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Polysubstance abuse and traumatic brain injury: Quantitative magnetic resonance imaging and neuropsychological outcome in older adolescents and young adults

LISA H. BARKER,[1] ERIN D. BIGLER,[2] STERLING C. JOHNSON,[3] CAROL V. ANDERSON,[4] ANTONIETTA A. RUSSO,[5] BARBARA BOINEAU,[6] AND DUANE D. BLATTER[7]

[1]Audie L. Murphy Memorial Veterans Hospital, San Antonio, TX
[2]Brigham Young University, Provo, UT
[3]Dartmouth College, Hanover, NH
[4]Brigham Young University, Provo, UT
[5]University of California, San Francisco, CA
[6]Heritage Residential Treatment Center, Provo, UT
[7]LDS Hospital, Salt Lake City, UT

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Abstract

Few studies have examined the consequences of alcohol and drug abuse on TBI though they commonly co-occur. Both TBI and substance abuse independently result in neuropathological changes in the brain such as ventricular enlargement and cortical atrophy, thus it is reasonable to hypothesize that the combination of the two would result in more significant cerebral damage. In this study, 3 groups of patients—traumatically brain injured (TBI) with substance abuse ($N = 19$), TBI without substance abuse ($N = 19$), and substance abuse with no TBI ($N = 16$)—were compared with normal controls ($N = 20$) on several quantitative MRI (QMRI) measures. Since TBI most frequently occurs in older adolescents and young men, we examined only male participants between 16 and 30 years of age. Comparing young substance abusers to controls resulted in no QMRI differences. When controlling for head injury severity, the effects of substance abuse in combination with TBI resulted in greater atrophic changes than seen in any other group. TBI and substance abuse patients' neuropsychological test performances also were examined, and no differences were found among patient groups on any measures. These findings have implications for the deleterious interaction of substance abuse combining with TBI to result in greater neuropathological changes that can be detected by QMRI techniques. (*JINS*, 1999, *5*, 593–608.)

Keywords: Substance abuse, Traumatic brain injury, Quantitative neuroimaging

INTRODUCTION

Various studies of traumatic brain injury (TBI) consistently have found substance abusers at high risk for fatal and nonfatal injury (Cherpitel, 1996; Dikmen et al., 1993; Drubach et al., 1993, 1994; Emmerson et al., 1988; Kraus & Sorenson, 1994; Kraus et al., 1989; Kreutzer et al., 1990; Mearns & Lees-Haley, 1993; Mercer & Jeffery, 1995; Robertson et al., 1994; Soderstrom et al., 1997; Solomon & Malloy, 1992; Sparadeo et al., 1990). Research findings have reported a positive blood alcohol level (BAL) in 32 to 73% of patients admitted to hospitals for brain injury (Dikmen et al., 1995; Galbraith et al., 1976; Kraus & Sorenson, 1994; Kreutzer et al., 1990; Rimel et al., 1982; Solomon & Malloy, 1992; Sparadeo et al., 1990). Likewise, other substances of abuse such as cocaine, methamphetamine, and marijuana are found more frequently in TBI victims (Francis et al., 1995; Mercer & Jeffery, 1995; Skurtveit et al., 1995; Tomaszewski et al., 1996) and often occur in combination with alcohol (Martin et al., 1996a, 1996b; Meyer, 1995). However, the relationship between TBI and substance abuse has not been well defined. Also, only limited

Reprint requests to: Erin D. Bigler, P.O. Box 25543, Department of Psychology, Brigham Young University, Provo, UT 84602-5543. E-mail: erin_bigler@byu.edu

attention has been paid to the role of intoxication or substance abuse in neuropathological and cognitive sequelae as well as rehabilitation outcome associated with cerebral injury (Bogner et al., 1997; Brooks et al., 1989; Corrigan, 1995; Emmerson et al., 1988; Kelly et al., 1997; Sander et al., 1997; Solomon & Malloy, 1992; Sparadeo & Gill, 1989; Rönty et al., 1993). This is often the case because patients with substance abuse problems are excluded from TBI studies to control for effects of preinjury conditions (Dicker, 1989; Kaplan & Corrigan, 1992; Robertson et al., 1994). Indisputably, substance abuse is associated with a greater likelihood of being involved in an accident (Cherpitel et al., 1995; Vinson et al., 1995). Whether the presence of substance abuse has an added deleterious effect to the injury remains in question and is the focus of this investigation.

Neuroimaging and Brain Morphology in Substance Abuse and TBI

Independent of any traumatic brain injury, it has been documented that chronic alcohol abuse can lead to demonstrable changes on computerized tomography (CT) and magnetic resonance (MR) imaging. Neuroimaging studies have shown ventricular and sulcal enlargement in both Korsakoff and non-Korsakoff alcoholics (Aasly et al., 1993; Christie et al., 1988; Jernigan et al., 1991a, 1991b; Litton et al., 1993; Nicolas et al., 1997; Pfefferbaum et al., 1992; Rosse et al., 1997). Additionally, lesions or parenchymal volume loss have been noted in the diencephalon (Jernigan et al., 1991a; Paller et al., 1997), mamillary bodies (Bigler et al., 1989), cerebellum (Cala et al., 1978), orbital frontal regions (Jacobson & Lishman, 1990; Jernigan et al., 1991a, 1991b), parietal and superior frontal cortex along with mesial temporal cortex (Jernigan et al., 1991b; Sullivan et al., 1996), and corpus callosum (Hommer et al., 1996). In addition, using MR imaging and neuropathological analysis some research suggests that white matter is more adversely affected than gray matter structures (Charness, 1993; Harper et al., 1985; Pfefferbaum et al., 1992; Sullivan et al., 1996). Similarly, substances of abuse other than alcohol can lead to similar pathological changes, identified by MR imaging (Aasly et al., 1993; Brown et al., 1992; Pascual-Leone et al., 1991; Strickland et al., 1998). Age and chronicity of substance abuse consistently emerge as important interacting variables in neuroimaging studies with substance abusers (Mann et al., 1989; Pfefferbaum et al., 1992; Shear et al., 1994; Wilkinson & Carlen, 1980). Older, more chronic abusers show exaggerated problems on neuroimaging and neuropsychological tests (Nicolas et al., 1997; Shear et al., 1994; Sullivan et al., 1996; Wilkinson & Carlen, 1980).

Similarly, atrophic brain changes are associated with TBI. For example, following TBI ventricular and sulcal enlargement as well as atrophic changes in corpus callosum, diencephalon, fornix and hippocampus have been demonstrated (Anderson & Bigler, 1995; Bigler et al., 1996b, 1997; Gale et al., 1995; Johnson et al., 1994, 1996; Wood & Bigler, 1995). Ventricular expansion (hydrocephalus ex vacuo) that accompanies brain injury typically is interpreted as an indication of disproportionate loss of white over gray matter, because of white matter vulnerability secondary to the shearing effects and diffuse axonal injury of TBI (Johnson et al., 1994, 1996).

Combined Effects of TBI and Substance Abuse

Several studies have examined the effects of substance abuse and TBI, demonstrating that polysubstance or ethanol abuse is related to indicators of injury severity. For example, it has been demonstrated that patients with a positive BAL on admission have a lower Glasgow Coma Score or elevated severity rating of injury (Bigler et al., 1996b; Brickley & Shepherd, 1995; Gurney et al., 1992; Kaplan & Corrigan, 1992; Sparadeo et al., 1992). They also may have a lower cognitive status at time of discharge and a higher mortality rate, though results have been conflicting (Fuller, 1995; Kaplan & Corrigan, 1992; Ruff et al., 1990; Sparadeo et al., 1992). Excessive users typically have a much lower rate of good outcome following injury (Charness, 1993; Rönty et al., 1993; Ruff et al., 1990), and patients with a history of alcohol abuse may show more long-term neurobehavioral and occupational problems than patients with no abuse history (Rönty et al., 1993; Sabhesan et al., 1987). Finally, the likelihood of seat belt use is reduced by alcohol, which increases the likelihood of multiple trauma and longer lengths of stay (Kaplan & Corrigan, 1992).

Mechanisms of Injury

There are several potential shared mechanisms of neurologic sequelae common to both TBI and substance abuse (Gualtieri, 1990; Koob & Nestler, 1997; McCann et al., 1997). For example, neuropathologic sequela associated with excitotoxic reaction may result from either TBI or substance abuse (Charness, 1993; Filley & Kelly, 1993; Gualtieri, 1990; Lucas et al., 1997; Novack et al., 1996; Salazar, 1992). Likewise, blood-flow dynamics may be influenced by either TBI or substance abuse (Gean, 1994; Volkow, 1987). For example, the spasmogenic actions of ethanol on cerebral blood vessels may act in concert with other blood-flow changes to facilitate cerebral infarctions (see Altura & Altura, 1989; Hillborn & Kaste, 1981) along with other biochemical factors that may result in greater degree of hemorrhage once bleeding occurs (DeCrescito et al., 1974; Flamm et al., 1977; Rönty et al., 1993). Also, direct biochemical and metabolic alterations associated with alcohol abuse may be responsible for CNS damage (Beghi et al., 1995; Kelly, 1995; Oscar-Berman et al., 1997; Ruff et al., 1990; Solomon & Malloy, 1992). Cocaine is known to precipitate autonomic and metabolic instability, alterations in cerebral perfusion and can cause vascular brain injury (Kaufman et al., 1998; Mendoza et al., 1992; Sharkey et al., 1991;

Volkow et al., 1988; Woods, 1992). Pathologically increased neuroexcitation also may be responsible for neural injury as a consequence of trauma and/or substance abuse (Choi & Rothman, 1990; Fadden et al., 1989; Kelly, 1995). Lastly, substance abuse may alter respiratory functions which in turn may affect neural integrity in the traumatically injured brain (Pfenninger et al., 1987).

Performance on Neuropsychological Measures

On neuropsychological tests, alcohol abusers without known head injury have shown a consistent pattern of diminished performance on tasks of memory and learning, visual–spatial abilities, abstract reasoning, and problem solving, while performing at relatively normal levels on measures of immediate memory (Bergman et al., 1980; Bondi et al., 1998; Browning et al., 1992; Cala et al., 1978; Chick et al., 1989; Goldstein & Shelly, 1980; Jernigan et al., 1991b; Leckliter & Matarazzo, 1989; Mearns & Lees-Haley, 1993; Moss et al., 1994; Shear et al., 1992; Tarter et al., 1995). Similar deficits may be associated with polysubstance abuse (Ardila et al., 1991; Freilich & Byrne, 1992; Grant et al., 1978; Horner, 1997; Mittenberg & Motta, 1993; Moss et al., 1994; O'Malley et al., 1992; Purcell et al., 1995; Rosselli & Ardila, 1996; Sweeney et al., 1989). Marijuana abusers have shown deficits in short term or working memory (Fletcher et al., 1996) and more lasting effects have been implicated in chronic marijuana users (Block & Ghoneim, 1993; Pope et al., 1995; Pope & Yurgelun-Todd, 1996). In comparison, TBI patients also commonly display deficits in memory, executive functioning, attentional processes, and on perceptuomotor tasks as well (Bigler, 1988; Bigler et al., 1996b, 1997; Johnson et al., 1994; O'Shanick & O'Shanick, 1994; Solomon & Malloy, 1992).

Despite the inference suggesting worse outcome in the substance abusing TBI victim, some recent neuropsychological studies have demonstrated surprisingly few differences between non-BAL and BAL TBI patients, particularly with mild injury (Dikmen et al., 1993; Kaplan & Corrigan, 1992; Solomon & Malloy, 1992). Furthermore, in an animal model investigation, acute ethanol administration actually had a protective effect in reducing cognitive deficits following TBI (Janis et al., 1998). In contrast, a recent study Kelly et al. (1997) found greater neuropsychological deficits in substance abusers who sustained a TBI than TBI subjects without substance abuse. Such contrasting findings underscore the need to carefully examine the putative deleterious role that substance abuse may play in TBI outcome.

Summary and Statement of the Problem

In summary, both long-term as well as the acute effects of substance abuse at the time of injury may be additive influences at the time of injury, which leads to greater injury effects to the brain at the time of TBI. To examine potential adverse consequence of either a history of substance abuse and/or abuse at the time of TBI, we examined a group of TBI participants who were age-, education-, and GCS-matched but differed according to their history of substance abuse (SA). One TBI group had no history of substance abuse (TBI–no-SA) while the other did (TBI–SA). However, just a comparison between these two groups is insufficient to examine the problem, because substance abuse may be already associated with structural abnormalities independent of any TBI. To test this, a comparison group is required that has no history of head injury, but of substance abuse—a no-TBI, but SA group (no-TBI–SA). Since the majority of head injuries occur in older adolescent and young adult participants, all groups need to be young and compared to normal controls, who have no history of substance abuse or TBI. Accordingly, these four groups were examined. This study addressed two problems: First, do older adolescent polysubstance abusing individuals have quantitatively different MRI findings than do normal controls? Second, and more importantly, do TBI participants with a history of substance abuse (TBI–SA) have greater morphological brain changes than TBI participants without any substance abuse (TBI–no-SA), substance abusers without TBI (no-TBI–SA) or normal controls?

We examined only young male individuals as a means to control effects of sex, aging, and length of substance abuse since the majority of head injuries occur in young men (Goldstein & Levin, 1990; Naugle, 1990). In our TBI research, we have demonstrated reliable trauma-induced changes in various brain CSF, hippocampal, and corpus callosum measures (Bigler et al., 1996b, 1997; Blatter et al., 1997; Johnson et al., 1996). The best overall indicator of brain integrity is the ventricle-to-brain ratio, which is a measure of total ventricular volume divided by total brain volume (higher score reflective of greater brain atrophy). The hippocampus was targeted because of its vulnerability to injury, with the significance of hippocampal volumetrics understood only in the context of temporal horn findings (e.g., temporal horn dilation can be a consequence of either hippocampal atrophy or temporal lobe atrophy, or some combination). The corpus callosum measure represents a straightforward and direct method to assess white matter integrity.

METHODS

Research Participants

TBI groups

Two groups of 19 male patients between the ages of 16 and 30 years were selected from a population of TBI patients at LDS hospital qualifying for participation in the LDS Hospital–Brigham Young University TBI (LDSH–BYU TBI) project. Subsequent to sustaining a motor vehicle related TBI, the majority of patients were initially treated in the LDS Hospital Emergency room, transferred to the Shock–Trauma unit for stabilization, and ultimately transferred to

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the Rehabilitation Department. A limited number of patients were treated initially at other facilities, but ultimately seen at LDS Hospital. All patients were hospitalized with an admitting TBI diagnosis that met criteria according to the TBI Model Systems Data Base definition (Dahmer et al., 1993). The entire project had standard IRB approval and all patients who participated in this study received a research MR and follow-up neuropsychological testing at no cost. Participants were tested and scanned at least 6 weeks post-injury, as research has shown that degenerative changes tend to stabilize by this time after injury (Bigler et al., 1992).

Determination of substance abuse in the TBI patient group (TBI–SA) utilized a medical chart review. Archival classification of substance abuse was made when hospital admission records reflected detectable blood alcohol levels (BALs) or a positive drug screen, and/or when psychological or social work hospital summaries objectively detailed a substance abuse history, according to the guidelines established by DSM IV as follows: A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by one (or more) of the following occurring within a 12-month period (for this study within the 12-month period preceding the TBI): (1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home; (2) recurrent substance use in situations in which is physically hazardous; (3) recurrent substance use-related legal problems; and (4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of substance use (American Psychiatric Association, 1994). BALs have been shown to be good indicators of preinjury alcohol problems (Dikmen et al., 1995). Every effort was taken to ensure accurate classification of TBI–SA and TBI–no-SA patients. In 7 cases, TBI–SA group placement (substance abuse history) was verified through personal communication with the patient or his family when they were contacted for follow-up evaluations. Substance abuse classification and pattern of abuse is presented in Table 1.

Likewise, TBI–non-substance-abusing comparison group participants (TBI–no-SA) were selected through a similar medical chart review, and subjects were utilized when BAL was nondetectable, with no substances indicated on drug screen, and/or no history of drug or alcohol abuse, according to the above standards. Again, heavy social drinkers were excluded from the control group. In 3 cases where some questions existed about the accuracy of placement, group placement (lack of substance abuse history) was verified via personal communication.

In the TBI–SA group, the mean BAL was 0.19 mg/dl ($SD = 0.07$; $N = 8$), well over the state legal driving limit of 0.08 mg/dl. Four participants had significant toxicology screens (positive for marijuana, amphetamines, and cocaine). Nine had no significant BAL or toxicology screen but did have a significant history of substance abuse at the time of injury. Four of these 9 participants with histories of substance abuse were suspected of being intoxicated at the time of their injuries, although no BAL or drug screen studies were available. No difference was found on any demographic, neuropsychological or MR morphological measure between those patients with available significant BALs and toxicology screens on hospital admission, and those patients without, but with documentable history of abuse. Accordingly, all "substance abuse" participants were combined into a single TBI–SA group.

Polysubstance abuse comparison group

The polysubstance abusing–non-TBI comparison group (SA–no-TBI) consisted of 16 male participants between the ages of 16 and 18 years (with the exception of 1 participant age 15 years, 7 months administered the same battery of testing to maintain consistency) who were in-patients at a residential treatment facility (RTF) for adolescents, specifically placed for their history of polysubstance abuse. These adolescents had been referred by either the juvenile court system, Child Protective Services, other treatment agencies, or parents specifically for their substance abuse disorder. Potential participants were referred by the staff psychologist and chemical dependency counselor of the RTF, after which a thorough overview of their pretreatment history was com-

Table 1. Substance abuse information for TBI-SA group

Condition	*N*	Drugs used
Positive BAL and/or TOX screen	10	
BAL only		
Significant TOX screen only	2	(Amphetamines and THC)
BAL and TOX screen	2	(Amphetamines, THC, and cocaine)
*History of substance abuse only	9	
History of problem drinking	9	
Reportedly intoxicated at time of injury, no BAL reported	4	
History of known inpatient alcohol abuse treatment	1	
Known DUI/DWI history	2	
Known history of other drug (non-ETOH) abuse	2	
Total	19	

*All participants met DSM–IV criteria for *substance abuse*.

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pleted via medical chart review. Potential participants were ranked according to the number of independent indicators of substance abuse (legal charges or school charges related to substance use, abuse, or possession; previous treatment specifically for substance abuse; and previous diagnoses of substance abuse or dependence made by licensed professionals). The SA–no-TBI participants selected were the 16 individuals with the greatest number of independent indicators of substance abuse and no history of TBI or neurological insult resulting in a loss of consciousness. All participants in the study had at least two independent indicators of substance abuse. History of learning disability or psychiatric disorder did not result in exclusion. Based on self-reports and collateral interviews at the time of admission, SA–no-TBI participants consumed an average of 63.10 drinks ($SD = 86.82$) in the 30 days prior to their admission to the residential treatment center. The mean number of illicit substances abused within the same time period was 3.20 ($SD = 1.87$); substances included marijuana, methamphetamine and other stimulants, cocaine, and hallucinogens, but not alcohol. SA–no-TBI subjects were tested an average of 8.25 months postadmission (5.03), indicating that they were free of any acute effects of substance abuse when tested.

Normal controls

Twenty male control participants were selected from the LDS Hospital neuroimaging normative data base for inclusion in the study (Blatter et al., 1995). These normative data base participants were relatives of TBI participants, or hospital and university staff and their friends and family. All received identical MR imaging, were between the ages of 18 and 30, and had no history of TBI. No neuropsychological studies were available on these individuals. All reported no substance abuse based on self-report only. No chart review was possible.

Assessment Procedures

TBI participants in this study were individually matched for age, sex, injury severity (by GCS), and education (see Blatter et al., 1997). Normal controls and SA–no-TBI participants were matched for sex and general age grouping for neuroimaging comparisons. Since the SA–no-TBI group was younger (16–18), no attempt was made to match for education. However, by utilizing such a young group the influence of age and excessive substance abuse was controlled; in addition, quantitative magnetic resonance imaging (QMRI) findings are similar during these years, minimizing aging effects (Blatter et al., 1995). All participants received identical MR sequences, and all save the normal controls were administered identical neuropsychological test batteries, although some TBI participants were not able to complete all neuropsychological tests.

Neuropsychological assessment

Neuropsychological outcome measures were obtained from all participants according to the standardized administration directions for each test (for a complete review of these tests, see Bigler, 1988; Lezak, 1995). The measures of specific interest administered included the Wechsler Memory Scale–Revised (WMS–R; Wechsler, 1987), Rey Auditory Verbal Learning Test (RAVL; Rey, 1964), Rey–Osterrieth Complex Figure Design (RCFD, Osterrieth, 1944), this test was scored based on the criteria presented by Lezak (1995); Warrington Recognition Memory Test (WRMT, Warrington, 1984); Wechsler Adult Intelligence Test–Revised (WAIS–R, Wechsler, 1981), and from the Halstead–Reitan Neuropsychological Test Battery, Trails A and B (Reitan & Wolfson, 1979).

Neuroimaging

MR images were acquired at 1.5 T, on a GE Signa scanner. Both 4x and 5x software platforms were in use during the course of the study. Sagittal T1 weighted (500/11/2;TR/TE/excitations) images were acquired and used for localization. Using the sagittal image as a reference, coronal intermediate and T2-weighted fast spin-echo images were acquired extending from the splenium of the corpus callosum anteriorly to the tip of the temporal lobe. These coronal images were used for hippocampal and temporal horn quantification. Axial intermediate and T2-weighted (3000/31/90/1) spin-echo images were also acquired to include from the foramen magnum to the convexity of the inner table of the skull. Axial images were used for quantification of all other structures, except corpus callosum which was obtained from the midsagittal T1-weighted image The slice thickness was 5 mm with an interspace gap of 1.5 or 2 mm. A 22 cm field of view (FOV) was used with a 256×192 acquisition matrix. Flow compensation, an inferior saturation pulse, and variable bandwidth were used. This sequence was part of our standard clinical protocol and the details have been published elsewhere (Bigler et al., 1997; Blatter et al., 1995, 1997).

Volumetric image analysis

For volumetric analysis, the images were processed using ANALYZE (Biomedical Imaging Resource, Mayo Foundation, Rochester, Minnesota; see Robb, 1995) running on SPARC 10 workstations (SUN Microsystems, Mountain View, California). Because ANALYZE requires the multispectral segmentation only with 8-bit images, the original 16-bit images were converted by linear interpolation to 8-bit images using the load command. The images were then archived permanently on optical disc using a lossless compression algorithm. A multistep volume analysis was then performed using several image processing tools available in ANALYZE, including multispectral tissue segmentation, interactive image editing, and region-of-interest pixel counting. The multispectral tissue segmentation was performed

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in a manner similar to that described previously (Blatter et al., 1995). Regions of cerebral spinal fluid (CSF), white matter, and gray matter were defined by the user and plotted in a two-dimensional feature space where the pixel signal intensity in the T2 weighted sequence is the value on the *x*-axis and the pixel intensity in the intermediate-weighted image is the *y*-axis. For whole brain white and gray matter and all CSF measures, except temporal horn, images in the axial plane were used. For the hippocampus and temporal horn, coronal images were used. A *k*-nearest-neighbor multispectral algorithm was then applied to the pixels of the entire section. For axial images, because of nonhomogeneity in the sensitivity of the radio frequency coil, the same feature-space map could not be successfully applied to all the images of the study, particularly the more inferior sections, in which the sensitivity of the radio frequency coil was slightly decreased. For these sections, separate feature-space maps were generated.

The classified images were edited using a manual trace tool to remove pixels representing the calvarium and extracranial soft tissues. The inner table of the skull was used as the landmark for separation of intracranial versus extracranial compartments. All of the pixels assigned to each segmented category (gray matter, white matter, CSF) were then summed over all of the classified, edited images from foramen magnum to vertex. Following segmentation, regions of interest (ROI) including the target ventricular system components were either traced manually along the proper segmented boundary and/or the outline was performed automatically, if the existing segmented boundary accurately defined the structure.

Methods for quantification techniques of the target structures of this study have been published in great detail elsewhere (see Bigler et al., 1996b, 1997; Blatter et al., 1995). Briefly, total brain volume was determined by summing all white and gray matter pixels and then multiplying by the voxel dimension. Total ventricular volume was obtained by summing the measurements of the lateral ventricles, the third and fourth ventricles, and the temporal horn measures. Total CSF was a combination of total ventricular volume and subarachnoid CSF. The ventricle-to-brain ratio (VBR) was calculated by dividing the total ventricle volume by total brain volume and multiplying by 100. Intra- and interrater reliabilities exceeded a correlation of .90 for all measures reported herein, except third ventricle which was $r = .86$.

Corpus callosum surface area measurements were obtained from the processing tools in IMAGE (Rasband, 1993). Measurements were taken in the midsagittal plane, the entire view of the corpus callosum in this plane was traced, with the image magnified to 4 times its normal size (see Johnson et al., 1996, for further discussion of these methods).

Design and Statistical Analysis

The current study utilized a simple four-group factorial design as follows: The experimental group consisted of the TBI-polysubstance abusing (TBI–SA) participants and three comparison groups: (1) TBI–non-substance-abusing (TBI–no-SA), (2) polysubstance-abusing–non-TBI (SA–no-TBI), and (3) normal controls. Several types of data analyses were performed. Due to the retrospective and clinical nature of the study, some individuals did not complete all of the neuropsychological testing. Likewise, SA–no-TBI participant terminated from the treatment center before scanning was performed, so MR information was not available. Imaging data were incomplete on 2 of the TBI–SA and 1 of the TBI–no-SA participants, and their data were not included in some of the image analyses. For multivariate analysis, there was one logical MANOVA to run based ventricular measures; the other MR morphological data were analyzed by two one-way ANOVAS (total hippocampal volume and corpus callosum surface area). The MANOVA included all ventricular measures (lateral, third, fourth, temporal horn, and VBR). The hippocampus ANOVA included total hippocampal volume based on the combined volume of the left and right hippocampus. The other one-way ANOVA utilized the midsagittal corpus callosum surface area across the groups. For neuropsychological test performance, four MANOVAs investigated (1) WMS–R, (2) RAVL, (3) WRMT and (4) WAIS–R IQ and Trails B. The WMS–R analysis was made up of all five WMS-R index scores: General Memory, Delayed Recall, Attention/Concentration, Verbal and Visual Memory. The RAVL MANOVA included both interference and recognition trials. The WRMT MANOVA compared performance on Words and Faces, the two subscales for this memory test. Finally, the WAIS–R IQ and Trails B MANOVA examined Full Scale, Verbal, and Performance IQ and Trails B. A one-way ANOVA examined performance on the Rey–Osterrieth Complex Figure delayed recall trial across groups.

In the presence of a significant MANOVA, *post-hoc* comparisons were then performed between groups with significant univariate findings, employing Bonferroni's corrections to control for family-wise error. Individual matching of TBI participants with no substance abuse to TBI participants with substance abuse was undertaken and planned independent *t* tests (or their nonparametric equivalent) were conducted to verify comparability between the group means for both TBI groups on initial GCS, age, and education. Pearson product–moment correlations were computed for QMRI and neuropsychological variables to examine the relationship between memory performance and brain structure–degree of atrophy. To further explore the morphologic basis to neuropsychological performance, various regression analyses were performed via a backwards elimination procedure using SPSS statistical software (Norusis, 1990).

RESULTS

Demographic information is summarized in Table 2. Although the mean TBI-SA GCS score was slightly lower, the difference was not significant [$t(35) = -1.32$, $p > .05$]. Age was not significantly different for TBI and the normal control groups; however, because of the age restriction

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Table 2. Mean age, education, and GCS scores of all groups

Variable	TBI–SA ($N = 19$) M	(SD)	TBI–no-SA ($N = 19$) M	(SD)	SA–no-TBI ($N = 16$) M	(SD)	Normal controls ($N = 20$) M	(SD)
Age	23.74	(4.05)	21.16	(4.82)	16.31	(0.60)	23.80	(2.71)*
Education	11.95	(0.97)	11.89	(1.21)	9.82	(1.08)	**	
GCS	6.36	(3.08)	7.82	(3.56)	N/A		N/A	

*$p < .05$. **information not available.

in the SA–no-TBI group, it was significantly younger [$F(3,70) = 17.21$, $p < .05$]. An independent samples t test also demonstrated that the TBI groups did not differ on mean level of education [$t(36) = .15$, $p > .05$]. Normal controls and SA–no-TBI groups were not matched for education. Correlational and regression analyses were performed by combining all three groups that had neuropsychological and QMR data (i.e., combining the TBI–no-SA, TBI–SA and SA–no-TBI groups).

MR Morphometric Findings

Table 3 presents means, standard deviations, and statistical results from QMRI findings for the four groups. Figure 1 provides comparison of VBR, hippocampal and temporal horn findings across the four groups. MANOVA results showed significant multivariate main effects (see Table 3). With the exception of the IV ventricle measure, subsequent univariate analyses were significant for all ventricular and VBR comparisons. Levene's test for homogeneity of variance revealed significant heterogeneity of variance for this MANOVA. Subsequently, using Box's altered degrees of freedom $(1, n - 1)$, a very conservative correction for heterogeneity of variance, a critical value for univariate significance was set: [$F(1,14) = 4.60$, $p < .05$]. When compared with this value, all univariate F values were still significant. *Post-hoc* comparisons showed mean VBR, a global indicator of brain atrophy, was greatest in the TBI–SA, although statistically this differed significantly from only the SA–no-TBI and control groups. Similar findings were obtained for lateral ventricle, III and temporal horn ventricular measures. Based on the significant ANOVA, although mean hippocampal volume was lowest in the TBI–SA group, *post-hoc* comparisons indicated that the TBI–SA and TBI–no-SA groups did not significantly differ, but both TBI groups clearly differed from the SA–no-TBI and controls. Corpus callosum surface area was significantly smaller in the TBI groups when compared to the SA–no-TBI and normal control groups, but the TBI groups did not differ.

Although matched on injury severity, as previously mentioned the TBI–SA group had slightly lower yet insignificantly different GCS scores. Nonetheless, it seemed appropriate to examine the VBR and temporal horn volume measures, two of the QMR measures demonstrating the most prominent atrophic change in the TBI–SA group (see Table 3), using GCS as a covariate. With GCS as a covari-

Table 3. Multivariate, univariate, and *post-hoc* comparisons for mean MRI volumes

Analysis	Wilks's Lambda	E	df	Participant group: Group 1: TBI–SA M	(SD)	Group 2: TBI–no-SA M	(SD)	Group 3: SA–no-TBI M	(SD)	Group 4: Normal M	(SD)
Multivariate analysis:											
CSF and ventricles	0.49	3.223***	15,166								
Univariate analyses											
Ventricle to brain ratio (VBR)		8.909***	3,64	2.96	(1.97)	2.14	(1.04)	1.15	(0.45)	1.29	(0.38)
Lateral ventricle		7.126***	3,64	23.64	(22.82)	23.44	(10.89)	12.69	(4.91)	16.65	(5.71)
Third ventricle		13.626***	3,64	1.93	(1.04)	1.57	(0.81)	0.78	(0.26)	0.70	(0.20)
Fourth ventricle		0.431	3,64	1.92	(0.80)	1.92	(0.84)	1.94	(0.58)	1.71	(0.57)
Total temporal horn		7.400***	3,64	2.22	(2.43)	1.13	(1.03)	0.25	(0.15)	0.42	(0.38)
Univariate analyses											
Total hippocampus		7.332***	3,45	4.59	(0.71)	4.70	(0.72)	5.37	(0.55)	5.84	(0.55)
Corpus callosum (surface area)		2.820*	3,59	642.36	(183.07)	642.27	(149.36)	764.72	(106.78)	723.93	(111.92)

*$p < .05$. **$p < .01$. ***$p < .001$.

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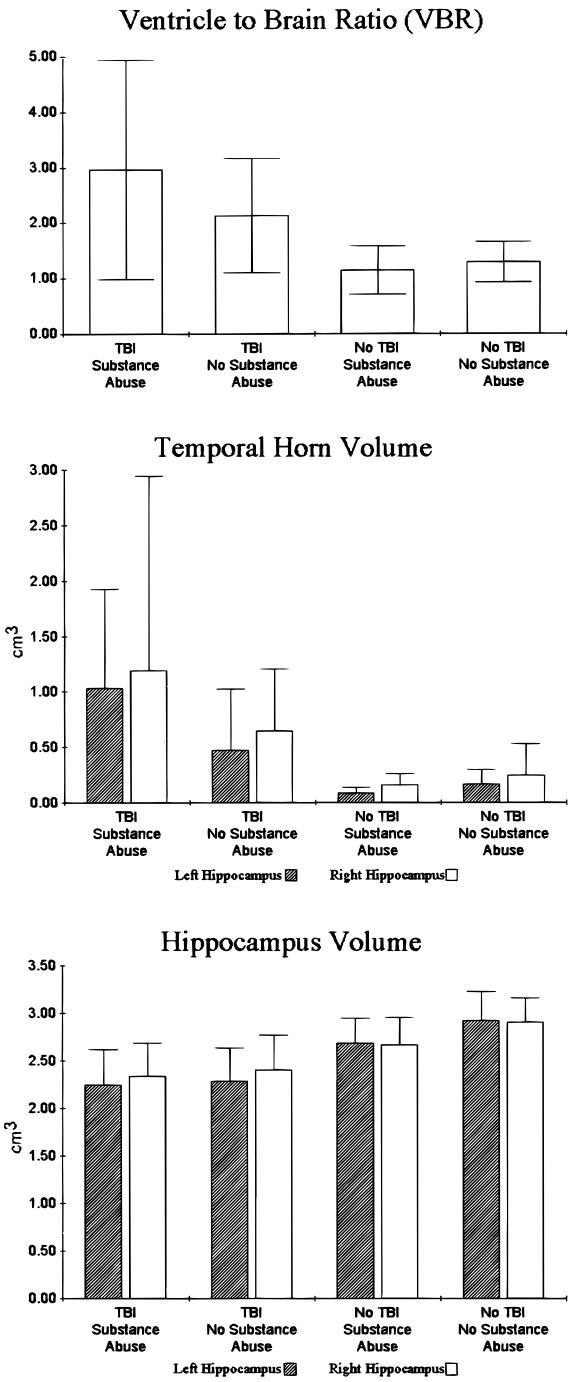

Fig. 1. Graphic depiction of QMR findings. Top: VBR findings across the four groups. Bar represents standard deviation, in this and subsequent figures. Middle: left and right mean temporal horn volumes and (bottom) left and right hippocampal volumes across the four groups. Although statistical analysis was based in combined left and right hippocampal and temporal horn volumes, graphical depiction in this figure gives mean values for each structure.

ate, VBR difference between the TBI–SA and no-SA groups nearly reached significance [$F(2,33) = 3.8$; $p = .063$]. As for temporal horn, no significant difference between the two TBI groups was observed [$F(2,33) = 1.85$, $p = .184$] with GCS as a covariate.

Neuropsychological Outcome Measures

Results of neuropsychological testing are presented in Table 4. Two TBI–no-SA patients had no applicable neuropsychological testing information available. No control participants had neuropsychological data and therefore not part of any analysis. Because of sample size inequality across the different neuropsychological measures, due to some TBI participants not completing some tests, four separate MANOVAs and a singular one-way ANOVA examining the between-participants factor of group membership and neuropsychological performance were performed. No significant multivariate effect for group was found. Due to the nonsignificant MANOVAs, no further analyses were performed for neuropsychological measures.

Correlational and Regression Findings

Results of correlational analyses between QMRI and neuropsychological variables are presented in Table 5. Correlational analyses included combined data from the TBI groups and the SA–no-TBI group. Generally, weak and nonsignificant correlations between MR imaging measures and memory scores were found. Trails B did significantly correlate with temporal horn, hippocampal, and VBR estimates.

Results of regression analyses are summarized in Table 6. A backward elimination procedure was utilized to examine the relative contribution of the neuroimaging predictor variables (QMRI findings) to each of the dependent variables (neuropsychological test scores). These analyses were performed across all groups (except normal controls who had no neuropsychological testing). The brain structures that most consistently contributed to neuropsychological outcome were corpus callosum and some measure of ventricular size. Hippocampal measures were consistently related to performance on memory tasks.

DISCUSSION

Does Substance Abuse Result in Brain Volumetric Changes in Older Adolescents?

The current study is unique in the sense that two MR comparison groups were utilized—a normal control and a substance abuse comparison group—both without history of head injury. Comparison on the various morphometric measures indicates no significant difference between the adolescent substance abuse group and adolescent–young adult control participants. Aasly et al. (1993) found that volumetric measures of the ventricular system in young polysubstance abusers did not differ significantly from controls, consistent with the current findings. Most of the literature examining the deleterious effects of substance abuse has demonstrated this to be a function of length of substance abuse, with older abusers to be more likely to have MR ab-

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Table 4. Mean scores on neuropsychological measures by group

Measure	Wilks's Lambda	*E*	*df*	Group means and standard deviations: TBI–SA (*N* = 19) *M*	(*SD*)	TBI–no-SA (*N* = 17) *M*	(*SD*)	SA–no-TBI (*N* = 16) *M*	(*SD*)
Multivariate analyses									
WMS–R	0.734	1.103	10,66						
General Memory Index				85.67	(20.44)	94.00	(19.49)	84.75	(13.17)
Verbal Memory Index				82.11	(17.65)	90.57	(15.94)	82.44	(11.72)
Visual Memory Index				96.13	(21.31)	103.62	(20.19)	100.06	(16.21)
Attention/Concentration				89.13	(19.27)	94.75	(10.57)	88.19	(13.95)
Delayed Recall				82.23	(22.88)	90.85	(22.81)	80.50	(16.50)
RAVL	1.817	2.014	4,76						
Interference				7.69	(4.92)	7.80	(3.91)	10.31	(2.73)
Recognition (no. correct)				11.92	(2.97)	13.07	(1.59)	12.88	(3.01)
WRMT	0.887	0.957	4,62						
Words (raw score)				44.22	(8.51)	44.70	(5.50)	47.25	(2.70)
Faces (raw score)				36.44	(5.10)	36.10	(7.96)	39.94	(4.99)
WAIS–R	0.77	1.431	8,82						
Full Scale IQ				85.22	(15.03)	89.40	(13.24)	96.44	(13.71)
Verbal IQ				84.11	(14.90)	91.44	(9.94)	97.00	(12.56)
Performance IQ				88.33	(16.34)	90.53	(18.57)	96.06	(15.58)
Trails B (seconds)				106.28	(61.07)	110.20	(53.82)	67.44	19.81)
Univariate analysis									
ROCF		0.164	2,35						
Delayed recall (raw score)				17.38	(7.66)	18.05	(8.82)	19.22	(9.17)

normalities (Jacobson & Lishman, 1990; Nicolas et al., 1997; Pfefferbaum et al., 1992; Shear et al., 1994). The current findings using quantitative MR measurements suggest that, as a group, young (16–18 years of age) polysubstance abusers do not exhibit QMRI differences.

Does Substance Abuse Result in Greater Pathologic Brain Changes in TBI?

Results of quantitative MR analyses demonstrate consistent group differences when TBI participants were compared to

Table 5. Correlation matrix: Neuropsychological test performance and quantitative MRI

Measure	WMS–R	RAVL Rec	Rey–ODR	Warr. Words	Warr. Faces	FSIQ	Trails B
VBR	.023 $p = .889$ $N = 38$	−.218 $p = .188$ $N = 38$	−.223 $p = .198$ $N = 35$	−.308 $p = .081$ $N = 33$	−.272 $p = .125$ $N = 33$	−.287 $p = .062$ $N = 43$	.344 $p = .024$ $N = 43$
Total temporal horn	−.076 $p = .648$ $N = 39$	−.261 $p = .109$ $N = 39$	−.261 $p = .124$ $N = 26$	−.247 $p = .167$ $N = 33$	−.311 $p = .078$ $N = 33$	−.258 $p = .091$ $N = 44$	−.333 $p = .027$ $N = 44$
Total hippocampus	.022 $p = .901$ $N = 35$	.285 $p = .097$ $N = 35$	.218 $p = .223$ $N = 33$	.348 $p = .065$ $N = 29$	.232 $p = .226$ $N = 29$	.208 $p = .205$ $N = 39$	−.328 $p = .042$ $N = 39$
Corpus callosum	−.173 $p = .307$ $N = 37$	−.227 $p = .176$ $N = 37$	.059 $p = .739$ $N = 34$	−.02 $p = .913$ $N = 32$	−.003 $p = .989$ $N = 32$	.05 $p = .754$ $N = 42$	−.12 $p = .448$ $N = 4$

Note. WMS–R, Wechsler Memory Scale–Revised; RAVL Rec, Rey Auditory Verbal Learning–Recognition Trial; Rey–ODR, Rey Osterrieth Complex Figure–Delayed Recall; Warr, Warrington Recognition Memory; FSIQ, Full Scale IQ; Trails B, Trail Making Test.

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Table 6. Results of regression analyses showing best quantitative predictors for each neuropsychological outcome measure

Predicted neuropsychological variable	Best predictors	R^2	F	df	N	p
ROCF Delayed Recall	III Ventricle	.154	4.907	1,21	36	.035
WMS–R Delayed Recall	CC, Total hippocampus	.208	3.536	2,27	31	.043
RAVL Recognition	CC, Total hipp., III	.477	8.194	3,27	31	.001
WRMT Recognition	CC, Total hipp., IV	.397	4.833	3,22	31	.010
WAIS–R VIQ	Total temporal horn	.143	5.694	1,34	43	.023
Trails B	Total hipp., Total temp. horn	.182	3.566	2,32	43	.040

Note. CC = corpus callosum; III = third ventricle; IV = fourth ventricle; Total hipp. = total hippocampus; Total temp. horn = total temporal horn.

their non-TBI counterparts. Both TBI groups displayed trauma-induced degenerative changes compared to both control groups, with the TBI–SA group consistently exhibiting the most atrophy. With the exception of the IV ventricle measure, the TBI–SA group displayed greater amounts of atrophy on all other measures. When level of injury was further controlled by covarying GCS, the TBI–SA group had an increased VBR value that approached significance ($p = .06$) compared to the TBI–no-SA group and was markedly different from the no-TBI–SA and control groups (see Figure 1). The no-TBI–SA group did not differ reliably from the control group on any morphometric measure. Accordingly, implications of this study are that substance abuse may result in greater amounts of neural degeneration when brain injury occurs and that this effect, at least in teenagers and young adults, is *not* superimposed on an already structurally altered brain, since the non-TBI polysubstance abuse participants did not have brain morphometry that differed from controls.

Associative Neuropathological Factors in Substance Abuse

The significance of these findings is that major structural differences attributed solely to substance abuse were not present in this young, substance abuse only, non-TBI comparison group. Thus, the changes associated with trauma in substance abuse TBI participants probably were not superimposed on preexisting gross structural defects. However, one additional possibility warranting exploration is the prospect that a subset of substance abuse subjects could have had underlying structural anomalies associated with one of the other potential coexisting neuropsychiatric factors that often accompany substance abuse.

For example, as indicated in the Methods section, substance abuse participants were not excluded due to history of learning disability (LD) or concomitant psychiatric disorder. Since there is a relationship between history of LD and substance abuse and LD is associated with a higher incidence of minor morphometric abnormalities on MR imaging (see Bigler, 1992), it is conceivable that some substance abusers who are also LD may have associated minor brain abnormalities that could be detected by QMRI analyses. To test this out, the clinical records of each substance abuse, non-TBI participant were reviewed for determination of possible LD. On admission all SA–no-TBI participants routinely received, through the RTC, a comprehensive psychometric exam including academic testing. SA–no-TBI participants with probable LD were separated by a review of the existing clinical records. LD classification was based on Woodcock-Johnson Achievement standard scores below 77, or a 30-point difference between FSIQ and achievement measures (Farnham-Diggory, 1986). In addition, history of severe learning problems or diagnosed learning disability was used to confirm identification of LD group inclusion. Using such criteria, 6 of the 16 SA–no-TBI participants were identified as probable learning disordered (learning disordered substance abuse, or LDSA). No significant difference was found between the LDSA and non-LD substance abuse (non-LD–SA) groups for variables of substance abuse or for months spent in residential treatment [LDSA M months = 9.83, $SD = 6.31$; non-LD–SA M months = 7.3, $SD = 4.17$; $t(14) = -.97$, $p < .05$]. Expected differences between LDSA and non-LD–SA groups were subsequently found on WRAT–3 achievement measures (administered to all SA–no-TBI participants as part of the research battery), validating our learning disability distinction [WRAT–3 Spelling SS: LDSA $M = 67.17$, $SD = 7.94$; non-LD–SA $M = 101.20$, $SD = 7.44$; $F(14)=66.39$, $p < .001$; Arithmetic SS: LDSA $M = 75.83$, $SD = 8.42$; non-LD–SA $M = 98.60$, $SD = 12.37$; $F(14) = 13.74$, $p < .01$; Reading SS: LDSA $M = 74.50$, $SD = 12.63$; non-LD–SA $M = 100.20$, $SD = 8.24$; $F(14) = 21.98$, $p < .001$].

Because the TBI–SA group exhibited the greatest difference on temporal horn volume and VBR, VBR and temporal horn volumes were compared between the LDSA and the non-LDSA groups (see Table 7). Although mean VBR was larger in the LD group ($M = 1.43$, $SD = 0.63$) compared to the non-LD substance abuse group ($M = 1.00$, $SD = 0.23$), the difference was not significant [$t(12) = -1.92$,

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Table 7. Quantitative MRI estimates: SA–no-TBI group with and without learning disabilities compared with TBI–SA group

Quantitative MR measure	Non-learning disabled SA–no-TBI ($N = 10$)		Learning disabled SA–no-TBI ($N = 6$)		TBI–SA ($N = 18$)	
	M	(*SD*)	*M*	(*SD*)	*M*	(*SD*)
VBR	1.00	(0.23)	1.43	(0.63)	2.96	(1.98)**
Lateral ventricle	11.07	(2.71)	15.60	(6.87)	32.64	(22.82)*
Total temporal horn	0.25	(0.12)	0.23	(0.21)	2.22	(2.43)**
Total brain	1414.61	(94.77)	1321.22	(113.06)	1318.05	(133.15)

*$p < .05$. **$p < .01$.

$p = .079$]. Also, the LDSA group mean VBR was within 1 standard deviation of that of the normal control group (see Table 2). Temporal horn volumes were nearly identical for the two groups, with no significant differences noted. Thus, it does not appear that gross structural aberration that would predate an acquired brain injury is present in young substance abusers, even those with significant LD.

The Interactive Effect of Substance Abuse and TBI

A number of mechanisms are potentially involved in the deleterious interactive effects of substance abuse resulting in the potential for greater morphologic abnormality following brain injury. At the time of injury due to impact various pathophysiological sequences ensue for hours to days post-injury (Jessell, 1991; Narayan et al., 1996). Some type of exacerbation of excitoxic reaction (see Coyle, 1987) has been suggested as a mechanism of action wherein substance abuse may interact with the effects of TBI (Bigler et al., 1996a). We know of no specific animal or human study that has empirically addressed the explicit issue of excitotoxicity and interactive effects of substance abuse within the context of TBI. Some of the data from the current study would actually argue against the excitotoxic hypothesis occurring at the hippocampal level, however. The hippocampus has been a target structure under investigation because of known excitoxic reactions to certain pathologic states (i.e., anoxia, TBI) or substance abuse (Ellison & Switzer, 1993; Eskay et al., 1994; Lishman, 1990; Lovinger, 1993, 1989; Smith et al., 1993; but see Harding et al., 1997). However, in the current study, although the hippocampus was significantly atrophic in both TBI groups, the TBI–SA group hippocampal volume was not significantly smaller than the TBI–no-SA group. Had excitoxicity been the major factor, it would seem plausible that hippocampal volume in the TBI–SA group would be significantly smaller.

DeCrescito et al. (1974) and Flamm et al. (1977) demonstrated that alcohol intoxicated cats at the time of TBI sustained greater mass lesions and more extensive edema than cats administered intravenous saline. They interpreted their findings in the context of vascular compromise and metabolic reactions associated with alcohol intoxication and TBI. Vascular mediated pathology exacerbated by substance abuse, in particular alcohol and cocaine, remains a distinct possibility for explication of our greater morphologic abnormality in the substance abuse group. Ethanol can result in increased permeability of the blood brain barrier, and larger areas of leaking endothelium following brain injury (Kelly, 1995). It also is known to severely impair platelet aggregation and thus prolong bleeding time following an injury (Kelly, 1995; Rönty et al., 1993). Cocaine abuse may affect blood pressure and cerebral blood flow (Kaufman et al., 1998; Muir & Ellis, 1995). TBI itself often results in vascular compromise to contused and/or edematous tissue, particularly in the temporal lobe region (Dowling et al., 1996; Gean, 1994). Possibly, it is the combination of pathologically altered vascular reactions in the substance abuse TBI group that leads to greater morphologic abnormalities. However, the issue of substance abuse related blood flow abnormalities and neurologic sequelae remains a complicated one (see Sharkey et al., 1991).

Neuropsychological Performance, TBI and Substance Abuse

Across the three groups that received neuropsychological tests—TBI–SA, TBI–no-SA, and SA–no-TBI—neuropsychological testing demonstrated no differences between groups. Such findings are consistent with the fact that poly-substance abusers tend to have neuropsychological deficits as do TBI patients. While the TBI–SA group often had the poorest neuropsychological performance, there were no significant differences in neuropsychological test performance found for the additional effect of substance abuse in TBI.

Correlational and Regression Analyses

Consistent with other research from our lab (see Bigler et al., 1996a, 1996b, 1997), the relationships between morphologic measures including hippocampal volumes and memory were weak. We have interpreted this as being related to

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the ubiquitous nature of memory and the fact TBI participants are assessed at various stages of recovery, where functioning may be distributed outside the boundaries of the structure in question. Regression analyses suggested a combination of white matter (corpus callosum), hippocampal, and ventricular measures to be the best predictors of memory function. Temporal horn was best for Verbal IQ and a combination of temporal horn and hippocampal volume were best predictors of Trail Making performance.

Limitations

This study needs to be viewed as preliminary. The findings are of distinct heuristic value and may have important clinical relevance to outcome from TBI in substance abusing persons. However, undoubtedly the biggest limitation of this study is its retrospective, archival design and limited sample size. It will be important to replicate this study with a prospective, longitudinal design where better control can be exercised over the degree, type, and chronicity of substance abuse, potential sex differences, and injury severity. In the current study, because of its archival nature, time postinjury for scanning and neuropsychological assessment could not be controlled. Recently, we have shown that the optimal time period for maximizing neuroimaging with neuropsychological outcome measures occurs between 70 and 210 days postinjury (see Blatter et al., 1997). It is likely that some of the weak relationships between QMRI measures and neuropsychological outcome are a reflection of variability in time postinjury between MR scanning and neuropsychological assessment.

Conclusions

In summary, the combination of substance abuse and TBI in older adolescent–young adult participants appears to result in greater brain atrophy than cannot be explained simply by the presence of TBI, severity of injury or substance abuse alone. While a number of limitations are present in the current design, these findings do have implications for the deleterious interactive effects of substance abuse and head injury. Based on the findings reported herein, additional research is suggested to examine the potential effects of concomitant substance abuse with the effects of head injury.

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