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Reprint of The effect of *N*-acetylcysteine and working memory training on cocaine use, craving and inhibition in regular cocaine users: correspondence of lab assessments and Ecological Momentary Assessment☆

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HIGHLIGHTS

- Beneficial effects of NAC on objective measures of cocaine use and related problems
- No effects on subjective measures of cocaine use and craving
- No effects involving WM-training
- EMA data on treatment effects on use/craving correspond to lab data.

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ABSTRACT

Introduction: Effective treatment for cocaine use disorder should dampen hypersensitive cue-induced motivational processes and/or strengthen executive control. Using a randomized, double-blind, placebo-controlled intervention, the primary aim of this study was to investigate the effect of N-Acetylcysteine (NAC) and working memory (WM)-training to reduce cocaine use and craving and to improve inhibition assessed in the laboratory and during Ecological Momentary Assessment (EMA). The second aim was to examine correspondence between laboratory and EMA data.

Methods: Twenty-four of 38 cocaine-using men completed a 25-day intervention with 2400 mg/day NAC or placebo and WM-training as well as two lab-visits assessing cocaine use, craving and inhibition (Stop Signal task). Additionally, cocaine use, craving and cognition (Stroop task) were assessed using EMA during treatment, with 26 participants completing 819 assessments.

Results: Cocaine problems according to the Drug Use Disorder Identification Test (DUDIT) decreased more after NAC than after placebo, and the proportion of cocaine-positive urines at lab-visit 2 was lower in the NAC group. No NAC effects were found on craving. For cocaine use and craving, results from the lab data were generally similar to EMA results. NAC also showed some effects on cognitive control: improved inhibition assessed with the Stop Signal task in the lab, and decreased classic Stroop performance during EMA. There were no significant effects of number of completed WM-training sessions.

Conclusions: Overall this study revealed mixed findings regarding the treatment of cocaine use disorders with NAC and WM-training. The effect of NAC on inhibition should be further investigated.

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1. Introduction

In Europe, more than half of patients entering cocaine use disorder (CUD) treatment were in treatment before (EMCDDA, 2016), highlighting the need for more effective treatments. Dual process models of addiction posit that maladaptive drug use results from the combination of hyper-reactive motivational processes and suboptimal self-regulation (Bechara, 2005; Wiers et al., 2007). Sensitized motivational processes are thought to activate tendencies to approach the substance, while deficient ability and motivation to self-regulate makes it hard to resist these urges (van Deursen et al., 2015). Cognitive control consists of different components, including inhibition and working memory (WM; Miyake et al., 2000). Deficits in these processes have been suggested to be risk factors for the development and persistence of substance use disorders (SUD; Khurana et al., 2017), but they could also be a consequence of (chronic) substance use (Schulte et al., 2014; de Wit, 2009). New treatments could dampen hypersensitive motivational processes and/or strengthen executive control.

Several studies have aimed to treat SUDs by targeting different processes in the dual process model (review: Wiers et al., 2013). First, WM-training has been used by several studies to strengthen cognitive control processes in various SUDs (for reviews, see Bickel, Moody, & Quisenberry, 2014; and Shipstead, Redick, & Engle, 2012), with some reports of positive effects on WM and reductions in substance use (Houben, Wiers, & Jansen, 2011; Rass et al., 2015), and on other neurocognitive functions related to SUDs (Bickel et al., 2011). Second, although only uncontrolled studies (Amen et al., 2011; Mardikian et al., 2007) and in a small placebo-controlled study (LaRowe et al., 2006), administration of medications like *N*-acetylcysteine (NAC) have shown positive results on cocaine craving and cocaine use cessation, possibly mediated by a normalization of the glutamate homeostasis. Increased glutamate concentrations have been associated with increased impulsivity (Schmaal et al., 2012), indicating that NAC could potentially restore affected cognitive functions. This has been found for several cognitive functions (Skvarc et al., 2017), but whether NAC also has an effect on cognitive control in SUDs remains to be investigated. Although studies exist on the effect of NAC on induced craving (in which WM is used as a distractor; Amen et al., 2011) and the positive effect of NAC on attentional bias (Bolin et al., 2017), in our study we specifically examined the effect of NAC to improve cognitive control in SUDs.

Apart from lab assessments, cocaine use, craving and cognition were also assessed using Ecological Momentary Assessment (EMA). EMA minimizes recall bias, permits more intensive assessment of experiences (Stone et al., 2007), while taking the environmental context into account, and can thus be beneficial in practice oriented clinical trials (Kowalczyk et al., 2015; Moran et al., 2016). EMA can also be useful in validating laboratory assessments. For example, one can identify the conditions under which data from laboratory assessments are associated with EMA data (Linas et al., 2016; Litt, Cooney, & Morse, 2000; Ramirez & Miranda, 2014) and when they are not (Shiffman et al., 2015).

The primary aim of this study was to investigate whether 25-days of treatment with 2400 mg/day NAC combined with WM-training is effective in reducing cocaine use, craving and inhibition in a randomized, double-blind, placebo-controlled trial. Measures of cocaine use, craving and inhibition were assessed during lab-visits before and after treatment. The hypothesis was that NAC would have a beneficial effect on cocaine use, craving and inhibition compared to placebo. In addition, it was hypothesized that this effect would be more pronounced in those who performed more WM-training sessions, as the number of completed training sessions was expected to be related to effects on cognitive control (Klingberg, 2010). A second aim was to examine the correspondence between lab data and EMA data in participants with CUD.

2. Materials and methods

2.1. Participants

Thirty-eight male regular cocaine users with the desire to reduce their cocaine use participated. Only males were selected to increase the homogeneity of the sample of a disorder with a higher prevalence among males (van Laar et al., 2016). Inclusion criteria were: age 18–55 years, using cocaine ≥ 4 times per month, and ≥ 2 criteria for CUD according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) in the past year. A minimum of two DSM-5 criteria was used to ascertain the presence of a cocaine use disorder. Exclusion criteria were: smoking (crack-) cocaine, > 2 DSM-5 criteria for heroin dependence in the past year, MRI-ineligibility, and medication interacting with NAC. Crack-cocaine was an exclusion criterion due to its different addictive liabilities (van Laar et al., 2016). However, since polysubstance use is typical for most cocaine users in the community and in treatment (van Laar et al., 2016), polysubstance use was not used for participant selection (except for heroin use).

Informed consent was attained at the start of lab-visit 1. The Ethical Review Board of the Academic Medical Center (AMC) of the University of Amsterdam approved the study.[1]

2.2. Procedure

Participants entered a 25-day double-blind placebo-controlled intervention and visited the AMC before and after the intervention. During lab-visits, participants filled out questionnaires, provided urine samples and performed the stop signal task. All questionnaires that were used to assess effects of treatment and were therefore repeated at the second lab-visit, were adjusted to specifically refer to the period between lab-visits. Between lab-visits, participants were given 2400 mg/day NAC or placebo and performed online WM-training. In addition, they carried a Personal Digital Assistant (PDA) around as they went about their daily lives, on which they answered questions on cocaine use and craving, and performed Stroop tasks (Fig. 1).

2.3. Assessments

2.3.1. Sample characteristics

A proxy of intellectual functioning (IQ) was assessed using the Dutch version of the National Adult Reading Test (Schmand et al., 1991). Nicotine dependence severity was assessed using the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991). The Alcohol Use Disorder Identification Test (AUDIT; Babor, Kranzler, & Lauerman, 1989) assessed the level of alcohol use and related problems. Motivation to change cocaine use behavior was assessed using the Readiness to Change Questionnaire (RCQ; Rollnick et al., 1992). The presence of cocaine metabolites in urine samples was tested by means of immuno-assays, where a cut-off of 300 μg/L benzoylecgonine indicated a positive test for cocaine.

2.3.2. Clinical assessments

Measures of cocaine use were obtained from interview and Time-Line Follow-Back method (Sobell & Sobell, 1992). The Drug Use Disorder Identification Test (DUDIT; Berman et al., 2003) assessed cocaine use and related problems. Craving was assessed using the Questionnaire for Cocaine Urges (QCU; Ollo et al., 1995), the Obsessive Compulsive

[1] This study is part of a larger intervention study on the effect of NAC and WM training on cocaine cessation, craving, and several neurobiological measures, and is registered with the Netherlands Trial Registry (number: NTR4474). The other assessments will be reported in separate papers. Due to slow enrollment, the design was adapted and the active control condition of the WM-training was dropped. From the 12th participant onward, every participant received working memory training.

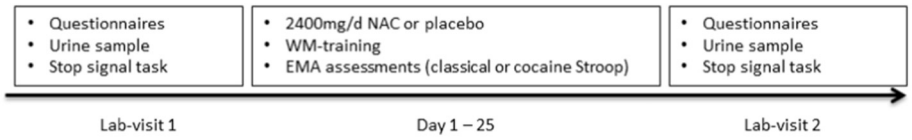


Fig. 1. Graphical timeline of study events.

Drug Use Scale (OCDUS; Franken, Hendriks, & van den Brink, 2002), the desire and intention factor of the Desire for Drug Questionnaire (DDQ; Franken et al., 2002), and a Visual Analogue Scale (VAS) ranging from 1 to 10 on which participants had to indicate their craving at the start of each session.

2.3.3. Stop signal task

Inhibition was assessed with a Stop Signal task (Logan, Cowan, & Davis, 1984). During go trials, participants had to indicate the direction of an airplane (left/right) by pressing corresponding arrow keys. During stop trials, the stop stimulus (white cross superimposed on the airplane) was presented after the go stimulus, and participants were to inhibit their response. The difficulty of stopping was varied by adjusting the interval between the go and stop stimulus (stop signal delay, SSD), resulting in a critical SSD to which participants were able to successfully inhibit their response on approximately 50% of the stop trials. The stop signal reaction time (SSRT, time required to successfully process the stop signal) was computed by subtracting the SSD from the mean go reaction time. Longer SSRTs indicate poorer response inhibition.

2.3.4. EMA assessments

The PDA hardware and software are described in Waters, Marhe, and Franken (2012). Participants had to complete up to three random assessments (RA) per day. The interval between participant-scheduled wake-up and bed-times was divided into three equal "periods", and one RA was scheduled at a random time during each period. RAs could be delayed by five minutes up to four times. Participants also completed self-initiated assessments when experiencing craving or when they missed an RA (make-up assessment).

During each assessment, participants answered questions about cocaine use ("Did you use cocaine since the last assessment?", responses: "Yes"/"No") and craving ("I have a strong urge to use cocaine right now" assessed on 7-point scale, "strongly disagree" to "strongly agree"). Next, participants completed either a classical Stroop (about 50%) or a cocaine Stroop (about 50%). Participants were instructed to identify the color of the word as quickly as possible, while ignoring the meaning of the word. Participants pressed response buttons indicating the color of the words. In the classical Stroop, words were presented in the same color as its meaning (congruent trial, e.g. "RED" in red ink), or in a different color as its meaning (incongruent trial: "RED" in blue ink). Interference is represented by the difference in reaction times when responding to congruent vs. incongruent trials, with a larger difference indicating a greater effect of interference. The cocaine Stroop presented cocaine-related or matched neutral words in the same colors with the same instructions. Interference on the cocaine Stroop task was represented by the difference in reaction time to cocaine-related and neutral words, with a larger difference indicating more difficulty ignoring the meaning of the cocaine-related words. The Stroop task was randomly selected (without replacement) from one of 24 sequences of words, with stimuli presented in random order. Each task began with 24 practice trials of meaningless symbols, followed by either a classic Stroop task composed of 48 trials (24 congruent, 24 incongruent trials) or a cocaine Stroop task composed of 48 trials of cocaine-related words (*cocaine, coke, dealer, high, line, powder, score, snort*; 24 trials) and matched neutral words (*blanket, stove, cabinet, furnace, lamp, railing, oven, attic*; 24 trials; see Waters et al., 2012 for scoring of Stroop tasks).

2.4. Interventions

2.4.1. Pharmacological intervention

Based on a blocked randomization design, participants received either NAC capsules or identical looking placebo capsules for 25 days, and were instructed to take two capsules, twice per day (a total of 4 capsules per day, resulting in 2400 mg/day NAC or placebo). This dosage was based on previous positive results with this dose reported for treatment retention and reduction in cocaine, nicotine, and cannabis use, and was found to be tolerable and safe (Gray et al., 2012; Knackstedt et al., 2009; Mardikian et al., 2007; Schmaal et al., 2011). Blinding was preserved by using identical sequentially numbered containers and by encapsulating the capsules twice to hide the characteristic smell of NAC. Medication adherence was measured by counting the number of capsules returned at lab-visit 2.

2.4.2. WM-training

Participants were instructed to perform daily online WM-training, consisting of 3 tasks: a backward digit span task, a complex span task, and a visuospatial WM-task. During the backward digit span (Klingberg et al., 2002), consecutively presented digits had to be reproduced in reversed order. During the complex span task (Unsworth et al., 2005), participants had to solve a math operation before being presented with a letter. After a sequence of math operations and letters, they had to indicate the presented letters chronologically in a 4 × 3 letter matrix. During the visuospatial WM task, an adapted version of the Corsi Block tapping task with a dual task included, participants were presented with a 4 × 4 grid of blue squares. In one square at a time, two three-digit numbers appeared and participants' task was to indicate the highest number, by pressing the up or down arrow next to the grid. After each sequence, participants needed to indicate the order of blocks in which the numbers appeared.

Tasks were performed in random order and consisted of 30 trials. The backward digit span task and the complex span task always started with a sequence of n = 3, whereas the visuospatial task started with a sequence of n = 2. Tasks were adaptive: difficulty increased after two consecutive correct trials and decreased after two consecutive incorrect trials. After every task, participants were given feedback regarding their performance.

2.5. Statistical analyses

For lab data, treatment effects on cocaine use, craving and inhibition were assessed using hierarchical multiple linear regression (continuous outcomes) or logistic regression (binary outcomes). For continuous lab outcomes, the difference score between lab-visits was entered as the dependent variable. Due to slow enrollment, the design was adapted and the active control training was dropped, resulting in a continuous measure of number of completed WM-training sessions (WM-sessions). For all regression analyses, Group (NAC vs. placebo) and WM-sessions (first block), and Group × WM-sessions interaction (second block) were entered as predictors.

For EMA data, linear mixed models (LMMs; PROC MIXED in SAS for continuous outcomes, PROC GLIMMIX for binary outcomes) were used to examine the effect of Group (NAC vs. Placebo) and WM-sessions (continuous variable) on EMA and TLFB data. LMMs allow for the fact that subjects differ in the number of observations available for analysis, and take into account clustering of data by subjects. For all models using PROC MIXED, a random (subject-specific) intercept and an

autoregressive model of order 1 (AR1) for the residuals within subjects was used. Group (NAC vs. Placebo) and WM-sessions were included as level 2 variables. In all models, day of study, and assessment type (RA vs. participant-initiated) were included as level 1 covariates. The effect of assessment type is not examined in the current paper. For craving assessed on the PDA, lab Visit 1 craving was included as a level 2 covariate. For cocaine use assessed on the PDA or by TLFB, mean cocaine use (grams per day) at the TLFB assessment at Visit 1 was included as a covariate.

The primary results for LMMs were parameter estimates for the main effect of Group and main effect of WM-sessions. In a separate model, the Group × WM-sessions interaction term was added and the parameter estimate reported. In exploratory analyses, to examine if the effect of Group or WM-sessions changed over time, we also tested the Group × Day and WM-sessions × Day interaction terms.

WM-sessions was not significantly associated with any baseline variable.

The NAC and placebo groups differed in age (Supplementary Table 1) and therefore additional analyses were performed with age added as a predictor (Supplementary Table 3).[2]

All tests were 2-tailed with α set to 0.05; p-values < 0.10 are also noted. Effect sizes are presented in Table 2 and Supplementary Table 3 as unstandardized (B) and standardized (beta) regression coefficients for continuous lab measures, and parameter estimates for EMA data.

3. Results

3.1. Participants

Of the 38 participants who entered the study, 14 dropped out before lab-visit 2 (see Fig. 2). Many participants forgot to return their container at the second lab-visit, or failed to inform us on the number of remaining capsules. In addition, as can be seen in the CONSORT chart, the adherence to WM-training was low. Demographic and baseline differences are reported in Supplementary Table 1. There we no between-group differences in the mean number of met DSM-5 cocaine use disorder criteria (NAC: 7.65(1.84), placebo: 7.24(2.63)). Summary statistics are reported in Table 1. The results of the analyses on all outcome variables are reported in Table 2.

3.2. Lab assessments

3.2.1. Cocaine use

Of the 24 men who completed the study only 2 of the 9 subjects in the NAC group (22%) did not use cocaine between the two visits. There was no significant between-group difference in proportion abstainers (22% vs. 0%; $p = 0.13$, Fisher's exact test), number of abstinent days (20.89 days vs. 21.07 days; Mann Whitney $U = 60$, $p = 0.65$) or days until relapse (6.43 days vs. 8.33 days: $\chi^2(1) = 1.216$, $p = 0.27$).

There was a main effect of Group on DUDIT score, with the NAC group showing a greater reduction than the placebo group (-7.85 vs. -1.73). There was also a statistical trend for main effect of Group on proportion of positive urine screens at lab-visit 2, controlling for lab-visit 1 screens ($OR = 0.17$), with the NAC group showing lower proportions of positive urine screens than the placebo group.

3.2.2. Craving

A statistical trend towards a significant Group × WM-sessions interaction effect was found on VAS-craving, indicating more positive effects of WM-sessions for the NAC group ($B = 0.44$ (0.10), $p = 0.005$) than for the placebo group ($B = 0.04$ (0.13), $p = 0.73$).

[2] Results of baseline comparisons between completers and dropouts are displayed in Supplementary Table 2.

3.2.3. Inhibition (stop signal task)

There was a main effect of Group on SSRT score, with the NAC group showing a greater improvement in inhibition than the placebo group (-20.77 vs. -2.59).

3.3. EMA assessments

Of the 38 participants, 26 participants (68.42%) provided EMA data, completing a total of 819 assessments (442 RAs, 377 participant-initiated assessments). The mean number of assessments completed was 31.50 ($SD = 15.03$, $Range = 8–54$). Ten of 17 NAC participants ($M = 33.70$ assessments, $SD = 14.89$) and 16 of 21 Control participants ($M = 30.13$, $SD = 15.43$) provided data.

3.3.1. Cocaine use

There were no significant effects. In an exploratory analysis, we noted that although the Group × Day interaction was not significant, cocaine use was lower in the NAC group than in the placebo group after day 23 (unadjusted for age, $B = -2.06$, $SE = 0.87$, $p = 0.02$; adjusted for age, $B = -2.43$, $SE = 1.01$, $p = 0.02$).

3.3.2. Craving

There were no significant effects.

3.3.3. Inhibition (Stroop)

For the classic Stroop, there was a main effect of Group, with the NAC group showing a greater Stroop effect than the placebo group. For the cocaine Stroop, there were no significant effects.

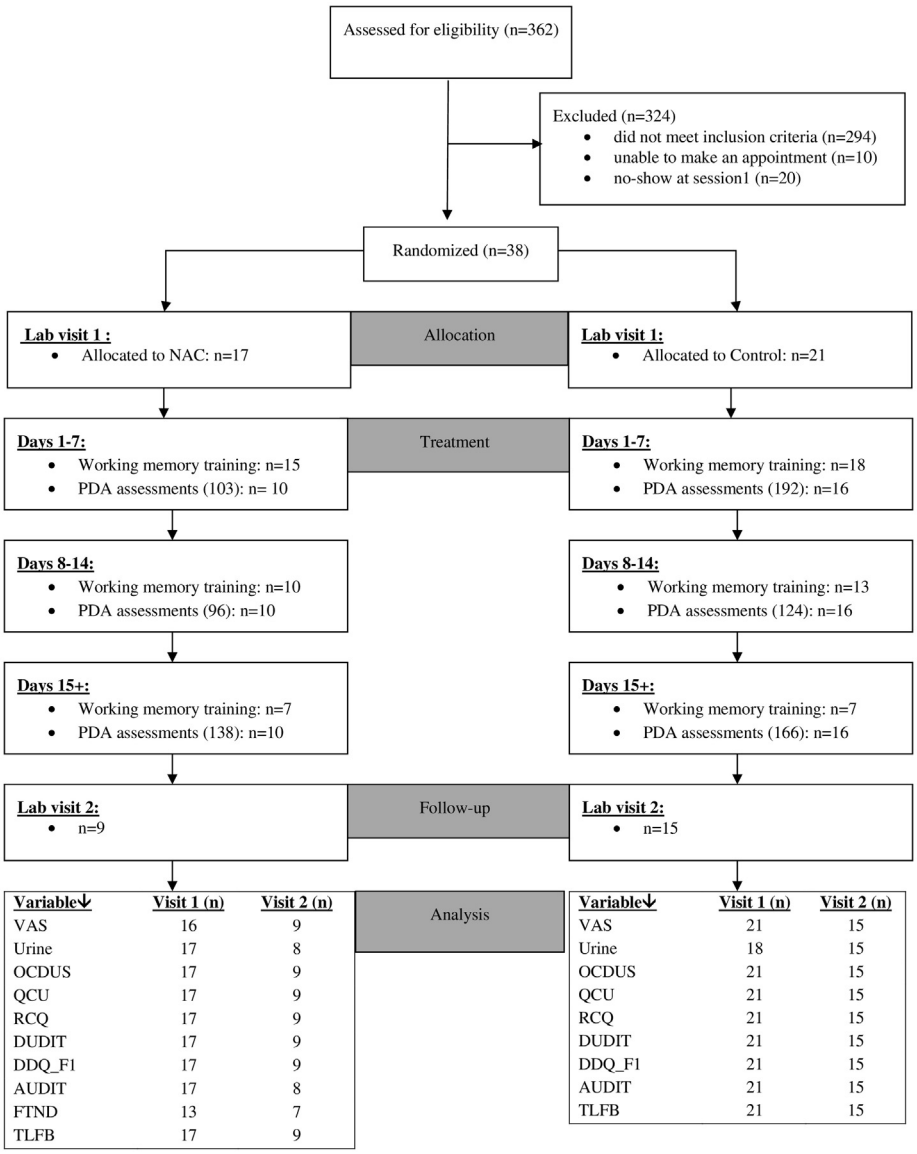
3.4. Correspondence lab - EMA

We examined the correspondence between lab and EMA data. Cocaine use according to the TLFB at baseline was significantly associated with reported use according to EMA ($PE = 2.06$, $SE = 0.65$, $p = 0.002$). Cocaine use according to the TLFB during the study period was also significantly associated with reported use according to EMA ($PE = 3.95$, $SE = 0.83$, $p = 0.0001$). Use reported during EMA was higher in the three days prior to lab-visit 2 in participants with a positive urine test at that visit (Mean Use = 24.74%) than those with a negative urine test (Mean Use = 4.17%; Wilcoxon rank sum = 26.0, $p = 0.01$).

For cocaine craving, VAS-craving at baseline was significantly associated with craving during the first week of EMA ($PE = 0.30$, $SE = 0.08$, $p = 0.0002$). As expected, the association became weaker over time (VAS-craving 1 × Day interaction, $PE = -0.012$, $SE = 0.004$, $p = 0.001$). VAS-craving at lab-visit 2 was significantly associated with craving during the last week of EMA ($PE = 0.34$, $SE = 0.14$, $p = 0.01$), but the association became weaker with data from earlier days (VAS-craving 2 × Day interaction, $PE = 0.009$, $SE = 0.004$, $p = 0.03$).

4. Discussion

This study investigated the effect of NAC and WM-training on cocaine use, craving and inhibition. Overall the results were mixed: an effect of NAC was found on cocaine use and problems (DUDIT), which was supported by a lower percentage of positive urine scores at post-test after NAC than after placebo in the age-adjusted analysis. However, no significant NAC effects were found on craving and self-reported abstinence. Furthermore, an effect of NAC on inhibition was found, with the NAC group showing larger improvements on the stop signal task. However, the NAC group also showed a larger classic Stroop interference effect than the placebo group during EMA, indicating poorer rather than better cognitive control. Compliance with the WM-training was low and subsequently showed very few if any effects. Finally, robust associations were found between craving/use reported in the lab



Variable↓	Visit 1 (n)	Visit 2 (n)
VAS	16	9
Urine	17	8
OCDUS	17	9
QCU	17	9
RCQ	17	9
DUDIT	17	9
DDQ_F1	17	9
AUDIT	17	8
FTND	13	7
TLFB	17	9

Variable↓	Visit 1 (n)	Visit 2 (n)
VAS	21	15
Urine	18	15
OCDUS	21	15
QCU	21	15
RCQ	21	15
DUDIT	21	15
DDQ_F1	21	15
AUDIT	21	15
TLFB	21	15

Fig. 2. CONSORT Flow Diagram. Numbers reflect number of cases (e.g., b2 = data from 2 participants were lost due to participant error). Field week 1 = days 1–7; Field week 2 = days 8–14; Field week 3 = days 15 + .
AUDIT, Alcohol Use Disorder Identification Test; DDQ_F1, the desire and intention factor of the Desire for Drugs Questionnaire; DUDIT, Drug Use Disorder Identification Test; FTND, Fagerström Test for Nicotine Dependence; NAC, *N*-acetylcysteine; OCDUS, Obsessive Compulsive Drug Use Scale; PDA, Personal Digital Assistant; QCU, Questionnaire on Cocaine Urges; RCQ, Readiness to Change Questionnaires; TLFB, Time-Line Follow-Back; VAS, Visual Analogue Scale.

and craving/use reported during EMA.

Our mixed findings regarding NAC effects on cocaine use and craving can be compared to previous research that did find clear significant reductions on these outcomes (Amen et al., 2011; LaRowe et al., 2006; Mardikian et al., 2007). Methodological differences are relevant in this comparison, such as the application of lower doses of NAC in some studies (e.g. LaRowe et al., 2006) or the use of open label or crossover designs (Amen et al., 2011; Mardikian et al., 2007), instead of a randomized double-blind design. Some other studies also did not find significant effects of NAC on cocaine use cessation (LaRowe et al., 2007; LaRowe et al., 2013). We based our dosage of NAC on Schmaal et al. (2012), who found a normalization of increased glutamate concentrations with 2400 mg. Nevertheless, the poor bioavailability of NAC (Olsson et al., 1988) might have contributed to the mixed findings, whereas the high dropout in the current study has decreased power to detect potential effects. LaRowe et al. (2013) also found that NAC medication was associated with a longer period of abstinence and reduced craving in already abstinent participants (LaRowe et al., 2013), which is supported by reviews of McClure et al. (2014) and Nocito Echevarria et al. (2017).

To the best of our knowledge, this is the first study reporting the effect of NAC on cognitive control (improved inhibition) in SUD. However, the results are ambiguous; NAC resulted in improved inhibition compared to placebo as measured with the stop signal task, which is in line with the conclusions of a review by Skvarc et al. (2017), but also yielded an enhanced classical Stroop effect, indicating reduced cognitive control. It could be argued that the classical Stroop is not a valid measure of inhibition, but of attentional processes (Cox, Fadardi, & Pothos, 2006; Johnson, 2004). Moreover, effects on cognitive control were reduced to a non-significant trend when controlling for age (Supplementary Table 3). Future research should investigate the effect on cognitive control more elaborately, preferably with bigger sample sizes, different types and severities of SUDs and a non-using control group, before definitive conclusions can be drawn.

In contrast to previous studies (Bickel et al., 2011), there appeared to be no effect of WM-training on any of the outcomes. One explanation could be the high rate of drop out, possibly resulting in insufficient power to detect an effect of WM-training. 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 (Muraven, 2010). Hence, it is possible that effects could be found in a larger sample after more training, although it should be noted that support for generalization of WM improvement to other tasks has been mixed (Verdejo-Garcia, 2016).

Table 1
Descriptive statistics for the effect of Treatment group.

	Baseline (Lab-visit 1)		Days 1–7 (EMA/TLFB)		Days 8–14 (EMA/TLFB)		Days 15 + (EMA/TLFB)		Follow-up (Lab-visit 2)	
	NAC N = 17	Control N = 21	NAC	Placebo	NAC	Placebo	NAC	Placebo	NAC N = 9	Control N = 15
Proportion PDA use	–	–	13.59%	14.46%	13.54%	13.71%	9.42%	15.66%	–	–
WM-sessions	–	–	3.59 (2.15)	3.57 (2.34)	2.59 (2.71)	2.48 (2.42)	2.18 (3.21)	1.57 (2.79)	–	–
Cocaine use										
Gram/week	2.59 (1.97)	2.47 (2.16)	–	–	–	–	–	–	0.97 (0.87)	1.52 (2.28)
UsingDays/week	3.06 (1.61)	2.11 (1.66)	–	–	–	–	–	–	1.22 (0.89)	1.38 (1.63)
Gram/UsingDay	0.78 (0.33)	1.23 (0.84)	–	–	–	–	–	–	0.75 (0.31)[b]	0.88 (0.48)
Urine screen (% pos)	70.59%	61.11%	–	–	–	–	–	–	37.50%	73.33%
DUDIT	22.18 (5.55)	19.00 (5.24)	–	–	–	–	–	–	14.33 (6.93)	17.27 (5.90)
Grams per day (TLFB)	–	–	0.09 (0.24)	0.16 (0.44)	0.15 (0.34)	0.19 (0.47)	0.16 (0.38)	0.25 (0.51)	–	–
Craving										
VAS (1 − 10)	3.81 (2.79)[a]	4.14 (2.83)	–	–	–	–	–	–	2.89 (1.76)	3.27 (2.84)
OCDUS	16.06 (5.88)	14.00 (5.64)	–	–	–	–	–	–	11.00 (4.24)	12.80 (6.89)
QCU	21.12 (10.92)	23.19 (11.87)	–	–	–	–	–	–	13.89 (3.76)	19.93 (10.32)
DDQ_F1	17.47 (10.51)	20.00 (10.49)	–	–	–	–	–	–	11.22 (3.83)	16.27 (10.93)
PDA craving (1–7)	–	–	2.38 (1.45)	2.64 (1.83)	2.25 (1.46)	2.31 (1.74)	2.31 (1.52)	2.34 (1.82)	–	–
Cognition										
SSRT	237.11 (37.23)	235.59 (39.56)	–	–	–	–	–	–	216.34 (37.84)	233.00 (43.53)
Classic Stroop (ms)	–	–	143.61 (166.74)	138.67 (136.28)	199.64 (178.75)	114.21 (151.26)	154.32 (178.88)	93.48 (102.50)	–	–
Cocaine Stroop (ms)	–	–	39.58 (146.57)	18.38 (93.79)	0.66 (131.23)	− 15.80 (93.80)	3.37 (120.39)	1.52 (89.98)	–	–

Note. Unless stated otherwise, data are Means (SD). For lab visits, n = 17 (NAC, visit 1), n = 9 (NAC, visit 2), n = 21 (Control, visit 1), n = 15 (Control, visit 2). For EMA data, 10 NAC subjects and 16 Control subjects contributed EMA data. Number of assessments: NAC (days 1–7 = 103; days 8–14 = 96; days 15 + = 138); Control (days 1–7 = 192; days 8–14 = 124; days 15 + = 166). Stroop data reflect assessments in which there were fewer than 25% errors. DDQ_F1, the desire and intention factor of the Desire for Drug Questionnaire; DUDIT, Drug Use Disorder Identification Test; DVs, Dependent Variables; IVs, Independent Variables; OCDUS, Obsessive Compulsive Drug Use Scale; PDA, Personal Digital Assistant; QCU, Questionnaire on Cocaine Use; SSRT, Stop Signal Reaction Time; VAS, Visual Analogue Scale; WM-session, number of completed working memory training sessions.

[a] n = 16.

[b] n = 7.

Cocaine use/craving assessed during lab-visits was robustly associated with cocaine use/craving assessed using EMA, cross-validating both types of assessment in this population. However, future research using larger samples can determine the degree of concordance between EMA and biological measures of use in European users. For instance, Linas et al. (2016) reported moderate to good concordance between cocaine use assessed during EMA and cocaine use assessed using sweat patches and self-reports in the laboratory in a larger sample of 109 illicit drug users. Moreover, as noted above, in the current study findings for Group and WM-training effects on use/craving were similar for lab and EMA data. Interestingly, an exploratory analysis revealed that reported cocaine use was lower in the NAC than in the placebo group in the last few days of EMA, while there was also a significant effect indicating an increased proportion of negative urines in the NAC group at lab-visit 2 when controlling for age (Supplementary Table 3). Although tentative, these data illustrate the utility of EMA data for examining treatment effects in fine-grained sequences of data.

More generally, EMA and laboratory studies are complementary methods with different strengths. For example, EMA data have higher ecological validity, permit more fine-grained examination of changes over time, and facilitate examination of within-subject associations. Future studies would benefit from combining laboratory and EMA methods to permit a more comprehensive examination of emotional and behavioral processes in CUD.

Strengths of this study include recruiting a challenging outpatient population for a placebo controlled, double-blind study targeting both motivational and executive processes, and using a multimethod design. This study also has some limitations. First, the substantial drop-out before lab-visit 2 resulted in smaller analytical samples and lower statistical power. However, also in studies with larger sample sizes, attrition may play a large role, especially in eHealth interventions, where attrition levels are typically high (Eysenbach, 2005). Second, there was no Stroop assessment at baseline. Third, only male participants were included. Even though this increases sample homogeneity, no generalizations can be made to female regular cocaine users. Fourth, even though we analyzed potential beneficial effects of WM-training, there was no control condition for the WM-training (it was dropped given slow enrollment). Furthermore, measures of WM improvements are included in a different paper (Schulte et al., 2017) as this was part of a neuroimaging protocol. Fifth, since many participants dropped out, forgot to return their container at the second lab-visit or failed to inform us on the number of remaining capsules otherwise, it remains unclear whether poor medication adherence contributed to the mixed results. In addition, the WM-training effect may be confounded by the repeated performance of the Stroop tasks, which can also be considered a task on cognitive control. Finally, a large number of tests were conducted, with no correction for multiple comparisons. Therefore, the current results should be considered as exploratory and hypothesis-generating pending confirmatory testing in larger samples.

In conclusion, even though the study did not reveal univocal positive effects of NAC and WM-training on cocaine use and craving, the results show beneficial effects of NAC on experienced cocaine use related problems and inhibition assessed in the lab. Future studies should examine the effects of NAC on cognition in more detail in both lab and field settings, preferably using larger groups, including a placebo group, and higher doses of NAC in a randomized control design. Furthermore, the correspondence between lab and EMA data indicates that EMA could be a reliable tool to study various detailed effects of treatment.

Table 2
Results for treatment effects on cocaine use, craving and cognition.

IVs →	Data	Group						WM-sessions						Group × WM-sessions					
DVs ↓		*B*	*SE B*	*β*	*95% CIs*		*p*	*B*	*SE B*	*β*	*95% CIs*		*p*	*B*	*SE B*	*β*	*95% CIs*		*p*
Cocaine use																			
Gram/week	LAB	0.13	0.57	0.04	− 1.21	1.46	0.85	0.01	0.05	0.04	− 0.09	0.10	0.87	0.08	0.10	0.34	− 0.13	0.30	0.42
UsingDays/ week	LAB	− 0.71	0.46	− 0.34	− 1.02	0.88	0.88	− 0.02	0.03	− 0.10	− 0.08	0.05	0.64	0.02	0.07	0.10	− 0.14	0.17	0.83
Gram/ UsingDay	LAB	0.13	0.18	0.16	− 0.25	0.51	0.48	0.01	0.01	0.24	− 0.01	0.04	0.29	0.00	0.03	− 0.004	− 0.07	0.07	0.99
DUDIT	LAB	− 4.82	1.94	− 0.48	− 8.85	− 0.78	**0.02**	− 0.14	0.14	− 0.20	− 0.30	0.28	0.92	− 0.11	0.31	− 0.14	− 0.76	0.53	0.72
Urine screen (%pos)	LAB	− 1.80	1.04		− 3.85	0.25	**0.09**	0.02	0.08		− 0.14	0.19	0.83	− 0.12	0.18		− 0.47	0.24	0.51
Cocaine Use	TLFB	− 0.02	0.07		− 0.16	0.12	0.76	0.01	0.01		− 0.00	0.02	0.19	− 0.00	0.01		− 0.03	0.02	0.78
Cocaine Use	EMA	− 0.12	0.39		− 0.88	0.64	0.76	0.04	0.03		− 0.01	0.10	0.13	− 0.03	0.07		− 0.15	0.10	0.69
Craving																			
VAS	LAB	1.32	1.40	0.20	− 1.61	4.25	0.36	0.15	0.10	0.32	− 0.05	0.35	0.14	0.40	0.20	0.73	− 0.02	0.81	**0.06**
OCDUS	LAB	− 1.09	2.63	− 0.09	− 6.55	4.38	0.68	0.04	0.18	0.04	− 0.34	− 0.42	0.84	0.22	0.42	0.23	− 0.65	1.10	0.60
QCU	LAB	− 1.11	5.45	− 0.04	− 12.44	10.21	0.84	0.21	0.38	0.12	− 0.58	1.00	0.58	1.05	0.84	0.51	− 0.71	2.81	0.23
DDQ_F1	LAB	1.36	4.18	0.07	− 7.32	10.05	0.75	0.32	0.29	0.23	− 0.29	0.92	0.29	0.76	0.65	0.47	− 0.60	2.11	0.26
Craving	EMA	− 0.22	0.39		− 0.98	0.54	0.57	0.04	0.03		− 0.02	0.09	0.20	− 0.02	0.07		− 0.16	0.11	0.72
Cognition																			
SSRT	LAB	− 39.68	17.00	− 0.44	− 75.04	− 4.32	**0.03**	1.73	1.19	0.28	− 75.04	− 4.32	0.16	2.00	2.70	0.270	− 3.62	7.62	0.47
Classic Stroop	EMA	74.01	35.92		3.39	144.64	**0.04**	− 3.54	2.64		− 8.73	1.65	0.18	2.20	1.84		− 1.42	5.82	0.23
Cocaine Stroop	EMA	12.80	10.18		− 7.22	32.82	0.21	0.32	0.76		− 1.18	1.82	0.68	2.33	1.62		− 0.86	5.52	0.15

Note. Data are unstandardized parameter estimates, *B* (*SE*), from multiple regression (LAB) or linear mixed models (EMA, TLFB). For LAB data, standardized *β* is also shown for continuous dependent variables. Group is coded as 0 = Placebo, 1 = NAC. WM-sessions is a continuous variable. For LAB data, dependent variables are difference scores (see text). DDQ_F1, the desire and intention factor of the Desire for Drug Questionnaire; DUDIT, Drug Use Disorder Identification Test; DVs, Dependent Variables; IVs, Independent Variables; OCDUS, Obsessive Compulsive Drug Use Scale; QCU, Questionnaire on Cocaine Use; SSRT, Stop Signal Reaction Time; VAS, Visual Analogue Scale; WM-session, number of completed working memory training sessions. All statistical tests reaching trend level significance ($p < 0.1$) and lower are bold.

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Author contribution

Mieke H.J. Schulte, Reinout W. Wiers, Anna E. Goudriaan, and Wim van den Brink designed the study and wrote the protocol. Denise S. van Deursen and Malte Friese designed the visuospatial working memory task. Mieke H.J. Schulte and Wouter J. Boendermaker designed the backward digit span and the complex span task, and Wouter J. Boendermaker programmed the working memory training. Emily Brede and Andrew J. Waters contributed to the design and implementation of EMA assessments. Mieke H.J. Schulte acquired the data. Mieke H.J. Schulte and Andrew J. Waters undertook statistical analyses and wrote the first version of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

No potential conflict of interest.

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