JOURNAL OF NEUROTRAUMA 26:1077–1082 (July 2009)

DOI: 10.1089/neu.2008.0849

Original Article

Does Traumatic Brain Injury Increase Risk for Substance Abuse?

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Abstract

Wars in Afghanistan and Iraq have resulted in thousands of military personnel suffering traumatic brain injury (TBI), including closed-head injuries. Of interest is whether these individuals and other TBI survivors are at increased risk for substance use disorder (SUD). While it has been well established that drug or alcohol intoxication itself increases probability of suffering a TBI in accidents or acts of violence, little is known about whether the brain insult itself increases the likelihood that a previously non-drug-abusing individual would develop SUD. Might TBI survivors be unusually vulnerable to addiction to opiate analgesics compared to other pain patients? Similarly, it is not known if TBI increases the likelihood of relapse among persons with SUD in remission. We highlight challenges in answering these questions, and review neurochemical and behavioral evidence that supports a causal relationship between TBI and SUD. In this review, we conclude that little is known regarding the directionality of TBI increasing drug abuse, and that collaborative research in this area is critically needed.

Key words: addiction; closed-head injury; cognition; drug abuse; drug dependence; traumatic brain injury

Introduction

According to the National Center for Injury Prevention and Control (of the Centers for Disease Control and Prevention), 1.4 million Americans per year sustain a traumatic brain injury (TBI), resulting in 235,000 hospitalizations *(www.cdc.gov/ncipc/tbi/TBI.htm)*. The number of TBI survivors in the United States has been dramatically increased by veterans returning from the wars in Iraq and Afghanistan. According to statistics from the Department of Veterans Affairs (VA), as of 2008 about 1800 U.S. troops have suffered penetrating head wounds during tours in Iraq or Afghanistan, and as many as 30% of troops who engaged in combat having suffered at least a mild TBI as a result of concussive blast effects from improvised explosive devices (Tanielian et al. 2008).

It has been well established that TBI can cause chronic headaches and other pain (Nampiaparampil, 2008), cognitive impairments (McDonald et al., 2002; Salmond et al., 2005), and increased risk of affective disorder (Hibbard et al., 1998; Rogers and Read, 2007) and Alzheimer's disease (Van Den Heuvel et al., 2007). Virtually nothing is known, however, about whether TBI itself increases the risk of substance use disorder (SUD), especially in persons with no psychological of psychiatric risk factors for SUD at the time of injury. The connection between SUD and TBI is almost entirely in the directionality of the drug or alcohol use or abuse *causing* TBI, chiefly in motor vehicle accidents, falls, or involvement in acts of violence (Taylor et al., 2003). This literature has established that SUD, and especially drug or alcohol intoxication itself, increases the risk of suffering a TBI (Cherpitel, 2007; Taylor et al., 2003), impairs recovery from TBI (Corrigan, 1995; Jorge et al., 2005), and may increase risk of drug abuse in psychologically vulnerable individuals following TBI (Horner et al., 2005).

Drug and Alcohol Use as a Risk Factor for TBI or Impaired TBI Recovery

In epidemiological surveys, emergency room patients have reported elevated incidence of recent drug and alcohol use (Cherpitel and Ye, 2008a), and have also shown high incidence of actual presence of alcohol or other drugs at the time of injury (Cherpitel and Ye, 2008b; Vitale and van de Mheen, 2006). Moreover, drug or alcohol abuse can exacerbate the effects of TBI. Jorge et al. (2005) reported that alcohol abuse or dependence following TBI impaired vocational outcome, possibly by exacerbating the neurological sequelae of the injury itself. Similarly, Corrigan et al. (1995) reported that substance abuse following TBI portended a poorer trajectory of rehabilitation following injury. However, because premorbid drug or alcohol abuse was frequently characteristic of persons who abused substances after the injury, poorer clinical outcomes could not be confidently attributed to post-injury

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substance use (as opposed to pre-morbid substance use or other collateral psychological characteristics). Similarly, in a sample of over 1600 TBI subjects, Horner et al. (2005) reported that a pre-existing substance abuse diagnosis at time of injury was predictive of heavy drinking following the injury. The effects of alcohol or illicit drug abuse on worsening TBI recovery may not extend to nicotine addiction, however, inasmuch as nicotine administration reduced the neurocognitive deficits in rodents following controlled cortical impacts (Verbois et al., 2003).

Challenges to Establishing TBI–Drug Abuse Causality in Clinical Surveys

There are several methodological barriers to establishing whether TBI alone increases risk of SUD in individuals who are otherwise psychologically normal at the time of the injury. First, TBI is a heterogeneous diagnosis that falls on a three-point spectrum, based on subjective impressions of severity. Reports frequently consolidate multiple sources of injury (e.g., focal versus global) into a single category for analysis. Also, closed head injury (concussive) TBI often reveals no morphological signature evident in clinical scans. In some reports, TBI has been simply inferred from self-report of having lost consciousness. Second, because pre-injury histories of substance problems have been suspected in as many as two-thirds of rehabilitation patients (Corrigan, 1995), for most individuals neurocognitive and behavioral symptomatology post-injury cannot be specifically attributed to either the TBI, or to pre-injury substance abuse or abuse risk.

Third, in prospective clinical investigations, the relationships between TBI, drug abuse, and neurocognitive outcomes are poorly characterized, because (a) studies of TBI effects on cognition almost always exclude applicants with significant histories of drug use, and (b) studies of cognition in drug abusers almost always exclude applicants with histories of head injury. Similarly, despite considerable comorbidity between affective disorders and TBI, the clinical care settings differ between brain rehabilitation and psychiatry, and can depend on the specific symptomatology cited by the patient.

Fourth, organic brain syndromes resulting from TBI that might predispose the subject to drug seeking are thwarted (and thus masked) by either the intense clinical monitoring of patients during the course of rehabilitative care, or by severe physical disability itself (Taylor et al. 2003). Studies with a shorter span of follow-up may therefore miss the acquisition of a trait propensity for substance abuse (Bombardier et al., 2003). Critically, other reports show an initial "honeymoon" from SUD symptoms, which transition to increased risk at longer follow-up (Ponsford et al., 2007). Finally, with regard to study of veterans, despite how TBI among returning troops is widespread (Tanielian et al., 2008), TBI is heavily intertwined with post-traumatic stress disorder (PTSD) from events related to the injury, and many veterans with PTSD symptoms do not report them over concerns about professional advancement, thus limiting investigation of milder military TBI cases (Tanielian et al., 2008).

Epidemiological Evidence that TBI Alone Increases the Risk of Drug or Alcohol Abuse

Despite the limitations described above, there is some limited evidence that TBI can increase drug or alcohol use in persons with no histories of significant substance use prior to the injury. In a sample of 100 TBI subjects, Hibbard et al. (1998) reported that the subset of subjects with no Axis I disorder prior to injury showed increased rates of SUD and depression relative to community controls. Similarly, a survey of health-maintenance organization enrollees found that TBI survivors with no evidence of mental illness or substance abuse-related service utilization in the year prior to injury had a 4.5 odds ratio of substance abuse within the first year post-injury, dropping to 1.4 at 25–36 months post-injury (Fann et al., 2004). Rates of treatment-seeking for other psychiatric disorders, however, were much higher than for substance abuse among these enrollees. The 386 respondents who self-reported a severe TBI in the New Haven NIMH Epidemiologic Catchment Area Study reported increased rates of drug abuse or dependence compared with community controls even after controlling for alcohol use prior to injury (Silver et al., 2001).

In a military sample, of the roughly two million service personnel discharged from American armed forces in 1992, roughly two thousand had been diagnosed with a TBI. Those with a mild TBI were 2.6 times more likely to be discharged for alcoholism or drug use, while those with a moderate TBI were 5.4 times more likely (Ommaya et al., 1996). Severe TBI subjects, however, did not have increased incidence for a substance-abuse-related discharge. For these subjects, their potential for drug-seeking was likely unrealized due to disability. The incidence of onset of substance abuse after discharge was not assessed.

We caution here that some portion of increased rates of drug or alcohol use in TBI survivors compared to community controls in cross-sectional comparisons may be a coping response to the psychosocial stressors of disability or pain (Nampiaparampil. 2008) and not a consequence of proximal neurobiological sequelae of *brain injury* itself. Critically, in another study, post-injury drug abuse rates among TBI survivors did not differ from patients treated for other bodily traumas (Kolakowsky-Hayner et al., 2002). Moreover, in another survey, the rate of post-injury alcoholism symptomatology is also higher than community samples in patients with spinal cord injuries (Tate et al., 2004), where drinking was greatest in patients who reported the most pain. Inclusion of additional patient comparison groups comprised of non-TBI pain patients would clarify findings in future research.

TBI Could Increase Risk for SUD by Disrupting Incentive-Motivation Neurocircuitry

It is well-established that cues for (Schultz, 2007) and delivery of (Di Chiara and Bassareo, 2007) both drugs and natural rewards recruits mesolimbic dopaminergic (DA) neurocircuitry. There is some emerging evidence that TBI disrupts DA pathways. Controlled impacts unilaterally administered to the parietal cortex of rats resulted in blunted striatal DA release after electrical stimulation of medial forebrain bundle, as well as decreased DA transporter (DAT) expression in ipsilateral striatum and blunted ipsilateral DA clearance brain-wide (Wagner et al., 2005). Similarly, human TBI survivors show reduced DAT in single photon emission computed tomography (SPECT) study (Donnemiller et al., 2000). Rats with a TBI showed an increase in tyrosine hydroxylase (the rate-limiting step in catecholamine synthe-

sis), in the nigrostriatal system compared to control rats (Yan et al., 2007). This TH upregulation has been interpreted as a compensatory response to decreased DA tone (Yan et al., 2007).

While there are several studies on the neurochemical and behavioral sequelae of controlled cortical injuries in rodents, we can find no reports that examine drug-related behavior subsequent to experimentally applied injury, such as conditioned place preference to drug-associated locations, or rates of drug self-administration under different schedules. We attribute this to a lack of transdisciplinary research approaches or investigator teams. Existing behavioral studies to date are conceptually tangential at best. One study reported that rats administered a controlled TBI showed a deficit in novelty exploration (Wagner et al., 2007). This conforms to anecdotal clinical reports of decrements in general motivation in many TBI patients, and does not suggest that TBI patients who are drug naïve would seek drugs for the sake of novelty. Similarly, another study found that TBI in mice results in memory and passive avoidance deficits, as well as a depressed-like state in forced swimming (Milman et al., 2005).

Other evidence of TBI-induced disruption of incentive-motivation neurocircuitry may be found if human TBI subjects also show blunted cortical signatures of reward-prediction-errors akin to substance abusers. The temporal difference reinforcement learning (TDRL) theory (O'Doherty et al., 2003) posits that mesolimbic neurocircuitry fosters associations between environmental cues and rewards by encoding violations of expected reward or expected nonreward, and this is thought to be dependent on phasic DA activity (Schultz, 2007). A related electrocortical signature of non-delivery of expected reward has been detected as "error-related negativity" (ERN) (Taylor et al., 2007), where ERN in controls is sensitive to parametric manipulation of probability of reward delivery, and has thus been attributed to striatal DA activity (Holroyd and Coles, 2002). Interestingly, TBI subjects showed a deviant ERN response to violations of reward expectancy compared to controls (Larson et al., 2007). Controls showed greater ERN to non-reward outcomes in a high reward-probability context, but did not differentiate between outcomes in a low-reward probability context. In contrast, TBI subjects showed no differentiation between reward and non-reward trials in the high reward-probability context, but significantly larger ERN following reward stimulus presentation in the low reward-probability context. Critically, blunted ERN has also been reported in cocaine-dependent patients (Franken et al., 2007), and also reflects findings of blunted cortical error processing in substance abusers in fMRI studies (Kaufman et al., 2003) and blunted error-induced behavior correction in behavioral (Hester et al., 2007) studies.

Finally, pharmacological intervention studies provide another hint of a dopaminergic component to TBI, in that administration of (dopaminergic) stimulants improves cognition in TBI patients (Arciniegas and Silver, 2006; Tenovuo, 2006). Therefore, just as schizophrenics are thought to smoke cigarettes to normalize neurotransmitter-mediated deficits in cognition, it is possible that exogenous enhancement of DA transmission by DAT blockers like cocaine or other stimulants might normalize this circuitry, providing a possible abuse risk with chronic administration. However, better evidence of DA disruption in TBI would be if stimulants were to improve executive cognitive function (ECF) in TBI patients to a greater extent than improvements among baseline-performance-matched non-TBI subjects. This is an interesting avenue for future research.

TBI Could Increase Risk for SUD by Causing Persistent Executive Cognitive Deficits

TBI, especially to the orbitofrontal cortex (OFC), can cause an organic personality disorder (OPD) conducive to substance abuse. Critically, the OFC is especially vulnerable to TBI—both to direct blows to the head as well as to exposure to percussive shock waves—because movement of the brain within the skull can lead to abrasions of the OFC along the sharp ridges of the orbital surface of the skull. Problematic in TBI research is that OFC abrasions are poorly detected—for two reasons: (1) they may not be morphologically evident, even with MRI, and (2) they may not be behaviorally evident in that OFC abrasions typically do not lead to gross clinical signs of TBI (e.g., speech impairments, orientation to time and place or general memory) or to impairments on classical neuropsychological tests. Franulic et al. (2000) reported that among sequentially admitted TBI patients with no significant histories of substance use, roughly one-third met ICD-10 criteria for an acquired OPD based on interviews with family members. Compared to TBI patients without OPD, the OPD patients had a greater incidence of closed (versus open) head injury, as well as increased mood lability and hostility compared to patients with no OPD diagnosis. This was despite minimal deficits in numerous neuropsychiatric tests and fewer days of hospitalization post-injury.

The link between behavioral and social impairment to OFC specifically has been established in studies of patients with known OFC injury due to cerebrovascular incidents or surgical lesions (Bechara and Van Der Linden, 2005). Frontal damage patients have also shown diminished self-awareness of inappropriate social behaviors in controlled laboratory observations (Beer et al., 2006), which could be the basis of a diagnosis of OPD, the classic example being Phineas Gage (Damasio et al., 1994). As with lesion patients, TBI subjects are also characterized by several ECF deficits in laboratory tasks (Levin, 1998), including blunted self-awareness (Bach and David, 2006). Because most of these reports have used artificial "cold"-cognitive tasks, how these decrements would affect decisions to use drugs is unclear. However, as these are relatively recent findings, most studies of TBI have not included appropriate assessments of OFC function, so it is unknown whether the functional consequences of TBI may include disruptions in OFC function.

With regard to reward-directed decision-making, TBI survivors have shown increased preference for small-immediate rewards over larger-delayed rewards compared to controls in delay-discounting (DD) choice tasks (Dixon et al., 2005; McHugh and Wood, 2008). This aversion to delayed gratification is akin to individuals addicted to a variety of substances (Reynolds, 2006). This suggests that TBI survivors, especially those with frontal damage, may be impaired in their ability to generate or invoke a mental representation of potential deferred aversive consequences of drug use. Conversely, in an experiential DD task, where subjects have to actually wait out the selected delays to reward delivery in the testing session, TBI subjects held out for the large reward

choice at progressively long delays, and did not maximize earnings like controls (Schlund 2002), indicating more of a strategic deficit. In a betting game, TBI survivors also made more impulsive choices, and responded suboptimally to changes in reward probability (Salmond et al., 2005). While these findings do not provide direct evidence of drug use vulnerability, poor ECF in decision-making tasks is a harbinger for drug abuse generally (Bechara, 2005).

OFC lesions may also alter "agency" or the perception of self as the actor or instigator of behavior. Beer et al. (2006) reported increased incidence of inappropriate laboratory social behavior in subjects with OFC lesions compared to subjects with dorsolateral frontal lesions. Moreover, OFC-lesion subjects showed embarrassment about their behavior only after being a shown a video of their behavior (i.e., from a third-person perspective), also suggesting a deficit in the processing of self as the agent of behavior. These findings collectively suggest that TBI with accompanying OPD may reflect OFC damage and may be a sub-group at risk for TBI-related substance abuse.

Where Do We Go from Here?

Rogers and Read (2007) recently asserted: "In conclusion, the data do not support the correct temporal sequence [*TBI increasing subsequent substance abuse]* and suggest TBI is a minimal, short-term risk factor for substance abuse. Rather, the prevalence of substance abuse after TBI appears to reflect enduring, pre-morbid abuse patterns and coping strategies. As such, TBI is more often a consequence than a cause of substance abuse and substance abuse has been consistently identified as a risk factor for TBI . . . However, it is important to identify the presence of substance abuse in TBI survivors, as alcohol and drug abuse have been clearly identified as impediments to recovery."

Although their conclusion seems definitive, we believe it is premature, because their review is based on variable findings from epidemiological reports, most of which suffer from the methodological shortcomings with respect to establishing directionality of causality mentioned above. Furthermore, experiments probing specific behavioral and neurotransmitter properties following TBI in persons with no substance use or abuse history show that TBI in many individuals results in ECF deficits or behavioral traits (i.e., OPD) that are characteristic of *uninjured* persons who either have, or are at risk for, a drug use disorder.

It is clear that interdisciplinary preclinical studies, as well as much more carefully controlled longitudinal human studies, are needed to address two key questions: (a) whether TBI alone increases risk of drug abuse in the absence of pre-injury psychobiological risk factors for drug abuse, or (b) the degree to which TBI increases drug abuse (or triggers relapse) in persons with histories of SUD. This is particularly critical with the high incidence of TBI in returning soldiers from Iraq and Afghanistan. Collaborations are needed between preclinical head-injury researchers and preclinical drug abuse researchers to conduct experiments on the effects of controlled brain injuries on drug-related behavior in animals. The fruits of such preclinical collaborations, together with more focused epidemiological research, could provide more direct evidence that TBI itself is a risk factor for the development of drug abuse, and could potentially justify further clinical interventions.

Conclusion

1. Numerous reports document a high incidence of (pre-injury) drug and alcohol abuse in persons receiving care for TBI, where in many cases, the subject was intoxicated at the time of injury. That drug abuse increases risk for TBI, and impairs recovery from TBI, has essentially been established.
2. Persons with pre-injury histories of drug or alcohol abuse are at increased risk for relapse to abuse or dependence following TBI.
3. Existing studies attributing psychiatric disorders to TBI suffer methodological shortcomings and cannot confidently attribute subsequent psychiatric disorders to the pathophysiological consequences of the brain trauma itself (as opposed to the psychosocial stressor of disability).
4. There are almost no published investigations that have focused on whether individuals with no histories of drug use prior to a TBI had increased incidence of drug use following the TBI.
5. There are no published preclinical investigations on the effects of an experimentally induced TBI on specific measures of drug sensitivity, such as conditioned place preference to, or self-administration of, drugs of abuse.
6. Behavioral evidence from "clean" TBI survivors is mildly suggestive of decision-making deficits that may increase risk for drug abuse.

Acknowledgments

We thank Dr. John Corrigan for his advice and perspective.

Author Disclosure Statement

No competing financial interests exist.

References

Arciniegas, D.B., and Silver, J.M. (2006). Pharmacotherapy of posttraumatic cognitive impairments. Behav. Neurol. 17, 25–42.

Bach, L.J., and David, A.S. (2006). Self-awareness after acquired and traumatic brain injury. Neuropsychol. Rehabil. 16, 397–414.

Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. Nat. Neurosci. 8, 1458–1463.

Bechara, A., and Van Der Linden, M. (2005). Decision-making and impulse control after frontal lobe injuries. Curr. Opin. Neurol. 18, 734–739.

Beer, J.S., John, O.P., Scabini, D., and Knight, R.T. (2006). Orbitofrontal cortex and social behavior: integrating self-monitoring and emotion-cognition interactions. J. Cogn. Neurosci. 18, 871–879.

Bombardier, C.H., Temkin, N.R., Machamer, J., and Dikmen, S.S. (2003). The natural history of drinking and alcohol-related problems after traumatic brain injury. Arch. Phys. Med. Rehabil. 84, 185–191.

Cherpitel, C.J. (2007). Alcohol and injuries: a review of international emergency room studies since 1995. Drug Alcohol Rev. 26, 201–214.

Cherpitel, C.J., and Ye, Y. (2008a). Drug use and problem drinking associated with primary care and emergency room utilization in the US general population: data from the 2005 national alcohol survey. Drug Alcohol Depend. 97, 226–230.

Cherpitel, C.J., and Ye, Y. (2008b). Trends in alcohol- and drug-related ED and primary care visits: data from three U.S. national surveys (1995–2005). Am. J. Drug Alcohol Abuse 34, 576–583.

Corrigan, J.D. (1995). Substance abuse as a mediating factor in outcome from traumatic brain injury. Arch. Phys. Med. Rehabil. 76, 302–309.

Damasio, H., Grabowski, T., Frank, R., Galaburda, A.M., and Damasio, A.R. (1994). The return of Phineas Gage: clues about the brain from the skull of a famous patient. Science 264, 1102–1105.

Di Chiara, G., and Bassareo, V. (2007). Reward system and addiction: what dopamine does and doesn't do. Curr. Opin. Pharmacol. 7, 69–76.

Dixon, M.R., Jacobs, E.A., Sanders, S., Geurcio, J.M., Soldner, J., Parker-Singler, S., Robinson, A., Small, S., and Dillen, J.E. (2005). Impulsivity, self-control, and delay discounting in persons with acquired brain injury. Behav. Intervent. 20, 101–120.

Donnemiller, E., Brenneis, C., Wissel, J., Scherfler, C., Poewe, W., Riccabona, G., and Wenning, G.K. (2000). Impaired dopaminergic neurotransmission in patients with traumatic brain injury: a SPECT study using ^{123}I-beta-CIT and ^{123}I-IBZM. Eur. J. Nucl. Med. 27, 1410–1414.

Fann, J.R., Burington, B., Leonetti, A., Jaffe, K., Katon, W.J., and Thompson, R.S. (2004). Psychiatric illness following traumatic brain injury in an adult health maintenance organization population. Arch. Gen. Psychiatry 61, 53–61.

Franken, I.H., van Strien, J.W., Franzek, E.J., and van de Wetering, B.J. (2007). Error-processing deficits in patients with cocaine dependence. Biol. Psychol. 75, 45–51.

Franulic, A., Horta, E., Maturana, R., Scherpenisse, J., and Carbonell, C. (2000). Organic personality disorder after traumatic brain injury: cognitive, anatomic and psychosocial factors. A 6-month follow-up. Brain Inj. 14, 431–439.

Hester, R., Simoes-Franklin, C., and Garavan, H. (2007). Post-error behavior in active cocaine users: poor awareness of errors in the presence of intact performance adjustments. Neuropsychopharmacology 32, 1974–1984.

Hibbard, M.R., Uysal, S., Kepler, K., Bogdany, J., and Silver, J. (1998). Axis I psychopathology in individuals with traumatic brain injury. J. Head Trauma Rehabil. 13, 24–39.

Holroyd, C.B., and Coles, M.G. (2002). The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. Psychol. Rev. 109, 679–709.

Horner, M.D., Ferguson, P.L., Selassie, A.W., Labbate, L.A., Kniele, K., and Corrigan, J.D. (2005). Patterns of alcohol use 1 year after traumatic brain injury: a population-based, epidemiological study. J. Int. Neuropsychol. Soc. 11, 322–330.

Jorge, R.E., Starkstein, S.E., Arndt, S., Moser, D., Crespo-Facorro, B., and Robinson, R.G. (2005). Alcohol misuse and mood disorders following traumatic brain injury. Arch. Gen. Psychiatry 62, 742–749.

Kaufman, J.N., Ross, T.J., Stein, E.A., and Garavan, H. (2003). Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. J. Neurosci. 23, 7839–7843.

Kolakowsky-Hayner, S.A., Gourley, E.V., 3rd, Kreutzer, J.S., Marwitz, J.H., Meade, M.A., and Cifu, D.X. (2002). Post-injury substance abuse among persons with brain injury and persons with spinal cord injury. Brain Inj. 16, 583–592.

Larson, M.J., Kelly, K.G., Stigge-Kaufman, D.A., Schmalfuss, I.M., and Perlstein, W.M. (2007). Reward context sensitivity impairment following severe TBI: an event-related potential investigation. J. Int. Neuropsychol. Soc. 13, 615–625.

Levin, H.S. (1998). Cognitive function outcomes after traumatic brain injury. Curr. Opin. Neurol. 11, 643–646.

McDonald, B.C., Flashman, L.A., and Saykin, A.J. (2002). Executive dysfunction following traumatic brain injury: neural substrates and treatment strategies. Neurorehabilitation 17, 333–344.

McHugh, L., and Wood, R.L. (2008). Using a temporal discounting paradigm to measure decision-making and impulsivity following traumatic brain injury: a pilot study. Brain Inj. 22, 715–721.

Milman, A., Rosenberg, A., Weizman, R., and Pick, C.G. (2005). Mild traumatic brain injury induces persistent cognitive deficits and behavioral disturbances in mice. J. Neurotrauma 22, 1003–1010.

Nampiaparampil, D.E. (2008). Prevalence of chronic pain after traumatic brain injury: a systematic review. JAMA 300, 711–719.

O'Doherty, J.P., Dayan, P., Friston, K., Critchley, H., and Dolan, R.J. (2003). Temporal difference models and reward-related learning in the human brain. Neuron 38, 329–337.

Ommaya, A.K., Salazar, A.M., Dannenberg, A.L., Ommaya, A.K., Chervinsky, A.B., and Schwab, K. (1996). Outcome after traumatic brain injury in the U.S. military medical system. J. Trauma 41, 972–975.

Ponsford, J., Whelan-Goodinson, R., and Bahar-Fuchs, A. (2007). Alcohol and drug use following traumatic brain injury: a prospective study. Brain Inj. 21, 1385–1392.

Reynolds, B. (2006). A review of delay-discounting research with humans: relations to drug use and gambling. Behav. Pharmacol. 17, 651–667.

Rogers, J.M., and Read, C.A. (2007). Psychiatric comorbidity following traumatic brain injury. Brain Inj. 21, 1321–1333.

Salmond, C.H., Menon, D.K., Chatfield, D.A., Pickard, J.D., and Sahakian, B.J. (2005). Deficits in decision-making in head injury survivors. J. Neurotrauma 22, 613–622.

Schlund, M.W. (2002). Effects of acquired brain injury on adaptive choice and the role of reduced sensitivity to contingencies. Brain Inj. 16, 527–535.

Schultz, W. (2007). Behavioral dopamine signals. Trends Neurosci. 30, 203–210.

Silver, J.M., Kramer, R., Greenwald, S., and Weissman, M. (2001). The association between head injuries and psychiatric disorders: findings from the New Haven NIMH Epidemiologic Catchment Area Study. Brain Inj. 15, 935–945.

Tanielian, T., Jaycox, L.H., Schell, T.R., Marshall, G.N., Burnam, M.A., Eibner, C., Karney, B.R., Meredith, L.S., Ringel, J.S., and Vaiana, M.E. (2008). *Invisible Wounds of War: Summary and Recommendations for Addressing Psychological and Cognitive Injuries.* Rand Corp.: Santa Monica, CA. Available at: *http://rand.org/pubs/monographs/2008/RAND_MG720.1.pdf).* Accessed May 1, 2009.

Tate, D.G., Forchheimer, M.B., Krause, J.S., Meade, M.A., and Bombardier, C.H. (2004). Patterns of alcohol and substance use and abuse in persons with spinal cord injury: risk factors and correlates. Arch. Phys. Med. Rehabil. 85, 1837–1847

Taylor, L.A., Kreutzer, J.S., Demm, S.R., and Meade, M.A. (2003). Traumatic brain injury and substance abuse: a review and analysis of the literature. Neuropsychol. Rehabil. 13, 165–188.

Taylor, S.F., Stern, E.R., and Gehring, W.J. (2007). Neural systems for error monitoring: recent findings and theoretical perspectives. Neuroscientist 13, 160–172.

Tenovuo, O. (2006). Pharmacological enhancement of cognitive and behavioral deficits after traumatic brain injury. Curr. Opin. Neurol. 19, 528–533.

Van Den Heuvel, C., Thornton, E., and Vink, R. (2007). Traumatic brain injury and Alzheimer's disease: a review. Prog. Brain Res. 161, 303–316.

Verbois, S.L., Hopkins, D.M., Scheff, S.W., and Pauly, J.R. (2003). Chronic intermittent nicotine administration attenuates traumatic brain injury-induced cognitive dysfunction. Neuroscience 119, 1199–1208.

Vitale, S., and van de Mheen, D. (2006). Illicit drug use and injuries: a review of emergency room studies. Drug Alcohol Depend. 82, 1–9.

Wagner, A.K., Postal, B.A., Darrah, S.D., Chen, X., and Khan, A.S. (2007). Deficits in novelty exploration after controlled cortical impact. J. Neurotrauma 24, 1308–1320.

Wagner, A.K., Sokoloski, J.E., Ren, D., Chen, X., Khan, A.S., Zafonte, R.D., Michael, A.C., and Dixon, C.E. (2005). Controlled cortical impact injury affects dopaminergic transmission in the rat striatum. J. Neurochem. 95, 457–465.

Yan, H.Q., Ma, X., Chen, X., Li, Y., Shao, L., and Dixon, C.E. (2007). Delayed increase of tyrosine hydroxylase expression in rat nigrostriatal system after traumatic brain injury. Brain Res. 1134, 171–179.

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