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Research report

Long-term deficits in risky decision-making after traumatic brain injury on a rat analog of the Iowa gambling task

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HIGHLIGHTS

- TBI chronically decreases optimal decision-making, independent of learning history.
- Motor impulsivity increases across time for 10 weeks post-injury.
- Amphetamine did not strongly affect acquisition TBI rats' decision-making.
- Amphetamine reduced motor impulsivity in TBI rats.

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ABSTRACT

Traumatic brain injury (TBI) affects 2.8 million people annually in the United States, with significant populations suffering from ongoing cognitive dysfunction. Impairments in decision-making can have major implications for patients and their caregivers, often enduring for years to decades, yet are rarely explored in experimental TBI. In the current study, the Rodent Gambling Task (RGT), an Iowa Gambling Task analog, was used to assess risk-based decision-making and motor impulsivity after TBI. During testing, rats chose between options associated with different probabilities of reinforcement (sucrose) or punishment (timeout). To determine effects of TBI on learned behaviors versus the learning process, rats were trained either before, or after, a bilateral frontal controlled cortical impact TBI, and then assessed for 12 weeks. To evaluate the degree to which monoamine systems, such as dopamine, were affected by TBI, rats were given an amphetamine challenge, and behavior recorded. Injury immediately and chronically decreased optimal decision-making, and biased rats towards both riskier, and safer (but suboptimal) choices, regardless of prior learning history. TBI also increased motor impulsivity across time, reflecting ongoing neural changes. Despite these similarities in trained and acquisition rats, those that learned the task after injury demonstrated reduced effects of amphetamine on optimal decision-making, suggesting a lesser role of monoamines in post-injury learning. Amphetamine also dose-dependently reduced motor impulsivity in injured rats. This study opens up the investigation of psychiatric-like dysfunction in animal models of TBI and tasks such as the RGT will be useful in identifying therapeutics for the chronic post-injury period.

1. Introduction

Traumatic brain injuries (TBIs) are a serious health problem in the United States with over 2.8 million resulting in hospital visits every year (Center for Disease Control, 2017). Brain injury is a leading contributor to life-long disabilities, and increases the risk of neurodegenerative disease (Plassman et al., 2000; Thurman et al., 1999; Zaloshnja et al., 2008). Despite the significance of this problem, there are no therapies approved specifically for the treatment of chronic TBI. Some of the most long-term, difficult to manage, and pervasive deficits associated with TBI are impairments revolving around cognition and executive function, including various memory deficits, poor impulse control, and reduced decision-making capacity. Often, impairments can result in symptoms resembling those found in psychiatric disorders such as gambling disorder or bipolar disorder (Kräplin et al., 2014; Zgaljardic et al., 2015). In particular, impairments in decision-making and impulsivity, are likely to contribute to poor quality of life, and may result in significant issues for both patients with TBI, and their

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caregivers (Marsh et al., 1998). While impulsive deficits are relatively common in the acute phase (e.g. impulsive aggression, 35% incidence; Dyer et al., 2006), they also extend into the chronic post-injury phase, and even occur in cases of milder brain injury (Bjork et al., 2016; Goswami et al., 2016). These impulsive deficits may also interact with decision-making capacity in TBI survivors.

Decision-making is not a unitary construct, and constitutes many different dimensions. Ultimately, selection of options comes down to the evaluation of various costs and benefits associated with each choice. While this is decidedly general, there are several types of decision-making that are substantially altered in both psychiatric and TBI populations. In particular, impulsive decision-making, in which the cost is often a time delay, and the benefit is a larger reinforcer (e.g., money, food), is frequently impaired after brain injury (Dixon et al., 2005; McHugh and Wood, 2008). Another form, risk-based decision-making, in which choices are made between different probabilistic outcomes (e.g., win or lose money), is also notable for its involvement in TBI-related deficits (Cotrena et al., 2014; Levine et al., 2005; Newcombe et al., 2011). Thus, the consequences of TBI strongly resemble psychiatric disease with regard to decision-making tendencies and may have common neural mechanisms. In particular, dopaminergic dysfunction has been identified following experimental and clinical TBI (Wagner et al., 2005; Wagner et al., 2014), and the monoamines, in general, are strongly involved in a number of decision-making processes, providing a potential mechanistic link (Ozga et al., 2018).

To enable causal study of psychiatric deficits after TBI and aid in the development of treatments, animal models are necessary. The experimental brain injury field has developed a number of models relevant for replicating the human sequelae of TBI in rodents and other species (O'Connor et al., 2011). However, the vast majority of studies in experimental TBI have largely focused on cognitive outcomes that are less relevant for chronic psychiatric-related dysfunction (e.g., spatial learning). Recently, our group has published studies demonstrating deficits in impulse control, attention, and impulsive decision-making lasting up to four months with continuous testing, which resemble reports in human patients (Vonder Haar et al., 2016; Vonder Haar et al., 2017). However, no animal studies have evaluated whether rodent models of TBI can successfully replicate the deficits in risky decisions that occur in human brain injury populations.

A common paradigm for studying risky decisions in patients is the Iowa Gambling Task (IGT) (Bechara et al., 1994). In this task, participants choose a card from four different decks, and either gain or lose money. Two choices are associated with large wins, but also significant losses ("risky"), while the other yield small gains, but relatively small losses ("safe"/optimal). To maximize monetary gain, participants must learn these contingencies. In psychiatric populations (e.g., substance dependence, gambling disorder), patients display increased preference for risky options, at the cost of maximizing return (Bechara, 2003; Brevers et al., 2013), and similar effects are observed after TBI (Cotrena et al., 2014; Levine et al., 2005; Sigurdardottir et al., 2010). To investigate these phenomena in animals, many different procedures are used (for reviews, see Bailey et al., 2016; de Visser et al., 2011b). One model that is particularly attractive due to its translational validity is the Rodent Gambling Task (RGT). The RGT is a relatively direct analog of the IGT, and presents rats with two low-risk options, and two high-risk options. However, it also layers on an aspect of impulsive action (requires withholding a response over a delay) that is not included in the IGT to enable concurrent investigations into motor impulsivity (Zeeb et al., 2009). A previous *meta*-analysis of over 200 animals demonstrated a significant correlation between impulsivity and poor decision-making in rats on this task (Barrus et al., 2015). Given that motor impulsivity is substantially increased after TBI in rats (Vonder Haar et al., 2016), it is likely that risky decisions would be affected in a similar fashion. In the current study, we evaluated effects of a bilateral frontal controlled cortical impact TBI on risk-based decision-making and motor impulsivity in the RGT, in the chronic post-injury period and assessed the role of monoaminergic systems by administering an amphetamine challenge.

2. Results

2.1. Recovery from surgery

Recovery was tracked with daily detailed post-surgical monitoring until rats were deemed "recovered" (stable weight, no overt motoric deficits or agitation to handling; minimum of three days monitoring). All sham rats (including craniotomy and intact) were considered recovered within one day. The weight of all sham rats only dropped to approximately 98% of pre-surgery baseline before recovering to 100% or more by the second day. TBI rats took between 1 and 5 days (mean: 1.28) to recover normal motor function, and between 1 and 3 days (mean: 1.38) to react normally to gentle handling. The weight of TBI rats dropped to 91% of baseline, and remained slightly below (93–97%) throughout the duration of testing.

2.2. Effects of TBI on Rodent gambling task

2.2.1. Choice

In the RGT, optimal reinforcement rates may be obtained by choices preferring the 2-pellet option, and preference for the 3- and 4-pellet options are considered "risky" (see Section 4 & Fig. 1). To determine if brain injury altered choice behavior, a linear mixed-effects regression with baseline choice as a covariate (Pct Choice ~ Group*Choice Option*Week + Baseline Choice; see Supplemental Table S1 for full statistics) was carried out for the Trained rats. The three-way interaction was significant ($p < 0.001$). The regression model was then examined for each choice option. For the all choice options, there was a significant effect of TBI (p's < 0.001), and a significant TBI × week interaction for the 2-pellet and 4-pellet options (p's < 0.009), such that for the 2-pellet option, the Sham group very slightly declined, while the TBI group remained at a low level of choice relative to baseline, while TBI animals increased choice of the 4-pellet option across time. The effects were large and persistent across the 12-week post-injury period (see Fig. 2).

For rats tested in acquisition, effects of TBI were assessed in a linear mixed-effects regression (Pct Choice ~ Group*Choice Option*Week; see Table S1 for full statistics), and the three-way interaction was significant ($p = 0.012$). For these rats, there were significant effects of TBI across all choice options (p's < 0.001), and a significant TBI x week interaction for the 3-pellet option ($p = 0.002$), such that the TBI group increased preference over time, while sham animals declined. All of these effects were similar in magnitude to those trained prior to injury, and choice profiles at 12 weeks ultimately resembled those trained before surgery (see Fig. 2).

2.2.2. Other variables

The RGT may also be used to measure several other variables of interest to gain insight into a host of other behavioral processes (see Section 4): premature responses (motor impulsivity), omitted responses (motivation), pellets earned (overall efficiency), response latency (choice-specific slowing), and reinforcer collection latency (motor/motivational effects). A linear mixed-effects regression (Outcome ~ Group*Week [+ Baseline in Trained groups]) was performed for all other behavioral variables. For premature responses in the Trained groups, there was a significant TBI x week interaction ($p < 0.001$), such that TBI rats increased their premature responding across several weeks of testing. A similar interaction effect ($p = 0.024$) was also observed for the Acquisition rats with regard to impulsive responding. On omitted responses, Trained TBI rats started off quite high, but quickly reduced to sham levels, as indicated by a significant TBI x week interaction ($p < 0.001$). There was also a significant TBI × week interaction ($p = 0.044$) for the Acquisition rats, but this