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Letter to the Editor

N-acetylcysteine improves EEG measures of auditory deviance detection and neural synchronization in schizophrenia: A randomized, controlled pilot study

Dear Editor,

N-acetylcysteine (NAC) is an amino acid thought to have effects on the *N*-methyl-D-aspartate (NMDA) receptor, a key target for treatment of schizophrenia. NAC has been shown to improve negative symptoms (Farokhnia et al., 2013), cognition (Conus et al., 2018), and electroencephalogram (EEG) measures of sensory processing in schizophrenia (Retsa et al., 2018).

We examined EEG during two early auditory processing paradigms. One, mismatch negativity (MMN), is a measure of auditory deviance detection that is of considerable interest in schizophrenia. Second, auditory steady-state response (ASSR), includes oscillations in the beta-gamma range and is a measure of neural synchronization. Deficits in MMN and beta-gamma oscillations are associated with clinical symptoms and poor functioning in schizophrenia (Javitt and Sweet, 2015; Wynn et al., 2010), and hence are targets for intervention (Braff and Light, 2004). NAC in particular has been shown to improve MMN and gamma oscillations (Carmeli et al., 2012; Lavoie et al., 2008). Only one previous study examined the effect of NAC on MMN in schizophrenia (Lavoie et al., 2008) and none have examined measures of ASSR.

We examined the effects of NAC in patients with schizophrenia in an 8-week randomized, double-blind, placebo-controlled study, assessing MMN and ASSR (total power and intertrial coherence), negative symptoms, and cognition. We hypothesized that NAC would improve EEG measures, negative symptoms, and cognition.

Twenty-six stable, medicated outpatients meeting DSM-5 criteria for schizophrenia were recruited from the VA Greater Los Angeles Healthcare System (VAGLAHS) and outpatient clinics in Los Angeles, and randomized to either NAC or placebo. Data from 19 participants were analyzed due to study drop-out (four participants) and unusable EEG data (three participants). Data for nine participants assigned to NAC and ten assigned to placebo were analyzed. For analyzed participants, Mean (SD) age was 47.7 (8.3) years for NAC group, 50.4 (12.5) years for placebo group; 67% male (NAC) and 75% male (placebo), with no differences between analyzed groups on demographics. All participants provided written informed consent in accordance with procedures approved by the Institutional Review Board at VAGLAHS. This study was registered with ClinicalTrials.gov (identifier: NCT01885338).

N-acetylcysteine 600 mg and matching placebo capsules were obtained from Vital Nutrients (Middletown, CT). Participants randomized to NAC received a total daily dose of 2400 mg. All subjects who completed the study were found to be 100% compliant based on interview and pill counts. Participants underwent EEG testing and clinical and cognitive assessments at baseline, and after 4 and 8 weeks of treatment, and change from baseline to the 8-week endpoint was pre-specified.

MMN was measured with a duration deviant auditory oddball paradigm, and amplitude was measured as the mean activity between 140–240 ms at electrode Fz. Participants watched a silent movie during the paradigm. Stimuli consisted of 50 ms (standard) or 100 ms (deviant) 1000 Hz tones. A total of 1800 trials were presented, 10% of which were deviants. For ASSR, we used a series of tone click-trains presented at 20, 30 or 40 Hz. Stimuli consisted of 500 ms long trains of a 1 ms 1000 Hz tone click presented at 20, 30, or 40 Hz. A total of 200 trials per condition were administered. Total power (POW) and intertrial coherence (ITC) were assessed at electrode Fz.

Age and gender-corrected normed T-scores for the global composite from the MATRICS Consensus Cognitive Battery (MCCB) were obtained. We assessed negative symptoms with the Clinical Assessment Interview for Negative Symptoms total score.

The primary statistical analyses utilized a generalized linear mixed model, separately examining EEG, cognitive, and negative symptom measures across baseline and week 8 as the within-group factor and treatment as a between-group factor. Cohen's *d* effect sizes were calculated for between-group differences in change from baseline to week 8.

Mixed model analysis revealed an interaction effect between group and time wherein POW at 40 Hz stimulation was significantly increased in patients treated with NAC compared to patients treated with placebo ($F_{(1,17.6)} = 4.92$, $p = .04$). Mixed model analysis also revealed an interaction between group and time wherein ITC at 20 Hz stimulation was significantly increased in patients treated with NAC compared to patients treated with placebo ($F_{(1,15.6)} = 11.68$, $p = .004$), and there was also a main effect of time ($F_{(1,15.6)} = 9.14$, $p = .008$). The group by time interaction for ITC survives Bonferroni correction for multiple testing. See Table 1 for means and SD as well as effect sizes of the group differences for change from baseline to 8 weeks.

For cognition and negative symptoms, there were no main effects of treatment group or treatment group × time interaction, and effect sizes of the group differences were small. The treatment was generally well-tolerated, with gastrointestinal complaints representing the most commonly reported side effect (in two participants).

This is the first study to demonstrate an NAC-associated increase in neural synchronization assessed with ASSR in schizophrenia. POW at 40 Hz stimulation was improved with NAC and ITC was improved at 20 Hz stimulation. The gamma band, including 40 Hz frequency has been a focus of interest in schizophrenia with several studies showing impairment in patients in this range (Zhou et al., 2018). As these EEG indices of neural synchronization are thought to be dependent on NMDA receptor function, improvements in EEG measures with NAC treatment may occur though NAC's actions on glutamate and the antioxidant glutathione (Steullet et al., 2016). We did not see improvement in MMN, which is inconsistent with some past reports of improvement of MMN in schizophrenia. This lack of finding may be due to the small sample of the study, the short duration of treatment, or the relatively low

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Table 1
Group differences between NAC and placebo on EEG measures of auditory deviance, auditory entrainment, cognition, and negative symptoms. NAC = N-acetylcysteine; MMN = mismatch negativity; MCCB = MATRICS Consensus Cognitive Battery.

	Placebo mean (SD)		NAC mean (SD)		F (df) Group by time interaction	Significance (p value)	Effect size of between-group difference (Cohen's d, NAC change – placebo change)
	Baseline	Week 8	Baseline	Week 8			
MMN	−0.89 (0.67)	−1.01 (1.28)	−0.74 (1.15)	−1.45 (0.55)	1.06 (1, 17.9)	0.318	−0.337
Power							
20 Hz	0.05 (0.07)	0.03 (0.10)	0.09 (0.12)	0.16 (0.16)	3.87 (1, 16.4)	0.066	0.848
30 Hz	0.09 (0.12)	0.13 (0.31)	0.11 (0.14)	0.31 (0.37)	2.07 (1, 17.8)	0.168	0.721
40 Hz	0.21 (0.24)	0.04 (0.13)	0.27 (0.45)	0.73 (0.90)	4.92 (1, 17.6)	0.040*	0.983
Intertrial coherence							
20 Hz	0.14 (0.05)	0.14 (0.06)	0.17 (0.09)	0.24 (0.13)	11.68 (1, 15.6)	0.004**	1.613
30 Hz	0.18 (0.12)	0.21 (0.17)	0.25 (0.14)	0.33 (0.22)	0.70 (1,15.9)	0.416	0.406
40 Hz	0.28 (0.19)	0.28 (0.30)	0.35 (0.20)	0.49 (0.22)	2.06 (1, 16.2)	0.170	0.602
MCCB composite	35.7 (9.9)	36.9 (13.0)	31.3 (14.2)	32.1 (12.8)	0.00 (1, 14.7)	0.962	0.038
CAINS	22.2 (8.5)	23.1 (10.3)	17.9 (6.4)	17.5 (4.9)	0.26 (1, 15.1)	0.621	−0.250

* Indicates $p < .05$.
** Indicates $p < .01$ and survives Bonferroni correction for multiple testing (EEG measures).

dose of NAC compared to other studies (Conus et al., 2018). The results of this study should be interpreted with caution until replication in a larger sample size with a longer duration of treatment. Nonetheless, these findings contribute to a growing literature on the utility of NAC adjunctive treatment to improve neural function in schizophrenia.

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Contributors

Drs. Davis, Wynn, Green, and Marder designed the study. Drs. Davis and Wynn collected data for the study. Drs. Wynn, Yang, and Hellemann conducted the data analyses. Dr. Yang wrote the first draft of the manuscript. Drs. Yang, Wynn and Green edited the manuscript and assisted with interpretation of the findings.

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