Glutamatergic and Immuno-oxidative Stress Abnormalities in Major Depressive Disorder: Links to Early Childhood Maltreatment and Lifetime Stress

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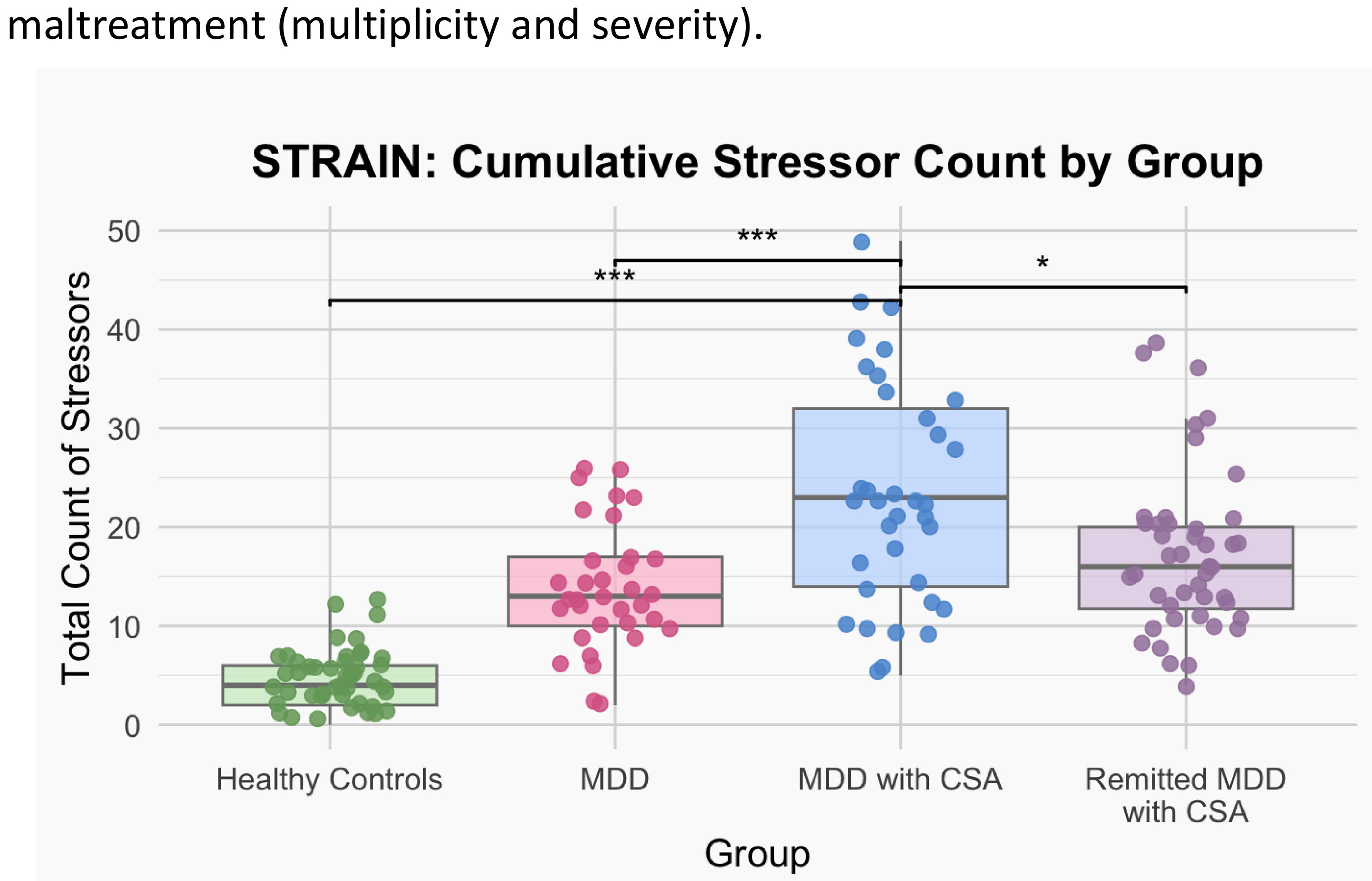
Background

- In major depressive disorder (MDD), magnetic resonance spectroscopy (MRS) studies report reduced glutamate concentrations in the medial prefrontal cortex (mPFC), along with altered glutamine levels. Concurrently, oxidative stress ($NAD^+/NADH$ redox balance) is elevated and may further impair glutamate-glutamine cycling.[1,2]
- **Here, we investigated: (i) the impact of depression and childhood sexual abuse (CSA) on glutamate and oxidative stress in the mPFC, and (ii) whether childhood maltreatment (abuse and neglect) and lifetime stress (acute and chronic) moderate these relationships.**
- We hypothesized participants with depression and CSA would have lower glutamate and higher oxidative stress levels. We also predicted that childhood maltreatment would be linked to decreased glutamate levels.

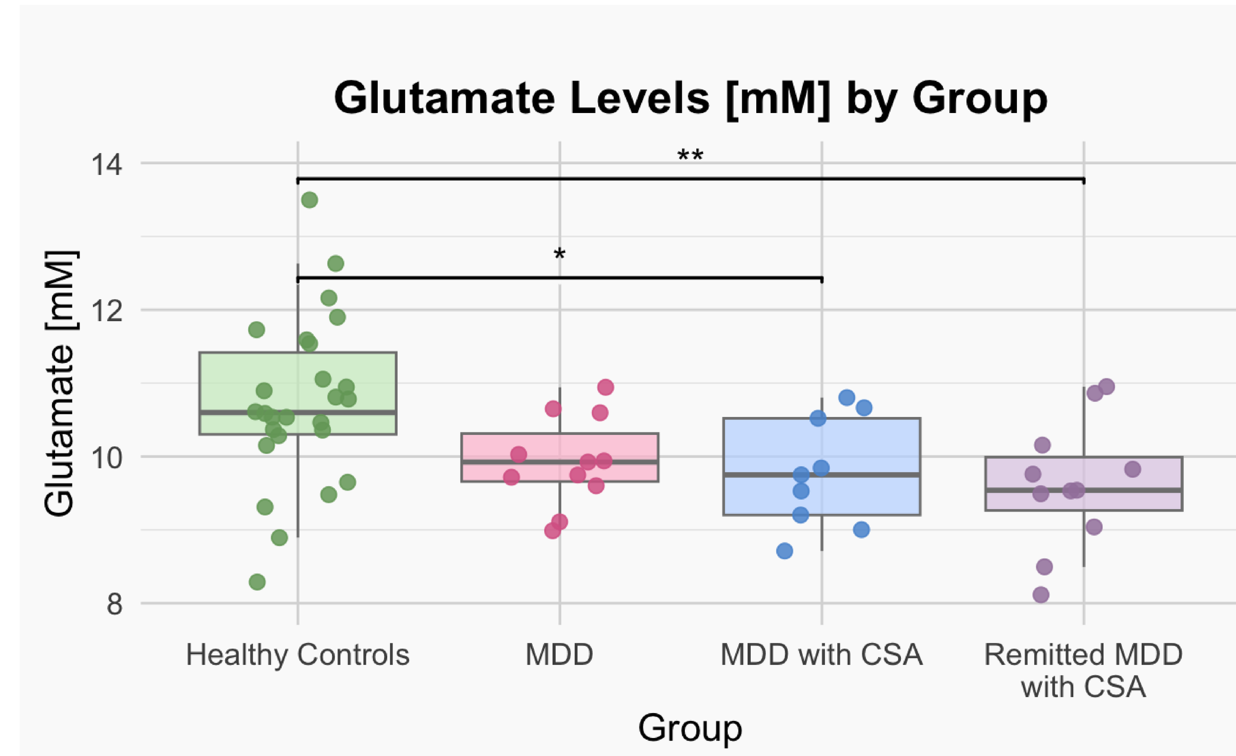
Study Methods

- Sample: 60 females (ages 20-32 years) across 4 groups: 26 Healthy Controls (**HC**s); 11 with **MDD**; 10 with MDD and CSA occurring between ages 11-18 (**MDD/CSA**); 13 with remitted MDD and CSA between ages 11-18 (**rMDD/CSA**).
- Participants completed the Maltreatment and Abuse Chronology of Exposure (MACE), Lifetime Stress and Adversity Inventory (STRAIN), and underwent a 4T MRS scan.[3,4]
- Between-group differences in glutamate, oxidative stress, and STRAIN were tested using separate 1-way ANOVAs.
- Oxidative stress was quantified by the redox ratio (NAD+/NADH).[5]
- Multiple linear regression models were run in R to test the relationships between glutamate and glutamine metabolite levels and childhood maltreatment (multiplicity and severity).



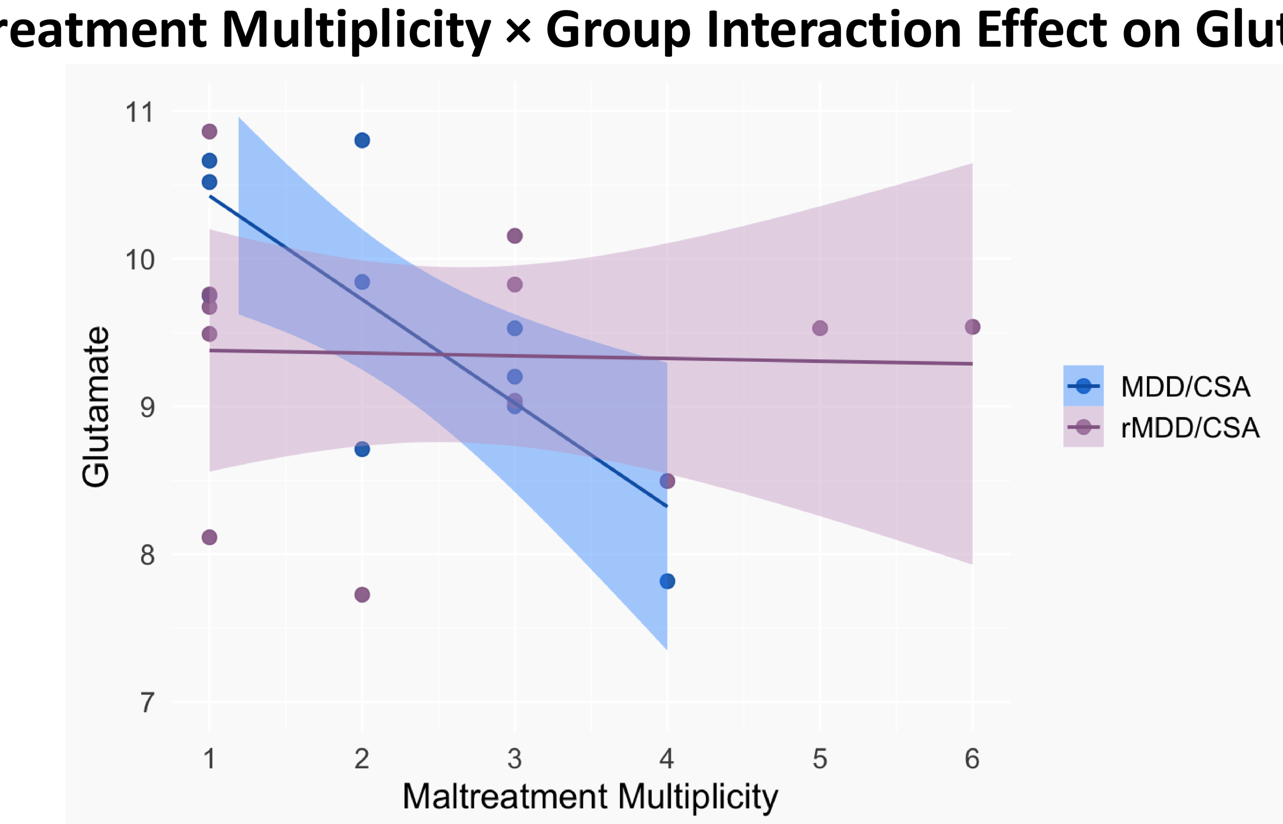
MDD/CSA participants reported highest lifetime stressor count [$F(3, 160)=47.95$, $p<0.001$] and severity [$F(3,160)=49.63$, $p<0.001$].

Glutamate and Glutamine Metabolites



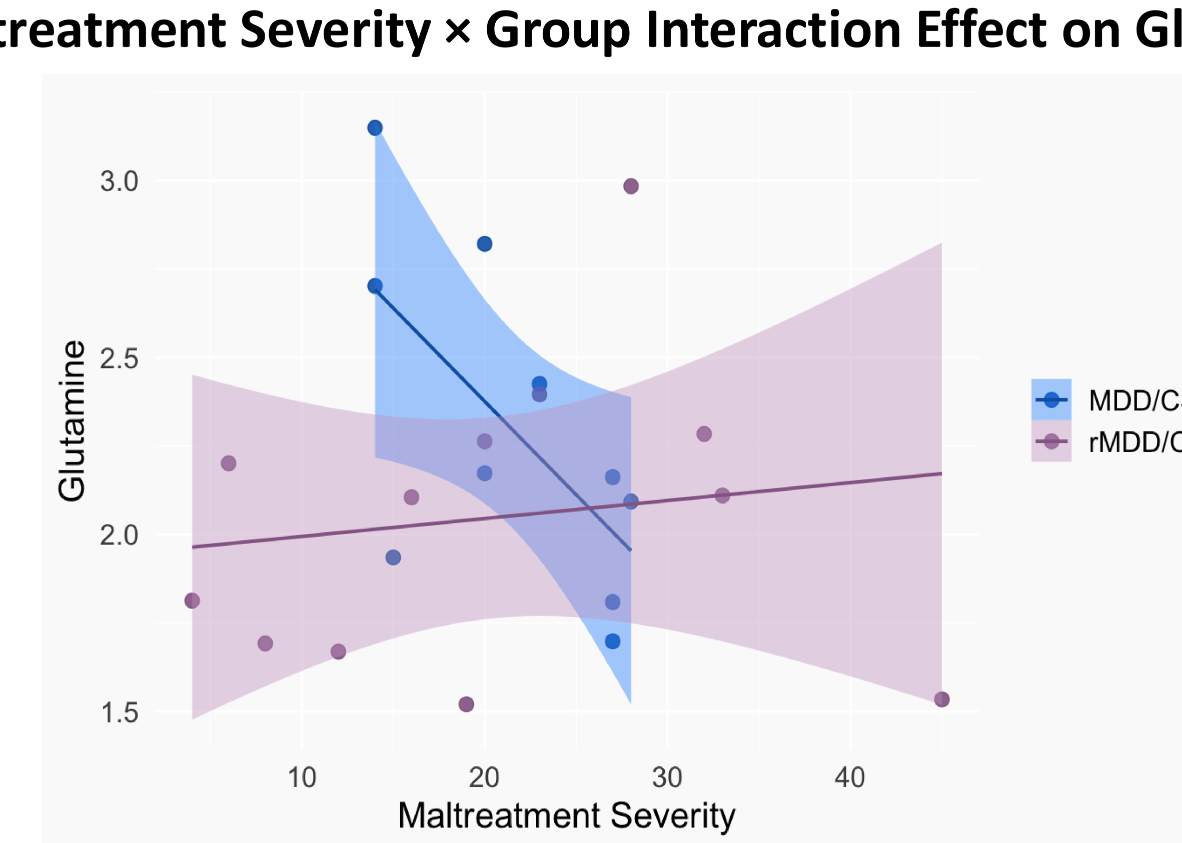
Glutamate levels differed by group [$F(3,56)=4.50$, $p=0.007$] with lower glutamate in rMDD/CSA [$d=-1.16$, $p=0.013$] and MDD/CSA [$d=-1.04$, $p=0.05$] relative to HC.

Maltreatment Multiplicity × Group Interaction Effect on Glutamate



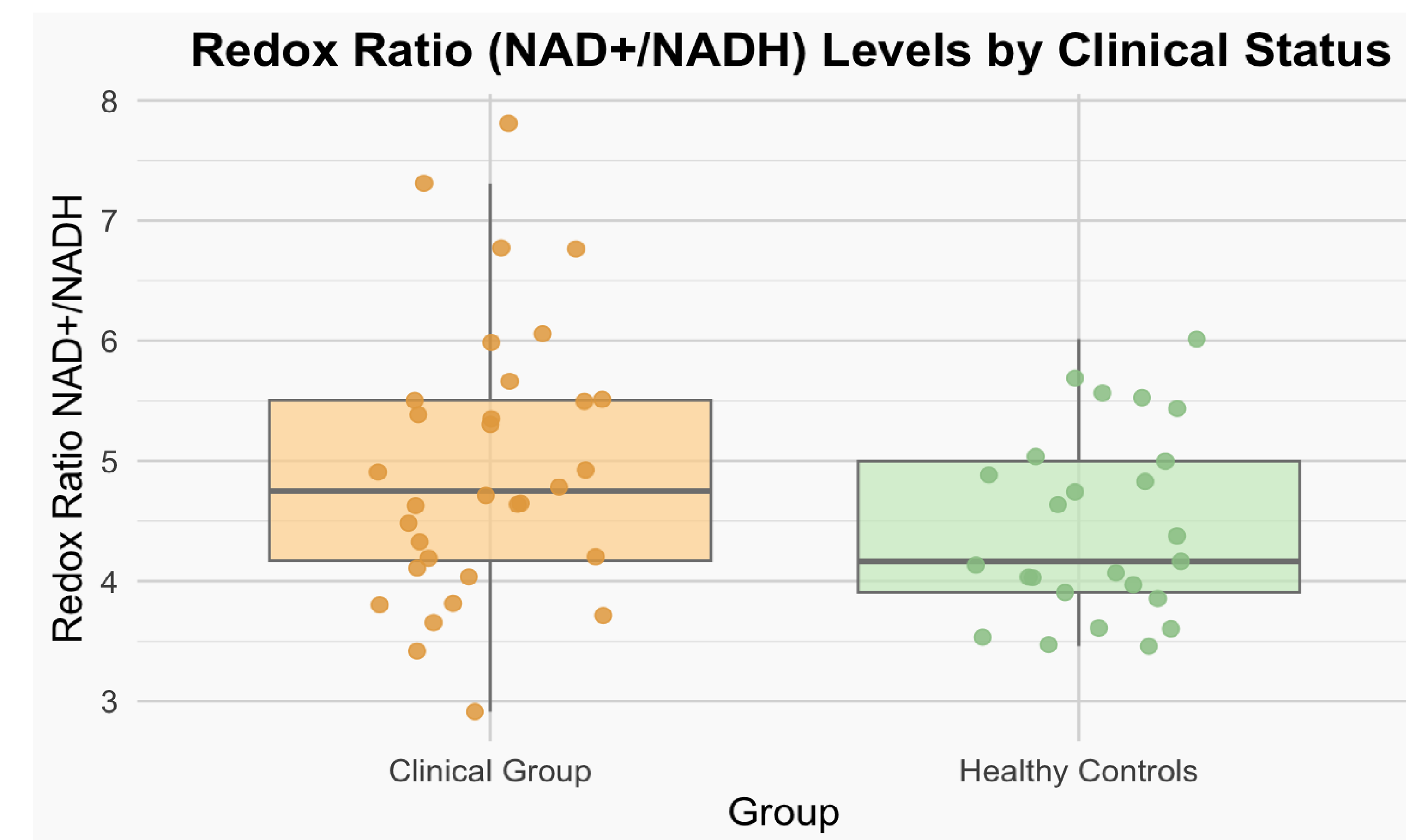
Maltreatment multiplicity was negatively associated with glutamate only in MDD/CSA participants [interaction effect: $t(18)=-2.67$, $p=0.015$]

Maltreatment Severity × Group Interaction Effect on Glutamine



Maltreatment severity was negatively associated with glutamine only in MDD/CSA participants [interaction: $t(18)=-2.17$, $p=0.043$].

Oxidative Stress



All three clinical groups combined (rMDD/CSA, MDD, MDD/CSA) had higher oxidative stress relative to HC [$t(53.95)=1.97$, $d=0.5$, $p=0.05$].

Discussion

- **Decreased glutamate and glutamine metabolites were linked to childhood maltreatment multiplicity and severity in MDD/CSA females.**
- These findings suggest that different forms of adversity can biologically embed and contribute to long-term vulnerability in individuals with depression and CSA.
- Depression reduces glutamate and glutamine levels, disrupting excitatory signaling and potentially driving its persistent mood and cognitive symptoms.
- Unlike previous studies with emphases on MDD, our sample of young adult females characterized by CSA offers novel insights into the interplay of specific adversity and MDD on neurotransmission among vulnerable subpopulations with depression.

References and Acknowledgement

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