N-acetylcysteine effects of glutathione and glutamate in schizophrenia: *A preliminary MRS study*

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BACKGROUND

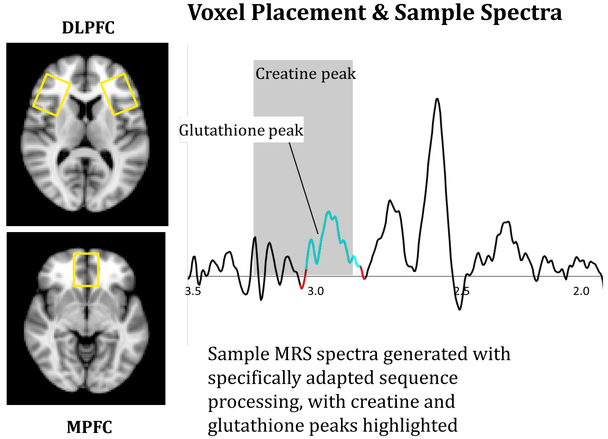
- Recent research suggests that negative symptoms in schizophrenia may arise from dysfunction of the glutamate system: decreased signaling from glutamate receptors on inhibitory neurons leads to excessive glutamate activity in prefrontal cortex
- This can arise from decreased levels of glutamate in the synapse or from the presence of excessive oxidizing species around the receptors leading to receptor hypofunction
- Glutathione, an important molecule against oxidative stress in the CNS, has shown to be decreased in schizophrenia patients
- N-acetylcysteine (NAC), a dietary supplement, may potentially affect schizophrenia by normalizing inhibitory tone on glutamatergic neurons and increasing glutathione concentrations, and has been associated with decreased negative symptoms
- In a randomized controlled small trial, we used magnetic resonance spectroscopy (MRS) to investigate whether treatment with NAC can alter the concentrations of glutamate and glutathione in the prefrontal cortex and improve negative and cognitive symptoms

METHODS

- Thirty-one participants were recruited from outpatient clinics at the West LA VA Hospital and UCLA, all meeting DSM-5 criteria for either schizophrenia or schizoaffective disorder
- Participants were randomly assigned to either 1200 mg twice daily oral NAC or placebo treatment group for eight weeks
- We measured glutathione with a magnetic resonance spectroscopy (MRS) editing sequence specifically adapted for glutathione, and glutamate with PRESS, in the medial prefrontal cortex (MPFC) and dorsolateral prefrontal cortex (DLPFC)
- We also measured positive, negative, and cognitive symptoms before and after the NAC treatment

- We performed a mixed model analysis of GSH/Cr and glutamate/Cr to examine the group x treatment effects
- Voxel placement and sample spectra from one of the patients is shown below

Voxel Placement & Sample Spectra

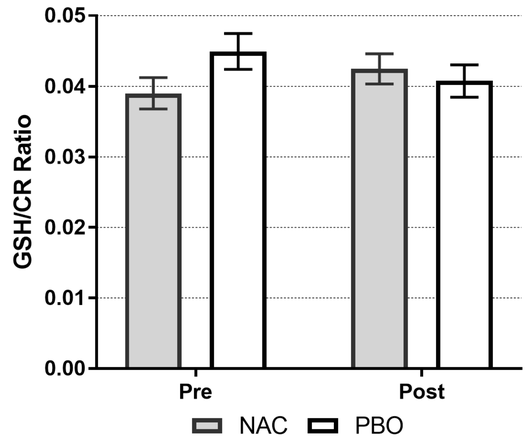


Sample MRS spectra generated with specifically adapted sequence processing, with creatine and glutathione peaks highlighted

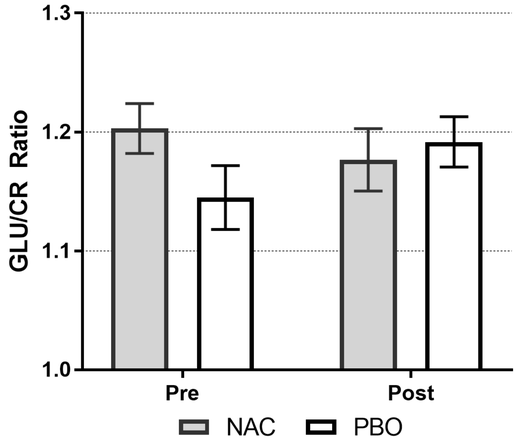
RESULTS

- Glutathione was increased in the MPFC of patients treated with NAC compared to placebo F (1,30.2) = 4.86, p = .035
- We also found a trend-level decrease in glutamate in MPFC of patients treated with NAC compared to placebo, F(1,30) = 4.04, p = .054.
- These changes were not observed in DLPFC
- We did not find any other significant interactions

Glutathione



Glutamate



DISCUSSION

- The data presented here suggest that NAC may improve symptoms of schizophrenia through supporting the antioxidant defense system by increasing glutathione in the prefrontal cortex
- NAC may also promote a downregulation of glutamate levels in prefrontal regions by improving NMDA receptor functioning on inhibitory neurons
- A longer treatment period (i.e. six months) may be required to see measurable clinical effects of NAC but two months of administration appears to be sufficient to see changes in glutathione levels

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