A Prospective Study of the Influence of Acute Alcohol Intoxication Versus Chronic Alcohol Consumption on Outcome Following Traumatic Brain Injury

Rael T. Langea,b,c, *, Jason R. Shewchukc,d, Alexander Rauscherc,c,f, Michael Jarrettc,e, Manraj K.S. Heranc,d, Jeffrey R. Brubacherc,d, Grant L. Iversong,h

a Defense and Veterans Brain Injury Center, Bethesda, MD, USA
b Walter Reed National Military Medical Center, Bethesda, MD, USA
c University of British Columbia, Vancouver, Canada
d Vancouver General Hospital, BC, Canada
e UBC MRI Research Center, Vancouver, BC, Canada
f UBC Brain Research Center, Vancouver, BC, Canada
g Harvard Medical School, Boston, MA, USA
h Red Sox Foundation and Massachusetts General Hospital Home Base Program, Boston, MA, USA

*Corresponding author at: Defense and Veterans Brain Injury Center, Walter Reed National Military Medical Center, Building 8, Room 2264, 8901 Wisconsin Avenue, Bethesda, MD 20814, USA. Tel.: +1-240-997-5284. E-mail address: rael.t.lange@us.army.mil; rael.lange@gmail.com (R.T. Lange)

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Abstract

The purpose of the study was to disentangle the relative contributions of day-of-injury alcohol intoxication and pre-injury alcohol misuse on outcome from TBI. Participants were 142 patients enrolled from a Level 1 Trauma Center (in Vancouver, Canada) following a traumatic brain injury (TBI; 43 uncomplicated mild TBI and 63 complicated mild–severe TBI) or orthopedic injury [36 trauma controls (TC)]. At 6–8 weeks post-injury, diffusion tensor imaging (DTI) of the whole brain was undertaken using a Philips 3T scanner. Participants also completed neuropsychological testing, an evaluation of lifetime alcohol consumption (LAC), and had blood alcohol levels (BALs) taken at the time of injury. Participants in the uncomplicated mild TBI and complicated mild–severe TBI groups had higher scores on measures of depression and postconcussion symptoms ($d = 0.45–0.83$), but not anxiety, compared with the TC group. The complicated mild–severe TBI group had more areas of abnormal white matter on DTI measures ($p < .05; d = 0.54–0.61$) than the TC group. There were no difference between groups on all neuropsychological measures. Using hierarchical regression analyses and generalized linear modeling, LAC and BAL did provide a unique contribution toward the prediction of attention and executive functioning abilities; however, the variance accounted for was small. LAC and BAL did not provide a unique and meaningful contribution toward the prediction of self-reported symptoms, DTI measures, or the majority of neuropsychological measures. In this study, BAL and LAC were not predictive of mental health symptoms, postconcussion symptoms, cognition, or white-matter changes at 6–8 weeks following TBI.

Keywords: Alcohol intoxication; Traumatic brain injury; Concurrent; Diffusion tensor imaging; Lifetime alcohol abuse

Introduction

Alcohol intoxication is a significant risk factor for traumatic brain injury (TBI) (Canadian Institute for Health Information, 2002; Corrigan, 1995; Cowie, Brubacher, Lee, Lee, & Simons, 2005; Heinemann, Doll, Armstrong, Schnoll, & Yarkony, 1991; McKinley, Kolakowsky, & Kreutzer, 1999; Miller, 1994; Sparadeo & Gill, 1989). The prevalence of positive blood alcohol levels (BALs) in patients presenting to a trauma center following a TBI ranges from 33% to 72% (Corrigan, 1995; Dikmen, Machamer, Donovan, Winn, & Temkin, 1995; Gurney et al., 1992; Kraus, Morgenstern, Fife, Conroy, & Nourjah, 1989;
Kreutzer, Doherty, Harris, & Zasler, 1990; Solomon & Malloy, 1992; Sparadeo & Gill, 1989; Sparadeo, Strauss, & Barth, 1990), with 37%–53% having BALs that exceed the legal limit (Gurney et al., 1992; Kraus et al., 1989; Rimel, Giordani, Barth, & Jane, 1982). Alcohol-related TBI has also been found to be predictive of a recurrent TBI; the majority of which are also alcohol related (Winquist et al., 2008).

Day-of-injury alcohol intoxication has significant implications for the diagnosis, management, treatment, and recovery from TBI. Elevated BALs at the time of injury have been reported to be associated with lower levels of consciousness on admission (Edna, 1982), longer hospitalization stays (Brismar, Engstrom, & Rydberg, 1983; Gururaj, 2004; Kaplan & Corrigan, 1992; Kraus et al., 1989; Sparadeo & Gill, 1989), greater neurological impairment at discharge (Kraus et al., 1989), increased severity of brain injury on CT scans (Cunningham, Maio, Hill, & Zink, 2002), higher mortality rates, longer duration of agitation during treatment (Sparadeo & Gill, 1989), longer time to rehabilitation admission (Kaplan & Corrigan, 1992), and worse global outcome (Ruff et al., 1990; Sparadeo & Gill, 1989). In contrast, however, researchers have reported that day-of-injury alcohol intoxication has also been reported to have no influence on duration of hospital stay (De Guise et al., 2009; Shandro et al., 2009; Talving et al., 2010) and is consistently associated with decreased mortality rates following TBI (Berry et al., 2010, 2011; Lustenberger et al., 2011; O’Phelan, McArthur, Chang, Green, & Hovda, 2008; Salim, Ley, et al., 2009; Salim, Teixeira, et al., 2009; Talving et al., 2010).

Researchers examining neuropsychological and neuropathological outcomes following TBI have reported that individuals who are intoxicated at the time of injury tend to have worse cognitive recovery (Bombardier & Thurber, 1998; Kelly, Johnson, Knoller, Drubach, & Winslow, 1997; Tate, Freed, Bombardier, Harter, & Brinkman, 1999; Wilde et al., 2004) and greater atrophic changes in the brain (Barker et al., 1999; Wilde et al., 2004) compared with those who are sober. Specifically, they (i) show greater trauma-induced degenerative changes following injury as indicated by higher ventricle-to-brain ratio and lower whole brain volume (i.e., gray and white matter) (Barker et al., 1999; Wilde et al., 2004) and (ii) perform worse on measures of visual–spatial ability, immediate and delayed memory, processing speed, and executive functioning (Bombardier & Thurber, 1998; Kelly et al., 1997; Tate et al., 1999; Wilde et al., 2004). There are some exceptions to this, however. Some researchers have reported no effect of BAL on neurocognitive outcome following TBI (Kaplan & Corrigan, 1992; Schutte & Hanks, 2010; Turner, Kivlahan, Rimmele, & Bombardier, 2006). Paradoxically, in one study, intoxicated TBI patients had better neuropsychological outcome in the first 2 weeks following TBI compared with their sober counterparts (Lange, Iverson, & Franzen, 2008). Nonetheless, the relation between acute alcohol intoxication and worse outcome following TBI appears to be supported by the literature.

The mechanisms by which day-of-injury alcohol intoxication might affect outcome from TBI are poorly understood. Two types of contributing factors have been proposed: acute and chronic alcohol factors. Acute alcohol factors refer to the hypothesis that individuals who are intoxicated at the time of injury may experience an increased magnitude of brain injury due to the presence of a variety of negative physiological responses to ethanol not present in a person who is sober at the time of injury (e.g., hemodynamic and respiratory depression, and/or blood–brain barrier impairment; Alexander, Kerr, Yonas, & Marion, 2004; Altura & Altura, 1999; Mautes et al., 2001; Wilde et al., 2004; Zink et al., 2001). Chronic alcohol factors refer to the hypothesis that worse outcome following intoxicated TBI is an artifact of the high base rate of chronic alcohol abuse in these patients (i.e., up to 75%; Bombardier, 1995). That is, acutely intoxicated patients are more likely to be chronic alcohol abusers (Bogner, Corrigan, Mysiw, Clinchot, & Fugate, 2001; Corrigan, Bogner, Mysiw, Clinchot, & Fugate, 2001; Dikmen, Donovan, Loberg, Machamer, & Temkin, 1993; Kolakowsky-Hayner et al., 1999; Kreutzer, Doherty, et al. 1990; Kreutzer, Harris, Myers, & Zasler 1990; McKinley et al., 1999; Rimel et al., 1982; Sparadeo & Gill, 1989; Tobis, Puri, & Sheridan, 1982), and poor cognitive outcome following TBI simply reflects the deleterious effects of pre-injury chronic alcoholism (e.g., Barker et al., 1999; Charness, 1993; Dikmen et al., 1993; Maers & Lees-Haley, 1993; Nixon, 1999; Pfefferbaum et al., 1992; Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1996) rather than magnified brain injury associated with alcohol intoxication.

The adverse effects of alcoholism on cognition and the brain are well documented. Numerous studies show that chronic alcoholics (Akshoomoff, Delis, & Keiffer, 1989; Beatty, Katzung, Moreland, & Nixon, 1994; Errico, Nixon, Parsons, & Tassy, 1990; Kramer, Blusewicz, Robertson, & Preston, 1989; Muuronen, Bergman, Hindmarsh, & Telakivi, 1989; Paraherakis, Charney, & Gill, 2001; Parsons, 1998) perform worse on a variety of cognitive measures (e.g., attention, memory, processing speed, and executive functioning; Brandt, Butters, Ryan, & Bayog, 1983; Errico, Parsons, & King, 1991; Gordon, Kennedy, & McPeake, 1988; Grant, 1987; Nixon, 1999; Parsons & Nixon, 1993) and have various structural and functional changes in the brain (Barker et al., 1999; Charness, 1993; Fein, Fletcher, & Di Scalfani, 1998; Harper, Kril, & Holloway, 1985; Jensen & Pakkenberg, 1993; Jernigan, Butters, & Cermak, 1992; Muuronen et al., 1989; Parsons, Sinha, & Williams, 1990; Pfefferbaum et al., 1992; Sachs, Russell, Christman, & Cook, 1987; Sullivan et al., 1996), such as white-matter atrophy (Harper et al., 1985; Pfefferbaum & Sullivan, 2002; Pfefferbaum et al., 1992, 2000; Sullivan et al., 1996). Chronic alcohol abuse commonly affects the corpus callosum (Pfefferbaum, Rosenbloom, & Sullivan, 2002; Rosenbloom, Sullivan, & Pfefferbaum, 2003; Sullivan & Pfefferbaum, 2003) and in particular the areas of the genu and splenium (Ma et al., 2005; Pfefferbaum, Adalsteinsson, & Sullivan, 2006;
Pfefferbaum & Sullivan, 2002, 2005; Pfefferbaum et al., 2000). Diffusion tensor imaging (DTI) studies have also found reduced corpus callosum white-matter integrity in individuals with a history of alcoholism (Pfefferbaum & Sullivan 2005; Pfefferbaum et al., 2002, 2000; Schulte, Sullivan, Muller-Oehring, Adalsteinsson, & Pfefferbaum 2005).

To date, few researchers have attempted to examine the relative contributions of acute versus chronic alcohol factors on outcome from TBI and the results have been mixed. Although some studies support day-of-injury alcohol intoxication as more influential in determining neuropsychological and neuropathological outcome (Brooks et al., 1989; Tate et al., 1999), others have found pre-injury alcohol abuse to be more influential (Lange, Iverson, & Franzen, 2007), or have reported that both factors are of equal importance (Wilde et al., 2004), or are non-contributory (Vickery et al., 2008). Therefore, the extent to and mechanisms by which day-of-injury intoxication might affect outcome from TBI remain unclear.

The purpose of this study is to disentangle the relative contributions of day-of-injury alcohol intoxication (acute alcohol factor) and pre-injury alcohol misuse (chronic alcohol factor) on the neuropsychological outcome (i.e., neurocognition and self-reported symptoms) and white-matter changes in the brain following TBI 6–8 weeks post-injury. It was hypothesized that both pre-injury lifetime alcohol consumption (LAC) and day-of-injury BAL will be associated with worse neurocognitive outcome, higher self-reported symptoms, and more extensive white-matter changes at 6–8 weeks post-injury; however, BAL will account for more variance than LAC.

### Method

#### Participants

Participants were 142 patients [106 TBI and 36 trauma control (TC)] prospectively recruited from the Emergency Department of Vancouver General Hospital (Level 1 Trauma Center) between June 2007 and April 2012. Patients were identified for potential inclusion in the study via daily reviews of consecutive Emergency Department admissions. Patients were initially considered for recruitment and consent if they presented to the Emergency Department after sustaining a TBI (i.e., TBI group), or they had sustained a soft tissue or orthopedic injury (i.e., TC group).

All participants were enrolled in the study if they were (i) between 19 and 55 years old, (ii) were injured as a result of a traumatic injury (e.g., fall, motor-vehicle accident, assault, etc.), and (iii) had a BAL obtained at the time of injury. Exclusion criteria included (i) lack of proficiency in conversational English; (ii) educated in a language other than English after age 10; (iii) history of a neurological disorder (e.g., stroke or multiple sclerosis), TBI, learning disability, ADHD, or psychiatric illness requiring hospitalization; (iv) the presence of any contraindication to MRI; (v) history of significant drug abuse other than alcohol; (vi) the presence of upper body injuries restricting the use of hands or arms; and (vii) difficulties with eyesight.

Participants were included in the TC group if (i) they sustained a soft tissue or orthopedic injury below the neck; (ii) there was no evidence of an altered state of consciousness as indicated by a reduction in Glasgow Coma Scale (GCS) score, or the presence of a loss of consciousness (LOC), posttraumatic amnesia (PTA), or posttraumatic confusion; and (iii) there was no evidence of physical head trauma, whiplash, or cervical strain based on medical chart review (e.g., the absence of lacerations/contusions to the head, the absence of complaints of head, neck, or back pain). In a small number of cases (n = 3, 8.3%), participants had undergone a head CT but had no evidence of intracranial abnormality.

Participants were included in the TBI group if they (i) presented to the Emergency Department following head trauma and (ii) had evidence of a closed TBI as indicated by at least one of the following: (i) witnessed LOC of at least 1 min duration, (ii) PTA of >15 min, (iii) GCS score of <15, and (iv) the presence of intracranial abnormality on day-of-injury CT scan. Classification of brain injury severity was based on the duration of LOC, duration of PTA, GCS scores, day-of-injury CT scans, and structural MRI scans 6–8 weeks post-injury as follows: (i) uncomplicated mild TBI: LOC < 30 min, GCS = 13–15, PTA < 24 h, and no trauma-related intracranial abnormality on day-of-injury CT or 6–8 weeks structural MRI scan; (ii) complicated mild TBI: LOC < 30 min, GCS = 13–15, PTA < 24 h, and trauma-related intracranial abnormality on day-of-injury CT scan and/or 6–8 weeks structural MRI scan; (iii) moderate TBI: LOC = 30 min–24 h, GCS = 9–12, or PTA = 1–7 days (at least one criterion must be in the moderate range and other criteria could be in the mild or moderate range); and (iv) severe TBI: LOC > 24 h; GCS = 3–8, or PTA > 7 days (at least one criterion must be in the severe range and other criteria could be in the mild, moderate, or severe range). Of the 106 TBI patients, the breakdown by injury severity was as follows: 43 uncomplicated mild, 46 complicated mild, 14 moderate, and 3 severe. For the purposes of this study, the TBI group was categorized into two broad groups: (i) uncomplicated

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1 Note that the second and more stringent criterion for ESL was only introduced in 2009 after the evaluation of a series of patients whose neurocognitive profile was considered to be affected by not having an English-based education (e.g., intact scores on all measures except language-based measures).
mild TBI group \(n = 43\) and (ii) complicated mild–severe TBI group \(n = 63\); i.e., 46 complicated mild TBI, 5 moderate TBI, and 12 severe TBI combined).

A substantial minority of the sample were seeking compensation at the time of evaluation \(n = 49, 34.5\%\); the majority were not seeking compensation \(n = 84, 59.9\%\) or were uncertain \(n = 8, 5.6\%\). Of those who were seeking compensation, the majority had filed an accident insurance claim \(n = 35, 71.4\%\), with a smaller proportion having retained a lawyer and initiated personal injury litigation \(n = 11, 22.4\%\), or a Workers Compensation Board claim \(n = 3, 6.1\%\).

**Participant Selection**

Participants were selected from a larger sample of 188 patients enrolled in the study (123 TBI and 65 TC). Participants were initially included in the sample as follows: (i) completed the entire neuropsychological test battery \(n = 188, 100\%\) of entire sample), (ii) completed a comprehensive evaluation of LAC \(n = 187, 99.5\%\) of entire sample), (iii) scored above the recommended cutoff score for providing adequate effort on the Test of Memory Malingering \(n = 188, 100\%\) of entire sample), (iv) behavioral observations during the neuropsychological evaluation did not provide suspicion of questionable motivation or attention that may have negatively influenced test performance \(n = 186, 98.9\%\) of entire sample), (v) neurocognitive performance was not considered influenced by ESL \(n = 181, 96.3\%\) of entire sample), (vi) successfully completed MRI scanning \(n = 187, 99.5\%\) of entire sample), (vii) structural MRI scans were considered complete and interpretable by a neuroradiologist \(n = 186, 99.5\%\) of those who completed MRI scanning), (viii) MRI scans were not significantly affected by motion artifact for the purposes of DTI post-processing \(n = 183, 97.9\%\) of those who completed MRI scanning), and (ix) no evidence of pre-injury neurological abnormalities (e.g., meningioma, cistern mass, and venous anomaly) detected on MRI scans \(n = 183, 97.9\%\) of those who completed MRI scanning). Application of these criteria resulted in retaining 163 participants (113 TBI and 51 TC, with 25 subjects excluded).

In addition to these criteria, the structural MRI scans were further examined for the presence of white-matter hyperintensities (WMHIs). The presence of pre-existing WMHIs can influence the results of DTI research in that healthy controls with WMHIs show evidence of other white-matter changes on DTI, distal to those hyperintensities (Iverson et al., 2011; Lange et al., 2013). Those individuals in the TC group that had two or more WMHIs were excluded \(n = 15\). Those participants in the TBI group who had did not show evidence of trauma-related structural abnormalities (i.e., uncomplicated mild TBIs), but who had two or more WMHIs, were also excluded \(n = 7\). There is no way of knowing whether one or more WMHIs, visualized several weeks following a TBI (especially MTBI), is pre-existing or trauma related. In the control group, we made the assumption that they are pre-existing. Therefore, for this study, to control for the likelihood that some or even most of the isolated hyperintensities were pre-existing, we decided to use this as an exclusion criterion for both groups. If we include pre-existing hyperintensities in one group and not the other, we bias the study. Of course, we bias the study if we exclude trauma-related WMHIs, too. We struggled with this issue methodologically and ultimately decided to exclude a small number of subjects with MTBI \(n = 7\), at the risk of reducing generalizability, to avoid the biasing effect of including pre-existing white-matter findings in the MTBI sample. The final sample included 142 participants (106 TBI and 36 TC).

**Measures and Procedure**

Participants completed a 1-h MRI brain scan and a 5-h neuropsychological assessment battery that included measures of neurocognitive functioning, self-reported mental health and postconcussion symptoms, and pre-injury alcohol use \(\sim 6–8\) weeks post-injury \(M = 47.0\) days, \(SD = 6.1\). All participants gave written informed consent in accordance with the Clinical Research Ethics Board at the University of British Columbia, Vancouver, Canada.

**Self-report measures.** Participants completed the Beck Depression Inventory—Second Edition (BDI-II), Beck Anxiety Inventory (BAI), and the British Columbia Post-Concussion Symptom Inventory (BC-PSI). The BDI-II (Beck, Steer, & Brown, 1996) and BAI (Beck & Steer, 1993) are both 21-item self-report questionnaires. Participants are asked to rate each item on a four-point scale ranging from 0 to 3. A total score is calculated by summing all 21 items on each measure separately, giving a total score on each measure with a range from 0 to 63.

The BC-PSI (Iverson, Zasler, & Lange, 2007) is a symptom inventory based on ICD-10 (American Psychiatric Association, 2000) criteria for postconcussional syndrome that requires the test taker to rate the frequency and intensity of 13 symptoms (i.e., headaches, dizziness/light-headedness, nausea or feeling sick, fatigue, sensitivity to noises, irritability, sadness, nervousness/tension, temper problems, poor concentration, memory problems, reading difficulty, and sleep disturbance) as well as the effect of three co-occurring life problems on daily living (i.e., greater present versus past effects of alcohol consumption, worrying and dwelling on symptoms, and self-perception of brain damage). The three life problems are rated on a scale from one to five, where 1 = “not at all” and 5 = “very much.” The 13 symptoms are rated on a six-point Likert-type rating scale that measures...
the frequency (i.e., “how often”) and intensity (“how bad”) of each symptom in the past 2 weeks. Frequency ratings range from 0 = “not at all” to 5 = “constantly.” Intensity ratings range from 0 = “not at all” to 5 = “very severe problem.” For each of the 13 symptoms, the two ratings are multiplied together (how often \times how bad) to create a single score for each item. These product-based scores are then converted to item scores that reflect both the frequency and intensity of symptom endorsement (range = 0–4).

**Neurocognitive measures.** The neurocognitive measures consisted of 16 tests from the Neuropsychological Assessment Battery (NAB; Stern & White, 2003). The NAB is a comprehensive, co-normed (across all tests) neuropsychological test battery that consists of 24 individual tests designed to assess cognitive functioning across five domains: Attention, Language, Memory, Spatial, and Executive Functioning. The normative sample is large and the coverage of neuropsychological abilities assessed is broad. The NAB can be used in a fixed or flexible manner. Only 16 of the 24 tests were selected for use in order to reduce administration time. The administration of the 16 selected tests results in the acquisition of 23 scores of interest. In order to reduce the number of cognitive variables for the analyses, the 23 scores of interest were used to generate index scores for each of the five cognitive domains. The Attention and Memory indexes were generated as per the instructions in the manual. For the Language, Spatial, and Executive Functioning Indexes, however, not all tests included in these indexes were administered. As such, these indexes were prorated. These three indexes were calculated by generating a prorated “Sum of T-scores” and then converting the prorated “Sum of T-scores” to a standard score using the look-up table in the NAB normative manual (White & Stern, 2003). The prorated sum of T-scores for the three indexes was calculated by averaging the demographically adjusted T-scores across all available tests that are included in each index. The mean T-score was then multiplied by the number of tests that are used to generate the full version of the index. For the Language index, two of five possible tests were used (i.e., Oral Production and Naming). For the Spatial Index, two of four possible tests were used (i.e., Visual Discrimination and Design Construction). For the Executive Functioning index, three of four possible tests were used (Categories, Mazes, and Word Generation). A NAB Total Index was also generated using the standard scores derived for the five indexes above as per the instructions in the manual.

As part of the larger neurocognitive test battery, participants were also administered the (i) Test of Memory Malingering (Tombaugh, 1996) to evaluate the possibility of the patient providing poor effort during neuropsychological testing, (ii) Reynolds Intellectual Screening Test (Reynolds & Kamphaus, 2003) to assess current level of intellectual ability, and (iii) Wechsler Test of Adult Reading (The Psychological Corporation, 2001) to assess premorbid level of intellectual ability. In addition, participants completed a semi-structured interview designed to gather information about their past and present medical, psychiatric, and personal history. Detailed information regarding the duration of PTA was obtained during this interview and reconstructed using collateral information obtained from hospital records.

**Alcohol measures.** Two measures of alcohol use were obtained: (i) day-of-injury alcohol intoxication (acute alcohol variable) and (ii) LAC (chronic alcohol variable). Day-of-injury alcohol intoxication was determined using BALs obtained in the Emergency Department of Vancouver General Hospital as part of standard clinical care. BALs at the hospital are measured using a high-volume analyzer (i.e., Beckman CX7, Model 7566, Beckman Instruments, Inc. Fullerton, CA, USA) and are reported as millimoles per liter. For comparative purposes, 21.7 mmol/L equals 100 mm/dl or 0.10 gm%.

Pre-injury LAC was estimated using the Cognitive Lifetime Drinking History (CLDH) interview (Russell et al., 1997, 1998). The CLDH is a widely used (Barba et al., 2004; Fan et al., 2006; Freudenheim et al., 2003; Hayashi et al., 2004; McCann et al., 1999; Russell et al., 1998, 2001; Schunemann et al., 2002a, 2002b; Stranges et al., 2004) computer-assisted interview designed to assess lifetime drinking patterns, utilizing cognitive techniques to maximize respondents’ ability to recall their past alcohol consumption. The CLDH asks detailed questions relating to the consumption of four types of alcohol: beer, wine, wine coolers, and liquor. Questions elicit information relating to (i) quantity of alcohol consumed, (ii) frequency of alcohol consumption, (iii) duration of alcohol consumption, and (iv) typical drink size consumed over “drinking intervals” across the lifespan (among other questions). The drinking intervals, which represent a person’s regular pattern of drinking within a certain life period, are identified with the aid of a “life events calendar” (e.g., marriage, job change, etc.) that provides cognitive cues designed to trigger memories of respondents past drinking intervals/patterns. The CLDH produces numerous scores/data relating to alcohol consumption patterns, frequency, quantity, and type of alcohol consumed across the lifespan. However, for the purposes of this study, only one score is of interest: total LAC (measured in ounces). This measure takes into account both (i) quantity/frequency of drinking and (ii) duration of drinking across the lifespan.

**Neuroimaging.** All MRI data were acquired on a Philips Achieva 3T scanner equipped with Dual Nova Gradients (maximum gradient strength 80 mT/m, maximum slew rate 200 mT/m/s) and an eight-channel head coil. Partial parallel imaging was performed using sensitivity encoding (SENSE) (Pruessmann, Weiger, Scheidegger, & Boesiger, 1999). The total data acquisition time was 43 min. The MRI protocol included: (i) axial T2-weighted turbo spin-echo scan (TR = 3000 ms, TE = 80 ms, flip angle = 90°,
acquisition matrix = $320 \times 245$, field of view = $240 \times 192 \times 139$ mm$^3$, acquired voxel size = $0.75 \times 0.78 \times 4$ mm$^3$, reconstructed voxel size = $0.47 \times 0.47 \times 4$ mm$^3$, SENSE factor of 1.2 along the left–right direction, 2 averages; (ii) axial T2-weighted fluid attenuated inversion recovery (FLAIR) scan, TR = 10,000 ms, TE = 10 ms, acquisition matrix = $304 \times 194$, field of view = $240 \times 193 \times 139$ mm$^3$, acquired voxel size = $0.79 \times 0.99 \times 4.00$ mm$^3$, reconstructed voxel size = $0.47 \times 0.47 \times 4.00$ mm$^3$, SENSE factor of 1.6 along the left–right direction; and (iii) DTI scan (TR = 5618 ms, TE = 75 ms, flip angle = 90°, acquisition matrix = $96 \times 95$, field of view = $240 \times 240 \times 125$ mm$^3$, acquired voxel size = $2.50 \times 2.50 \times 2.50$ mm$^3$, reconstructed voxel size = $1.88 \times 1.88 \times 2.50$ mm$^3$, SENSE factor of 2.4 along the front-back direction, 15 diffusion directions, 3 averages). Sagittal 3D T1-weighted, axial T1-weighted spin echo, and axial and coronal 2D T2-weighted gradient echo scans were also obtained but are not directly relevant to this study.

All images were reconstructed for the scanner. All DTI scans were visually inspected for motion artifacts by looking at each individual diffusion weighted scan and at the non-weighted scan. If any of these images showed significant signs of motion, the participant was excluded. The FLAIR and T2-weighted scans were assessed for WMHIs by a neuroradiologist (JRS or MKSH). DTI data were processed using FSL (Smith et al., 2004). Eddy current and head motion correction were done via a linear, affine registration (FLIRT; Greve & Fischl, 2009; Jenkinson & Smith, 2001; Jenkinson, Bannister, Brady, & Smith, 2002). Non-brain voxels were removed using FSL’s brain extraction tool (Smith, 2002). DTI eigenvalues (where the principle diffusion axis and $\lambda_1$ is along the principle diffusion axis and $\lambda_2$ and $\lambda_3$ are orthogonal to $\lambda_1$) were calculated using software in FSL’s diffusion toolbox, from which the relevant DTI parameters (fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity) were derived.

To identify regions of interest (ROIs), the FA maps of all subjects were registered into MNI152 space via FLIRT (12 degrees of freedom, cost function = correlation ratio) and the nonlinear registration tool FNIRT (Andersson, Jenkinson, & Smith, 2007a, 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999) (Jacobian range = 0.1 – 10). The transformation defined in the FA registration was used in turn to register MD, AD, and RD parameter maps into the same MNI152 space. After registration, all scans were visually inspected to assure the quality of the registration. Subjects with abnormal CT scans showed either no abnormalities on DTI or minor signal loss in the cortex that had no apparent effect on the registration.

Fifty individual ROIs were identified according to the International Consortium of Brain Mapping DTI-81 white-matter labels atlas (Mori, Wakan, & VanZijl, 2004). The ROIs included the (i) genu, body, and splenium of corpus colossum; (ii) forceps minor, fornix, and middle cerebellar peduncle; and (iii) two unilateral symmetrical ROIs (left/right) each for the anterior corona radiata, anterior limb of internal capsule, cerebral peduncle, cingulum, corticospinal tract, external capsule, inferior cerebellar peduncle, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, internal capsule, medial lemniscus, posterior corona radiata, posterior limb of internal capsule, posterior thalamic radiation, retrolenticular part of internal capsule, sagittal stratum, superior cerebellar peduncle, superior corona radiata, superior fronto-occipital fasciculus, superior longitudinal fasciculus, tapetum, and uncinate fasciculus.

Four summary scores were calculated for each participant and used in all statistical analyses. The four summary scores represent the number of ROIs with FA, MD, RD, and AD values that fell below/above a specified cutoff score for each participant. Cutoff scores were identified by calculating the means and standard deviations (SDs) for FA, MD, RD, and AD values in each of the 50 ROIs using the 38 TC subjects who did not have a single WMHI visible on MRI (the remaining control subjects had an isolated WMHI; previous studies have shown that having two or more WMHIs are associated with worse DTI scores in regions distal to the lesions; Iverson et al., 2011; Lange et al., 2013). FA values that were $>2$ SDs below the mean, and MD, RD, and AD values that were $>2$ SDs above the mean, were classified as reflecting an ROI with “reduced white-matter integrity.” For the purposes of this study, we refer to these values as “abnormal.” It should be noted, however, that these scores are only abnormal in the sense that they are unlikely to occur in the TC sample. These scores are believed to reflect unusually low (i.e., FA) or unusually high (i.e., MD, RD, and AD) values that are indicative of reduce white-matter integrity.

**Statistical Analysis: Unique Contribution of Alcohol Use**

For the neurocognitive and symptoms measures, in order to examine the influence of day-of-injury alcohol intoxication (i.e., BAL) and pre-injury alcohol use (i.e., LAC) on outcome from TBI, a series of hierarchical regression analyses were undertaken to determine the percent variance accounted for by day-of-injury BAL and pre-injury LAC toward the prediction of these measures. Two hierarchical regression analyses were undertaken for each of the outcome measures separately as the dependent variables, and BAL and LAC as the independent variables. There were three main steps for these analyses. In order to control for the effects of brain injury severity and certain demographic variables on some outcome measures, duration of PTA (in minutes) was used as a covariate and forced into the regression on the first step, followed by the two alcohol factors in two subsequent, alternating steps [i.e., Regression 1 = Covariates (Step 1) $\rightarrow$ BAL (Step 2) $\rightarrow$ LAC (Step 3); Regression 2 = Covariates (Step 1) $\rightarrow$ LAC (Step 2) $\rightarrow$ BAL (Step 3)]. In this manner, the significance of each alcohol factor was evaluated over and above all other variables on the
final step of the hierarchy using $R^2_{\text{change}}$ statistics. For the regression on self-reported symptoms, age, education, and gender were also included as covariates in Step 1. However, age, gender, and education were not included as covariates for the neurocognitive measures because these scores are already demographically adjusted for these variables.

For the DTI measures, in order to examine the influence of BAL and LAC on outcome from TBI, a series of generalized linear models (GLMs) were used to explore the unique contribution of BAL and LAC toward the prediction of these measures, using a nested model approach. Two negative binomial GLMs were used for each of the outcome measures separately as the dependent variables, and BAL, LAC, and selected covariates (i.e., age, gender, and PTA) as the independent variables. The unique contribution of each alcohol variable toward the prediction of the DTI measures was examined by entering the covariates and one alcohol variable in the first model (GLM-1), followed by the covariates and both alcohol variables in the second model (GLM-2). In order to explore the influence of BAL and LAC separately, the first model was run twice using each of the two alcohol variables separately (i.e., GLM-1A = covariates and BAL; GLM-1B = covariates and LAC). To determine the best fitting model, a difference score was calculated using the Akaike Information Criterion (AIC) statistics generated from both models ($\text{AIC}_{\text{GLM2}} - \text{AIC}_{\text{GLM1}}$). A large positive AIC difference score ($\text{AIC}_{\text{diff}}$) indicates that the inclusion of the alcohol variable in GLM-2 improved the model fit and therefore provided a unique contribution toward the prediction of the DTI measures. $\text{AIC}_{\text{diff}}$ was interpreted as recommended by Hilbe (2009) as follows: $< 6 = \text{no difference in models}; > 6 = \text{first model is preferred}$.

**Results**

**Demographics and Injury Characteristics**

Descriptive statistics and group comparisons of demographic and injury characteristics are presented in Table 1 (continuous variables) and Table 2 (categorical variables). There were no significant main effects (using ANOVA and $\chi^2$ analyses) for age, education, gender, ethnicity, LAC, mechanism of injury, days tested post-injury, current intellectual ability, or estimated premorbid intellectual ability (all $p > .05$). There were significant main effects for day-of-injury BAL ($p = .002$) and GCS scores ($p = .029$). The uncomplicated MTBI group and the complicated mild–severe TBI group had a higher day-of-injury BAL compared with the TC group (medium and large effect sizes, respectively). In addition, the uncomplicated MTBI group had a higher day-of-injury GCS score compared with the complicated mild–severe TBI group (medium effect size).

**Neuropsychological and DTI Measures**

Descriptive statistics, group comparisons, and effect sizes (Cohen, 1988) for the neurocognitive measures, self-reported symptoms, and DTI measures, by group, are presented in Table 3. There were no significant main effects (ANOVA) for the NAB Total Index ($p = .574$) or the five individual NAB Indexes (range: $p = .247–.789$). For the self-reported symptoms, there were significant main effects (using Kruskal–Wallis $H$-tests due to non-normal distribution) for BDI-II total ($p = .016$) and BC-PSI total ($p < .001$) scores, but not for the BAI total score ($p = .178$). Pairwise comparisons (using Mann–Whitney $U$-tests) revealed that participants in the uncomplicated mild TBI and complicated mild–severe TBI group had higher scores on the BDI-II and BC-PSI compared with the TC group (all $p < .05$; medium to large effect sizes).

For the DTI measures, there were significant main effects (Kruskal–Wallis $H$-tests) for the number of abnormal AD scores ($p = .039$), but not for FA, MD, or RD scores (all $p > .104$). Pairwise comparisons (Mann–Whitney $U$-tests) revealed that participants in the complicated mild–severe TBI group had a greater number of abnormal FA, MD, RD, and AD scores compared with the TC group (all $p < .05$; medium-large effect sizes) but not the uncomplicated mild TBI group (all $p > .05$; small effect sizes). There were no statistically significant differences in the number of abnormal FA, MD, RD, and AD scores when comparing the uncomplicated mild TBI and TC group; however, there were medium effect sizes for all these comparisons ($d = 0.35–0.45$), with trends for the uncomplicated mild TBI group having more areas of abnormal white matter.

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2 Hierarchical regression analyses are not appropriate for use with the DTI measures. The four DTI summary measures reflect “count” data. Therefore, statistical methods such as generalized linear models (i.e., Poisson log linear or negative binomial) that are designed specifically for use with count data were used for these measures.

3 A Poisson log linear GLM was not appropriate for use due to the over dispersion of the dependent variable (all dispersion ratios were $>3.0$). When using a negative binomial GLM, all dispersion ratios were within normal limits (i.e., $<1.3$).
Table 1. Demographic and injury severity characteristics

<table>
<thead>
<tr>
<th></th>
<th>1. Uncomplicated MTBI</th>
<th>2. Complicated mild–severe TBI</th>
<th>3. Trauma controls</th>
<th>Cohen’s Effect Sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.4</td>
<td>8.5</td>
<td>34.2</td>
<td>11.1</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.6</td>
<td>2.2</td>
<td>14.8</td>
<td>2.2</td>
</tr>
<tr>
<td>LAC (ounces)</td>
<td>6071.8</td>
<td>7289.2</td>
<td>6368.3</td>
<td>9082.7</td>
</tr>
<tr>
<td>Day-of-injury BAL</td>
<td>28.4</td>
<td>27.1</td>
<td>20.1</td>
<td>27.3</td>
</tr>
<tr>
<td>Days tested post-injury</td>
<td>46.1</td>
<td>5.6</td>
<td>48.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Lowest GCS &gt; 30 min</td>
<td>14.4</td>
<td>0.7</td>
<td>13.6</td>
<td>2.3</td>
</tr>
<tr>
<td>RIST Index</td>
<td>110.0</td>
<td>9.5</td>
<td>107.5</td>
<td>9.3</td>
</tr>
<tr>
<td>WTAR reading</td>
<td>107.1</td>
<td>7.1</td>
<td>106.0</td>
<td>7.4</td>
</tr>
<tr>
<td>Premorbid IQ (Dem + WTAR)</td>
<td>110.8</td>
<td>7.3</td>
<td>109.8</td>
<td>7.4</td>
</tr>
</tbody>
</table>

Notes: N = 142 (43 uncomplicated mild TBI, 63 complicated mild–severe TBI, 36 trauma control).
LAC = lifetime alcohol consumption; BAL = blood alcohol level (in mg/dl); GCS = Glasgow Coma Scale; RIST = Reynolds Intellectual Screening Test; WTAR = Wechsler Test of Adult Reading; TBI = traumatic brain injury.
a, b, and c subscript letters denote a statistically significant difference (p < .05).

Table 2. Demographic and injury severity characteristics

<table>
<thead>
<tr>
<th></th>
<th>Uncomplicated MTBI</th>
<th>Complicated mild–severe TBI</th>
<th>Trauma control</th>
<th>χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>N</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
<td>76.7</td>
<td>47</td>
<td>74.6</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>23.3</td>
<td>16</td>
<td>25.4</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>N</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>36</td>
<td>83.7</td>
<td>55</td>
<td>87.3</td>
</tr>
<tr>
<td>Asian/East-Indian/other</td>
<td>7</td>
<td>16.3</td>
<td>8</td>
<td>12.7</td>
</tr>
<tr>
<td>Mechanism of injury</td>
<td>N</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>MVA</td>
<td>15</td>
<td>34.9</td>
<td>22</td>
<td>34.9</td>
</tr>
<tr>
<td>Non-MVA</td>
<td>28</td>
<td>65.1</td>
<td>41</td>
<td>65.1</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>N</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>None</td>
<td>3</td>
<td>7.0</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Transient</td>
<td>10</td>
<td>23.3</td>
<td>12</td>
<td>19.0</td>
</tr>
<tr>
<td>&lt;5–30 min</td>
<td>28</td>
<td>65.1</td>
<td>41</td>
<td>65.1</td>
</tr>
<tr>
<td>&gt;30 min</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>4.8</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>4.7</td>
<td>6</td>
<td>9.5</td>
</tr>
<tr>
<td>Posttraumatic amnesia</td>
<td>N</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&lt;15 min</td>
<td>10</td>
<td>23.3</td>
<td>4</td>
<td>6.3</td>
</tr>
<tr>
<td>15 min–24 h</td>
<td>33</td>
<td>76.7</td>
<td>49</td>
<td>77.8</td>
</tr>
<tr>
<td>&gt;24 h</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>15.9</td>
</tr>
<tr>
<td>CT scan</td>
<td>N</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Not ordered</td>
<td>2</td>
<td>4.7</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Normal</td>
<td>41</td>
<td>95.3</td>
<td>24</td>
<td>38.1</td>
</tr>
<tr>
<td>Abnormal</td>
<td>0</td>
<td>0</td>
<td>38</td>
<td>60.3</td>
</tr>
<tr>
<td>MRI scan</td>
<td>N</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Normal</td>
<td>43</td>
<td>100</td>
<td>8</td>
<td>12.7</td>
</tr>
<tr>
<td>Abnormal</td>
<td>0</td>
<td>0</td>
<td>55</td>
<td>87.3</td>
</tr>
</tbody>
</table>

Notes: N = 142 (43 uncomplicated mild TBI, 63 complicated mild–severe TBI, 36 trauma control).
MVA = motor-vehicle accident; CT = computed tomography; MRI = structural magnetic resonance imaging; TBI = traumatic brain injury.
aCalculated using a 2 × 2 table by combining (i) “None” and “Transient” and (ii) “<5–30 min” and “>30 min.” “Missing” was not included.
bCalculated using a 2 × 2 table by combining (i) “None” and “<15 min” and (ii) “<15 min–24 h” and “>24 h.”
cCalculated using a 2 × 2 table by combining (i) “Not Ordered” and “Normal” and (ii) “Abnormal.”
Table 3. Descriptive statistics, group comparisons, and effect sizes for all measures across groups

<table>
<thead>
<tr>
<th></th>
<th>1. Uncomplicated MTBI</th>
<th>2. Complicated mild–severe TBI</th>
<th>3. Trauma controls</th>
<th>Cohen’s Effect Sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAI total</td>
<td>8.2</td>
<td>8.4</td>
<td>7.4</td>
<td>7.0</td>
</tr>
<tr>
<td>BDI-II total</td>
<td>9.7</td>
<td>9.5</td>
<td>10.0</td>
<td>7.9</td>
</tr>
<tr>
<td>BC-PSI total</td>
<td>10.4</td>
<td>10.2</td>
<td>12.2</td>
<td>10.2</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAB Total Index</td>
<td>105.7</td>
<td>14.3</td>
<td>104.2</td>
<td>14.5</td>
</tr>
<tr>
<td>NAB Attention Index</td>
<td>104.6</td>
<td>11.0</td>
<td>103.6</td>
<td>14.9</td>
</tr>
<tr>
<td>NAB Memory Index</td>
<td>101.1</td>
<td>13.4</td>
<td>101.5</td>
<td>13.3</td>
</tr>
<tr>
<td>NAB Language Index</td>
<td>103.8</td>
<td>17.9</td>
<td>101.6</td>
<td>19.8</td>
</tr>
<tr>
<td>NAB Spatial Index</td>
<td>107.9</td>
<td>16.5</td>
<td>107.3</td>
<td>14.9</td>
</tr>
<tr>
<td>NAB Executive Index</td>
<td>104.9</td>
<td>16.3</td>
<td>102.6</td>
<td>16.6</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># abnormal FA scores</td>
<td>3.2</td>
<td>4.8</td>
<td>3.7b</td>
<td>3.2</td>
</tr>
<tr>
<td># abnormal MD scores</td>
<td>3.4</td>
<td>4.9</td>
<td>5.1b</td>
<td>3.4</td>
</tr>
<tr>
<td># abnormal RD scores</td>
<td>3.5</td>
<td>5.8</td>
<td>5.1b</td>
<td>3.5</td>
</tr>
<tr>
<td># abnormal AD scores</td>
<td>2.8</td>
<td>3.2</td>
<td>4.0b</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Notes: N = 142 (43 uncomplicated mild TBI, 63 complicated mild–severe TBI, 36 trauma control).

BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-Second Edition; BC-PSI = British Columbia Postconcussion Inventory; NAB = neuropsychological assessment battery; FA = fractional anisotropy; MD = mean diffusivity; RD = radial diffusivity; AD = axial diffusivity.

1Group comparisons for the neuropsychological measures were undertaken using ANOVA. 2Group comparisons for the neuroimaging measures were undertaken using Kruskal–Wallis H-tests (across three groups) and Mann–Whitney U-tests (pairwise comparisons) due to non-normal distribution of scores. 3Prorated Index scores

*p < .05; a, b, c superscript letters reflect significant pairwise differences.

Influence of LAC and BAL: Neuropsychological Measures

Summary statistics for the series of hierarchical regression analyses designed to examine the influence of BAL and LAC on outcome from TBI, using the entire TBI sample, are presented in Table 4. Due to the large amount of data generated in these analyses, data are only provided relating to $R^2$, $R^2_{\text{change}}$, and Sig. $F_{\text{change}}$. The inclusion of pre-injury LAC at Step 3 of the hierarchical regression analyses did not make a statistically significant contribution toward the prediction of the self-reported symptoms or neurocognitive measures (Column C: $F_{\text{change}}$, all $p > .05$; <3.3% of unique variance across all measures), with the exception of the Executive Functioning Index ($p = .047$) that accounted for 4.6% of unique variance. The inclusion of day-of-injury BAL at Step 3 of the hierarchical regression analyses also did not make a statistically significant contribution toward the prediction for all measures (Column D: $F_{\text{change}}$, $p > .05$) accounting for <3.6% of unique variance across all measures). Of note, LAC and BAL combined accounted for <5.8% of unique variance across all measures (i.e., Column B: range = 0.9–5.8%).

Summary statistics for the series of hierarchical regression analyses using the complicated mild–severe TBI group is presented in Table 5. The inclusion of pre-injury LAC at Step 3 of the hierarchical regression analyses did not make a statistically significant contribution toward the prediction of the self-report measures, but did make a statistically significant contribution toward the prediction of 3 of the 6 NAB indexes (i.e., Total Index, Attention Index, and Executive Functioning Index; Column C: $F_{\text{change}}$, $p = .005–.047$). The inclusion of LAC increased the variance accounted for by only 6.4%–13.9% across these three indexes. Similarly, the inclusion of day-of-injury BAL at Step 3 of the hierarchical regression analyses did not make a statistically significant contribution toward the prediction of the self-report measures, but did make a statistically significant contribution toward the prediction to 4 of the 6 NAB indexes (i.e., Total Index, Attention Index, Spatial Index, and Executive Functioning Index; Column D: $F_{\text{change}}$, $p = .008–.022$). The inclusion of BAL increased the variance accounted for by only 6.3%–10.8% across these four indexes. Including BAL and LAC simultaneously (Column B) made a statistically significant contribution to the NAB Total Index (13.5%), Attention Index (9.7%), and Executive Function Index (16.2%).

Influence of LAC and BAL: DTI Measures

Summary statistics for the series of GLMs designed to examine the influence of BAL and LAC on outcome from TBI, using the entire TBI sample, are presented in Table 6. Results from GLM-2 revealed that the covariates, BAL, and LAC combined was a
### Table 5. Summary of hierarchical regression analysis: influence of LAC and day-of-injury BAL on symptom and neurocognitive measures in the complicated mild–severe TBI group

<table>
<thead>
<tr>
<th>Dependent variables</th>
<th>Column A</th>
<th>Column B</th>
<th>Column C</th>
<th>Column D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Variance</td>
<td>% Variance accounted for by LAC and BAL</td>
<td>Unique % variance accounted for by LAC</td>
<td>Unique % variance accounted for by BAL</td>
</tr>
<tr>
<td>Covariate(s)†</td>
<td>Step 1: Covariates; Steps 2 and 3: LAC and BAL</td>
<td>Steps 1 and 2: Covariates + BAL; Step 3: LAC</td>
<td>Steps 1 and 2: Covariates + LAC; Step 3: BAL</td>
<td></td>
</tr>
<tr>
<td>R² (%)</td>
<td>p</td>
<td>R² change (%)</td>
<td>Sig. F change</td>
<td>R² change (%)</td>
</tr>
</tbody>
</table>

**Self-reported symptoms**
- BAI total: 17.2, .001, 2.7, .188, .4, .506, 1.4, .186
- BDI-II total: 12.9, .007, .6, .694, .5, .497, .6, .417
- BC-PSI total: 11.0, .018, 2.8, .201, .6, .190, 2.3, .106

**Neurocognitive measures**
- NAB Total Index*: 1.2, .269, 4.5, .091, 3.3, .061, 3.1, .070
- NAB Attention Index: .856, .9, .632, .5, .495, .8, .372
- NAB Memory Index: .870, .9, .641, .6, .419, .916
- NAB Language Index*: 2.1, .137, 1.5, .446, 1.1, .276, 1.0, .296
- NAB Spatial Index*: 2.6, .099, 3.8, .130, 1.8, .165, 3.4, .056
- NAB Executive Index*: .825, 5.8, .04, 4.6, .028, 3.6, .051

Notes: N = 63 complicated mild–severe TBI.

R² = the amount of variance accounted for by the variable(s); R² change = the amount of variance accounted for by the variable above and beyond the previously entered variable(s) in the hierarchy; Sig. F change = p-value relating to the R² change; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-Second Edition; BC-PSI = British Columbia Postconcussion Inventory; NAB = Neuropsychological Assessment Battery.

†For the self-reported symptoms, the covariates included age, education, gender, and PTA. For the neurocognitive measures, only PTA was included. These scores are already demographically adjusted for age, gender, and education.

*Prorated Index scores.

---

### Table 4. Summary of hierarchical regression analysis: influence of LAC and day-of-injury BAL on symptom and neurocognitive measures in the entire TBI group

<table>
<thead>
<tr>
<th>Dependent variables</th>
<th>Column A</th>
<th>Column B</th>
<th>Column C</th>
<th>Column D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Variance</td>
<td>% Variance accounted for by LAC and BAL</td>
<td>Unique % variance accounted for by LAC</td>
<td>Unique % variance accounted for by BAL</td>
</tr>
<tr>
<td>Covariate(s)†</td>
<td>Step 1: Covariates; Steps 2 and 3: LAC and BAL</td>
<td>Steps 1 and 2: Covariates + BAL; Step 3: LAC</td>
<td>Steps 1 and 2: Covariates + LAC; Step 3: BAL</td>
<td></td>
</tr>
<tr>
<td>R² (%)</td>
<td>p</td>
<td>R² change (%)</td>
<td>Sig. F change</td>
<td>R² change (%)</td>
</tr>
</tbody>
</table>

**Self-reported symptoms**
- BAI total: 17.2, .001, 2.7, .188, .4, .506, 1.4, .186
- BDI-II total: 12.9, .007, .6, .694, .5, .497, .6, .417
- BC-PSI total: 11.0, .018, 2.8, .201, .6, .190, 2.3, .106

**Neurocognitive measures**
- NAB Total Index*: 1.2, .269, 4.5, .091, 3.3, .061, 3.1, .070
- NAB Attention Index: .856, .9, .632, .5, .495, .8, .372
- NAB Memory Index: .870, .9, .641, .6, .419, .916
- NAB Language Index*: 2.1, .137, 1.5, .446, 1.1, .276, 1.0, .296
- NAB Spatial Index*: 2.6, .099, 3.8, .130, 1.8, .165, 3.4, .056
- NAB Executive Index*: .825, 5.8, .04, 4.6, .028, 3.6, .051

Notes: N = 106 (43 uncomplicated mild TBI, 63 complicated mild–severe TBI).

R² = the amount of variance accounted for by the variable(s); R² change = the amount of variance accounted for by the variable above and beyond the previously entered variable(s) in the hierarchy; Sig. F change = p-value relating to the R² change; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-Second Edition; BC-PSI = British Columbia Postconcussion Inventory; NAB = Neuropsychological Assessment Battery.

†For the self-reported symptoms, the covariates included age, education, gender, and PTA. For the neurocognitive measures, only PTA was included. These scores are already demographically adjusted for age, gender, and education.

*Prorated Index scores.
significant predictor of the number of abnormal FA (p = .034), MD (p < .001), RD (p < .001), and AD (p < .001) scores. However, LAC and BAL were found to be poor predictors of all DTI measures (all p > .131). \( \text{AICdiff} \) scores between GLM-2 and GLM-1A revealed no difference between models (range: \( \text{AICdiff} = 0.4 \) to 2.0), indicating that the inclusion of LAC into the model did not make a significant unique contribution toward the prediction of the DTI measures. Similarly, \( \text{AICdiff} \) scores between GLM-2 and GLM-1B revealed no difference between models (range: \( \text{AICdiff} = 1.1 \) to 2.0), indicating that the inclusion of BAL into the model did not make a significant unique contribution toward the prediction of the DTI measures.

Summary statistics for the GLMs using the complicated mild–severe TBI sample are also presented in Table 6. The GLM-2 revealed that the covariates, BAL, and LAC combined was a significant predictor of the number of abnormal MD (\( p < .05 \)), FA (\( p < .01 \)), RD (\( p < .01 \)), and AD (\( p < .01 \)) scores, but not abnormal FA scores (\( p > .07 \)). LAC and BAL were again found to be poor predictors of the DTI measures (all \( p > .16 \)). \( \text{AICdiff} \) scores between GLM-2 and GLM-1 revealed no difference between models (range: \( \text{AICdiff} = < 0.1 \) to 1.5), indicating that the inclusion of LAC into the model did not make a significant unique contribution toward the prediction of the DTI measures. Similarly, \( \text{AICdiff} \) scores between GLM-2 and GLM-1B revealed no difference between models (range: \( \text{AICdiff} = 0.8 \) to 2.0), indicating that the inclusion of BAL into the model did not make a significant unique contribution toward the prediction of the DTI measures.

### Exploratory Subgroup Analyses

Exploratory subgroup analyses were undertaken using the entire TBI sample (including uncomplicated mild, complicated, mild, moderate, and severe TBI). A group of patients who had elevated BAL levels at the time of injury (i.e., \( \geq 21 \text{ mmol/L} \); U.S. equivalent = 100 mg/dl) and pre-injury LAC scores in the bottom 25% of the entire sample were selected to represent a higher risk group with more pronounced alcohol-related histories \( (n = 19; \text{“High BAL/LAC” group}) \). Similarly, a group of patients who had low BAL levels at the time of injury (i.e., \( < 21 \text{ mmol/L} \) and pre-injury LAC scores in the bottom 25% of the entire sample were selected to represent a low-risk group with no alcohol-related histories \( (n = 50; \text{“Low BAL/LAC” group}) \). The BAL cutoff value was selected to be consistent with the values used in the extant literature to classify alcohol intoxication.

Comparison of demographic and injury-related characteristics (using ANOVA and \( \chi^2 \) analysis) revealed no significant group differences for age (\( p = .07 \)), ethnicity (\( p = .26 \)), education (\( p = .21 \)), duration of LOC (\( p = .22 \)) or PTA (\( p = .42 \)), GCS scores (\( p = .41 \)), intracranial abnormality on day-of-injury CT scan (\( p = .166 \)) or 6-week structural MRI scan (\( p = .479 \)), estimated premorbid IQ (\( p = .746 \)), or post-injury obtained IQ (\( p = .819 \)). It should be noted, however, that although not statistically significant (likely due to small sample size), there was a medium effect size for age (\( d = 0.49 \)). The High BAL/LAC group \( (M = 38.0 \text{ years}, SD = 10.5) \) was slightly older compared with the Low BAL/LAC group \( (M = 32.8 \text{ years}, SD = 10.8) \). There were significant differences between groups for gender \( (p = .042) \), mechanism of injury \( (p = .013) \), and days tested post-injury \( (p = .046, d = 0.55) \). The High BAL/LAC group had a higher number of males \( (89.5\%); \text{Low BAL/LAC} = 64.0\% \), fewer people who were injured in a motor-vehicle-related accident \( (15.8\%; \text{Low BAL/LAC} = 50.0\%) \), and they were tested on average slightly earlier post-injury \( (45.0 \text{ days} \text{[SD} = 6.2]) \); Low BAL/LAC = 48.3 days \text{[SD} = 6.0]) \).
Comparison of the neuropsychological measures revealed no significant group differences for all neurocognitive measures \((p = .465-.957)\) and self-reported symptom scales \((p = .170-.767)\). There were, however, medium effect sizes found for BAI total \((d = 0.43)\) and BC-PSI total \((d = 0.39)\) scores. On these measures, there was a trend toward the Low BAL/LAC group (BAI: \(M = 8.4, SD = 9.5\); BC-PSI: \(M = 13.5, SD = 11.3\)) to report a greater number of anxiety and postconcussion symptoms (High BAL/LAC group: BAI, \(M = 5.1, SD = 3.2\); BC-PSI, \(M = 9.4, SD = 8.1\)). For the DTI measures, there were significant group differences, and large effect sizes, for the number of low MD scores \((p = .005, d = 0.78)\) and RD scores \((p = .003, d = 0.84)\). The High BAL/LAC group had a greater number of low MD scores \((M = 9.1, SD = 7.5)\) and RD scores \((M = 9.8, SD = 3.7)\) compared with the Low BAL/LAC group (number of low MD scores: \(M = 3.9, SD = 6.3\); number of low RD scores: \(M = 3.7, SD = 6.8)\). When adjusting for the influence of age (using ANCOVA), the group differences for MD \((p = .012)\) and RD \((p = .007)\) scores remained. Although not significantly different, medium effect sizes were found for the number of low FA scores \((d = 0.45)\) and AD scores \((d = 0.49)\). For these measures, there was a trend toward the High BAL/LAC group to have a greater number of low FA \((M = 5.6, SD = 4.8)\) and AD scores \((M = 5.8, SD = 3.5)\) compared with the Low BAL/LAC group (number of low FA scores: \(M = 3.4, SD = 5.2\); Number of low AD scores: \(M = 3.5, SD = 4.8)\)). When adjusting for the influence of age (using ANCOVA), the lack of statistical group differences for FA \((p = .195)\) and AD \((p = .085)\) remained.

**Discussion**

The primary purpose of this study was to disentangle the relative contributions of day-of-injury alcohol intoxication and pre-injury alcohol misuse on the neuropsychological outcome (i.e., cognitive functioning and self-reported symptoms) and white-matter changes in the brain following TBI at 6–8 weeks post-injury. It was hypothesized that both pre-injury LAC and day-of-injury BAL would be associated with worse neuropsychological outcome and reduce white-matter integrity in the brain at 6–8 weeks post-injury, and that BAL would account for more variance than LAC. This hypothesis was not supported by the results. Overall, the results of this study found that neither day-of-injury BAL nor pre-injury LAC, had a statistically significant influence on (i) measures of attention, memory, language, spatial ability, or executive functioning; (ii) anxiety, depression, and postconcussion symptoms; and (iii) the integrity of white-matter structures in the whole brain using advanced neuroimaging (i.e., DTI).

When compared with those studies that have examined the influence of one of these alcohol variables separately, our results are inconsistent with a large number of studies that have documented the adverse effects of alcoholism on neurocognitive functioning and reduced white-matter integrity (e.g., Barker et al., 1999; Jensen & Pakkenberg, 1993; Nixon, 1999; Pfefferbaum & Sullivan, 2005; Pfefferbaum et al., 2000; Schulte et al., 2005; Sullivan et al., 1996). Similarly, our results are inconsistent with much of the literature that has found an association between day-of-injury alcohol intoxication and worse neurocognitive functioning and reduced white-matter integrity (Barker et al., 1999; Bombardier & Thurber, 1998; Kelly et al., 1997; Tate et al., 1999; Wilde et al., 2004). However, as in our study, a significant minority of studies found no influence of day-of-injury BAL on neurocognitive outcome following TBI (Kaplan & Corrigan, 1992; Lange et al., 2007; Schutte & Hanks, 2010; Turner et al., 2006). Paradoxically, in one study, patients who were intoxicated at the time of injury actually performed better on neurocognitive measures compared with those who were sober (Lange et al., 2008).

When our results are compared with the small number of studies that have examined the influence of the two alcohol variables concurrently, there is again little consistency with the current study. Our results are somewhat consistent with one study that found no association between day-of-injury BAL or pre-injury alcohol use with functional status post-injury (Vickery et al., 2008). However, our results are inconsistent with other studies that have found that (i) day-of-injury BAL, but not pre-injury alcohol consumption, was associated with neurocognitive outcome post-injury (Brooks et al., 1989; Tate et al., 1999); (ii) pre-injury alcohol consumption, but not day-of-injury BAL was associated with neurocognitive outcome post-injury (Lange et al., 2007), or (iii) both BAL and pre-injury alcohol use were associated with neuropsychological and neuropathological outcome post-injury (Wilde et al., 2004).

The inconsistency of our results with the extant research literature prompts a number of hypothesized explanations and discussion points. First, the lack of influence of day-of-injury BAL and pre-injury LAC found here may be due to the possibility that the alcohol measures used in this study were problematic, in that they lacked sufficient sensitivity. For the self-reported symptom measures and neuroradiological measures, this hypothesis is clearly not the case. When compared with the TC group, both the uncomplicated MTBI and complicated mild–severe TBI group reported higher rates of depression and postconcussion symptoms (but not anxiety), and had a greater number of abnormal FA, MD, RD, and AD scores in the whole brain. For the neurocognitive measures however, this possibility is uncertain. In our study, there were no differences for all neurocognitive measures across the three groups. It should be noted that previous research has found that the neurocognitive measures used in our study are sensitive to various neurological conditions such as TBI, dementia, aphasia, HIV/AIDS, multiple sclerosis, and adult ADHD (White & Stern, 2003). It is not clear why this was also not found here. It is possible that our use of prorated scores for some of the NAB measures has compromised the psychometric integrity of these measures. However, similar results were found when using...
prorated versus non-prorated NAB indexes and this explanation is considered unlikely. It is also possible that we have recruited a sample of patients with TBIs who are somewhat above average in pre-injury intelligence (see Table 1), resilient, motivated to perform well in this research study, and who have had a generally favorable outcome from injury. None of the patients with TBIs, for example, required inpatient rehabilitation services. It is important to note that this is not the first study to report such findings. Using quantitative MRI methods, Bigler and colleagues (1996) showed that neuropathological changes were evident in patients who had sustained a TBI and who had a history of pre-injury alcohol abuse, whereas these differences were less distinct or undetectable when using neurocognitive measures.

Second, the lack of influence of pre-injury LAC found here may also be due to the absence of a sufficient sample of individuals with pre-injury problematic alcohol consumption. The National Institute of Alcohol Abuse and Alcoholism (NIAAA, National Institute on Alcoholism and Alcohol Abuse, 2005) defines heavy drinking as follows: (i) for women: 8 or more drinks per week or 4 or more drinks on a single occasion (i.e., binge drinking) and (ii) for men: 15 or more drinks per week or 5 or more drinks on a single occasion. In our TBI sample, the number of alcoholic drinks typically consumed each week prior to their injury was as follows: 0–5 drinks (46.2%), >5–10 drinks (23.6%), >10–20 drinks (17.0%), >20–30 drinks (6.6%), and >30–56 drinks (6.6%). The number of binge drinking events per year was as follows: 0–12 days (49.1%), 15–26 days (13.2%), 30–52 days (13.2%), 78–156 days (17.0%), and 208–365 days (7.5%). When applying the NIAAA criteria, more than half (51.9%) of the TBI sample met criteria for heavy drinking. However, it is important to appreciate that only 1 in 4 people who meet the NIAAA criteria actually qualify for a diagnosis of alcohol abuse or alcohol dependence (National Institute on Alcoholism and Alcohol Abuse, 2005). If only 25% of the sample who met NIAAA criteria for heavy drinking actually had a serious substance abuse problem, then only 13% of the total sample would be in this subgroup (Note: we did not evaluate criteria for alcohol abuse/dependence and the actual prevalence of these disorders in our sample unknown). Past studies that have demonstrated a negative association between lifetime alcohol misuse and neurocognitive or neuropathological outcome typically include participants with diagnosed alcohol dependence or abuse (e.g., Barker et al., 1999; Fein et al., 1998; Nixon, 1999; Pfefferbaum et al., 1992, 2000, 2002; Pfefferbaum & Sullivan, 2005; Schulte et al., 2005; Sullivan et al., 1996). Thus, the relatively small percentage of people with severe substance abuse problems in this sample has likely minimized, or masked, the possible influence of pre-injury LAC in this sample. In our exploratory subgroup analyses, when we compared “extreme” alcohol groups by combining both BAL and LAC criterion together, individuals who were “high-risk” alcohol consumers (i.e., intoxicated at the time of injury and in the highest 25% of pre-injury alcohol consumers) had a larger number of DTI abnormalities when compared with those individuals who were “low-risk” alcohol consumers (i.e., sober at the time of injury and in the lowest 25% of pre-injury alcohol consumers). There were, however, no differences between these extreme groups on any of the neurocognitive or self-reported symptom measures.

Third, similar to the above point, the lack of influence of day-of-injury BAL found here may also be due to the absence of a sufficient sample of individuals who were intoxicated at the time of injury. Approximately half of the TBI sample (54.7%) had a BAL below the legal limit of alcohol intoxication (i.e., <100 mg/dl). However, of the remaining sample, 17.9% had a BAL of 100–199 mg/dl, 19.8% a BAL of 200–299 mg/dl, 6.6% a BAL of 300–399 mg/dl, and <1% a BAL of >400 mg/dl. These data show that there was substantial variation of the sample that exceeded the legal limit of alcohol intoxication (45.3%) and a substantial proportion of the sample that had BALs that were 2–4 times the legal limit (27.3%). As such, the sample used in this study is considered to include a sufficient number of individuals who were intoxicated at the time of injury and the lack of representativeness of this variable is not considered to be a contributory factor to these results.

Fourth, in a previous study by some of the current authors (Lange et al., 2008), we hypothesized that the lack of influence of day-of-injury BAL could manifest as a result of TBI severity characteristics in the group under investigation. If indeed the hypothesis is true that day-of-injury BAL increases the magnitude of brain injury due to the presence of a variety of negative physiological responses to alcohol not present in a person who is sober at the time of injury (Alexander et al., 2004; Altura & Altura, 1999; Barker et al., 1999; Mautes et al., 2001; Wilde et al., 2004; Zink et al., 2001), it would seem logical to assume that as TBI severity increases, the negative effects of day-of-injury BAL would also increase. Of particular mention are those participants who have sustained an uncomplicated MTBI. Uncomplicated MTBIs are the mildest forms of TBI. Permanent cognitive, psychological, or psychosocial problems due to the biological effects of this injury are uncommon following these injuries (Binder, Rohling, & Larrabee, 1997; Carroll et al., 2004). Therefore, any negative effects of day-of-injury BAL are likely to be minimized in this group due to less brain insult. Conversely, any negative effects of day-of-injury BAL is likely to be maximized in a group of participants who have sustained a brain injury of greater severity (i.e., complicated mild–severe TBI group). In this study, when we combined the uncomplicated MTBI and complicated mild–severe TBI groups, we found no influence of day-of-injury BAL on all outcome variables. It is possible that the inclusion of the uncomplicated MTBI group in these analyses “washed out” any effects of BAL. However, when we examined the complicated mild–severe TBI group alone, the lack of influence of day-of-injury BAL on all measures remained, with the exception the NAB Executive Index. Nonetheless, the unique variance accounted for by BAL was small and not considered clinically meaningful.
Finally, the lack of influence of day-of-injury BAL found here may also be due to methodological differences across studies. Many studies in this area suffer from methodological limitations that preclude us from understanding the effects of day-of-injury alcohol on outcome following TBI (including some of our own; Lange et al., 2007, 2008). The most significant problem is the failure to adequately measure and control for the effects of pre-injury alcoholism (other past methodological problems include the failure to evaluate patients within the same time frame post-injury; retrospective analyses of a convenience sample; not using BAL to define patients who are “intoxicated”). Given the known influence of alcohol abuse on neuropsychological and neuropathological functioning (e.g., Barker et al., 1999; Fein et al., 1998; Parsons et al., 1990; Pfefferbaum et al., 1992, 2000, 2002; Pfefferbaum & Sullivan, 2005; Schulte et al., 2005; Sullivan et al., 1996), it is possible that previous studies that have found an association between day-of-injury BAL and poor outcome, have not controlled for pre-injury alcohol factors, and have drawn erroneous conclusions (Bombardier & Thurber, 1998; Kelly et al., 1997). There is one exception to this, however. In a carefully controlled study by Tate and colleagues (1999), these authors concluded that BAL at hospital admission predicted poorer performance on several neuropsychological measures and “accounted for a significant, unique portion of the variance in these cognitive measures beyond that of variables known to moderate recovery from TBI, including age, [education], TBI severity, and history of alcohol abuse” (p. 776). The results of the study by Tate and colleagues (1999) is in stark contrast to the only other carefully controlled study available in this area —, that is, the current study —that found no effect of BAL. Although the study by Tate and colleagues (1999) did differ to the current study in some aspects of the methodology (e.g., retrospective chart review; included a higher number of participants with alcohol abuse; designation of pre-injury alcohol use relied on medical record review; patients were not evaluated at the same time post-injury), it is difficult to account for this discrepancy.

To our knowledge, the current study is one of the most carefully controlled prospective research studies to date, designed specifically to assess the relative contribution of day-of-injury alcohol intoxication versus pre-injury alcohol use on outcome from mild, moderate, and severe TBI. In order to address the methodological limitations of past studies, we employed a prospective research design that (i) recruited patients from a Level I trauma center; (ii) included patients with well-defined TBI severity; (iii) evaluated patients at the same time period post-injury; (iv) comprehensively evaluated outcome by including neurobehavioral, neurocognitive, and neuroradiological measures; (v) used BAL levels detected on admission to measure day-of-injury alcohol intoxication; (vi) comprehensively evaluated, and controlled for, pre-injury alcohol consumption; and (vii) included a sample of TCs as a comparison group.4 In sum, our results do not support the tenet that day-of-injury alcohol consumption is associated with worse outcome following TBI. When considering the literature as a whole (including this study), it appears unlikely that day-of-injury alcohol intoxication has an adverse effect on outcome following TBI. Rather, an association between day-of-injury BAL and worse outcomes found in past studies might reflect the influence of pre-injury alcohol consumption, or some other unknown and/or unrelated factor(s).

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References


4 As part of this study design, we also included a 12-month post-injury follow-up evaluation. These data are currently being collected by our group and are not reported here.


