Take control

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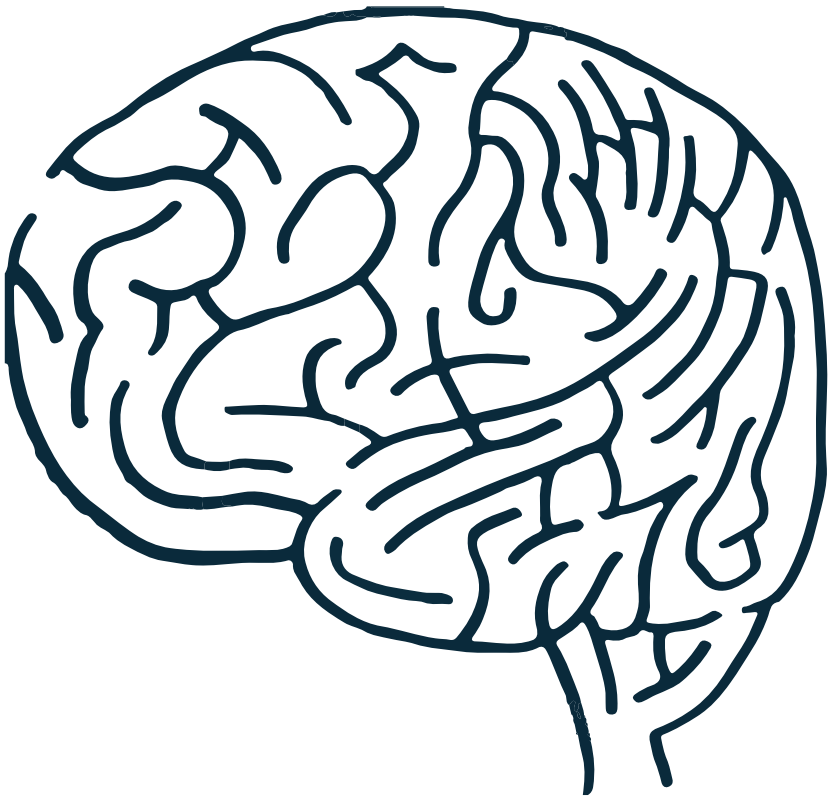
Chapter 1

General introduction and outline of the thesis



GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Substance use disorders (SUDs) have been proposed to be a chronic relapsing disorder, characterized by compulsive seeking and consumption of a substance, and a diminished ability to control this behavior despite negative consequences. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classifies SUDs on a severity scale based on the number of criteria: mild 2-3/11 criteria, moderate 4-5/11 criteria, and severe ≥ 6/11 criteria.

As reported in the 2016 World Drug Report (UNODC, 2016), SUDs come with major public health problems, which have an immense societal and economic impact. Globally, 29 million people suffer from SUDs, and it is estimated that there were 207.400 substance-related deaths in 2014 in people aged 15-64, a number that has been stable over the years. The development and implementation of effective treatments could lead to a substantial decrease in the number of people suffering from SUDs and thereby decreasing the number of SUD-related deaths (e.g. Rehm, Shield, Gmel, Rehm, & Frick, 2013).

The concept of addiction has changed substantially over the years, and it was only in the late 1990s that it was proposed to be a brain disease (e.g. Leshner, 1997), a proposal that has been criticized by part of the scientific community (e.g. Heyman, 2009; Lewis, 2017) The recognition of the role of SUD-related neurobiological abnormalities is mirrored by an increasing body of research employing neuroimaging techniques in SUDs. This has allowed researchers to gain a better understanding of brain processes implicated in SUDs, from the level of neurotransmitters to the level of activation of brain regions and neural networks. The changing concept of addiction is also reflected in the description of the disorder in the latest edition of the DSM: DSM-5. In previous editions of the DSM (DSM-III until DSM-IV) the importance of biological or genetic models were included, in DSM-5 the description of SUD is expanded with the inclusion of the involvement of the brain reward system as a central component to the initiation and maintenance of addiction (Nathan, Conrad, & Skinstad, 2016), and the inclusion of behavioral addiction (e.g. gambling disorder; Petry, Blanco, Stinchfield, & Volberg, 2013).

However, SUD treatments are only moderately effective, as indicated by substantial relapse rates. For example, 20% of the Dutch population are regular smokers, of whom 65% tried to quit at least once (Trimbos, 2014). Furthermore, over 50% of Europeans entering treatment for cocaine use had received treatment before (EMCDDA, 2016). SUDs are associated with abnormal motivational and cognitive processes and changes in brain function and structure. Currently available evidence-based treatments for SUDs focus on conscious psychological processes (e.g. cognitive behavior therapy: CBT) or neurotransmitter abnormalities (e.g. naltrexone in the treatment of alcohol use disorder). In addition, treatments based on affected implicit

processes such as cognitive bias modification (CBM) have also become available, such as the modification of attentional biases, automatic memory associations and approach biases. Targeting underlying, implicit and explicit motivational and cognitive processes and brain functions provides novel avenues for the development of new treatment strategies and better treatment results.

The aim of this chapter is to provide a theoretical background on neurocognitive processes affected in SUD that serves as a foundation for the development of treatment strategies. First, an overview is provided on cognitive functions and associated brain activity in SUDs, based on the Dual Process Model of addiction. Next, changes in neurotransmitter concentrations associated with deviating neurocognitive functioning underlying SUD will be discussed. Thereafter, two novel approaches to treat SUD will be discussed, which can be viewed as targeting either side of the Dual Process Model, i.e. the administration of N-acetylcysteine and working memory training. Finally, ecological momentary assessment (EMA) is discussed as a useful tool for assessments during clinical trials.

COGNITIVE FUNCTIONS AND ASSOCIATED BRAIN ACTIVITY IN SUDS

Dual Process Models of addiction state that an imbalance between two qualitatively distinct types of processes are involved in the development and persistence of SUDs, on the one hand hyper-reactive motivational processes and on the other hand deficient reflective processes (Bechara, 2005; Gladwin et al., 2011; Wiers et al., 2007). Impulsive motivational processes include automatic appraisals of stimuli in terms of motivational or emotional significance and automatic associations between stimuli and responses (Bechara et al., 2006; Wiers et al., 2008). These impulsive processes are fast and rely on learning mechanisms that are influenced by repetitive experiences, and elicit behavior based on associative (unconscious) links rather than more sophisticated reasoning (Strack & Deutsch, 2004). Reflective processes comprise cognitive control processes such as inhibition and working memory (WM) and behavior aimed at long-term goals. Reflective processes are typically slow and allow a high degree of behavioral and cognitive flexibility, and lead to behavioral decisions based on explicit (conscious) knowledge (Strack & Deutsch, 2004). Sensitized motivational processes activate tendencies to approach the substance, while deficient ability (diminished cognitive control) and motivation to self-regulate makes it hard to resist these urges (van Deursen et al., 2015).

The disrupted balance between motivational and regulatory processes is also reflected by increased neural activity in brain areas associated with motivational processes and decreased activity in brain areas associated with cognitive control, respectively. For instance, increased neural responses to substance related cues (cue

reactivity) are thought to reflect motivational processes related to substance use and relapse (Carter & Tiffany, 1999) and have been reported for several brain regions associated with addiction. Brain regions predominantly associated with cue reactivity across addictive substances include the anterior cingulate cortex (ACC) and ventral striatum (Kühn & Gallinat, 2011; Schacht, Anton, & Myrick, 2013). The ACC can be differentiated into functionally distinct areas, such as the dorsal and rostral part. The dorsal part (dACC) is associated with cognitive control functions such as inhibition, whereas the rostral part (rACC) is associated with the salience of emotional and motivational information (Bush, Luu, & Posner, 2000). The ventral striatum, together with the dorsal striatum, is involved in the shift from initial substance use to compulsive substance use and dependence (Everitt & Robbins, 2005; Sjoerds, van den Brink, Beekman, Penninx, & Veltman, 2014; Vollstädt-Klein et al., 2010).

Areas in the prefrontal cortex (PFC) have often been associated with cognitive control processes. The role of prefrontal cortical areas in addiction can be explained by the Impaired Response Inhibition and Salience Attribution model (I-RISA; Goldstein & Volkow, 2002) as dependent of the type of behavior related to SUD, i.e. activated during behaviors related to the (desire to) use of a substance and deactivated during withdrawal. These regions also modulate the salience of a reinforcer and expectation, and the ability to control and inhibit automatic prepotent responses. In addition, neuroimaging studies have revealed that hypoactivation of the dorsolateral PFC (DLPFC) is associated with worse performance of behavioral tasks tapping into motoric and cognitive control processes, and associated with more substance use and a higher probability of relapse (Goldstein & Volkow, 2011). In addition, in prefrontal areas, decreased neural activity in response to substance related cues is present in SUD groups compared to controls (Goldstein & Volkow, 2011), underscoring changes in brain activity associated with the disbalance in motivational and reflective processes.

DEVIATING NEUROTRANSMITTERS ASSOCIATED TO SUDS

Dopamine, and its role in the brain reward system, has been the major neurotransmitter associated with addiction (e.g. Volkow, Wang, Fowler, & Tomasi, 2012, but see Nutt, Lingford-Hughes, Erritzoe, & Stokes, 2015 for a critical appraisal on the role of dopamine-mediated reward in addiction). The use of most substances is associated with an increase of dopamine in brain regions associated with positive reinforcement and reward, such as the nucleus accumbens (NAcc) in the ventral striatum. However, chronic substance use – in particular stimulants – leads to disrupted dopamine functioning by decreasing (i.e. blunting) dopamine production and downregulating dopamine receptors. This disrupted functioning is thought to contribute to a decreased ability to experience pleasure in normally pleasurable

activities (anhedonia) and insensitivity to drug rewards, leading to enhanced craving and loss of control over drug intake (Volkow, Wang, Fowler, Tomasi, & Telang, 2011).

More recently the role of glutamatergic and GABA-ergic mechanisms in SUDs has become more prominent (e.g. Li, Semenova, D'Souza, Stoker, & Markou, 2013). Glutamate is the main excitatory neurotransmitter and is stored in glia cells as glutamine (Gln), which is essential for normal brain functioning and to prevent excitotoxicity (Ramadan, Lin, & Stanwell, 2013). Gln is taken up into neurons to be used in the synthesis of glutamate or GABA (the main inhibitory neurotransmitter). In turn, glutamate and GABA released from neurons are taken up into glia cells, and converted to Gln (Bak, Schousboe, & Waagepetersen, 2006; Hertz & Zielke, 2004). Glutamate and GABA play a key role in the regulation of the excitation/inhibition balance in the brain and in personality traits associated with addiction, such as impulsivity (Schmaal, Goudriaan, van der Meer, van den Brink, & Veltman, 2012; Silveri et al., 2014).

Animal studies emphasize the importance of glutamatergic and GABA-ergic modulation of the NAcc in addiction (Kalivas, 2009; Scofield & Kalivas, 2014; Vanderschuren & Kalivas, 2000). Repeated administration of cocaine has been found to decrease extracellular glutamate in the NAcc (Baker et al., 2003) and putamen (Yin & Knowlton, 2006), and results in reduced firing rates of glutamatergic projections from the medial prefrontal cortex to the NAcc (Sun & Rebec, 2006). Glutamate also seems to be important in the continuation of and relapse into substance use, by mediating cocaine-induced drug seeking behavior (Cornish & Kalivas, 2000; McFarland, Lapish, & Kalivas, 2003). In addition, the GABA system has been associated with abstinence and withdrawal. Several neuroadaptations leading to deviations in GABA have been associated with abstinence and withdrawal, such as a decrease in the GABA-synthesizing enzyme glutamic acid decarboxylase (Sherif, Tawati, Ahmed, & Sharif, 1997), an upregulation of benzodiazepine-sensitive $GABA_A$ receptors (Staley et al., 2005) and a down-regulation of the expression of gephyrin (an important regulator of GABA-ergic neurotransmisston) at postsynaptic density sites of the medial PFC (Yang et al., 2017).

Several human Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) studies in SUD patients have investigated the existence and direction of glutamate and GABA alterations in various frontal brain regions, including the dACC and rACC, but the results are inconsistent, i.e. both increased levels of glutamate (Bauer et al., 2013; Lee et al., 2007; Mon, Durazzo, & Meyerhoff, 2012; Schmaal, Veltman, Nederveen, van den Brink, & Goudriaan, 2012), decreased (Durazzo et al., 2016; Ende et al., 2013; Hermann et al., 2012; Mashhoon et al., 2011; Prescot, Renshaw, & Yurgelun-Todd, 2013; Yücel et al., 2007) and normal levels of glutamate have been found in substance

use disorder patients (Chang, Ernst, Strickland, & Mehringer, 1999; Gallinat & Schubert, 2007). Similarly, the results with regard to GABA concentrations are also inconsistent, i.e. both decreased (Abé et al., 2013; Prescot et al., 2013; Silveri et al., 2014) and normal levels of GABA have been found in SUD patients (Mon et al., 2012). These inconsistencies are independent on voxel placement, type of substance or other substance use characteristics such as withdrawal.

NEW TREATMENT METHODS THAT TARGET UNDERLYING MECHANISMS IN SUDs

Several treatment strategies have been suggested in recent years, such as pharmacological interventions aimed at targeting aberrant glutamate concentrations (e.g. acamprosate, modafinil and N-acetylcysteine (Reissner & Kalivas, 2010)), and cognitive interventions aimed at targeting implicit or explicit cognitive processes including CBM and WM-training (Wiers, Gladwin, Hofmann, Salemink, & Ridderinkhof, 2013). The following two paragraphs will focus on the body of evidence for N-acetylcysteine and working memory training as possible treatment strategies.

N-ACETYLCYSTEINE

Opportunities to treat addiction arise from pharmacotherapies that target aberrant glutamate concentrations (e.g. acamprosate, topiramate). A drug that may offer new possibilities for the treatment of substance dependence by targeting glutamate is N-acetylcysteine (NAC), a drug that is commonly sold as an over-the-counter mucolytic agent in cough medicine, but is also used in the acute treatment of acetaminophen overdose. NAC is a cystine prodrug that activates the cystine/glutamate antiporter [or x(c)] system to synthesize glutathione by supplying additional cystine. The x(c)-system also functions as an antiporter protein, transporting intracellular glutamate from glial cells into the extracellular environment and extracellular cystine into glial cells, resulting in a normalization of extracellular glutamate levels (Baker, Xi, Shen, Swanson, & Kalivas, 2002).

In rodents, NAC has been found to increase extracellular glutamate levels in the NAcc (Baker, McFarland, Lake, Toda, & Kalivas, 2003), to normalize the excitatory characteristics of PFC projections to the NAcc (Kalivas, 2009) and to prevent cocaine-primed drug seeking (Baker et al., 2003). Studies in humans have also shown promise. In a randomized, placebo-controlled crossover study, a single dose of 2400 mg NAC normalized increased dACC glutamate levels in cocaine dependent individuals (Schmaal et al., 2012b). Also various beneficial clinical effects have been reported, such as reduced marijuana use and craving (Gray, Watson, Carpenter, & Larowe, 2010), reduced methamphetamine craving (Mousavi et al., 2015), positive

results on cocaine craving and cocaine use cessation (Amen et al., 2011; LaRowe et al., 2006; Mardikian, LaRowe, Hedden, Kalivas, & Malcolm, 2007), reduced cigarette smoking (Knackstedt et al., 2009) and reduced rewarding effects of smoking (Schmaal et al., 2011). However, there are also some studies that did not find beneficial effects of NAC on cocaine use or craving (LaRowe et al., 2007, 2013). Additionally, NAC has been found to have a beneficial effect on cognition, including inhibition and cognitive control (Skvarc et al., 2017), but whether this holds true in SUDs remains to be seen. However, given that there is only one human study investigating the neurobiological effects of NAC in SUD, more research is warranted to further investigate this potential effect and its association with clinical and cognitive effects.

TRAINING COGNITIVE CONTROL

Novel paradigms have been developed to train cognitive functions, among which are training paradigms to improve cognitive control processes. Cognitive control consists of different components, including inhibition and working memory (WM; Miyake et al. 2000). WM is the capacity to temporarily store and manipulate information (Baddeley, 2010). WM-training has been used by several studies to strengthen cognitive control in various psychiatric disorders, including SUD (for reviews, see Bickel et al. 2014; and Shipstead et al. 2012). Although improvements in WM do not always generalize to other tasks than the training task itself (Verdejo-Garcia, 2016) or transfer to other cognitive functions (Shipstead et al., 2012), positive effects have been reported for reductions in substance use (Houben, Wiers, & Jansen, 2011; Rass et al., 2015) and for other neurocognitive functions related to SUD (Bickel, Yi, Landes, Hill, & Baxter, 2011). Moreover, improvements in WM performance have been associated with increased neural activity in prefrontal and parietal brain areas after training (Olesen, Westerberg, & Klingberg, 2004). However, there have also been negative findings (e.g. Wanmaker, 2014) and it is as-yet unknown whether WM-training induced reductions in cocaine use are associated with alterations in neural activity in frontal brain regions.

AMBULATORY ASSESSMENT: IMPROVING MEASUREMENTS OF MOTIVATION AND COGNITION IN SUD RESEARCH

Most studies on SUDs are conducted within the laboratory using assessment techniques that do not take into account changes in environmental factors. While this provides researchers with a controlled environment, the ecological validity is low. Ambulatory techniques such as ecological momentary assessment (EMA) minimize recall bias, permit more intensive assessment of experiences (Stone, Shiffman, Atienza, & Nebeling, 2007) and can be used in clinical trials (Kowalczyk et al., 2015; Moran et al., 2016). EMA could be a reliable tool to study various detailed effects of

treatment. For instance, more positive explicit attitudes towards substances and elevated attentional bias towards drug cues have been reported in heroin-inpatients while experiencing the temptation to use, in daily life (Waters, Marhe, & Franken, 2012). Furthermore, individuals who relapsed reported increased attentional bias and craving compared to abstainers while experiencing temptation, as measured with EMA (Marhe, Waters, van de Wetering, & Franken, 2013). These studies emphasize the ability of EMA, and ambulatory assessment in general, to identify which individuals are at risk of relapse at what moment. Although laboratory assessments will always be necessary and unavoidable in certain situations (e.g. assessing neuroimaging measures), ambulatory assessments could be a useful addition to acquire fine-grained information on treatment effects. The correspondence between lab data and EMA data for regular cocaine using participants was further elucidated in this dissertation.

AIMS AND OUTLINE OF THE THESIS

SUDs have been associated with hyper-reactive motivational processes and suboptimal reflective processes, which have been associated with altered brain functioning. This provides opportunities to develop treatments aimed at targeting these affected processes, more specifically to dampen motivational excitation and improve cognitive control. NAC has shown to have beneficial effects in the dampening of motivational processes (e.g. craving) possibly by normalizing the disbalance in glutamate. Novel training paradigms have been developed to improve cognitive control functions, with WM-training as a promising candidate. However, there is still little evidence on the clinical effects of WM-training and the association with neurobiological changes.

The first aim of this dissertation was to investigate the neurocognitive and neurochemical mechanisms underlying substance use disorders, specifically with respect to the neurotransmitters glutamate and GABA and their association with impulsivity. The second aim was to investigate the effect of NAC on glutamate normalization and smoking cessation. The third aim was to investigate the combined effect of NAC and WM-training on cocaine use cessation, craving, cognition, and brain activity associated with craving and working memory in regular cocaine users. Finally, the correspondence between data acquired under lab conditions and data collected using ecological momentary assessment (EMA) was investigated.

Chapter 2 is a systematic review of neurocognitive recovery using neuropsychological assessments before and after sustained abstinence from substance use, and discusses how these results can be implemented in the development of new treatment strategies.

Chapter 3 focusses on potential differences in GABA and glutamate concentrations in the dACC and impulsivity between cigarette smokers, smoking polysubstance users, and healthy controls. Proton magnetic resonance spectroscopy (^{1}H-MRS) is used to assess glutamate and GABA concentration in the dACC. Associations between impulsivity and the level and severity of substance use with glutamate and GABA concentrations are also explored.

Chapter 4 investigates the effect of NAC on smoking cessation, craving and glutamate and GABA concentrations in the dACC. Glutamate and GABA concentrations before and after treatment are assessed by means of ^{1}H-MRS. First, it was explored whether smokers differ in neurotransmitter concentrations from non-smokers. Second, in a double-blind placebo controlled design, smokers received 2400 mg/day NAC or placebo for two weeks.

Chapter 5 investigates the effect of NAC and WM-training on the reduction of cocaine use, craving and inhibition. Regular cocaine users received 2400 mg/day NAC and daily online WM-training for 25 days. Additionally, it was investigated if there is correspondence between data acquired in the lab and data acquired by means of Ecological Momentary Assessment (EMA).

Chapter 6 focusses on the effect of NAC and WM-training on neural mechanisms of cue reactivity and WM, and associated behavior (cue-induced craving and WM performance, respectively). Regular cocaine users received 2400 mg/day NAC and daily WM-training for 25 days and underwent the imaging protocol before and after training.

Finally, in **Chapter 7** the results of the studies are summarized and discussed. Methodological considerations, clinical implications and recommendations for future studies are discussed as well. **Chapter 8** provides a Dutch summary of the results.