The relationship between alcohol consumption, impulsivity and neurophysiological indices of inhibitory control: an experimental study using transcranial direct current stimulation.
Preface

“Some beautiful paths can’t be discovered without getting lost.” (Erol Ozan)

Before the start of my dissertation I couldn’t have imagined what a journey it would become. At the end I found it a challenging though fruitful experience and I’m happy that I had the chance to work on an interesting project.

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Abstract

Impaired response inhibition, the motor component of impulsive action, is known to be one of the main cognitive mechanisms in initiating and maintaining alcohol use. The right inferior frontal gyrus (rIFG) has been identified as a neural correlate of response inhibition. Previous research has indicated that anodal transcranial direct current stimulation (tDCS) over rIFG boosts response inhibition on a behavioral level. The current study assesses if this effect can also be observed on the N2P3 complex, neurophysiological correlates that are associated with response inhibition. In addition, the present study also assesses the relationship between trait impulsivity and response inhibition. In addition, the potential role of individual differences in trait impulsivity and alcohol use on behavioral and neurophysiological measures of response inhibition is investigated.

A sample of healthy subjects (N=40) were randomly assigned to either active tDCS (n = 20) or sham tDCS (n = 20) condition. At baseline, every participant was asked to perform a Go/No-Go task, a paradigm which is known to measure response inhibition, and an oddball face detection task, that was used as control. During the execution of both tasks, event-related potentials (ERP) were measured. After a 20-minute neuromodulation session, participants were confronted again with both tasks.

On a behavioral level, no differences between both groups were observed on the Go/No-Go task. Commission errors (not able to inhibit a prepotent response) were similar in both tDCS and sham condition. On a neurophysiological level reduced P300 amplitudes were observed post stimulation in the tDCS condition, indicating that fewer cognitive resources were needed. Furthermore a significant relationship between the attentional impulsiveness and commission errors was observed at baseline. This was not replicated on a neurophysiological level, indicating that individuals, who have problems with focused attention, used similar levels of cognitive effort in comparison with individuals who are better in keeping focus. Furthermore, trait impulsivity and self-reported alcohol use did not alter the effect of response inhibition within our sample.

Overall, the present data indicate that boosting rIFG enhances response inhibition through decreased neural activity needed to perform an inhibitory control task. In addition, a relationship between trait impulsivity and response inhibition was observed. However the specific role of individual differences in trait impulsivity and alcohol use on the effect of tDCS remains unclear.
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Introduction

Impulsivity is repeatedly described as both a determinant and consequent of alcohol use (de Wit, 2009; Jentsch & Taylor, 1999; Verdejo-Garcia, Lawrence, & Clark, 2008; von Diemen, Bassani, Fuchs, Szobot, & Pechansky, 2008). Impaired response inhibition - the inability to inhibit a response once it has been started - has been identified as one of the main cognitive mechanisms in approach behavior, alcohol abuse and difficulties abstaining (Bari & Robbins, 2013). A sample of healthy participants was used to investigate whether the underlying neurobiological working mechanism of response inhibition can be influenced using a neuromodulation technique. Better understanding of this process will increase insight in a biological vulnerability factor that initiates and maintains drinking behavior. In the course of time, increased knowledge can help in the prevention of alcohol abuse and development of better treatment methods. This is needed because treatment remains difficult and complicated (O'Brien, 2008), often resulting in relapse (Finney, Hahn, & Moos, 1996; Heinz, Beck, Grüsser, Grace, & Wrase, 2009). In the first chapter, alcohol and its adverse effects are explained together with societal and economic costs. In the second chapter the broad concept of impulsivity, which is closely related to alcohol use, abuse and relapse, will be explained including the aspect of response inhibition. In the third chapter, the neurophysiological correlates of response inhibition will be described and in the fourth chapter, a neuromodulation technique used to boost response inhibition will be elucidated. At the end a clarification of hypotheses and summary will be given.

Adverse Effects of Alcohol

Alcohol has always taken an important role in human culture. Consumption of alcohol is part of most societies and harmful use of alcohol causes a wide range of health and social consequences for the drinker, his environment and society (Rehm et al., 2009b; WHO, 2014). According to the most recent report of the World Health Organization (WHO, 2014), harmful use of alcohol is one of the most important factors leading to burden of disease and mortality worldwide. In 2012, adverse use of alcohol accounted for about 3.3 million deaths or 5.9% of all global deaths and around 5.1% of the total global burden and disease could be attributed to alcohol use.

Alcohol related problems are not solely restricted to health but impose significant social and economic costs on society. According to the WHO (2014) there are three distinct categories of expenses. The first category is associated with direct economic burden. These can be understood as costs directly related to wellbeing and health such as hospitalizations, medical care, ambulant and nursing home care, but
also expenses associated to police, unemployment and the justice system. These costs represent 9 to 24% of the total amount related to alcohol, which means that an extensive fraction of costs does not fall within this type of expenses (van Gils, Hamberg-van Reenen, van den Berg, Tariq, & de Wit, 2010). The second category is the indirect expenses. Loss in employee efficiency can play an essential role in the economic feasibility of an entire society (Room et al., 2002). Factors such as unemployment, absenteeism and reduced productivity cause lost working years and diminished income (Anderson & Baumberg, 2006; Thavorncharoensap & Teerawattananon, 2009). Lastly there are the intangible expenses. These costs are vague and difficult to measure and are interrelated with factors such as anguish and pain resulting in deteriorated quality of life. These costs are not only linked with drinkers themselves but family and other related individuals also bear these costs (Anderson & Baumberg, 2006; Thavorncharoensap & Teerawattananon, 2009). In total it’s assumed that social costs attributable to alcohol represent between 1.3% and 3.3% of the gross domestic product (Rehm et al., 2009a).

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM5) utilizes alcohol use disorder (AUD) as an overarching definition of disorders related to alcohol (American Psychiatric Association, 2013). According to DSM5, AUD is characterized as a syndrome with a broad range of symptoms. First, there’s a pattern of compulsive use of alcohol as a consequence of a diminished ability in controlling preoccupation with acquiring alcohol. Second, as a consequence, recurrent alcohol abuse has destructive effects on psychological, physical, social and occupational functioning. And third, the repeated use of alcohol has lead to physiological dependence with both high tolerance and withdrawal symptoms making an individual vulnerable to relapse after cessation of drinking. Alcohol dependency (AD), the most severe form of AUD, is characterized as alcohol abuse combined with symptoms such as tolerance, withdrawal, and an uncontrollable drive to drink. AD is considered to be a multi-factorial chronic relapsing disorder with biological, genetic and psychosocial factors associated with its development (Addolorato, Leggio, Abenavoli, & Gasbarrini, 2005; Farren & Tipton, 1999). In 2004, AD was responsible for 85000 deaths (85% males, 15% females) in Europe, which is equal to 60% of all alcohol related deaths (Rehm, Shield, Rehm, Gmel, & Frick, 2012). About 65 to 70% of patients who are diagnosed with AUD go into remission within a period of three years and only a minority experience relapse (Dawson, Goldstein, Ruan, & Grant, 2012; Tuithof, ten Have, van den Brink, Vollebergh, & de Graaf, 2013). In contrast, individuals with chronic recurrent AD are linked with increased risk of relapse (Tuithof, ten Have, van den Brink, Vollebergh, & de Graaf, 2014). AD is treated both pharmacologically and
psychotherapeutically, but treatment remains difficult and complicated (Anton et al., 2003). The detoxification process is the first step in treating alcohol addiction, but relapse after treatment is a major concern for health workers. In a period between 6 months and 1 year after treatment, 40 to 80% of individuals who underwent therapy typically restart alcohol use (Finney et al., 1996; Heinz et al., 2009), and relapse is more likely to happen in the first 3 months following detoxification (Pelc et al., 1997). Clinically it’s vital to identify the means that predict and initiate relapse given that the long-term effect of treatment is modest (O’Brien, 2008).

In summary, alcohol related problems are diverse and lead to a high burden of disease as well as a high mortality rate (WHO, 2014). Furthermore, alcohol related problems are not solely limited to health but also impose significant societal and economic costs (WHO, 2014). Problematic use of alcohol can result in AUD or AD. Treatment remains difficult and complicated (Anton et al., 2003). Most individuals who undergo therapy typically restart alcohol use in a period between 6 months and 1 year after treatment (Finney et al., 1996; Heinz et al., 2009). For this reason, it’s important to understand the processes that initiate and maintain hazardous drinking behavior. Evidence suggests an important role of impulsivity (de Wit, 2009; Jentsch & Taylor, 1999; Verdejo-Garcia et al., 2008; von Diemen et al., 2008). Both trait and state aspects of impulsivity have been identified as potential influencers of alcohol use and abuse. As a result it’s critical to understand the relationship between impulsivity and alcohol.

Vulnerability for Alcohol Use and Misuse: Impulsivity

Impulsivity.

In literature, impulsivity is repeatedly defined as one of the most important behavioral characteristics that functions as a determinant and consequent of alcohol and substance use (de Wit, 2009; Jentsch & Taylor, 1999; Verdejo-Garcia et al., 2008; von Diemen et al., 2008). Impulsivity is often associated with maladaptive or inappropriate behavior. High levels of trait impulsivity are considered a risk factor for approach behavior towards substances, substance abuse and difficulties abstaining (de Wit, 2009). But also momentary state-dependent factors can impair the process of decision making and inhibition, resulting in an increase of impulsive behavior, which impact the risk of substance use (de Wit, 2009).

Impulsivity is researched at several different levels. The field of personality psychology focuses on behavioral aspects of impulsivity. They regard impulsivity as an underlying trait of personality which has a certain degree of stability over time and uses
self-report questionnaires or observations to measure trait impulsivity. The field of neuropsychology approaches impulsivity as a construct with different aspects and assumes that these aspects are transitory states which are sensitive to environmental influences (Verdejo-Garcia et al., 2008). It uses neurocognitive computer tasks that focus on behavior and are commonly accepted as more objective measures in comparison to self-report questionnaires which are prone to biases in social desirability and demand characteristics (Verdejo-Garcia et al., 2008). The field of cognitive neuroscience uses techniques such as event-related potentials (ERP) to understand how these neurocognitive processes work.

Research indicates that correlations between behavioral measures of impulsivity in laboratory tasks and self-report questionnaires are often non-existent (Bari & Robbins, 2013; Stevens et al., 2014). Two possible explanations arise. First, the reason for this inconsistency could be because of the multidimensional characteristics of impulsivity (Evenden, 1999). Second, it’s possible that impulsive tendencies aren’t stable and vary within a person depending on the current state of the individual (Bari & Robbins, 2013). A combination of measures can be used to detect associations between both types of measures (Bari & Robbins, 2013).

In sum, impulsivity is repeatedly described as predictor and outcome of alcohol and substance abuse (de Wit, 2009; Jentsch & Taylor, 1999; Verdejo-Garcia et al., 2008; von Diemen et al., 2008). Furthermore it’s a broad concept which is researched on several distinct levels using their own set of tools. However, overlap between measures remains low because one can assume that impulsivity isn’t a unitary construct (Evenden, 1999) and that tendencies within the individual can vary over time (Bari & Robbins, 2013).

Next the cognitive and biological processes of impulsivity are explained. For this purpose a model is used which elaborates on the underlying neurobiological working mechanisms of impulsive behavior.

Cognitive and biological processes of impulsivity.

Impulsive behavior is associated with more than one specific brain region or process (Bechara, 2005). It’s the result of a discrepancy between two distinctive neural systems that interact with each other: a bottom-up impulsive system and a top-down reflective system (Bechara, 2005; Heatherton & Wagner, 2011). In the impulsive system, the amygdala is an essential neural component involved in prompting affective and emotional cues triggered by the likes of pleasure or by pain, which result in an instant reaction (Bechara, 2005). In the reflective system, the prefrontal cortex is an essential neural component involved in triggering affective and emotional cues with
long-term results (Bechara, 2005), and can be viewed as more of a proactive mechanism (Bari & Robbins, 2013). Impulsivity can be the outcome of failure to engage in prefrontal control in the top-down reflective system of the brain (Bechara, 2005; Heatherton & Wagner, 2011). This means that an individual at that certain moment lacks the ability to reflect and think about consequences before making a choice (Bechara, 2005). After mastering social rules, the reflective system has control over the impulsive system but cannot restrain it completely. Therefore it can still overrun the reflective system (Bechara, 2005). A hyperactive bottom-up system can overrule the reflective system especially when there’s a great sensitivity and attention bias towards strong reward impulses (Bechara, 2005; Heatherton & Wagner, 2011).

Impulsivity can be split into two distinct neurocognitive components each relating separately to either top-down or bottom-up system. The first neurocognitive component is the top-down process of impulsive choice which depends on temporal discounting of reward and occurs when a person prefers an instantaneous small reward over a bigger reward in the long term (Dalley, Everitt, & Robbins, 2011). This delayed discounting of reward is associated with the top-down reflective system. A typical task for measuring decision-making behavior is the Iowa Gambling Task (Bechara, 2003). The second neurocognitive component is the bottom-up process of impulsive action. This process is often characterized as having deficits in response inhibition and corresponds with failures in the ability to restrain inappropriate actions or thoughts (Dalley et al., 2011; Stevens et al., 2014).

Because impulsive action affects both actions and thoughts, it comprises of both a cognitive and motor component (Stevens et al., 2014). The cognitive component of interference control appears when people have difficulties restraining information which diverts attention (Nigg, 2000) and is typically measured with the Stroop Color Word Test (Stroop, 1935). Response inhibition, the motor component of impulsive action, is determined by the ability to voluntary restrain a response which has already been initiated (Dalley et al., 2011; Stevens et al., 2014). Two common tasks to measure response inhibition are the Go/No-Go task (Chambers, Garavan, & Bellgrove, 2009; Dalley et al., 2011; Verbruggen & Logan, 2008) where a behavior which hasn’t been started yet has to be withheld, and the Stop Signal Task (Verbruggen & Logan, 2008), where an action which has been initiated needs to be interrupted (Schachar et al., 2007).

Research indicates that impairment of response inhibition is closely related to alcohol (Dick et al., 2010; Field, Kiernan, Eastwood, & Child, 2008; Noel et al., 2016). Impaired response inhibition has been linked with approach behavior towards alcohol, cessation problems and relapse (Field et al., 2008; Nigg et al., 2006; Petit et al., 2014;
Petit, Kornreich, Noël, Verbanck, & Campanella, 2012; Wetherill, Squeglia, Yang, & Tapert, 2013). Focusing on the observable motor component of response inhibition allows objective measurement of the underlying physiological processes (Stevens et al., 2014; Verdejo-Garcia et al., 2008). For this reason, the current study focuses solely on the motor component. Response inhibition is of importance because it is linked to behavior that involves self-regulation (Barkley, 1997). It is considered as an essential component in regulating ongoing behavior and enabling reflective behavior (Bari & Robbins, 2013). Therefore, poor response inhibition is associated with more impulsive and stimulus-driven behavior, and also with an inability to identify if current behavior hinders attaining objectives in the long-term (Bari & Robbins, 2013). Impaired response inhibition relates to approach behavior towards substance use and abuse. Some studies indicate that deficits in response inhibition can predict alcohol abuse (Nigg et al., 2006) and that adolescents who evolved to heavy drinkers showed less response inhibition before the commencement of heavy drinking behavior (Wetherill et al., 2013). Impaired response inhibition makes it harder for an individual to stop alcohol use and promotes the continuance of drinking (Field et al., 2008). Research also shows that the use of psychoactive substances can alter executive control functions and produce deficits in response inhibition (Verdejo-Garcia et al., 2008; Verdejo-García, Perales, & Pérez-García, 2007). In addition, chronic alcohol use is linked with serious cognitive defects having an effect on inhibition even after detoxification treatment (Noël, Van der Linden, Schmidt, & et al., 2001) and there are also indications that alcohol use can trigger impulsive behavior (Goldstein & Volkow, 2002; Jentsch & Taylor, 1999).

In summary, impulsive behavior consists of two distinct neural systems that interact with each other, a bottom-up impulsive system and a top-down reflective system. Impulsive action occurs when individuals have difficulties in restraining particular behavior and is linked to impulsive action. Response inhibition can be understood as the motor component of impulsive action. Impaired response inhibition is associated with problems in impulsive and reflective behavior and promotes the continuation of drinking. Studies also indicate that this process can predict alcohol abuse and that substance use can generate deficits in response inhibition.

**Relationship between response inhibition and trait impulsivity.**

Impaired response inhibition relates to approach behavior towards substance use and abuse, but trait impulsivity is also often linked to impulse-control disorders and substance abuse disorders (Whiteside & Lynam, 2001). Studies have indicated that individuals with an impulsive personality often have problems inhibiting responses (de Wit, 2009). In general, research shows that correlations between trait impulsivity
measures and laboratory tasks seldom emerge (Bari & Robbins, 2013; Stevens et al., 2014). However, some researchers suggest that a link between both measures exist. Aichert et al. (2012) found a small but significant relationship between trait impulsivity and response inhibition within a sample of healthy subjects. Participants who score high on trait impulsivity were likely to have impaired response inhibition on a Go/No-Go task. Gorlyn, Keilp, Tryon, and Mann (2005) observed a significant association between the impulsivity trait of motor impulsiveness and the performance of an SST within a sample of healthy subjects. In addition, Perales, Verdejo-Garcia, Moya, Lozano, and Perez-Garcia (2009) found some support that trait impulsivity is linked to the neurocognitive mechanism involved in response monitoring and inhibition while performing a Go/No-Go task. On the other hand, other researchers could not find a significant relationship between response inhibition and trait impulsivity (Reynolds, Ortengren, Richards, & de Wit, 2006). Furthermore, Horn, Dolan, Elliott, Deakin, and Woodruff (2003) argued that factors such as a lower IQ might be more important than trait impulsivity itself in determining performance on a response inhibition task.

A combination of measures can be used to detect associations between both types of measures (Bari & Robbins, 2013). Assessing both could therefore further enlighten the relationship between trait impulsivity and response inhibition.

**Brain areas associated with response inhibition.**

The role of the frontal lobe as the basis of cognitive control has been predominantly in literature, and nowadays there’s a consensus that the brain consists of a network of intertwined cortical and subcortical regions, all associated with response inhibition (Bari & Robbins, 2013; Chambers et al., 2009). Tagging all the brain areas involved in response inhibition is complex because it isn’t restricted to one single brain area. Lesions and damage to the frontal regions of the brain are often associated with impairment of cognitive control. Depending on the task at hand different cortical and subcortical regions in the brain are activated and differ in responsibilities, some are responsible for maintaining concentration, while other regions are in charge of detecting conflicts, error monitoring or interpreting rules of a task (Bari & Robbins, 2013). Many regions have been linked with response inhibition and the current view is that behavioral inhibition is an interaction between the right Inferior Frontal Cortex (IFC), insula, dorsomedial areas such as pre-Supplementary Motor Area (pre-SMA) and basal ganglia (Aron, 2011; Bari & Robbins, 2013; Sharp et al., 2010). This view is supported by studies looking into both connectivity and causality (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Duann, Ide, Luo, & Li, 2009).
There’s extensive evidence suggesting that the right Inferior Frontal Gyrus (rIFG) situated in the right IFC is one of the main areas responsible for inhibiting motor responses. Functional magnetic resonance imaging (fMRI) research pointed out that the blood oxygen level (BOLD) in rIFG is increased during an inhibition task compared with baseline (Aron, Robbins, & Poldrack, 2004) and patients with lesions in rIFG do worse than controls when performing inhibitory control tasks (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003). Furthermore, individuals who are able to inhibit more quickly than others, have elevated activation in rIFG when compared with individuals who react slower (Aron et al., 2007). Moreover there’s accumulating evidence that patient populations, especially patients with attentional deficit hyperactivity disorder (ADHD), show aberrant rIFG activation when compared with controls (Dickstein, Bannon, Xavier Castellanos, & Milham, 2006; Rubia et al., 2010; Sowell et al., 2003). Some suggest that due to the converging evidence supporting the role of rIFG in successful inhibition, the right hemisphere system mediates inhibitory control (Chambers et al., 2009).

Although numerous studies indicate that rIFG plays an extensive role in the inhibition process, not all evidence is in line with this trend. In some studies patients with lesions in left IFG (lIFG) showed impairment when performing inhibition tasks (Swick, Ashley, & Turken, 2008), which means that lIFG’s role might be more extensive in the process. Other research couldn’t find response inhibition issues in brain-damaged patients with impaired rIFG (Dimitrov et al., 2003; Picton et al., 2007). This research indicates that generalization of the function of rIFG is difficult. The task of rIFG seems to be more extensive. Furthermore, research pointed out that rIFG also functions in detecting salient cues that are not always followed with the inhibition of a motor response (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). According to these findings, the function of rIFG is also related to attentional switching between stimuli, and connecting bottom-up processes where stimuli grab attention with top-down processes of executing planned behavior (Hampshire et al., 2010; Sharp et al., 2010). Based on these findings, a definite conclusion about the role of rIFG cannot be made yet and future research is needed. It’s assumed that rIFG has a function in the process of response inhibition interacting with other areas such as pre-SMA and basal ganglia (Aron, 2011; Sharp et al., 2010). Therefore, in spite of the extensive proof of the contribution of the rIFG, the specific process which it regulates still has to be determined (Bari & Robbins, 2013; Cai et al., 2016).

In sum, there’s evidence that rIFG plays an important role in the process of response inhibition but a straightforward conclusion about the exact role of rIFG cannot be made yet. The aim of the current study is to investigate the relationship between
rIFG and response inhibition within a sample of healthy subjects. This is important because impaired response inhibition is associated with approach behavior towards alcohol use, problems with cessation of drinking and relapse. Due to these problems, a challenge arises to create and develop new techniques to enhance inhibitory control. Better understanding of the relationship between response inhibition and rIFG could help in this process. To study the effect of rIFG, an experimental approach is needed to establish a causal relationship. Therefore, transcranial Direct Current Stimulation (tDCS) will be used as a causal interference technique and event-related potentials (ERP) to investigate the process of response inhibition in the human brain.

**Event-Related Potentials (ERP) of Response Inhibition**

A widespread experimental measure of response inhibition is the Go/No-Go paradigm (Bari & Robbins, 2013; Folstein & Van Petten, 2008; Huster, Enriquez-Geppert, Lavallee, Falkenstein, & Herrmann, 2013; Luijten et al., 2014; Pires, Leitao, Guerrini, & Simoes, 2014). In a Go/No-Go task there are two types of stimuli. Subjects are instructed to react as quickly as possible to regular “Go” trials but have to withhold their response on irregular “No-Go” trials. It’s assumed that participants need their inhibitory control mechanism to suppress the tendency of an automatic response. ERP research pinpoints two ERP components (N200 and P300), often referred to as the N2/P3 complex (Folstein & Van Petten, 2008; Huster et al., 2011; Ramautar, Kok, & Ridderinkhof, 2006), which is augmented during No-Go trials in comparison to Go trials. This difference in amplitudes between Go and No-Go trials suggests that both N200 and P300 are a reflection of the brain activity associated with inhibitory control.

N200 is regarded as the second negative peak; which emerges between 200 – 300 ms after presenting a stimulus (Folstein & Van Petten, 2008; Luijten et al., 2014; Polich, 2007). It’s assumed that N200 corresponds with activity in lateral frontal and/or medial brain areas (Huster et al., 2013). Brain areas most commonly associated with N200 are the inferior frontal cortex which includes rIFG (Lavric, Pizzagalli, & Forstmeier, 2004), left IFC (Huster, Westerhausen, Pantev, & Konrad, 2010), mid cingulate cortex (MCC; Bekker, Kenemans, & Verbaten, 2005) and medial PFC including anterior cingulate cortex (ACC; Huster et al., 2011; Kok, Ramautar, De Ruiter, Band, & Ridderinkhof, 2004).

P300 occurs after N200 and reflects a later stage in the process of inhibition. Where N200 is more of an index of the initiation of motor inhibition, P300 is more closely related to the behavior of inhibiting the motor response itself (Huster et al., 2013; Luijten et al., 2014; Pires et al., 2014). P300 is a long-lasting positive wave which peaks between 300 and 500 ms after stimulus onset and comprises of at least two
subcomponents: P3a reflects stimulus-Driven orientation to salient changes in both regular and novel stimuli while P3b is more closely related to appraisal of stimuli and working-memory (Huster et al., 2013; Polich, 2007). When sensory input is processed, a novel or unexpected stimuli that captures attention activates the frontal lobe, producing P3a while memory updating processes activate tempo-parietal regions resulting in a P3b (Polich, 2007). Brain areas associated with P300 are linked with pre-motor and motor areas (Kok et al., 2004; Ramautar et al., 2006), which suggest that P300 is probably more directly related to the actual process of motor inhibition itself whereas N200 seems to be more closely attached to non-motor processing phases such as conflict and error monitoring (Huster et al., 2013; Pires et al., 2014). Based on previous research, it can be assumed that both N200 and P300 are distinct features in the process of response inhibition and can potentially be considered as indicators of neural deficits within substance dependent populations (Luijten et al., 2014).

**Relationship between N2/P3 complex and alcohol related problems.**

There’s some evidence showing an association between No-Go P300 amplitudes and vulnerability to alcohol dependency. According to a number of studies, alcoholics are less precise, commit more commission errors and show lower P300 amplitudes in both Go and No-Go trials when compared to controls, which suggests deficiencies in both response activation and response inhibition (Kamarajan, Porjesz, Jones, Choi, et al., 2005). Furthermore, the reduced amplitude during the processing of No-Go trials is an indicator of a decrease in frontal lobe activity (Kamarajan, Porjesz, Jones, Choi, et al., 2005). There’s also a less potent difference between Go and No-Go trials in alcoholics compared to controls, supporting the notion that controls are better in differentiation between Go and No-Go trials when compared with alcoholics (Kamarajan, Porjesz, Jones, Choi, et al., 2005). Moreover, a decreased No-Go P300 was also found in offspring of alcoholics and can be interpreted as a potential neurocognitive marker in developing alcoholism or substance use disorders (Kamarajan, Porjesz, Jones, Chorlian, et al., 2005). In an alcohol-related context, cues that point to alcohol are more salient for heavy social drinkers when compared with light social drinkers, and a delayed P300 has been found with heavy social drinkers compared to light drinkers (Petit et al., 2012). There’s also evidence revealing a diminished P300 amplitude in heavy social drinkers compared to light drinkers (Oddy & Barry, 2009). Both the idea of the influence of alcohol-related context where cues take hold of the attention (Oddy & Barry, 2009; Petit et al., 2012) combined with deficits in cognitive control mechanisms (Kamarajan, Porjesz, Jones, Choi, et al., 2005; Kamarajan, Porjesz, Jones, Chorlian, et al., 2005) are in line with the dual process
approach, which states that alcoholics have insufficient response inhibition and an attentional bias towards alcohol-related cues. On the other hand, other research is less conclusive. In a group of young heavy drinkers larger P300 amplitudes were found in both Go and No-Go trials, with rIFC more active during successful inhibition (López-Caneda et al., 2012). Another similar longitudinal fMRI study revealed that future heavy social drinkers had less activation in neural systems linked with response inhibition prior to onset of drinking when compared with continuous non-drinkers, but showed more activation after onset in frontal, parietal and cerebellar areas of the brain, motivating researchers to infer the existence of preceding differences and a possible latent neural vulnerability (Wetherill et al., 2013). Furthermore, it also suggests that starting to drink may lead to modification in brain functioning (Wetherill et al., 2013). In a recent study, Petit et al. (2014) have argued that behavioral data in combination with ERP can be used to predict relapse in recently detoxified alcoholics. In a Go/No-Go task performed at the end of a detoxification cure, No-Go P300 was the only parameter contrasting future relapsers from non-relapsers (Petit et al., 2014).

The relation between alcohol and N200 remains unclear and research is scarce compared to P300. A study investigating the effect of alcohol on error processing and response inhibition found N200 differences between regular and irregular trials but this effect was not altered through alcohol intake (Ridderinkhof et al., 2002). In Go/No-Go experiments, there were no group differences in No-Go N200 found between alcoholics and controls (Kamarajan, Porjesz, Jones, Choi, et al., 2005), between heavy and light drinkers (Petit et al., 2012) and between abstinent drug users and controls (Morie et al., 2014). A recent longitudinal study from Korucuoğlu, Gladwin, and Wiers (2015) suggests that a potential deficiency in monitoring might be a vulnerability marker for alcohol abuse in adolescents. At baseline, adolescents were exposed to alcohol-related cues versus non-alcohol cues and were divided in a placebo versus alcohol condition. Changes in alcohol use within subjects were assessed for a period of six months. Both conflict monitoring (N200) and error detection (ERN) processes were examined. No-Go N200 amplitude was larger for alcohol cues, while alcohol intake decreased No-Go N200 for alcohol cues. Differences at baseline predicted alcohol use 6 months later. This suggests that cues which are seen as rewards stimulate approaching behavior. In addition these results indicate that larger N200 for inhibition might be necessary (Korucuoğlu et al., 2015).

To summarize, evidence of the relation between N2/P3 complex and alcohol use still remains inconclusive. However, the relationship between cognitive control and N2/P3 is more robust. There’s supporting evidence that noninvasive brain stimulation of rIFG with tDCS increases cognitive control (Ditye, Jacobson, Walsh, & Lavidor,
2012; Jacobson, Javitt, & Lavidor, 2011), a process which is associated with problems of impulsive and reflective behavior (Bari & Robbins, 2013) and often impaired within subjects showing alcohol related problems (Field et al., 2008; Noël et al., 2001; Wiers et al., 2007). P300 and N200 can be used as neurophysiological correlates to measure the effect of tDCS, and the present study aims to examine the influence of tDCS on the No-Go N2/P3 complex. Current research on this topic is practically non-existent. If lower amplitudes in No-Go N2/P3 after tDCS stimulation can be observed within our sample of healthy subjects, then this might suggest that potential relapers, such as recently detoxified alcoholics, may profit from additional tDCS sessions apart from pharmacological and psychotherapeutic treatments. This is motivated by the findings that lower amplitudes imply that reduced brain activity is required in order to achieve response inhibition.

**Transcranial Direct Current Stimulation (tDCS)**

TDCS is a paradigm to administer noninvasive brain stimulation. It can be distinguished from other methods such as Transcranial Magnetic Stimulation (TMS) because tDCS does not evoke neuronal action potentials (Nitsche et al., 2008). To induce tDCS, two electrodes are placed on the skull and a weak direct current flows through the brain from anode to cathode creating a static electric field (Nitsche et al., 2008). The direct current spontaneously elicits excitability and activity of neurons and impacts firing of action potentials of underlying neurons due to sub-threshold changes in the resting membrane potential (Creutzfeldt, Fromm, & Kapp, 1962; Purpura & McMurtry, 1965). Because tDCS does not actually activate neurons but rather increases sensitivity of neurons, it’s described as a neuromodulation technique (Nitsche et al., 2008). Direct current stimulation is capable of inducing long-lasting (up to one hour) effects in humans after the stimulation was finished (Nitsche & Paulus, 2001; Poreisz, Boros, Antal, & Paulus, 2007). The effects on cortical activity and excitability differ according to the positioning of the electrodes and different subpopulations of neurons appear to have diverse thresholds for modulation (Stagg & Nitsche, 2011). Polarity and the positioning of electrodes have an important role in the orientation of the electric field. The anode represents the positively charged electrode, whereas the cathode serves as the negatively charged electrode. One electrode is placed over the scalp on the cortical area to be stimulated while the reference electrode is positioned over another region (e.g. supra-orbital, DLPFC, etc.) or extracranial (e.g. neck or shoulder) (DaSilva, Volz, Bikson, & Fregni, 2011). Excitation can be achieved by anodal stimulation while inhibition can be accomplished by cathodal stimulation (Nitsche & Paulus, 2000). It has to be noted that the effect of excitation and
inhibition is mainly seen in motor studies, with a focus on the physiological motor response during the execution of tasks, but rarely in cognitive research (Jacobson, Koslowsky, & Lavidor, 2012). In addition, anodal and cathodal stimulation elicit widespread neuronal network changes in regional cerebral blood flow (rCBF) and in cortical and subcortical sensory processing regions of the brain (Lang et al., 2005; Zheng, Alsop, & Schlaug, 2011).

The original focus of research with direct current stimulation was mainly on motor regions of the cortex. Priori et al. (1998) concluded that anodal scalp direct current, alternated with a negative cathodal direct current restrained the excitability of the human motor cortex as assessed with motor evoked potentials (MEP). Other researchers found an opposite effect. According to Nitsche and Paulus (2000) anodal stimulation of the motor cortex enhances excitability, while cathodal stimulation inhibits the effect. This discrepancy is probably due to the positioning of electrodes, both excitation and inhibition effects are commonly acquired in motor studies (Jacobson et al., 2012). Since those pioneering studies most of the researcher’s aim was based on motor regions. A second domain of interest is the impact of tDCS when applied over non-motor regions to measure cognitive functions. Cognitive studies cover a very broad domain. Effects on language have been described. Anodal stimulation over Wernicke’s area had a positive effect on acquiring novel vocabulary within aphasic patients (Floel, Rosser, Miichka, Knecht, & Breitenstein, 2008) and language processing in healthy individuals (Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008). In another study, tDCS over left Frontal Cortex enhanced naming accuracy within stroke patients suffering from aphasia. (Baker, Rorden, & Fridriksson, 2010). Furthermore, Manenti et al. (2015) showed effects of anodal tDCS over right DLFPC on verb retrieval. Attention and perception is another cognitive area of interest. For example: effects of anodal stimulation of posterior parietal cortex (PPC) were discovered on visual stimuli and attentional skills (Bolognini, Fregni, Casati, Olgiati, & Vallar, 2010) and spatial orientation (Bolognini, Olgiati, Rossetti, & Maravita, 2010). There’s also growing evidence suggesting an effect of direct current stimulation on memory. For instance, an improvement of working memory was found with anodal stimulation of the DLPFC (Boggio et al., 2006; Brunoni & Vanderhasselt, 2014). Lastly, effects on executive functions and cognitive control are explored, which is especially relevant in the context of the current study. There’s supporting evidence that anodal tDCS over left PFC increases cognitive control (Vanderhasselt et al., 2013). In a study of Jacobson et al. (2011), the anode was placed on rIFG and cathode on orbito-frontal cortex as reference. Anodal stimulation on rIFG in a SST resulted in diminished impulsive behavior and improved inhibitory control. In a follow-up study, which also used anodal
stimulation on rIFG and left orbito-frontal cortex as reference, the effect of direct current on rIFG combined with behavioral training resulted in better performances on a repeated-measures SST, in comparison with the group only receiving behavioral training, which implies that tDCS could have an additional effect upon behavioral training (Ditye et al., 2012).

A recent study of den Uyl, Gladwin, and Wiers (2015), using the same setup with anodal stimulation on rIFG and contralateral supraorbital region as reference, examined whether stimulation of rIFG had an effect on craving within a group of heavy social drinkers. Unfortunately, no effect of rIFG stimulation on craving was found, whereas stimulation of DLPFC effectively resulted in a diminished effect of craving. Important to note of course is that craving and response inhibition are two distinct concepts which both relate to addiction, but one could argue that improved inhibition would have an effect on inhibiting craving-related thoughts (den Uyl et al., 2015). Nevertheless, the effect of tDCS on the process of response inhibition is important enough to remain under investigation, because an impaired process of inhibition impacts the risk of substance use (de Wit, 2009) and abuse (Field et al., 2008; Noël et al., 2001; Wiers et al., 2007).

To summarize, tDCS has been around for a while (Zago, Ferrucci, Fregni, & Priori, 2008) and is a paradigm capable of inducing long-lasting effects on humans even after stimulation has finished (Nitsche et al., 2008). Research has mainly focused on the motor regions of the brain but the effects on cognitive functions have also been explored within both healthy and patient groups. The present study investigates the effects of anodal stimulation on rIFG and its effect on response inhibition within a group of healthy subjects. Previous evidence is scarce within this line of research but there are indications that stimulating this zone augments behavioral control of responses (Ditye et al., 2012; Jacobson et al., 2012).

**Hypothesis and Goals**

The main aim of the current study is to investigate whether tDCS stimulation versus sham over rIFG will improve response inhibition in healthy individuals confirming earlier research by examining No-Go P300 and No-Go N200 components. Based on previous research it’s assumed that improved cognitive control will result in better performance doing a response inhibition task. An experimental Go/No-Go task is employed twice to measure response inhibition together with an oddball face detection task as control. P300 and N200 are interpreted as neurophysiological correlates to assess the effect of tDCS. The present study is the first to our knowledge to assess whether anodal tDCS over rIFG will improve inhibiting prepotent responses within a
group of healthy subjects while performing a Go/No-Go task and if this effect is observable on the N2/P3 complex. Petit et al. (2014) showed that No-Go P300 was the best predictor for relapse within a sample of recently detoxified alcoholics. For treatment purposes this is interesting because if change in P300 No-Go amplitudes can be observed, potential relapers may profit from tDCS, in addition to other type of treatments. Prior studies have indicated that individuals with more risky drinking behavior have more difficulties inhibiting their responses as reflected with lower amplitudes on P300 in both Go and No-Go conditions (Chen et al., 2007; Kamarajan, Porjesz, Jones, Chorlian, et al., 2005; Petit et al., 2014). Moreover, certain research suggests the possibility of preexisting differences in brain activity in response inhibition prior to the onset of hazardous drinking behavior (Wetherill et al., 2013). This infers the existence of potential preceding differences and a possible underlying neural susceptibility. It has also been noted that group differences can predict nearly identical or opposed responses to tDCS (Berryhill, Peterson, Jones, & Stephens, 2014). Therefore, the influence of trait impulsivity (BIS-11), alcohol use (AUDIT) is also investigated, because these factors are known to affect ERP (Petit et al., 2014; Petit et al., 2012; Sehlmeyer et al., 2010). Based on the aforementioned literature, we present the following hypotheses:

**Effect of tDCS on mood:** the *first goal* of the current dissertation is to investigate the effect of tDCS on mood states. Previous research suggested that effects of mood can influence the neurocognitive process of response inhibition (Boehler, Hopf, Stoppel, & Krebs, 2012; Dreisbach & Goschke, 2004; Kato, Endo, & Kizuka, 2009), therefore mood states are measured at the beginning and the end of the experiment. However, we are mainly interested in the effect of tDCS on mood itself. A recent review, that investigated the effect of neuromodulation and stimulation techniques over prefrontal areas, has indicated that effects after a single rTMS/tDCS session commonly fail to produce significant changes in self-reported mood (Remue, Baeken, & De Raedt, 2016). Therefore we hypothesize that a single session will not alter mood states within healthy subjects.

**Effect of tDCS on response inhibition:** the *second goal* is to explore if tDCS over rIFG will effectively enhance response inhibition within our sample. There’s extensive evidence suggesting that the right inferior frontal gyrus (rIFG) situated in the right IFC is one of the main areas responsible for inhibiting motor responses (Aron et al., 2007; Aron et al., 2003; Aron et al., 2004; Dickstein et al., 2006; Rubia et al., 2010; Sowell et al., 2003). Prior research has indicated that stimulating this region with tDCS boosts response inhibition, resulting in fewer commission errors while performing an SST (Ditye et al., 2012; Jacobson et al., 2011). On a neurophysiological level, P300
has been identified as a potential correlate of response inhibition (Huster et al., 2013; Luijten et al., 2014; Pires et al., 2014). The current study will assess whether differences in P300 amplitude can be observed pre- and post tDCS stimulation while performing a Go/No-Go task. Furthermore N200 will also be assessed, although this process is more closely related to non-motor processing phases such as conflict- and error monitoring (Huster et al., 2013; Pires et al., 2014). On a behavioral level we hypothesize that anodal tDCS over rIFG will boost the effect of response inhibition confirming the effects observed in previous research. We expect fewer commission errors while performing the Go/No-Go task after stimulation. We expect that this effect will solely emerge within the tDCS condition but not in the placebo sham condition. Furthermore, on a neurobiological level, we hypothesize a decrease of P300 amplitude after stimulation while performing the Go/No-Go task. We expect that this effect will only show within the tDCS condition but not in the placebo condition. In addition we expect this effect will only be seen on P300 but not on N200 amplitudes.

**Relationship between trait impulsivity and response inhibition:** The third goal is to examine the relationship between trait impulsivity and response inhibition at baseline. Trait impulsivity and response inhibition have both often been linked with substance use and abuse. Therefore we look into the associations between trait impulsivity, behavioral measures of response inhibition and neurophysiological correlates. The Barratt Impulsiveness Scale (BIS-11; Patton, Stanford, and Barratt, 1995) is employed as a measure of trait impulsivity. Prior research showed small but significant associations between measures of trait impulsivity and response inhibition. Aichert et al. (2012) found a small but significant relationship between BIS impulsivity and commission errors on a Go/No-Go task within a sample of healthy subjects. Gorlyn et al. (2005) observed a significant association between motor impulsiveness and reaction times performing an SST. However, other researchers could not find similar results (Cyders & Coskunpinar, 2011; Reynolds et al., 2006) and some researchers suggest that other factors such as lower IQ might be more important (Horn et al., 2003). We hypothesize that if a significant relationship between trait impulsivity and response inhibition emerges at baseline, this effect will be small (Aichert et al., 2012; Gorlyn et al., 2005; Perales et al., 2009).

**Influence of trait impulsivity on the effect of tDCS.** Previous research didn’t investigate the influence of factors such as trait impulsivity on the effect of tDCS on response inhibition. Studies have indicated that an impulsive personality often has problems inhibiting responses (de Wit, 2009) and impairment of response inhibition has been linked to high levels of trait impulsivity (Gorlyn et al., 2005). Do stable trait aspects such as motor impulsiveness (acting without thinking), attentional
impulsiveness (difficulties with focused attention) and non planning impulsiveness (not planning and thinking without forethought before making a decision) alter the effect of tDCS on commission errors and P300 while performing a Go/No-Go task? Therefore, the fourth goal is to examine whether the effect of tDCS on behavioral and neurophysiological measures is moderated by trait impulsivity.

**Influence of self-reported alcohol use on the effect of tDCS.** Lastly, we investigate whether self-reported alcohol use influences the effect of tDCS on response inhibition. Research shows that the use of psychoactive substances can alter executive control functions and produce deficits in behavioral aspects of response inhibition (Verdejo-Garcia et al., 2008; Verdejo-Garcia et al., 2007). In addition, evidence suggests that preexisting differences exist in response inhibition prior to the onset of drinking (Wetherill et al., 2013) and alcohol abuse is linked with stable cognitive defects (Noël et al., 2001). For this reason we look if self-reported alcohol use (AUDIT) influences the effect of tDCS on behavioral and neurophysiological measures of response inhibition (Go/No-Go).
Methods

Subjects

Subjects in the current study were recruited within undergraduates and healthy individuals who were thoroughly screened and joined voluntarily in return for payment. In the past, gender differences in response inhibition have been demonstrated (Li, Huang, Constable, & Sinha, 2006). Therefore only right-handed males were selected. All of the participants were between 18 and 30 years old. Volunteers were informed of all the aspects of the experiment and were only included in the study if they met the exclusion criteria for tDCS. Exclusion criteria consisted of the following: (1) personal family history of epilepsy, (2) Recent neurosurgical treatment, (3) pacemaker or other electrical equipment (4) within ear prosthesis (5) current major medical or physical problem, (6) history of psychopathology or psychiatric disorder, (7) Current substance use or a history of substance use such as alcohol and drugs, (8) skin lesions on forehead and (9) visual impairments.

Material and Instruments

Apparatus.

EEG.

A Quick-Cap with 32 mounted electrodes (ANT® Neuro, Enschede, The Netherlands) was used to measure EEG activity at baseline and posttest. The cap was placed using standard (10 – 20 system) and intermediate positions (Fpz, Fp1, Fp2, Fz, F3, F7, F4, F8, FC1, FC5, FC2, FC6, Cz, C3, C4, T7, CP5, CP1, CP2, CP6, T8, P7, P3, Pz, P4, P8, POz, O1, Oz, O2), with the mastoid behind the ear used as a reference (see figure 1). The EEG device was amplified by battery-operated amplifiers with a gain of 30,000 and a bandpass of 0.01 – 100 Hz (ANT® Neuro, Enschede, The Netherlands) was used. Position of the ground (AFz) is located between frontal zero (Fz) and frontoparietal zero electrode (Fpz). Impedance of every electrode was kept under 10 kΩ. eeprobe™ software (ANT® Neuro, Enschede, the Netherlands) was employed to measure EEG at a sampling rate of 1,024 Hz. Trials disrupted by blinking or movement were manually removed using the Semlitsch, Anderer, Schuster, and Presslich (1986) method. Epochs were created from -200 ms to 800 ms after onset of stimulus with -200 to 0 considered as pre-stimulus baseline. Data were filtered with a 30 Hz low-pass filter.
tDCS.

In our present study, DC-STIMULATOR (neuroConn GmbH, Ilmenau, Germany) was used as tDCS device with an adjustable current up to 5000 µA. The machine has a maximum duration of 30 minutes and fade in/fade out can be set between 1 and 120 seconds. NeuroConn’s DC-STIMULATOR composes of 4 elements. A 9 V battery as power supply, an ampere meter for measuring current strength, a potentiometer as resistor allowing electric current adjustment and two electrodes. In the present study, 2 rubber 35 cm² electrodes were applied to avoid electrochemical polarization together with a NaCl solution. The anodal electrode was placed over the cortical area associated with rIFG and corresponds with to the F8 electrode (See figure 1). The cathodal electrode was positioned over the extra-cephalic left superior region of the trapezius muscle in the participant’s neck. This type of setup has been used in previous studies investigating the effect on rIFG (Enticott et al., 2012). In the present experiment we used a weak 2mA direct electric current administered over a period of 20 minutes. The current, flowing from anode to cathode creates an electric static field (Nitsche et al., 2008), resulting in underlying neurons becoming more sensitive and impacting depolarization of action potentials as a consequence of sub-threshold changes in the resting membrane potential (Creutzfeldt et al., 1962; Purpura & McMurtry, 1965). During sham stimulation, the tDCS ramps up during a period of 30 seconds just like in the active tDCS condition, but is immediately followed by a fade out. This generates an active placebo condition and makes it difficult for participants to discern between sham and active stimulation.

Figure 1. Positions of the 32 electrodes.
Experimental tasks.

**Go/No-Go.**

A computerized Go/No-Go task was assessed. Participants were confronted with a total of 186 expected Go trials (letter M) and 80 unexpected No-Go trials (letter W). Letters had a size of 500x400 mm in Arial font. Participants were asked to press as quickly as possible with their right index finger on a designated key on the gamepad when confronted with the letter “M” while inhibiting their response when confronted with the letter “W”. The letters appeared over a period of 200 ms followed by a black screen over a duration of 1300 ms (See figure 2 for an illustration). Subjects had a maximum of 1,500 ms to press before the next letter would appear. Participants were asked to sit as still as possible in a comfortable position and were instructed to try to refrain from blinking due to potential interference with the EEG.

**Face detection task.**

ERPs of an oddball task were also recorded. This task measures cognitive processes that are not related to inhibition. During this task, participants were confronted with a visual oddball using a face detection task. The task had two types of stimuli. A frequent female face was presented 150 times and an infrequent male face 50 times. Participants were instructed to press as quickly as possible when confronted with the infrequent male face (See figure 2 for an illustration). Subjects had to press a designated button on a gamepad using their right index finger. Each picture was shown for a period of 700 ms, and between stimuli a black screen was displayed over a random duration between 350 and 700 ms. Participants had 1,200 ms to react.

*Figure 2.* Trials in both Go/No-Go (left). Trials in face detection task (right).
Questionnaires.
At the beginning and the end of the experiment a visual analogue scale (VAS) was administered to measure the current state of the participant on tiredness, powerfulness, angriness, tenseness, depressiveness and cheerfulness. Moreover, demographic data such as age, education, nationality, and language were assessed, and participants were explicitly asked if they were currently using subscribed medication due to physical complaints or psychopathology. Furthermore, subjects were inquired if they had a history of mood disorders, alcohol abuse or addiction, neurological disorders and if there were accounts of psychiatric and neurological problems within the participant's family using the Mini International Neuropsychiatric Interview (M.I.N.I).

The present study used the AUDIT (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993) and BIS-11 (Lijffijt & Barratt, 2005; Patton et al., 1995) questionnaires.

The Mini International Neuropsychiatric Interview (MINI).
The Mini International Neuropsychiatric Interview (M.I.N.I.) is short diagnostic structured interview used to assess 17 DSM-IV disorders including 16 axis I disorders and one personality disorder (D. V. Sheehan et al., 1998). In our present study the M.I.N.I. SCREEN 5.0.0./English version (M.I.N.I. screen; D. Sheehan & Lecrubier, 2006) was used as a screener to assess previous episodes of the aforementioned axis I and II disorders. The M.I.N.I. screen is a 20-item questionnaire using a yes/no-coding scheme. It measures symptoms such as depressive feelings, anxiety, irritation, shame and indicators related to trauma. The M.I.N.I screen also assesses information about substance abuse. Participants had to elaborate on their use of alcohol, tobacco, illicit drugs and prescribed medicine in the past 12 months. The M.I.N.I has been found to be a valid tool with high kappa coefficients ranging between 0.88 and 1.0 for inter-rater reliability and kappa's between 0.76 and 0.93 for test-retest reliability (Lecrubier et al., 1997). The psychometric qualities haven’t been assessed yet by the COmmissie TestAangelegenheden Nederland (COTAN).

Alcohol Use Disorder Identification Test (AUDIT).
The Alcohol Use Disorder Identification Test (AUDIT) is a 10-item self-report questionnaire, which consists of 10 items and is used to assess the pattern of alcohol use and alcohol-related problems within an individual (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001; Saunders et al., 1993). This questionnaire was developed by the WHO as a simple screening instrument to detect extreme drinking patterns, and as a brief assessment tool. The translated version is based on the original version of Saunders et al. (1993). The AUDIT uses a 5-point Likert-scale. Participants can score
between 0 and 4 on each item with an individual scoring a maximum of 40 on the test. Total scores above 8 are possible indicators for perilous and harmful use of alcohol, as well as possible alcohol dependence (Babor et al., 2001). Audit scores in the range of 8 - 15 are associated with moderate levels of alcohol problems whereas scores of 16 and above correspond with more severe alcohol related problems (Miller, 1995). A score surpassing 20 indicates problematic use and points out that professional help is advised (Babor et al., 2001). Furthermore, the test consists of 3 types of items. The first type measures drinking behavior and potential hazardous alcohol use. Questions inquire how much an individual usually drinks and also the frequency of drinking and heavy drinking. The second type of items gauges alcohol dependency and especially measures problems with impaired control over drinking and problems with cessation of drinking. The last type of items inquire about alcohol-related problems such as memory loss, injury of others and feelings of guilt and remorse. There’s accumulating support for the criterion validity of the AUDIT as a screener for both mild and severe alcohol-related problems, and can be described as a reliable and valid instrument which is relatively free of cultural bias and can be employed in multiple settings (Reinert & Allen, 2007). Currently there isn’t a COTAN approval for the AUDIT.

**Barratt Impulsiveness Scale (BIS).**

The Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) is a 30-item self report questionnaire assessing the personality trait of impulsivity and is divided in three different components using oblique rotations. The first component is *motor impulsiveness* (BIS – Motor Impulsiveness) which can be understood as acting on the spur of the moment and refers to doing things without thinking, taking quick decisions and acting impulsively. The second component is *non-planning impulsiveness* (BIS – Non Planning), which relates to not planning and thinking without forethought before making a decision. *Attentional impulsiveness* (BIS – Attentional) is the last component and can be described as having difficulties with focused attention on a task. The BIS-11 uses a 4-point Likert scale with scores ranging between “rarely/never”, “Occasionally”, “Often” and “Almost Always/Always”. There are 8 attentional-, 11 motor- and 11 non-planning impulsivity items. In the present study, a translated version of the BIS-11 was used (Lijffijt & Barratt, 2005). Although reliability and validity scores over studies vary, the BIS-11 has good psychometric characteristics with Cronbach’s alphas ranging between .71 and .83 for the total score over cultures (Stanford et al., 2009). Currently COTAN hasn’t reviewed and evaluated the BIS-11.
ERP N2/P300 Components

Epochs were created for the Go/No-Go and face detection task, beginning 200 ms before the onset of stimuli and lasting 800 ms afterwards.

In the Go/No-Go task, trial type (Go vs. No-Go) and response (key press on go trials, no key press on No-Go trials) were recorded. Erroneous responses (no key press on Go-trials, key press on No-Go trials) were removed from subsequent analyses. An ANOVA was performed, excluding trials from analysis due to errors or artifacts (EOG, movements) with Time (pre vs. post) and Trial type (Go vs. No-Go) as within-subject factors, and Group (tDCS vs. sham) as between-subject factor. No effects emerged, indicating that the included trials for further ERP analyses were comparable across groups and conditions (all p's > .05). To determine the inhibitory No-Go effect, mean Go waveforms were subtracted from mean No-Go waveforms (Falkenstein, Hoormann, & Hohnsbein, 1999; Petit et al., 2014), resulting in N2d and P3d waves. N2d and P3d values were computed for each individual subject using frontocentral electrodes (Fz, FC1, FC2, FC5, FC6 and Cz) (Petit et al., 2014). N2d was computed through averaging electrical activity recorded within the 200-300 ms interval after stimulus onset and P3d through averaging values within the 300-580 ms interval.

In the oddball task, trial type (deviant vs. frequent) and response type (key press on deviant stimuli, no key press on frequent stimuli) were recorded. Erroneous responses (no key press on deviant stimuli key press on frequent stimuli) were excluded from subsequent analyses. An ANOVA was performed excluding trials from analysis due to errors with Time (pre vs. post) and Trial type (deviant vs. frequent) as within-subject factors, and Group (tDCS vs. sham) as between-subject factor. No effects were observed, indicating that the included trials for further ERP analyses were comparable across groups and conditions (all p's > .05). To determine the effect on the oddball task, P300 was investigated and emerges in the parietal areas of the brain after the detection of a deviant stimulus (Polich, 2007). The P300 component was defined using the electrodes associated with the parietal area of the brain (P3, Pz, P4, POz). For each participant P3d was computed by averaging values within the 300-580 ms interval. To determine P3d, mean frequent waveforms were subtracted from mean deviant waveforms resulting in a P3d wave.

Procedure

A double blind randomized between subjects design was used. Participants were randomly assigned to receive either active tDCS or sham tDCS. Every participant was tested individually in a laboratory and had to complete a series of tasks twice. Participants were placed in front of a 15 inch Dell laptop at approximately 60
centimeters and used a gamepad to complete each task. Before the start of the experiment, subjects were asked to sign an informed consent and started filling in the questionnaires. Meanwhile, an ERP cap was applied on the head of the participant. At baseline, the subject had to complete two distinct tasks. The first task was a face detection task that was used as a control task. This control task was used to ensure that tDCS stimulation of rIFG specifically enhanced cognitive control within subjects. During the task, participants needed to react as quickly as possible on male faces while ignoring female faces. The second task was a Go/No-Go task aimed at measuring response inhibition via ERP. During this task participants were asked to react as quickly as possible when the letter 'M' was shown on the screen and to inhibit their response when the letter 'W' was shown. After completion of both tasks, subjects were asked to wash and dry their hair as quickly as possible. Next, tDCS electrodes were applied on the skull and active/sham stimulation was applied for exactly 20 minutes. During this time, participants were asked to fill in the questionnaires. After stimulation, participants were asked to wash and dry their hair again. EEG was applied on the scalp and participants had to do both face detection and Go/No-Go task in the same order again. Afterwards participants had the chance of completing their questionnaires, if they hadn’t finished during stimulation phase. At the end of the experiment, participants received a compensation of 25 euro’s and were inquired if they thought they were in either sham or active tDCS condition. Participants were allowed to end the experiment at any given time during administration. The experiment took approximately 1h30m and was approved by the ethical comity of UZ Ghent.

Statistical Plan

Analyses were performed using SPSS 22.0®, with the level of significance set at 0.05. The assumptions of normality for both tDCS and sham group were assessed using the Shapiro-Wilk test and homogeneity of variance was evaluated using the Levene’s Test for the Equality of Error Variances. Furthermore sphericity was appraised using Mauchly's Test of Sphericity. Greenhouse-Geisser correction was applied when the assumption of sphericity did not hold. Outliers within our self-report data were corrected using outlier labeling rule (Hoaglin & Iglewicz, 1987).

Demographics and self-report data. Independent sample t-tests were conducted, to examine if statistically significant differences could be observed on self-report data (AUDIT, BIS – Attentional, BIS – Motor Planning, BIS – Non Planning) by dichotomous variable Group (tDCS vs. sham).

Effect of tDCS on mood. Based on recent review, we expect that mood states will not be altered through tDCS (Remue et al., 2016). Mood states were assessed at
the beginning and the end of the experiment. To explore whether tDCS or sham stimulation affected mood states, a repeated-measures MANOVA was conducted to assess if mean differences over Time (Pre vs. Post) emerged on VAS scales (Fatigue, Vigour, Anger, Tension, Depressed and Cheerful) by Group (tDCS vs. sham).

**Effect of tDCS on response inhibition:** on a behavioral level we hypothesize that anodal tDCS over rIFG will boost the effect of response inhibition confirming the effects observed in previous research. To investigate the effect of tDCS on reaction times and accuracy for both Go/No-Go and face detection task, repeated-measures analysis of variance (ANOVAs) were conducted. If a significance was found, paired sample t-tests were carried out to evaluate the difference. $\eta^2_p$ was used as measure of effect size. For interpreting .01, .10 and .25 were used as cut-off scores and represent small, medium or great effects respectively (Cohen, 1988). Furthermore, on a neurobiological level, we hypothesize a decrease of P300 amplitude after stimulation while performing the Go/No-Go task. We expect that this effect will emerge only in the tDCS condition. Repeated-measures ANOVAs were performed to investigate the effect of tDCS on N2/P3 complex. An independent sample t-test with Group (tDCS vs. sham) as between-subject factor was conducted to assess if observed differences on N2/P3 emerged prior or post stimulation. If significance was observed, paired sample t-tests were used to appraise the disparity.

**Trait impulsivity and response inhibition:** Prior research showed small but significant associations between measures of trait impulsivity and response inhibition. We hypothesize that if a significant relationship between trait impulsivity measures (BIS – Attentional, BIS – Non Planning, BIS – Motor Planning) and No-Go P300 emerges at baseline, this effect will be small (Aichert et al., 2012; Gorlyn et al., 2005; Perales et al., 2009). To investigate whether a statistically significant relationship between trait impulsivity (BIS – Attentional, BIS – Non Planning, BIS – Motor Planning), commission errors and No-Go P300 could be observed, a Pearson product-moment r correlation was conducted. Cohen’s standard is used to evaluate the correlation coefficient, where .10 represents a weak association between two variables, .30 represents a moderate association, and .50 represents a strong association (Cohen, 1988). A Bonferroni adjusted alpha level of .017 per test was used (.05/3) to correct for multiple comparisons (three comparisons for commission errors and three comparisons for No-Go P300).

**Influence of trait impulsivity on the effect of tDCS.** We examined whether trait impulsivity moderates the effect of tDCS on response inhibition. To examine whether after controlling for trait impulsivity, differences between Group (tDCS vs. sham) on No-Go P300 by Time (Pre vs. Post) emerge, three repeated-measures
analysis of covariance (ANCOVA) were conducted with BIS – Non Planning, BIS – Motor Planning and BIS – Attentional as covariates. The purpose was to partial-out the effects of the covariates and Group on P300 to determine if the effect of tDCS on P300 delta is moderated by trait impulsivity measures or not.

**Influence of self-reported alcohol use on the effect of tDCS.** We looked into the effect of self-reported alcohol use (AUDIT) on behavioral and neurophysiological measures of response inhibition (Go/No-Go). To examine whether after controlling for AUDIT scores, differences between Group (tDCS vs. sham) on No-Go P300 and commission errors by Time (Pre vs. Post) emerge, two repeated-measures analysis of covariance (ANCOVA) were conducted. The purpose was to partial-out the effect of alcohol use and Group on P300 to determine if the observed effect of tDCS on both P300 delta and commission errors is due to alcohol use or if the differences are independent of the effect of alcohol use.
Results

Demographics and Self-Report Data
An independent sample \( t \)-test was performed to compare means between tDCS and sham group on self-report data. The assumption of equal variances was met (all \( p \)'s > .05). The Shapiro-Wilk test assumed a non-normal distribution for BIS – Motor Planning within the sham group (\( p = .48 \)). Therefore we standardized the scores for BIS – Motor Planning. There were no significant differences between tDCS and sham for Age, \( t(1,29) = -.641, p = .527 \), BIS – Attentional, \( t(1,29) = .542, p = .592 \), BIS – Motor Planning, \( t(1,29) = .261, p = .796 \) and BIS – Non Planning, \( t(1,29) = -.945, p = .352 \). However, there was a marginally statistically significant difference in the scores for AUDIT in the tDCS, \( (M = 10.4, SD = 3.8) \) and sham \( (M = 7.8, SD = 3.7) \) conditions; \( t(1,29) = -1.934, p = .063 \). Table 1 summarizes the means and standard deviations for the demographical and self-report data.

Table 1. Characteristics of tDCS and Sham participants presented as means (standard deviations).

<table>
<thead>
<tr>
<th></th>
<th>tDCS ( (n = 15) )</th>
<th>Sham ( (n = 16) )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>21.9 (3.1)</td>
<td>21.3 (1.7)</td>
<td>0.527</td>
</tr>
<tr>
<td>Alcohol problems (AUDIT)</td>
<td>10.4 (3.8)</td>
<td>7.8 (3.7)</td>
<td>0.063</td>
</tr>
</tbody>
</table>

BIS-11
<table>
<thead>
<tr>
<th></th>
<th>tDCS ( (n = 15) )</th>
<th>Sham ( (n = 16) )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIS – Attentional</td>
<td>13.2 (3.6)</td>
<td>13.9 (3.4)</td>
<td>0.592</td>
</tr>
<tr>
<td>BIS - Motor Planning*</td>
<td>13.5 (4.2)</td>
<td>13.9 (4.5)</td>
<td>0.796</td>
</tr>
<tr>
<td>BIS - Non Planning</td>
<td>30.1 (4.3)</td>
<td>29 (6.4)</td>
<td>0.352</td>
</tr>
</tbody>
</table>

All values are \( p > .5 \) (NS)
*BIS – Motor Planning: Unstandardized score

Effect of tDCS on Mood

A 2X2 Repeated Measures MANOVA with Time (pre vs. post) as within-subject factors and Group (tDCS vs. sham) as between-subject factor was carried out to detect changes in mood. Mood scores evaluated with VAS (fatigue, vigour, anger, tension, depressed and cheerful) were used as multiple dependent variables. Differences in VAS prior and post stimulation for both tDCS and sham group are presented in table 2.

Analyses revealed a main effect of Time on depressed, \( F(1,28) = 5.981, p = .021 \), indicating that in general participants reported fewer depressed feelings at the end of the experiment. No effect of Time was found for fatigue, \( F(1,28) = 0.678, p = \)
.417, vigour, $F(1,28) = 0.741, p = .397$, anger, $F(1,28) = 1.916, p = .177$, tension, $F(1,28) = 2.254, p = .144$, and cheerful, $F(1,28) = 0.438, p = .513$.

No effect of Group was found for all mood scales: fatigue, $F(1,28) = 0.874, p = .358$, vigour, $F(1,28) = 0.595, p = .447$, anger, $F(1,28) = 0.001, p = .982$, tension, $F(1,28) = 0.020, p = .888$, depressed, $F(1,28) = 0.014, p = .907$ and cheerful, $F(1,28) = 1.607, p = .215$.

Furthermore, no interaction effects between Time and Group were found for all mood scales: fatigue, $F(1,28) = 0.761, p = .390$, vigour, $F(1,28) = 0.412, p = .526$, anger, $F(1,28) = 0.140, p = .711$, tension, $F(1,28) = 0.010, p = .923$, depressed, $F(1,28) = 0.013, p = .911$, and cheerful, $F(1,28) = 2.285, p = .142$.

These scores indicate that no short-term mood changes due to tDCS stimulation were observed.

**Table 2. Mean ratings and standard deviations for the VAS measures before, and 60 minutes after tDCS or SHAM stimulation.**

<table>
<thead>
<tr>
<th>Active tDCS (n = 15)</th>
<th>Sham Placebo (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre</strong></td>
<td><strong>Post</strong></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.25 (1.37)</td>
</tr>
<tr>
<td>Vigour</td>
<td>6.05 (2.00)</td>
</tr>
<tr>
<td>Anger</td>
<td>0.89 (0.82)</td>
</tr>
<tr>
<td>Tension</td>
<td>2.05 (2.20)</td>
</tr>
<tr>
<td>Depressed</td>
<td>1.045 (0.94)</td>
</tr>
<tr>
<td>Cheerful</td>
<td>6.50 (1.98)</td>
</tr>
</tbody>
</table>

**Effect of tDCS on Behavioral Measures**

**Go/No-Go task.**

Analyses were performed on reaction times, omissions and commission errors using three 2 (Time; pre vs. post) x 2 (Group; tDCS vs. sham) repeated-measures ANOVAs. Time was defined as within-subject factor and Group as between-subject factor. Reaction times and accuracy (i.e. a correct button press within the response time-out window in go trials and not responding when required in no-go trials) were examined as dependent variables. Mean reaction times to go trials, omissions and commission errors to no-go trials are presented by Group in table 3.
Reaction time measures on Go-trials. Analyses revealed a significant main effect of the between-subject factor Group, $F(1,29) = 6.460, p = .017, \eta^2_p = .162$, observed power = .690. Subjects in the sham group reacted faster on Go trials. There were no effects for Time, $F(1,29) = 1.956, p = .172$ and Time X Group, $F(1,29) = 1.051$, $p = .314$.

Omission errors (not responding in No-Go trials). Results showed no effects for Time, $F(1,29) = 0.272, p = .606$, Group, $F(1,29) = 1.719, p = .200$, and Group X Time, $F(1,29) = 3.515, p = .071$. Furthermore, mean performance in both groups was in 99% of the trials correct which indicates a possible ceiling effect.

Inhibition errors on No-Go trials (commission errors). The main effect for Time, $F(1,29) = 5.702, p = .024, \eta^2_p = .164$, observed power = .636, indicates a test-retest effect with fewer errors committed post stimulation (over active and sham). However no effect of Group, $F(1,29) = .364, p = .551$, and Group X Time. ($F(1,29) = 2.599, p = .118$) emerged indicating that performance within both groups was similar and accuracy between tDCS and sham did not vary.

Of note, A significant negative correlation between reaction times on Go-trials and accuracy in sham, $r = -.536, p = .032$, indicates a potential speed-accuracy tradeoff within the sham group. Faster reaction times on Go-trials correlated with more commission errors during No-Go trials. Within the tDCS group, there was no significant correlation between reaction times on Go-trials and accuracy, $r = -.363, p = .183$.

Table 3. Go/No-Go Task. Reaction times and standard deviations to Go stimuli for pre-post, sham-tDCS.

<table>
<thead>
<tr>
<th></th>
<th>tDCS ($n = 15$)</th>
<th>Sham ($n = 16$)</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Go RTs (ms) – pre</td>
<td>325 (39)</td>
<td>303 (43)</td>
<td>314 (42)</td>
</tr>
<tr>
<td>Go RTs (ms) – post</td>
<td>322 (47)</td>
<td>283 (34)</td>
<td>302 (45)</td>
</tr>
<tr>
<td>Omission error rates (/186) – pre</td>
<td>184 (3.2)</td>
<td>184 (1.4)</td>
<td>184 (2.4)</td>
</tr>
<tr>
<td>Omission error rates (/186) – post</td>
<td>183 (5.1)</td>
<td>185 (0.6)</td>
<td>184 (3.6)</td>
</tr>
<tr>
<td>Commission error rates (/80) – pre</td>
<td>16 (8.8)</td>
<td>18 (9.3)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Commission error rates (/80) – post</td>
<td>15 (9.6)</td>
<td>15 (8.3)</td>
<td>15 (8.8)</td>
</tr>
</tbody>
</table>

Face detection task.

Analyses of the oddball task were performed on reaction times, omission errors and false alarms using repeated-measures ANOVAs. Time (pre vs. post) was defined
as within-subject factor and Group (tDCS vs. sham) as between-subject factor. Analyses are presented in Table 4.

**Reaction time measures.** Analyses of reaction times revealed a main effect of Time, $F(1,29) = 6.867, p = .014, \eta^2_p = .191$, observed power = .717. Both groups reacted faster post sham/tDCS stimulation suggesting a possible learning effect in both groups. The main effect of Group, $F(1,29) = 3.894, p = .050, \eta^2_p = .118$, observed power = .479, illustrates that participants were quicker in the sham condition. There was no interaction between Time X Group ($F(1,29) = 0.018, p = .895$).

**Omission errors (not responding on infrequent stimuli).** Time, $F(1,29) = 0.795, p = .380$, Group, $F(1,29) = 1.790, p = .191$, and Time X Group, $F(1,29) = 0.372, p = .547$, showed no significant effects. Again, mean performance in both groups was in 99% of the trials correct indicating a potential ceiling effect.

**False alarms (responding on frequent stimuli).** The main effect of Time, $F(1,29) = 7.429, p = .011, \eta^2_p = .204$, observed power = .750, implies that both groups had more false alarms post stimulation. Also, no effect of Group, $F(1,29) = 0.215, p = .647$ and Time X Group, $F(1,29) = 0.002, p = .956$, emerged.

Table 4. The Face Detection task. Reaction times and standard deviations to deviant stimuli and error rates for pre-post, sham-tDCS.

<table>
<thead>
<tr>
<th></th>
<th>tDCS (n = 15)</th>
<th>Sham (n = 16)</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Go RTs (ms) – pre</td>
<td>415 (34)</td>
<td>395 (29)</td>
<td>405 (33)</td>
</tr>
<tr>
<td>Go RTs (ms) – post</td>
<td>405 (30)</td>
<td>384 (32)</td>
<td>394 (32)</td>
</tr>
<tr>
<td>False Alarms (/140) – pre</td>
<td>0.33 (0.6)</td>
<td>0.44 (0.5)</td>
<td>0.39 (0.5)</td>
</tr>
<tr>
<td>False Alarms (/140) – post</td>
<td>0.93 (1.2)</td>
<td>1 (1.18)</td>
<td>1 (1.18)</td>
</tr>
<tr>
<td>Omissions (/60) – pre</td>
<td>59.4 (1.5)</td>
<td>59.8 (0.3)</td>
<td>59.6 (1.1)</td>
</tr>
<tr>
<td>Omissions (/60) – post</td>
<td>59.8 (0.5)</td>
<td>59.9 (0.2)</td>
<td>59.8 (0.4)</td>
</tr>
</tbody>
</table>

**Effect of tDCS on N2/P3 Complex**

**Go/No-Go task.**

To investigate whether an effect of tDCS could be observed on the N2/P3 complex, repeated measures ANOVAs were performed with Time (pre vs. post) as within-subject factor and Group (tDCS vs. sham) as between-subject factor. A mean value for N200 and P300 amplitudes was calculated, based on the averages for pre- and post stimulation (mean amplitude average for Fz, FC1, FC2, FC5, FC6, Cz).
Analyses on N200 didn’t reveal an effect of Time, $F(1,29) = 0.0002$, $p = .986$, Group, $F(1,29) = 0.400$, $p = .532$, and Time $\times$ Group, $F(1,29) = 2.012$, $p = .167$.

Analyses on P300 were performed next. The factors Time, $F(1,29) = 0.272$, $p = .606$, and Group, $F(1,29) = 0.838$, $p = .368$, did not reach significance. However, an effect of Time $\times$ Group, $F(1,29) = 4.525$, $p = .042$; $\eta^2_p = .135$, observed power = .538, was observed. An independent sample $t$-test was conducted to evaluate the difference between sham and tDCS on No-Go P300 values, prior and post stimulation. There was a significant difference in No-Go P300 amplitudes post stimulation between sham, $M = 3.407$, $SD = 1.98$, and tDCS, $M = 1.942$, $SD = 1.55$, $t(1,29) = 2.278$, $p = .030$. Prior to stimulation, no effect emerged on No-Go P300 between sham, $M = 2.782$, $SD = 2.67$, and tDCS, $M = 3.061$, $SD = 1.94$, $t(1,29) = -.396$, $p = .695$, indicating that a difference in No-Go P300 only appeared post stimulation. Paired sample $t$-tests were used to investigate the difference pre-post for each group separately. An amplitude difference in the tDCS group was observed, $t(14) = 2.299$, $p = .037$, with a decrement of amplitudes post stimulation, while no difference emerged in the sham group, $t(15) = -0.999$, $p = .333$, confirming our previous results.

In summary these data indicate that administering active tDCS over the rIFG has an effect on P300, a neurophysiological correlate of response inhibition. An independent sample $t$-test indicated that both groups differed post stimulation. Paired sample $t$-tests illustrated that this decrease of amplitude was only observed within tDCS participants whereas this decrement was not observable within sham participants.

**Face detection task.**

An oddball task was performed as a control task to test whether the effect is viable for any cognitive task or specific for response inhibition. Again, a repeated-measures ANOVA was carried out on P300 with Time (Pre vs. Post) as within-subject factor and Group as between-subject factor. A mean value for P300 amplitudes was calculated, based on the averages for pre- and post stimulation (Pz, P3, P4, Poz). Within the oddball task, P300 occurs in the parietal areas of the brain. For this reason we used the typical parietal electrode setup (Pz, P3, P4, Poz) to obtain individual P300 values. No effect emerged of Time, $F(1,29) = 2.038$, $p = .164$, Group, $F(1,29) = 0.022$, $p = .822$, and Time $\times$ Group, $F(1,29) = 0.025$, $p = .875$ (see figure 3). Next the electrodes (Fz, FC1, FC2, FC3, FC5, FC6, Cz) used during the Go/No-Go task were observed. Similar results were observed. No effect of Time, $F(1,29) = 0.035$, $p = .852$,
Group, $F(1,29) = 0.047, p = .830$, and Time X Group, $F(1,29) = 0.000, p = .988$, was observed.

Figure 3. Amplitude differences between tDCS and sham, pre/post stimulation on both Go/No-Go task and face detection task.

Correlations between Trait Impulsivity and Response Inhibition.

In this part we investigated if individual differences in trait impulsivity correlated with P300 amplitude and commission errors on No-Go trials, prior to stimulation.
Bonferroni correction was applied to counteract the problem of multiple comparisons (three comparisons for the behavioral and three comparisons for the neuropsychological variable). Analyses revealed a moderately strong correlation between BIS – Attentional and commission errors, $r = .429$, $p = .016$, indicating that participants that have difficulties maintaining focus on tasks committed more response inhibition errors during No-Go tasks. Correlations between trait impulsivity, commission errors and No-Go P300 at baseline are presented in table 6.

Table 6. Correlation table between behavioral and neurophysiological measures of response inhibition and trait Impulsivity measures ($n = 31$)

<table>
<thead>
<tr>
<th>Variables</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. BIS - Attentional</td>
<td>.450*</td>
<td>.509**</td>
<td>.149</td>
<td>.429*</td>
</tr>
<tr>
<td>2. BIS - Motor Planning</td>
<td>-</td>
<td>.738**</td>
<td>-.198</td>
<td>.343</td>
</tr>
<tr>
<td>3. BIS - Non Planning</td>
<td>-</td>
<td>-</td>
<td>-.091</td>
<td>.183</td>
</tr>
<tr>
<td>4. No-Go P300 (Pre)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>.043</td>
</tr>
<tr>
<td>5. Commission errors (Pre)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*p <= .05. ** p <= .01

*p-values less than .0167 were deemed significant after Bonferroni adjustment.

Influence of Trait Impulsivity on the Effect of tDCS.

Analysis was only performed on P300 for No-Go trials, since prior analyses indicated that no effects on behavioral measures and the neurophysiological correlate of N200 emerged. To determine whether the observed effect of tDCS on P300 was due to potential confounding variables, repeated-measures ANCOVAs were performed with Time (pre vs. post) as within-subject factor and Group (tDCS vs. sham) as between-subject factor. Self-report measures (BIS – Attentional, BIS – Non Planning and BIS – Motor Planning were included as covariates. For each covariate a separate repeated measures ANCOVA was conducted. Levene’s tests were performed to assess the assumption of homogeneity of variances. Equality of variances was never violated for the present analyses ($p$'s > .179). Also, the assumption of homogeneity of regression slopes was analyzed but never broken ($p$'s > .379). Results indicate that BIS – Attentional, $F(1,28) = 0.407$, $p = .529$, BIS – Motor Planning, $F(1,28) = 1.204$, $p = .282$ and BIS – Non Planning, $F(1,28) = .049$, $p = .827$, didn’t influence the effect of tDCS on No-Go P300.
Influence of Self-Reported Alcohol Use on the Effect of tDCS.

Because AUDIT scores were marginally significant between sham and tDCS group, analyses were performed on both No-Go P300 and commission errors for No-Go trials.

A repeated-measures ANCOVA was conducted to determine a statistically significant difference between tDCS and sham on pre- and post stimulation P300 in No-Go trials controlling for the effect of AUDIT scores. Time (pre vs. post) was defined as within-subject factor and Group (tDCS vs. sham) as between-subject factor. Levene’s test was performed to assess the assumption of homogeneity of variances. Equality of variances was never violated (p's > .228). Also, the assumption of homogeneity of regression slopes was analyzed but never broken, $F(1,29) = .263, \ p = .770$. Analysis showed no significant effect of Group on P300 after controlling for AUDIT, $F(1,28) = 0.016, \ p = .906$. These results suggest that the effect of tDCS on No-Go P300 wasn’t influenced by alcohol use.

Next, a repeated-measures ANCOVA was conducted to assess if mean differences between tDCS and sham exist on commission errors, controlling for the effect of AUDIT scores. Again, Time (pre vs. post) was defined as within-subject factor and Group (tDCS vs. sham) as between-subject factor. Levene’s test indicated equal variances (p's > .678). Homogeneity of regression slopes was not broken, $F(1,29) = 2.599, \ p = .118$. Analysis showed no significant effect of Group on commission errors after controlling for AUDIT, $F(1,29) = 0.364, \ p = .551$. These results indicate that the effect of tDCS on commission errors wasn’t influenced by alcohol use.
Discussion

The goal of the present study was to examine the influence of tDCS vs. sham on response inhibition. Impaired response inhibition is known to as a risk factor for both substance use (de Wit, 2009) and abuse (Field et al., 2008; Noël et al., 2001; Wiers et al., 2007). Studies have indicated that impaired response inhibition can predict alcohol abuse (Nigg et al., 2006) and pre-existing differences in response inhibition can be observed between individuals before the onset of drinking (Wetherill et al., 2013). It also makes it harder for alcohol dependent patients to stop drinking, often resulting in difficulties abstaining (Field et al., 2008). Better understanding of this process can therefore help in the prevention of alcohol abuse and development of better treatment methods. This is needed because treatment continues to be difficult (O’Brien, 2008), often resulting in relapse (Finney et al., 1996; Heinz et al., 2009). There’s evidence that rIFG plays an important role in the process of response inhibition. To study rIFG and its relationship with response inhibition, ERP and tDCS were utilized to increase insight. Neuromodulation through tDCS gives us a causal interference technique to investigate whether stimulating rIFG effectively improved response inhibition and ERP provides the tools to examine this process in the human brain.

To conduct our research, a sample of right-handed males aged between 18 and 30 was investigated. Participants who received active tDCS were expected to have improved response inhibition in comparison with their counterparts in the sham condition. Every participant was tested individually and had to complete a series of tasks twice. The first task was a face detection task which is associated with cognitive processes that are not related to inhibition. During this task participants faced a visual oddball task with frequent and infrequent face stimuli. Participants were instructed to react as quickly as possible when confronted with an infrequent stimulus. The second task was a Go/No-go task and is assumed to be a measure of response inhibition. Participants were asked to react as quickly as possible to frequent “M” letters and inhibit their response when confronted with infrequent “W” letters. During this task, ERP was used to measure neural components (P300 and N200) that are linked with response inhibition. After having completed the face detection task and Go/No-Go task at baseline, participants received either sham of active tDCS for a period of exactly 20 minutes. After stimulation was finished, participants were asked to complete both tasks in the same order again.

Comparing tDCS and sham revealed no significant differences between self-reported trait impulsivity (BIS-11) at baseline. However a marginally significant difference between sham and tDCS on AUDIT scores was observed at baseline. This
is important to note since prior research indicated the potential influence of these factors on ERP. Previous research has denoted that heavy social drinkers committed more commission errors than light drinkers when confronted with alcohol-related cues, which was reflected by a delayed P300 component (Kreusch et al., 2014; Petit et al., 2012). However differences independent of context have also been observed (Petit et al., 2014). Therefore we assessed if AUDIT scores moderated the effect of tDCS on neurophysiological- and behavioral measures of response inhibition. Results indicated that AUDIT scores didn’t influence the effect of tDCS on response inhibition (cf. infra).

Effects of mood were analyzed. Subjective mood reports did not alter after a single session of tDCS over rIFG. Early research supported the idea of the effect of neurostimulation over prefrontal zones on mood after a single session, but recent studies couldn’t reproduce these effects (Remue et al., 2016). As expected, our results don’t support the notion that neuromodulation- and stimulation techniques over prefrontal cortex produce significant changes in mood after a single session. Furthermore this indicates that our results were not influenced by mood, and that tDCS itself did not influence mood states within our sample of healthy subjects.

Effect of tDCS on response inhibition was analyzed. We hypothesized that anodal tDCS over rIFG would enhance the effect of response inhibition. On a behavioral level, tDCS did not influence response times and accuracy measures (i.e., reaction times, commission errors and omissions) on the Go/No-Go task. This was not in line of our expectations. Previous research using an SST paradigm, which specifically targets the motor component of impulsivity, found evidence that anodal tDCS over the rIFG enhanced the ability of refraining responses and observing a significant reduction in reaction times (Cai et al., 2016; Ditye et al., 2012; Jacobson et al., 2011; Stramaccia et al., 2015). Similar research using TMS resulted in comparable effects (Chambers et al., 2006; Verbruggen, Aron, Stevens, & Chambers, 2010). However, other studies are in line with our findings and failed to find or replicate the effect of tDCS on behavioral measures (Berryhill et al., 2014; Dambacher et al., 2015). A possible explanation for these results could be the type of task that was given to our subjects. Participants need to be engaged and properly stimulated for the tasks at hand. The possibility exists that our group of young healthy subjects needed a more challenging task to impact behavioral changes. On the other hand, we did find evidence on a neurophysiological level (cf. infra). This could mean that non-invasive brain stimulation possibly affects the relationship between different behavioral constructs rather than the behavior itself. If this is true, then more complex tasks are required to measure changes on a behavioral level, though not too complex because at
that point too many resources might be needed for performing the task, that are more related to other processes.

Furthermore, a significant negative correlation between reaction times on Go-trials and accuracy on No-Go trials was observed in sham indicating the possibility of a speed-accuracy trade-off. Reaction times in Go-trials were associated with fewer commission errors on No-Go trials, which means that participants who reacted slower were less prone to make mistakes during No-Go trials and were better at inhibiting their responses then fast responders. This suggests that not only task characteristics determined performance but also the strategy which was applied by our participants. Although the participants were given the instruction to react as quickly as possible, it seems that differences in approach were used when performing the test. This difference in strategy could have potentially influenced the effect on behavioral measures, and is a possible explanation why no differences between sham and tDCS on behavioral measures could have been observed. Lastly a ceiling effect was also perceived on No-Go trials making discrimination among subjects difficult. This could have potentially impacted behavioral measures and can also be seen as a possible explanation why no differences between sham and tDCS were observed.

Although no effect on behavior was observed while performing a Go/No-Go task, ERP did show an effect on neurophysiological measures. The N2/P3 complex was used as neurophysiological measure of the effect of tDCS. On the Go/No-Go task, a significant decrease in P300 amplitude was observed after tDCS stimulation on No-Go trials. This decrement can be interpreted as a marker for the effect of tDCS on rIFG. Lower P300 amplitudes post stimulation suggests that participants who received active tDCS needed fewer cognitive resources to perform the Go/No-Go task. This change in P300 could not be observed after sham stimulation, indicating that the effect was due to tDCS. In addition, this effect on P300 did not emerge on the oddball task; a task which targets parietal areas in the brain and is not related to response inhibition. This indicates that the observed reduced brain activation was specifically needed to achieve response inhibition. Based on these findings we can assume that response inhibition was indeed facilitated after 20 minutes of tDCS stimulation confirming our hypothesis. These results support the notion that P300 is indeed a correlate of response inhibition as observed in prior research (Huster et al., 2013; Luijten et al., 2014; Pires et al., 2014) and also supports the idea of the relationship between rIFG and response inhibition (Aron et al., 2007; Aron et al., 2003; Aron et al., 2004; Dickstein et al., 2006; Rubia et al., 2010; Sowell et al., 2003). N200 was also investigated. Anodal tDCS over rIFG did not reveal any effect on N200. This is in line with our expectations. N200
seems to be more closely related to aspects such as conflict- and error monitoring (Huster et al., 2013; Pires et al., 2014), but less with response inhibition itself.

Next we investigated if trait impulsivity correlated with behavioral and neurophysiological measures of response inhibition at baseline. Previous research has indicated that correlations between behavioral measures of impulsivity in laboratory tasks and self-report questionnaires are often non-existent (Bari & Robbins, 2013; Stevens et al., 2014). However, the relationship between trait impulsivity and response inhibition remains interesting because impaired response inhibition, together with trait impulsivity have both been linked to alcohol use and problems that are related to alcohol. A Bonferroni adjusted alpha level of .017 per test was used to correct for multiple comparisons (three comparisons for commission errors and three comparisons for No-Go P300). One association was deemed significant which is in line with prior research. Others studies also observed small yet significant associations between trait impulsivity and response inhibition (Aichert et al., 2012; Gorlyn et al., 2005; Perales et al., 2009). Within the present study, the correlation between attentional impulsiveness and commission errors, $r = .429$, $p = .016$, was significant. Therefore it can be interpreted as a potential indicator of a significant relationship between one aspect of trait impulsivity and response inhibition. High scorers on attentional impulsiveness can be described as individuals who have difficulties keeping focused while performing a task and it seems that this group had more difficulties inhibiting their responses at baseline. Participants who score high on this trait might have found it hard to keep their attention and stay focused when performing the Go/No-Go task, resulting in more commission errors. These findings are in line with the idea that an impulsive personality has more difficulties with response inhibition (de Wit, 2009) and the notion that impairment of response inhibition is often linked with high levels of trait impulsivity (Gorlyn et al., 2005). Interestingly the effect in the present study was only observable on neurophysiological measures. This could indicate that although subjects who have problems keeping focused, committed more commission errors during No-Go trials. However, the cognitive effort they used to perform the task was similar when compared with less impulsive subjects. This suggests that although the outcome is different, subjects with problems keeping attention did put in the same effort as others.

Next, we assessed if trait impulsivity (BIS – Attentional, BIS – Non Planning, BIS – Motor Planning) predicted change and moderated the effect on No-Go P300 amplitudes. Previous research didn’t investigate the influence of trait impulsivity measures on the effect of tDCS. In the present study, BIS – Attentional, BIS – Motor Planning and BIS – Non Planning did not significantly change the effect of tDCS on No-Go P300 amplitudes in both tDCS and sham group. This suggests that the observable
effect of tDCS in No-Go trials could not be explained through trait impulsivity, indicating that the effect of tDCS stimulation was similar between individuals with different levels of trait impulsivity. This could suggest that both low and high scorers on trait impulsivity equally benefit from the effect of tDCS. However, it’s important to note that the current study used a sample of normal healthy subjects. The range within our sample was probably too small to find any significant effect and therefore scores might have been too restricted to find an effect.

We also wondered if alcohol use predicted the effect of tDCS on both behavioral and neurophysiological measures. Previous research had indicated that alcohol can produce deficits in behavioral aspects of response inhibition (Verdejo-Garcia et al., 2008; Verdejo-García et al., 2007) and suggest the existence of preexisting differences between individuals prior to the onset of drinking (Wetherill et al., 2013). In the current study we did not find an effect of self-reported alcohol use on the effect of tDCS. However it’s important to note that healthy subjects were used in the current study. Participants in the present study don’t report to many alcohol related problems. This indicates that the range was probably too small to find any significant effect.

We can conclude that tDCS over rIFG did result in diminished P300 amplitudes within a sample of healthy individuals when performing a Go/No-Go task. Lower amplitudes are linked with reduced brain activity needed for response inhibition. The fact that we did find a difference in P300 amplitudes within the tDCS condition supports the reliability of the Go/No-Go paradigm in assessing response inhibition on a neurophysiological level. However, no changes were observed on a behavioral level. A possible reason could have been the type of task, which might have been too easy or tedious for our sample of healthy subjects. Another reason could have been due to the speed-accuracy trade-off which was observed. Participants in the sham group differed in strategy when performing the task, possibly resulting in an absence of effect on behavioral level. Furthermore, no effect emerged on N200. This was as expected because N200 is assumed to be more closely related to aspects such as conflict- and error monitoring, but less with response inhibition itself. Effects of tDCS on mood were also absent and therefore in line with our expectations. Previous research has also indicated that a single 20 minutes tDCS session over prefrontal areas of the brain commonly fails to alter self-reported mood. Furthermore we assessed the relationship and influence of self-report measures. Alcohol use and trait impulsivity could not predict the change that was observed on P300 within No-Go trials. In addition, correlations between trait impulsivity and response inhibition were investigated. A significant relationship between attentional impulsiveness and commission errors was found. This suggests that participants, who had more difficulties keeping focused, committed more
errors during No-Go trials. Interestingly, this effect was not observable on neurophysiological measures, indicating that participants with problems focusing applied similar levels of cognitive effort when compared with other participants in our sample. Furthermore, trait impulsivity did not influence the effect of tDCS on response inhibition, suggesting that the effect observed cannot be explained through trait impulsivity. This also suggests that both high and low impulsive subjects might benefit equally from tDCS. However, a sample of healthy subjects was used. Therefore, scores might have been too restricted to find an effect. Lastly, self-reported alcohol use did not influence the effect of tDCS on response inhibition within our sample. This absence of effect also has to be interpreted cautiously since our sample consisted solely of healthy subjects. Participants within our sample didn’t report a lot of alcohol related problems. As a result the range of scores on the AUDIT scale was probably too small to find a significant effect.

**Limitations and future research**

Clearly our study has some limitations. The main restriction was probably the size of our sample. A small sample size prevented us from detecting highly significant interactions within our data. Moreover we only selected healthy male participants between 18 and 30 years old. Results gathered within this group make it difficult to generalize to a more clinical population of alcohol dependent individuals. Since the sample only consisted of young males, we can only speculate if these results would have been obtained within a group of female participants. Furthermore participants within the tDCS group only received a single 20 minutes session of tDCS over rIFG. It still remains unclear how long the effect of neuromodulation lasts since EEG was measured within a time frame of 1 hour after administration. Since we couldn’t observe any behavioral changes in reaction times, omissions and commission errors, we could argue that the Go/No-Go task has its own limitations. The task might be too tedious or not challenging enough for participants. A more complex task could be more suited to detect changes in behavior if it enhances motivation for the task within subjects. Furthermore we could also wonder if a more complex task would enhance the effect of response inhibition over a prolonged time. Lastly we did observe changes on P3d but no effect was observed on N2d. Possibly a more complex task would alter the performance on the N2d component. Also, existing studies have suggested that the effect of neuromodulation is performance dependent, with stronger effects for participants with a lower initial performance level (Cai et al., 2016; Hsu, Tseng, Liang, Cheng, & Juan, 2014). Within our study we chose to stimulate rIFG. Although rIFG is commonly accepted as an important region for inhibitory control (Aron et al., 2007;
Aron et al., 2003; Aron et al., 2004; Dickstein et al., 2006; Rubia et al., 2010; Sowell et al., 2003), not all evidence is in correspondence with this tendency (Dimitrov et al., 2003; Picton et al., 2007) and the exact role of rIFG upon the act of response inhibition still remains unclear. rIFG seems to be involved in early stages of detecting novel stimuli and attentional switching, functioning as a connector between bottom-up and top-down processes (Hampshire et al., 2010) which indicate the broader function of rIFG. Furthermore rIFG isn’t solely responsible for response inhibition and interacts with areas such as pre_SMA and basal ganglia (Aron, 2011; Sharp et al., 2010). It is stated that rIFG stimulation could smoothen the process of response inhibition by augmenting arousal and motivation (Cai et al., 2016). In addition other regions next to rIFG were stimulated too. These issues need to be addressed in future studies in the field of response inhibition. The current study also failed to find a conclusive relationship between individual differences in trait impulsivity and alcohol use on the effect of tDCS on response inhibition. Future research should aim to further investigate the underlying processes that are related to response inhibition.

Conclusions

The goal of the present study was to assess if neuromodulation through tDCS improves response inhibition within a sample of healthy subjects and the role of individual differences in trait impulsivity and alcohol use. Impaired response inhibition is identified as an important cognitive mechanism in approach behavior towards alcohol, abuse and relapse. To assess the effect of tDCS on response inhibition, two tasks were assessed. A Go/No-Go task which typically measures inhibiting prepotent responses and an oddball face detection task that was used as control. At the beginning and end of the experiment we appraised mood states. As expected, mood wasn’t altered through the effect of tDCS. Concerning the Go/No-Go task, we predicted an increase in behavioral performance after tDCS stimulation within the experimental condition as reflected through improved accuracy. The present study could not confirm this hypothesis. Both sham and tDCS did not differ in behavioral performance on the Go/No-Go task post stimulation. However, we also hypothesized that improved response inhibition would be visible on P300 amplitude. The results did confirm this hypothesis. Although no difference could be observed on behavioral level, a decrease in amplitude on the Go/No-Go task between pre- and post stimulation was observed within the tDCS condition, indicating that fewer cognitive resources were used post stimulation. We also hypothesized that no change on N200 would emerge, which was also confirmed. In addition the role of trait impulsivity was examined. Trait impulsivity and response inhibition have both often been linked with substance use and abuse.
Prior research found small but significant associations between both types of measures. The present study found a significant relationship between attentional impulsiveness and response inhibition at baseline. Individuals who score high on attentional impulsiveness had more problems inhibiting prepotent responses on a behavioral level. This was not replicated on a neurophysiological level, indicating that cognitive effort didn’t differ between high and low scorers on attentional impulsiveness. Furthermore, trait impulsivity did not alter the effect of tDCS on response inhibition, suggesting that the observed effect cannot be explained through trait impulsivity. Lastly, self-reported alcohol use did not moderate the effect of tDCS on response inhibition. However, this absence of effect has to be interpreted with care because only healthy subjects were included in our sample. To conclude, the current study did find an effect of tDCS on response inhibition, but also failed to obtain a convincing relationship between individual differences in trait impulsivity and alcohol use on the effect of tDCS on response inhibition. Future research should therefore keep on focusing on the underlying processes that are associated with response inhibition.
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