



*Take Control: Developing and Testing Novel Treatments of Substance
Dependence by Targeting Underlying Neurocognitive Processes*

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English Summary



Developing and Testing Novel Treatments of Substance Dependence
by Targeting Underlying Neurocognitive Processes

Substance Use Disorders (SUDs), commonly referred to as addictions, come with major public health problems, which have an immense societal and economic impact. However, SUD treatments are only moderately effective as indicated by high relapse rates. Dual Process Models of Addiction state that SUDs are the result of two distinct processes. On the one hand, there are hyper-reactive motivational ('impulsive') processes, which result in an automatically triggered tendency to approach or use a substance (e.g. cue-reactivity and craving). On the other hand, there are suboptimal regulatory control processes, such as inhibition and working memory (WM), which result in behavioral choices based on explicit choices. The imbalance between motivational and regulatory processes is associated with neural adaptations with increased neural activity in brain areas and circuits associated with motivational processes and decreased neural activity in brain areas and circuits associated with cognitive control processes. In addition, hyper-reactive motivational processes are associated with an imbalance in glutamate concentrations in the dorsal anterior cingulate cortex (dACC). In this dissertation, these neural adaptations were used as targets for experimental treatments of smoking and cocaine use cessation, i.e. dampening of hyper-reactive motivational processes and improving cognitive control.

New pharmaceutical compounds, including N-acetylcysteine (NAC), have been proposed to normalize the glutamate imbalance in the dACC. This results in a normalization of motivational processes, and potentially reduces cue-induced craving. In addition, novel training paradigms have been developed to improve cognitive control functions, including working memory training (WM-training). However, very little is known about the neural bases of the changes involved in these new treatments and their relationship with clinical outcomes. Finally, although clinical and laboratory assessments will always be necessary and unavoidable in certain situations (e.g. assessing neuroimaging measures), ambulatory assessments such as ecological momentary assessment (EMA) could be a useful addition to acquire fine-grained and contextualized information on treatment effects. The correspondence between laboratory data and EMA data for regular cocaine using participants is further elucidated in this dissertation.

First, some of the underlying mechanisms of substance dependence were explored. In the review of neurocognitive recovery after abstinence (chapter 2), most functions appeared to recover when substance use is discontinued for a long period. Partial or no recovery could represent either pre-existing risk factors for the development of SUDs or sustained neurocognitive impairments and associated changes in brain structures and/or functions due to long-term substance use. In chapter 3 and chapter 4 differences in glutamate and gamma-aminobutyric acid (GABA) between substance users and non-users were investigated. There was a difference (increase) in glutamate, but not GABA, concentrations in the dACC between substance users (smokers and smoking polysubstance users) and non-users. There were no differences in dACC glutamate or GABA concentrations between the different substance using groups. Although there were also differences in impulsivity between groups (smoking polysubstance users highest, non-users lowest), impulsivity was not correlated with glutamate or GABA concentrations in the dACC. Furthermore, NAC did not have an effect on dACC glutamate concentrations in smokers in chapter 4. Given that both the NAC and placebo group showed a decrease in smoking and craving, no firm conclusions could be drawn about the effect of NAC on smoking cessation and craving. In chapter 5 and chapter 6, no effect was found of NAC and/or WM-training on cocaine use cessation, craving, or neural cue reactivity, but NAC was associated with a decrease in objective measures of cocaine use (urinalysis) and a decrease in cocaine use related problems. NAC also resulted in a decrease in WM associated activity

in the VLPFC. The effects of NAC on cognition were ambiguous, with findings of increased, decreased and unaffected performance on cognitive tasks. There was, however, an indication of an effect of WM-training on WM associated activity in the VLPFC in the NAC group. Finally, there was correspondence between the lab assessments and the EMA assessments with respect to measures of substance use and craving, but not with respect to cognitive measures, which indicates that EMA can be used as a measure for daily life assessment of craving.

In conclusion, this dissertation provided an overview of recovery of neurocognitive functions and associated brain structures and functions after a substantial period of substance use cessation. More specifically, the association of glutamate and GABA concentrations with (various aspects of) substance use was further investigated. However, little evidence was found for clinical, cognitive or neurobiological effects of NAC and/or WM-training. The main limitations were small sample sizes due to substantial dropout and the lack of a non-using control group. Future studies should aim to increase sample sizes by increasing intrinsic and/or extrinsic motivation of participants to complete the study. In addition, a non-using control group should be included to establish the presence of baseline differences with unaffected neurocognitive functions and associated neurobiological mechanisms. Also, several suggestions were made for future studies and clinical purposes to increase the efficacy of NAC and WM-training. These suggestions primarily concerned the timing of these interventions in treatment. Clearly, more research is needed to investigate underlying mechanisms of SUDs and the efficacy of NAC and WM-training for the treatment of SUDs.