



Effects of traumatic brain injury on cognitive functioning and cerebral metabolites in HIV-infected individuals

Kenny Lin¹, Michael J Taylor¹, Robert Heaton¹, Donald Franklin¹, Terry Jernigan¹, Christine Fennema-Notestine¹, Allen McCutchan¹, J Hampton Atkinson¹, Ronald J Ellis¹, Justin McArthur², Susan Morgello³, David Simpson³, Ann C Collier⁴, Christina Marra⁴, Benjamin Gelman⁵, David Clifford⁶, and Igor Grant¹, for the CHARTER group

¹University of California San Diego, San Diego, CA, USA

²Johns Hopkins University, Baltimore, MD, USA

³Mt. Sinai School of Medicine, New York, NY, USA

⁴University of Washington, Seattle, WA, USA

⁵University of Texas Medical Branch, Galveston, TX, USA

⁶Washington University, St. Louis, MO, USA

We explored the possible augmenting effect of traumatic brain injury (TBI) history on HIV (human immunodeficiency virus) associated neurocognitive complications. HIV-infected participants with self-reported history of definite TBI were compared to HIV patients without TBI history. Groups were equated for relevant demographic and HIV-associated characteristics. The TBI group evidenced significantly greater deficits in executive functioning and working memory. N-acetylaspartate, a putative marker of neuronal integrity, was significantly lower in the frontal gray matter and basal ganglia brain regions of the TBI group. Together, these results suggest an additional brain impact of TBI over that from HIV alone. One clinical implication is that HIV patients with TBI history may need to be monitored more closely for increased risk of HIV-associated neurocognitive disorder signs or symptoms.

Keywords: Head injury; HIV associated neurocognitive disorder; Neuropsychological performance; Magnetic resonance spectroscopy; N-acetylaspartate.

INTRODUCTION

Though not known as a primarily neurodegenerative disease, human immunodeficiency virus (HIV) infection has been linked to cognitive impairment as well as cerebral metabolic changes. HIV has been shown to cause significant impairments of varying severity in higher order brain functions (HIV-associated neurocognitive disorders: HAND). Currently, a set of research diagnostic criteria have been proposed to categorize HAND into three conditions: asymptomatic neurocognitive impairment, HIV-associated mild neurocognitive

disorder, and HIV-associated dementia (Antinori et al., 2007). Neuropsychological deficits in attention and learning have the highest prevalence (61% and 57%, respectively) in HIV+ patients (Grant, 2008); as HIV disease progresses from early to later stages, executive functioning, information-processing speed, and motor functioning are associated with the greatest decline (Reger, Welsh, Razani, Martin, & Boone, 2002).

The precise neuroanatomical basis of the cognitive effects of HIV is still uncertain. Structural and functional brain imaging has revealed loss of gray and white matter volumes, increased white matter abnormality, and

CNS HIV Antiretroviral Therapy Effects Research (CHARTER) is supported by award N01 MH22005 from the National Institutes of Health.

Address correspondence to Igor Grant, Department of Psychiatry (0680), School of Medicine, University of California, San Diego, La Jolla, CA 92093–0680, USA (E-mail: igrant@ucsd.edu).

changes in perfusion and glucose metabolism associated with HIV (Wohlschlaeger, Wenger, Mehraein, & Weis, 2009). One indication of neuronal injury is reduced N-acetylaspartate (NAA), a putative marker of neuronal health and integrity, on magnetic resonance spectroscopy (MRS) imaging (Schuff et al., 2006). Increased HIV viral load and decreased CD4+ T-cell counts have been associated with decreased levels of NAA in the frontal white matter, frontal gray matter, and basal ganglia regions, suggesting that HIV infection may result in loss of neuronal integrity (Taylor et al., 2007). Even when asymptomatic, persons with HIV infection may have decreased NAA levels in the basal ganglia region (Paul et al., 2007).

With advanced ARV (antiretroviral) regimens, HIV-infected individuals are living longer and in better health now than before. Paradoxically, HAND remains prevalent. For example, a recent study by the CHARTER (CNS HIV Antiretroviral Therapy Effects Research, where CNS denotes central nervous system) group reported that 40–50% of people in HIV care, with the majority receiving HAART (highly active antiretroviral therapy), have neurocognitive impairments (Heaton et al., in press). While the reasons for HAND persistence are unclear, one possibility is that certain coexisting (comorbid) factors might increase the brain's vulnerability to HIV injury. Among such comorbidities, traumatic brain injury (TBI) is commonplace.

Since TBI still remains as a largely unexplored condition within the HIV population, we were interested in its potential effects in HIV-infected people. TBIs involve disruption of normal brain function that can be caused by a physical insult to the head, subjecting it to sudden acceleration and deceleration forces (Silver, McAllister, & Arciniegas, 2009). The incidence of new TBIs each year in the United States is 2 million, which is approximately 35 times greater than the incidence of new HIV infection per year (Centers for Disease Control, 2009a, 2009b). The high prevalence of TBI in the general population suggests that TBI may be a common comorbidity in HIV+ persons that requires further investigation.

The prevalence of HIV+ patients who have suffered from at least one TBI has not been reported systematically. However, in the 1,599 cases studied in the CHARTER (CNS HIV Antiretroviral Therapy Effects Research) program at the University of California, San Diego, approximately 21% reported head injury.

Following a traumatic brain injury, people can experience a wide range of impairments in the cognitive, emotional, physical, and psychosocial domains and interactions amongst them (Hernández, 2006). People with moderate to severe TBI history can experience a range of cognitive deficits, with one of the most prevalent being difficulty in applying optimal strategies for learning and memory (Vakil, 2005).

MRS studies have confirmed that TBI patients also evidence lower NAA levels (Weiss, Galanaud, Carpentier, Naccache, & Puybasset, 2007). Mild traumatic brain injury patients have also been shown to exhibit a 12% deficit in WBNA (whole brain N-acetylaspartate), suggesting a loss in neuronal health following a head injury (B. A. Cohen et al., 2007).

To explore the possibility that TBI might enhance the effects of HIV on the brain, we performed comprehensive neuropsychological assessments with HIV-infected persons who did and did not have histories of TBI. We hypothesized that neurocognitive function in those with TBI would be worse than in those without, particularly in areas of cognition that have been implicated in each etiology—that is, working memory, attention, and executive function. We also performed a nested study on a subset of cases to examine changes in brain metabolites via MRS. Since HIV and TBI are each associated with decreases in NAA levels, we hypothesized that people with both HIV and TBI would evidence greater NAA reductions, suggestive of more neuronal injury.

METHOD

Participants

HIV-infected participants from the multisite CHARTER study were categorized into either the traumatic brain injury group (HIV+TBI+) or no traumatic brain injury group (HIV+TBI-) based on self-reported medical history. In the CHARTER protocol participants are queried about head injury on two separate occasions: during a structured neuromedical history preceding the neurological examination; and during a neuropsychological screening that preceded testing. To increase the level of certainty that a substantial head injury had indeed occurred, we defined cases as those reporting definite head injury on the two different interviews. Out of the total 1,599 participants in the CHARTER database, 635 participants reported inconsistent information and were excluded from analysis. The remaining 964 participants were then categorized into one of the following groups, in order of increasing severity: no TBI ($N = 634$); had concussions or head injuries with brief (i.e., less than 30 minutes) or no loss of consciousness (TBI Level 1, $N = 214$); experiencing loss of consciousness greater than 30 minutes (TBI Level 2, $N = 93$); complicated by neurological deficits lasting greater than 2 weeks (TBI Level 3, $N = 17$), and having permanent residual neurological and motor impairments (TBI Level 4, $N = 6$).

The 214 cases in TBI Level 1 were excluded from analysis to ensure that only those with definite a TBI were analyzed. We also excluded the 6 cases in TBI Level 4 as they had permanent residua by definition. The final TBI group (HIV+ TBI+) that we used for analysis included the 110 participants from either TBI Level 2 or Level 3. All participants were ambulatory patients who had recovered and were able to both function normally and participate in the study.

Neuropsychological study

For the neuropsychological study, we selected from the HIV participants with negative TBI history (HIV+TBI-) those that matched the HIV+TBI+ on the demographic characteristics of age, sex, education, and ethnicity,

TABLE 1
 Characteristics of groups with neuropsychological assessment and magnetic resonance spectroscopy subset

	<i>NP assessment</i>				<i>MRS subset</i>			
	<i>HIV+TBI+</i> (<i>N</i> = 110)	<i>HIV+TBI-</i> (<i>N</i> = 590)	<i>t value</i> or χ^2	<i>p</i> value	<i>HIV+TBI+</i> (<i>N</i> = 17)	<i>HIV+TBI-</i> (<i>N</i> = 84)	<i>t value</i> or χ^2	<i>p</i> value
Age (years)	43.6 (8.4)	43.6 (8.0)	-0.13	.45	47.5 (6.3)	47.1 (5.9)	-0.25	.80
Education (years)	12.3 (2.8)	12.6 (2.3)	1.19	.88	13.2 (3.2)	13.1 (2.1)	-0.15	.88
WRAT-3 Reading	91.5 (17.3)	90.7 (16.7)	-0.47	.32	96.1 (15.9)	93.5 (15.7)	-0.61	.54
Sex (% male)	89.2	74.9	12.10	.001	100.0	84.5	5.17	.08
Ethnicity (% non-White)	56.4	59.5	0.37	.54	58.8	57.1	0.02	.90
No. of ARVs	2.2 (1.5)	2.1 (1.6)	-0.55	.29	2.3 (1.6)	2.4 (1.5)	0.37	.71
ARV history (% currently using)	69.1	65.6	0.51	.47	70.6	75.0	0.14	.70
% on HAART	69.1	64.4	0.91	.34	70.6	73.8	0.07	.78
Nadir CD4	213.3 (188.5)	219.9 (210.7)	0.31	.62	215.2 (212.4)	174.5 (152.6)	-0.93	.35
% AIDS ^a	60.0	61.5	0.08	.77	64.7	70.2	0.20	.65
Plasma HIV ^b (% detectable)	65.1	70.7	1.31	.25	47.1	44.6	0.04	.85
CSF HIV ^b (% detectable)	37.4	38.6	0.05	.83	37.5	29.5	0.39	.53
% HCV seropositive	33.3	31.8	0.10	.75	41.2	33.3	0.38	.54

Note. For *t* value or χ^2 : Variables with standard deviations have a *t* value; variables with % values have a χ^2 value. NP = neuropsychological. MRS = magnetic resonance spectroscopy. WRAT-3 = Wide Range Achievement Test-Third Edition. ARV = antiretroviral. HAART = highly active antiretroviral therapy. CSF = cerebrospinal fluid. HCV = hepatitis C virus. Standard deviations in parentheses. ^aBased on 1993 Centers for Disease Control (CDC) classification (Centers for Disease Control, 1992). ^bBased on limit of detection = 50 copies.

as well as on HIV-associated characteristics of current antiretroviral status, antiretroviral history, nadir CD4, plasma HIV viral loads, CSF (cerebrospinal fluid) HIV viral loads, AIDS or non-AIDS classification, and presence of hepatitis C (HCV) infection. Wide Range Achievement Test-Third Edition (WRAT-3) Reading scores were also used as added matching criteria to ensure general intellectual equivalence across the groups (Keogh, Major, Omori, Gándara, & Reid, 1980). This resulted in a sample of 590 HIV+TBI- and 110 HIV+TBI+ participants whose characteristics are summarized in Table 1.

Neuropsychological assessment

The neuropsychological test battery, given to all CHARTER participants, evaluates eight cognitive ability areas: overall vocabulary, working memory, executive functioning, attention and speed of information processing, learning, memory, verbal fluency, and psychomotor (Table 2; Heaton et al., in press).

Each participant's level of neuropsychological impairment was determined by calculating deficit scores for each domain of cognitive functioning. More specifically, results for each test were converted to demographically adjusted *T*-scores ($M = 50$, $SD = 10$) accounting for age, sex, education, and ethnicity using published normative conversions. The resulting *T*-scores were then converted

to deficit scores using the following conversions: *T*-scores $>40 =$ deficit score of "0," *T*-scores of 35-39 = "1," *T*-scores of 34-30 = "2," *T*-scores of 29-25 = "3," *T*-scores of 24-20 = "4," and *T*-scores $\leq 19 =$ "5." In addition, a global deficit score (GDS) was calculated to summarize the overall level of impairment by averaging the deficit scores across domains. Scores on the GDS range from 0 to 5 as above, with a higher value signifying a greater level of impairment. A GDS of greater than 0.5 is consistent with definite mild impairment (Heaton, Miller, Taylor, & Grant, 2004).

Patient's self assessment of neurocognitive functioning

At each visit, participants were administered the Patient's Assessment of Own Functioning Inventory (PAOFI), which asked them to evaluate their own neurocognitive function. The PAOFI assesses whether or not participants had complaints about their own functioning in areas such as sensory, motor, memory, or other cognitive domains and, if so, the level of severity. Scores on the PAOFI are derived by summing the relevant questions in each area. The total PAOFI score was obtained by averaging all the other functioning scores (Chelune, Heaton, & Lehman, 1986).

Depression and substance use assessment

Participants were also compared for potential differences in depressive symptoms and substance abuse, as these can have independent effects on neuropsychological performance. Depressive symptoms were assessed using the Beck Depression Inventory (BDI; Richter, Werner, Heerlein, Kraus, & Sauer, 1998). Participants were also given a Composite International Diagnostic Interview (CIDI), which permits diagnosis of participants with mood disorders according to the *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV)*; American Psychiatric Association, 1994) criteria (Cooper, Peters, & Andrews, 1998). The mood disorders specifically assessed for CHARTER participants included major depressive disorder (MDD) and dysthymia. The CIDI was also used to diagnose a substance use abuse or dependency disorder, and we define “history of substance use disorder” as any individual who met criteria for substance abuse or dependency, either

currently or in the past. Data were also gathered on current use of prescription medications with psychotropic effects, including antidepressants, sedatives, and opioid analgesics.

Magnetic resonance spectroscopy (MRS) study

In the CHARTER study, a subset of participants (HIV+TBI+, $N = 17$; HIV+TBI-, $N = 84$) entered a longitudinal MRS substudy based on their willingness to participate and not having any contraindications to MRI imaging (e.g., metal in the body); subjects were not excluded for any other reason. These participants were equated on the same characteristics and thus were comparable to all subjects in the larger neuropsychological study (Table 2). The metabolites selected for inspection, N acetylaspartate (NAA), myo-inositol (MI), and choline (CHO) are thought to reflect several neuropathologic

TABLE 2
The neuropsychological battery

<i>Ability area</i>	<i>Neuropsychological test</i>	<i>Assesses</i>
Overall vocabulary	WRAT-3 Reading	Premorbid verbal ability
Working memory	Paced Auditory Serial Addition Task WAIS-III Letter-Number Sequencing	Ability to work with information in short-term store
Executive functioning	Wisconsin Card Sorting Test Trail Making Test Part B	Abstracting ability (abstract reasoning, evaluating, planning, and decision making)
Attention/ speed of information processing	WAIS-III Digit Symbol WAIS-III Symbol Search Trail Making Test Part A	Selecting and evaluating input under time pressure; associated with speed of information processing
Learning	Hopkins Verbal Learning Test, Immediate Recall Trials 1-3 Brief Visuospatial Memory Test, Immediate Recall Trials 1-3 Story Memory Test, Learning Rate Trial 1 Recall Figure Memory Test Learning Rate Trial 1 Recall	Learning of explicit and implicit memories, logical memory, and nonverbal memory
Memory	Hopkins Verbal Learning Test, Delayed Recall Brief Visuospatial Memory Test, Delayed Recall Story Memory Test, % Loss Figure Memory Test % Loss	Delayed recall of explicit and implicit memories, logical memory, and nonverbal memory
Verbal fluency	Controlled Oral Word Association Test Animal (Category) Fluency Test	Fluency (spontaneous generation of words)
Psychomotor	Grooved Pegboard Test	Performance of motor tasks

Note. WRAT-3 = Wide Range Achievement Test-Third Edition. WAIS-III = Wechsler Adult Intelligence Scale-Third Edition.

processes relevant to HIV and TBI. NAA is produced by neuronal mitochondria only and thus serves as a useful marker for neural integrity. Choline and myo-inositol indicate inflammation and glial changes; these two are known to be increased in HIV+ patients. Creatine is a control marker, commonly accepted as a marker of cellular energy stores (Taylor et al., 2007).

To obtain measurements of these markers, we used a clinical, General Electric 1.5-Tesla scanner at the 5 CHARTER research sites for short-echo proton magnetic resonance spectroscopy. The settings used include an echo time of 35 ms and a repetition time of 3,000 ms. The regions of interest (ROIs) were the right frontal lobe white matter, midline frontal lobe gray matter, and basal ganglia, including the head of the right caudate nucleus (Taylor et al., 2007).

Spectral analyses were accomplished using LCModel, Version 5.2-1. This program analyzes in vivo spectra as a linear combination of a basis set of complete model spectra of metabolites in vitro. Metabolite concentrations were calculated correcting for partial volume of CSF in each ROI. On the day of each scan, a chemical phantom provided by the CHARTER coordinating center was scanned. After processing, metabolites for each participant were adjusted for site differences by dividing the in vivo values by the phantom values (Provencher, 1993).

Statistical analysis

Statistical analyses were performed using the JMP software program (SAS Institute, Inc., Cary, NC). Neuropsychological and neurological imaging data were compared between groups with and without reported head injury using *t* tests for independent samples. These

analyses were conducted at one-tailed tests based on the a priori hypotheses presented above. Cohen's *d* is reported as a measure of effect size (J. Cohen, 1988).

RESULTS

On neuropsychological assessments we found that the HIV+TBI+ group had significantly worse deficit scores than the HIV+TBI- group in working memory and executive function, and a trend toward worse overall performance as reflected in the GDS (Table 3). Executive function (Cohen's *d* = 0.20), working memory (Cohen's *d* = 0.21), and GDS (Cohen's *d* = 0.14) all exhibit a small effect size. The remaining cognitive ability areas (attention and speed of information processing, learning, memory, verbal fluency, and psychomotor) showed no significant differences between the two groups (Table 3).

On self-assessment the HIV+TBI+ group reported more total complaints on the PAOFI (Cohen's *d* = 0.21), with significantly elevated scores in the areas of memory (Cohen's *d* = 0.31) and sensory functioning (Cohen's *d* = 0.25); all effect sizes for the PAOFI were small (Table 3).

In the MRS study, the HIV+TBI+ group displayed significantly lower NAA levels in frontal gray matter and basal ganglia, but not in frontal white matter, than did the HIV+TBI- group (Table 4). Frontal gray matter (Cohen's *d* = 0.59) and basal ganglia (Cohen's *d* = 0.58) exhibit a medium effect. Between the two groups, myo-inositol, creatine, and choline were not found to be significantly different (Table 4).

The only significant correlations between neuropsychological (NP) and MRS values were between frontal gray matter (FGM) NAA and GDS. The correlation between FGM NAA and GDS for the TBI group was $r = .55$, $p = .02$, while the correlation for the group without

TABLE 3
NP and PAOFI data comparisons between TBI and non-TBI groups

	HIV+TBI+ (N = 110)	HIV+TBI- (N = 590)	<i>t</i> value	<i>p</i> value
NP deficit score				
Working memory	0.71 (0.97)	0.54 (0.76)	-2.02	.02*
Executive function	0.73 (1.07)	0.56 (0.81)	-1.89	.03*
Attention/speed of information processing	0.36 (0.73)	0.31 (0.63)	-0.77	.22
Learning	0.96 (1.11)	0.83 (1.01)	-1.22	.11
Memory	0.70 (1.01)	0.73 (1.03)	0.33	.63
Verbal fluency	0.39 (0.69)	0.36 (0.70)	-0.38	.35
Psychomotor	0.59 (0.98)	0.53 (0.92)	-0.66	.26
Global	0.62 (0.65)	0.54 (0.57)	-1.31	.09
PAOFI				
Memory	3.06 (2.91)	2.19 (2.81)	-2.98	.002*
Cognitive	1.48 (2.23)	1.23 (2.20)	-1.05	.15
Language	2.13 (2.51)	1.71 (2.50)	-1.60	.06
Motor	0.46 (0.86)	0.44 (0.71)	-0.34	.37
Sensory	0.61 (0.84)	0.42 (0.73)	-2.44	.007*
Total score	7.25 (7.36)	5.71 (7.29)	-2.03	.02*

Note. Standard deviations in parentheses. NP = neuropsychological. Patient's Assessment of Own Functioning Inventory. TBI = traumatic brain injury. $p < .05$.

TABLE 4
MRS data comparison between TBI and no-TBI groups

		HIV+ TBI+ N = 17	HIV+TBI- N = 84	t value	p value
Frontal white matter	N-Acetylaspartate	1.18 (0.13)	1.21 (0.14)	0.85	.20
	myo-inositol	1.71 (0.34)	1.63 (0.40)	-0.84	.20
	Creatine	1.01 (0.20)	0.97 (0.15)	-0.75	.23
	Choline	1.06 (0.17)	0.98 (0.18)	-1.56	.06
Frontal gray matter	N-Acetylaspartate	1.04 (0.16)	1.12 (0.13)	2.18	.02*
	myo-inositol	1.31 (0.33)	1.42 (0.28)	1.48	.93
	Creatine	1.00 (0.19)	1.02 (0.15)	0.56	.29
	Choline	0.79 (0.19)	0.78 (0.14)	-0.39	.35
Basal ganglia	N-Acetylaspartate	1.21 (0.17)	1.29 (0.13)	2.17	.02*
	myo-inositol	1.35 (0.21)	1.41 (0.26)	0.73	.77
	Creatine	1.17 (0.25)	1.21 (0.21)	0.69	.25
	Choline	0.99 (0.18)	0.97 (0.15)	-0.48	.32

Note. Standard deviations in parentheses. MRS = magnetic resonance spectroscopy. TBI = traumatic brain injury. $p < .05$.

TBI was $r = .32$, $p = .003$. Fisher's r -to- z transformation was used to test the difference between these two correlations, which were not significantly different even using a one-sided test ($p = .16$).

Depressive symptoms (BDI scores) did not significantly differ between HIV+TBI+ and HIV+TBI- groups (Table 5). Alcohol use disorders were somewhat more prevalent in HIV+TBI+ (61.7% vs. 51.2% for HIV+TBI-). The other substance categories (cannabis, cocaine, methamphetamine, opioid, hallucinogen, sedative, and inhalants) showed no statistically significant differences between groups (Table 5). There was no significant difference in the proportions of participants with lifetime history of mood disorders (57.4% for TBI+; 51.5% for TBI-) or with mood disorders at time of evaluation (18.2% for TBI+; 15.1% for TBI-).

Although the difference in proportion with alcohol disorders was not large, we conducted a series of two-way analyses of variance (ANOVA) with TBI and alcohol

disorder as independent variables and the various neuropsychological, PAOFI, and MRS scores as dependent. None of the 2×2 ANOVAs for the NP deficit and PAOFI scores was statistically significant. The R^2 values for each of these models ranged from .001 to .007, meaning that the highest proportion of variance explained was 0.7%. Less than 1% of the variance in MRS measures was accounted for by the combination of TBI and history of alcohol use disorder. In the case of FGM NAA, the 2×2 ANOVA model was statistically significant overall ($R^2 = .05$, $p = .01$); however, the interaction between TBI and history of alcohol use disorder was not statistically significant ($p = .16$). In the case of basal ganglia (BG) NAA, the overall model was statistically significant ($R^2 = .03$, $p = .05$), and there was a trend towards a significant interaction between TBI and history of alcohol use disorder ($p = .06$). Further analysis revealed that subjects with history of alcohol use disorder and TBI had the lowest NAA in the basal ganglia.

TABLE 5
Depression and substance dependence comparisons in TBI and non-TBI groups

	HIV+TBI+ (N = 110)	HIV+TBI- (N = 590)	t value	χ^2	p value
BDI	15.1 (10.5)	14.1 (13.6)	-0.73		.23
With history of use disorder of:					
Alcohol (%)	62.7	51.2		5.02	.03*
Cannabis (%)	3.6	2.5		0.39	.53
Cocaine (%)	6.4	7.3		0.12	.73
Opioid (%)	1.8	5.4		3.26	.07
Meth (%)	0.91	3.1		2.06	.15
Hallucinogen (%)	0.0	0.17		0.34	.56
Sedative (%)	0.0	0.17		0.34	.56
Inhalant (%)	0.0	0.17		0.34	.56

Note. History of use disorder includes "abuse" and "dependency," as defined by the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV)* criteria, either currently or in the past (American Psychiatric Association, 1994, 2000). Standard deviations in parentheses. TBI = traumatic brain injury. BDI = Beck Depression Inventory. $p < .05$.

Proportions of participants with diagnoses of multiple substance use were not significantly different between TBI+ (53.6%) and TBI- (47.6%) groups. There was also no significant difference in proportions with current psychotropic use between TBI+ (54.5%) and TBI- (58.1%) groups.

DISCUSSION

The results of this study indicate that HIV-infected participants who report substantial TBI, defined as a history of loss of consciousness greater than 30 minutes or complicated by neurological symptoms persisting more than 2 weeks after the injury, were significantly more impaired in working memory and executive functioning than the HIV+ TBI- group. Consistent with our neuropsychological test results, the HIV+TBI+ group also reported more neurocognitive problems, including memory and sensory complaints.

From our MRS subset, we found that HIV and TBI together were associated with decreased NAA in the frontal gray matter and basal ganglia brain regions when compared to HIV participants without TBI. Our results are consistent with studies that have showed decreased levels of NAA associated with HIV alone and TBI alone; they also suggest greater reduction in neuronal integrity in those regions among the HIV+TBI+ group (Taylor et al., 2007).

Our groups were well equated on many factors that could have independently contributed to worse NP performance or metabolite changes. These matching factors included age, education, race/ethnicity, reading proficiency, and several HIV disease and treatment characteristics, including nadir CD4 count. Though individuals within the HIV+TBI+ group were somewhat more likely to be male (89% vs. 75% for HIV+TBI-), our use of gender-adjusted norms available for most of the neuropsychological tests make it unlikely that gender influenced the results. Furthermore, a study on neuropsychological performance in mild TBI patients revealed no statistically significant differences between male and female patients (Tsushima, Lum, & Geling, 2009). The groups also had equivalent levels of depressive symptoms (typically in the mild severity range) as well as current and past diagnoses of MDD, dysthymia, or both. Substance disorders were also comparable, with the exception of alcohol disorders, which were about 10% higher in the HIV+TBI+ group. However, analyses taking alcohol disorder diagnosis into account did not reveal any systematic effect for alcohol on CNS outcomes.

From these data, we believe it is accurate to say that a history of more than minimal TBI in the setting of HIV is associated with mild enhancement of neurocognitive symptoms and signs, as well as more evidence of metabolite change in the brain. At the same time, the effect sizes for neuropsychological performance are surprisingly small (in the 0.15 range), given that these were more than minimal injuries by history. The effect sizes on reported cognition were somewhat higher (0.21 to 0.31) and were not explained by differences in mood.

This, coupled with the more robust effect on the metabolite NAA in the MRS substudy, opens the possibility that TBI may be associated with more lingering brain effects than are being captured by neuropsychological testing.

Our data are also consistent with another study that demonstrated that people who are HIV+TBI+ have significantly greater number of symptoms associated with mild TBI than do an HIV+TBI- group. The authors used the TIRR (The Institute for Rehabilitation Research) symptom checklist, which included the cluster of 25 symptoms specific to mild TBI that were higher in those with previous head injuries (Jaffe, O'Neill, Vandergoot, Gordon, & Small, 2000). Though the authors were the first to state the importance of recognizing the functional impact of TBI within the HIV population, our report has further explored what the impact is through analysis of neuropsychological tests, spectroscopy information, depressive symptoms, alcohol and drug abuse, and biological markers of HIV infection and AIDS disease.

Although the effects of TBI on HIV neurocognitive outcomes have not received wide attention, there are indications that history of TBI can amplify the effects of other neurological diseases. For example, traumatic brain injury appears to increase the risk of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease (Formisano et al., 2009; Van Den Heuvel, Thorton, & Vink, 2007). Persisting difficulties with abstraction associated with alcoholism may also be amplified by head injury history (Adams & Grant, 1986).

The mechanisms of the reinforcing effects of HIV and TBI on brain function are unknown. Reduction in NAA is consistent with neuronal injury associated with TBI leading to a disruption of neuronal mitochondrial activity, which subsequently leads to cognitive compromise. The lower NAA levels may also be compatible with the common neural injury mechanism of increased excitotoxicity: TBI alone could potentiate large fluxes of calcium that induce apoptosis in neurons associated with cognition (Greenwood, 1991).

TBI has also been associated with inflammation (Cederberg & Siesjö, 2010). However, given that in the MRS substudy there were no significant differences between HIV+TBI+ and HIV+TBI- in levels of myoinositol and choline, metabolites indicative of inflammation, it appears that an inflammatory process may not be linked to the TBI-associated cognitive worsening that follows. Instead, the patterns in our data (e.g., NAA reduction in TBI+) suggest that persistent neuronal injury may be a factor. Since TBI has been linked to increased blood brain barrier (BBB) permeability, it is possible that mechanisms associated with increased BBB permeability can enhance HIV's penetration and virulence in HIV+TBI+ individuals (Fay et al., 2009; Moody, 2006). Viral proteins and inflammatory mediators could disrupt BBB regulation, allowing increased leukocyte migration and inducing subsequent neuronal damage and death (Roberts, Buckner, & Berman, 2010).

Our analyses were based on a study limited to HIV-infected people. Therefore, though our results are compatible with a model of additivity, without examining

HIV-uninfected groups that have TBI we cannot be certain whether these are additive or interactive effects. Because this was an exploratory study, we did not rigorously control for multiple comparisons, and thus the data must be regarded as preliminary. Furthermore, since our study was retrospective, some details about the TBIs were unavailable. It is possible that the TBI group itself differed in some way that we did not account for. A potential future prospective study could integrate more clinical information about a participant's head injury such as the location of initial insult, Glasgow Coma Scale rating, or more precision on duration of unconsciousness. Future studies could also utilize functional magnetic resonance imaging (fMRI) information as another means to evaluate neuropsychological performance simultaneously with metabolic imaging.

Looking at the number of head injuries that a person experienced could also have been worthwhile (such data were not systematically gathered in CHARTER), as neuropsychological tests of memory, attention, and motor function have shown worse performance with repeated head injury (Hestad, Updike, Selnes, & Royal, 1995). For example, HIV- individuals with multiple TBIs, when compared to those with a single TBI, exhibit significantly poorer memory and executive functioning (Belanger, Spiegel, & Vanderploeg, 2010). Given that these two neurocognitive domains are the same as those that showed significant deficits in our study, it would be interesting to determine whether there are cumulative effects of multiple TBI on HIV-associated neurocognitive decline.

Despite some limitations, our study does indicate that TBI may increase vulnerability to brain dysfunction in HIV-infected individuals. If confirmed, the results indicate that those involved with HIV care need to take head injury into account in their neurological evaluation and clinical management of HIV patients.

Original manuscript received 7 May 2010
Revised manuscript accepted 16 August 2010
First published online 10 January 2011

REFERENCES

- Adams, K. M., & Grant, I. (1986). Influence of premorbid risk factors on neuropsychological performance in alcoholics. *Journal of Clinical and Experimental Neuropsychology*, 8(4), 362–370.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.
- Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., et al. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*, 69(18), 1789–1799.
- Belanger, H. G., Spiegel, E., & Vanderploeg, R. D. (2010). Neuropsychological performance following a history of multiple self-reported concussions: A meta analysis. *Journal of the International Neuropsychological Society*, 16, 262–267.
- Cederberg, D., & Siesjö, P. (2010). What has inflammation to do with traumatic brain injury? *Child's Nervous System*, 26, 221–226.
- Centers for Disease Control. (1992). 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *Morbidity and Mortality Weekly Report*, 41, 1–19.
- Centers for Disease Control. (2009a). *HIV/AIDS basic statistics*. Retrieved February 26, 2009, from <http://www.cdc.gov/hiv/topics/surveillance/basic.htm>
- Centers for Disease Control. (2009b). *Traumatic brain injury*. Retrieved March 27, 2009, from <http://www.cdc.gov/ncipc/tbi/TBI.htm>
- Chelune, G. J., Heaton, R. K., & Lehman, R. A. W. (1986). Neuropsychological and personality correlates of patients' complaints of disability. In R. E. T. Gerald Goldstein (Ed.), *Advances in Clinical Neuropsychology*, 3, 95–126.
- Cohen, B. A., Inglese, M., Rusinek, H., Babb, J. S., Grossman, R. I., & Gonen, O. (2007). Proton MR spectroscopy and MRI-volumetry in mild traumatic brain injury. *American Journal of Neuroradiology*, 28, 907–913.
- Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.
- Cooper, L., Peters, L., & Andrews, G. (1998). Validity of the Composite International Diagnostic Interview (CIDI) psychosis module in a psychiatric setting. *Journal of Psychiatric Research*, 32(6), 361–368.
- Fay, T. B., Yeates, K. O., Taylor, H. G., Bangert, B., Dietrich, A., Nuss, K. E., et al. (2009). Cognitive reserve as a moderator of postconcussive symptoms in children with complicated and uncomplicated mild traumatic brain injury. *Journal of the International Neuropsychological Society*, 19, 1–12.
- Formisano, R., Cicinelli, P., Buzzi, M. G., Brunelli, S., Zafonte, R., Vinicola, V., et al. (2009). Blink reflex changes in parkinsonism following severe traumatic brain injury correlates with diffuse axonal injury. *International Medical Journal of Experimental and Clinical Research*, 15(3), 101–106.
- Grant, I. (2008). Neurocognitive disturbances in HIV. *International Review of Psychiatry*, 20(1), 33–47.
- Greenwood, J. (1991). Mechanisms of blood-brain barrier breakdown. *Neuroradiology*, 33(2), 95–100.
- Heaton, R. K., Clifford, D. B., Franklin, Jr, D. R., Woods, S. P., Ake, C., Vaida, F., et al. (in press). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy. *Neurology*.
- Heaton, R. K., Miller, W., Taylor, M. J., & Grant, I. (2004). *Revised comprehensive norms for an expanded Halstead-Reitan Battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults*. Lutz, FL: Psychological Assessment Resources.
- Hernández, T. D. (2006). Post-traumatic neural depression and neurobehavioral recovery after brain injury. *Journal of Neurotrauma*, 23, 1211–1221.
- Hestad, K., Updike, M., Selnes, O. A., & Royal, W., III. (1995). Cognitive sequelae of repeated head injury in a population of intravenous drug users. *Scandinavian Journal of Psychology*, 36(3), 246–255.
- Jaffe, M., O'Neill, J., Vandergoot, D., Gordon, W. A., & Small, B. (2000). The unveiling of traumatic brain injury in an HIV/AIDS population. *Brain Injury*, 14(1), 35–44.
- Keogh, B. K., Major, S. M., Omori, H., Gándara, P., & Reid, H. P. (1980). Proposed markers in learning disabilities research. *Journal of Abnormal Child Psychology*, 8(1), 121–131.
- Moody, D. M. (2006). The blood-brain barrier and blood-cerebral spinal fluid barrier. *Seminars in Cardiothoracic and Vascular Anesthesia*, 10(2), 128–131.
- Paul, R. H., Yiannoutsos, C. T., Miller, E. N., Chang, L., Marra, C. M., Schifitto, G., et al. (2007). Proton MRS and neuropsychological correlates in AIDS dementia complex: Evidence of subcortical specificity. *Journal of Neuropsychiatry and Clinical Neuroscience*, 19, 283–292.

- Price, R. W., Epstein, L. G., Becker, J. T., Cinque, P., Gisslen, M., Pulliam, L., et al. (2007). Biomarkers of HIV-1 CNS infection and injury. *Neurology*, *69*, 1781–1788.
- Provencher, S. W. (1993). Estimation of metabolite concentrations from localized in vivo proton NMR spectra. *Magnetic Resonance in Medicine*, *30*, 672.
- Reger, M., Welsh, R., Razani, J., Martin, D., & Boone, K. B. (2002). A meta-analysis of the neuropsychological sequelae of HIV infection. *Journal of the International Neuropsychological Society*, *8*, 410–424.
- Richter, P., Werner, J., Heerlein, A., Kraus, A., & Sauer, H. (1998). On the validity of the Beck Depression Inventory. A review. *Psychopathology*, *1*(3), 160–168.
- Roberts, T. K., Buckner, C. M., & Berman, J. W. (2010). Leukocyte transmigration across the blood-brain barrier: Perspectives on neuroAIDS. *Frontiers in Bioscience*, *15*, 478–536.
- Schuff, N., Meyerhoff, D. J., Mueller, S., Chao, L., Sacrey, D. T., Laxer, K., et al. (2006). N-Acetylaspartate as a marker of neuronal injury in neurodegenerative disease. *Advances in Experimental Medicine and Biology*, *576*, 241–363.
- Silver, J. M., McAllister, T. W., & Arciniegas, D. B. (2009). Depression and cognitive complaints following mild traumatic brain injury. *American Journal of Psychiatry*, *166*, 653–661.
- Taylor, M. J., Schweinsburg, B., Alhassoon, O. M., Gongvatana, A., Brown, G. G., Young-Casey, C., et al. (2007). Effects of human immunodeficiency virus and methamphetamine on cerebral metabolites measured with magnetic resonance spectroscopy. *Journal of Neurovirology*, *13*, 150–159.
- Tsushima, W. T., Lum, M., & Geling, O. (2009). Sex differences in the long-term neuropsychological outcome of mild traumatic brain injury. *Brain Injury*, *10*, 809–814.
- Vakil, E. (2005). The effect of moderate to severe traumatic brain injury (TBI) on different aspects of memory: A selective review. *Journal of Clinical and Experimental Neuropsychology*, *27*(8), 977–1021.
- Van Den Heuvel, C., Thorton, E., & Vink, R. (2007). Traumatic brain injury and Alzheimer's disease: A review. *Progress in Brain Research*, *161*, 303–316.
- Weiss, N., Galanaud, D., Carpentier, A., Naccache, L., & Puybasset, L. (2007). Clinical review: Prognostic value of magnetic resonance imaging in acute brain injury and coma. *Critical Care*, *11*(5), 230.
- Wohlschlaeger, J., Wenger, E., Mehraein, P., & Weis, S. (2009). White matter changes in HIV-1 infected brains: A combined gross anatomical and ultrastructural morphometric investigation of the corpus callosum. *Clinical Neurology and Neurosurgery*, *111*(5), 422–429.