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The effect of N-acetylcysteine on brain glutamate and gamma-aminobutyric acid concentrations and on smoking cessation: A randomized, double-blind, placebo-controlled trial

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Abstract
Using data form a 14-day double-blind trial with 48 smokers randomized to either N-acetylcysteine (2400 mg) or placebo, we tested the effect of N-acetylcysteine on glutamate and gamma-aminobutyric acid concentrations in the dorsal anterior cingulate cortex and on smoking cessation. Smoking related behaviors and neurotransmitter concentrations in the dorsal anterior cingulate cortex were assessed before and after treatment. Forty-seven non-smoking males served as baseline controls. Smoking showed higher baseline glutamate but similar gamma-aminobutyric acid concentrations than non-smokers. There were no treatment effects on dorsal anterior cingulate cortex neurotransmitter concentrations, smoking cessation, craving, or withdrawal symptoms. These results confirm glutamate disbalance in smokers, but not efficacy of N-acetylcysteine.

Keywords
Proton magnetic resonance spectroscopy, gamma-aminobutyric acid, glutamate, N-acetylcysteine, smoking cessation, tobacco dependence

Null Results in Brief

Substance dependence is associated with deviating glutamate and gamma-aminobutyric acid (GABA) concentrations in the dorsal anterior cingulate cortex (dACC). However, the literature is inconclusive on the direction of these neurotransmitter deviations (e.g. Durazzo et al., 2016; Schmaal et al., 2012). Pilot studies with N-acetylcysteine (NAC), a glutamatergic agent, show treatment promise (review: Deepmala et al., 2015). A first study (Schmaal et al., 2012) showed a direct effect of NAC on glutamate concentration in the dACC of cocaine dependent individuals. The aim of the current study was to test the effect of NAC on glutamate and GABA concentrations in the dACC in smokers and smoking cessation. Smokers were hypothesized to differ in dACC glutamate and GABA concentrations from non-smokers, and smokers receiving NAC were hypothesized to show normalization of these neurotransmitter concentrations and higher success-rates in smoking cessation.

Forty-eight male 15–55 year-old smokers (15+ cigarettes/day and Fagerström Test for Nicotine Dependence (FTND≥3) participated in a 14-day randomized, double-blind trial with 2400 mg/d NAC or placebo. Exclusion criteria were psychoactive medication, other mental and neurological disorders and magnetic resonance imaging (MRI)-ineligibility. MRI and psychological testing was done one day before and after treatment. Forty-seven matched non-smoking males served as baseline controls. Glutamate and GABA concentrations in the dACC were assessed with proton magnetic resonance spectroscopy (1H-MRS; for details see Waddell et al., 2007). Due to overlap in the spectral assignment of glutamate, glutamine and glutathione (Glx) concentrations are reported as proxy for glutamate. Breath CO concentration was assessed with a smokerlyzer. For questionnaire analysis, see Table 1 and 2. Our local Ethics Committee provided institutional review board approval. An extensive method description is available on request.

Between-group differences were assessed with independent sample t-tests. Linear mixed model analyses were conducted to analyze treatment effects. Bayes factors quantified evidence for the null hypothesis.

There were no between-group differences in quality parameters of MRS spectra (Table 1) or medication compliance (Table 2). Smokers and non-smokers differed significantly in AUDIT-scores

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### Table 1. Baseline comparison of demographic, sample description measures and neurotransmitter concentrations.

|                    | Controls (n=47) | Smokers (n=48) | NAC (n=24) | Placebo (n=24) | t (df) | p-Value |
|--------------------|----------------|----------------|------------|----------------|--------|---------|
| **Age**            | 33.23 (11.24)  | 35.08 (9.83)  | –          | –              | 0.854 (93) | 0.40    |
|                    |                |                | –          |                | –      |         |
| **IQ (NART)**      | 106.55 (8.20)  | 105.29 (8.25) | 106.58 (7.54) | 104.00 (8.88) | –      |         |
|                    |                |                | –          |                | –      |         |
| **AUDIT**          | 5.30 (3.67)    | 6.81 (3.31)    | –          | –              | 2.094 (92) | 0.04    |
|                    |                |                | –          |                | –      |         |
| **FTND**           | –              | –              | 6.54 (3.09) | 7.08 (3.56)    | 0.563 (46) | 0.58    |
|                    |                |                | –          |                | –      |         |
| **RCQ**            | –              | –              | 6.04 (1.90) | 5.71 (1.57)    | –      |         |
| **Smoking years**  | –              | –              | 18.78 (9.64) | 16.29 (9.70)  | –      |         |
| **Glx**            | 0.62 (0.10)    | 0.67 (0.13)    | –          | –              | 1.955 (71) | 0.05    |
|                    | –              | –              | –          | –              | –      |         |
| **GABA**           | 0.20 (0.05)    | 0.19 (0.09)    | 0.67 (0.12) | 0.68 (0.14)    | 0.246 (32) | 0.81    |
|                    | –              | –              | –          | –              | –      |         |
| **CRLB**           | 4.05 (1.02)    | 4.06 (0.85)    | 0.19 (0.07) | 0.20 (0.11)    | 0.090 (38) | 0.93    |
|                    | –              | –              | –          | –              | –      |         |
| **FWHM**           | 0.05 (0.02)    | 0.05 (0.02)    | 4.25 (0.93) | 3.89 (0.76)    | –      |         |
|                    | –              | –              | –          | –              | –      |         |
| **SNR**            | 4.33 (1.03)    | 4.21 (0.95)    | –          | –              | –      |         |
|                    | –              | –              | 4.13 (0.96) | 4.28 (0.96)    | 0.464 (32) | 0.65    |

AUDIT: Alcohol Use Disorder Identification Test; CRLB: Cramer Rao Lower Bound; FTND: Fagerström Test for Nicotine Dependence; FWHM: Full Width at Half Maximum; GABA: gamma-aminobutyric acid, referenced to creatine; Glx: composite measure of glutamate and glutamine, referenced to creatine; 1H-MRS: proton magnetic resonance spectroscopy; NAC: N-acetylcysteine; NART: National Adult Reading Test; RCQ: Readiness to Change Questionnaire; SD: standard deviation; SNR: signal to noise ratio.

Test results of baseline comparisons between smokers and controls, and between the smokers stratified into the NAC group and placebo group are represented on different rows, respectively. Twelve and eight non-smokers at baseline, and two smokers at follow-up were excluded for Glx analyses, and eight smokers and four non-smokers at baseline, and five smokers at follow-up were excluded for GABA analyses due to technical 1H-MRS failures.
concentrations were in line with previous results, the current study failed to replicate the normalization of dACC Glx concentrations or treatment effects of NAC.

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Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: This study is registered at the Netherlands Trial Registry (www.trialregister.nl; number: NTR3576).

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Table 2. Effects of treatment on composite measure of glutamate and glutamine (Glx), referenced to creatine, and gamma-aminobutyric acid (GABA), referenced to creatine, concentrations, and smoking outcomes as measured by smoking behavior, craving, and withdrawal symptoms.

|                      | NAC group | Placebo group | χ² (df) | p-Value | BF01 |
|----------------------|-----------|---------------|---------|---------|------|
|                      | Baseline  | Follow-up     | Baseline | Follow-up |     |
|                      | n=24      | n=19          | n=24     | n=20     |     |
| Mean (SD)            | Mean (SD) | Mean (SD)     | Mean (SD) | Mean (SD) |     |
| #pills taken         | –         | 52.7 (11.3)   | –        | 50.8 (7.85) | –0.557 (33) | 0.58 |
| Neurotransmitters    |           |               |          |          |      |
| Glx                  | 0.67 (0.12) | 0.64 (0.17) | 0.68 (0.14) | 0.62 (0.19) | 0.7 (1.66) | 0.40 |
| GABA                 | 0.19 (0.11) | 0.17 (0.06) | 0.20 (0.07) | 0.19 (0.06) | 0.216 (1,66) | 0.64 |
| Smoking behavior     |           |               |          |          |      |
| Proportion quit (%)d | –         | 7.90          | –        | 18.40    | 1.642 (1) | 0.18 |
| Abstinent daysd      | –         | 4.11 (4.90)   | –        | 6.45 (5.73) | 150    | 0.25 |
| Days until relapsedd | –         | 3.18 (4.87)   | –        | 4.25 (5.07) | 0.89 (1) | 0.34 |
| Cigarettes/weekd     | 23.47 (6.42) | 1.68 (0.46) | 21.44 (7.10) | 1.53 (0.51) | 0.048 (1,87) | 0.82 |
| Breath CO            | 22.27 (14.46) | 14.23 (10.95) | 17.25 (10.10) | 8.58 (11.44) | 0.001 (1,45.22) | 0.98 |
| Craving              |           |               |          |          |      |
| QSU                  | 28.92 (11.83) | 25.53 (12.26) | 31.67 (13.35) | 24.40 (13.82) | 0.520 (1,44.19) | 0.48 |
| Craving (VAS)        | 32.87 (33.09) | 32.77 (25.91) | 46.25 (30.23) | 31.75 (30.70) | 0.718 (1,44.51) | 0.40 |
| Withdrawal symptoms  |           |               |          |          |      |
| M-NWS                | 17.54 (8.23) | 15.26 (10.27) | 17.42 (8.91) | 15.10 (10.15) | 0.004 (1,43.42) | 0.95 |

BF01: Bayes Factor of H0 against H1; CO: carbon monoxide; M-NWS: Minnesota Nicotine Withdrawal Scale; NAC: N-acetylcysteine; QSU: Questionnaire for Smoking Urges; SD: standard deviation; VAS: Visual Analogue Scale.

*Values of p represent chi-squared tests; †values of p represent non-parametric t-test; ‡values of p represent results of interaction effects group×time; ‘measured using the Timeline Followback method.

References

Deepmala Slattery J, Kumar N, et al. (2015) Clinical trials of N-acetylcysteine in psychiatry and neurology: A systematic review. *Neurosci Biobehav Rev* 55: 294–321.

Durazzo TC, Meyerhoff DJ, Mon A, et al. (2016) Chronic cigarette smoking in healthy middle-aged individuals is associated with decreased regional brain N-acetylaspartate and glutamate levels. *Biol Psychiatry* 79: 481–488.

Lee E, Jang D, Kim J, et al. (2007) Alteration of brain metabolites in young alcoholics without structural changes. *Neuroreport* 18: 1511–1514.

McClure EA, Gipson CD, Malcolm RJ, et al. (2014) Potential role of N-acetylcysteine in the management of substance use disorders. *CNS Drugs* 28: 95–106.

Schmaal L, Veltman DJ, Nederveen A, et al. (2012) N-acetylcysteine normalizes glutamate levels in cocaine-dependent patients: A randomized crossover magnetic resonance spectroscopy study. *Neuropsychopharmacology* 37: 2143–2152.

Waddell KW, Avison MJ, Joers JM, et al. (2007) A practical guide to robust detection of GABA in human brain by J-difference spectroscopy at 3T using a standard volume coil. *Magn Reson Imaging* 25: 1032–1038.