Neurostimulation in alcohol dependence: The effect of repetitive transcranial magnetic stimulation on cognitive functioning and craving

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CHAPTER 1

INTRODUCTION
1. ALCOHOL DEPENDENCE

Harmful alcohol consumption ranks among the top five worldwide contributors of disease, disability and death (Lim et al., 2013; Whiteford, Ferrari, Degenhardt, Feigin, & Vos, 2013; World Health Organization, 2011), and alcohol dependence is a common disorder with a 12-month prevalence of 2-3% in the United States (Compton, Thomas, Stinson, & Grant, 2007; Kessler, Chiu, Demler, & Walters, 2005), 4% in Europe (Wittchen et al., 2011), and 0.7-3.7% in the Netherlands (Bijl, Ravelli, & Van Zessen, 1998; De Graaf, Ten Have, & Van Dorselaer, 2010; Monitor., 2012). Alcohol dependence is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as a pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by the following behaviours: spending significant time on obtaining, consuming, thinking about, or recovering from alcohol, loss of control over the amount and frequency of intake, attempts to cut down, reduced social involvement, tolerance, and withdrawal symptoms during abstinence (American Psychiatric Association, 1994).

The DSM-IV included two separate disorders with a difference in severity; alcohol abuse and alcohol dependence (American Psychiatric Association, 1994). In the latest edition, the DSM-5, alcohol dependence and alcohol abuse have been merged into “alcohol use disorder” based on almost the same DSM-IV criteria, but with the abuse criterion “substance-related legal problems” replaced by “craving”, i.e. the very strong urge to drink (American Psychiatric Association, 2013; O’Brien, 2011). This disorder is measured on a continuum, ranging from mild to medium and severe depending on how many of the 11 criteria are met (American Psychiatric Association, 2013).

2. NEUROBIOLOGY OF ADDICTION

The societal view on addiction has changed greatly over the past decades; addiction was considered a moral weakness in the 19th century, a symptom of an underlying personality disorder in the beginning of the 20th century and a social response or learned inappropriate behaviour in the 1970’s. The development of neuroimaging techniques, including functional Magnetic Resonance Imaging (fMRI) in the 1990s has led to an abundance of studies into the neural correlates of substance dependence, from which several neurobiological models on addiction have emerged (Garavan & Weierstall, 2012; Koob & Volkow, 2010; Leshner, 1997; Yucel & Lubman, 2007). A common factor in these theories is that substance dependence is often described as a dual process disorder with deficits in cognitive control (Feil et al., 2010; Hester, Lubman, & Yucel, 2010; Ravaglia et al., 2002) and hypersensitivities in the reward system (Adinoff, 2004; Everitt & Robbins, 2005; Kalivas & Volkow, 2005) of the brain.

The brain reward system includes the ventral tegmental area and nucleus accumbens, and uses neurotransmitters (e.g. dopamine, endogenous opioid peptides and γ-aminobutyric acid [GABA]) to transfer signals regarding the pleasurable effects of stimuli (Diana, 2011; Heinz et al., 2004; Knutson, Adams, Fong, & Hommer, 2001; Volkow, Wang, Fowler, Tomasi, & Telang, 2010). Although drug and alcohol both influence the reward system, their mechanism of action is slightly different. The intake of cocaine,
heroin and amphetamine is followed by high and short bursts of extracellular dopamine release in these areas, which are associated with the pleasurable effect of drugs (Di Chiara et al., 2004; Ikemoto & Panksepp, 1999). Alcohol intake, on the other hand, increases GABA, endorphine and serotonin levels, whereas it diminishes glutamate levels, which taken together are associated with its rewarding, anxiolytic and relaxing effects. The (pleasurable) response to drugs or alcohol becomes blunted after prolonged periods of intake, because the availability of dopamine and GABA is reduced due to habituation. The reward system becomes sensitized and conditioned to drug or alcohol cues and more drug or alcohol is required to elicit the pleasurable effects (Di Chiara & Bassareo, 2007; Robinson & Berridge, 1993). These conditioned responses lead to increased valuation of drugs (salience) and attentional bias for drug-related cues which is associated with craving and compulsive drug seeking (Cornish & Kalivas, 2001; Field, Munafò, & Franken, 2009). After extended periods of drugs and alcohol use the immediate effects are no longer pleasurable, because it merely alleviates (withdrawal) symptoms caused by the decreased dopamine and GABA levels (Koob et al., 2004; Wise & Koob, 2014). Drug or alcohol seeking and consumption becomes associated with negative reinforcement (Heilig et al., 2010) and the brain response shifts to dorsal parts of the striatum which may be related to habitual drug use, as evidenced by animal research (Everitt & Robbins, 2005).

The control system is a circuit of brain areas implicated in executive functioning, consisting of the prefrontal cortex, including the anterior cingulate (ACC) and dorsolateral prefrontal cortex (dIPFC) (Buhle et al., 2013; Miller, 2000). These areas of the brain are involved in planning, working memory, cognitive flexibility, error monitoring, motor inhibition, cognitive control over emotions (Buhle et al., 2013; Miller, 2000; Ochsner & Gross, 2005) and control over craving (Kober, Kross, Mischel, Hart, & Ochsner, 2010; Volkow, Fowler, et al., 2010). Substance dependence is related to decreased functioning of the control system (Kalivas & Volkow, 2005), which results in decreased control over the amount, frequency and location of consumption (Baler & Volkow, 2008). The imbalance between a ‘strengthened’ reward system and a ‘weakened’ control system seems to be related to the chronic, relapsing features of addiction.

3. NEUROIMAGING

Functioning of the reward and control systems can be measured with various neuroimaging techniques, including functional magnetic resonance imaging (fMRI), which measures the ratio of oxygenated and de-oxygenated blood (Sharp et al., 2011). This ratio is known as the Blood Oxygenation Level Dependent (BOLD) effect. Changes in BOLD response reflect consumption of oxygen which is a correlate for brain activity. This thesis describes studies using two types of fMRI; task based and resting-state fMRI. Task-based fMRI requires participants to perform a computer task inside the fMRI scanner, while brain activity is measured. With this technique we can identify areas of the brain which are implicated in the task that was performed. Resting state functional magnetic resonance imaging (rsfMRI) measures spontaneous fluctuations in brain activity at rest and identifies temporally correlated brain regions and brain networks (Laird et al., 2011; Smith et al., 2009; Van Den Heuvel & Hulshoff Pol, 2010).
4. RESTING STAGE FMRI

Resting state functional magnetic resonance imaging has been used to identify the above mentioned control (Damoiseaux et al., 2006; Janes et al., 2010; Laird et al., 2011; Smith et al., 2009) and motivation networks (Damoiseaux et al., 2006; Janes et al., 2010; Laird et al., 2011; Müller-Oehring, Jung, Pfefferbaum, Sullivan, & Schulte, 2014; Smith et al., 2009) in healthy controls and more recently in alcohol dependent patients (Camchong, Stenger, & Fein, 2013a, 2013b; Camchong, Stenger, & Fein, 2013; Müller-Oehring et al., 2014). These studies show that resting state connectivity within and between the reward/motivation network and the cognitive control network is compromised in ADPs, but methodological differences limit generalizability and comparability of these studies. In this thesis, we present a study which investigates differences in reward and control systems between alcohol dependent patients and healthy controls based on a data-driven technique which improves generalizability and comparability of the results.

5. COGNITIVE FUNCTIONING IN ALCOHOL DEPENDENT PATIENTS

This thesis focusses on two functions of the brain's control system; cognitive flexibility and emotion regulation, which will be discussed briefly in this introductory chapter.

5.1 Cognitive Flexibility

Cognitive flexibility is a prerequisite for goal directed behavior and involves executive decision making preceding switching behavior (Lezak, 2004). It is a inhibitory process which has been defined as the ability to adjust one's thinking from old to new situations (Moore & Malinowski, 2009). Impairments in cognitive flexibility may be related to the compulsive use of drugs and/or alcohol, which is one of the key elements in the development and persistence of substance dependence. This relationship has mostly been described in animal studies (Everitt & Robbins, 2005; Stalnaker, Takahashi, Roesch, & Schoenbaum, 2009), but evidence in actual substance dependent patients is limited although some studies report impaired cognitive flexibility in gamblers (Odlaug, Chamberlain, Kim, Schreiber, & Grant, 2011), cocaine (Cunha, Nicastri, de Andrade, & Bolla, 2010) internet (Dong, Lin, Zhou, & Lu, 2014) and alcohol dependent patients (Chanraud et al., 2007). Cognitive flexibility has been associated with prefrontal white matter (WM) integrity in healthy controls, showing that lower WM integrity is associated with worse performance (van Schouwenburg, O'Shea, Mars, Rushworth, & Cools, 2012). Although both cognitive flexibility (Chanraud et al., 2007) and WM integrity have found to be aberrant in patients with alcohol dependence (Pfefferbaum, Desmond, Galloway, Glover, & Sullivan, 2001; Pfefferbaum, Rosenbloom, Rohlfing, & Sullivan, 2009; Pfefferbaum & Sullivan, 2005), the relationship between the two has never been tested. This thesis therefore incorporates a study assessing underlying functional and structural brain differences related to cognitive flexibility in healthy controls, problematic drinkers and alcohol dependent patients.
5.2 Emotion regulation

Showing our emotions is not always socially acceptable and handling emotions is central to our daily functioning (Gross, 2013). Two important strategies for emotion regulation are suppression and reappraisal. Emotions may be suppressed by trying not to think about them, whereas reappraising emotions is defined as ‘changing the impact of a certain thought or stimulus through cognitive reinterpretation’ (Gross & John, 2003). Applying reappraisal strategies instead of suppression strategies is related to more and stronger social connections, higher quality of life and better cognitive performance in stressful situations in healthy controls (Gross & John, 2003). Neuroimaging studies in healthy controls show that reappraisal or ‘emotion regulation’ is related to prefrontal inhibition (control system) of the amygdala (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Buhle et al., 2013). The amygdala is central to the processing of (negative) emotion, and reappraising negative emotions reduces amygdala activity while activity in prefrontal control areas increase (Buhle et al., 2013).

In alcohol dependent patients, negative emotions and stress are known to provoke alcohol craving and consumption (Sinha et al., 2008; Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006). In fact, the experience of negative emotions and stress have been indicated as primary contributors to relapse (Sinha, 2011). The experience of negative emotion triggers a craving response in the reward system (Sinha et al., 2008; Sinha et al., 2006). Normally the cognitive control system regulates emotions, but in alcohol and nicotine dependent patients these mechanisms are weakened which may lead to diminished control over emotions and craving (Holahan, Moos, Holahan, Cronkite, & Randall, 2001; Kober, Kross, et al., 2010; Kober, Mende-Siedleckic, et al., 2010). At the start of this study, emotion regulation differences between alcohol dependent patients and healthy controls had been assessed using questionnaires (Berking et al., 2011; Stasiewicz et al., 2012), but there were no studies that assessed differences in performance on an emotion regulation task or whether neural recruitment during emotion regulation differed between alcohol dependent patients and healthy controls. Given the relevance of negative emotions in relapse, this thesis addresses whether or not there are differences in emotion regulation abilities and neural recruitment during an emotion regulation task between alcohol dependent patients and healthy controls.

6. TREATMENT OPTIONS FOR ALCOHOL DEPENDENCE

The currently available treatment options for alcohol dependence include pharmacotherapy (disulfiram, naltrexone, acamprosate) and cognitive behavioural therapy which often includes some form of emotion regulation training (Axelrod, Perepletchikova, Holtzman, & Sinha, 2011; Berking et al., 2008). After an initially successful period of abstinence an estimated 50% of patients relapse into alcohol use within the first year (Jonas et al., 2014; Moos & Moos, 2006; Schippers & Broekman, 2006). These high relapse rates indicate that research into new treatment possibilities is warranted. One of these new techniques is non-invasive neurostimulation, or repetitive transcranial magnetic stimulation (rTMS), because some studies have shown that rTMS may decrease craving (chapter 2), may enhance cognitive functioning (Guse, Falkai, &
Wobrock, 2010), and change the experience of negative emotion (Baeken et al., 2010). Neurostimulation may therefore serve to decrease craving levels and increase cognitive functioning, including the regulation of emotions. This thesis therefore assesses the beneficial effects of neurostimulation on craving, emotion regulation abilities and related brain function in alcohol dependent patients and healthy controls.

7. NEUROSTIMULATION

The first attempts at neurostimulation were made in the early 1900’s, but these ventures were unsuccessful and the idea was abandoned. The first successful neurostimulation study was performed decades later by Barker and colleagues in 1985 (Barker, Jalinous, & Freeston, 1985), when they applied Transcranial Magnetic Stimulation (TMS) to the primary motor cortex and were able to move the contralateral hand by stimulating this brain area.

TMS is applied from outside the brain by placing an electromagnetic coil against the scalp. The electric current running through the coil creates a magnetic field that traverses through the skull and generates an electrical current in the brain directly under the coil. The electrical current in the brain stimulates nerve cells and alters brain activity in that area (Kobayashi & Pascual-Leone, 2003). In the extensive research in the years after the first study (Barker et al., 1985), TMS proved to be able to either excite or inhibit brain activity, depending on the stimulation parameters (George & Aston-Jones, 2010). Inhibiting brain areas causes a temporary disruption of functions related to the stimulated area, an effect which is known as a ‘virtual lesion’ (Pascual-Leone, Walsh, & Rothwell, 2000). Virtual lesion studies have been key in mapping functions of the brain, as it was now possible to make causal connections between brain areas and their function. The virtual lesion approach is an example of a ‘single pulse’ application of TMS, but other possibilities include paired pulse and repetitive TMS (Feil & Zangen, 2010; George & Aston-Jones, 2010). Paired-pulse TMS couples two pulses in a very short timeframe (2-5ms) and has mainly been used in cortical inhibition and excitation studies (Feil & Zangen, 2010). Repetitive TMS (rTMS) uses low (<1hz) or high (>1hz) frequency trains of TMS pulses, which either inhibit or excite activity in the stimulated brain area (George & Aston-Jones, 2010). Repetitive TMS induces effects that remain for an extended period of time after the actual stimulation has ended (Eisenegger, Treyer, Fehr, & Knoch, 2008) and extend beyond the stimulation location. High-frequency stimulation of the dlPFC increases dopamine release in the caudate nucleus (Strafella, 2001) and may attenuate activity in the dorsal anterior cingulate cortex (De Ridder, Vanneste, Kovacs, Sunaert, & Dom, 2011).

Many psychiatric disorders are characterised by deficient brain functioning, and due to the lasting effects of rTMS this technique may be used to improve brain function (Addolorato, Leggio, Hopf, Diana, & Bonci, 2012; Slotema, Dirk Blom, Hoek, & Sommer, 2010). These clinical applications have mainly been studied in depressed patients, which resulted in an FDA approval for the treatment of (treatment resistant) depression with high-frequency rTMS of the dorsolateral prefrontal cortex (dlPFC) (Dell’Osso, 2011; FDA, 2008). During rTMS treatment, the patient receives multiple sessions of rTMS over
the course of a few weeks and the depression symptoms gradually decrease (Dell’Osso, 2011). More recent studies show that rTMS also bears promise for the treatment of substance dependence, since there are indications that it may decrease craving (see Chapter 2: (Camprodon, Martinez-Raga, Alonso-Alonso, Shih, & Pascual-Leone, 2007; Fecteau, Fregni, Boggio, Camprodon, & Pascual-Leone, 2010; Mishra, Nizamie, Das, & Praharaj, 2010) as well as improve cognitive functioning (Fecteau et al., 2010) including improved emotion regulation (Baeken et al., 2010; De Raedt et al., 2010). In order to clarify the possibly beneficial effects of rTMS for alcohol dependent patients, this thesis investigates the effects of rTMS on craving, emotion regulation and resting state connectivity in this patient group.

8. OUTLINE OF THE THESIS

The main objective of this thesis is to assess whether there are behavioural and neural differences related to (1) emotion regulation and (2) cognitive flexibility between alcohol dependent patients and healthy controls, and if rTMS can (3) improve emotion regulation, (4) change related brain function and (5) reduce craving. Finally, we assess (6) differences in pre-frontal resting state networks and (7) the effects of rTMS on these resting state networks. In order to evaluate and answer these points several studies are presented.

Chapter 2 investigates the effects of non-invasive neurostimulation on craving by conducting a meta-analysis of existing studies. We assess the effects of both rTMS and transcranial direct current stimulation (tDCS) on multiple types of craving (smoking, alcohol, food), hypothesizing that active stimulation significantly outperforms sham stimulation.

Chapter 3 is a pilot study, assessing whether rTMS increases emotion regulation abilities in healthy controls and whether the effects differed between stimulation of the left or right hemisphere. In line with theories on side-lateralized emotion processing we hypothesize that right sided stimulation improves emotion regulation to a greater extent than left sided stimulation.

Chapter 4 assesses differences in behavioural and neural response during emotion regulation between alcohol dependent patients and healthy controls, and the effects of right-sided rTMS on emotion regulation, craving and related brain activity. We hypothesize that alcohol dependent patients are significantly impaired in the regulation of negative emotion and that active rTMS improves emotion regulation and reduces craving.

Chapter 5 assesses brain function during cognitive flexibility and white matter integrity in alcohol dependent patients, problematic drinkers, and healthy controls. We hypothesize that alcohol dependent patients and problematic drinkers, when compared to healthy controls, show reduced white matter integrity combined with an increase in brain activity during a cognitive flexibility task.
Chapter 6 investigates differences in prefrontal control and limbic resting state networks between alcohol dependent patients and healthy controls, and the effect of rTMS on these networks. We expect differences in resting state connectivity between the alcohol dependent patients and healthy controls in both networks, and that rTMS will influence resting state connectivity in these networks.

Chapter 7 provides a general discussion of the findings which are presented throughout this thesis and discusses limitations and recommendations for future research.