Limbic morphometry correlates of mood disoders in traumatic brain injury

A. A. Capizzano[1], R. E. Jorge[1], L. Acion[1], J. Nicoll Toscano[1], M. Brumm[1], L. McCormick[1], and R. G. Robinson[1]

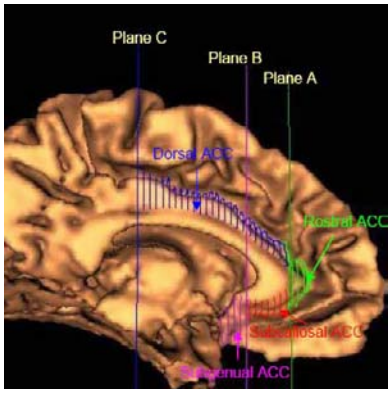
[1]Psychiatry Department, University of Iowa Hospitals and Clinics, Iowa City, Iowa, United States

BACKGROUND

Traumatic brain injury is a leading cause of disability and mortality among young subjects. Animal studies showed delayed progression of neuronal loss and gliosis up to 1 year after TBI involving susceptible regions such as the hippocampus (1). Mood disorders with major depression or mixed features affect about a third of TBI survivors negatively impacting cognitive and social functioning (2). Brain structure correlates of primary unipolar or bipolar MD reflect limbic involvement with anterior cingulate cortex (ACC) and hippocampal atrophy (3). The anatomical correlates of MD in TBI have been less well characterized. The purpose of this study was to extend our previous finding of reduced hippocampal volumes in TBI patients with MD at 3 months of trauma (4) by assessing volumetric differences in the subregions of the ACC between MD and no MD TBI patients.

METHODS

A total of 44 TBI patients were assessed by a psychiatrist with the present state examination (PSE) and structured clinical interview for DSM-IV diagnoses (SCID) interviews. Diagnosis of MD was made according to the DSM-IVcategory of mood disorder due to general medical condition (here: TBI). Patients were scanned 3 months after trauma with a 1.5 T GE Signa system at the University of Iowa Hospitals & Clinics. The imaging protocol included the following sequences: 1) Coronal T1-weighted (TR/TE = 24/5, flip = 40°, 2 NEX, FOV = 26, matrix = 256 x 192, 1mm thickness); 2) Coronal T2-weighted (TR/TE = 3000/104, 2 NEX, FOV = 24, matrix = 256 x 192, 4mm thickness); 3) Coronal PD-weighted (TR/TE = 3000/28, 1 NEX, FOV = 26, matrix = 256 x 192, 3mm thickness); 4) Coronal FLAIR (TR/TE/TI = 9002/165/2200, 1 NEX, FOV = 24, matrix = 256 x 192, 4mm thickness). Image processing was carried out with the BRAINS2 software package. This software permits coregistration of different sequences, automated image segmentation and Talairach-defined regions identification, cortical surface generation, multi-planar telegraphing and volume measurements (5). Right and left hippocampi were manually traced onto coronal and sagittal reformatted T1, T2, and segmented images following locally developed anatomic guidelines (6). The right and left ACC were traced onto alternating coronal slices and the brain surface image after recently defined guidelines (7). The ACC was further parcellated into the following subregions: dorsal, rostral, subgenual and subcallosal (Figure). Both hippocampal and ACC tracing methods were validated showing high reproducibility.



RESULTS

Out of 44 TBI patients studied, 24 developed MD with major depression or mixed features during the first 3-month period after TBI (MD group) whereas 20 did not present with such disorders (no MD group). Mean age (SD) for MD patients was of 36.2 years (13.0), whereas for no MDs was 36.8 (16.7) (Wilcoxon $\chi 2$= 0.01, df=1, p=0.93). There was no difference in sex distribution: 15 out of 24 MD patients (62.5%) were males against 10 out of 20 of the no MD group (50%) (Fisher Exact Test, p=0.54). No significant differences in severity of TBI as measured with the Glasgow coma scale (GCS) were present between the groups: MD had 11.8 (2.3) GCS against 12.2 (2.7) for the no MDs (Wilcoxon $\chi 2$= 1.3, df=1, p=0.24). Mean volumes (in cc) and SD of the left and right hippocampus and ACC subregions for the MD and no MD groups are shown in the table, where "*" indicates significant differences between the two groups.

REGION	MD (n=24)	NO MD (n=20)
Left hippocampus	1.83* (0.36)	1.92 (0.21)
Right hippocampus	1.83* (0.30)	1.93 (0.24)
Left dorsal ACC	3.23 (0.49)	3.03 (0.44)
Right dorsal ACC	3.63 (0.73)	3.37 (0.53)
Left rostral ACC	1.54 (0.49)	1.42 (0.43)
Right rostral ACC	1.87 (0.61)	1.69 (0.64)
Left subgenual ACC	0.57 (0.12)	0.54 (0.16)
Right subgenual ACC	0.61 (0.23)	0.55 (0.16)
Left subcallosal ACC	0.43 (0.19)	0.43 (0.14)
Right subcallosal ACC	0.48 (0.16)	0.49 (0.13)

An ANCOVA model controlling for total intracranial volume (TIV) and GCS scores showed that hippocampal volumes were reduced in the MD group compared to the no MD group both on the left and right sides (F=7.1, p=0.01 and F=9.2, p=0.004 respectively). Multivariate Analysis of Variance (MANOVA) was used to test for differences between groups in the four ACC regions per side. Each region was separately analyzed using a repeated measures model including group, brain side (repeated effect), TIV, and gender. We also considered some of the interactions between these factors (i.e. group by brain side). No significant effect for group in any of the ACC regions was detected after correction for multiple comparisons. Finally, total hippocampal volume was a significant predictor of bilateral subgenual + subcallosal ACC volumes in a repeated measures analysis using side as repeated factor and controlling for TIV ($F(1,42)=6.39$, $p<0.02$). This association was not changed when introducing group as a predictor in the model and was not specific for group. Neither dorsal nor rostral ACC were associated with hippocampal volume.

CONCLUSION

Mood disorders associated with TBI appear to have different brain structural correlates than primary mood disorders, displaying bilateral hippocampal atrophy with relative sparing of the ACC. Different phenomenology of primary versus post-TBI mood symptoms might contribute to volume differences. Furthermore, family history of mood disorders has been implicated as a contributor to subgenual ACC atrophy in major depression (8). The correlation between subgenual + subcallosal ACC with hippocampal volumes warrants longer follow-up to detect potentially delayed changes in the ventral ACC. Finally, these results suggest different mechanisms involved in TBI MD reflecting higher hippocampal vulnerability to TBI-induced neuropathology.

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