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Research Article

Analysis of Various Automated Structural Computing Methods Inpatient with Early Traumatic Brain Injury

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Abstract. *Aim:* To assess Surface Based Morphometry (SBM) and Voxel Based Morphometry (VBM), the automated computation methods to demonstrate volume and thickness changes in brain among early Traumatic Brain Injury (TBI) and their correlation with cognitive test scores. *Methods:* 22 mild to moderate TBI patients and 20 age, gender matched healthy individuals were recruited (mean ± SD, age range: 27.7 ± 6.5 years). MRI scans were acquired in the Siemens 3T Magnetom Skyra Scanner. TheT1-weighted magnetization preparation rapid acquisition gradient echo (MP-RAGE) sequence used for morphometric analysis provided excellent gray-white matter contrast. The structural data was processed using SBM and VBM methods with statistical significance of $P < 0.05$ corrected for multiple comparisons. *Results:* both methods did not show any significant changes in brain measures after correcting for false discovery rate. However, on correlating neuropsychological score with structural changes, SBM demonstrated significant voxels survived in animal naming and Token Test after correcting for multiple comparisons. No significant change was found while using VBM. *Conclusion:* The study emphasizes the similarities in the results obtained after using different automatedmethods. Our findings suggest that SBM is more sensitive as compared to VBM in detecting structural changes correlated with Neuropsychological scores during early phase of TBI.

Keywords: Volex based morphometry, surface based morphometry, early phase of head injury, volumetric software

1. Introduction

The advances in neuroinformatics have led to develop various software that are widely used to document quantitative brain measure changes. Volex based morphometry (VBM) and surface based morphometry (SBM) are the first in this field. The results of these software are unique as they use default algorithms and atlas. Exploring them on same MPRAGE data

may give clue that how that software are unique in brain measures.

The computated automated imaging field has opened a new avenue to analyze the Grey matter (GM), white matter (WM) and Cerebrospinal fluid (CSF) volume and thickness. Quantitative MRI studies have revealed differences in the volume of particular brain structures in several neurological & psychiatric conditions including depression [1], posttraumatic stress disorder [2, 3], schizophrenia [4, 5], Alzheimer's disease [6, 7], Obsessive Compulsive disorder [8, 9].

Our study is focused on Traumatic brain injury (TBI), which is a heterogeneous disorder resulting from a variety of causes, extending from trivial and transient injuries to catastrophic damage and ranging from focal to diffuse injuries, with patients having varied outcomes. Any brain injury is a disruption in the network of interconnected pathways from a holistic perspective of integrative brain function dependent on complex neural networks that underlie human behavior and cognition [10, 11].

The goal of this study was to characterize the performance of two widely used automated SBM and VBM methods of brain segmentation in a manner that would significantly augment the existing literature by expanding the scope of the analyses within a head injured patient cohort.

2. Material and Methods

It is a prospective study conducted at National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore. We have a dedicated trauma center led by the department of neurosurgery. The data was collected during January to August 2010. The study was approved by the Institute Ethics Committee. Informed written consent was obtained from all participants or their legal guardian (custodian is an institute or firm).

2.1. Subject. Twenty two right handed patients with mild to moderate brain injury ($N = 22$, Males: 17, females: 5, mean age 27.7 ± 6.5 years) were recruited. Exclusion criteria included neuropsychiatric illness/symptoms, alcoholic or drug dependence, past history of head injury, neuro infection, acute/chronic neurological diseases and any contraindication to MRI. All patients' traumatic details were documented on standard proforma. Their admission Glasgow coma scale (GCS) ranged from 9 to 15, 13 patients had mild GCS scores of 14–15 and 9 patients had moderate GCS score for 13–9 no patients in study group needed resuscitation. All patients were evaluated with CT scan and managed accordingly. The patients were followed up with mean duration of 13 weeks (range 6 to 26weeks) for neurological, neuropsychological, and neuroimaging examinations. Summary of demographic characteristics and Neuropsychological scores of the subject groups are depicted in Table 1.

2.2. Healthy volunteers. Twenty healthy right handed healthy volunteers were selected with matching to age and gender to that of brain injured group. They consisted of 16 men and 4 woman with a mean (SD) age of 27.1(6.3) years. They were scanned on the same scanner with the same MRI protocols as the brain injured patients but did not undergo neuropsychological examination.

2.3. Method of data acquisition. MRI scans were acquired in the Siemens 3T Magnetom Skyra Scanner. The T1-weighted Magnetization preparation rapid acquisition gradient echo (MP-RAGE) sequence used for morphometric analysis provided excellent gray-white matter contrast. TR 1600ms, TE 2.13ms, Slice Thickness 0.9 mm, Slices per slab 176, FOV 240 mm, Voxel Size $0.9 \times 0.9 \times 0.9$ mm, acquisition time 3 min 44 seconds.

2.4. Data analysis. We followed the two different automated methodologies to evaluate the GM changes and test the repeatability of results, by comparing the two methods (different methodologies).

2.5. SBM analysis. Initially MR images were converted to an analyzable format (.mgz) using buit-in function mri_convert. Compatible scans were then preprocessed using FreeSurfer version 5.1.0 (released on 24 May 2011 Martinos Center, Harvard University, Boston, MA) on a -HP-Z200-Workstation 3.0.0-15-generic #24-Ubuntu (Linux) SMP. The work-flow for reconstruction of cortical structures and calculation of various measures consist the following steps [12, 13]:

Pre-processing: Motion correction performed and MR image is conformed to 1 mm size and 256 voxels for all directions.

Non-uniform Intensity Correction: Non-parametric, non-uniform intensity normalization is performed on the MRI image.

Registration: A transformation matrix to Talairach space is calculated for later steps using twelve degrees of freedom affine transformation.

Intensity normalization: Fluctuations in scan intensity are corrected and scan intensities are collectively adjusted to achieve a mean white matter intensity of 110.

Skull Stripping: The skull and meningeal surfaces are removed from the scan, leaving only the brain with cerebrum, brain stem and cerebellum.

WM segmentation: Merged the cortical and subcortical components, Intensities normalized according to segments and brain mask were created for further ambiguous edge creation using pretest command.

Filling: Filled the pre-tessellated areas according to seed calculation for cerebral cortex and erased the brain stem and cerebellum to parcellate the two hemispheres respectively in

Table 1: Summary of demographic characteristics, neuropsychological test and concussion symptoms of the subject groups.

Patient	Demographic Details and NeuroPsychological Tests Scores										
ID	Age	Gender	GCS Score	Duration	DSST	ANT	TT	AVLT Total	AVLT LTPR	CFT Copy	CFT DR
1	38	M	6	6	28	12	5	5	95	50	15
2	26	M	12	12	3	10	20	5	80	15	20
3	19	F	23	23	67	5	20	30	90	95	60
4	29	M	14	14	12	20	10	5	30	20	25
5	21	M	10	10	9	5	30	5	5	95	5
6	36	F	12	12	19	5	30	5	5	50	50
7	22	M	14	14	12	5	10	5	5	15	15
8	22	M	10	10	15	25	30	5	15	5	5
9	26	M	12	12	9	60	30	30	10	5	5
10	33	M	12	12	38	30	20	30	40	40	25
11	22	M	10	10	0	25	40	40	40	0	0
12	30	F	8	8	7	40	20	15	10	50	30
13	19	M	12	12	91	9	20	5	40	30	40
14	40	M	24	24	13	70	10	20	15	95	60
15	20	M	11	11	18	5	5	5	5	5	5
16	24	M	12	12	33	5	60	95	15	30	20
17	25	M	14	14	27	10	25	40	20	95	70
18	30	M	10	10	61	30	70	40	10	34	25
19	37	F	24	24	3	5	50	20	95	95	10
20	25	M	7	7	97	95	30	60	15	5	10
21	35	M	9	14	0	5	5	5	95	5	5
22	32	F	15	26	66	10	50	15	5	50	15

GCS-Glasgow coma scale, DSST-digit symbol substitution test, ANT-animal naming test, TT-token test, AVLT-auditory verbal learning test, LTPR-long term percent retention, CFT-complex figure test, DR-delayed recall.

its cortical structures for measuring cortical thickness and volume of individual cortical structures.

Tessellation and topology correction: Tessellated hemispheres respectively smoothed, inflated, cortex unfolded, fixed in topology and again corrected for topology using genetic search on the basis of maximum likelihood method.

Surface reconstruction, Registration and parcellation: First white surface is constructed for repositioning the cortical surface to gray/white boundary of each hemisphere. Topology corrected images were smoothed, inflated and curvature calculated .This helped in surface registration and pial surface construction in the end using class statistics Surface volume, thickness and area calculated from parcellated cortex by applying anatomical stats on a parcellated image of each hemisphere.

Labeling: Final volume labels are applied to cortical and sub-cortical structures based on the prior probabilities of voxel identity assigned by the atlas in addition to the probability of voxel identity based on the tissue class assignment of surrounding voxels, and volumetric statistics are computed.

2.6. Statistical analysis. A cross-subject general linear model (GLM), fit at each vertex, was used to test group-wise differences in surface measures between TBI patients and healthy volunteers. Individual subject's thickness and volume measures were smoothed using a full width half maximum (FWHM) kernel of 10mm. Group difference t-stat maps were false-discovery-rate (FDR) corrected (for multiple comparisons across vertices) at $P < 0.05$ [14]. GLM analysis was also repeated to find out correlation between cortical thickness and volumetric changes with different Neuropsychological tests performed between TBI patients and healthy volunteer's. The effect of age and total intracranial volume and thickness differences was regressed out as a nuisance regressor in GLM design [15]. The significant quantitative measurement of structural changes noted at $P < 0.05$ corrected for FDR at $P < 0.15$ [19].

VBM Analysis: We used VBM for structural MR image grey matter concentration and volumetric difference analysis among control and head injury patient and also correlation of changes with different cognitive functions. We performed analysis with the help of script previously designed by Neurological institute, university college of London (www.fil.ion.ucl.ac.uk/spm). Structural images were

Table 2: Significant regions among traumatic patients with cognitive domains.

Animal Naming Test (ANT)	**Token Test (TT)**
Left hemisphere Thickness, FDR - 0.15	**Right hemisphere thickness, FDR – 0.15**
Inferior parietal	Inferior parietal
Superior parietal	
Precentral	

FDR-false discovery rate.

reoriented and registered in the AC-PC plane according to the standard T1 template and further processed according to optimal VBM protocol described by Good et al. [16].

Normalization: partially segmented images were normalized in to grey and white matter template on the basis of prior grey/white matter differentiation.

Segmentation and extraction of normalized whole brain image: Stereotactic structural images segmented into grey and white matter, CSF and non CSF partitions and again extracted to remove remaining non brain voxels which could still remain outside the brain margins on segmented grey/white matter images.

Correction for volume changes (modulation): Due to nonlinear spatial normalization, the volumes of certain brain regions may grow, whereas others may shrink. In order to preserve the volume of a particular tissue (grey or white matter or CSF) within a voxel, a further processing step is incorporated. This involves multiplying (or modulating) voxel values in the segmented images by the Jacobian determinants derived from the spatial normalization step. In effect, an analysis of modulated data tests for regional differences in the absolute amount (volume) of grey matter, whereas analysis of unmodulated data tests for regional differences in concentration of grey matter (per unit volume in native space) [17]. In this study we analyzed both modulated and un-modulated data.

Smoothing: Each optimally normalized segmented, modulated and unmodulated image smoothed at 8-mm FWHM so that the differences can be identified accurately.

2.7. Statistical analysis. We followed the statistical methodology applied for Voxel-Based Morphometric Study of Aging [16]. The normalized, smoothed, segmented data were analyzed using statistical parametric mapping (SPM8). Global effects of age were examined by multiple regressions of summed voxel values of GM, WM, CSF, and total intracranial volume (TIV) in a linear model. Regionally specific differences in GM between the control and TBI groups were assessed statistically using a two-tailed contrast (testing for either an increased or decreased probability of a voxel being grey matter). We tested for volumetric changes in GM by including the modulation of segmented data. Concentration changes were assessed by using the segmented images directly. Normalization for global differences in voxel intensity across scans was or affected by inclusion of the global mean voxel value as a confounding covariate in an ANCOVA analysis, while preserving regional differences in grey matter [18]. Significance levels for the T statistics were set at $P < 0.05$, corrected for multiple comparisons. We also performed multiple regression analysis between neuropsychology scores and structural changes to find out correlation at significant level $P < 0.05$ corrected for FDR at $P < 0.15$ [19].

3. Results

3.1. SBM results: Grey matter changes. After deriving t-stat maps, we found no significant changes in the grey matter TBI patients compared to healthy controls. Correlation analysis between neuropsychological tests and volume changes showed significant changes in different brain regions as elaborated in Table 2.

3.2. VBM Results: Grey matter concentration changes. After deriving t-stat maps we found no significant changes of GM in TBI patients compared to healthy controls. In multiple regression analysis corrected for multiple comparisons, no significant correlation was found between the neuropsychological scores of different tests and gray matter volume and thickness changes.

4. Discussion

In this study, we assessed GM changes in TBI patients (selected for 3month of duration after injury to see the effect of minimal perturbation on cognitive functions) relative to age and gender-matched healthy controls using SBM & VBM methods and correlated TBI patients brain measure changes with different cognitive tests performed.

Our results suggest no spatial overlaps between SBM and VBM methodologies across TBI and healthy individuals. SBM demonstrates shows that brain measure changes correlate with neuropsychological scores of Animal Naming Test (ANT) and Token test (TT) in early TBI and healthy individuals while VBM analysis showed no significant difference. This shows poor sensitivity of VBM in identifying the initial changes in mild to moderate or early stage TBI patient. Although the current study basically agrees with most of the prior volumetric and VBM investigations where a widespread pattern of atrophy is reported in patients with chronic TBI, there are important differences in the specific pattern of volume loss that merit further discussion.

In Voxel based tissue density calculation any misregistration during the normalization process can potentially lead researchers to falsely identify registration errors as

true anatomic differences [20]. However, the brains of TBI survivors present a great challenge to this process because they can exhibit severe global and focal atrophy. These structural abnormalities manifested in the brains of TBI subjects violate the basic assumptions of small deformations and/or simple intensity relationships used in many existing image registration methods [21]. VBM involves segmenting the normalized brain into different tissue types. Since segmentation requires a good separation of intensities, hypointense lesional areas of TBI patients pose another challenge for the VBM method. Thus, the results of prior VBM studies may be confounded by unreliability in segmenting affected brain regions.

FreeSurfer (SBM) has its efficient algorithms for segmentation and tissue classification even though it is trained on the FS40 data This data is adjusted for the Caucasian race and does not accurately train data in our setting and this introduces some bias in the evaluation of the study because other methods [22]. Use of different software versions and operating systems also affect the resultant grey matter changes in several brain regions when analyzed using FreeSurfer [23]. A study on schizophrenia suggested apparent reduction in GM density in patients relative to healthy matched controls using VBM while no significant voxels were seen in SBM-derived cortical thickness measures [24]. It was concluded from this study that the scales and algorithms of SBM for evaluating the changes in patients with schizophrenia have limitations which need to be taken into consideration.

The literature on early mild to moderate head injured brain measure changes and their correlation with neuropsychological test scores are very few. Our study is the first one in which the gray matter thickness and volume abnormalities in early mild to moderate range TBI were examined simultaneously with greater precision. We believe new observations from the current study may provide clues regarding the complex neuro-metabolic cascade that is responsible for manifesting cognitive deficits. The quantitatively brain measure changes documented give the hint that FreeSurfer may be a better volumetric software to assess early cortical changes that are responsible for neuropsychiatric deficits. Findings from this study add the current understanding that quantitatively brain measure can be documented even among early TBI patients. Hence neuro rehabilitation can be initiated early after a head injury that may reduce deficits over the long run.

4.1. Limitations. Our results demonstrate that optimized Cortical GM volumetric and thickness changes between groups and neuropsychological tests with SBM or VBM may be prone to significant errors when presented with data collected from the mild to moderate head injury patients. As the patient data was collected in early mild and moderate stages of head injury, the diffused quantitative changes are very small to be detected using the above mentioned methodologies. The lack of significant changes in VBM analysis makes it a limiting factor to do further statistical tests for comparing the two methodologies.

5. Conclusion

In summary, this is one of the few studies addressing reliability and validity of automated Surface and Voxel based methods in Traumatic Brain injury in early mild to moderate category. In early phase of injury SBM may be better tool to detect brain measure changes in correlation with cognitive deficits and adds additional information regarding in-vivo regional pathophysiological changes. Further studies are required to integrate both GM and WM changes in order to understand the in-vivo ongoing injury cascade.

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