Prefrontal Metabolite Alterations in Individuals with Posttraumatic Stress Disorder: A 7T Magnetic Resonance Spectroscopy Study

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BACKGROUND

Converging lines of evidence point to glutamatergic dysfunction in posttraumatic stress disorder (PTSD) [1-3]. Although some in vivo magnetic resonance spectroscopy (MRS) studies have shown abnormalities in glutamate in individuals with PTSD [4], no PTSD MRS studies have used 7T, which has better signal-to-noise ratio and spectral resolution, thereby providing better spectral quality and higher sensitivity to detect more metabolites. We currently lack PTSD MRS studies of the lateral prefrontal cortex [4] despite its role in emotion regulation and cognition, which are affected in individuals with PTSD [5]. The objective of this study was to use 7T proton MRS to investigate glutamate and other neurometabolite concentrations in the left dorsolateral prefrontal cortex (DLPFC) of participants with PTSD, trauma-exposed participants without PTSD, and participants without trauma exposure. We hypothesized that individuals with PTSD would have lower glutamate levels compared to trauma-exposed individuals without PTSD and individuals without trauma exposure [6,7]. Additionally, we explored the relationship between glutamate and psychiatric symptom severity as well as potential alterations in other neurometabolites.

METHODS

Participants:

- Life Events Checklist (LEC-5) extended version – DSM-5 Criterion A based on worst event
- PTSD Checklist (PCL-5) – DSM-5 diagnostic rule and total score ≥ 30
- Beck Depression Inventory (BDI-II), Beck Anxiety Inventory (BAI), and Multiscale Dissociation Inventory (MDI)

Imaging:

- Siemens 7T MR scanner with a 32-channel head coil
- Structural images acquired for voxel placement and segmentation
- Spectra acquired from the left DLPFC (25×25×25 mm) using FASTESTMAP shimming and ultra-short TE STEAM (TE/TR/TM = 5/10,000/45 ms, 4 kHz spectral bandwidth, 2048 points, 32 averages) with outer volume suppression and VAPOR water suppression [8]

MRS analysis:

- Osprey for eddy current correction, fitting with LCModel, voxel coregistration and segmentation with SPM12, and water-scaled quantification with corrections for tissue fractions and relaxation
- Spectra excluded for poor water suppression (n = 1) and creatine line width > 30 Hz (n = 2)
- Metabolites excluded from statistical analysis if CRLB > 20%, except for NAAG and Lac for which the threshold was 30%

Statistical analysis:

- ANCOVA controlling for age and sex (Bonferroni-corrected p<0.0036 (0.05/14 metabolites)) followed by post-hoc t-tests
- Pearson correlation between glutamate and psychiatric symptoms (Bonferroni-corrected p<0.0125 (0.05/4 symptom scales))

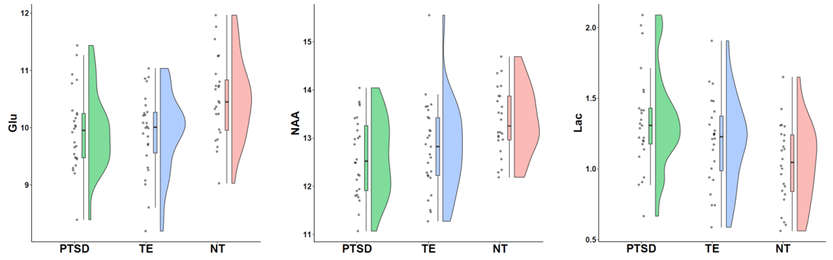
RESULTS

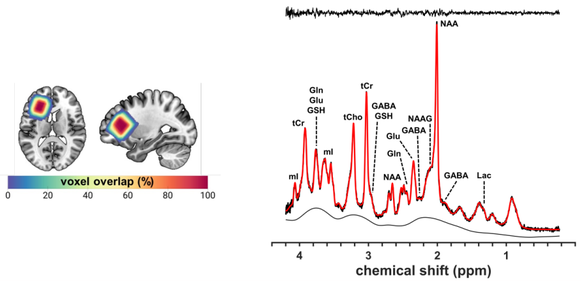
Participants: Age and sex were not significantly different among the groups. PCL-5 total score was significantly higher in PTSD vs. Trauma. BDI and BAI were significantly higher in PTSD vs. Trauma and in PTSD vs. No Trauma. BAI was significantly higher in Trauma vs. No Trauma. MDI was higher in PTSD vs. Trauma and in PTSD vs. No Trauma.

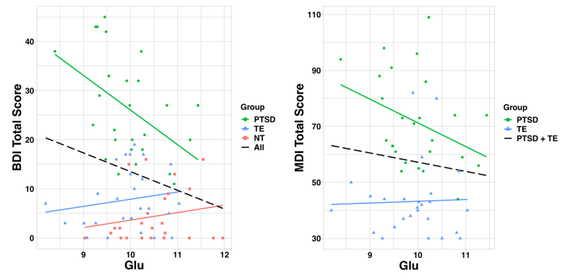
MRS: SNR, linewidth, and CRLB were not significantly different among the groups. There was a significant group difference in glutamate ($F(2,71) = 6.17$, $p = 0.003$). Glutamate was lower in the PTSD group compared to the NT group ($p_{Tukey} = 0.005$) and lower in the TE group compared to the NT group ($p_{Tukey} = 0.02$). There was a significant group difference in NAA ($F(2,72) = 6.20$, $p = 0.003$). NAA was lower in the PTSD group compared to the NT group ($p_{Tukey} = 0.002$). There was a significant group difference in lactate ($F(2,68) = 6.18$, $p = 0.003$). Lactate was higher in the PTSD group compared to the NT group ($p_{Tukey} = 0.002$). There were no significant group differences for the other metabolites. Glutamate was negatively correlated with BDI scores in the PTSD group (PTSD: $r = -0.47$, $p = 0.01$). There was a trend-level negative association between glutamate and MDI scores in the PTSD group ($r = -0.36$, $p = 0.07$).

	PTSD	Trauma (TE)	No Trauma (NT)	Statistics
N	27	27	26	
Age, years	27.9 (8.3)	31.6 (9.2)	29.1 (11.0)	$F(2,77) = 1.06$, $p = 0.35$
Sex, F/M	21 / 6	14 / 13	16 / 10	$X^2(2) = 4.01$, $p = 0.14$
PCL-5	50.9 (11.6)	11.5 (9.6)	---	$t(52) = 13.6$, $p < 0.001$
BDI-II	26.4 (10.2) [a]	8.0 (6.1)	4.8 (6.0)	$F(2,77) = 61.2$, $p < 0.001$
BAI	25.4 (9.9) [a]	8.2 (6.8) [b]	2.7 (3.3)	$F(2,77) = 71.6$, $p < 0.001$
MDI	72.9 (17.5) [a]	43.0 (13.1)	36.9 (7.9)	$F(2,77) = 54.7$, $p < 0.001$

[a] PTSD vs. Trauma and PTSD vs. No Trauma: $p_{Tukey} < 0.001$
[b] Trauma vs. No Trauma: $p_{Tukey} = 0.02$







DISCUSSION

In this first 7T MRS study of PTSD, we observed that individuals with PTSD had lower glutamate, lower NAA, and elevated lactate compared to individuals without trauma. Glutamate was also reduced in trauma-exposed individuals without PTSD compared to those without trauma exposure. The results of our study add to the growing evidence of glutamatergic dysfunction in individuals with PTSD. We also provide evidence of abnormal levels of NAA and lactate, which is consistent with prior studies of PTSD and other psychiatric disorders. Further research is needed to unravel the precise mechanisms underlying glutamate alterations in individuals with PTSD and their implications for the development and treatment of the disorder. Interventions that enhance glutamatergic function and promote neuronal health are promising targets for drug development. High-field MRS offers insight into the neurometabolic abnormalities associated with PTSD and is a powerful tool to probe trauma- and stress-related neurotransmission and metabolism in vivo.

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