The effect of N-acetylcysteine and working memory training on glutamate concentrations in the dACC and rACC in regular cocaine users-A randomized proof of concept study

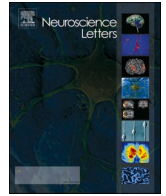Schulte, M.H.J.; Goudriaan, A.E.; Boendermaker, W.J.; van den Brink, W.; Wiers, R.W.

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Research article

The effect of N-acetylcysteine and working memory training on glutamate concentrations in the dACC and rACC in regular cocaine users – A randomized proof of concept study

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ABSTRACT

Introduction: Current treatments for cocaine use disorder (CUD) are not very effective and better treatments are needed. This study investigates the effectiveness of a combined intervention that targets the assumed underlying glutamate pathology in cocaine users. To this end, the combined effects of N-acetylcysteine (NAC) and working memory (WM) training on glutamate concentrations in the dorsal and rostral ACC were investigated in a randomized, double-blind placebo-controlled design.
Methods: In this study, 38 regular cocaine-using men were randomized to either 25-days with 2400 mg/day NAC and WM-training or 25 days with placebo with WM-training. Cocaine use, impulsivity, and glutamate concentrations in the dACC and rACC using proton Magnetic Resonance Spectroscopy were assessed at baseline and after treatment.
Results: Twenty-four participants completed the study, of which 9 received NAC and 15 received placebo. There were no baseline correlations of glutamate concentrations in the dACC or rACC with cocaine use measures or impulsivity. Additionally, there were no effects of NAC, WM-training, or the combination thereof on (changes in) glutamate concentrations in the dACC or rACC.
Discussion: This randomized proof of concept study could not confirm our hypotheses. Possible explanations are insufficient power and the possible absence of deviant baseline glutamate concentrations in the included participants. Future studies should consider larger samples and a non-using control group to confirm baseline deviations in glutamate in cocaine users.

1. Introduction

Currently available treatments of cocaine dependence are not very effective and there is a pressing need for more effective treatments (EMCDDA, 2016). Investigating the effectiveness of a pharmacological intervention combined with behavioral training targeting underlying neurocognitive processes could contribute to the development of more effective treatments. Substance use disorders (SUD) have been associated with a variety of alterations in neurobiological functioning, such as an imbalance in the glutamate homeostasis in the nucleus accumbens

(see e.g. [1] or [2]). Several pre-clinical studies on addiction have investigated glutamate concentrations in other brain regions, including the dorsal Anterior Cingulate Cortex (dACC) and the rostral ACC (rACC). However, the findings regarding ACC Glx concentrations in SUD patients are inconsistent. For example, some studies found increased levels of Glx [3,4], whereas other studies found decreased levels of Glx [5,6] and some studies reported normal levels of Glx [7–9]. These discrepancies in findings may have resulted from differences in the type of substance that was used (e.g., alcohol, cocaine or tobacco) and the different stages of SUD (e.g., short-term abstinence, long-term abstinence or no

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abstinence).

Moreover, dACC Glx concentrations were positively associated with cognitive (dys)functions such as impulsivity in healthy controls [10] and cocaine dependent patients [3]. However, similar associations were not reported in smokers or cocaine using polysubstance users [11][1]. Working memory (WM) is regarded to be a central (cognitive) cognitive function [12] that is related to impulsivity in such a way that people with low WM capacity are less capable to control impulsive behaviors, including substance use behaviors [13,14]. This study investigated the effectiveness of an intervention to reduce cocaine use by targeting the underlying glutamate brain pathology through the administration of N-acetylcysteine in combination with working memory (WM) training.

Studies on the effect of N-acetylcysteine (NAC), a cysteine prodrug, on brain glutamate concentrations are limited and findings are inconsistent with both positive effects [3,15] and absence of effects [16]. However, this discrepancy could have resulted from the fact that the two positive studies focused on the dACC, whereas the negative study focused on the nucleus accumbens. Furthermore, ^{1}H MRS studies are not always able to differentiate between glutamate, glutamine, and other components due to overlap in spectral assignment. The term Glx (a composite measure) is often used [17], and will also be used as a proxy measure of glutamate when referring to data from the current study.

Positive clinical effects of NAC in the treatment of SUD have also been reported. In an umbrella review including 5 systematic reviews (including 59 studies comprising 2184 participants suffering from different SUDs), NAC was found to reduce craving and prevent relapse especially in cocaine users and in cannabis users [18]. The effects of NAC on cognitive control, including impulsivity, are inconsistent [19,20] and the same is true for the effects of WM-training on working memory [21–26].

The aim of the current randomized controlled study was to investigate the effects of NAC and WM-training on glutamate concentrations in the dACC and the rACC separately, given their association with distinct cognitive functions [27]. Since NAC and WM-training have individually resulted in inconsistent effects, it could be beneficial to investigate their combined effects. First, it was investigated whether there were baseline associations of glutamate concentrations in the dACC and rACC with cocaine use and impulsivity. Impulsivity is a multi-faceted construct [28] and was therefore measured using a self-report questionnaire and neurocognitive tasks assessing impulsive choice and impulsive action. It was expected that in both brain areas there would be a positive association of glutamate concentrations with the amount of cocaine that was used, as well as with impulsivity. Regarding the treatment effect, NAC was expected to decrease Glx concentrations in the dACC and rACC compared to placebo. Moreover, this effect on Glx was expected to be more pronounced in participants who completed more WM-training sessions.

2. Material and methods

The results of the current paper were part of a larger study (see [19,29])[2]. A brief description of the methods is provided here, a more detailed description can be found as supplementary materials.

Thirty-eight male 18–55 year-old regular cocaine-using men (snorting ≥4 times per month, DSM5 ≥ 2 criteria) participated in a 27-day double-blind placebo controlled trial with 2400 mg/d NAC or placebo and active WM-training. Exclusion criteria were smoking (crack-) cocaine, ≥2 DSM-5 criteria for heroin dependence in the previous year, MRI-ineligibility, and medications interacting with NAC. MRI and psychological testing were done one day before and after testing. Informed consent was acquired at the start of the first lab-visit. The Ethical Review Board of the Academic Medical Center of the University of Amsterdam approved the study.

Several questionnaires were used to assess baseline demographic and clinical measurements during lab-sessions at baseline and after the 25-day intervention. Impulsivity was assessed using self-report (Barrat Impulsiveness Scale; [30]), as well as by means of behavioral tasks to assess impulsive action (Stop Signal Task; [31], see [19] for a detailed description) and impulsive choice (Delay Discounting Task; [32]).

For the 25-day intervention, participants were randomly allocated to either NAC or placebo. Simultaneously, participants performed online WM-training, consisting of three tasks. Each task consisted of 30 trials and were adaptive to the participants' performance.

Imaging data was collected using a Philips 3.0 T MRI scanner (Philips Healthcare, Best, the Netherlands) at the Academic Medical Center in Amsterdam. For a detailed description of imaging acquisition and pre-processing, see supplementary methods.

Dependent on the outcome variable, treatment effects were analyzed using hierarchical multiple linear regression or multivariate regression analyses. Due to between-group differences, age was added as a covariate in both regression analyses, whereas baseline dACC Glx concentrations were added in the regression analyses investigating the treatment effect in the dACC.

3. Results

3.1. Participants

Of the 38 included participants, 24 (63%) completed the study of which 9 participants received NAC and 15 participants received placebo.[3] There were no between-group differences in dropout rate ($\chi^2(1)$ = 1.380, p = .24). Adherence to WM-training was low (NAC: 9.67(6.27) of 25 sessions; placebo: 9.13(7.75) of 25 sessions). Between-group differences in baseline measurements of the 24 participants who completed the study are displayed in Table 1. The NAC group was significantly older (p < .01), reported a longer duration of frequent cocaine use (p = .02), had a lower Glx concentration in the dACC (p = .05), and tended to have a higher DDT (AUC) score (p = .07). At baseline, there were no significant correlations of the Glx concentrations in the dACC or rACC with cocaine use measures or impulsivity measures (see Table 2).

3.2. Treatment effects on cocaine use

There were no significant between-group differences in cocaine use between the two study visits. Out of all participants who completed the study, only 2 of the 9 participants from the NAC group and 0 of the 15 participants form the placebo group remained abstinent from cocaine between the two visits (22% vs. 0%; NNT = 4.5; p = .13). The mean number of days until relapse was 6.43 (SD = 6.61) days for the NAC group and 8.33 (SD = 6.03) days in the placebo group (f = 0.15; p = .27). For a full report on the treatment effects on cocaine use see Schulte et al. [19].

3.3. Treatment effects on dACC and rACC Glx concentrations

Although the between-group baseline differences in dACC Glx were

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[1] The cocaine using polysubstance users from this study were from an independent sample.

[2] This study is part of a more extensive intervention study on the effect of NAC and working memory training on cocaine cessation, craving, and several neurobiological measures, and is registered with the Netherlands Trial Registry (number: NTR4474). The effects on cocaine use cessation, craving, cognitive functions, and fMRI assessments are reported in Schulte et al. [4,29]. Due to slow enrollment, the design was adapted and the placebo WM training was dropped.

[3] When comparing dropouts to completers at baseline, there was a difference in years of frequent cocaine use (dropouts < completers, p=.02). See supplementary Table 1 for all baseline comparisons between dropout and completers.

Table 1

Baseline between-group comparisons of demographics, cocaine use, impulsivity and glutamate concentrations in the dACC and rACC of participants who completed the study.

	NAC	Placebo	$t(df)^a$/ $\chi^2(df)^b$/U^c	p-value
	N = 9	N = 15		
	M(SD)	**M(SD)**		
WM-sessions	9.67(6.27)	9.13(7.75)	−0.175 (22)[a]	0.86
Demographics				
Age	44.78(8.72)	32.40(7.74)	−3.620 (22)[a]	**<0.01**
IQ	106.11(6.97)	103.50 (7.78)	0.304(22)[a]	0.42
Drinker (%)	100	100		
AUDIT	19.44(5.18)	15.47(6.71)	41.5[c]	0.12
Smoker (%)	80.0	77.8	0.02(1)[b]	0.90
FTND	3.00(2.00)	5.15(3.08)	1.661(18)[a]	0.11
Cannabis (%)	22.2	33.3	0.336(1)[b]	0.56
Cannabis (joints/ week)	4.33(11.73)	9.01(19.10)	0.660(22)[a]	0.52
XTC (%)	44.4	13.3	2.904(1)[b]	0.09
XTC (days/week)	0.10(0.12)	0.09(0.26)	−0.111 (22)[a]	0.91
Other[d] (%)	22.2	6.7	1.244(1)[b]	0.27
Other[d] (days/week)	0.05(0.10)	0.19(0.72)	0.551(22)[a]	0.59
RCQ	46.33(7.70)	44.47(6.49)	48.5[b]	0.26
Cocaine use				
Age first use	26.22(10.26)	21.27(7.51)	−1.365 (22)[a]	0.19
€/week	114.44 (75.52)	99.11 (70.61)	−0.930 (21)[a]	0.36
Duration frequent use (y)	14.22(8.00)	6.66(6.50)	−2.492 (21)[a]	**0.02**
DSM-IV criteria	7.33(2.12)	7.33(2.72)	0.000(22)[a]	0.99
Gram/week	1.90(1.67)	2.58(2.37)	0.668(22)[a]	0.51
UsingDays/week	2.35(1.14)	2.43(1.83)	0.106(22)[a]	0.92
Gram/UsingDay	0.74(0.38)	1.00(0.40)	1.574(22)[a]	0.13
Urine screen (% pos)	69.2	55.6	0.43(1)[b]	0.51
DUDIT	21.22(4.74)	19.33(6.02)	−0.802 (22)[a]	0.43
Impulsivity				
BIS-11	72.11(8.62)	70.67 (13.58)	−0.285 (22)[a]	0.78
SSRT (ms)	246.38 (43.43)	224.27 (39.39)	−1.284 (22)[a]	0.21
DDT (AUC)	2272.39 (1083.55)	1462.60 (965.39)	−1.902 (22)[a]	0.07
Glx				
dACC	1.48(0.27)	1.67(0.17)	2.060(20)[a]	**0.05**
Excluded scans (%)	11.11	6.67	0.145(1)[b]	0.70
rACC	1.74(0.16)	1.82(0.27)	0.713(20)	0.48
Excluded scans (%)	11.11	0	1.626(1)	0.20

Note. [a] independent samples *t*-test, [b] non-parametric *t*-test, [c] Fisher's exact test. [d] Other substances include GHB n = 1), 2CB (n = 2) and ketamine (n = 1). Glutamate is presented as Glx (glutamate + glutamine), referenced to creatine. AUC, Area Under the Curve; AUDIT, Alcohol Use Disorder Identification Test; BIS-11, Barrat Impulsiveness Scale; dACC, dorsal Anterior Cingulate Cortex; DDT, Delay Discounting Task; DSM, Diagnostic and Statistical Manual of Mental Disorders; DUDIT, Drug Use Disorder Identification Test; FTND, Fagerström Test for Nicotine Dependence; NAC, N-acetylcysteine; rACC, rostral Anterior Cingulate Cortex; RCQ, Readiness to Change Questionnaire; SD, Standard Deviation; SSRT, Stop Signal Reaction Time.

no longer present at follow-up (t(20) = −0.184, p = −0.86), there were no significant effects of NAC, the number WM-training sessions completed or the combination thereof on Glx concentrations in the dACC. Specifically, group and WM-training (block 1) did not significantly contribute to the regression model (F(4, 17) = 2.141, p = .12, R^2 = 0.335, f^2 = 0.50). Adding the group by WM-sessions interaction (block 2) to the model did not have an effect on the significance of the model (F (5, 16) = 2.125, p = .12, R^2 = 0.399, f^2 = 0.66). Post-hoc power analyses

for both blocks revealed around 80% power (block 1: 78%; block 2: 83%) to detect treatment effects with a large effect size.

Regarding rACC Glx, there also were no effects of group, the number of WM-training sessions or the combination thereof on Glx concentrations in the rACC. Specifically, group and WM-training (block 1) did not significantly contribute to the regression model (F(3, 18) = 1.005, p = .41, R^2 = 0.143, f^2 = 0.17). Adding the group by WM-sessions interaction (block 2) to the model did not have an effect on the significance of the model (F(4, 17) = 0.940, p = .47, R^2 = −0.181, f^2 = 0.22). Post-hoc power analyses revealed 34% power to detect treatment effects with a small effect size for block 1 and 35% power to detect treatment effects with a medium effect size for block 2. Detailed information on coefficients for both regression models can be found in (see Table 3).

4. Discussion

The current study did not find an effect of 2400 mg/day NAC and/or the number of WM-training sessions on glutamate/glutamate (Glx) concentrations in the dACC or the rACC. Although positive effects of NAC on glutamate concentrations in the dACC have been reported in cocaine-dependent patients [3], the current results are in line with previous studies that showed no effects of NAC on glutamate concentrations [16,4]. Similar to our previous report [4], the lack of effect could be explained by insufficient power due to considerable dropout or ongoing substance use (see [19]). Additionally, because the current study did not include a non-using control group, it is unclear whether the glutamate concentrations in our cocaine using participants were affected at baseline. The absence of baseline correlations with cocaine use or impulsivity measures might suggest that the dACC and rACC Glx concentrations were indeed unaffected. However, the NAC group showed significantly lower baseline dACC Glx concentrations compared to the placebo group. In line with Yang et al. [33], the former also showed a significant longer duration of frequent cocaine use. This is also in line with the glutamate homeostasis hypothesis of addiction [1] and may indicate that glutamate concentrations were affected by cocaine use to some extent in the present study. However, whether this constitutes a decrease, as reported by Yang et al. [33], or an increase, as reported by Schmaal et al. [3], remains an open question.

The absence of a significant effect of WM training on Glx concentrations in the dACC or rACC could also be explained by the absence of a top-down effect on cocaine use or impulsivity (reported in [19]. For example, if WM training would have influenced cognitive control, it would have been expected to mediate the reducing effect on Glx concentrations in the ACC regions. However, the high dropout rate and low WM training adherence may have resulted in insufficient power to detect an effect of WM training. This appeared to be the case for the analyses regarding rACC Glx concentrations (±35% power), but not for the analyses regarding dACC Glx concentrations (±80% power). Additionally, participants had to quit cocaine use when their self-control was still low, whereas it has been suggested that strengthening self-control before attempting to quit could be more effective [34]. Future research could consider improving adherence to WM-training by increasing motivation intrinsically by means of motivational interviewing [35] or extrinsically by means of gamification [36] or adding contingency management.

This study has both strengths and limitations. Strengths of this study include recruitment of a challenging population of regular cocaine users, a placebo group in a double-blind randomized design, targeting motivational as well as executive processes, and using a multi-method design. Limitations include substantial dropout before the second visit, resulting in only 9 participants receiving NAC and 15 participants receiving placebo. This might have led to insufficient power to detect an effect, especially with respect to the effect of NAC on rACC Glx concentrations. Second, as there was no non-using control group, baseline differences in dACC and rACC glutamate concentrations could not be confirmed. In addition, the groups showed significant baseline

Table 2

Correlation between Glx concentrations in the dACC and rACC with cocaine use variables and impulsivity at baseline of those who completed the study.

	Age first use	€/week	Duration frequent use (y)	DSM-IV criteria	Gram/week	UsingDays/week	Gram/UsingDay	DUDIT	BIS-11	SSRT (ms)	DDT (AUC)
dACC	0.03	−0.20	−0.33	0.22	−0.31	−0.20	−0.30	0.001	0.03	0.12	−0.19
rACC	0.17	−0.38	−0.06	0.05	−0.20	−0.34	0.05	−0.16	−0.21	−0.03	0.06

Note. Values represent Pearson correlation coefficients. None of the correlations reached the significance level of 0.05.
AUC, Area Under the Curve; DDT, Delay Discounting Task; DSM, Diagnostic and Statistical Manual of Mental Disorders; DUDIT, Drug Use Disorder Identification Test; SSRT, Stop Signal Reaction Time.

Table 3

Results for treatment effects on Glx measures in the dACC and rACC.

IVs →	Group						WM-session						Group x WM-session					
DVs ↓	B	SE B	β	95% CI		p	B	SE B	β	95% CI		p	B	SE B	β	95% CI		p
dACC Glx	0.04	0.18	0.06	-0.34	0.43	.82	0.01	0.01	0.13	-0.02	0.03	.64	0.03	0.02	0.57	-0.02	0.08	.21
rACC Glx	0.14	0.12	0.30	-0.12	0.40	.28	0.01	0.01	0.28	-0.01	-.02	.23	-0.02	0.02	-0.43	-0.05	0.02	.39

Note. Dependent variables are difference scores between lab-sessions.
dACC, dorsal Anterior Cingulate Cortex; DVs, Dependent Variables; IVs, Independent Variables; rACC, rostral Anterior Cingulate Cortex.

differences in age, duration of cocaine use, Glx concentration in the dACC, and DDT score, which may have contributed to the absence of treatment effects. In addition, there was no placebo WM-training and the number of sessions was not randomly divided between NAC and placebo group. Third, only males were included. Although this increases sample homogeneity, no generalizations can made to female cocaine users.

5. Conclusion

This study did not find the expected effect of NAC and WM-training on Glx concentrations in the dACC or rACC in regular cocaine users. Possible explanations are insufficient power due to considerable dropout and low WM training adherence. Future research should aim to further elucidate the effectiveness of NAC and WM training in the treatment of SUDs, for instance in a stepped approach in which cognitive control is improved after which cessation is achieved and maintained by administering NAC, in paradigms including a non-drug-using control group.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neulet.2021.136146.

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