N-Acetylcysteine changes glutamate levels in cocaine dependent subjects: an open label ^{1}H MRS pilot study

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Introduction

Disturbances in glutamate homeostasis play an important role in addiction, especially in relapse.

Treatment with N-acetylcysteine has proven to restore glutamate homeostasis and prevent relapse into drug seeking behavior in preclinical studies.

Proton magnetic resonance spectroscopy (^{1}H MRS) provides a noninvasive means of examining metabolites such as glutamate in the human brain.

Until date, the effects of NAC on brain glutamate concentrations in humans have not yet been examined.

Aim

- **To investigate glutamate changes in the anterior cingulate after administration of NAC in cocaine dependent subjects compared to healthy controls.**
- To delineate the relationship between glutamate concentrations, impulsivity and cocaine use.

Methods

Subjects

- Cocaine dependent (CD) subjects with comorbid alcohol problems
- Age and education matched healthy controls (HC)

	Cocaine dependent	Controls
N	9	11
Age	35.6 ± 6.5	36.7 ± 9.8
IQ	91.4 ± 6.7	95.1 ± 14.7

N-acetylcysteine administration

- Single dose 2400 mg one hour before scanning

^{1}H MRS protocol

- Open label design
- 2 scan sessions: Baseline-NAC (counterbalanced)
- PRESS sequence, TR/TE = 38/2000
- Voxel (5.0 x 1.6 x 1.0 cm) placed in left dorsal anterior cingulate cortex (BA24/32), **see Fig. 1**

Questionnaire

- Barratt Impulsiveness Scale, Version 11 (BIS-11)

Fig. 1: A voxel was placed in the dorsal ACC (BA24/32) for obtaining an ^{1}H MRS spectrum

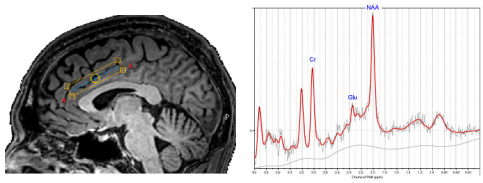
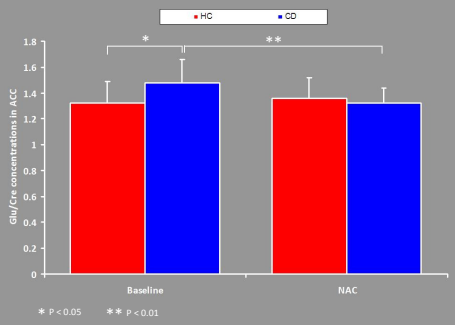
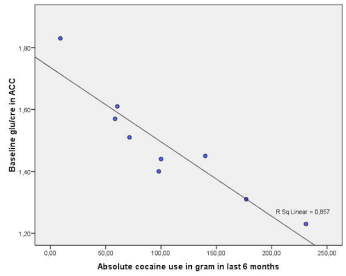


Fig. 2: Glu/cre concentrations in ACC at baseline and after NAC admininstration



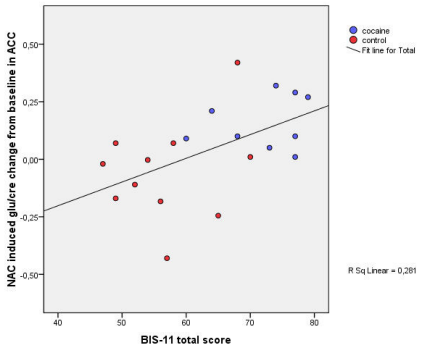
At baseline, glu/cre concentrations were significantly higher in the CD group compared to the HC group. NAC significantly reduced glu/cre concentrations in the CD group, while it had no effect in the HC group.

Fig. 3a: Correlation between baseline glu/cre and absolute cocaine use in last 6 months in CD group



A

Fig. 3b: Correlation between NAC induced glu/cre changes and cognitive impulsivity at baseline across groups



B

Methods

- At baseline, **CD subjects displayed higher glu/cre concentrations in the dorsal ACC** compared to HC subjects, **see Fig. 2**
- The glu/cre concentrations at baseline were negatively correlated with absolute cocaine use in the last 6 months (r=-0.93), **see Fig. 3A**
- Across groups, BIS-11 total score and cognitive and nonplanning impulsivity subscales were positively correlated with glu/cre levels at baseline (total r=0.53; cognitive r=0.62; nonplanning r=0.49)
- **After NAC administration, glu/cre levels were significantly reduced in the CD group,** while it had no effect in the HC group, **see Fig. 2**
- Subjects with higher impulsivity scores at baseline had the highest NAC induced glu/cre reduction (BIS-11 total r=0.53, **see Fig. 3B**; cognitive r=0.58; nonplanning r=0.59)

Conclusions

NAC restored the disturbed glutamate concentration within the ACC in cocaine dependent subjects found at baseline.

This could be an important implication for treatment, because disturbed glutamate concentrations have been related to relapse and treatment with NAC to prevention of relapse.

Higher impulsivity was associated with elevated glutamate levels within the dorsal ACC, a brain area involved in cognitive control. Impulsive subjects benefit most from NAC in terms of glutamate reduction.

Cocaine dependent subjects with the lowest amount of cocaine use in the last six months had lower glutamate levels at baseline. These subjects were also more impulsive at baseline and longer abstinent from cocaine.

No potential conflicts of interest

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