive function after such trauma has been the Morris water maze (MWM), a task designed to measure hippocampal function (Morris, 1984). While this has proven to be very effective in rapidly assessing the effects of TBI on spatial learning and reference memory in animals, it is difficult to ascertain changes associated with a variety of other executive functions using this task. More recent studies have begun to make use of a wider variety of paradigms to measure cognition, including several methods based on standard operant techniques, which are the focus of this review.

To date, no pharmacological agents have been approved for the treatment of TBI, either in the acute or the chronic period. In particular, it is unclear whether patients with injury-induced psychiatric conditions represent a special population with regard to pharmacotherapies, and the degree to which commonly prescribed drugs are appropriate for patients with a TBI. Thus, the purpose of the present review is to (i) survey the literature on executive function assessments following human and animal brain injury; (ii) describe monoaminergic-systems changes following TBI that may influence how deficits in executive function respond to pharmacological intervention; and (iii) discuss considerations for behavioral pharmacology and pharmacotherapies in TBI.

Executive function following traumatic brain injury

Impulsivity

Impulsivity is a multifaceted concept describing actions with the potential to provide short-term gain at a cost to long-term benefits. The construct can be subdivided into motor impulsivity (i.e. failure to inhibit responding), choice impulsivity (i.e. inability to wait for delayed reinforcers or issues with delayed gratification), and sometimes risk-taking (i.e. choosing larger outcomes that are uncertain over smaller outcomes that are certain). Human studies suggest that deficits involving impulsivity following TBI are particularly problematic because of their wide impact on daily function (Rochat *et al.*, 2010; James *et al.*, 2014) and animal models with high translational validity have been developed within each realm of impulsive behavior.

Motor impulsivity

Motor impulsivity, also known as response disinhibition, refers broadly to acting without thinking. Response

inhibition can be further divided into ‘stopping’ and ‘waiting’ impulsivity (Schachar *et al.*, 2007; Robinson *et al.*, 2009), in which ‘stopping’ impulsivity refers to the inability to stop an action that has already been initiated, while ‘waiting’ impulsivity refers to the inability to inhibit responding for an extended duration (i.e. premature responding). One of the clinical manifestations of increased motor impulsivity is impulsive aggression, which is also correlated with criminal behavior after TBI (Alderman, 2003; Dyer *et al.*, 2006; Wood and Thomas, 2013). Impulsive aggression is operationalized as a quick, impulsive, aggressive response following minimal provocation (Barratt *et al.*, 1997), and in its verbal form is relatively common during acute recovery post-TBI (35–38%; according to Dyer *et al.*, 2006), although physical aggression may also be present (Dyer *et al.*, 2006; Rao *et al.*, 2009). Thus, deficits in motor impulsivity post-TBI have the potential to drastically impact quality of life for individuals with TBI, and their close relations.

Clinical evidence: There are several procedures for assessing motor impulsivity in humans, including go/no-go tasks (Donders, 1969), stop-signal tasks (SST; Logan, 1994), and continuous performance tasks (CPT; Rosvold *et al.*, 1956). For humans, reinforcers are presented typically in the form of ‘points’ such as those delivered in a game.

During go/no-go tasks, response inhibition is evaluated by pairing a cue (e.g. tone, symbol) with each type of trial – ‘go’ and ‘no-go’ trials – to aid in discrimination between the two alternatives. In general, if responding is inhibited during the ‘no-go’ signal, a reinforcer is delivered, while responses are punished with a timeout. The opposite occurs during ‘go’ signals, with reinforcement of responses and punishment of nonresponding. The SST is a more complex version of go/no-go, where response inhibition is tested further as participants must inhibit an action that is already in progress. A rapid response sequence is trained on two different options to receive a reinforcer. At random intervals within the session, a stimulus is presented (typically a tone), which signals that response inhibition will be reinforced. Stopping difficulty is increased by parametrically manipulating the delay to presentation of the ‘stop’ trial signal, and the signal is not given until a motor action is already in progress. Specifically, the task is designed to measure the longest delay under which an already-initiated action can be inhibited. Those with poorer inhibitory control will require shorter delays and have increased stop-signal reaction times (Logan, 1994). Nativ *et al.* (1994) and Rochat *et al.* (2013) used the SST to assess stopping impulsivity of patients following moderate-to-severe TBIs as compared with healthy controls matched for handedness or age. Stimuli were different colored lights and participants were instructed to respond as quickly as possible in the presence of one color and to stop responding in the presence of the alternative color.

During this procedure, TBI patients had significantly longer latencies to inhibit responding relative to controls, which is indicative of poorer response inhibition and resistance to performance interference following injury.

CPTs are a popular tool for assessing sustained attention and waiting impulsivity in various clinical populations (Riccio *et al.*, 2002). Such tasks require subjects to respond when target stimuli are present (i.e. a specific tone or light) and to inhibit responding when alternative, distractor stimuli are present (Rosvold *et al.*, 1956). Duncan *et al.* (2005) and Chen *et al.* (2012) used visual versions of the CPT to assess sustained attention and motor impulsivity at 2 years and 1 month postmild concussive TBI, respectively, as compared with age-matched, sex-matched, and education-matched controls. Together, results from these studies indicate that TBI patients have omission errors, commission errors, and reaction times that are comparable to non-TBI participants, and that regardless of whether tested during acute or chronic recovery, mild concussive TBI does not affect performance on visual CPTs.

Preclinical evidence. Given the significance of motor impulsivity problems in the clinical population, analogs of the tasks described above have been designed to assess motor impulsivity in preclinical animal models. Many of the tasks map onto the human assessments quite directly; however, reinforcers are typically delivered in the form of food.

Similar to the clinical evidence discussed above, preclinical evidence using rats and mice suggests that mild concussive experimental TBI produces deficits in stopping impulsivity in the go/no-go task, indicated by increased latencies to inhibit responding when no-go stimuli are presented (Hehar *et al.*, 2015; Mychasiuk *et al.*, 2015). In addition to a significant main effect of TBI on response inhibition, both of these studies also found that deficits for male rats were significantly more pronounced than those for female rats, suggesting that sex may play a prominent role in how TBI affects response inhibition. A similar deficit in latency to stop responding has been shown when utilizing the SST in rats. In particular, following severe focal TBI to the bilateral medial frontal cortex, response inhibition was impaired in rats when assessed using a SST, indicated by increased stop-signal reaction times and these deficits were exacerbated in rats that underwent voluntary exercise during acute recovery (Crane *et al.*, 2012).

In contrast to the stop-signal and go/no-go tasks, differential reinforcement of low-rate responding (DRL) schedules of reinforcement (Ferster and Skinner, 1957) are free-operant arrangements and do not have designated 'stop' trials. Such reinforcement schedules are designed to evaluate waiting impulsivity and include a temporal duration in which lack of responding is reinforced. Specifically, if the time between two consecutive

responses is greater than some duration (set by the experimenter), reinforcement occurs. If responding occurs before the duration elapses, the timer is reset. For example, on a DRL 20 s schedule, subjects must space two consecutive responses by at least 20 s to receive reinforcement. Severe focal injuries to the bilateral frontal cortex in rats impaired performance on a DRL 20 s schedule and deficits persisted until 11 months post-injury (Lindner *et al.*, 1998), with TBI animals showing an ~15% reduction in efficiency.

Another behavioral task developed for studying motor impulsivity of nonhuman animals is the five-choice serial reaction time task (5CSRTT), which is considered an analog of human CPTs (Carli *et al.*, 1983). During this procedure, subjects must wait a period of time until the brief illumination of one response option (commonly 0.5 s duration), after which a response to that alternative is reinforced. Because of the brief presentation of the stimulus, combined with punishment for incorrect or omitted responses, the task sets up a prepotent motor response, which is required to be inhibited for some duration (commonly 5 s, although longer and variable versions exist). Following reinforcer delivery, the next trial may be initiated immediately. Failure to inhibit leads to a timeout. Because each session is limited in duration, excessive premature responding leads to delays in reinforcement or even reduced total reinforcement. In one study utilizing the 5CSRTT in rats, mild, moderate, and severe focal TBI to the bilateral frontal cortex resulted in a significant increase in premature responding, and deficits persisted for 14 weeks postinjury (Vonder Haar *et al.*, 2016).

Summary: While there are relatively few clinical and preclinical studies on response inhibition following TBIs, the existing evidence suggests that motor impulsivity (both, stopping and waiting impulsivity) increases following even mild injuries. The use of a variety of procedures for assessing motor impulsivity, as well as injury models, suggests that this is a robust phenomenon in the preclinical literature. Further work is needed to dissociate the mechanisms by which TBI reduces response inhibition in an effort to develop treatment strategies specific to TBI-induced motor impulsivity.

Choice impulsivity

Choice impulsivity is a term that captures decisions that result in immediate gains at the cost of long-term benefits. Commonly, this is referred to as 'discounting' the value of future reinforcers/rewards, which is thought to be because of the cost associated with waiting. One of the most common ways for choice impulsivity to be measured is through tasks that manipulate delays and reinforcer magnitudes parametrically to determine individual levels of temporal discounting, and impulsive choice is operationalized as preference for smaller, immediate reinforcers over larger, delayed reinforcers. Large-scale

increases in choice impulsivity may result in overall poor decision-making, which can cause financial difficulties, physical health problems, and overall adverse life outcomes (Hamilton and Potenza, 2012; Boyle *et al.*, 2013).

Clinical evidence: Impulsive choice is assessed primarily using various delay discounting procedures. In general, such procedures involve discrete-trials choices between a smaller, more immediate reinforcer and a larger, delayed reinforcer. For humans, reinforcers are hypothetical monetary rewards in most cases. Although the basic premise of delay discounting procedures is the same, several variations exist, which differ in the way that delays and/or reinforcer amounts are presented to subjects (Vanderveldt *et al.*, 2016). For example, during the 'adjusting-amount procedure' (Du *et al.*, 2002), the magnitude of the smaller reinforcer is titrated during each trial until a point of indifference is calculated, which is defined as the magnitude at which the subject chooses each magnitude/delay alternative with equal frequency. In general, greater choice for the smaller, more immediate reinforcer is considered impulsive and results in indifference points at smaller magnitudes.

Evidence from clinical TBI studies suggests that patients display increased impulsive choice following TBI, reporting that TBI patients choose smaller, immediate reinforcers over larger, delayed reinforcers more than healthy controls matched for age, sex, and educational status (Dixon *et al.*, 2005; McHugh and Wood, 2008; Sellitto *et al.*, 2010; Wood and McHugh, 2013). Such deficits in choice impulsivity have been reported following assessment on adjusting-amount procedures using various hypothetical monetary amounts as well as following mild, moderate, and severe concussive TBI to the frontal cortex (Dixon *et al.*, 2005; McHugh and Wood, 2008; Sellitto *et al.*, 2010; Wood and McHugh, 2013). Indeed, it seems as though deficits in choice impulsivity may be frontally mediated given that patients with TBI outside of the frontal lobe show performance similar to that of healthy controls (Sellitto *et al.*, 2010). However, given the cross-sectional nature of clinical data in TBI patients, a temporal pathway between occurrence of TBI and choice impulsivity cannot be discerned.

Preclinical evidence: Despite the high translational validity of delay discounting procedures for assessing choice impulsivity, only one study has used it in the field of experimental TBI, using the Evenden and Ryan (1996) procedure. During this procedure, delays to the larger reinforcer are systematically increased across blocks of trials within each session while reinforcer magnitudes are held constant. In general, choices are between one food pellet delivered immediately and three food pellets delivered after a delay. During the first block of trials, the delay to both reinforcer options is 0 s, and the delay to the larger reinforcer increases systematically across blocks within sessions. Choice for the smaller, immediate

reinforcer is considered impulsive in conditions where reinforcement can be maximized by maintaining exclusive choice for the larger, delayed reinforcer. Following severe or mild focal TBI to the bilateral frontal cortex in rats, impulsive choice increased, indicated by significantly more choice for the smaller, immediate reinforcer for TBI rats relative to shams (Vonder Haar *et al.*, 2017). Not surprisingly, deficits in choice impulsivity were initially quite pronounced following severe TBI, but actually recovered to sham levels. Surprisingly, while mild TBI animals had relatively small increases in impulsivity relative to shams, their deficits persisted for the 8 weeks of testing. These results suggest that pure tissue damage may not be a primary mechanism driving impulsivity after TBI.

Summary: Impulsivity is a major issue for individuals living with TBI. Notably, high levels of impulsivity could also be a contributing risk factor to TBI in clinical populations. However, at least in one study, choice impulsivity was increased following experimental TBI, lending support for a directional relationship between clinical TBI and enhanced impulsive decision-making. Despite this, preclinical data suggest that the persistence of such deficits may be dependent upon the severity of injury. Given that only one study has examined effects of experimental TBI on choice impulsivity, further research is needed to expand upon these findings using alternative delay discounting procedures and injury models.

Risk-taking

Risk-taking behaviors may be somewhat controversial to include with impulsivity, as impulsivity is defined commonly to include actions/choices that will have long-term detrimental effects. By contrast, risky decisions only probably lead to long-term problems. However, they are part of a cluster of symptoms identified in TBI patients, have considerable overlap with impulsive behaviors, and can lead to similar negative outcomes.

Clinical evidence

Numerous procedures exist for assaying risk-taking behaviors in humans, including probability-discounting tasks, various gambling tasks, the Balloon-Analog Risk Task (BART), and others (Bechara *et al.*, 1994; Rogers *et al.*, 1999; Lejuez *et al.*, 2002). The most common assessment for use with clinical populations is the Iowa Gambling Task (IGT; Bechara *et al.*, 1994). During the IGT, 100 discrete-trials choices are presented between four decks of cards, two of which are relatively 'safe' and two of which are 'risky'. The two 'safe' options are set up to return the highest overall rate of reinforcement (\$50 with frequent penalties ranging from \$25 to \$75, or \$50 with infrequent penalties of \$250), while the 'risky' options give large amounts, but low overall rates of reinforcement (\$100 with frequent penalties ranging from \$100 to \$350, or \$100 with infrequent penalties of \$1250).

MacPherson *et al.* (2009) and Cotrena *et al.* (2014) found no differences in choice on the IGT between frontal TBI patients and healthy controls matched for age and education status during the first 60 trials of the task (both groups were largely indifferent between alternatives). However, between trials 61 and 100, TBI patients remained indifferent between options while controls chose the two 'safe' options significantly more, suggesting that control participants may have been more sensitive to the contingencies associated with each alternative. Xiao *et al.* (2013) observed a similar pattern of results with frontal TBI patients, although deficits in risky decision-making were observed as early as trial 21 out of 100.

An alternative assessment for risk-taking behavior is the Cambridge Gambling Task (CGT; Rogers *et al.*, 1999), which has the major advantage of presenting known probabilities, and thus potentially achieving a more pure measurement of risk preference. During this task, participants are presented with 10 boxes, some of which are red and some blue, representing the probability for that trial. There is a token hidden in one box and participants must wager an amount on the box color in which they believe the token is located. Participants 'win' the wagered amount if they were correct or 'lose' if it is in the other color box. The primary risk-taking outcome measure is 'risk adjustment' and is calculated as the percentage of points risked across more-certain to less-certain probabilities. In addition, the latency between trial presentation and when participants place a bet is measured, and reduced deliberation times are reflective of enhanced motor impulsivity. When matched for age and education status, TBI patients had higher risk adjustment on the CGT at 4 and 6 months postinjury (Salmond *et al.*, 2005; Newcombe *et al.*, 2011). Brain injury patients also showed reduced deliberation times, lending additional support for impaired response inhibition following frontal TBI.

An alternative means for assessing risk tolerance is the BART (Lejuez *et al.*, 2002), in which discrete trials are presented that begin with an un-inflated balloon on a computer screen. Participants click a button to inflate the balloon and gain two points per click. If the balloon is over-inflated, it may burst and participants lose all points acquired during the trial. The burst point varies unpredictably across trials such that participants cannot develop a rule for how many times to click before the balloon bursting. At any point during the trial, they may click an alternative button to 'cash out' their acquired points and move on to the next trial. During this procedure, a balance is needed between tolerating some risk, but not too much, to maximize returns. The primary dependent measure is risk tolerance, which is calculated as the average number of clicks to inflate the balloon per trial, excluding trials in which the balloon burst: more clicks are indicative of greater risk tolerance and greater risk-taking behavior. In the single study utilizing the

BART with TBI patients, adolescents at least 12 months postinjury were assessed and compared with healthy control participants matched for handedness, age, sex, race/ethnicity, and maternal education status (Chiu *et al.*, 2012). During this task, no differences in risk tolerance were observed between TBI and controls. The differences in findings between the BART and IGT/CGT are interesting, and may be because of differences in clinical samples (adolescent vs. adult), but also suggest that different risk-taking assessments may tap into alternative forms of risk-based decision-making.

Preclinical evidence

Risk-taking behavior has been largely unstudied in animal models of TBI. Recently, our laboratory has performed one such study using a rodent analog of the IGT, referred to as the rodent gambling task (RGT; Zeeb *et al.*, 2009). The primary difference between the IGT and RGT is that the rodent version has a distinct, most-optimal option, while on the IGT, the two 'risky' choices and the two 'safe' choices are equivalent to one another. As in the IGT, rats make choices among four options, two 'safe' and two 'risky'. Each choice is associated with a different number of sucrose pellets for 'wins' (1–4), and different penalties for 'losses' (5–40 s timeout), with the two-pellet option conferring the highest overall rate of reinforcement, followed by the one-pellet option (Winstanley and Clark, 2016). Following severe focal TBI to the bilateral frontal cortex of rats, there was a significant shift in choice away from the most-optimal option (Shaver TK, Ozga JE, Zhu B, Anderson KG, Martens KM, Vonder Haar C, unpublished data). Notably, this shift in choice preference reflected an increased preference for both the safer, slightly sub-optimal one-pellet option, as well as the riskier three-pellet and four-pellet options, highlighting a complex decision-making phenotype. These deficits persisted for 12 weeks postinjury, and occurred even if rats were extensively pretrained on the task before injury.

Summary

The clinical literature emphasizes risk-taking as a major concern for patients with TBI. However, phenotypes are complex, as illustrated by differences in the BART and other gambling tasks. Further, preclinical evidence is quite limited, and identifies a more generalized deficit that may not be selective to risk-taking, but instead, may be more reflective of a generalized change in reinforcement/punishment sensitivity. Further research will be needed to identify which aspects of cognitive-behavioral therapies may be directed toward these patients.

Behavioral flexibility

Behavioral flexibility refers to the ability to adapt to changing reinforcement contingencies and is often contrasted with perseveration. It is typically assessed with discrimination-reversal procedures of varying complexity,

several of which have been used in the fields of clinical and experimental TBI (Berg, 1948; Daum *et al.*, 1989; Sherer *et al.*, 2003; Hashimoto and Toshima, 2005; Myers *et al.*, 2006; Martens *et al.*, 2012; Martens *et al.*, 2013; Bondi *et al.*, 2014; Vonder Haar *et al.*, 2014a; Chou *et al.*, 2016).

Clinical evidence

In simple discrimination-reversal learning, subjects are trained to discriminate between two response alternatives that are distinguished by set stimuli (e.g. lights, shapes) and that discrimination is subsequently reversed. During the task, discrete trials are presented in which responding associated with the 'correct' stimulus is reinforced, while responses to other alternatives are on extinction. Once discrimination occurs reliably, the contingencies are reversed and the number of trials required to shift to a predefined mastery criterion is taken as a measure of behavioral flexibility, in which more trials are indicative of less flexibility. During simple discrimination-reversal assessments using lights, tones, or shapes as discriminative stimuli, TBI patients require more trials to reach mastery criteria relative to non-TBI patients matched for age and handedness (Daum *et al.*, 1989; Hashimoto and Toshima, 2005; Myers *et al.*, 2006) and never meet such criteria in some cases (Daum *et al.*, 1989; Hashimoto and Toshima, 2005).

Another flexibility measurement, the Wisconsin Card Sorting Task (Berg, 1948), is commonly used in neuropsychiatric testing. In the task, participants are given several cards in a deck and asked to sort them, but are not told how the cards should be sorted. There are multiple classification systems (e.g. color, shape, number,) and each time the participant sorts a card, the experimenter tells them whether the classification is correct or not. However, after 10 cards are sorted correctly, the classification system changes and the number of trials required for participants to adapt to the new classification is taken as a measure of behavioral flexibility. On this task, patients with moderate-to-severe TBI are impaired and require more trials to meet mastery criterion (Sherer *et al.*, 2003). However, this task is not sufficient in and of itself to delineate those with the worst TBI-related deficits (Greve *et al.*, 2002, 2009).

Preclinical evidence

Animal models largely mirror the clinical tasks with regard to assessing flexibility, with stimuli (e.g. lights, odors, tones) and response options (e.g. lever press, nose poke) that are relevant for the animal. Severe focal TBI to the frontal cortex impairs behavioral flexibility using simple discrimination-reversal tests in rats and mice. Specifically, TBI animals show a range of deficits from small (additional trials or sessions to criterion) to major (never achieving criterion) during postacute and early chronic recovery periods (2–5 weeks postinjury; Martens

et al., 2012; Bondi *et al.*, 2014; Vonder Haar *et al.*, 2014a, 2014b; Chou *et al.*, 2016). In addition to acute impairments, Chou *et al.* (2016) suggest that deficits persist for 5.5 months postinjury.

Additional complexity can be added to discrimination-reversal tasks in nonhuman animals by utilizing complex multimodal discriminative stimuli (e.g. odor+texture, light+location), and shifting the discrimination only along one dimension of discriminability. This procedure, known as attentional set-shifting (Birrell and Brown, 2000), is roughly analogous to the Wisconsin Card Sorting Task used with humans. This results in a subtler shift in reinforcement contingencies (50% reinforced rather than extinction), which can make for a more difficult task. This form of learning is also impaired following unilateral parietal focal injury in rats, although only at higher injury severities (Bondi *et al.*, 2014), but unaffected by unilateral frontal focal injury (Chou *et al.*, 2016).

Summary

Impairments in flexibility affect an individual's ability to appropriately change in response to their environment in a fundamental way, and may contribute to a poorer quality of life for individuals with TBI who report these symptoms. This phenomenon has been replicated in the preclinical literature, but only after relatively severe injuries, potentially limiting its applicability to the clinical condition. However, these data may serve as a starting point for the evaluation of pharmacotherapies, and could be extended to more complex discrimination-reversal procedures and more mild injury models.

Working memory

Working memory (WM) refers to the ability to remember a given stimulus over a relatively short time frame (commonly seconds to minutes). The assessment of WM typically involves presenting a stimulus, removing it for a given delay, and then testing for recall.

Clinical evidence

Numerous procedures exist for assessing WM in humans using verbal, visual, and spatial modalities (Dunning *et al.*, 2016). Two common procedures that have been used in the field of clinical TBI are the digit-span and *n*-back tasks (Asloun *et al.*, 2008; Levin *et al.*, 2002; Chen *et al.*, 2012). The digit-span task measures verbal WM and presents a sequence of numbers as the stimulus, which subjects are then asked to reproduce after a brief delay. Sequence length is gradually increased with each correct response. The primary dependent measure in this task is the number of digits correctly remembered in sequence, with fewer digits indicating impaired WM. Digit span is commonly included as part of the Wechsler Adult Intelligence Test battery, and so has been fairly extensively tested. While it is relatively common to find some level of impairment post-TBI (Scherwath *et al.*,

2011; Woods *et al.*, 2011), there are studies that report no effect after milder TBI (Demery *et al.*, 2010; Chen *et al.*, 2012). In addition, some researchers have noted that this task may be confounded by the motivation of the individual, potentially exacerbating measurements in TBI populations (Clark *et al.*, 2014; West *et al.*, 2011).

Similar to the digit-span task, the *n*-back task presents a sequence of stimuli (commonly numbers or letters), one at a time. During each stimulus presentation, the participant is instructed to identify whether the current stimulus is the same as the one presented *n* trials (commonly 2 or 3) before the current stimulus. Thus, if *n* = 3, the participant must identify when the current stimulus matches the one presented three trials before the current stimulus, typically with a mouse click or button press. Task difficulty increases as *n* increases and thus, the primary dependent measure is typically the proportion of correct responses at 2-back or 3-back, with smaller proportions indicating impaired WM. Levin *et al.* (2002) assessed WM of adolescents five years postmild or postsevere TBI compared with healthy controls, matched for age and parental education status, using 1-back, 2-back, and 3-back tasks. Adolescent patients with brain injuries demonstrated reduced WM performance on all three task levels. Similarly, adult patients with severe or mild TBI showed reduced WM performance on 1-back, 2-back, and 3-back tasks compared with matched control participants (Asloun *et al.*, 2008; Chen *et al.*, 2012).

Preclinical evidence

Despite the potential impact on daily function in clinical populations, memory impairments following experimental TBI have primarily been studied using the MWM, and largely focused on reference memory as opposed to WM. However, alternative measures for assessing WM deficits include variants of the MWM as well as delayed match-to-sample (DMTS) tasks. Here, we limit our discussion to these, given that they are highly dependent upon executive function relative to the traditional reference MWM.

Morris water maze variants

The traditional form of the MWM is ubiquitous in the field of experimental TBI. In this task, animals are placed in a tank of water, and may escape by locating a submerged platform. Animals gradually reduce their latency to escape using visual cues located around the room, typically considered a measure of reference memory that is highly hippocampal-dependent (Morris, 1984). Several variations of the MWM have been implemented aimed at assessing WM. These variations include a moving platform wherein the animals' ability to track changing locations of the platform is assessed (Hamm *et al.*, 1996; Hoane *et al.*, 2003). During testing, the platform is submerged in a new quadrant of the MWM tank. After the platform is placed in its new location, animals are placed

into the tank and given a brief period of time to locate the platform. If the platform is not located by the animal after the time interval elapses, the experimenter guides the animal to the platform. Following the first trial, considered an 'information' trial, additional trials are conducted with several minutes separating the start of each trial, and latencies to find the platform are taken as a measure of WM function. Because of the length of this delay, these procedures are considered different from delayed match-to-sample parameters described below, although there is considerable overlap. Longer latencies on this procedure have been indicative of WM deficits following moderate bilateral parietal (Hamm *et al.*, 1996), severe frontal (Hoane *et al.*, 2003, 2004, 2005; Kokiko *et al.*, 2006) and severe unilateral parietal TBIs (Quigley *et al.*, 2009; Swan *et al.*, 2011) during acute recovery. Evaluation of chronic deficits has been limited, but unpublished data suggest that WM impairments do not resolve after focal, frontal TBI (Fig. 1).

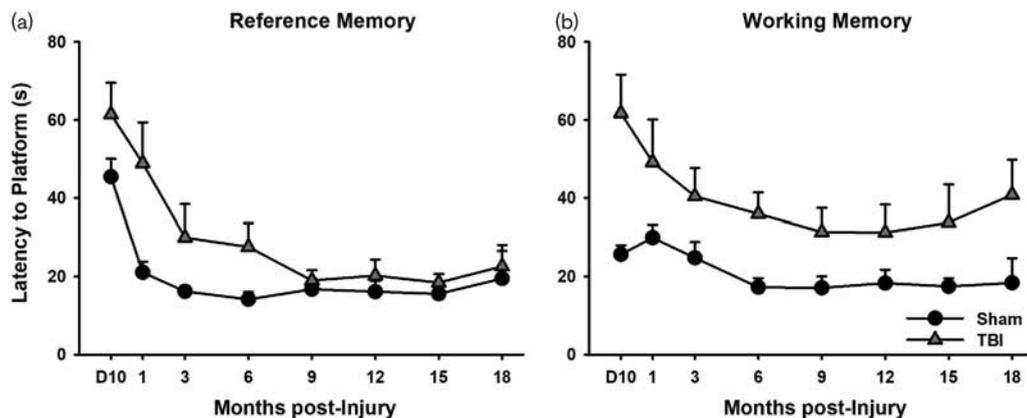
Delayed match-to-sample

In general, DMTS procedures include a sample stimulus, followed by two comparison stimuli, and choice for one of the two comparison stimuli is recorded. Choice for the comparison stimulus that matches the sample stimulus is reinforced, while choice for the novel comparison stimulus results in extinction or timeout. Following accurate discrimination between the two comparison stimuli and correct 'matching' to some criterion, a delay is introduced such that the animal must remember which sample stimulus was presented for a period of time before the comparison stimuli are presented. A 'non-match' version of this procedure follows an opposite rule in which animals must identify the stimulus that is novel after the delay.

Various DMTS procedures have been used in the field of experimental TBI where stimuli are associated with spatial location. In one study that used an operant chamber for WM assessment in rats (Lindner *et al.*, 1998), one lever was extended into the chamber and a response on that lever resulted in lever retraction (sample stimulus). Following an intertrial interval, which varied from 0 to 50 s, both levers were extended into the chamber (i.e. comparison stimuli) and animals were trained to respond on the lever that did not match the sample stimulus (non-match-to-sample). Following severe focal injuries to the lateral sensorimotor cortex, rats demonstrated a transient impairment, while those that received severe bilateral frontal cortex injuries, had deficits that lasted up to 11 weeks postinjury.

Although operant techniques represent a common procedure for testing WM, various maze assessments are more prevalent in experimental TBI (e.g. T-mazes and eight-arm radial mazes). In general, T-mazes have included a platform that allows animals to escape from a tub of water (Whiting and Hamm, 2006; Hoskison *et al.*,

Fig. 1



Long-term, selective deficits in working memory after traumatic brain injury (TBI) (Martens KM, Vonder Haar C, Swan AA, Emery MA, Clayton ER, Peterson TC, Hoane MR, unpublished data). Rats (3 months of age) received a bilateral frontal, focal TBI and were tested up to 18 months postinjury. (a) TBI caused deficits in the reference version of the Morris water maze ($P=0.012$), which resolved by 9 months postinjury. (b) TBI also caused deficits in a working memory version of the task where the platform was moved to a novel location daily, but these never resolved ($P=0.004$).

2009). During one variation of this procedure, a divider is placed on one side of the maze during forced-exposure trials, so that the animal is forced to enter that side and reach a platform to escape from the water (sample stimulus). Immediately or after a delay, a free-choice trial is given in which the divider is removed and the animal can enter either side of the maze (comparison stimuli). When the animal enters the same side of the maze as that presented during the forced-exposure trial, the choice is reinforced by escaping the water. Using this procedure, Whiting and Hamm (2006) found that when the delay between sample and comparison stimuli was relatively short (i.e. 15 s), matching of sham animals and those experiencing moderate lateral focal TBI reached ~90% accuracy. Although performance was disrupted at relatively long delays (e.g. 30 and 120 s) for both groups (80 and 75% respectively for sham), it was disrupted to a larger degree following injury, with TBI animals displaying an ~15% reduction in accuracy relative to sham. Similarly, performance was disrupted at 5 and 10 s delays following unilateral parietal TBI in rats relative to sham animals (Kline *et al.*, 2002; Hoskison *et al.*, 2009; Dash *et al.*, 2010; Kobori *et al.*, 2011; Titus *et al.*, 2016) and in one study, deficits persisted until at least 16 weeks postinjury (Hoskison *et al.*, 2009; Dash *et al.*, 2010; Kobori *et al.*, 2011; Titus *et al.*, 2016).

Similar to results from DMTS and T-maze tasks, animal studies suggest that WM, as measured by the eight-arm radial maze, is impaired after mild to severe focal unilateral TBI (Lyeth *et al.*, 1990; Enomoto *et al.*, 2005; Taylor *et al.*, 2008; Sebastian *et al.*, 2013; Shin *et al.*, 2016). The typical radial maze paradigm involves delayed nonmatch to sample. Reinforcers are placed in four of the eight arms, and animals must remember locations they have already visited. Deficits, as measured by number of

errors (repeated visits), on this task after TBI may be quite long lasting, as one study identified deficits even when testing began 6 weeks after injury (Sebastian *et al.*, 2013).

Summary

Deficits in WM after TBI are robust in the preclinical literature and relatively common in clinical practice across many different approaches to testing. Most interesting is the animal finding that WM deficits happen regardless of location of injury. Given that WM is commonly considered to be frontal-dependent, this suggests that there is more at work than mere tissue loss, and that other factors, such as long-term alteration to neurotransmission, may play a role. Whereas motivational deficits are emphasized as a potential confound in clinical work, the animal research appears quite reliable in this regard, perhaps by using salient reinforcers such as escape from water or palatable sucrose pellets.

Monoaminergic system changes following traumatic brain injury

The brain regions that play prominent roles in executive function tasks discussed above include the frontal cortex, striatum (which includes the nucleus accumbens and caudate-putamen), and hippocampus (Baron *et al.*, 1985; Hicks *et al.*, 1993; McDonald *et al.*, 2002; Chudasama and Robbins, 2006). These regions, and the circuits they form, are intimately dependent upon proper monoaminergic function. In the following sections, dopamine (DA), serotonin (5-hydroxytryptamine, 5-HT), and nor-epinephrine (NE) changes following TBI are discussed, with an emphasis on changes in brain regions known to be critical for executive function. It should be noted that although changes to monoaminergic systems are

discussed in terms of disruptions, such changes may not necessarily be detrimental but rather, may reflect compensatory adaptations.

Dopamine

DA is a prominent signaling system with widespread effects and is critical for frontal-dependent, striatal-dependent, and hippocampal-dependent executive function (Beaulieu and Gainetdinov, 2011; Haber, 2014; Trantham-Davidson and Chandler, 2015). DA is heavily concentrated in striatal regions, and serves a strong signaling function within the prefrontal cortex. Changes to the DA system have been suggested to underlie chronic behavioral and cognitive dysfunction following TBI (Bales *et al.*, 2009). This injury-induced disruption occurs directly, but also by indirect glutamatergic and GABAergic signaling alterations (Bales *et al.*, 2009).

Clinical evidence

There are limited data available regarding the relationship between clinical TBI and DA transmission, and a small portion of such data are equivocal. Using positron emission and single-photon emission tomography, clinical imaging studies converge on moderate and severe TBI-related reductions in striatal DA transporter densities when compared with healthy control participants matched for age and educational status (Donnemiller *et al.*, 2000; Wagner *et al.*, 2014). However, effects of clinical TBI on DA receptor densities and metabolism are less clear. Studies suggest that striatal D2 receptor binding is altered following moderate or severe TBI, although there are reports of both up-regulation and down-regulation (Donnemiller *et al.*, 2000; Wagner *et al.*, 2014). Similarly, it seems as though DA turnover is significantly altered following severe TBI (both increases and decreases have been reported; Bareggi *et al.*, 1975; Porta *et al.*, 1975; Vecht *et al.*, 1976; Majchrzak *et al.*, 1979; Massucci *et al.*, 2004). Such discrepant evidence may be because of contributing sex differences and/or genetic profiles (Wagner *et al.*, 2007, 2014) in which DAergic transmission is more heavily impacted for female patients and for those with certain functional genetic variants (Wagner *et al.*, 2007).

Preclinical evidence

Given the sparse and sometimes conflicting evidence for DA system changes following clinical TBI, as well as the cross-sectional nature of the data that precludes the detection of a causal relationship between TBI and DAergic transmission, the field of experimental TBI has focused on evaluating DA changes at each step in the process of neurotransmission – synthesis, distribution, and breakdown – using highly reproducible animal models of injury.

Tyrosine hydroxylase (TH) is the rate-limiting enzyme that is responsible for converting the amino acid

L-tyrosine to L-DOPA. Given that L-DOPA is the immediate precursor for DA synthesis, changes in TH levels lead to alterations in DA signaling. Preclinical work suggests that TH may be influenced differentially across brain regions and time. Notably, disruptions in TH activity may not be apparent during the acute post-TBI phase (Huger and Patrick, 1979), but rather manifest themselves later during recovery (Yan *et al.*, 2001, 2007; Shin and Dixon, 2011; Shin *et al.*, 2011, 2012). Increased TH in the frontal cortex and substantia nigra have been observed following severe focal TBI in rats (Yan *et al.*, 2001, 2007), but only at chronic time points (28+ days postinjury). In the same model of injury, Shin *et al.* (2011, 2012) determined the functional ability of TH to convert L-tyrosine to L-DOPA, with a similar lack of differences early postinjury, but decreases in TH function for TBI rats at 1 and 4 weeks postinjury. While the effect of TBI on TH activity has primarily been examined in the striatum and substantia nigra of rats (Yan *et al.*, 2001, 2007; Shin and Dixon, 2011; Shin *et al.*, 2011, 2012), mRNA levels for TH are elevated after mild blast injury in the locus coeruleus and raphe nucleus (Kawa *et al.*, 2015), and protein levels and functional capacity of TH are elevated after moderate focal injury in the prefrontal cortex (Kobori *et al.*, 2006). Together, the evidence suggests that TH function is disrupted following various experimental TBIs, but the nature of disruption may be dependent upon both the region of interest, and the time point at which it is measured (i.e. increase or decrease in activity). Vesicular storage of DA and other monoamines may also be altered after TBI as some alleles of the vesicular monoamine transporter are associated with cognitive dysfunction after TBI in patients (Myrga *et al.*, 2016), and vesicular monoamine transporter is down-regulated after experimental TBI, albeit only in female rats (Xu *et al.*, 2016).

Given that TH activity is disrupted post-TBI, it follows that DA release and basal DA concentrations also experience alterations. Indeed, evidence from high-performance liquid chromatography and western blot studies with rats suggests that there are initial increases in DA levels in the frontal cortex and striatum postmild blast or postsevere focal TBI that persists for at least 28 days (Massucci *et al.*, 2004; Kobori *et al.*, 2006; Kawa *et al.*, 2015). While higher DA levels have been measured post-mortem after TBI, in-vivo recordings of DA release from presynaptic neurons using fast scan cyclic voltammetry or microdialysis show significantly lower levels for severe and moderate focal-TBI rats up until 8 weeks postinjury when compared with sham rats (McIntosh *et al.*, 1994; Wagner *et al.*, 2005; Shin and Dixon, 2011; Huang *et al.*, 2014a; Chen *et al.*, 2015, 2017). In turn, DA transporter down-regulation may be due to the significant, chronic reduction in frontal and striatal DA release following TBI, leading to a reduction in DA reuptake and clearance from the synapse (Yan *et al.*, 2002;

Wagner *et al.*, 2005; Wilson *et al.*, 2005; Huang *et al.*, 2014a; Shimada *et al.*, 2014). The effect of TBI on DA transporter down-regulation is true not only for the frontal cortex and striatum (Yan *et al.*, 2002; Wagner *et al.*, 2005; Wilson *et al.*, 2005), but also for the midbrain (Shimada *et al.*, 2014), and occurs even in the case of mild TBI (Yan *et al.*, 2002; Wagner *et al.*, 2005; Wilson *et al.*, 2005; Huang *et al.*, 2014a; Shimada *et al.*, 2014). This is perhaps because of the action of DA as an excitotoxic agent, in which elevated levels in the acute post-TBI phase may lead to excitotoxicity and oxidative damage, resulting in lower levels of DA release at chronic time points and compensatory changes in DA transporter densities (Olney *et al.*, 1990; Wagner *et al.*, 2005). Moreover, DA transporter down-regulation appears to be a chronic effect and persists for at least 28 days postinjury for rats (), although additional time points have not been evaluated.

In rat models, some have reported transient (<24 h) reductions in D1 receptor density in the striatum after TBI (Henry *et al.*, 1997), but another study observed a complex relationship at 24 days postinjury of decreased D1 receptor density in dorsal striatum, and increased D1 levels in the nucleus accumbens, but only after mild TBI (Vonder Haar *et al.*, 2016). Moreover, no changes in striatal D2 receptor densities have been recorded across multiple time points (Henry *et al.*, 1997; Wagner *et al.*, 2005, 2008; Vonder Haar *et al.*, 2018).

In addition to reuptake by transporters, the second mechanism by which DA is removed from the synapse is by enzymatic degradation; the enzymes catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO) break down DA into its primary metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid. Although there have been no studies assessing effects of TBI on COMT or MAO directly, existing evidence suggests that DA metabolism may be affected acutely post-TBI. However, there is some discrepancy in the preclinical TBI field, in which some work suggests that there are heightened levels of DOPAC and homovanillic acid of rats in the short term, corresponding with elevated DA levels (Massucci *et al.*, 2004; Shin and Dixon, 2011; Shin *et al.*, 2012), while others report reduced levels of such metabolites in mice and rabbits during acute recovery (Edvinsson *et al.*, 2009; Shen *et al.*, 2011). In addition, DOPAC/DA ratios (a measure of DA turnover) are significantly altered in rats postinjury (both increases and decreases have been reported; Massucci *et al.*, 2004; Shen *et al.*, 2011), giving evidence for altered DA metabolism and not simply an up-regulation or down-regulation of DOPAC as a response to changes in DA levels. However, by 7 days postinjury, no differences were found between sham and injured rats, suggesting that DOPAC levels (and potentially COMT and/or MAO levels) become normative during the postacute recovery period (Shin and Dixon, 2011; Shin *et al.*, 2012).

Summary

In addition to chronic, detrimental effects of TBI on DA synthesis, distribution, and breakdown, moderate focal TBI results in a significant, progressive loss of DA neurons in the substantia nigra (Wagner *et al.*, 2009; Hutson *et al.*, 2011; van Bregt *et al.*, 2012), which may be representative of the established link between TBI and the development of Parkinson's disease (Semchuk *et al.*, 1993). Thus, TBI has widespread effects on the DAergic system, affecting all aspects of DA neurotransmission. Given the evidence from both experimental and clinical TBI fields, treatment has focused largely on providing DAergic pharmacotherapies (e.g. D-amphetamine, methylphenidate) for TBI patients to aid in symptom reduction following injury by increasing DA signaling (Bales *et al.*, 2009), although these pharmacotherapies are not without potential pitfalls (see below: Special Considerations for Pharmacotherapy following TBI). Moreover, given the unique time course of changes to DA after TBI, the exact timing of pharmacotherapies will be of critical importance.

Norepinephrine

Of all the monoaminergic systems, NE has received the least attention in regard to alterations following TBI. DA is converted to NE by the rate-limiting enzyme, DA- β -hydroxylase. Therefore, the disruptions in TH or DA activity discussed above also contribute to alterations in NE activity.

Clinical evidence

The two clinical TBI studies that evaluated changes in NE signaling relative to non-TBI control participants suggest that brain injury increases NE metabolism, indicated by heightened levels of NE's primary metabolite, 3-methoxy-4-hydroxyphenylglycol. However, this was only measured at between one and 12 days postinjury (Markianos *et al.*, 1992, 1996). Although NE has not been a prime target of interest for clinical TBI research, selective NE reuptake inhibitors are a relatively common treatment for depression and anxiety, and may also improve attention, all of which suffer some impairment in TBI patients (Hibbard *et al.*, 1998; Jorge and Robinson, 2003; Juengst *et al.*, 2017). Thus, further clinical work investigating NE activity following clinical TBI is needed.

Preclinical evidence

Experimental work suggests that brain injury leads to significant increases in NE levels in the prefrontal cortex, hippocampus, cerebellum, and hypothalamus of rats (at 2 h, 7 days, and 14 days), which corresponds with increased TH levels at these same time points (Huger and Patrick, 1979; Kobori *et al.*, 2006; Kawa *et al.*, 2015). In addition, acute increases in NE occur specifically at the site of injury, followed by a return to levels comparable to those of sham rats by as early as one week postinjury (McIntosh *et al.*, 1994; Levin *et al.*, 1995;

Dunn-Meynell *et al.*, 1998; Fujinaka *et al.*, 2003). Thus, the evidence suggests that relatively acute disruptions occur during NE synthesis and distribution/release following injury in experimental studies, although clinical work is needed to validate these findings in TBI patients. In addition to significant increases in basal NE, early studies suggested that α 1A receptor subtypes are transiently reduced at the injury site and may persist until 30 days postinjury in rats (Prasad *et al.*, 1992; Levin *et al.*, 1995), while more current work reports increased α 1A receptor mRNA in the medial prefrontal cortex following TBI (Kobori *et al.*, 2011).

Summary

While NE transmission is likely disrupted following TBI, research is lacking in specificity of the nature of those disruptions. It is likely that NE signaling disruption following TBI could influence executive function through the locus coeruleus innervation of the prefrontal cortex (Logue and Gould, 2014). In particular, whether densities of other receptor subtypes are altered, what changes occur at the NE transporter, and the degree to which these changes may contribute to behavioral dysfunction remain open questions. It may also be a clinical concern that elevated NE levels have been detected after TBI, yet selective NE reuptake inhibitors may be used clinically for a host of conditions in these patients. Overall, research regarding TBI and NE disruption is lacking and there is a critical need for both clinical and preclinical work.

Serotonin

Although more research has been conducted on 5-HT compared with NE, relatively little work has investigated the mechanisms by which TBI disrupts 5-HT signaling.

Clinical evidence

Clinical studies suggest that 5-HT transmission is indeed disrupted following TBI, revealed by significant changes in 5-HT metabolites in the cerebrospinal fluid of TBI patients (both increases and decreases have been reported; Porta *et al.*, 1975; Vecht *et al.*, 1976; Majchrzak *et al.*, 1979; Markianos *et al.*, 1992, 1996). Discrepancies in the nature of such changes in 5-HT metabolite levels may be explained, at least in part, by measurement time points, with 5-HT being elevated during the acute post-TBI phase and reduced during chronic recovery (Porta *et al.*, 1975; Vecht *et al.*, 1976; Majchrzak *et al.*, 1979; Markianos *et al.*, 1992, 1996). The mood-altering effects of 5-HT have been a primary area of focus, given that the development of mood disorders such as depression and anxiety are prevalent following brain injury (Hibbard *et al.*, 1998; Jorge and Robinson, 2003; Juengst *et al.*, 2017) and the most common treatment for such disorders are selective 5-HT reuptake inhibitors (SSRIs; Ciuna *et al.*, 2004). Although effects have not been assessed directly, it is possible that 5-HT signaling disruption following TBI

may also influence executive function (Cifariello *et al.*, 2008). Indeed, some have reported significant inverse correlations between 5-HT signaling and impulsive behavior (Harrison *et al.*, 1997; Dalley *et al.*, 2002), and inverse relations have been identified between 5-HT metabolites and aggression levels, although these may also be mediated by DA signaling (Coccaro *et al.*, 2010).

Preclinical evidence

Tryptophan hydroxylase (TPH) is the rate-limiting enzyme that is responsible for interacting with the amino acid tryptophan and converting it to 5-HT, which is then acted upon by DOPA decarboxylase to create 5-HT. Although TPH is significantly increased in the dorsal raphe nucleus and locus coeruleus in rats acutely following mild blast TBI (i.e. up until 24 h), by 48 h post-TBI, TPH levels return to those that are comparable to sham rats (Kawa *et al.*, 2015). Similarly, acute changes have been observed in rat basal 5-HT levels post-TBI (10 min; Busto *et al.*, 1997), suggesting that acute disruptions in TPH production directly affect 5-HT levels. However, there is some discrepancy as to whether 5-HT levels return to normal early during recovery. Some have reported a return to sham levels by seven days postinjury (Kawa *et al.*, 2015), while others suggest that 5-HT levels are elevated until at least 2 weeks postinjury (Mustafa *et al.*, 2017). Such discrepant findings may be because of the use of different injury models across studies, in which mild TBI induced by weight drop may affect 5-HT transmission longer into the recovery period than that induced by blast (Kawa *et al.*, 2015; Mustafa *et al.*, 2017). Given the limited and sometimes conflicting evidence, further preclinical work is needed to dissociate the mechanisms by which TBI affects 5-HT levels.

In addition to relative acute and transient disruptions in 5-HT synthesis and basal concentrations post-TBI, there are no changes in 5-HT_{2A} receptor densities in the motor, prelimbic, agranular, sensory, or cingulate cortices of rats at 15 days postinjury (Dam *et al.*, 2013), although more acute time points have not been assessed. In contrast, significant increases in 5-HT_{1A} densities in the hippocampus have been shown at 15 days postinjury (Wilson and Hamm, 2002), which may contribute to memory deficits that are seen following TBI (Dale *et al.*, 2016). Changes in other 5-HT receptors have not been evaluated after TBI, potentially because of a lack of strong radioligands for human patients, or because of the inherent complexities in studying the numerous receptors and their actions.

In terms of 5-HT deactivation, moderate or severe TBI produces significant, chronic reductions in 5-HT transporter densities in the frontal and cingulate cortices of rats (Abe *et al.*, 2016). At the same time, moderate TBI leads to chronic increases in 5-HT transporter densities in the raphe nucleus while having no effect on densities in the hippocampus, thalamus, or amygdala of rats (Dam

et al., 2007). Together, the evidence suggests that 5-HT reuptake is dysregulated following TBI, but the nature of such disruption may depend upon injury type and brain region. In addition to 5-HT deactivation by reuptake, 5-HT enzymatic degradation may be disrupted following TBI, which is in line with clinical evidence. Indeed, significant reductions in 5-HIAA in the rat hippocampus have been observed at 30 min post-TBI (Eschun *et al.*, 1992), although additional time points have not been assessed.

Summary

Given the significant reduction in 5-HT transporters in the frontal cortex, a critical region for executive function (McDonald *et al.*, 2002; Chudasama and Robbins, 2006), as well as disruptions in 5-HT metabolism, it is possible that disruptions in 5-HT breakdown and removal from the synapse contribute to behavioral impairments after TBI, although effects have not been assessed directly. In addition to replicating the results discussed above using alternative models of experimental TBI, the efficacy of commonly prescribed SSRIs (i.e. 5-HT transporter antagonists) on executive function following TBI should be assessed thoroughly given that a large portion of TBI patients experience postinjury depression and/or anxiety (Hibbard *et al.*, 1998; Jorge and Robinson, 2003; Juengst *et al.*, 2017) and are likely to be prescribed such pharmacotherapies.

Special considerations for pharmacotherapy following traumatic brain injury

Reduced sensitivity to reinforcement

TBI patients show significant impairments in executive function, which may be due, in part, to insensitivity to contingencies and natural reinforcement processes. Executive function tasks include reinforcing (and often concurrent punishing) consequences for appropriate responding, with optimal responding in these tasks producing higher rates of reinforcement. However, individuals with TBIs show reduced sensitivity to and awareness of reinforcement contingencies (Schlund and Pace, 2000; Schlund *et al.*, 2001; Schlund, 2002a, 2002b; Larson *et al.*, 2007), and are slower to adapt choices following changes in reinforcing contingencies compared to non-TBI controls (Schlund *et al.*, 2001; Schlund, 2002a, 2002b). All of these processes are directly dependent on DAergic signaling, and a large literature has demonstrated the role of DA in primary reinforcement (Cameron *et al.*, 2014; Shnitko and Robinson, 2015), reward expectation (Schultz *et al.*, 1997; Cocker *et al.*, 2016), and punishment salience (Tomer *et al.*, 2014; van der Schaaf *et al.*, 2014; Jean-Richard-Dit-Bressel *et al.*, 2018). Despite these large effects in patients, sensitivity to contingencies may not be impacted at the most basic level. As such, one study examined responding under basic schedules of reinforcement (e.g. fixed ratio, fixed interval, variable ratio, variable interval) between sham

and rats undergoing experimental TBI and found no notable deficits in TBI rats (Vonder Haar *et al.*, 2016). However, in the same model of TBI, rats displayed substantial deficits in simple discriminations (Martens *et al.*, 2012; Vonder Haar *et al.*, 2014a, 2014b) and aberrant (but not purely disadvantageous) choice behavior on the RGT (Shaver TK, Ozga JE, Zhu B, Anderson KG, Martens KM, Vonder Haar C, unpublished data), suggesting that discrimination between concurrently available contingencies may be reduced, which may drive executive function deficits in TBI patients. Given the scope of this problem, augmented behavioral therapies may need to be developed specific to patients with brain injury in order to appropriately serve this population (Knight *et al.*, 2002; Wood and Alderman, 2011). These foundational problems should also be considered when assessing executive function in animal models of TBI.

Altered pharmacology after traumatic brain injury

While pharmacotherapies to treat TBI remain a primary interest of the medical community, several concerns have been raised about factors that may alter the efficacy of these treatments. We have opted to focus primarily on mechanisms of monoaminergic dysfunction because of their suspected role in executive impairment; however, it should be noted that effects of TBI extend far beyond the monoamines. Notably, altered pharmacokinetics have been observed by multiple mechanisms after TBI and for many different drugs. In particular, hepatic cytochrome-P450 enzymes are upregulated, and protein-depot binding in blood may be reduced, resulting in faster metabolism of many substances (Empey *et al.*, 2006; Anderson *et al.*, 2015). Parsing these metabolic changes is further compounded by disruption of the blood-brain barrier (Stowe *et al.*, 2000; Hay *et al.*, 2015; Prakash and Carmichael, 2015), potentially resulting in higher than normal drug concentrations, and/or other interfering proteins reaching neural tissue as blood-brain barrier permeability shifts after injury. Together, these factors present challenges to both the experimental researcher and the clinician regarding concentration and frequency of dosing, and may help explain the numerous treatment failures experienced in the field of TBI.

While alterations to pharmacokinetics are concerning, fully understanding the changes in pharmacodynamics after TBI are an even more difficult challenge. Monoaminergic metabolism, as well as receptor and transporter densities are all altered at some point following TBI, leading to the question of whether drugs exert the same effects in TBI as non-TBI populations (McAllister *et al.*, 2011a), or whether TBI patients represent a unique subgroup with regard to conventional pharmacotherapies. In addition, alterations in monoaminergic signaling are varied during acute versus chronic recovery, and thus, how pharmacotherapies affect executive function at different time points is also important for a full understanding of pharmacotherapy following TBI.

Dopaminergic therapies

DA pharmacotherapies, such as amantadine hydrochloride, bromocriptine, D-amphetamine, and methylphenidate (DA agonists), are reported to have cognitive-enhancing (i.e. attention and working memory) effects in TBI patients during chronic recovery (see Bales *et al.*, 2009; Liepert, 2016 for reviews). Therefore, these and other pharmacotherapies (apiprazole, L-deprenyl, and methamphetamine) aimed at increasing DA signaling have been tested following experimental TBI. Several of these drugs show promise in reducing chronic signaling deficits following injury, such as increasing DA levels in the striatum and substantia nigra while also reducing neuronal death (Zhu *et al.*, 2000; Wagner *et al.*, 2008, 2009; Rau *et al.*, 2012; Huang *et al.*, 2014a, 2014b; Wang *et al.*, 2014; Tan *et al.*, 2015; Phelps *et al.*, 2017). In turn, performance is improved acutely for TBI animals on traditional tasks for assessing cognitive deficits, such as the MWM and novel-object recognition tasks, following administration of such therapeutic agents (Zhu *et al.*, 2000; Wagner *et al.*, 2008, 2009; Rau *et al.*, 2012; Huang *et al.*, 2014a, 2014b; Wang *et al.*, 2014; Tan *et al.*, 2015; Leary *et al.*, 2017; Phelps *et al.*, 2017). At the same time, pharmacotherapies that reduce DA signaling, such as haloperidol and resperidone, exacerbate acute MWM deficits, in both TBI and non-TBI animals (Wilson and Hamm, 2002; Kline *et al.*, 2007, 2008; Hoffman *et al.*, 2008), giving support for a significant contribution of reduced DA signaling in cognitive dysfunction.

Most recently, work has focused on investigating how DA therapies may affect higher-order executive function using tasks such as those discussed earlier in this review. Similar to memory-related assessments, drugs that increase DA signaling (amantadine and D-amphetamine) reduce chronic deficits in motor impulsivity in TBI animals on the 5CSRTT (Vonder Haar *et al.*, 2016), although effects of amantadine were accompanied by potential psychomotor slowing or motivational issues across groups. Perhaps most interesting was the fact that D-amphetamine selectively reduced impulsivity, but only in severely-injured rats; an effect that we have observed again recently (Fig. 2). This provides strong evidence that those with TBI may not respond to pharmacologic treatments in the same manner as those without such injury.

Indeed, human studies using functional MRI give evidence for less activation in various brain regions for TBI patients following acute dosing of bromocriptine when compared with healthy control participants (McAllister *et al.*, 2011a). Thus, TBI patients may not respond in the same way as non-TBI patients to pharmacotherapy, both neurochemically or behaviorally. In addition, DA agonistic therapies may not have the same effect on all types of executive function, as evidenced by methylphenidate aiding in chronic recovery of working memory function in TBI patients (Liepert, 2016). These factors may become

even more confounding when considering that mixed in with positive findings are studies claiming efficacy without achieving statistical significance (Kim *et al.*, 2006), evidence for similar rates of recovery under placebo or nondrug conditions (Pavlovskaya *et al.*, 2007), and differential drug effects between TBI and non-TBI animals (Vonder Haar *et al.*, 2016; Shaver TK, Ozga JE, Zhu B, Anderson KG, Martens KM, Vonder Haar C, unpublished data), null drug effects (Wilson and Hamm, 2002; Ripley *et al.*, 2014), as well as the need to consider natural aging- or sex-related changes in monoamine metabolism and drug responsiveness. When combined with studies that have identified altered DA pharmacology in TBI patients, it is clear that additional research is needed using animal models to determine whether current DAergics may be effective in treating complex cognitive dysfunction such as decision-making.

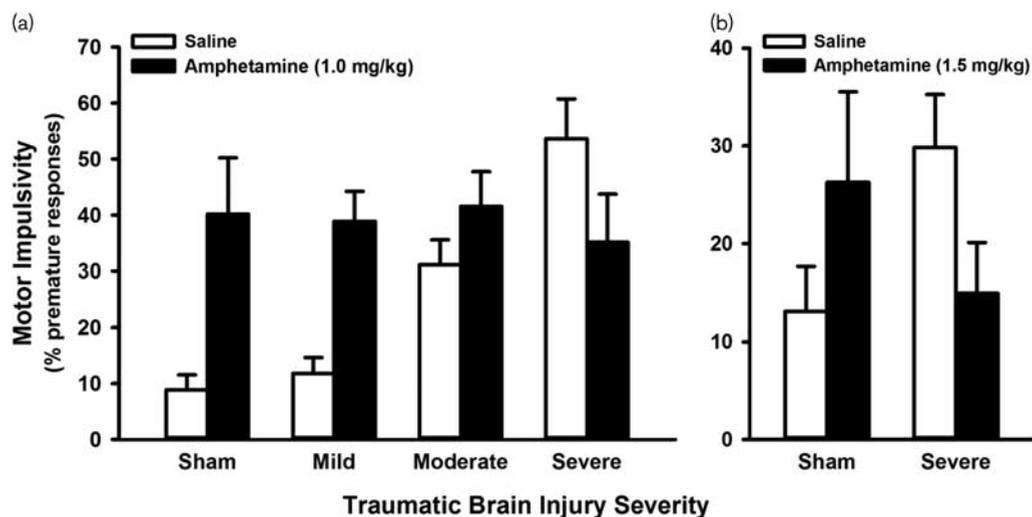
Noradrenergic therapies

Although NE signaling deficits have been observed following TBI, evaluations of cognitive performance following administration of pharmacotherapies targeting the NE system are relatively sparse and conflicting. Some have suggested that too much NE signaling is a cause for concern in the acute recovery phase of TBI patients, with $\alpha 1$ receptor antagonists (e.g. prazosin) improving MWM performance in rats with experimental TBI at 14 days postinjury (Kobori *et al.*, 2011). However, others have suggested that too little NE may be the issue. In clinical assessments, guanfacine, an $\alpha 2A$ receptor agonist, improved working memory deficits following mild TBI at one month postinjury (McAllister *et al.*, 2011b), although preclinical assessments have reported no effect of guanfacine on MWM performance at 14 days postinjury (Kobori *et al.*, 2011). There is also mixed evidence following administration of atomoxetine, a NE reuptake inhibitor, in which clinical assessments suggest no effect on attentional deficits at one year or more postinjury (Ripley *et al.*, 2014), while preclinical work suggests improved working memory and response inhibition following atomoxetine treatment during both, acute and chronic recovery of TBI animals (i.e. 14 days and 12 weeks; Reid and Hamm, 2008; Vonder Haar *et al.*, 2016). In addition to the sparse, and sometimes conflicting, evidence, atomoxetine has a low binding affinity for the DA transporter (Bymaster *et al.*, 2002); thus, its effects on executive function may not be due to its action on NE per se but rather by its effects on DA.

Serotonergic therapies

The majority of work with 5-HT agents has focused on improving disruptions in mood, such as depression and anxiety. However, executive function deficits are prevalent in patients with depressive disorders (Alves *et al.*, 2014), and 5-HT agents may simultaneously improve executive function and mood (Gualtieri *et al.*, 2006). Few studies have investigated how 5-HT pharmacotherapies

Fig. 2



Differential effects of amphetamine challenge on motor impulsivity after traumatic brain injury (TBI). (a) High-dose amphetamine significantly reduced impulsivity on the five-choice serial reaction time task, but only for animals with a severe focal TBI ($P=0.002$) (adapted with permission from Vonder Haar *et al.*, 2016, copyright 2016 American Chemical Society). (b); High-dose amphetamine significantly reduced impulsivity on the rodent gambling task in animals with a severe focal TBI ($P=0.011$) (Ozga JE, O' Hearn CM, Shaver TK, Lake AD, Vonder Haar C, unpublished data). Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

may impact cognitive function directly either following clinical or experimental TBI. Similar to DA agonists, various 5-HT agonists (N-n-propyl-3-ethoxyquinoxaline-2-carboxamide, 8-OH-DPAT, repinotan, buspirone, and fluoxetine) produce increases in basal 5-HT levels as well as reduced neuronal cell loss and contusion volume following experimental TBI, corresponding with a reduction in acute and chronic anxiety-like (elevated plus maze, marble burying, and open field) and depressive-like (sucrose preference) behaviors (Kline *et al.*, 2001, 2012; Cheng *et al.*, 2007, 2008; Olsen *et al.*, 2012; Monaco *et al.*, 2014; Bhatt *et al.*, 2017).

In addition to emotion-related behaviors, a variety of 5-HT_{1A} receptor agonists improve acute and chronic MWM performance in TBI animals, suggesting that deficits in 5-HT signaling post-TBI contribute to cognitive deficits (Kline *et al.*, 2001, 2012; Cheng *et al.*, 2007, 2008; Olsen *et al.*, 2012; Monaco *et al.*, 2014; Bhatt *et al.*, 2017). However, others have reported no effect on acute MWM performance in TBI animals following systemic fluoxetine administration, an SSRI that is prescribed commonly for depression and anxiety (Wilson and Hamm, 2002). Given the limited evidence for how 5-HT-enhancing drugs may affect cognitive function, in conjunction with a lack of work using higher-order executive function tasks, further work is needed to evaluate how common 5-HT pharmacotherapies (SSRIs, in particular) affect working memory, decision-making, and impulsivity.

Efficacy of pharmacotherapies

Reports showing mixed efficacy of pharmacotherapies in TBI populations (both human and nonhuman animal) are likely due to several factors, including timing of treatment during recovery. As an example, NE antagonists have shown promise in reducing hippocampally dependent cognitive deficits, while agonists have been shown to produce no improvements during acute recovery (Kobori *et al.*, 2011). In contrast, during chronic recovery, NE agonists reduce cognitive function deficits (McAllister *et al.*, 2011b; Vonder Haar *et al.*, 2016), although the magnitude of effect is small. In addition to the timing of drug administration, alterations in monoaminergic pharmacodynamics may lead to differences in dosing guidelines needed to produce significant effects on executive function for TBI populations. Indeed, some have suggested that increased doses of DAergic therapies are needed to affect executive function following TBI in rats (Bondi *et al.*, 2014; Vonder Haar *et al.*, 2016; Leary *et al.*, 2017; Shaver TK, Ozga JE, Zhu B, Anderson KG, Martens KM, Vonder Haar C, unpublished data), which is reflective of altered pharmacokinetics or pharmacodynamics following injury. Thus, the efficacy of traditional pharmacotherapies for reducing executive function deficits likely depends upon when during recovery and in what doses drugs are administered. Together, changes in pharmacodynamics and pharmacokinetics following TBI pose challenges to clinicians and researchers, and may explain the high frequency of treatment failures that exist in the field.

Deficits in executive function and monoaminergic signaling may also help to explain the heightened prevalence of alcohol, cocaine, opioid, marijuana, and amphetamine use disorders in TBI populations compared with those without such injuries (Walker *et al.*, 2003; O'Phelan *et al.*, 2008; Golub and Bennett, 2013; Singh *et al.*, 2014; Ma *et al.*, 2015; Ramesh *et al.*, 2015). Given the large-scale alterations to monoaminergic systems following TBI, increased drug-seeking behaviors, particularly of psychostimulants, may represent an effort to 'self-medicate'. While this simple pharmacological argument is attractive, it is unlikely to account for the entirety of substance abuse after TBI. In particular, research has showed that impulsivity is intimately linked to the development of substance abuse (Perry *et al.*, 2005; Dalley *et al.*, 2007), and thus may be a mediating factor. Further, deficits in behavioral flexibility are likely to promote continued drug dependence, even in the face of detrimental outcomes (Istin *et al.*, 2017). Given that TBI patients demonstrate deficits in all of these domains, these are likely contributors to initiation, exacerbation, and maintenance of substance abuse following injury. However, data on increased incidence after TBI are a classic case of correlation (i.e. does substance abuse cause TBI or does TBI cause substance abuse?), with a lack of concrete prospective studies in humans. Importantly, a number of brain injuries occur while under the influence of various substances, particularly alcohol, with some studies ranging as high as 47% (Andelic *et al.*, 2010). Despite this figure, some studies report no relationship between previous substance abuse and brain trauma (Lange *et al.*, 2014) while others identify relationships only within injury subgroups (Andelic *et al.*, 2010), and indeed, alcohol intoxication at the time of injury is associated with reduced injury severity in humans and animals (Andelic *et al.*, 2010; Goodman *et al.*, 2013; Kanbak *et al.*, 2013; Raj *et al.*, 2015).

The argument for TBI as causal to addiction is much stronger when considering the animal evidence. To date, few studies have examined voluntary drug self-administration after TBI. However, these studies largely converge on the conclusion that animals with injury self-administer more drug, or escalate their intake more quickly, across both alcohol and cocaine (Lim *et al.*, 2015; Mayeux *et al.*, 2015; Weil *et al.*, 2016; Vonder Haar *et al.*, 2018), although such self-administration may depend upon injury type, severity, and substance, as one group found no changes in cocaine intake after blast injury (Muelbl *et al.*, 2018), while others have seen increased alcohol intake after blast (Lim *et al.*, 2015), and increased cocaine after mild or severe focal injury (Vonder Haar *et al.*, 2018). Moreover, studies have found interesting subgroup differences within TBI animals with regard to acquisition of drug self-administration (Lim *et al.*, 2015; Vonder Haar *et al.*, 2018), in which some TBI rats show faster acquisition of drug self-administration than others,

suggesting potential biological or behavioral mediators of resilience that warrant investigation. In particular, both DA-related markers (e.g. DA-regulated and cAMP-regulated neuronal phosphoprotein) and multiple inflammatory markers (e.g. cytokines, glial activation) have been affiliated with increased intake (Vonder Haar *et al.*, 2018) or greater sensitivity or preference for drugs of abuse (Lowing *et al.*, 2014; Merkel *et al.*, 2017a, 2017b). As research moves forward, a potential propensity to substance abuse should be a prime consideration when evaluating therapeutics, especially when considering implementation in clinical populations.

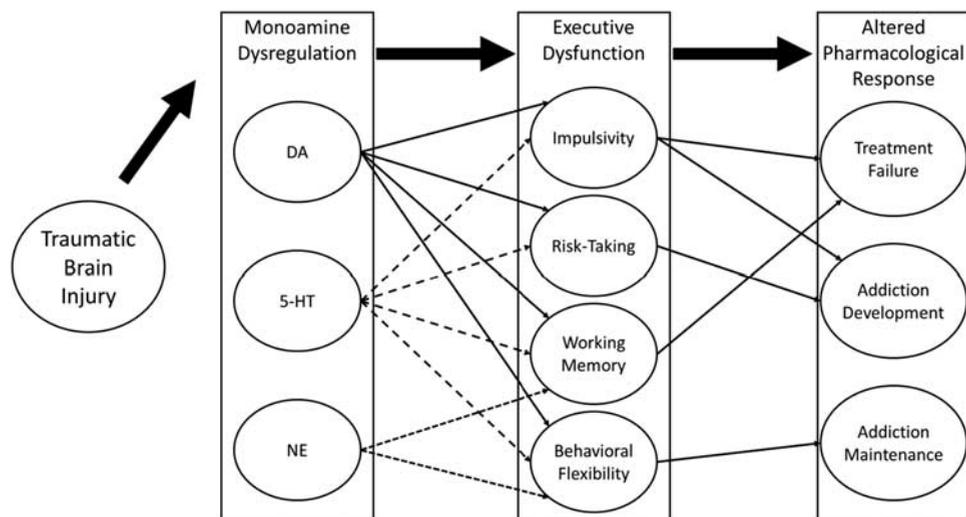
Conclusion

In this review, we have identified major changes in executive function following TBI, namely impulsivity, behavioral flexibility, and working memory (Fig. 3). These deficits are present in both human patients, and in animal models of brain injury. While the clinical effects are well-established, the animal literature lags behind. Much of the focus of the experimental TBI field has been on relatively simple assessments of learning and memory, such as the MWM, to the neglect of more complex cognitive function. Further studies are needed to characterize executive function deficits across the many existing injury models in order to generate a more clinically-relevant behavioral phenotype which may then be used to effectively screen treatment options.

Moreover, these deficits in executive function may be driven by the major alterations in monoaminergic neurotransmission such as dopamine, norepinephrine, and serotonin (Fig. 3). However, the field is limited in its consensus on the exact nature of these changes, and there appear to be important factors related to injury type and severity, as well as time from injury. More research is needed at both the clinical and preclinical level to resolve major conflicts (e.g. up-regulation and down-regulation of DA receptors; increased NE despite cognitive impairments that may be alleviated by NE agonists) so that we may better understand the time course of these changes and target therapeutics appropriately.

Finally, these changes in both executive function and monoaminergic status may in turn complicate developing, administering, and achieving efficacious results not only with novel compounds, but also with traditional treatments for psychiatric-like symptoms experienced by these individuals. In particular, reduced sensitivity to contingencies surrounding the individual may limit the efficacy of pharmacotherapies or require an integrated approach with cognitive-behavioral therapies. In addition, altered doses, or less conventional drugs may be required to treat behavioral symptoms, accounting for monoaminergic alterations. Finally, the abuse potential for drugs, particularly psychostimulants which may remediate impulse control issues, needs to be carefully

Fig. 3



Schematic representation of dysfunction after traumatic brain injury (TBI). Monoamine disruptions are common starting mere hours after injury, with some continuing for months or longer. Monoamines influence various types of executive function, and this dysregulation after TBI may account for some of the common behavioral disturbances that are observed. Finally, both altered monoamines and functional impairments may converge to explain several post-TBI complications, including numerous therapeutic failures, and increased propensity for substance abuse and dependence. Notably, the intertwined nature of altered functional and structural changes make it difficult to fully parse the separate factors that challenge clinical treatment of TBI. DA, dopamine; 5-HT, 5-hydroxytryptamine; NE, norepinephrine.

considered given links between substance abuse and TBI populations.

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Conflicts of interest

There are no conflicts of interest.

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