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Cerebral Volume Loss, Cognitive Deficit, and Neuropsychological Performance: Comparative Measures of Brain Atrophy: II. Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) results in a variable degree of cerebral atrophy that is not always related to cognitive measures across studies. However, the use of different methods for examining atrophy may be a reason why differences exist. The purpose of this manuscript was to examine the predictive utility of seven magnetic resonance imaging (MRI) - derived brain volume or indices of atrophy for a large cohort of TBI patients ($n = 65$). The seven quantitative MRI (qMRI) measures included uncorrected whole brain volume, brain volume corrected by total intracranial volume, brain volume corrected by the ratio of the individual TICV by group TICV, a ventricle to brain ratio, total ventricular volume, ventricular volume corrected by TICV, and a direct measure of parenchymal volume loss. Results demonstrated that the various qMRI measures were highly interrelated and that corrected measures proved to be the most robust measures related to neuropsychological performance. Similar to an earlier study that examined cerebral atrophy in aging and dementia, these results suggest that a single corrected brain volume measure is all that is necessary in studies examining global MRI indicators of cerebral atrophy in relationship to cognitive function making additional measures of global atrophy redundant and unnecessary. (*JINS*, 2011, *17*, 308–316)

Keywords: MRI, TBI, Cognition, Atrophy, Brain/behavior relationships, CNS

INTRODUCTION

Measures of brain volume and/or global cerebral atrophy have been central in understanding the nature of several neurologic disorders, cognitive dysfunction, as well as normal brain development and aging (Jack et al., 1999; Killiany et al., 2000; Levine et al., 2008; Maxwell, MacKinnon, Stewart, & Graham, 2010; Smith, Snowden, Wang, & Markesbery, 2000; Xu et al., 2000, 2010). Previously, we examined seven common quantitative and statistical methods used to examine global brain atrophy among a cohort of older patients from the Cache County Memory and Aging study (Bigler et al., 2004). That study demonstrated relatively consistent findings between the measures of brain atrophy and cognitive variables with no one single variable statistically superior to the other, although the ventricle-to-brain ratio (VBR) tended to be the best overall indicator related to cognitive outcome. While the study underscored the importance of correcting for brain size differences, the main observation was that any one of the seven corrected brain volume measurements was sufficient when examining the association between cognitive function and quantitative magnetic resonance imaging (qMRI) variables in aging and age-associated degenerative disease.

The study by Bigler et al. (2004) only examined subjects 65 and older and included those with and without dementia. Numerous other neurological conditions result in global cerebral atrophy (Brewer, 2009) the presence of which likely influence cognitive performance. However, the question remains unanswered as to whether these various methods that correct for head size differences have equivalent relationships in other disorders. For example, traumatic brain injury (TBI) is known to result in diffuse parenchymal volume loss (Levine et al., 2008; Maxwell et al., 2010; Xu et al., 2010), in which the

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degree of volume loss is associated with clinical outcome and degree of cognitive deficit (Bendlin et al., 2008; Bergeson et al., 2004; Bigler et al., 2000; Christensen et al., 2008; Gur et al., 2000; Ng et al., 2008). The pattern of diffuse volume loss from TBI obviously has a different etiology than that observed in aging and progressive degenerative disorders, and therefore, the question arises as to whether there is a best method for head size correction in TBI, when examining neuropsychological outcome and its relationship to cerebral atrophy.

For this reason, we revisit the topic of global atrophy measurement methods among a cohort of TBI patients to determine if there is a "preferred" method of measurement when examining the effects of TBI. In this study, we examine the same seven qMRI measures of global brain volume and/or atrophy as performed in the investigation by Bigler et al. (2004) and analyze their association with cognitive performance in adult TBI patients.

METHODS

Patient Cohort

Participants for this study included a cohort of TBI patients ($n = 65$) initially recruited from an inpatient neurorehabilitation unit from a Level I trauma center in Salt Lake City, Utah with qMRI and complete neuropsychological test data. All eligible patients were informed to the nature of the study and provided written consent. In addition, all data management and recruitment procedures were performed in accordance with local institutional review boards. Subject demographics for the TBI subjects are contained in Table 1. Briefly, subjects included TBI patients with a range of TBI injury severity (Glasgow Coma Scale [GCS] ranged from 3 to 15 with, a mean age of 27.66 years [$SD = 7.58$]).

On average, TBI patients were imaged and cognitively tested 34 months post-injury (range, 3.5 to 91 months), a point in their recovery where both brain and cognitive function are considered "stable" (Ng et al., 2008). Some of the subjects for this investigation have been part of earlier investigations and the methods of recruitment are outlined in those studies (see Bergeson et al., 2004; Blatter et al., 1995; Tate & Bigler, 2000).

MRI Acquisition and Segmentation Routine

Each of the patients and control participants underwent MRI using the same 1.5 Tesla (T) GE scanner at the LDS Hospital in Salt Lake City, Utah. A standardized set of sequences was used (see Bigler et al., 2000) across the sample and included a T1-weighted as well as a Proton Density (PD)/T2-weighted dual echo [repetition time (TR) = 3000/31, echo time (TE) = 90/1, field of view (FOV) = 24 cm, 1 mm × 1 mm in plane resolution, 5-mm-thick slices] sequences. For this study, we used the global quantitative measurements (described below) obtained from the dual echo sequence using a manual segmentation routine (Bigler et al., 2002). Using the commercially available software program Analyze® (Mayo Clinic, Rochester, MN), measures for grey/white matter parenchyma and cerebrospinal fluid (CSF) were derived using a two-channel (PD/T2) segmentation routine, where imaging voxels representing the different tissue types were manually selected for each set of images and processed using a k-nearest neighbor algorithm effectively assigning ranges of voxel intensities to the three tissue classes (CSF, gray and white matter). Once segmented into the various tissue types, the images were manually skull stripped leaving only the parenchyma and CSF for quantification (for a full description of segmentation method see Robb, 1995, 2001).

Quantitative MR Measurements

Though the details of the image analyses and quantification techniques were discussed in the previous manuscript (Bigler et al., 2004), we provided a brief description for each measure below (see Table 2 for summary). The three most basic measures examined here include total intracranial volume (TICV), total parenchymal brain volume (TBV), and total ventricular volume (TVV). TICV is a measure of the intracranial cavity contents and is derived by quantifying the total CSF, meninges, and brain parenchyma volumes inside the calvarium. It is generally accepted as a measure of head size as well as maximal brain growth (Bigler and Tate, 2001) given the dynamic interaction between the developing brain and skull growth (Blinkov & Glezer, 1968; Courchesne et al., 2000; Nellhaus, 1968; Peterson et al., 2000; Reiss, Abrams, Singer, Ross, & Denkla, 1996). TBV is simply a measure of gray and white matter in the cerebrum, cerebellum and brain stem. In degenerative or traumatic disorders, TBV is usually represented as total parenchymal brain volume adjusted in some manner for head size (i.e., TICV) to allow for more direct comparisons between participants (Cahn et al., 1998; Fama et al., 2000; Forstl et al., 1996; Jack et al., 1998; Killiany et al., 2000; Shear et al., 1995; Tanabe et al., 1997; Wilson et al., 1996). TVV is a measure of ventricular volume and is derived by summing the volumes of the four main ventricular spaces (the two lateral ventricles, III and IV ventricles). Qualitative

Table 1. Basic demographic information for the sample investigated

	Males ($n = 44$)	Females ($n = 21$)	Total ($n = 65$)
Age, mean (*SD*), yr	27.95 (7.75)	27.05 (7.38)	27.66 (7.58)
GCS, mean (*SD*)	9.07 (3.26)	8.38 (3.15)	8.85 (3.22)
Time post-injury, mean (*SD*), mo	34.27 (25.49)	46.30 (19.64)	38.16 (24.27)
Range of time post-injury, mo	3.20-91.63	8.70-77.10	3.20-91.63
Education, mean (*SD*), yr	12.18 (1.26)	12.29 (1.98)	12.21 (1.52)

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Table 2. Formula summaries for the various measures used to quantify global brain atrophy

Total intracranial volume (TICV)	Surface CSF + meninges + grey/white matter + ventricular CSF
Raw total brain volume (TBV)	Gray matter volume + white matter volume
Total ventricular volume (TVV)	Lateral ventricle volume + III and IV ventricular volumes
Total corrected brain volume (TBV[c])	$\left(\frac{\text{Subject TICV}}{\text{Mean TICV for the group}}\right) \times$ individual TBV
Parenchymal volume loss (PVL)	(Original estimated TBV[a]) − (current TBV)
Ventricle-to-brain ratio (VBR)	$\text{VBR} = \left(\frac{\text{TVV}}{\text{TBV}}\right) \times 100$
Brain-to-TICV ratio (TBV/TICV)	$\frac{\text{TBV}}{\text{TICV}}$
Ventricle-to-cranial ratio (VCR)	$\frac{\text{TVV}}{\text{TICV}}$

CSF = cerebrospinal fluid.
[a]Original Brain Volume = TICV − CSF Constant (Male CSF Constant = 85; Female CSF Constant = 90 (From Blatter et al., 1995).

and quantitative examination of the ventricles is generally accepted as a way of examining atrophy since intraventricular CSF is under pressure and any parenchymal volume loss results in passive expansion of the ventricles, or hydrocephalus *ex vacuo* (Bradley & Orrison, 2000).

Using TICV, TBV, and TVV, several additional ways for examining associations between brain size, disease variables, and cognition were examined. Five additional measures of atrophy including a total corrected brain volume (TBV[c]) measure suggested by Blatter et al. (1995) which is derived by normalizing the individual's TICV by the group's average TICV and then using this value to scale the TBV of each participant. Another measure is an estimate of parenchymal volume loss (PVL) derived by subtracting the current TBV from an estimated maximal TBV. The maximal TBV is estimated using TICV, which as stated above is generally considered an estimate of maximal brain growth. In terms of the volume occupied by the non-neural intracranial contents, Blatter et al. (1995) demonstrated that surface CSF occupied approximately 85 cm^3 for male subjects and 90 cm^3 for female subjects at maturity (age 16 to 25). So, an estimate of maximal brain volume or perhaps "premorbid" brain volume (provided normal development) is TICV minus the CSF constant reported above for males and females (Bigler et al., 2004). By subtracting the current brain volume from this maximal brain volume estimate, one can then estimate the amount of global atrophy.

We also examine the ventricle-to-brain ratio (VBR), which is a modification of early planimetric methods developed in the era of pneumoencephalography (Haug, 1962). VBR is derived by dividing the TVV by TBV and multiplying this value by 100. This measure captures both the expansion of the ventricular system and decreased brain volume in response to injury or disease (Bigler et al., 2000). Furthermore, by relying on whole brain ventricular volume and dividing this by brain volume, this current measure addresses earlier criticisms of the original planimetric method (Arndt, Cohen, Alliger, Swayze, & Andreasen, 1991; Raz, Raz, & Bigler, 1988a, 1988b), which relied on a single slice to determine VBR. The ventricle-to-cranial ratio (VCR) is a ratio of TVV to TICV multiplied by 100 and is considered a measure of ventricular expansion normalized by head size. We examine VCR due to the possibility that processes other than parenchymal atrophy influence ventricular expansion. We also examine the brain-to-intracranial volume ratio, which captures global brain size normalized by head size. See Table 2 for the exact formula for each variable considered in this study.

Neuropsychological Measurements

Neuropsychological function was assessed for the TBI patients using common clinical assessment measures administered while the patients were in rehabilitation and follow-up. From this clinical battery, tests examined in this manuscript were selected to maximize the overlap in measures examined in the previous study (Bigler et al., 2004) (see Table 3). Selecting overlapping tests would allow us to maximize our ability to draw similar or disparate conclusions about the data.

For this study, we examined cognitive performance using the Wechsler Adult Intelligence Scale-R Full Scale IQ (WAIS-R FSIQ), the symbol digit from the WAIS-R, Trail Making A and B, Controlled Oral Word Association (COWA), the Hooper Visual Organization Test, the immediate and delayed recall for the Logical Memory subtest from the Wechsler Memory Scale—Revised (WMS-R), the delayed recall and total score for the Rey Auditory Verbal Learning Test, and the immediate and delayed recall of the Rey Complex Figure. All tests were administered and scored according to standardize testing procedures. The dependent measures for each test was the raw score with the exception of the WAIS-R FSIQ, which was a standardized score (mean = 100; *SD* = 15). To be included in this study, cognitive testing needed to be completed within two weeks of the MRI examination.

Statistical Methods

The Pearson correlation coefficient was used to assess the degree of association between the seven brain atrophy measures and each neuropsychological test score in a similar manner to that of the earlier published manuscript (Bigler et al., 2004) to

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Table 3. Neuropsychological test battery used to assess cognitive function in TBI patients with the means (*SD*) for males and females

	Bigler et al., 2004 Paper	Current paper	Explanation	Males	Females	Total
IQ	Shipley Intelligence Test	WAIS-R FSIQ[a]	This is the composite score derived from the various subtests of the Wechsler Adult Intelligence Scale.	93.21 (13.34)	89.70 (12.58)	91.91 (13.06)
Attention/ executive function	Symbol Digit	Symbol Digit	Assesses attention by requiring participants to discriminate between visually presented targets and foils under timed conditions.	7.26 (2.12)	7.39 (3.18)	7.30 (2.50)
	Trail Making A	Trail Making A	Measures visual-scanning and attention abilities when dealing with a familiar sequence (numbers 1 through 25).	38.15 (30.46)	48.10 (38.62)	41.47 (33.41)
	Trail Making B	Trail Making B	Assesses sequencing and mental flexibility by requiring alternating between two familiar sequences (numbers and letters).	85.76 (44.03)	116.20 (72.63)	96.26 (56.83)
Language	Controlled Oral Word Association	Controlled Oral Word Association	Assesses word generation given a phonemic cue (in this case F, A, and S).	30.30 (11.77)	33.92 (8.94)	31.40 (11.02)
	Boston Naming	No equivalent test administered.	Not applicable.	N/A	N/A	N/A
Visual spatial function	No equivalent test administered.	Hooper	Assesses ability to visually integrate piecemeal information into whole perceptions.	26.89 (2.54)	26.94 (2.15)	26.90 (2.41)
Immediate memory	Logical Memory-Immediate	Logical Memory-Immediate	Assesses ability to learn and freely recall a novel story presented aurally.	22.49 (6.05)	23.15 (7.53)	22.73 (6.56)
	Construction	Rey Complex Figure-Immediate Recall	Assesses ability to recall and generate a novel complex geometric figure.	32.59 (6.18)	32.91 (3.12)	32.69 (5.34)
	Word List-Immediate	Rey Auditory Verbal Learning-Total Score	Assesses ability to learn and freely recall a list of words presented across several trials.	44.94 (12.46)	44.94 (12.80)	44.94 (12.44)
Delayed memory	Logical Memory-Delayed	Logical Memory-Delayed	Assesses ability to learn and freely recall a novel story presented aurally after a 30-minute delay.	18.00 (6.73)	19.26 (7.84)	18.46 (7.11)
	Benton Visual	Rey Complex Figure-Delayed Recall	Assesses ability to recall and generate a novel complex geometric figure after a 20-minute delay.	17.56 (7.50)	16.03 (6.75)	17.06 (7.23)
	Word List-Delayed	Rey Auditory Verbal Learning-Delayed Recall	Assesses ability to learn and freely recall a list of words after a 20-minute delay.	8.56 (3.98)	9.13 (3.40)	8.73 (3.78)

TBI = traumatic brain injury.
[a]WAIS R -FSIQ is reported as a standard value. All other neuropsychological measures in the table are represented as raw values.

facilitate a more direct comparison of the results from the two studies. The correlation coefficients within neuropsychological test were compared with a χ^2 test for multiple correlation coefficients based on Fisher's transformation of the correlation (Zar, 1996, p. 384). Fisher's transform ensures that correlation coefficients follow a normal distribution by taking the inverse hyperbolic tangent of the correlation (Zar, 1996, p. 376).

The χ^2 test compares atrophy measures within each neuropsychological test, but makes no attempt to compare the general performance of the measures across tests. Hence, general performance of atrophy measures was assessed by first assigning a rank to each atrophy measure within each neuropsychological test according to the strength of the absolute value of the correlation coefficient. The atrophy measure with the strongest correlation for a test was given a ranking of seven, while the weakest correlation received a ranking of one. For example, within the Logmem Immediate test, TBV^C, with a correlation of 0.348, is assigned a rank of 7, while TBV, with a correlation of 0.129, is assigned a rank of 1. A non-parametric Friedman Test was used to assess differences in the median rank of each atrophy measure. No difference in the median ranks would indicate that all the atrophy measures are similar and there is not a "best" measure of global atrophy. Difference in the median ranks, however, would suggest that one or more of the measures are on average "better" than the others across all neuropsychological tests. We also performed a repeated measures analysis to compare the atrophy measure profiles across neuropsychological tests. The repeated measures test, like the Friedman test, assesses general atrophy measure performance, but it takes into account that the measure may not be independent. We transformed the correlations to follow a normal distribution with Fisher's transform before applying the repeated measures model.

RESULTS

Previous to any analyses described below, we examined the normality of the various distributions for significant outliers and/or other potential problems with the distribution that might affect the statistical analyses. Examination of the brain measures revealed no normalcy issues and/or significant outliers. Examination of the neuropsychological test revealed no normalcy issues though a single outlier was noted for the Trail Making Test A.

Interrelationships of Brain Morphometry Measures

Although some measures did not show any correlation, the qMRI variables were generally interrelated regardless of whether or not a brain volume/atrophy correction procedure was performed (see Table 4).

Comparison of Brain Morphometry Measures With Neuropsychological Tests

The correlation coefficients (absolute value) between each individual brain measure and each neuropsychological test is shown in Figure 1.

Table 4. Correlation matrix showing the relationship between the various global brain atrophy metrics examined

	VBR	TBV^C	TVV	PVL	TBV/TICV
TICV	−0.22	0.28[a]	0.99[b]	−0.05	0.28[a]
VBR		−0.84 [b]	−0.22	0.81[b]	−0.83[b]
TBV^C	−0.84[b]		0.28[a]	−0.97[b]	1.00[b]
TVV	−0.22	0.28[a]		−0.05	0.28[a]
PVL	0.81[b]	−0.97[b]	−0.05		−0.97[b]
TBV/TICV	−0.83[b]	1.00[b]	0.28[a]	−0.97[b]	
VCR	0.99[b]	−0.79[b]	−0.23	0.77[b]	−0.79[b]

Note. TBV = total brain volume; VBR = ventricle-to-brain ratio; VCR = ventricle-to-cranial ratio; TICV = total intracranial volume; PVL = parenchymal volume loss; TVV = total ventricular volume.
[a]Correlation is significant at the .05 level (two-tailed).
[b]Correlation is significant at the .01 level (two-tailed).

According to the χ^2 test for comparing multiple correlation coefficients, no statistical differences were detected between the correlations of different brain measures within each neuropsychological test (see Table 5). However, both the Friedman Test of rank comparisons and the repeated measures analysis were significant ($P < 0.001$ in both cases), suggesting that several of the atrophy measures consistently demonstrated stronger correlation. For example, TBV^C, VCR, VBR, and TBV/TICV consistently yielded higher coefficients than the other atrophy measures.

Post hoc analysis of pairwise comparisons demonstrated that the brain measures can be divided into two groups. One grouping is comprised of the qMRI variables, TBV and TICV, which are not statistically different from each other. The second group is comprised of TBV/TICV, PVL, TBV^C, VBR, VCR, which also do not differ statistically from each other. However, these two groups of brain measures are significantly different, with the second group having consistently stronger correlations than the first.

"Best" Measure of a Single Atrophy Measure

As mentioned in the Bigler 2004 study, there are several limitations involved in selecting a "best" measure for defining cortical atrophy. The results of the χ^2 analysis did not reveal statistical differences atrophy measures within test, which suggests that the differences between measures are subtle. Furthermore, the χ^2 analysis also suggests that using only one neuropsychological test does not supply enough information to tell the whole picture. The results of both the Friedman test of rank comparisons and repeated measures analysis discussed above, do not point to a single "best" atrophy measure, but rather suggest that there are groups of measures that simultaneously perform better or worse than other groups of measures. For example, TBV^C had the highest correlation median rank (6.00) (see Table 5), which suggests that this measure tended to have stronger correlations with neuropsychological tests. However, pair-wise analyses of the median ranks indicated that VBR, TBV/TICV, and VCR (with median ranks 5.00, 5.00, and 4.50, respectively) were not significantly

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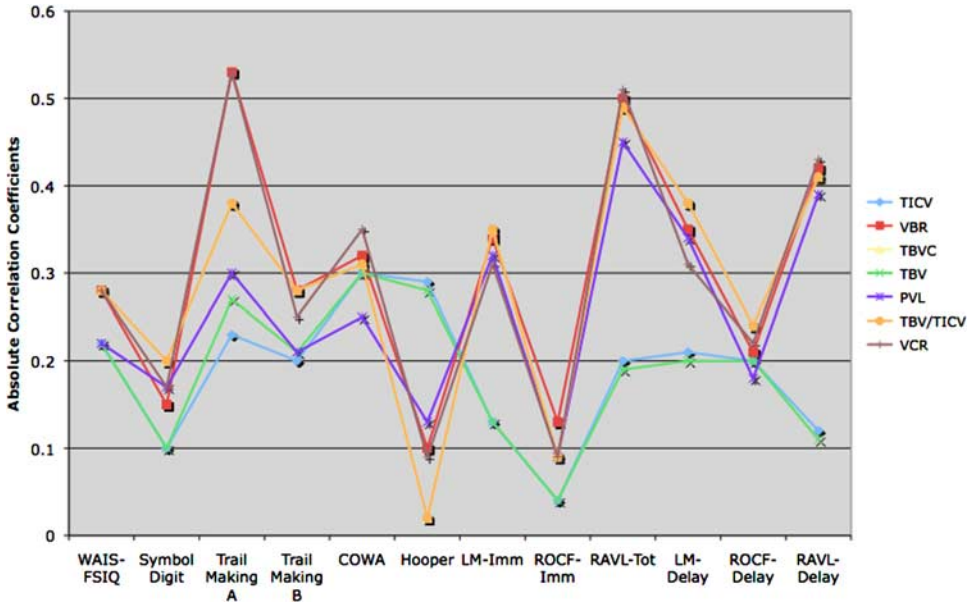

Fig. 1. Correlations between quantitative brain metrics and each neuropsychological test. The graphed correlation coefficient is the absolute value of the correlation coefficient. This allows the reader to compare the magnitude of the correlation coefficients across the range of tests.

different from each other, but were significantly higher than the remaining measures (with the exception of TBV^C). Although the rank results of the Friedman test do not indicate statistical superiority, they do suggest a trend, in which corrected measures perform similarly to each other. TICV and TVV had the lowest correlation median ranks (2.00). The repeated analysis lead to the same conclusions where *post hoc* pairwise comparison, as mentioned above, showed that TBV/TICV, PVL, TBV^C, VBR, VCR all had stronger correlations than TBV and TICV.

DISCUSSION

Measurement error and variability continue to be a challenge encountered in quantitative neuroimaging studies (Fjell et al., 2009; Jack, Theodore, Cook & McCarthy, 1995; Lancaster et al., 2000; Loewenstein et al., 2009). Therefore, the method chosen to quantify brain volume is of utmost importance when examining relationships between quantitative imaging findings and neuropsychological performance (Bigler et al., 2004; He et al., 2009; Jack et al., 1999; Killiany et al., 2000; Smith et al., 2000). The purpose of this investigation was to examine whether or not a preferred global qMRI method (whether corrected for head size or not) exists when examining the relationship between neuropsychological performance and brain atrophy in TBI patients. For each neuropsychological test, we compared the correlation coefficients of the different brain measures. Overall, measures of cerebral atrophy were highly interrelated though not uniform (see Table 4). Thus, the results suggest that no correction procedure or measure of atrophy showed a significantly higher correlation with the neuropsychological tests.

Specific to TBI patients, TBV^C, VBR, TBV/TICV, and VCR indicated higher correlations, with median rankings of 6.00, 5.00, 5.00, and 4.50 respectively. In contrast, the median rankings in the aging and dementia investigation by Bigler et al. (2004) demonstrated a different pattern. Higher correlations were noted for TBV^C, TBV/TICV, and VBR, with median rankings of 6.71, 6.00, and 5.00, respectively,

Table 5. Mean and median ranking of the seven morphometric measures relating to neuropsychological performance, as well as mean of the absolute value of the correlation of the atrophy measures

	Median rank	Mean rank	Mean of the absolute value of correlation
TBV^C	6.00	5.45	0.30
VBR	5.00	5.09	0.32
VCR	5.00	5.18	0.30
TBV/TICV	5.00	4.64	0.30
PVL	2.00	2.82	0.27
TVV	2.00	2.82	0.28
TBV	1.00	2.00	0.20

Note. TBV = total brain volume; VBR = ventricle-to-brain ratio; VCR = ventricle-to-cranial ratio; TICV = total intracranial volume; PVL = parenchymal volume loss; TVV = total ventricular volume.

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suggesting that these represented the best measures for detecting whole brain-cognitive relationships in dementia patients. As such, the top three measures in the aging/demented subjects (see Bigler et al., 2004) overlap with the highest rankings relating atrophy to cognitive outcome in TBI. Furthermore, being that the measures examined in these studies were global indices for quantifying brain volume, the slight differences in the ranking order may be due to the dynamic atrophy particular to TBI, in which there is an abrupt change followed by stabilization (Himanen et al., 2006).

Of interest, three tests appeared to be significantly related to most of the global brain measures; namely RAVL-immediate, RAVL-delayed, and Trail Making Part A. These three tests in the context of head injury lend themselves to interesting explanations especially when you consider that these tests are known to tap into distributed networks of the brain (Balthazar, Yasuda, Cendes, & Damasceno, 2010; Perry et al., 2009). Trail Making Part A is highly dependent on the integrity of the white matter as this task relies heavily on speed of processing. In addition, measures of immediate and delayed list learning depend on the integrity of both the hippocampus and the afferent/efferent hippocampal projections to and from multimodal cortical areas. As white matter damage in the form of traumatic axonal injury (TAI) and hippocampal injury are a well documented result of TBI, it is possible that these global measures capture various aspects of white matter damage associated with TBI and in particular, the neural networks that subserve memory and speed of processing.

Regardless of slight quantitative differences, both studies underscore the importance of correcting for head size irrespective of the disorder being examined. This is consistent with the fact that correction procedures account for intersubject variability in body and head size, as well as variability in brain volume due to gender differences (Carne, Vogrin, Litewka, & Cook, 2006; Dekaban & Sadowsky, 1978). Furthermore, in both studies, TBV^C, was the most robust method for correcting for head size. This measure, which normalizes the individual's TICV by the group's average TICV, may offer more meaningful clinical applications than other correction measures. In another study examining the utility of TICV as a correction factor when assessing TBV and the subcortical volumes of the temporal horn of the lateral ventricles and the hippocampus, corrections with TBV rather than TICV provided more robust measures of atrophy in distinguishing dementia/neuropsychiatric patients from controls (Bigler & Tate, 2001).

Combined, these two studies suggest that corrected measures capture similar information regarding brain atrophy whether looking at TBI or aging and dementia. Our findings in the TBI population reinforce the notion that only one of these corrected measures is necessary in studies of general brain morphometry and cognitive performance. This is because the high level of similarity between corrected measures would reflect redundancy in analysis if more than one measure is used. Consistent with our previous findings, uncorrected measurements of brain volume yielded the least reliable relationships with neuropsychological assessments. Therefore, the use of uncorrected values is inadvisable when examining atrophy–neuropsychological relationships in TBI investigations.

In an ideal research world, the only variance existing in the study would be due to the disease or injury processes under examination. However, this is obviously not the case in this study and it is apparent the additional variability exists limiting the ability of this study to be more definitive. For example, this study examined only a single imaging time point and these findings do not account for longitudinal progression of atrophy as seen in TBI (Blatter et al., 1995; Green et al., 2008; Ruttan, Martin Liu, Colella, & Green, 2008; Xu, 2010). This is particularly relevant to our data as there is significant inter-subject variability in the range for post-injury assessment and imaging (3.5 to 91 months). This variability may affect our data as there may be differences in the degree of recovery experienced across the individuals within the group, especially since we included a range of injury severity (Christensen et al., 2008; Ng et al., 2008). However, it should be noted that this sample is consistent with what one might expect to see in clinical practice and the fact that such robust relationships continue to persists across this range of post-injury assessment times is intriguing because it would seem to suggest that regardless of the individual trajectories of change in either measure, there remains an important relationship between these different measures. Also, our cross-sectional study does not account for factors such as severity of trauma-related injury or demographic variables that influence atrophy (Ng, 2009) and cognitive trajectories (Himanen et al., 2006; Green et al., 2008; Penna et al., 2010) as seen in TBI. Future studies may want to consider these additional factors (i.e., gender, age at injury, race, etc.), which influence morphological changes in the brain due to TBI and which may result in increased sensitivity to different qMRI variables from what we observed here. Also, because we only examined global measures of atrophy, the current study neglects possible focal and/or regional variations that may occur in the context of physical trauma. In future studies, it may be useful to examine more focal/regional atrophy, in addition to global atrophy measures.

In summary, our findings emphasize the importance of correcting for head size when evaluating atrophy in relation to neuropsychological performance for TBI patients. For this reason, we recommend using any one of the corrected measures as these measures are highly interrelated and reflect consistent relationships to neuropsychological performance without creating quantitative redundancies.

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