



# The effect of N-acetylcysteine and working memory training on neural mechanisms of working memory and cue reactivity in regular cocaine users

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## ABSTRACT

The current study investigated the combined effects of N-acetylcysteine and working memory (WM) training on behavioral and neural mechanisms of cue reactivity and WM in cocaine users in a randomized, double-blind design. Twenty-four of 38 cocaine-using men completed a 25-day treatment with either 2400 mg/day NAC or placebo. Both groups performed WM-training. During pre- and post-test lab-visits, neural mechanisms of cue reactivity and WM, and cue-induced craving and WM performance were assessed. Additionally, exploratory whole brain analyses were performed. Overall, the hypotheses were not confirmed, possibly due to small sample size, low WM-training adherence and/or ongoing substance use.

## 1. Introduction

The need for effective treatment of cocaine use disorder (CUD) is highlighted by high relapse rates (EMCDDA, 2016). Dual Process Models of addiction state that the development and persistence of substance use disorders results from the imbalance between hyper-reactive motivational processes and deficient reflective processes (Bechara, 2005; Gladwin et al., 2011). In addition, several neurobiological mechanisms underlying these aberrant cognitive processes have been associated with CUD (Stewart, 2008). For instance, cue reactivity and subjective craving have been associated with ongoing substance use and relapse (e.g. Carter and Tiffany, 1999). Distinct areas of the striatum and the anterior cingulate cortex (ACC) have been associated with aspects of cue reactivity (Bush et al., 2000; Everitt and Robbins, 2005; Kühn and Gallinat, 2011; Sjoerds et al., 2014; Vollstädt-Klein et al., 2010). In addition, working memory (WM) deficits have been associated with different stages of substance dependence (de Wit, 2009; Finn et al., 1999; Khurana et al., 2017; Schulte et al., 2014). The dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC) and the dorsal ACC have been associated with WM performance (Owen et al., 2005). Effective treatment for cocaine use disorder should dampen hypersensitive cue-induced motivational processes

and/or strengthen executive control.

N-acetylcysteine (NAC; Amen et al., 2011; LaRowe et al., 2006, 2007; Mardikian et al., 2007), has been associated with initial positive clinical effects and with beneficial effects on cognitive control (Skvarc et al., 2017). However, effects on cognition in CUD have been found to be ambiguous (Schulte et al., 2018). In addition, positive effects of WM-training have been reported (Bickel et al., 2011; Houben et al., 2011; Rass et al., 2015) but negative findings have also been reported (Wanmaker et al., 2017).

The aim of the current study was to investigate the combined effects of NAC and WM-training on neural mechanisms of cue reactivity and WM, and associated behavioral effects. Compared to placebo, NAC was expected to have beneficial effects on cue reactivity in the dACC, rostral ACC (rACC), and the dorsal and ventral striatum (DS and VS, resp.), and to decrease cue-induced craving. In addition, NAC was expected to increase activity in the dACC, DLPFC and VLPFC. These effects were expected to be more pronounced in subjects who completed more WM-training sessions.

## 2. Methods

The results of the current paper were part of a larger study (see

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Schulte et al., 2018 and supplementary methods).<sup>1</sup> 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  $\geq 4$  times per month, DSM-IV  $\geq 2$  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,  $\geq 2$  DSM-IV criteria for heroin dependence in the previous year, MRI-ineligibility, and medications interacting with NAC. MRI and psychological testing was 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. MRI-assessment consisted of a cue reactivity task and a WM-task (n-back) during fMRI. The cue reactivity task was adopted from Cousijn et al. (2013). Cue-induced craving was calculated by subtracting pre-cue reactivity craving from the post-cue reactivity craving, where positive values indicated increased craving (cue-induced craving). The n-back task was adapted from Cousijn et al. (2014), and consisted of blocks with different memory load levels (n); 0-back, 1-back, 2-back, and 3-back. For each memory load level, behavioral performance was assessed using mean reaction times (RTs) of correct responses and accuracy.

For the 25-day intervention, participants were randomly allocated to either NAC or placebo. Simultaneously, participants performed on-line 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 3.0T MRI scanner (Philips Healthcare, Best, the Netherlands) at the Academic Medical Center in Amsterdam. For a detailed description of imaging acquisition and preprocessing, 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 all regression analyses.

### 3. Results

Of the 38 included participants, 24 (63%) completed the study.<sup>2</sup> Results of analyses on treatment effects will be provided here, a comprehensive display can be found as supplementary material. There was no significant treatment effect on cue-induced craving (Table 1). There were no treatment effects on cue reactivity in the dACC, vACC, VS, or DS (see Table 1). With respect to WM performance, there were no significant treatment effects on RT or accuracy (see Table 1). There was no treatment effect on dACC or DLPFC activity on any working memory load. In the VLPFC, there was a main effect of group during 1-back vs. 0-back, but no main effect of WM-sessions and no group by WM-sessions interaction effect. During the 2-back vs. 0-back and 3-back vs. 0-back, there were no main effects of group, no main effects of WM-sessions, and no group by WM-sessions interaction effect (see Table 1).

<sup>1</sup> 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 and cognitive functions is reported in Schulte et al. (2018). Other assessments will be reported in separate papers. Due to slow enrollment, the design was adapted and the placebo WM training was dropped.

<sup>2</sup> When comparing dropouts to completers at baseline, there was a difference in years of frequent cocaine use (dropouts < completers,  $p = 0.02$ ) and cue reactivity in the dACC (dropouts < completers,  $p = 0.007$ ).

### 4. Discussion

With the exception of the effect of NAC on VLPFC activity during 1-back vs. 0-back, this study did not find an effect of NAC and/or WM-training on neural correlates of cue reactivity and WM, and associated behavior. The absence of an effect on cue reactivity in the DS and VS could be explained by the absence of baseline cue reactivity. For the dACC and rACC, the absence could be explained by habituation to the used stimuli or by insufficient power due to considerable dropout or ongoing substance use (see Schulte et al., 2018 for clinical outcomes). Although positive effects have been reported (e.g. Amen et al., 2011), this is not the first study to report no effects of NAC on craving (LaRowe et al., 2013). However, LaRowe et al. (2013) did report greater reductions in craving in abstinent participants, which is supported by reviews by McClure et al. (2014) and Nocito Echevarria et al. (2017). With respect to neural and behavioral correlates of WM, there was only a small effect of NAC in the VLPFC but not in other regions of interest. This differential effect could be explained by the fact that cognitive control encompasses several specific cognitive functions (Miyake et al., 2000), which may be represented in different prefrontal regions.

Although positive effects of WM-training have been reported (Houben et al., 2011; Rass et al., 2015), our results were in line with the largest study so far (Wanmaker et al., 2017). The relatively high dropout rate could have resulted in insufficient power to detect effects of WM-training. In addition, due to the absence of a baseline control group, we were not able to test for deviating baseline WM-performance. Future research should improve WM-training adherence, for example by increasing extrinsic motivation using game elements (Boendermaker et al., 2015) or contingency management (Petry, 2000), or by increasing intrinsic motivation using motivational interviewing (Miller and Rollnick, 2012).

This study has both strengths and limitations. Strengths of this study include the recruitment of a challenging outpatient population of regular cocaine users, a placebo group in a double-blind design, targeting both motivational and executive processes, and using a multimethod design. Limitations include substantial dropout before the second lab-visit, resulting in lower statistical power. In addition, although none of the participants reported adverse events, the dropout rate was higher in the NAC group compared to the placebo group. Second, it remains unclear whether any of the baseline measures were affected by cocaine use, since there was no non-using control group to compare baseline measures with. In addition, the groups showed significant baseline differences in age and duration of cocaine use, which could have contributed to the absence of treatment effects. Third, although including only males increases sample homogeneity, no generalizations can be made to female drug users. Fourth, even though potential beneficial effects of WM-training were investigated, there was no control condition for the WM-training (it was dropped given slow enrollment) and the number of WM-sessions was not randomly divided between the NAC and the control group.

In conclusion, this study did not find the expected effect of NAC and WM-training on cue-induced craving, WM performance and neural cue reactivity. There was an indication of an effect of NAC on WM-associated activity in the VLPFC. Possible explanations are reduced power due to substantial treatment dropout and low WM-training adherence. Future research should aim to further elucidate the efficacy of NAC and WM-training in SUD treatment, for instance their role as add-on to treatment as usual, and to improve treatment adherence in paradigms including control conditions. Even though NAC and WM-training seem promising treatment strategies, their clinical applications in various disorders need to be further elucidated.

### Contributors

MHJS, RWW, AEG, and WvdB designed the study and wrote the protocol. MHJS and WJB designed working memory tasks, and WJB

**Table 1**  
Results for treatment effects on craving, cue reactivity, *n*-back performance, and WM-associated brain activity.

IVs → DVs ↓	Group					WM-session					Group x WM-session							
	<i>B</i>	<i>SE B</i>	$\beta$	95% CI	<i>p</i>	<i>B</i>	<i>SE B</i>	$\beta$	95% CI	<i>p</i>	<i>B</i>	<i>SE B</i>	$\beta$	95% CI	<i>p</i>			
Cue induced craving	-0.90	1.28	-0.21	-3.60	1.79	0.49	-0.11	0.07	-0.35	-0.26	0.04	0.14	-0.02	0.16	-0.05	-0.35	0.31	0.92
<b>Cue reactivity</b>																		
dACC	-1.32	0.91	-0.48	-3.24	0.61	0.17	-0.03	0.04	-0.15	-0.12	0.06	0.51	-0.12	0.09	-0.57	-0.31	0.06	0.18
vACC	-0.15	1.33	-0.04	-2.96	2.66	0.91	-0.04	0.06	-0.16	-0.17	0.09	0.52	-0.16	0.13	-0.54	-0.43	0.11	0.25
DS	1.38	1.54	0.31	-1.87	4.63	0.38	-0.09	0.07	-0.28	-0.24	0.06	0.24	-0.17	0.15	-0.47	-0.49	0.15	0.28
VS	-0.88	0.74	-0.40	-2.45	0.69	0.25	-0.04	0.04	-0.23	-0.11	0.04	0.33	-0.10	0.07	-0.59	-0.25	0.05	0.17
<b>N-back RT</b>																		
0-back	-88.35	66.58		-228.81	52.12	0.20	-4.37	2.83		-10.34	1.59	0.14	5.15	5.42		-6.28	16.59	0.36
1-back	24.04	73.08		-130.13	178.22	0.75	-3.49	2.10		-10.04	3.06	0.28	3.00	5.95		-9.55	15.56	0.62
2-back	75.40	94.79		-124.59	275.38	0.44	-0.88	4.03		-9.38	7.62	0.83	3.25	7.72		-13.04	19.53	0.68
3-back	30.82	108.65		-198.41	260.05	0.28	-2.57	4.62		-12.31	7.17	0.59	6.14	8.85		-12.52	24.81	0.50
<b>N-back ACC</b>																		
0-back	0.03	0.16		-0.31	0.36	0.87	-0.11	0.01		-0.03	0.003	0.13	0.01	0.01		-0.02	0.03	0.73
1-back	0.08	.14		-0.21	0.37	0.56	-0.004	0.01		-0.02	0.01	0.55	0.004	0.01		-0.02	0.03	0.72
2-back	0.12	0.21		-0.32	0.56	0.57	-0.003	0.01		-0.02	0.02	0.71	-0.003	0.02		-0.04	0.03	0.87
3-back	0.19	0.20		-0.23	0.61	0.35	-0.002	0.01		-0.02	0.02	0.84	-0.01	0.02		-0.04	0.03	0.77
<b>N-back fMRI</b>																		
<b>1vs0-back</b>																		
dACC	0.01	0.25		-0.52	0.54	0.97	-0.006	0.01		-0.03	0.02	0.57	-0.003	0.02		-0.05	0.04	0.90
DLPFC	0.02	0.11		-0.22	0.26	0.88	1.36E-5	0.005		-0.01	0.01	0.99	<0.001	0.009		-0.02	0.02	0.96
VLPFC	-0.97	0.28		-1.56	-0.38	0.003	-0.02	0.01		-0.04	0.01	0.14	0.06	0.02		-0.01	0.11	0.017
<b>2vs0-back</b>																		
dACC	0.21	0.25		-0.32	0.74	0.41	0.002	0.01		-0.02	0.02	0.89	-0.01	0.02		-0.56	0.03	0.54
DLPFC	-0.15	0.28		-0.74	0.43	0.59	-0.006	0.01		-0.03	0.02	0.62	0.016	0.02		-0.03	0.06	0.51
VLPFC	-0.66	0.29		-1.27	-0.05	0.04	-0.009	0.01		-0.04	0.02	0.47	0.04	0.02		-0.01	0.09	0.13
<b>3vs0-back</b>																		
dACC	0.50	0.41		-0.37	1.36	0.25	0.01	0.02		-0.02	0.05	0.46	-0.05	0.03		-0.12	0.02	0.18
DLPFC	-0.17	0.19		-0.57	0.24	0.40	-0.005	0.008		-0.02	0.01	0.59	0.007	0.02		-0.03	0.04	0.66
VLPFC	-0.59	0.28		-1.18	0.005	0.05	-0.003	0.01		-0.03	0.02	0.79	0.04	0.02		-0.13	0.09	0.14

Note. Data are unstandardized parameter estimates, *B* (*SE*), from multivariate regression analyses. For hierarchical multiple linear regression analyses, standardized  $\beta$  is also shown. Group is coded as 0 = Placebo, 1 = NAC. WM-sessions is a continuous variable. Dependent variables are difference scores. ACC, accuracy; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; DS, dorsal striatum; RT, reaction times; vACC, ventral anterior cingulate cortex; VLPFC, ventrolateral prefrontal cortex; VS, ventral striatum.

programmed the working memory training. MHJS acquired the data. MHJS and AMK undertook statistical analyses. MHJS wrote the first version of the manuscript. All authors contributed to and have approved the final manuscript.

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## Conflicts of interest

There are no conflicts of interest.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2019.03.011](https://doi.org/10.1016/j.psychres.2019.03.011).

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