Exploring the association between self-reported sleep quality and prefrontal glutamate and GABA in individuals with posttraumatic stress disorder

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BACKGROUND

Posttraumatic stress disorder (PTSD) is often accompanied by poor sleep quality [1,2]. Converging lines of evidence point to glutamatergic and GABAergic dysfunction in PTSD [3-5]. Previous studies using magnetic resonance spectroscopy (MRS) have reported an association between insomnia severity and glutamate and GABA in the parieto-occipital cortex of individuals with PTSD [6,7]. The primary purpose of this study was to measure glutamate concentrations in the dorsolateral prefrontal cortex (DLPFC) of participants with PTSD, trauma-exposed participants without PTSD, and participants without trauma exposure [8]. In an exploratory analysis, we examined the correlation between self-reported sleep quality and DLPFC glutamate and GABA. We hypothesized that individuals with PTSD would have lower glutamate levels and worse sleep quality compared to trauma-exposed individuals without PTSD and individuals without trauma exposure. We further hypothesized that sleep quality would be correlated with glutamate and GABA levels.

METHODS

Participants [8]:

- 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
- Pittsburgh Sleep Quality Index (PSQI) in subset of participants

Imaging [8,9]:

- 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

MRS analysis [8,9]:

- 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%

Statistical analysis [8]:

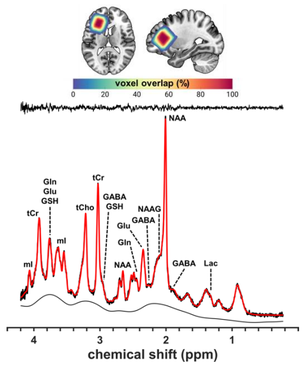
- ANCOVA controlling for age and sex (Bonferroni-corrected p<0.0036 (0.05/14 metabolites)) followed by post-hoc t-tests
- Pearson correlation between PSQI and glutamate and GABA

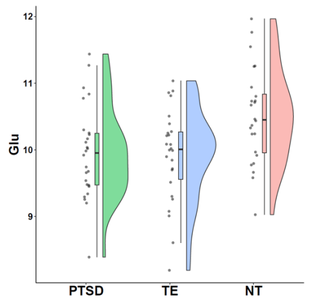
RESULTS

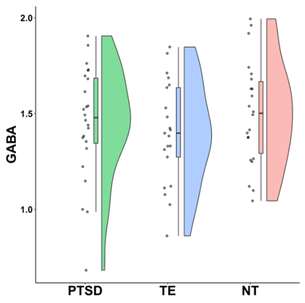
Participants: Age and sex were not significantly different among the groups. PCL-5 total score was significantly higher in PTSD vs. Trauma. There was a significant group difference in PSQI scores. PSQI was higher in the PTSD group compared to the TE group (p_{Tukey} = 0.007, Cohen's d = 0.88) and the NT group (p_{Tukey} < 0.001, Cohen's d = 1.66) and higher in the TE group compared to the NT group (p_{Tukey} = 0.03, Cohen's d = 0.78).

	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
PSQI	10.2 (3.8) n = 26	7.0 (3.8) n = 24	4.2 (3.0) n = 21	F(2,68) = 16.18, p < 0.001

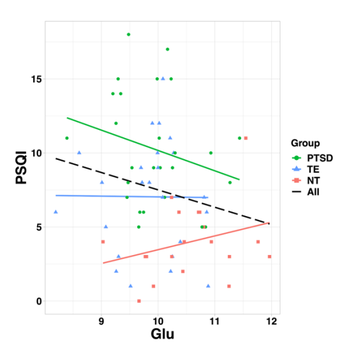
MRS: SNR, linewidth, and CRLB were not significantly different among the groups. As previously reported [8], there was a significant group difference in glutamate (F(2,71) = 6.17, p = 0.003). Glutamate was significantly lower in the PTSD group compared to the NT group (p_{Tukey} = 0.005, Cohen's d = 0.92) and significantly lower in the TE group compared to the NT group (p_{Tukey} = 0.02, Cohen's d = 0.80). GABA was not significantly different between the groups (F(2,62) = 0.66, p = 0.52).

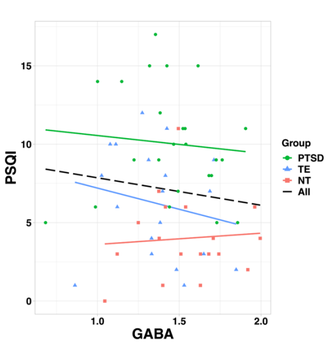






PSQI and MRS: There was a trend-level association between glutamate and PSQI in the combined sample (r(67) = -0.21, p = 0.08), but the correlations within each group were not significant (PTSD: r(24) = -0.25, p = 0.22; TE: r(22) = -0.01, p = 0.97; NT: r(17) = 0.28, p = 0.24). The correlation between GABA and PSQI was not significant (combined sample: r(59) = -0.12, p = 0.37; PTSD: r(22) = -0.09, p = 0.67; TE: r(17) = -0.20, p = 0.42; NT: r(16) = 0.07, p = 0.77).





CONCLUSION

We observed that individuals with PTSD had lower glutamate and worse sleep quality compared to individuals without PTSD. The results of our study add to the growing evidence of glutamatergic dysfunction in individuals with PTSD. We provide some preliminary evidence of an association between prefrontal glutamate and self-reported sleep quality, but more studies with larger samples are needed to validate this finding. Further research is needed to unravel the precise mechanisms underlying glutamate alterations in individuals with PTSD and the implications for the pharmacological and behavioral treatment of the disorder. Interventions that enhance glutamatergic function are promising targets for drug development.

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