Dissertation

Cognitive impairment and response inhibition deficits in alcohol use disorders: impact on relapse and neural processing

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1. Introduction

1.1. Alcohol use disorders: overview and prevalence

Alcohol is one of the most detrimental drugs, being ranked as the fifth harmful drug out of 20 different substances, it is more harmful than LSD and ecstasy (Nutt, King, Saulsbury & Blakemore, 2007). Alcohol use disorders (AUDs) are some of the most prevalent mental disorders worldwide (Grant et al., 2004; Kessler, Chiu, Demler, Merikangas & Walters, 2005; Rehm et al., 2015; Wittchen et al., 2010) with a lifetime prevalence rate of 30.3% in the U.S. (Hasin, Stinson, Ogburn, & Grant, 2007) and a worldwide 12 month-prevalence (*Global status report on alcohol and health,* 2014) of 4.1%, causing a high burden for disease (Whiteford et al., 2013). In Germany, 9.5 million people engage in risky alcohol consumption and 1.77 million are alcohol-dependent (*Drogen- und Suchtbericht*, 2015). AUDs involve detrimental patterns of alcohol consumption with a wide range of problems including lack of control over drinking, preoccupation with drinking and serious physical or mental damage due to alcohol consumption.

> Alcohol dependence (also known as alcoholism or alcohol dependence syndrome) is defined as a cluster of behavioural, cognitive, and physiological phenomena that develop after repeated alcohol use and that typically include a strong desire to consume alcohol, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to alcohol use than to other activities and obligations, increased tolerance, and sometimes a physiological withdrawal state. (*Global status report on alcohol and health,* 2014, p.13)

Recently, the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM–5*; American Psychiatric Association [APA], 2013) made several

changes to the diagnostic criteria of AUDs, integrating criteria for alcohol abuse and alcohol dependence (AD) into one unified diagnosis for AD with mild, moderate and severe classifications (Bartoli, Carrà, Crocamo & Clerici, 2015). As the recruitment and data collection of the present work commenced prior to the release of *DSM–5* (APA, 2013), diagnostic inclusion criteria used for patients were based on the criteria for alcohol dependence criteria of *DSM IV-TR* (APA, 2000) and *ICD-10* (WHO, 1992). It should also be noted that the epidemiological data in this section are likewise derived from diagnostic criteria of *DSM IV-TR*.

DSM IV-TR Criteria for alcohol dependence:

(A) A maladaptive pattern of drinking, leading to clinically significant impairment or distress, as manifested by three or more of the following occurring at any time in the same 12-month period:

- Need for markedly increased amounts of alcohol to achieve intoxication or desired effect; or markedly diminished effect with continued use of the same amount of alcohol
- The characteristic withdrawal syndrome for alcohol; or drinking (or using a closely related substance) to relieve or avoid withdrawal symptoms
- Drinking in larger amounts or over a longer period than intended.
- Persistent desire or one or more unsuccessful efforts to cut down or control drinking
- Important social, occupational, or recreational activities given up or reduced because of drinking
- A great deal of time spent in activities necessary to obtain, to use, or to recover from the effects of drinking
- Continued drinking despite knowledge of having a persistent or recurrent

physical or psychological problem that is likely to be caused or exacerbated by drinking.

(B) No duration criterion separately specified, but several dependence criteria must occur repeatedly as specified by duration qualifiers associated with criteria (e.g., "persistent," "continued").

(APA, 2000, p.192 & 213)

Alcohol dependence is a chronic disorder which is often accompanied by relapses with ongoing heavy alcohol consume. It is associated with a wide range of cognitive impairments which contribute to the maintenance of the disorder, the development of chronic symptoms and diminishing the success of therapy (Bates, Buckman & Nguyen, 2013). Therefore, it is of particular interest to identify factors that contribute to relapse and factors that predict abstinence and a positive long-term treatment outcome. Merely 10% of alcohol dependent patients (ADP) undergo therapy after an average time of 10-15 years of being alcohol dependent. Approximately 74.000 people die each year in Germany due to direct and indirect consequences of their alcohol abuse (*Drogen- und Suchtbericht*, 2015). AUDs constitute a serious and substantial public health problem with a national economic cost of 26.7 billion (for Germany, *Drogen- und Suchtbericht*, 2015) and were the most frequent cause of hospitalisation for men in 2013 (*Gesundheit in Deutschland,* 2015). Alcohol is also the third most significant risk factor for disease and early death in Europe (*Gesundheit in Deutschland,* 2015).

In this context, excessive drinking, known as 'binge drinking', is an important detrimental factor for health as it is associated with acute health endangerment such as intoxications and accidents (*Gesundheit in Deutschland,* 2015) and constitutes a strong risk factor for the development of AUDs. The standardized definition of a "binge", as proposed by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in

2004, is a pattern of alcohol drinking that results in a blood alcohol concentration (BAC) of 0.08 gram percent or higher. "For the typical adult, this pattern corresponds to the consumption of five or more drinks for males, or four or more drinks for females, in about two hours" (*NIAAA Newsletter,* 2004, p.3). A standard drink equals 0.5 oz of alcohol which equals one 5-oz glass of wine, one 12-oz beer or 1.5-oz glass of distilled spirits (*NIAAA Newsletter,* 2004). Another quantifiable method of defining binge-drinking is the binge-drinking score which consists of three questions of the Alcohol Use Questionnaire (Mehrabian & Russell, 1978; Townshend & Duka, 2002): the number of times drunk within the last six months, the number of drinks per hour and percentage of time being intoxicated when drinking (Townshend & Duka, 2005).

In Germany, binge drinking occurs most frequently in the age group of 18-29 year-olds (Hapke, v. der Lippe & Gaertner, 2013). Binge drinking therefore constitutes a very relevant issue for public health as it puts adolescents at a high risk for alcohol related health damage and the development of chronic AUDs (Hapke et al., 2013). The developmental period of adolescence is accompanied by increased risk-taking behaviour, making it a more likely period for engaging in excessive drinking, which in turn has potential long-lasting neurotoxic effects (Peeters, Vollebergh, Wiers & Field, 2013). Furthermore, the adolescent brain is still developing and especially brain areas involved in regulation of emotions and impulsive responses are only reaching maturity, making it more sensitive for neurotoxic effects of alcohol (Peeters et al., 2013).

1.2. Role of impulsivity and response inhibition

Recent models of addiction development (Everitt & Robbins, 2005; Everitt et al., 2008) propose a transition from voluntary, enjoyment guided consumption to automatized

and compulsive consumption patterns, marked by a loss of control. Impaired cognitive control has thus a particular relevance as it interferes with adequate and self-regulated behaviour. In the framework of the dual-system theory by Strack and Deutsch (2004), cognitive control processes belong to the reflexive system, which is characterised by considerate weighing up of values, probabilities and potential consequences of behaviour. In contrast, behavioural schemata in the impulsive system are driven by external cues, motivational orientation and associative learning processes.

Cognitive control processes in substance use disorders (SUDs) are often mentioned along with the terms impulsivity, impulse control, behavioural control or response inhibition. Cognitive control is thought to be a multi-dimensional construct that includes attentional and decisional processes and response inhibition/behavioural inhibition processes, and which reflects the ability to inhibit a prepotent (automatic) response (Crews & Boettiger, 2009; de Wit, 2009). In turn, impaired response inhibition is related to impulsivity and is often categorised as an impulsive reaction or behaviour, particularly in the context of SUDs. However, impulsivity itself is a much broader and multi-dimensional construct that includes personality traits and behavioural patterns (de Wit 2009; Dick et al., 2010). In the research literature impulsivity is defined as „the tendency to engage in inappropriate or maladaptive behaviours" (de Wit, 2009, p.23), for example, choosing a smaller, immediate reward over a larger, delayed reward (Aragues, Jurado, Quinto & Rubio, 2011) or the inability to wait and withhold a response (de Wit, 2009). The major types of processes in laboratory measures of impulsivity are impaired response inhibition and impaired decision making (delay discounting) (de Wit, 2009). However, there is evidence that other cognitive processes such as inattention play an important role for impulsivity too, but could also reflect a separate process that results in behaviours appearing impulsive (de Wit, 2009).

Impulsivity as a personality trait is related to rash or impulsive acts. However, there are different definitions and several personality processes identified, that lead to impulsive reactions (Dick et al., 2010). The most recent models propose five different personality dispositions for impulsive behaviour (Dick et al., 2010): positive urgency (acting rashly while experiencing extremely positive mood), negative urgency (acting rashly while experiencing extremely negative mood), lack of planning (acting without forethought), lack of perseverance (difficulty in tolerating boredom) and sensation seeking (searching for novel or thrilling stimulation). Those traits are usually measured with questionnaires, such as the Barratt impulsiveness scale (BIS-11) (Barrat & Patton, 1983) or the Sensation seeking scale (Zuckerman et al., 1964).

There is a large body of evidence showing that substance use and dependence are linked to impulsivity and impaired cognitive control processes (e.g. Aragues et al., 2011; de Wit, 2009; Dick et al., 2010; Yan & Li, 2009). Self-reported impulsivity and sensation seeking are thought to be related to early onset alcohol dependence and higher symptom severity in comparison to late onset alcohol dependence (Dom, Hulstijn & Sabbe, 2006). There is also research with prospective studies suggesting that impulsivity predicts the development of AUDs and could reflect a genetic vulnerability for SUDs (see Dick et al., 2010). Nigg et al. (2006) showed that poor response inhibition in early adolescence (12–14 years) predicted the escalation of alcohol use in late adolescence (15–17 years). Furthermore, preclinical studies in non-human primates and rodents corroborate these findings by showing similar associations between impulsivity and alcohol use (disorders) as in humans (see Dick et al., 2010).

Response inhibition has gained increasing interest in alcohol addiction studies. The most common paradigms used are the stop signal task (SST) and the go/no-go task.

While the SST measures the ability to cancel an ongoing speeded motor response (Lipszyc & Schachar, 2010), the go/no-go task assesses response restraint (Schachar et al., 2007). In the SST subjects have to respond as quickly as possible to a go-stimulus, but have to inhibit their response in a subset of trials when the go-stimulus is followed by a stop-signal (Lipszyc & Schachar, 2010). In the go/no-go task participants also have to react as quickly and accurately as possible to a go-stimulus to evoke a fast, prepotent motor response, however, in a subset of less-frequently presented no-go stimuli they should not react and therefore have to inhibit a possible response. If a subject fails to inhibit a reaction to a no-go stimulus it is referred to as a commission error, while not responding to a go-stimulus is called an omission error. There are many studies reporting an increased number of commission errors in ADP compared to HC (Bjork, Hommer, Grant & Danube, 2004; Noël et al., 2007; Petit et al., 2014), empathizing a role for impaired inhibitory control in alcohol dependence. Glass et al. (2009) reported that increased deficits in inhibitory control, as measured with the SST, are associated with severity of alcohol dependence. Another study (Li, Luo, Yan, Bergquist & Sinha, 2009) showed that impaired response inhibition in ADP compared to HC is accompanied by a decreased activation of the dorsolateral prefrontal cortex (dlPFC), which was more strongly pronounced in patients reporting an increase in alcohol craving. It has also been shown that alcohol intake is associated with an increased number of commission errors and is related to a decrease in response inhibition compared to a placebo drink (Dougherty, Marsh, Moeller, Chokshi & Rosen, 2000; Easdon, Izenberg, Armilio, Yu & Alain, 2005; Marczinski, Abroms, Van Selst & Fillmore, 2005). Moreover, studies with social drinkers (Loeber & Duka, 2009a; Loeber & Duka, 2009b; Loeber & Duka, 2009c) showed that acute alcohol ingestion (dose of 0.8 g ethanol/kg bodyweight) impairs behavioural instrumental reactions such as inhibition of reward associated reactions. Those results suggest that alcohol leads to

a more reward related impairment of response inhibition.

Corresponding to that, Goldstein and Volkow (2002) have proposed the I-RISA model (*I-RISA: impaired response inhibition and salience attribution*) in which both aspects, the impaired cognitive control and increased salience of the reward-associated drug cues, are combined. This combination supposedly leads to increased craving and more automatized behaviour, resulting in a high relapse risk. Research findings corroborate the I-RISA model and show that alcohol-associated cues elicit an increased emotional and attentional reaction in ADP compared with neutral cues (cue reactivity) (Carter & Tiffany 1999; Drummond, 2000; Loeber et al., 2009) and that ADP report stronger craving for alcohol when they are confronted with alcohol-associated cues (Gauggel et al., 2010; Muraven & Shmueli, 2006; Schneider et al., 2001).

To date, response inhibition and cue-reactivity in ADP have been mostly studied separately and there is a lack of studies investigating the effect of alcohol-related cues in response inhibition tasks and their relation to relapse behaviour and relapse prediction. Further, the results of the studies investigating response inhibition towards alcohol-associated stimuli show mixed findings: while some studies with social drinkers (Kreusch, Vilenne & Quertemont 2013; Kreusch, Quertemont, Vilenne & Hansenne, 2014; Weafer & Fillmore, 2012) and recently detoxified ADP (Noël et al., 2007) show a pronounced response inhibition deficit towards alcohol-related cues, there are research findings reporting no significant differences regarding inhibitory errors towards alcohol-associated stimuli (Nederkoorn, Baltus, Guerrieri & Wiers, 2009). Also it has to be noted, that the reported alcohol-cue specific impairment in response inhibition has been found in all subjects. There was only one study suggesting that ADP made more commission errors towards alcohol-associated cues compared with HC (Noël et al., 2007) and the interpretation of the findings has been criticised (Field

& Cole, 2007). Concordantly, a study with recently detoxified ADP assessed response inhibition towards alcohol and neutral cues with a go/no-go-task (Petit et al., 2014) and reported a general inhibition deficit in ADP compared with HC reflected by an increased number of commission errors, although the type of stimulus did not have any significant effect at all.

1.3. Cognitive impairment in alcohol use disorders

1.3.1. Overview about cognitive deficits

It is a well-known and reported fact that chronic, heavy alcohol consumption is associated with damage to the central nervous system, noticeable on a behavioural and physiological level (Bates, Bowden & Barry, 2002; Stavro, Pelletier & Potvin, 2013; Wilcox, Dekonenko, Mayer, Bogenschutz & Turner, 2014). Physiologically, the brain suffers from volume loss in different areas such as the frontal lobes, insula, basal ganglia, cerebellum and hippocampus (Wilcox et al., 2014) but also from functional changes in brain activity and abnormalities in metabolic activity, especially in prefrontal and temporal brain areas (Bates et al., 2002; Moselhy, Georgiou & Kahn, 2001; Nicolas et al., 1993; Parks et al., 2002). Regarding behavioural changes, chronic alcohol use can lead to cognitive impairments, difficulties in affect-regulation, enhanced impulsivity and personality changes (Bates et al., 2002; Stavro et al., 2013).

Regarding cognitive deficits, moderate to heavy alcohol use is related to reduced performance in visuospatial and immediate memory functions (Green et al., 2010) and among diagnosed ADP approximately between 50-70% show some degree of neurocognitive impairment compared to healthy controls (HC) (for a review see Bates, Buckman & Nguyen, 2013). The most severe neurological and cognitive symptoms

appear in Korsakoff's syndrome, Wernicke's encephalopathy and alcohol-related dementia, manifesting in mental confusion, severely impaired memory, amnesia and further cognitive decline (Krabbendam et al. 2000; Saxton, Munro, Butters, Schramke & McNeil, 2000). Most patients however, suffer from subtle to moderate and fortunately only transient cognitive impairment (Bates et al., 2013). However, those cognitive deficits are supposedly of crucial relevance for the development, the maintenance and the therapy of substance use disorders (SUDs) and will be described in more detail in the following paragraphs.

In a meta-analysis analysing 62 studies which assessed cognitive deficits in ADP compared to HC, Stavro and colleagues (2013) calculated effect size estimates for 12 different cognitive domains: intelligence quotient, verbal fluency/language, speed of processing, working memory, attention, problem solving/executive functions, inhibition/impulsivity, verbal learning, verbal memory, visual learning, visual memory and visuospatial abilities. Furthermore, they calculated effect sizes for ADP with a short time abstinence (< one month), intermediate term abstinence (2-12 months) and long-term abstinence (> 1 year). They reported moderate effect sizes for 11 domains for short term abstinence, with highest values for attention and lowest effect size for IQ. For intermediate term abstinence, the effect sizes were very similar except for inhibition/impulsivity which had a generally high effect size and a higher value than for short term abstinence. Effect sizes for attention and IQ were smaller in the intermediate term abstinence condition compared to the short term abstinence condition. These results show that significant cognitive deficits in multiple cognitive domains remain relatively stable during the first 12 months of abstinence. Only in the long term abstinence condition, effect sizes declined and ranged between small to moderate, emphasizing that regeneration of cognitive deficits is possible but it can take up to one

year of abstinence and even then minor to moderate deficits in cognitive functioning might still remain.

In line with the findings of the meta-analysis by Stavro et al. (2013), there is a large body of evidence across studies with ADP which report deficits in divided attention, automatic information processing, working memory, response inhibition, problem solving, visual-spatial abilities, episodic and autobiographical memory as well as planning and decision making (for a review see Bates et al. 2013; Wilcox et al., 2014). Interestingly, even in heavy-drinking and ADP who did not report any subjective cognitive deficits, impairment in cognitive processes affecting frontal-executive functions were found (Wollenweber et al., 2014).

Summarizing the reported findings, loss of cognitive control plays a key role in current neuropsychological research (Bates et al., 2013) and among the different markers of cognitive impairment in AUDs, response inhibition task performance and related brain activity, impulsivity questionnaire scores and brain volume loss are considered to be the most promising markers (Wilcox et al., 2014).

1.3.2. Causes of cognitive deficits

With respect to the aetiology and mechanisms of the cognitive deficits in AUDs, there are several explanations and hypotheses, including the neurotoxic effect of alcohol itself, thiamine deficiency, the excitotoxicity of neurotransmitters and brain injuries.

The two main aetiological factors discussed in alcohol research (see Bates et al., 2002) are the neurotoxic effect of alcohol leading to progressive cognitive deterioration (Butters, 1985; Parsons, 1994) and severe malnutrition, particularly deficiency of

thiamine. Thiamine deficiency can cause the Wernicke-Korsakoff-Syndrome, a condition involving vision changes, ataxia and impaired memory (Nardone et al., 2013; Thomson, Guerrini & Marshall, 2012).

The two major neurotransmitters alcohol is acting on are glutamate and Gamma-Aminobutyric Acid (GABA). Glutamate is involved in memory and learning processes through its effect on long-term potentiation (LTP). Acute alcohol exposure inhibits glutamate activity in the brain (Oscar-Berman, Shagrin, Evert & Epstein, 1997), presumably being responsible for blackouts after binge-drinking (Bates et al., 2002). The inhibition declines when alcohol consumption stops, such as during withdrawal, and subsequently leads to a flooding with glutamate, opening of receptors and rushing in of calcium ions, resulting in a state of hyperexcitation (Bates et al., 2002). The excitotoxicity is hypothesized to contribute to neurological symptoms, seizures (Grant, Valverius, Hudspith & Tabakoff, 1990) and to cognitive deficits (Bates et al., 2002). Similarly, with the inhibitory neurotransmitter GABA, chronic alcohol use leads to changes in the activity of GABA, namely a downregulation of postsynaptic GABA receptors. Through alcohol withdrawal, an overexcitation is caused. In addition to the neurotoxic effects of alcohol itself, withdrawal also presumably contributes to hallucinations and cognitive impairment (Bates et al., 2002). Consequently, drugs that stimulate GABA activity and enhance the affinity of GABA to receptors, such as Benzodiazepines, are given during alcohol withdrawal to prevent acute neural excitotoxicity and the development of more cognitive deficits.

Another contributing factor for cognitive deficits in AUDs are traumatic brain injuries, which are reported in a disproportionate number of people with heavy alcohol use (Jones, 1989; Weinstein & Martin, 1995). In head trauma victims, more than 50% show an alcohol- or drug disorder (Miller, 1995).

Furthermore, there is the possibility of preceding factors for cognitive deficits, such as familial alcoholism, childhood behavioural problems, age and education. Children of parents with AUDs show more cognitive impairment compared to children of parents without AUDs (Giancola, Martin, Tarter, Pelham & Moss, 1996; Peterson, Finn, & Pihl, 1992; Tarter & Edwards, 1986; Tarter, Hegedus, Goldstein, Shelly & Alterman, 1984), a finding that has led some authors to suggest those cognitive deficits may play a role as a risk factor. However, not all studies support the suggested link (Bates & Pandina, 1992; Schuckit, Butters, Lyn, & Irwin, 1987) and the conclusions drawn need further corroboration from longitudinal studies.

Certain psychiatric conditions or psychopathological abnormalities during child- and youthhood are linked to cognitive deficits and AUDs, such as antisocial behaviour and affective symptoms (Glenn, Errico, Parsons, King & Nixon, 1993).

Moreover, age and education may be additional contributing factors, as lower levels of education were reported to be a predictive factor for reduced cognitive functioning in treatment seeking patients with SUDs (Bates, Voelbel & Labouvie, 2002) and older drinking subjects show more alcohol-related cognitive impairment (Oscar-Berman et al., 1997; Wiseman, Souder & O'Sullivan, 1997). It has also been found that ADP at all ages show impaired cognitive functioning compared to age-matched HC, interpreted as becoming neuropsychologically older at an earlier stage than non-alcoholics and named as the premature or accelerated aging hypothesis (Ellis & Oscar-Berman 1989, Oscar-Berman & Marinković, 2007). This model was followed by the increased vulnerability hypothesis (Oscar-Berman & Marinković, 2003), proposing that older brains have a higher vulnerability to alcohol and undergo stronger impairment. Both hypotheses are supported by neuropathological and neuroimaging research findings (Chanraud et al., 2007; Oscar-Berman & Marinković, 2003).

1.4. Neurobiological aspects of alcohol use disorders and response inhibition

AUDs are associated with a number of structural and functional, neurophysiological changes and according to recent neuroscientific research alcohol dependence is considered to be an acquired disease of the brain (Volkow, Koob & McLellan, 2016). Macroscopic changes in alcohol dependence include cortical atrophy, ventricular expansion, thickening of the meninges and loss of neurons (de la Monte & Kril, 2014; Harper & Kril, 1989; Harper, Kril & Holloway, 1985). Neuroimaging studies showed significant brain tissue atrophy in cortical and subcortical areas (Pfefferbaum et al., 1992), e.g. in the cerebellum (Sullivan, Rosenbloom, Deshmukh, Desmond & Pfefferbaum, 1995), hippocampus (Pfefferbaum et al., 1992, Pfefferbaum et al., 1995), medial temporal and parietal cortices, thalamus, nucleus caudatus (Chanraud et al., 2007) and especially in areas of the frontal cortex (Chanraud et al., 2007; Pfefferbaum, Sullivan, Mathalon & Lim,1997; Rando et al., 2011). There is evidence that brain volume in ADP increases with continuous abstinence, meaning that atrophy might be reversible (Mann, 1992; Monnig, Tonigan, Yeo, Thoma & McCrady 2013). Rando et al. (2011) reported that reduced volumina of grey matter in medial-frontal and parietal-occipital regions in ADP can be predictive of relapse. In this context, Norman et al. (2011) found that adolescents eliciting significantly less activity in a set of brain areas, including the right inferior frontal gyrus (IFG), left dorsal and medial frontal regions, cingulate gyrus, motor cortex and inferior parietal lobules during inhibition in a go/no-go task, later (mean follow-up time of 4.2 years) showed heavy use of alcohol. Those findings suggest that hypoactivation in frontal areas could be a possible predictor of alcohol or substance abuse.

Research in the neuroscientific field of addiction has shed more light on the neural processes that lead to development of addictive behaviour and help us to understand

why those affected by addiction have so much trouble withstanding drug consumption. First, it is known that drugs activate the reward brain regions (the mesocorticolimbic system including area tegmentalis, hippocampus, nucleus accumbens and parts of the frontal cortex) and lead to high dopamine release (Di Chiara, 2002; Koob, 1992; Wise, 2008), which in turn elicits a reward signal triggering associative learning. In this way, formerly neutral contexts and cues become associated with reward. This is a crucial process leading to cue reactivity in addicted people, meaning that when confronted with an associated cue but not the drug itself, dopamine cells already start firing in anticipation of the reward (Schultz, 2002). As a short-term result, craving and motivation for drug-seeking is increased, often leading to heavy drug use (see Volkow et al., 2016) and in the long run formerly healthy and natural rewards become less rewarding (Volkow et al., 2016). In contrast to earlier theories, that proposed an increased sensitivity to rewarding effects of a drug in addicted subjects, it is now known that drug consume elicits much smaller dopamine release in addicted people compared to non-addicted people or people who never used drugs (Volkow et al., 2016). As a consequence, the addicted person gets less excited from drugs but also from daily life experiences, resulting in less motivation and anhedonia, further increasing the risk to take drugs in higher doses. Additionally, to the changes in the reward- and emotional processing brain systems, chronic drug use leads to structural and functional changes in prefrontal regions, including impaired signalling of dopamine and glutamate (Volkow et al., 2016). As prefrontal regions are strongly involved in cognitive control processes, the ability to act attentively, resist or stop urges are weakened in the addicted brain (Volkow et al., 2016). Studies with positron emission tomography (PET) illustrated decreased glucose metabolism in frontal brain areas in subjects with AUDs (Adams et al., 1993, Adams et al., 1998; Volkow et al., 1992) which has also been related with frontal cortical atrophy and impairments in

neuropsychological functioning (Boller et al., 1995; Ratti et al., 1999), including executive function (Adams et al., 1993). Dysfunction of frontal lobe areas is also associated with impaired inhibitory control, especially the dorsolateral and orbitofrontal cortex have been reported to be substantially involved in inhibition processes (Crews & Boettiger, 2009). Accordingly, subjects with alcohol dependence have shown decreased densities of neurons and glia cells in the orbitofrontal cortex (Miguel-Hidalgo, Overholser, Meltzer, Stockmeier & Rajkowska, 2006). Further, neuroimaging studies investigating response inhibition depict the involvement of a right lateralised network including the inferior frontal cortex (IFC), pre-supplementary motor area (pre-SMA), parietal cortex and in a few studies, thalamic areas (Bellgrove, Hester & Garavan, 2004; Garavan, Ross, Murphy, Roche & Stein, 2002; Liddle, Kiehl & Smith, 2001). Activity in the IFG and in the pre-SMA has been reported to be involved in successful inhibition processes (Lipszyc & Schachar, 2010), whereas unsuccessful inhibition (making commission errors) is associated with decreased activation in the IFG and adjacent subcortical areas (Lipszyc & Schachar,2010). However, Menon, Adleman, White, Glover and Reiss (2001) highlight that brain areas involved in successful and unsuccessful inhibition are only partially overlapping and there are also other regions such as the anterior cingulate cortex (ACC), left precuneus and anterior insula for which increased activity has been associated with unsuccessful stopping (Garavan et al., 2002). Altogether these neurophysiological findings support the above mentioned theories and models of addiction, such as the dual-process model by Strack and Deutsch (2004) and the I-RISA model by Goldstein and Volkow (2002). Addicted patients underlie an imbalance that makes it difficult to stop consuming a drug: on the one hand they suffer from a weakened cognitive control and on the other hand they experience decreased reward effects and automatized, craving related behaviour elicited by drug cues.

1.5. Prediction of abstinence and relapse behaviour

Predictive factors contributing to relapse and hindering recovery, are a positive family history of alcohol dependence (Moriyama, Muramatsu, Kato, Mimura & Kashima, 2006), heavy smoking (Durazzo, Rothlind, Gazdzinski, Banys & Meyerhoff, 2007), poor coping skills, lack of self-efficacy and depressive symptoms (Brown, Vik, Patterson, Grant & Schuckit, 1995; Miller, Westerberg, Harris & Tonigan, 1996; Yates, Booth, Reed, Brown & Masterson, 1993). Impairment of response inhibition has been shown to be predictive for relapse in recently detoxified ADP during a three month-follow up (Bowden-Jones, McPhillips, Rogers, Hutton & Joyce, 2005) and impulsivity traits were reportedly linked to craving and relapse (Evren, Durkaya, Evren, Dalbudak & Cetin, 2012). Moreover, Petit et al. (2014) illustrated a predictive association between a neurophysiological measure that is linked with behavioural inhibition deficits (P3d increase in an EEG) in ADP and relapse. Neuroimaging studies showed that increased activation in brain areas linked to impulse control, attentional bias towards alcohol cues and the reward system, were predictive for relapse in ADP (Beck et al., 2012; Braus et al., 2001; Grüsser et al., 2004).

Another major contributing factor for increased relapse risk that has been proposed by different researchers (Duka & Stephens, 2014; Fujiwara, Brand, Borsutzky, Steingass, & Markowitsch, 2008; Pitel et al., 2009), is the number of detoxifications a dependent person has undergone. Detoxifications have a crucial impact on the function of multiple brain processes, including cognitive control and therefore might increase the vulnerability for stress-induced relapse (Duka & Stephens, 2014). ADP with a lower number of detoxifications (< 2) had better recovery in behavioural measures of risk taking and decision making than ADP with a higher number of detoxifications (> 2) (Loeber et al., 2010).

1.6. Aims of the work

SUDs are marked by a loss of cognitive control and recent models of addictive behaviour proposed the contribution of two aspects for the development and maintenance of addiction: deficits in response inhibition and enhanced salience attribution to a drug related stimuli (Goldstein & Volkow, 2002). There is a large body of evidence showing impairments in cognitive control processes including response inhibition (e.g. Fernández-Serrano, Pérez-García, Schmidt Río-Valle & Verdejo-García, 2010; Stavro et al., 2013; Wilcox et al., 2014) as well as heightened impulsivity (e.g. Dick et al., 2010; Stavro et al., 2013) in people with AUDs. Binge drinking has also been found to be related with impaired response inhibition and impulsivity (Verdejo-García, Lawrence & Clark, 2008) and is of crucial relevance for the development of AUDs, especially in adolescents, increasing the risk for alcohol related health damages and the development of chronic AUDs in this group (Hapke et al., 2013). Other studies demonstrated the salience of alcohol related stimuli, namely cue reactivity (Carter & Tiffany 1999; Drummond, 2000; Loeber et al., 2009c). This work aims at combining both aspects to investigate whether a response inhibition deficit is significantly more pronounced towards alcohol related stimuli compared to neutral stimuli (cue-specific impairment of response inhibition) in groups of subjects consisting of binge drinkers, non-binge drinkers, ADP and HC.

As most of studies, regarding the impairment of cognitive control processes in ADP, have investigated only one or two to three cognitive domains, the aim of this work was to extensively assess several domains of cognitive control processes as cognitive control is a multidimensional construct (de Wit, 2009). Furthermore, little is known about factors contributing to relapse, which is why this work also aims at analysing which cognitive processes and other variables can be predictive for relapse.

Impairments in different cognitive control- and regulation processes in ADP and their association with relapse behaviour were investigated in a six-month follow-up time. Another aim was to study differential neural activation patterns during inhibition processes in ADP compared to HC with functional magnetic resonance imaging (fMRI). The results should not only contribute more crucial information to the body of evidence in this research field, but also provide conclusions for clinical work and psychotherapeutic treatments of alcohol dependence.

In detail, the following questions should be answered:

1. Do recently abstinent (since 1-3 weeks) ADP show deficits in cognitive control processes compared to HC and if so, in which particular components of cognitive control functions?

2. Is there a greater response inhibition deficit in general in ADP relative to HC and in binge-drinkers relative to non-binge drinkers?

3. Is a possible response inhibition deficit significantly pronounced towards alcohol related stimuli compared to neutral stimuli in ADP relative to HC and in binge-drinkers relative to non-binge drinkers?

4. Are trait-like impulsivity and deficits in response inhibition predictive of binge drinking?

5. Is the risk for relapse associated with deficits in cognitive control functions, particularly with a response inhibition deficit in ADP?

6. Do the possible deficits in cognitive control functions in ADP persist under abstinence over six months?

7. Do ADP and HC show different neuronal activity patterns during response inhibition towards alcohol related and neutral stimuli?

8. Is neural activity during response inhibition stimulus dependent?

1.7. Design and methods

In order to answer the above questions, the following procedures and methods were applied:

All subjects were screened before study participation regarding the inclusion and exclusion criteria, filled out different questionnaires and performed a response inhibition task with alcohol-related and neutral stimuli. The response inhibition task used in all three studies was a go/no-go task, which was modified to assess response inhibition in response to alcohol related stimuli (pictures of alcohol) and neutral stimuli (geometric figures). Subjects had to react as quickly as possible if a go-stimulus was displayed by pressing a button and they had to inhibit their reaction (not pressing the button) when a no-go stimulus was displayed. Subjects selected their 8 preferred pictures of alcoholic beverages out of 85 pictures before performing the task to ensure individual relevance of the alcoholic stimuli.

Trait impulsivity was assessed with the German version of the Barratt Impulsiveness Scale (BIS-11) (Preuss et al. 2008) to provide a self-report measure of impulsivity. Additionally, subjects filled out mood questionnaires and questionnaires regarding their alcohol intake and consumption patterns, which are described in more detail in the following articles.

A sample of social binge and non-binge drinkers (students) participated in study 1. Subjects were recruited from the undergraduate and postgraduate population of psychology students. Based on the calculation of a binge drinking score assessed with the Alcohol Use Questionnaire (AUQ) (Mehrabian & Russell, 1978), subjects were classified as binge or non-binge drinkers.

A sample of ADP and HC was recruited for participation in study 2 and study 3. In study

2 behavioural data regarding performance in several cognitive control tasks were assessed as well as questionnaire data. Study 3 focused on the assessment of neuroimaging data during response inhibition with fMRI.

All subjects of the sample participated in study 2, while for study 3 a part of the sample additionally underwent a fMRI scanning session, performing the go/no-go task. Imaging data were collected with a Siemens 3T Magnetom Tim/Trio MR scanner located at the Neuroradiology department in the University Hospital Heidelberg, Germany. ADP were recruited from the Psychiatric Center Nordbaden, Wiesloch, Germany during their detoxification treatment. At the time of neuropsychological assessment and/or fMRI scanning, ADP were abstinent from alcohol for at least six days and pharmacological detoxification treatment terminated at least three days before. HC were recruited via advertisements and flyers.

Study 2 comprised an extensive neuropsychological assessment of cognitive control functions. Additionally to the go/no-go task, four subtests of the CANTAB (Cambridge Cognition, Cambridge, United Kingdom; http://www.camcog.com), a computerized cognitive test battery, were administered: the rapid visual processing task (RVP) to assess visual-sustained attention and response initiation, the Cambridge gambling task (CGT) measuring decision-making and risk-taking behaviour, the intra/extra-dimensional set shift task (IED) for assessing rule acquisition and reversal learning and the choice reaction time task (CRT) to measure attentional processes. In order to investigate relapse behaviour, ADP were contacted monthly via telephone in the following six months after the first test session and all ADP were invited for a second catamnestic test session after six months.

Behavioural data in all three studies was analysed with the IBM SPSS Statistics software (Statistical Package of the Social Science, 20.0, respectively 22.0.) using

different statistical analyses including t-tests, χ^2 analyses, multivariate analyses of variance, Kaplan–Meier survival analysis, principal component analysis and regression analyses. FMRI data were analysed using SPM 8 (www.fil.ion.ucl.ac.uk/spm).

1.8. Statement of personal contribution to the publications

This dissertation is based on three articles (original contributions) which were part of a collaborative research work between the author (MC) and the co-authors and was supervised by SL. The work consisting of the three original contributions is a product of the intellectual environment of all authors. SL contributed mainly with her previous work which was the basis for the development of the research ideas in this dissertation. SL also contributed through supervision of the research work, the analyses and drafting of manuscripts. MC was responsible for planning and realisation of the studies. MC further developed the design and research ideas including the implementation of a new task (go/no-go-task) and creating stimulus material. In study 1, MC was responsible for the paradigm, assisted with the analysis and completion of the manuscript. For study 2 and study 3 MC recruited the subjects, did screenings and clinical interviews and collected behavioural data, questionnaire data as well as fMRI data. MC was responsible for all analyses in study 2 and 3, the interpretation and drafting of the manuscripts. MC is also fully responsible for writing all other parts (introduction, discussion, summary) of this dissertation.

2. Original contributions

2.1. Is binge drinking in young adults associated with an alcohol-specific impairment of response inhibition?[1]

[1] Czapla, M., Simon, J.J., Friederich, H.C., Herpertz, S.C., Zimmermann, P., & Loeber, S. (2015). Is binge drinking in young adults associated with an alcohol-specific impairment of response inhibition? *European Addiction Research, 21*(2), 105-13.

Abstract

Background/Aims: Little is known about the association of binge drinking with impulsivity related to trait- or state-like aspects of behavior. The aim of the present study was therefore to investigate whether binge drinkers compared to non-binge drinkers show an impairment of inhibitory control when confronted with alcohol-associated or control stimuli and whether this is reflected in self-reported impulsivity.

Methods: A go-/nogo task with pictures of alcoholic and non-alcoholic beverages as well as control stimuli was administered to binge drinkers and a gender-matched group of non-binge drinkers. All participants completed also the Barratt Impulsiveness Scale (BIS-11). **Results:** We found an alcohol-specific impairment of response inhibition for binge drinkers only, while the groups did not differ with regard to overall response inhibition to the experimental stimuli or self-reported impulsiveness (BIS-11). In addition, the number of commission errors in response to alcohol-associated stimuli was the only significant predictor of binge drinking. **Conclusion:** The findings of the present study suggest that when young adults have established binge drinking as a common drinking pattern, impairment of inhibition in response to alcoholic stimuli is the only significant predictor of binge drinking, but not general impulsive behavior.

Introduction

Recent models of addictive behavior suggest that an impairment of response inhibition and an enhanced salience attribution to alcohol-associated stimuli are two processes that contribute to the development and maintenance of addiction (Goldstein & Volkow, 2002). For example, Boog, Goudriaan, van de Wetering, Deuss and Franken (2013) proposed that rash impulsiveness and reward sensitivity are two aspects associated with addiction. According to this theory, rash impulsiveness reflects disinhibition, "a rash tendency to act upon acute impulses" and reward sensitivity describes a sensitivity to appetitive rewarding stimuli, which is overlapping with the concept and empirical evidence of enhanced salience attribution. In line with this, a large number of studies demonstrated that heavy drinking individuals and alcohol-dependent patients show impulsive behavior in questionnaire measures or neuropsychological tasks that assess response inhibition (Henges & Marczinski, 2012; Hildebrandt, Brokate, Eling and Lanz, 2004; Nederkoorn, Baltus, Guerrieri & Wiers, 2009; Noël et al., 2005; Noël et al., 2007; Rubio et al., 2007). In addition, appetitive responses to alcohol-associated cues have been found with different experimental paradigms using alcohol-associated and neutral stimuli (e.g., modified Stroop tasks, visual dot probe tasks; Loeber et al., 2009) and imaging methods have been applied to study the brain activity associated with these responses (Gruesser et al., 2004; Wrase et al., 2007).

While these studies primarily investigated the adverse effects of chronic alcohol use, only recently a growing research interest has emerged to assess whether impulsive behavior and impairment of inhibitory control are also associated with binge drinking (Carlson, Johnson & Jacobs, 2010; Scaife & Duka, 2010). Binge drinking is usually characterized as the consumption of large amounts of alcohol in a short time followed by a period of abstinence, as opposed to regular drinking patterns in which a person

might consume a similar amount of alcohol per week but without the extremes of alcohol intoxication (Scaife & Duka, 2010). In the United States as well as in European Countries binge drinking is quite common among college and university students and has been associated with negative social and health consequences as well as the development of problem drinking (Wechsler, Davenport, Dowdall, Moeykens & Castillo, 1994). As adolescence is a critical period of neuromaturation (Crews & Boettiger, 2009) and executive control processes undergo profound development during adolescence (Luna, Padmanabhan & O'Hearn, 2010), binge drinking seems to be especially harmful with regard to the development of cognitive control processes. Thus, several cross-sectional studies demonstrated that binge drinkers compared to non-binge drinkers are impaired with regard to a wide variety of executive functions (Parada et al., 2012; Scaife & Duka, 2010; Townshend & Duka, 2005), and especially deficits of response inhibition were shown in several studies (Henges & Marczinski, 2012; Nederkoorn et al., 2009). Only recently, the results of longitudinal studies using event-related potentials or brain imaging techniques demonstrated that young binge drinkers showed abnormal brain activity during tasks assessing learning and response inhibition without any impairment of behavioral responses (López-Caneda et al., 2012; Schweinsburg, McQeeny, Nagel, Eyler & Tapert, 2010; Schweinsburg, Schweinsburg, Nagel, Eyler & Tapert, 2011;). Importantly, it has also been demonstrated (López-Caneda et al., 2012) that some of these abnormalities emerged after only two years of binge drinking. These studies support the assumption of the adverse effects of binge drinking on brain development.

However, there are also a number of studies that demonstrate that trait-like impulsive behavior and difficulties in response inhibition might be a risk factor for the development of binge drinking (for a review see Verdejo-Garcia, Lawrence & Clark, 2008). For example, a prospective study (Nigg et al., 2006) found that deficits of

response inhibition predicted alcohol-related problems. In addition, several studies demonstrated that children at risk for the development of alcohol abuse show an impairment of response inhibition and less behavioral control (Hill et al., 2009; Nigg et al., 2004; Wiers, Gunning & Sergeant, 1998). Children at risk for alcohol abuse showed disruption in the laterality of the orbitofrontal cortex volume compared to control children and this was associated with genetic variations (Hill et al., 2009). In addition, reduced white matter volume in the right orbitofrontal cortex was related to increased impulsivity which might antecedent risky behavior. In line with this, it was reported that automatic alcohol approach tendencies predicted future drinking behavior of young adolescents with relatively weak response inhibition skills (Peeters et al., 2013).

Taken together, there is quite extensive evidence that the association between binge drinking and an impairment of response inhibition might be reciprocal (Wiers et al., 2007) with impulsive behavior and an impairment of response inhibition contributing to binge drinking which in turn leads to brain damage and a further impairment of response inhibition. As alcohol-associated stimuli acquire an incentive salience during the development of addictive drinking patterns, this impairment of response inhibition should be especially pronounced when confronted with alcohol-associated stimuli as suggested (Goldstein & Volkow, 2002). There are a few studies (Noël et al., 2005; Noël et al., 2007) that addressed the question whether an impairment of response inhibition is especially pronounced when alcohol-associated cues are presented. The findings of these studies indicated that alcohol-dependent patients show an impairment of response inhibition which is enhanced when alcohol-associated cues are presented. However, to our best knowledge, up to now only one study investigated whether binge drinkers show also an impairment of response inhibition which is especially pronounced when responses to alcohol-associated stimuli have to be inhibited (Nederkoorn et al., 2009). Thus, Nederkoorn and colleagues (2009) administered a

modified stop-signal task in which neutral as well as alcohol-associated, soft-drink and erotic visual stimuli were presented to participants classified either as heavy versus non-heavy drinkers or binge vs. non-binge drinkers. The results of this study indicated that female binge drinkers showed a stronger impairment of response inhibition than the other groups with no significant differences between the different picture categories. Although these findings are in line with previous studies reporting that female binge-drinkers show the strongest impairments of executive function (Townshend & Duka, 2005), they do not support the assumption of an impairment of response inhibition that is especially pronounced for alcohol-associated responses (Noël et al., 2005; Noël et al., 2007).

The aim of the present study was to enhance our understanding of the nature of the impairment of response inhibition being associated with binge drinking as this might contribute to the development of effective prevention strategies. It was demonstrated that for heavy drinking young adults a training in which participants have to repeatedly inhibit responses toward alcohol-related stimuli is effective to reduce excessive alcohol use (Houben, Nederkoorn, Wiers & Jansen, 2011). However, less is known whether this strategy would also address the needs of binge drinkers. We therefore developed a modified go-/nogo task in which stimuli of alcoholic and non-alcoholic beverages were presented and responses to alcoholic beverages had to be inhibited. As a control condition, blocks with geometrical figures were presented. We hypothesized that binge drinkers would show greater response inhibition deficits than non-binge drinkers in response to the geometrical as well as the alcohol-associated stimuli, while we expected a greater impairment of response inhibition to the presentation of alcohol-associated compared to geometrical stimuli for binge drinkers only. We administered also the Barratt Impulsiveness Scale as a trait measure of impulsivity and expected higher self-reported impulsive behavior for binge drinkers. In addition, we calculated a

multiple linear regression to assess the predictive validity of trait-like impulsive behavior and impairment of response inhibition with regard to binge drinking. As previous studies reported that female binge drinkers might be especially affected by the adverse effects of alcohol on prefrontal functioning, we included equal proportions of male and female participants in all groups and controlled in all analyses for gender effects.

Material and methods

Participants

Male and female social drinkers were recruited for this study from the undergraduate and postgraduate population of psychology students of the University of Wuppertal. For study inclusion participants had to be between 18 and 30 years old, in good physical health, and to be able to fill in questionnaire measures and complete computerized tasks. Alcohol- or drug dependence was defined as exclusion criterion. A pre-screening using a standardized interview was conducted with everyone who responded to the call for participants to check for inclusion and exclusion criteria. Alcohol consumption was assessed with the *Alcohol Use Questionnaire* (*AUQ*; Mehrabian & Russell, 1978) and participants who achieved a binge-drinking score of 24 or higher in the *AUQ* were classified as binge drinkers, while participants with a score of equal or less than 16 were classified as non-binge drinkers (Townshend & Duka, 2002). The binge-drinking score is based on the items related to speed of drinking (number of drinks per hour), the 'number of times being drunk in the last six months' and the percentage of times getting drunk when drinking (Townshend & Duka, 2002). Participants with a score higher than 16 but below 24 were not included in the study. The study adhered to the Declaration of Helsinki. Student participants received course credits for their participation in the study.

General procedure

After evaluation of inclusion/exclusion criteria, testing started with the assessment of demographic variables. Then a questionnaire was administered to control for current mood (Hörhold & Klapp, 1993) and participants also completed the *Barratt Impulsiveness Scale* (*BIS-11*; Preuss et al., 2008) to provide a self-report measure of impulsivity. Then a go-/no-go task using visual cues of alcoholic and non-alcoholic beverages as well as geometrical figures was administered to assess behavioral response inhibition. The test session was conducted by a research assistant trained in neuropsychological test administration and lasted about 50 minutes. All participants were instructed to abstain from the use of illicit drugs for at least 1 week and from the use of alcohol for at least 12 h before the test session to avoid confounding effects of alcohol or drug consumption.

Questionnaire measures

Alcohol Use Questionnaire (AUQ). The *AUQ* (Mehrabian & Russell, 1978) was used to assess alcohol consumption of participants and to classify binge- versus non-binge drinkers. The questions presented are related to the frequency and amount of alcohol consumption per week in the last six months, but also to drinking patterns like the speed of drinking and the frequency of getting drunk (i.e., experiencing loss of co-ordination, nausea, and/or inability to speak clearly).

Barratt-Impulsiveness-Scale (BIS-11). The German version of the *BIS* (Preuss et al., 2008) was administered to provide a subjective measure of impulsive behavior in everyday-life situations. This questionnaire comprises 30 items designed to assess general impulsiveness taking into account the multi-factorial nature of the construct (e. g., inattention, motor impulsivity, lack of planning behavior). For the present analysis

only the summary score was used as this is the most reliable outcome measure of the German version (Preuss et al., 2008).

Berlin mood questionnaire (Hörhold & Klapp, 1993). This questionnaire was used to assess the current mood of participants as this might confound the experimental outcome. A number of 30 adjectives related to different mood states is presented and participants rate on a five-point Likert scale how much these adjectives describe their current mood (0=not at all; 4=very much). Items can be grouped in six different mood states: anger, anxious depression, fatigue, listlessness, high spirits, or engagement.

Experimental paradigm

Go/no-go task. A go/no-go task using visual stimuli that displayed alcoholic beverages, non-alcoholic beverages or geometrical figures was used to assess impulsive behavior and impairment of response inhibition in response to different stimuli. The task was divided in two parts each lasting about ten minutes. In each part, four blocks with alcoholic/non-alcoholic beverages and four blocks with geometrical figures were presented with the sequence of blocks alternating. In the alcoholic/non-alcoholic beverages blocks, visual stimuli of non-alcoholic beverages served as go-stimuli and participants were instructed at the beginning of each block to respond as quickly as possible to pictures of non-alcoholic beverages by pressing the space bar. In contrast, participants should inhibit their responses when alcoholic beverages were displayed. In blocks with geometrical figures, a rectangle served as the go-stimulus and a circle as the no-go stimulus. At the start of the experimental task two short practice blocks were presented that were not scored. All pictures were 4 inches high and 6.67 inches wide and were displayed for 490 ms on a 15.4 inch color monitor of a Lenovo ThinkPad SL510. A total of 40 trials were presented within each block with 80% of the trials being go-trials. After each block there was a short break of 13 seconds and then a fixation

cross was presented for 1000ms before the target category for the following block was displayed on the screen.

Before the beginning of the task 85 pictures of different alcoholic beverages (beer, wine, and spirits) were shown to the participants and they were instructed to select eight pictures that displayed best their preferred alcoholic beverages. The non-alcoholic beverages consisted of a standard set of eight pictures displaying soft-drinks, water and juice. After the selection of the alcoholic pictures, participants rated each of the sixteen experimental stimuli with regard to liking ("How much do you like this beverage?"), valence ("How pleasant do you find this picture?") and arousal ("How much arousing do you find this picture?"). The analyses of these ratings indicated no significant overall differences between pictures displaying alcoholic or non-alcoholic beverages (all Ts≤1.49, all ps≥0.15). However, while binge-drinkers and non-binge drinkers did not differ with regard to liking, valence and arousal of non-alcoholic beverages (all Ts≤0.67, all ps≥0.14), binge-drinkers achieved higher scores than non-binge drinkers with regard to liking of alcoholic beverages (t(30)=-2.61, p<0.05) and rated pictures displaying alcoholic beverages as more pleasant than non-binge drinkers (t(-2.38, p<0.05). In contrast, the groups did not differ with regard to arousal in response to pictures of alcoholic-beverages (t(30)=-0.52, p=0.61).

For task presentation and recording of responses we used Presentation® software (Version 16.0, Neurobehavioral Systems, Inc., Albany, CA, USA). As dependent variable we calculated separately for alcoholic/non-alcoholic beverages blocks and geometrical figures blocks the number of commission errors (i.e. responses to no-go stimuli).

Statistical analysis

Differences between binge drinkers and non-binge drinkers with regard to drinking behavior, demographic variables and affective state were analyzed using t-tests, chi-square analyses and multivariate analysis of variance. To analyze differences in response inhibition a repeated measures analysis of variance was calculated for the number of commission errors as dependent variable with *binge drinking* (binge drinker, non-binge drinker) and *gender* (male, female) as between group factors and *category* (alcoholic/non-alcoholic, geometrical) as repeated measures factor. Data from one participant were excluded from the analysis of response inhibition as the results of an outlier analysis indicated that this participant achieved a commission error score higher than two standard deviations above the mean. An univariate analysis of variance was calculated to assess whether binge drinkers and non-binge drinkers and male and female participants, respectively, differed with regard to self-reported impulsivity (*BIS-11*). In all analyses the amount of alcohol in g consumed per week was entered as a covariate to control for a possible confounding effect due to the deleterious effects of the amount of alcohol consumed irrespective of binge drinking patterns as suggested by Townshend, Kamabouropoulos, Griffin, Hunt and Milani (2014). Effect sizes (partial eta^2) are reported to allow the reader an evaluation of the results given the possibility of lacking significance due to small sample sizes. In addition, a multiple linear regression analysis was calculated to analyze whether the different aspects of an impairment of response inhibition and impulsive behavior are significant predictors of the binge drinking score. The *BIS-11* summary score, the number of commission errors in response to alcoholic stimuli, the number of commission errors in response to geometrical figures, gender as well as the interaction effects of gender and the other variables were entered stepwise in the sequence reported here as predictor variables. All analyses were performed with IBM SPSS Statistics Version 20.

Results

Participant characteristics

Sixteen binge drinkers and 16 non-binge drinkers were included in the study with gender being equally distributed in both groups. Further demographic and drinking-related participant characteristics are displayed in Table 1. Binge drinkers consumed significantly more g ethanol per week ($t(18)=-4.45$, $p<0.001$) than non-binge drinkers and were significantly younger than non-binge drinkers ($t(30)=2.17$, $p<0.05$). The mean amount of ethanol consumed per week was entered as a covariate in the analyses [30], while age was not related to any of the dependent variables (Spearman correlation: all $r<\lfloor 0.43 \rfloor$, all $p≥0.11$) and was thus not entered as a covariate. Binge-drinkers and non-binge drinkers did not differ with regard to any of the variables of current mood as assessed with the *Berlin mood questionnaire* ($F(6,25)=0.34$, $p=0.91$) and none of these variables were significantly related to any of the dependent variables (all $rs≤-0.30$, $ps≥0.09$ uncorrected).

Table 1: Demographic and drinking-related characteristics of binge drinkers and non-binge drinkers.

	Binge drinkers (n = 16)	Non-binge drinkers (n = 16)
Gender [N male/female]	8/8	8/8
Age [Mean (SD)]	22.69 (2.50)	24.94 (3.32)*
Binge drinking score (AUQ) [Mean (SD)]	30.25 (4.34)	8.14 (4.12)*
g ethanol per week [Mean (SD)]	138.91 (88.21)	35.63 (29.04)*

Note: AUQ Alcohol Use Questionnaire [30], * p< 0.05

Behavioral disinhibition

We found a significant main effect of the repeated measures factor *category* (alcoholic/non-alcoholic, geometrical) ($F1,26)=15.34$, $p<0.05$, partial eta^2=0.37) which

was qualified by a significant category by group interaction (F1,26)=6.51, p<0.05, partial eta^2=0.20). The main effect of group did not achieve significance (F(1,26)=2,43, p=0.13, partial eta^2=0.09). As can be seen from Figure 1 these findings indicate, that binge drinkers but not non-binge drinkers committed more commission errors when responses to alcohol-associated cues compared to control stimuli had to be inhibited. (see Figure 1).
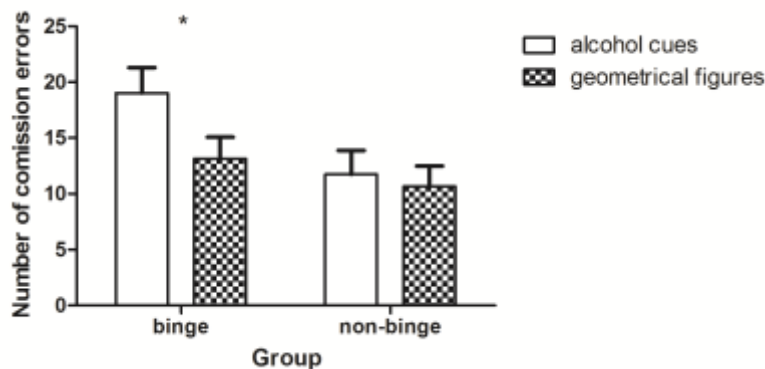

Figure 1: Binge drinkers committed significantly more commission errors when responses to alcoholic stimuli had to be inhibited (distractors) than when responses to geometrical figures had to be inhibited (p<0.05).

With regard to gender effects our results indicated neither a significant main effect of gender (F(1,26)=1.94, p=0.18, partial eta^2=0.07) nor any significant interaction effect (Fs≤2.46, ps≥0.13, partial eta^2≤0.09). All other main or interaction effects were also not significant (all Fs≤0.31, ps≥0.16).

Self-reported impulsivity

The results of the univariate analysis of variance indicated that binge drinkers and non-binge drinkers did not differ with regard to self-reported impulsive behavior in the *BIS-*

11 ($F_{(1,27)}=0.22$, $p=0.64$, partial $eta^2=0.008$). In addition, this analysis did also not indicate any main or interaction effects of gender (all $Fs \leq 1.32$, $ps \geq 0.26$) with regard to self-reported impulsivity.

Prediction of binge drinking

The results of the regression analysis in which we entered self-reported impulsivity (*BIS-11*), the number of commission errors in response to alcoholic and geometrical stimuli as well as gender as predictor variables indicated that the number of commission errors in response to alcohol-associated stimuli was the only significant predictor of the binge drinking score ($\beta=0.44$, $t=2.62$, $p<0.05$) and accounted for a significant proportion of the variance of the binge-drinking score ($R^2=0.19$, $F_{(1,29)}=6.87$, $p<0.05$). All other variables did not achieve significance, and we found no evidence for main effects of gender (all $ts \leq 1.50$, all $ps \geq 0.15$). However, the interaction effects gender by commission errors in response to alcohol-associated stimuli ($t=1.83$, $p=0.079$) and gender by commission errors in response to geometrical stimuli ($t=1.90$, $p=0.068$) only slightly failed to reach statistical significance. Given the marginal significance of the interaction effects of gender, separate linear regression analyses were calculated for male and female participants. The results of these analyses indicated no significant regression model for male participants, while for female participants the number of commission errors in response to alcohol-associated stimuli emerged as the only significant predictor of the binge drinking score ($\beta=0.58$, $t=2.64$, $p=0.02$) and accounted for a significant proportion of the variance ($R^2=0.33$, $F_{(1,14)}=6.96$, $p<0.05$).

Discussion

The aim of the present study was to investigate whether binge drinking is associated with an impairment of response inhibition when confronted with alcohol-associated stimuli to enhance our understanding of the nature of response inhibition deficits often reported for binge drinkers (Carlson et al., 2010; Henges & Marczinski, 2012; Nederkoorn et al., 2009; Scaife & Duka, 2010). We developed a modified go-/nogo task in which stimuli of alcoholic and non-alcoholic beverages were presented and responses to alcoholic beverages had to be inhibited. As a control condition, blocks with geometrical figures were presented. We assumed that binge drinkers would show greater response inhibition deficits than non-binge drinkers in response to the geometrical as well as the alcohol-associated stimuli. In addition, we hypothesized greater impairment of response inhibition to the presentation of alcohol-associated compared to geometrical stimuli for binge drinkers only. Our results indicated in line with our assumptions that binge drinkers, but not non binge drinkers, committed more commission errors in response to alcohol-associated than control stimuli. However, contrary to our hypothesis, binge drinkers and non-binge drinkers did not differ with regard to the overall number of commission errors in response to the different experimental stimuli and this was also reflected in self-reported impulsive behavior as the groups did not differ in the *BIS-11*. Thus, in contrast to previous studies that investigated whether binge drinking is associated with a general impairment of response inhibition, we did not find evidence for a deficit of response inhibition irrespective of the content of stimuli presented. For example, Townshend and Duka (2005) found that binge drinkers showed a lack of inhibitory control in the Vigilance Task from the Gordon Diagnostic System, a task which is similar to a go-/nogo task as participants have to inhibit their responses to a cue until the target stimulus appears (Townshend & Duka, 2005). In another study it was demonstrated that the number of

inhibition failures in a cued go-/nogo task with colored rectangles presented either in a vertical or horizontal orientation as go- or nogo-stimuli, was a significant predictor of binge drinking (Hildebrandt et al., 2004). Thus, it is important to consider task-specific aspects when investigating the association of binge drinking and deficits of response inhibition.

To our best knowledge there is up to now only one study that previously administered visual stimuli of different picture content to investigate whether binge drinking is associated with an impairment of response inhibition when alcohol-associated stimuli are presented (Nederkoorn et al., 2009). In this study, Nederkoorn and colleagues (2009) administered a stop-signal task and participants had to indicate as quickly as possibly by pressing one of two response buttons whether a picture was presented in a portrait or landscape view. The pictures were taken from four different categories: alcohol, soft-drink, neutral (shades of grey) or mild erotic. In 25% of the trials a stop-signal indicated that participants should inhibit their responses. Using the stop signal reaction time as dependent variable, the results of this study demonstrated no differences in response inhibition between binge and non-binge drinkers and no content-specific differences in response inhibition emerged. Thus, the results from this study (Nederkoorn et al., 2009) are in line with the present findings as no overall differences with regard to response inhibition deficits were observed between binge drinkers and non-binge drinkers, but in contrast to the present findings there was also no content-specific impairment observed for binge drinkers. There are a number of reasons that might explain these divergent findings. First of all, in a stop signal task participants are instructed to respond to a stimulus unless a stop-signal is presented, but do not need to first categorize stimuli and then to either respond or not as in a go-/nogo task. Thus, the two tasks might be related to different cognitive processes which

might be differentially affected by binge drinking. Another reason might be that the study by Nederkoorn and colleagues (2009) was primarily designed to assess the association between heavy drinking and response inhibition deficits and the authors report to have decided based on a correlation analysis of the AUDIT score (Saunders, Aasland, Babor, de la Fuente & Grant, 1993), binge drinking score and alcohol use to use alcohol use as the primary classification criterion and to check the main results for alternative classifications like binge drinking. Thus, we cannot exclude that the binge drinkers of our study differ from those of that previous study (Nederkoorn et al., 2009) with regard to important participant characteristics that might affect the findings (e.g., age, amount of alcohol use not reported separately for binge vs. non-binge drinkers in that study). This is especially important as different criteria were used in these two studies with regard to the classification of binge drinking. While we defined binge drinking based on the criteria developed by Townshend and Duka (2002) and relate to 'speed of drinking', the 'number of times being drunk in the last six months' and the 'percentage of times getting drunk when drinking', Nederkoorn and colleagues (2009) classified participants as binge drinkers based on their report of the number of days during the last two weeks on which they drank more than five units of alcohol on one occasion. This definition seems to be less specific compared to the criteria of Townshend and Duka (2002) and the sample of Nederkoorn and colleagues (2009) might also comprise participants with less severe binge drinking patterns.

Our finding of an alcohol-specific, but not general impairment of response inhibition, is in line with previous studies that investigated whether alcohol-dependent patients show an impairment of response inhibition that is especially pronounced when alcohol-associated compared to control stimuli are presented (Noël et al., 2005; Noël et al., 2007). The results of these studies are interesting with regard to the findings of the present study. Thus, Noël and colleagues (2005) administered a go-/nogo task in which

either alcohol-associated or neutral words were presented one after the other rapidly in the center of a computer screen. The words were arranged in eight test blocks with each block containing nine alcohol-associated and nine neutral words. At the beginning of each block a target category (i.e. either alcohol-associated or neutral) was defined and participants were instructed to respond to words of the target category as quickly as possible by pressing the space bar, but to withhold their response when distracters were presented. As dependent variables reaction times in go-trials and decision bias were calculated taking into account both hits and false alarms. The results of this study indicated that alcohol-dependent patients compared to healthy controls committed overall more commission errors and a significant group by target interaction was interpreted to indicate that this impairment of response inhibition was pronounced when alcohol-associated words were the targets (Noël et al., 2005). Noël and colleagues (2005) replicated this finding with alcohol-dependent patients without comorbid substance use and concluded that alcohol-dependent patients show a deficit of response inhibition which is enhanced when the responses to be inhibited are related to alcohol (Noël et al., 2007). However, the interpretation of these findings has been criticized (Field & Cole, 2007) as the results indicated that when alcohol-associated words were the target category, alcohol-dependent patients inappropriately responded to neutral words, while there seems to be no difference with regard to the responding to alcohol-associated words. As Noël and colleagues (2007) also found that alcohol-dependent patients showed longer reaction times when responding to alcohol-associated words as targets than control participants, it was suggested (Field & Cole, 2007) that these finding are more in line with avoidance or an impairment of cognitive processing of alcohol-related words in alcohol-dependent patients. Alternatively it has been proposed (Nederkoorn et al., 2009) that the findings of Noël and colleagues (2007) might also indicate an over-preparedness of alcohol-dependent

patients to detect alcohol-associated stimuli. Based on this criticism of the interpretation of the findings, we used in the present study a modified version of a go-/nogo task in which pictures displaying alcoholic beverages always had to be inhibited and pictures of non-alcoholic beverages always served as target stimuli. In addition, our control condition included geometrical figures only. Therefore, we can exclude that our finding of a larger deficit of response inhibition in binge drinkers when alcohol-associated pictures were presented compared to control stimuli is due to avoidance strategies. Thus, it can be hypothesized that binge drinkers show an impairment of response inhibition when alcohol-associated stimuli are presented, while alcohol-dependent patients seem to avoid alcohol-associated stimuli. It would be interesting for future studies to investigate in longitudinal studies if an alcohol-specific impairment of response inhibition changes over the course of time when drinking patterns are changing and problem drinking develops. At present, we only know that impulsive behavior and an impairment of response inhibition are risk factors for the development of problem drinking and addictive behavior (Verdejo-Garcia et al., 2008), and it is assumed that this association is reciprocal as chronic alcohol consumption further impairs cognitive control processes (Crews, Braun, Hoplight, Switzer & Knapp, 2000).

The results of our multiple linear regression analysis indicated that the only significant predictor of binge drinking was the number of alcohol-specific commission errors. This is an interesting finding as it might indicate that when binge-drinking has emerged not state-related aspects of an overall impairment of response inhibition or trait-like overall impulsive behavior predict further binge drinking, but that a specific impairment of response inhibition when alcohol-associated stimuli are presented contributes to binge drinking. It can be hypothesized that such an alcohol-specific impairment of response inhibition is induced by the harmful effects of binge drinking on the adolescent brain, possibly in combination with an increased incentive salience of alcohol-associated

cues for binge drinkers. In addition, our results deliver preliminary evidence that gender effects have to be taken into account as we found an interaction effect with gender that slightly failed to reach statistical significance. Separate regression analyses for male and female binge drinkers indicated that the number of commission errors in response to alcohol-associated pictures is only for female participants a significant predictor of the severity of binge drinking. In line with this, there are a number of studies (Hildebrandt et al., 2004; Townshend & Duka, 2005) that found that female binge drinkers are more impaired with regard to response inhibition than male binge-drinkers or female non-binge-drinkers, and it has been hypothesized that binge drinking is especially harmful to the female brain. However, our results with regard to gender should be interpreted with caution as the interaction effect of gender only reached marginally significance and further studies with larger sample sizes are warranted to analyze gender effects.

Some aspects of the present study are possible limitations and should be acknowledged when interpreting our findings. Firstly, the sample size of our study was rather small, thus we cannot exclude that differences between the groups with regard to confounding factors that we have not controlled for might have affected our findings. This should be especially taken into account with regard to the non-significant or only marginal significant findings with regard to gender effects. Thus, future studies with larger sample sizes are warranted to replicate our findings and to analyze gender effects in more detail. Secondly, we did not assess smoking status of participants and we cannot exclude that binge drinkers and non-binge drinkers might have differed with regard to smoking. Due to the rather short duration of our test session of only about 50 minutes, confounding effects due to smoke deprivation seem minimal. However, as shown by Luijten, Little and Franken (2011), smokers compared to non-smokers might show a general deficit of response inhibition. As our results indicated that binge

drinkers compared to non-binge drinkers showed an alcohol-specific, but not a general impairment of response inhibition, confounding effects due to smoking status are unlikely, but cannot be excluded. Thus, future studies are warranted that control for smoking status as binge drinkers might smoke more than non-binge drinkers. In addition, although participants were instructed to refrain from alcohol use 12 hours before the test-session, we did not control compliance with this instruction, for example by means of breath analysis. We thus cannot exclude that binge drinker's performance in the experimental task might have been affected by a hangover or sleep deprivation. Finally, the modified go-/nogo task we present here is a new and innovative measure to assess an alcohol-specific impairment of response inhibition and future studies are warranted to provide more information with regard to reliability and validity of this task. However, the task was derived from methodological considerations and concerns about the interpretation of the results from previous studies (Fied & Cole, 2007; Nederkoorn et al., 2009) and the present findings are promising that this task might be a suitable instrument to address research questions concerning content-specific aspects of response inhibition.

Conclusions

Taken together, the present study has demonstrated that binge drinkers compared to non-binge drinkers show an alcohol-specific impairment of response inhibition, but we found neither in self-reported nor behavioral measures evidence for an overall impairment of response inhibition. Interestingly, in a regression analysis, the number of commission errors in response to alcohol-associated cues emerged as the only significant predictor of binge drinking. In contrast, factors that are supposed to contribute to the development of binge drinking (like an overall impairment of response inhibition or trait-like impulsive behavior) were no significant predictors of binge

drinking. Thus, it can be assumed that when young adults have established binge drinking as a common drinking pattern, impairment of response inhibition when confronted with alcohol-associated stimuli is the only significant predictor of binge drinking. Future longitudinal studies are necessary to enhance our understanding of factors that contribute to binge drinking as this is important with regard to the development of effective interventions to prevent binge drinking (Field, Schoenmakers & Wiers, 2008).

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Conflict of interest disclosure

All authors report no potential conflicts of interest.

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2.2. The impact of cognitive impairment and impulsivity on relapse of alcohol-dependent patients: implications for psychotherapeutic treatment[2]

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[2] Czapla, M., Simon, J.J., Richter, B., Kluge, M., Friederich, H.C., Herpertz, S., Mann, K., Herpertz, S.C., & Loeber, S. (2016). The impact of cognitive impairment and impulsivity on relapse of alcohol-dependent patients: implications for psychotherapeutic treatment. *Addiction Biology, 21*(4), 873-84.

Abstract

Recent models of the development of addiction propose a transition from a pleasure-driven to a heavily automatised behaviour, marked by a loss of cognitive control. This study investigated the deficits in different components of cognitive control processes including behavioural inhibition in response to alcohol-related stimuli in alcohol dependent patients (ADP) and healthy controls (HC). The aims of the study were to identify which particular cognitive functions are impaired in ADP. Furthermore, we analysed the association between cognitive deficits and relapse rates and the reversibility of cognitive deficits under abstinence in a six month follow-up period. 94 recently detoxified ADP and 71 HC completed cognitive tasks as well as questionnaire measures assessing drinking behaviour and personality traits. Compared to HC, ADP showed poorer performance in response initiation, response inhibition, complex sustained attention and executive functions. Impairment in response inhibition was a significant predictor for relapse, yet the strongest predictor was the interaction between the number of previous detoxifications and response inhibition deficits. These findings indicate that interventions should take into account inhibitory deficits especially in ADP with a high number of previous detoxifications.

Keywords: cognitive impairment, go/no-go task, incentive salience, relapse, response inhibition

1. Introduction

A body of evidence shows that alcohol dependence is associated with deficits in a range of cognitive control functions (for a review see Fernandez-Serrano, Perez-Garcia & Verdejo-Garcia, 2011; Noël et al., 2013). Everitt et al. (Everitt & Robbins, 2005; Everitt et al., 2008) argue for a transition in addiction behaviour, from voluntary and pleasure-driven drinking habits at first to a strongly automatised, compulsive behaviour, characterized by a loss of control, which leads to the continuation of alcohol consumption despite negative consequences. Neuroimaging studies have shown that cognitive deficits in ADP are associated with significant changes in brain structure and function (e.g. Beck et al., 2012; Crews & Boettiger, 2009; Bari & Robbins, 2013) accompanied by relapse risk. Models of the aetiology and maintenance of addiction (e.g. Franken, 2003; Robinson & Berridge, 2000; 2008) propose that chronic alcohol consumption leads to a dysfunction of dopaminergic neurotransmission in the mesolimbic-mesocortical reward system causing hypersensitivity to alcohol and alcohol related stimuli (for a review see Heinz, Beck, Grüsser, Grace & Wrase, 2009; Jentsch & Pennington, 2014). When alcohol related stimuli become more salient, it results in an increase in craving for alcohol (Goldstein & Volkow, 2002). This increase in salience also relates to cue reactivity, a finding in addiction research describing physiological changes and increase in craving for a substance, when addicted individuals are exposed to substance-related cues (Carter & Tiffany, 1999; Drummond 2000).

However, Papachristou et al. (2013) point out that ADP show inter-individual differences in cue reactivity and propose impulsivity as a possible moderator for the impact of cue reactivity and craving. They showed that impulsivity and impaired response inhibition are predictive for cue-elicited craving during alcohol cue exposure.

This is in line with other studies indicating that impulsivity and novelty seeking are both related to craving and relapse (Evren, Durkaya, Evren, Dalbudak & Cetin, 2012). Some studies have focused on response inhibition in larger detail, suggesting a pronounced inhibition deficit for substance related stimuli (Noel et al., 2005; Noel et al., 2007; Weafer & Filmore, 2012). Noel et al. (2005) examined detoxified polysubstance abusers with alcoholism, who showed discrimination and inhibition deficits when alcohol-related words were the targets, indicating a cognitive bias towards information related to alcohol that might be responsible for relapse.

A similar study (Noel et al., 2007) with ADP using a go/no-go task with alcohol-related and neutral words found that ADP made more commission errors when alcohol-related words had been displayed, assuming an impairment in response inhibition for alcohol associated stimuli. However, this interpretation has been criticised (Field & Cole, 2007) and Nederkoorn et al. (2009) report contradicting findings demonstrating that there is no content-specific inhibition deficit in heavy drinkers. They propose that domain-specific differences between ADP and HC may be due to an over-preparedness to detect alcohol-related stimuli and differences in attention or approach tendencies. However, comparability is limited due to different populations that have been studied (social drinkers vs. ADP) and therefore such interpretations have to be treated with caution.

Findings from studies with social and problem drinkers provide further evidence that a deficit of response inhibition might be especially pronounced when alcohol-related stimuli are presented (Kreusch et al., 2013; Weafer & Filmore, 2012). Studies about the acute effects of alcohol also indicate that the effects of alcohol on disinhibition are cue-specific and restricted to inhibition of responses towards alcohol related stimuli (Adams, Ataya, Attwood & Munafo, 2013). A study by Christiansen et al. (2013)

demonstrated that craving is sensitive to the anticipated effects of alcohol and alcohol-approach tendencies are particularly sensitive to the anticipated effects of alcohol.

Recently the impact of detoxifications has been highlighted as a very important issue in relation to cognitive control deficits and relapse (Duka, 2011; Duka & Stephens, 2014), depicting that ADP with multiple detoxifications present more emotional and cognitive impairments than ADP with fewer detoxifications. Duka and Stephens (2014) argue that the process of detoxification may engender brain changes that lead to loss of control and therefore impair the ability to control future drinking.

In the scientific literature (de Wit, 2009; Fernandez Serrano et al., 2011; Jones et al., 2013) cognitive control, often referred to as impulsivity, is considered a multi dimensional construct including processes of attentional control, response inhibition and decision making (delay discounting). While Dougherty and colleagues (Dougherty, Marsh-Richard, Hatzis, Nouvion & Mathias, 2009) include impaired response initiation as an important component of impulsivity, meaning that ADP respond rapidly before a stimulus is completely processed. Other authors (Crews & Boettiger, 2009; Fernandez-Serrano et al., 2011) also emphasise the meaning of reversal learning in relation to addiction which is defined as the ability to adapt and is marked by a loss of executive function. We combined the above mentioned components of cognitive control and intended to assess the following processes entirely for the first time in relation to relapse: attention, response initiation, response inhibition, delay discounting and reversal learning.

We expected an overall impairment of cognitive control functions for ADP reflected by a significantly worse performance in the given tasks in comparison to HC. Following the above mentioned research findings that point out the crucial role of impulse control and cue reactivity towards alcohol related stimuli, we hypothesized ADP to show a

pronounced inhibition deficit for alcohol related stimuli compared to neutral stimuli, more precisely, expecting ADP to make more commission errors in alcohol stimuli trials. In regard to relapse, we anticipated cognitive deficits in the five underlying processes, particularly response inhibition and the number of previous detoxifications would be significant predictor variables. Lastly, we wanted to find out whether or which cognitive deficits in ADP are reversible after six month of abstinence, as the literature provides mixed findings (Fein, Torres, Price & Di Sclafani, 2006; Fernandez-Serrano et al., 2011; Stavro et al., 2013).

2. Materials and methods

2.1. Participants

From May 2011 to October 2013 171 volunteers were included in the study. One hundred of them were ADP (according to DSM-IV-criteria) who sought extended inpatient detoxification treatment at the Psychiatric Center Nordbaden, Wiesloch, Germany, for an average duration of 2-4 weeks. The extended detoxification is an evidence based treatment recommended by the guidelines of the German society for addiction research and addiction treatment that is commonly applied in the German psychiatric system. It involves alcohol withdrawal, accompanied by medication when needed and a cognitive behavioural based psychotherapeutic program including psychoeducation, individual and group therapy to enhance motivation for abstinence. All patients fulfilling the study criteria and providing written informed consent were included. Due to technical problems with the *CANTAB*, data from six patients had to be excluded from further analyses. The control group consisted of 71 HC recruited from the local community. HC had no alcohol-related problems based on information obtained from semi-structured interviews and questionnaires. All subjects received monetary compensation.

Exclusion criteria for both samples were current drug abuse or dependence other than nicotine or alcohol for patients, severe somatic, neurological or psychiatric diseases, serious complications in detoxification for patients, pregnancy, lactation period or suicidal tendencies. The study was approved by the Ethics Committee of the University of Heidelberg (Medical Faculty Mannheim) and adhered to the Declaration of Helsinki. All participants signed informed consent.

2.2. General procedure

Data assessment was conducted by a clinical psychologist trained in neuropsychological test administration and was divided in two sessions: in the first session patients were elaborately screened and interviewed with a standardized clinical interview, lasting 1 to 1.5 hours in total. The second session lasted about two hours and contained neuropsychological test administration and questionnaires. Information on past and recent alcohol consumption was obtained from the *Time Line Follow Back Interview* (*TLFB*; Sobell & Sobell, 1992). The *Alcohol Dependence Scale* (*ADS*; Skinner & Allen, 1982) was administered to assess the severity of alcohol dependence. Neuropsychological testing comprised four subtests of the *CANTAB* (Cambridge Cognition, Cambridge, United Kingdom; http://www.camcog.com) as well as an *Alcohol-Go/no-go-task (AGN)*. The four subtests of the CANTAB were presented in a randomized order. After a five minute break, the AGN was administered. For patients, neuropsychological assessment was performed at least three days after termination of medically supervised detoxification treatment and the mean duration of abstinence prior to the test session was 18.20 days (SD=10.05, range 6-76). For alcohol-dependent patients drinking behaviour as well as utilisation of further treatment offers after discharge from inpatient treatment was assessed in the six months following the test-session either via personal telephone interviews or during the follow-

up test-session. All patients were asked to take part in a second neuropsychological test-session at the end of the follow-up period.

2.3. Assessment of cognitive impairment

Four subtests of the CANTAB were administered to assess different components of cognitive control functions. Attentional processes were assessed by the *Choice Reaction Time Task* (CRT), which is a two-choice reaction time test with arrows pointing either to the left or right side. Outcome measures used in the analysis were the *standard deviation of the latencies for correct responses,* the *mean reaction time for correct responses, commission errors, omission errors and the total number of correct trials*. Deficits in the maintenance of attention manifest in a higher variance of reaction times and a higher number of commission and omission errors.

The *Rapid Visual Processing Task* (RVP) measures visual sustained attention and response initiation. Subjects view digits from 2 to 9 that appear consecutively in a pseudo-random order and are requested to detect target sequences (e.g. 3-5-7). The outcome variables were *RVP A'* (target sensitivity regardless of response tendency), *RVP B'* (tendency to respond regardless whether the target sequence is present), *mean latency* (time taken to respond), *total false alarms, total hits* (correct responses).

The Cambridge Gambling Task (CGT) assesses decision-making and risk-taking behavior. Outcome variables used in analysis were *delay aversion* (measure of delay discounting: assesses whether subjects preferably choose smaller but immediate rewards over larger and later rewards), *deliberation time (*mean latency to the subject's choice of which colour to bet on), *quality of decision making* (the proportion of trials on which the subject chose to gamble on the more likely outcome), *risk adjustment* (reflects the tendency to bet a higher proportion of the points on trials when the large majority of the boxes are the colour chosen than when a smaller majority of the boxes

are of the colour chosen), *risk taking* (mean proportion of the current points total that the subject chose to risk on gamble trials for which they had chosen the more likely outcome).

The *Intra/Extradimensional Set Shift Task* (IED) is a test of rule acquisition and reversal learning. It features visual discrimination and attentional set formation maintenance, shifting and flexibility of attention. Outcome measures used for analysis *were number of extra-dimensional shift errors, number of errors prior to the extra-dimensional shift, number of successfully completed stages, total errors adjusted* (measures the subject's efficiency by adjusting the errors for not attempted stages) and *reversal learning* (number of errors in stages where contingencies are reversed). In General difficulties in this task reflect impairment in executive functions, with *reversal learning* reflecting a specific impairment in cognitive flexibility.

2.4. *Assessment of response inhibition and impulsivity*

To assess impairment of response inhibition a go/no-go task that displayed visual stimuli of alcoholic beverages, non-alcoholic beverages or geometrical figures was used. To ensure individual relevance of the alcoholic stimuli presented, a total of 85 pictures of different alcoholic beverages (beer, wine, and spirits) were shown to the participants before the beginning of the task, and they were instructed to select eight pictures that displayed best their preferred alcoholic beverages. The non-alcoholic beverages consisted of a standard set of eight pictures displaying soft-drinks, water and juice. The pictures of both alcoholic and non-alcoholic beverages had the same background and similar visual features. After the selection of the alcoholic pictures, participants rated each of the sixteen experimental stimuli with regard to *likeability* ("How much do you like this beverage?"), *valence* ("How pleasant do you find this picture?") and *arousal* ("How much arousing do you find this picture?"). Bonferroni-

corrected t-tests indicated no significant differences between pictures displaying alcoholic or non-alcoholic beverages in HC (all ts≤1.99, all ps≥0.15). In ADP there were no significant differences between alcoholic and non-alcoholic pictures in *likeability* and *arousal* (all ts≤0.99, all ps≥0.98), while pictures of alcoholic beverages were rated significantly less pleasant than pictures of non-alcoholic beverages (t=-2.96, p=0.02).

The selection and rating of the pictures as well as the *AGN* were presented on a 15 inch colour monitor. For task presentation and recording of responses we used Presentation® software (Version 16.0, Neurobehavioral Systems, Inc., Albany, CA, USA).

The AGN-task (Figure 1) was divided in two parts each lasting about ten minutes. Each part comprised four blocks with alcoholic/non-alcoholic beverages and an alternating sequence of four blocks where geometrical figures were displayed. In the alcoholic/non-alcoholic beverages blocks, visual stimuli of non-alcoholic beverages served as go-stimuli and participants were instructed at the beginning of each block to respond as quickly as possible to pictures of non-alcoholic beverages by pressing the space bar. In contrast, participants should inhibit their responses when alcoholic beverages were displayed. In blocks with geometrical figures, a rectangle served as the go-stimulus and a circle as the no-go stimulus. A total of 40 trials were presented within each block with 80% of the trials being go-trials, thus one part consisted of 320 trials and both parts included 640 trials in total. All pictures were displayed for 490 ms and after each block there was a short break of 13 seconds and then a fixation cross was presented for 1000 ms before the target category for the following block was displayed on the screen. At the start of the experimental task two short practice blocks were administered that were not scored.

The number of commission errors (i.e. responses to no-go stimuli) for alcoholic beverage blocks and geometrical figure blocks were used as separate dependent variables.
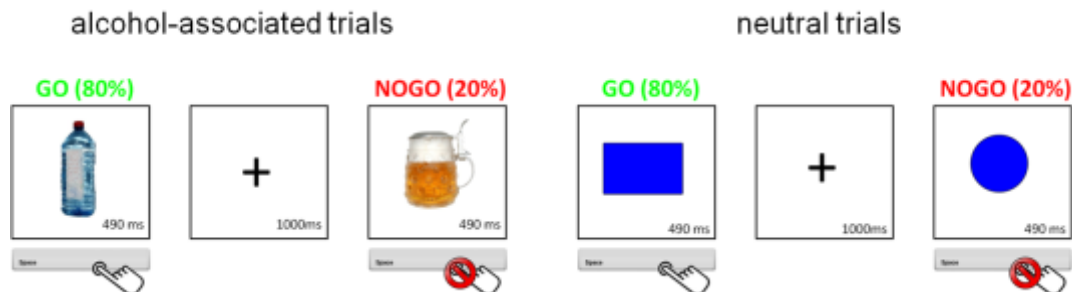

Figure 1: The *Alcohol-Go-Nogo-Task*: Trial procedure in alcohol-associated blocks (left) and neutral blocks (right).

The German version of the *Barratt-Impulsiveness-Scale (BIS-11)* (Preuss et al., 2008) was administered to provide a subjective measure of impulsive behaviour in everyday-life situations. The *BIS-11* comprises 30 items related to inattention, motor impulsivity and lack of planning behaviour. For the present analysis only the summary score of the *BIS-11* was used as this is the most reliable outcome measure of the German version (Preuss et al., 2008).

2.5. *Analysis of drinking behaviour and treatment utilisation during follow-up*

The *TLFB*-interview was used to assess drinking behaviour after discharge from inpatient treatment in the six months following the test-session. *Relapse* (yes/no) *and time until first relapse* (in days) were used as dependent variables for subsequent analyses. If patients reported abstinence, biological alcoholism markers (Gamma-glutamyl transferase, Alanine transaminase, mean corpuscular volume, Carbohydrate-deficient transferrin) were assessed to verify patients' information and relatives were asked whether they could confirm abstinence. In addition, the utilisation of further treatment offers was assessed. Patients were coded as utilising treatment offers during

the follow-up period when they reported regular visits of self-help groups, engagement in psychotherapeutic treatment, enrolment in a structured pharmacological treatment program (e.g. daily administration of disulfiram), and/or daycare treatment.

2.6. Statistical Analysis

T-tests (two-sided) and chi-square analyses using Fisher's exact test were used to examine differences between patients and controls with regard to demographic and drinking-related variables. To assess cognitive function, a multivariate analysis of variance with different outcome parameters of the *CANTAB tasks* as dependent variables was calculated. Respecting the special aspect of response inhibition, a repeated measures ANOVA was performed with the *number of commission errors* in the AGN as dependent variable, *category* (alcohol-associated vs. neutral) as within group factor and *group* (ADP vs. HC) as between group factor.

To analyse the predictive value of impairment of cognitive function and response inhibition for risk of relapse in the six months following the test-session, we first analysed relapse rates during follow-up using a Kaplan-Meier-Survival analysis and assessed the influence of the utilisation of treatment during follow-up by a log-rank test. Secondly, we performed a principal components analysis with varimax rotation and stepwise inclusion of all variables of cognitive function in which patients performed worse than healthy controls in order to classify similar measures assessed in different tests into homogenous factors and to reduce the number of predictors for the regression analysis. Factors were extracted based on the Kaiser criterion (eigenvalues greater than 1) and the Scree-test. Then, we calculated a stepwise binary logistic regression analysis with relapse as the dependent variable. As predictors we entered in the first step the number of previous detoxifications, in the second step the utilisation of treatment offers during the follow-up period as well as the factors extracted in the

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factor analysis. In the third step, the interaction terms of the number of previous detoxifications and the factors of cognitive function with follow-up treatment were entered. The number of previous detoxifications was corrected for the duration of dependence to control for confounding effects in line with prior findings that have shown the duration of dependence or amount of alcohol per week is not associated with deficits of response inhibition (Townshend et al., 2014). To further analyse significant interaction effects, a moderator analysis was calculated using the procedure PROCESS for SPSS by Andrew Hayes. The conditional effect of cognitive impairment on relapse was then investigated by entering cognitive impairment as predictor variable and the number of previous detoxifications as a moderator variable into this model, with low/high values of the moderator variable referring to the mean +/- 1 SD.

Recovery of cognitive performance during the follow-up period was analysed by separate repeated measures ANOVA with relapse (yes vs. no) as group variable. For all analyses a significance level of $\alpha \leq 0.05$ was considered as significant; missings in single questionnaire measures or due to technical problems were replaced with the mean. IBM SPSS Statistics (Statistical Package of the Social Science, 22.0.) was used for all analyses.

3. Results

3.1. Sample characteristics

Table 1 shows the sample characteristics for ADP and HC. The groups did not differ in age, gender and duration of education. As expected, we found a significantly greater number of drinking days as well as a significantly higher amount of alcohol consumed in the three months leading up to the test-session; patients also received a significantly higher score on the *Alcohol Dependence Scale*.

Table 1: Demographic characteristics and drinking related variables of alcohol-dependent patients and healthy controls at baseline

	Alcohol-dependent patients (n = 94)	Healthy control participants (n = 71)	Statistics (t/X², p-value)
Age (years) [Mean (SD)]	48.05 (9.26)	46.00 (12.02)	-1.20, 0.23
Gender [N (%)]			
Female [N (%)]	18 (19)	17 (24)	0.56, 0.29
Male [N (%)]	76 (81)	54 (76)	
Duration of education (years) [Mean (SD)]	12.99 (2.62)	13.63 (3.41)	1.36, 0.18
Number of drinking days (in the 3 months prior to testing-T1) [Mean (SD)]	51.94 (24.02)	13.10 (13.85)	-13.06, 0.00
Cumulative amount of ethanol (gr) (in the 3 months prior to T1) [Mean (SD)]	9.294.03 (6397)	452.78 (553.19)	-13.33, 0.00
Summary score *Alcohol Dependence Scale* (Skinner & Allen, 1982) [Mean (SD)]	15.85 (6.97)	1.21 (2.44)	-18.90, 0.00
Duration of alcohol dependence (years) [Mean (SD)]	11.45 (10.16)	n/a	n/a
Number of previous detoxifications (prior to T1) [Mean (SD)]	5.83 (7.48)	n/a	n/a

3.2. Impairment of cognitive function and response inhibition

With regard to cognitive function our results indicated an overall impairment of ADP when compared to HC [$F_{(20,144)}=2.14$; $p \leq 0.01$]. However, this impairment was not reflected in all measures of cognitive function (Table 2). Thus, clear evidence for cognitive impairment was found with regard to performance in the *Rapid Visual Information Processing Task* as patients achieved a significantly lower number of correct responses, had a higher number of commission errors (i.e. false alarms), needed longer to respond and were less sensitive to the task specific requirements (RVP-A). In addition, patients performed significantly worse than healthy controls in the *Intra/Extra Dimensional Set Shift Task* with regard to the number of stages completed and the number of errors, although not with regard to (pre-) shift errors or reversal learning (only marginally significant at $p<0.10$). While patients needed

significantly longer in the *Cambridge Gambling Task* to decide about their bets, and the difference with regard to risk adjustment reached marginal significance, we found no evidence for lower quality of decision making, higher risk taking, delay aversion or fast and impulsive choices. Patients also did not perform worse than controls in maintenance of attention during the *Choice Reaction Time Task*.

For response inhibition, we found that contrary to our hypothesis, ADP as well as HC made more commission errors when alcohol-associated stimuli were presented compared to neutral stimuli (main effect *category*) [$F_{(1,163)}=26.33$, $p<0.001$], whereas the interaction *category by group* did not achieve significance [$F_{(1,163)}=0.72$, $p=0.40$]. However, ADP showed an overall impairment of response inhibition as they had a higher number of commission errors than HC in response to alcohol-associated as well as neutral stimuli (main effect *group*) [$F_{(1,163)}=11.84$, $p=0.001$] (Figure 2; Table 2).

Table 2: Performance of alcohol-dependent patients and healthy controls in the different tasks of the *CANTAB* and the *Alcohol-Go-Nogo-task*

	Alcohol-dependent patients (n = 94)	Healthy control participants (n = 71)	Statistics (F, p-value)
Choice reaction time task			
Number of total correct trials [Mean (SD)]	99.27 (1.04)	99.48 (0.86)	1.97, 0.16
Latency correct trials[Mean (SD)]	327.05 (54.78)	327.85 (52.42)	0.01, 0.93
SD latency correct trials [Mean (SD)]	74.07 (38.45)	68.14 (26.27)	1.25, 0.27
Number of commission errors [Mean (SD)]	0.02 (0.15)	0.01 (0.12)	0.12, 0.73
Number of omission errors [Mean (SD)]	0.02 (0.15)	0.00 (0.00)	1.53, 0.22
Cambridge Gambling Task			
Quality decision making [Mean (SD)]	0.84 (0.17)	0.88 (0.16)	1.79, 0.18
Deliberation time [Mean (SD)]	3075.09 (1305.84)	2376.20 (724.15)	16.49, 0.00
Risk adjustment [Mean (SD)]	0.95 (1.00)	1.25 (1.01)	3.74, 0.06
Delay aversion [Mean (SD)]	0.24 (0.23)	0.26 (0.24)	0.18, 0.68
Risk taking [Mean (SD)]	0.53 (0.16)	0.51 (0.16)	0.67, 0.41
Intra extra dimensional set shift task			
Stages completed [Mean (SD)]	8.11 (1.62)	8.56 (0.98)	4.41, 0.04
Number of errors (total) [Mean (SD)]	35.91 (37.11)	24.79 (25.14)	4.74, 0.03
Pre-shift errors [Mean (SD)]	8.47 (6.64)	7.01 (4.78)	2.44, 0.12
Extra-dimensional shift errors [Mean (SD)]	10.96 (10.46)	9.35 (9.39)	1.04, 0.31
Reversal learning errors [Mean (SD)]	19.35 (21.11)	13.54 (16.66)	3.66, 0.06
Rapid visual information processing task			
Number of hits (total) [Mean (SD)]	15.21 (5.43)	17.49 (5.05)	7.58, 0.01
Mean latency [Mean (SD)]	454.13 (107.69)	411.67 (88.69)	7.30, 0.01
RVP-A [Mean (SD)]	0.88 (0.06)	0.91 (0.05)	9.10, 0.00
RVP-B [Mean (SD)]	0.87 (0.30)	0.91 (0.24)	0.87, 0.35
	2.69 (5.08)	1.38 (1.92)	4.27, 0.04

Number of false alarms (total) [Mean (SD)]			
Alcohol-Go-Nogo-task	13.81 (5.60)	10.56 (6.77)	11.84, 0.00*
Number of commission errors in response to alcohol-associated stimuli [Mean (SD)]	11.65 (5.52)	9.01 (5.87)	
Number of commission errors in response to neutral stimuli [Mean (SD)]			

Note: * main effect of group in repeated measures ANOVA, for further details see text

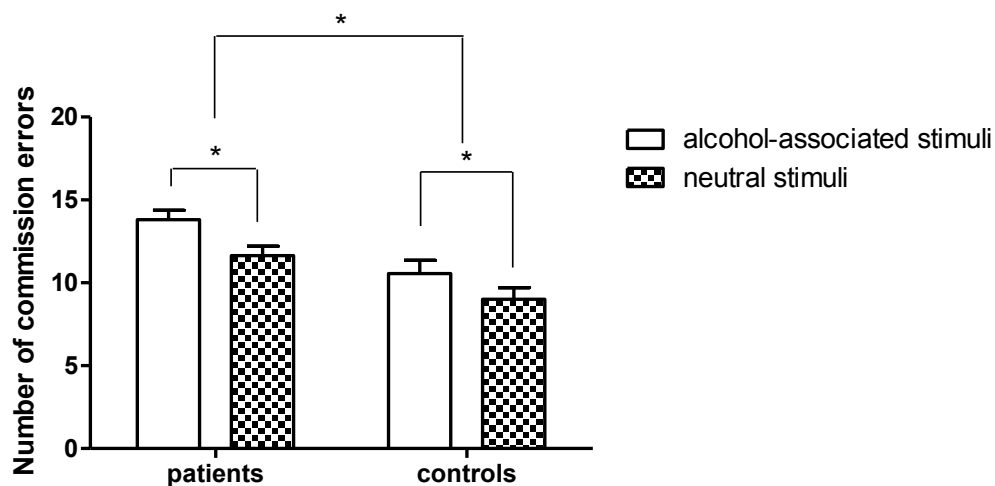Figure 2: Impairment of response inhibition to the presentation of alcohol-associated and neutral stimuli during the *Alcohol-Go-Nogo-task*, * p<0.05

With regard to self-reported impulsive behaviour we found that patients achieved significantly higher scores on the summary scale of the BIS [T(169)=-2.06, p=0.043; patients: mean=59.77, SD=10.54; control participants: mean=56.82, SD=7,33]. However self-reported impulsive behaviour was not significantly correlated with any of the measures of cognitive function or response inhibition [r≤|0.12|, p≥0.14].

3.3. Predictive validity of impairment of cognitive function and response inhibition for relapse

3.3.1 Relapse rates during follow-up

For the follow-up period complete data with regard to relapse and utilisation of further treatment offers was available for 81 of the ADP [86.17%]. 67.90% of the patients reported a relapse during the follow-up period. Conservative calculations assuming that patients who could not be contacted during follow-up (n=13) were relapsed, increased this number to 77.66%. We found a strong effect of utilisation of further treatment offers on the course of relapse [$\chi^2(1)=43.08$, $p<0.001$]. This finding indicates that patients who regularly attended to treatment offers like self-help groups or psychotherapy during follow-up, report a longer duration of time until the first relapse and an overall lower rate of relapse (Figure 3). Therefore, in the subsequent analyses, the variable *utilisation of further treatment offers* was used as an additional predictor variable.
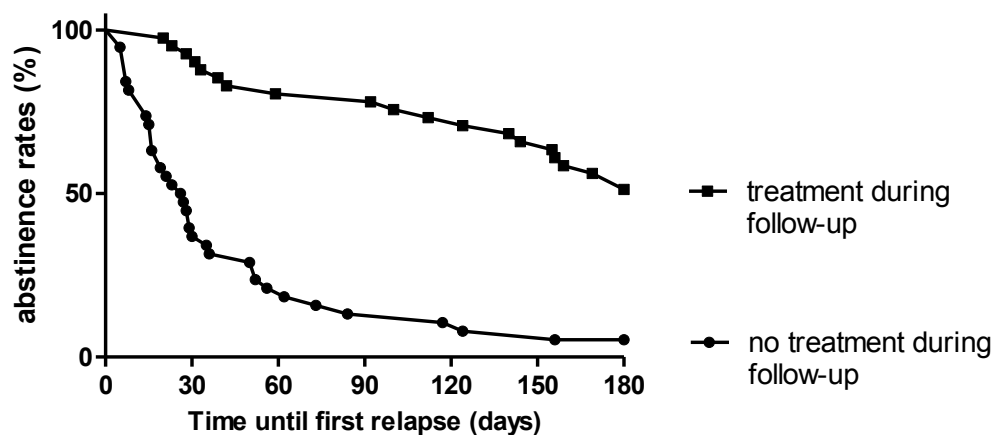

Figure 3:   Impact of utilization of treatment offers during the follow-up period on relapse

3.3.2. Classification and reduction of cognitive outcome parameters

The results of the principal components analysis suggested that three factors accounted for 59.38% of the variance. The factors were interpreted based on the highest respective loadings. The first factor [eigenvalue: 2.89, percentage of variance explained: 24.1] consisted of performance in the *Intra Extra/Dimensional Set Shift Task* [number of stages completed: factor loading = -0.96, total number of errors: factor loading = 0.96, errors with regard to reversal learning: factor loading = 0.93]. The second factor [eigenvalue: 2.50, percentage of variance explained: 20.79] comprised of performance in the *Rapid Visual Information Processing Task* [RVP-A: factor loading=0.89, total hits: factor loading=0.81, total false alarms: -0.64, mean latency: factor loading=-0.52] and risk adjustment in the *Cambridge Gambling Task* [factor loading=0.49]. The third factor [eigenvalue: 1.74, percentage of variance explained: 14.48] consists of response inhibition deficits shown in the *AGN* [number of commission errors in response to alcohol-associated stimuli: factor loading=0.94, number of commission errors in response to neutral stimuli: factor loading=0.90].

3.3.3. Prediction of relapse

The logistic regression analysis yielded a significant model in the third step [$\chi^2(3)=27.10$, $p<0.001$] explaining 42.6% of the variance (R^2 Nagelkerke). Prediction success was high, with an overall prediction rate of 80.0%; 93.3% correct prediction rate of relapse and 40.0% of abstinence. This lower prediction success of abstinence might be due to the low number of abstainers. As shown in Table 3 the *utilisation of treatment during follow-up*, *response inhibition deficits* (factor 3 of the principal components analysis) and the interaction of *response inhibition deficits* (factor 3) and the *number of previous detoxifications* significantly predicted relapse. Beta weights, significance levels and odds ratios for each predictor are shown in Table 3.

Table 3: Logistic regression results for predicting relapse

Predictors	Beta	df	p-value	Odds Ratios	95% Confidence Intervals	
					Lower	Upper
Utilization of treatment during follow-up	-1.55	1	0.002	0.21	0.08	0.56
Deficits of response inhibition (factor 3)	1.28	1	0.033	3.59	1.11	11.61
Deficits of response inhibition (factor 3) x Number of detoxifications (prior T1)	4.87	1	0.008	130.61	3.67	4651.75
Constant	1.62	1	0.000	5.04		

The effect of the *utilisation of further treatment offers* was rather weak with patients who did not attend further treatment being 0.21 times more likely to relapse than patients who attended to treatment. In contrast, the influence of *deficits of response inhibition* (factor 3) was strong with patients with higher deficits of response inhibition being 3.59 times more likely to relapse. However, the *interaction of factor 3 and the number of previous detoxifications* was the strongest predictor. Figure 4 shows the results of the moderation analysis that was run to elucidate this interaction effect.
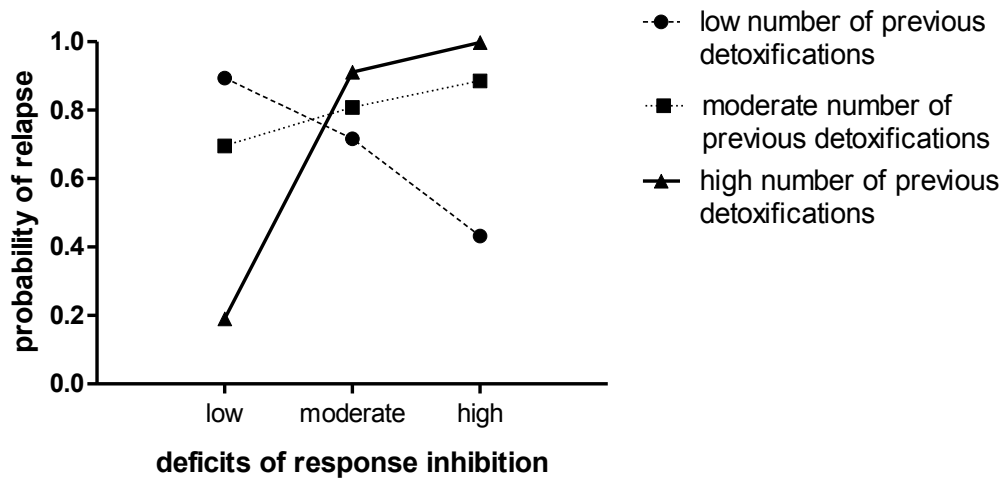
Figure 4: The conditional effect of *deficits of response inhibition* on relapse for patients with a low, moderate or high number of previous detoxifications.

Note: Number of previous detoxification was corrected for the duration of dependence; high/low number of previous detoxification is +/- 1 SD; *deficits of response inhibition* equals factor 3 of the principal components analysis

The results of the moderation analysis indicated that *deficits of response inhibition* (factor 3) was a significant predictor of relapse for patients with a higher number of previous detoxifications. In contrast, patients with a low number of previous detoxifications were most likely to relapse when they only had little impairment of response inhibition (Table 4).

Table 4: The conditional effect of deficits of response inhibition on relapse: Results of the moderation analysis

Value of the moderator (previous number of detoxifications related to the duration of dependence)	Beta	p-value	95% Confidence Intervals	
			Lower	Upper
1 SD below mean	-2.46	0.01	-2.32	-0.26
mean	1.23	0.22	-0.38	1.69
1 SD above mean	2.11	0.04	0.28	7.82

3.4. Changes of cognitive impairment and response inhibition during follow-up

44 ADP completed a second test session after six months. 32 of these 44 patients [72.72 %] reported a relapse during the follow-up, while twelve patients reported abstinence [27.72 %]. The results of a logistic regression analysis indicated that neither sociodemographic and drinking-related variables (Table 1) nor results with regard to cognitive function at the first test-session (factor 1 to 3) significantly predicted participation in the follow-up test-session [$\chi^2(11)$=11.22, p=0.43; overall prediction success: 50.0%].

With regard to changes of cognitive function we found a decline of the *deliberation time* in the CGT compared to the first test-session [diff mean = 256.71; F(1,42)=4.33, p=0.04]. However, there was no significant interaction effect with relapse [F1,42)=0.32, p=0.58]. In good keeping with this finding, there was a significant decline of the overall number of commission errors in the *deficits of response inhibition* in the AGN [diff mean=170.97; F(1,42)=23.34, p<0.001] indicating a decrease of deficits of response inhibition, but no significant interaction effect with relapse [F(1,42)=0.71, p=0.40]. None of the main or interaction effects achieved statistical significance in any of the other measures [all Fs≤3.21, all p≥0.07].

4. Discussion

Our results show that ADP possess impairments in several different cognitive control processes and add to the growing body of literature implicating an important role for cognitive deficits in ADP (reviewed in Stavro et al., 2013). Furthermore, we demonstrate that cognitive deficits in ADP mainly appear in the following areas of cognitive control functions: response initiation, complex sustained attention, response inhibition as well as a slight impairment in executive functioning and reversal learning.

However, ADP did not perform worse than HC in regard to decision making, delay discounting, and the maintenance of attention in a rather simple task, which partly contradicts our first hypothesis. Interestingly, we found no deficits with regard to attentional processes in the Choice Reaction Time Task, despite findings from several studies involving more complex tasks (Naim-Feil et al., 2014) that have reported such deficits. This indicates that ADP have a good functional level of simple attention which is supported by research findings suggesting that heavy social drinkers only differ from light social drinkers in tasks that are more complex (Bijl, de Bruin, Kenemans, Verbaten & Böcker, 2005). The lack of differences in the gambling task is partly supported by studies with ADP with comorbid gambling disorder (Zois et al., 2014) or polysubstance use (Van der Plaas et al., 2009) demonstrating that ADP showed no evidence of deficits in decision making and their betting was not different from that of HC.

Further, we demonstrate that ADP have a pronounced deficit in response inhibition. However, this deficit in ADP is not specific for alcohol-associated stimuli as both groups made more commission errors in alcohol stimuli trials than in neutral trials. While this finding is not in line with our initial hypothesis, these results are a valuable contribution to a research area in which previous findings of an alcohol-specific inhibition deficit (Noel et al., 2007) have been criticised (Field et al., 2007) or even disconfirmed (Nederkoorn et al., 2009). Thus, Nederkoorn et al. (2009) who reported similar results to our study, suggest that domain-specific differences between ADP and HC are more likely to be due to differences in attention or approach tendencies than to response inhibition. Concordantly, studies with social drinkers found similar patterns of attentional bias towards alcohol stimuli in both ADP and light social drinkers (Vollstädt-Klein et al., 2009) indicating that this bias is not exclusive for ADP.

With regard to the relapse risk in the six month follow up period, we found that deficits of response inhibition are a significant relapse predictor in conjunction with the number of previous detoxifications, thus confirming our main hypothesis regarding relapse prediction. Moreover, moderation analysis showed that patients with many previous detoxifications and large deficits in response inhibition showed the highest relapse risk. Several studies have indicated that a high number of previous detoxifications is associated with cognitive deficits (e.g. Loeber et al., 2009; 2010), and changes in brain structure and connectivity (for an overview see Duka & Stephens, 2014). This process may be associated with neurodegenerative processes in prefrontal areas that have been linked to elevated glutamate levels during acute alcohol withdrawal (Crews & Nixon, 2009). Thus, frequent detoxifications could lead to impairments in prefrontal functioning, reduced cognitive control and to increased vulnerability for stress-induced relapse (Duka & Stephens, 2014). In contrast, the moderation analysis showed that patients with a low number of detoxifications and high deficits in response inhibition were more likely to stay abstinent. In interpreting this somewhat unexpected finding it should be noted that the correct prediction rate for abstinence was only 40.0%, indicating that there are other unknown variables influencing the maintenance of abstinence. For example, this patient group might be more aware of the heightened risk of relapse after detoxification and more motivated to undergo further treatment. In addition, regarding the concept of response inhibition, the considerations by Jones et al. (2013) are noteworthy, suggesting that the ability to inhibit behaviour fluctuates in response to environmental and psychological triggers such as stress, motivational biases and individual differences and should be rather seen as a state than a trait. However, due to the limited size of the subgroup of patients who stayed abstinent it was not possible to further analyse these hypotheses in the present study but it seems important for future studies to consider protective factors for relapse.

Regarding our last hypothesis, the results of the current study demonstrate that cognitive deficits in general did not improve during a six month time of abstinence, which is in line with a recent meta-analysis (Stavro et al., 2013) demonstrating strong evidence that normalisation of cognitive function appears to generally require up to one year of abstinence. Future studies should investigate whether a specific training in inhibitory control functions can reduce observed deficits and reduce the relapse risk in ADP with a high number of detoxifications and pronounced deficits in inhibition control. Interestingly, our results do not show a moderation effect of follow-up treatment on relapse rate in this particular patient group, though generally follow-up treatment had a major impact on abstinence. This suggests that present treatment options are not sufficiently addressing these particular deficits, and emphasises the need for more personalized interventions. In this regard, previous studies have shown very promising results using computerized training programs such as the Cognitive Bias Modification (CBM) training which aims to modify approach bias towards alcohol associated stimuli and to reverse impairments in neurocognitive functions in ADP (Wiers et al., 2011). In addition, Houben et al. (2011) showed that alcohol intake could be significantly decreased by strengthening response inhibition for alcohol related cues by completing a training task similar to the go/no-go task. Taken together, the results of the present study indicate that cognitive control processes should be strengthened by employing interventions such as inhibitory control training especially in high risk patients with a high number of previous detoxifications.

5. Limitations

There are some limitations of the present study that should be acknowledged when interpreting the results. Firstly, the *AGN* task was designed so that alcohol-associated stimuli always served as nogo-stimuli in alcohol-associated blocks, but not as go-

stimuli. In contrast to other go/no-go tasks that found differences between stimuli categories our paradigm allows control for confounding effects of any approach bias induced by using alcohol-associated stimuli as go-stimuli. However, alcohol-associated blocks and geometrical stimuli differed with regard to picture complexity and we cannot exclude that this might account for the higher number of commission errors that both groups made in response to alcohol-associated stimuli. Thus, for future studies an improved version of the task is recommended to control for this effect. Secondly, due to practical reasons, the *AGN* was always administered at the end of the testing period. Therefore, although unlikely, we cannot exclude the possibility that order effects might have impacted the performance results. Due to limited personal resources, only ADP but not HC were tested twice, thus, we cannot rule out the possibility that learning effects, but not a recovery of cognitive impairment and response inhibition deficits accounted for the increased performance at the follow-up test session. However, previous studies and our own research has shown that there is little change over the course of six months with regard to cognitive function of healthy controls and that learning effects seem to be very low or not existent if the time span between the repeated test session is six months (e.g., Loeber et al., 2010).

Finally, we note that the patient sample for the follow-up analysis was limited by the contactabilty of the participants, resulting in missing information for some subjects on abstinence or relapse behavior. To account for this bias, we applied a conservative approach whereby all drop-outs were classified as relapsers.

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7. Authors contribution

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2.3. Do alcohol-dependent patients show different neural activation during response inhibition than healthy controls in an alcohol-related fMRI go/no-go-task?[3]

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[3] Czapla, M., Baeuchl, C., Simon, J.J., Richter, B., Kluge, M., Friederich, H.C., Mann, K., Herpertz, S.C., & Loeber, S. (2016). Do alcohol-dependent patients show different neural activation during response inhibition than healthy controls in an alcohol-related fMRI go/no-go-task? Manuscript prepared for submission.

Abstract:

Alcohol dependence is associated with impaired response inhibition and heightened cue reactivity towards alcohol related stimuli. Several brain areas, but mainly prefrontal structures have been linked to response inhibition in addiction. This study aimed at combining both aspects: salience of drug-associated cues and response inhibition using a go/no-go task with alcohol-associated stimuli during functional magnetic resonance imaging (fMRI). 19 abstinent alcohol dependent patients (ADP) and 21 healthy control subjects (HC) were compared on blood oxygen level dependent (BOLD) responses during successful inhibition of no-go stimuli and successful reactions to go-stimuli. ADP and HC did not significantly differ in their behavioural performance in the task. However, both groups performed worse during the inhibition of alcoholic-associated stimuli compared to neutral stimuli. On the neural level, ADP displayed enhanced BOLD activity relative to HC during successful response inhibition in several areas involved in visual processing, cognitive and impulse control, including occipital structures, anterior cingulate gyrus, medial frontal gyrus and medial orbitofrontal cortex. We interpret these findings as a possible compensation strategy for impaired cognitive processing. Furthermore, the results underline the impact of salience of alcohol related stimuli on response inhibition, which seems to affect both ADP and HC.

1. Introduction

Substance use disorders are strongly associated with impaired impulse control, meaning that addicted patients have significant problems to adequately inhibit their behaviour related to substance use (Crews & Boettiger, 2009; de Wit, 2009; Fernández-Serrano et al., 2011). One important aspect of adequate behavioural control is the ability to stop a prepotent motor response, referred to as response inhibition. In alcoholism, the loss of inhibition is part of a strong "bottom-up" and stimulus-driven urge that gets stronger over time, while "top-down" or knowledge driven processes get weaker and make it more difficult to withstand alcohol consumption, despite knowing about the damaging consequences (Fein& Cardenas, 2015). Several studies have reported deficits of response inhibition in alcohol-dependent patients (ADP) compared to healthy controls (HC) (Czapla et al., 2015; Naim-Feil et al., 2014; Noël et al., 2007, Salgado et al., 2009) and in heavy versus light social drinkers (Ames et al., 2014). There are mixed results whether a response inhibition deficit in ADP is general or specific to alcohol cues. Studies with social drinkers (Kreusch et al., 2013; Kreusch et al., 2014; Weafer & Fillmore, 2012) and with detoxified ADP (Czapla et al., 2015; Noël et al., 2007) demonstrated a pronounced response inhibition deficit when alcohol-associated stimuli were presented. Interestingly, of the above mentioned studies, only one study reported an interaction effect between group and stimulus category (Noël et al., 2007), whereas in the other studies all subjects showed a pronounced impairment in response inhibition towards alcoholic cues, emphasizing that the salience of alcoholic stimuli affects light drinkers too. However, there are also findings reporting no significant differences regarding inhibitory errors towards alcohol-associated stimuli in social drinkers (Nederkoorn et al., 2009; Rose & Duka, 2008).

FMRI studies have consistently demonstrated a strong involvement of frontal lobe activation in response inhibition (Aron & Poldrack, 2006; Konishi et al., 1999; Li et al., 2009; Lipszyc & Schachar, 2010; Simmonds et al., 2008). Successful inhibition is associated with a network of brain areas including the anterior cingulate cortex (ACC), the inferior frontal gyrus (IFG) and inferior parietal lobe, the lateral prefrontal cortex, subcortical regions including the basal ganglia and the thalamus (Steele et al., 2013; Steele et al., 2014) as well as pre-supplementary motor areas (Mostofsky et al., 2003) and occipital areas such as the cuneus (Chambers et al., 2009; Steele et al., 2013; Steele et al., 2014; Tian & Yao, 2008). Simmonds et al. (2008) reported a task-dependent brain activation with right dorsolateral prefrontal and inferior parietal circuits recruited under conditions of increased working memory (complex tasks) in comparison to simple go/no-go tasks. The pre-supplementary motor cortex (pre-SMA) has been shown to be involved in both simple and complex tasks, inferring that it is critical to response inhibition, irrespective of task demands (Simmonds et al., 2008). Regarding response inhibition in substance use disorders, there is a body of evidence pointing to a hypoactivation in the ACC, IFG and dorsolateral prefrontal cortex (dlPFC) in addicted patients (for an overview see Luijten et al., 2014). Claus et al. (2013) reported reduced neural activation in frontal networks during response inhibition in ADP as well as a negative association between reduced BOLD activity in the right inferior parietal lobe, right IFG/insula and pregenual ACC during successful inhibition in subjects with more severe alcohol use disorders. In an electroencephalographic (EEG) study using the source localisation method eLORETA, López-Caneda et al. (2012) reported, that binge drinkers showed greater activation in the right inferior frontal cortex during successful inhibition compared to non-binge drinkers. ADP also showed reduced activation in the dlPFC during failed response inhibition (Li et al., 2009) and less activity in different prefrontal regions, including the dlPFC, during

receipt of monetary reward (Forbes et al., 2014), compared to HC. Furthermore, greater negative correlation between function in these prefrontal regions and the bilateral nucleus accumbens has been reported in ADP (Forbes et al., 2014) as well as weaker functional connectivity between prefrontal areas and the striatum, which was also correlated with severity of alcohol dependence (Courtney et al., 2013). Zhu et al. (2015) reported an association between impaired connectivity in resting state networks and stronger impulsivity in ADP. Those findings point to a disrupted or weakened fronto-striatal circuitry in progressing chronic alcoholism, resulting in a diminished response inhibition. Accordingly, there is evidence that lesions in prefrontal areas (especially in the dlPFC) lead to higher impulsivity and disinhibition (Crews & Boettiger, 2009). In contrast to this, Ames et al. (2014) found that the dlPFC was significantly more active in heavy drinkers compared to light drinkers during nogo trials in a go/no-go task with alcoholic stimuli. The authors do not interpret this finding as a contradiction to previous findings, emphasizing that the increased salience of beer cues during no-go trials may have served as an attentional bias cue resulting in greater effort needed to withhold a response. They interpret their finding as an increased demand in task difficulty and decision making for the heavy drinkers, given the potential salience of the cues. Additionally, they report significantly greater activity among heavy drinkers in the anterior/mid cingulate cortex during no-go trials as well as increased activity in the right anterior insula.

In summary, it can be stated that there is a body of evidence reporting inhibition deficits in ADP with involvement of mainly prefrontal brain areas. However, there are mixed findings about specific neuronal activation processes during inhibition in ADP and whether a response inhibition deficit is significantly pronounced for alcohol related stimuli. To the best of our knowledge, there are no neuroimaging studies with ADP using a response inhibition task with alcohol related stimuli so far. Thus, the aim of this

study was to combine both aspects by using a go/no-go task with individualized alcohol cues selected according to patients' preferred alcoholic beverages. In line with previous findings, we expected that ADP would commit more inhibitory errors in the alcohol-specific go/no-go task (AGN task) than HC and that ADP would show a significantly different neuronal activation pattern during inhibition in areas associated with response inhibition, such as the dlPFC, ACC and IFG.

2. Methods

2.1. *Participants*

The participants of the present study were taken from a larger set of 171 volunteers who took part in a study about the effects of chronic alcohol consumption on different cognitive functions (Czapla et al., 2015). All volunteers of this sample who fulfilled no exclusion criteria for an fMRI scan were asked to participate which resulted in a sample of 48 participants who underwent the fMRI scan session while completing a response inhibition task. Of these 48 participants six subjects had to be excluded due to excessive head movements during fMRI recording and two had to be excluded due to technical problems with the response recording device resulting in a final sample of 40 participants (19 ADP and 21 HC). ADP were recruited at the Psychiatric Center Nordbaden, Wiesloch, Germany, where they underwent an inpatient detoxification treatment for an average duration of two to four weeks. The control group has been recruited via advertisements in local newspapers, bill-boards, flyers and online advertisements. HC had no alcohol-related problems based on information obtained from a short telephone interview and the Alcohol Use Disorders Identification Test (AUDIT), a ten-item screening questionnaire for detection of hazardous or harmful drinking (Bohn et al., 1995). Control subjects were only included if they had a score below eight points, which is the cut-off score indicating a strong likelihood of alcohol

misuse. The participants were included if they were right handed and had normal or corrected to normal visual abilities. Exclusion criteria for both samples were severe somatic, neurological or psychiatric diseases, pregnancy, lactation period, suicidal tendencies, current drug use or dependence other than nicotine or alcohol for patients as well as serious complications in the detoxification treatment. The study was approved by the Ethics Committee of the University of Heidelberg (Medical Faculty Mannheim) and adhered to the Declaration of Helsinki. All participants signed informed consent and received monetary compensation for their participation upon completing of all test-sessions (for ADP this included the follow-up appointment).

2.2. Procedure

Subjects participated in three sessions on separate days: in the first session they were elaborately screened and interviewed with the structured clinical interview for DSM-IV (Wittchen et al., 1997), lasting about one and a half hours in total. Information on past and recent alcohol consumption was obtained from the Time Line Follow Back Interview (TLFB; Sobell & Sobell, 1992). The Alcohol Dependence Scale (ADS; Skinner & Allen, 1982) was administered to assess the severity of alcohol dependence. The second session lasted about one hour and contained neuropsychological test administration and filling out sociodemographic and other questionnaires, which will not be further described here as the data from the second session has not been taken in account in the present study. In the third session patients underwent a fMRI scan consisting of structural scans and completing the AGN task, lasting about 40 minutes. For patients, neuropsychological assessment and MRI scanning was performed at least three days after termination of medically supervised detoxification treatment and the mean duration of abstinence prior to the test session was 19.16 days (SD=8.98, range=8-41). ADP were contacted monthly via telephone during a six-month period

after the first test session to assess possible relapses and drinking behaviour (see Czapla et al., 2015).

2.3. Experimental design

To assess impairment of response inhibition, an alcohol go/no-go task (AGN) that displayed visual stimuli of alcoholic beverages, non-alcoholic beverages or geometrical figures, was used. To ensure individual relevance of the alcoholic stimuli presented, a total of 85 pictures of different alcoholic beverages (beer, wine, and spirits) were shown to the participants before the beginning of the task, and they were instructed to select eight pictures that represented best their preferred alcoholic beverages. The non-alcoholic beverages consisted of a standard set of eight pictures displaying soft-drinks, water and juice. The pictures of both alcoholic and non-alcoholic beverages had the same background. After the selection of the alcoholic pictures, participants rated each of the sixteen experimental stimuli with regard to likeability ("How much do you like this beverage?"), valence ("How pleasant do you find this picture?") and arousal ("How much arousing do you find this picture?"). For task presentation and recording of responses we used Presentation® software (Version 16.0, Neurobehavioural Systems, Inc., Albany, CA, USA). The AGN task was presented with a rapid event related design format while subjects were lying in the scanner and their brain activity was monitored with BOLD fMRI. Participants' heads were restrained by using a head holder and head movement was restricted by using cushions inside a 32 canal head coil. Participants' responses were registered using a MRI compatible response pad (Current Design, Philadelphia, USA). The visual stimuli were back projected onto a screen through a mirror attached to the head coil. Subjects were instructed to respond as quickly as possible by pressing a button with the right index finger. The AGN-task was divided in two parts each lasting about ten minutes. Each part comprised four

blocks with alcoholic/non-alcoholic beverages and an alternating sequence of four blocks where geometrical figures were displayed. In the alcoholic/non-alcoholic beverages blocks, visual stimuli of non-alcoholic beverages served as go stimuli and participants were instructed at the beginning of each block to respond as quickly as possible to pictures of non-alcoholic beverages. In contrast, participants should inhibit their responses when alcoholic beverages were displayed (no-go trials). In blocks with geometrical figures, a rectangle served as the go stimulus and a circle as the no-go stimulus. A total of 40 trials were presented within each block with 80% of the trials being go trials, thus one part consisted of 320 trials and both parts included 640 trials in total. All pictures were displayed for 490 ms and after each block there was a short break of 13 seconds and then a fixation cross had been presented for 1000 ms before the target category for the following block was displayed on the screen. At the start of the experimental task, two short practice blocks were administered that were not scored. For further details and a figure displaying the trial procedure see Czapla et al. (2015).

Due to the fact that there were only a few - or in some cases - no incorrect responses to go stimuli (omissions) and a very low rate of incorrect responses to no-go stimuli (commission errors) in the HC sample, contrasts were only estimated for the conditions with "correct rejections of no-go stimuli (successful inhibition)" and "correct responses to go stimuli (hits)".

2.4. Imaging protocol

Imaging data were collected with a Siemens 3T Magnetom Tim/Trio MR scanner located at the Neuroradiology department in the University Hospital Heidelberg, Germany. 310 T2* -weighted transversal echo planar images (TR=2 s, TE=30 ms, flip angle=80°, 30 slices, slice thickness 4 mm, ascending interleaved slice order, voxel

dimensions 3 x 3 x 4 mm, field of view: 192 x 192 mm, 64 x 64 in-plane resolution) covering the whole brain, were acquired. An anatomical T1*-weighted structural scan was acquired using an MPRAGE sequence (TR=1.57 s; TE=2.63 ms; flip angle=9°; 192 sagittal slices; slice thickness 1mm, voxel dimensions 1 x 1 x 1 mm, field of view 256 x 256 mm, 256 x 256 mm in-plane resolution).

2.5. Behavioural data analysis

Analyses of behavioural data were carried out with the IBM SPSS Statistics software (Statistical Package of the Social Science, 22.0.). T-tests (two-sided) and chi-square analyses using Fisher's exact test were used to examine differences between patients and controls with regard to sociodemographic and drinking-related variables. To assess the performance in the AGN task a repeated measures analysis of variance (ANOVA) was performed with the number of commission errors in the AGN as dependent variable, category (alcohol-associated vs. neutral) as within group factor and group (ADP vs. HC) as between group factor. For all behavioural analyses a significance level of $\alpha \leq 0.05$ was considered as significant.

2.6. Preprocessing and functional MRI analyses

Preprocessing and statistical analyses of functional images were performed using SPM 8 (www.fil.ion.ucl.ac.uk/spm). The first five scans were discarded to avoid artefacts due to magnetic saturation effects and the remaining 305 images were preprocessed with the following steps: (1) slice time correction with the middle slice as reference slice, (2) realignment of scans to the first image to correct for head motion, (3) coregistration to the mean functional image and segmentation of the anatomical image using the new segment algorithm, (4) normalization of functional images to the Montreal Neurological Institute (MNI) space using SPM's DARTEL toolbox, (5)

smoothing with an 8 mm Gaussian kernel (full width at half maximum). Realignment parameters were examined for excessive head motion and subjects were excluded from the analysis if their scans contained more than 5% images of abrupt scan-to-scan head translations >0.5mm or rotations >0.5°. Furthermore, subjects were excluded if head motion drifts across an entire experimental run exceeded >3mm (translations) or >3° (rotations) respectively. This lead to the exclusion of six subjects. The data were high pass filtered (cut-off: 128 s) and corrected for temporal auto correlations using the AR (1) model. The preprocessed images were analysed statistically with a general linear model (GLM) approach, by convolving the correct responses to each type of stimulus with the canonical hemodynamic response function. Incorrect responses were not used for computing contrasts because there were not enough incorrect responses to have sufficient power to analyse them, but they were included as regressors in the design matrix. As some subjects didn't show any incorrect responses for certain stimulus categories, the number of regressors of interest varied between 7-10. Additionally the GLM included 6 movement parameters and the global mean as regressors of no interest. For the first level analyses we computed contrast images for each subject using the following contrasts with only correct trials:

(1) Alcohol_nogo > Non-alcohol_go; (2) Geometric_nogo > Geometric_go; (3) interaction: [(Alcohol_nogo > Nonalcohol_go) > (Geometric_nogo > Geometric_go)]; (4) main effect: [(Alcohol_nogo & Geometric_nogo) > (Non-alcohol_go & Geometric_go)].

Individual contrast images were entered in to a second level analysis and compared between the ADP and HC group by means of a 2-sample t-test for ADP > HC and HC > ADP. For the t-tests we used a family-wise error (FWE) corrected cluster level significance (Nichols & Hayasaka, 2003) of p<0.05 (at a cluster defining single-voxel

significance level of p<0.005 uncorrected). For the group comparisons this resulted in cluster sizes of k=129 (contrast 1), k=132 (contrast 2), k=124 (contrast 3) and k=137 (contrast 4). Within each statistically significant region, local maxima for signal increase were determined (voxels of maximum significance), and their location were expressed in terms of MNI coordinates.

3. Results

3.1. Sample characteristics

Table 1 shows the sample characteristics for ADP and HC. The groups did not differ in the proportion of males in each group, premorbid intelligence level (measured with a vocabulary based IQ test) and the duration of education. However, due to the drop-out of subjects on account of technical problems and excessive head movement during fMRI, the mean age of groups did not match with ADP being significantly older than HC. As expected, we found a significantly greater number of drinking days as well as a significantly higher amount of alcohol consumed in the three months leading up to the test-session in ADP. Patients also received a significantly higher score on the *Alcohol Dependence Scale.*

Table 1: Demographic characteristics and drinking related variables of alcohol- dependent patients and healthy controls at baseline

	Alcohol-dependent patients (n = 19)	Healthy control participants (n = 21)	Statistics (t/X^2, p-value)
Age (years) [Mean (SD)]	51.21 (7.36)	41.95 (9.99)	-3.30, 0.00
Gender [N (%)]			
Female [N (%)]	2 (10)	4 (19)	0.57, 0.66
Male [N (%)]	17 (90)	17 (81)	
Duration of education (years) [Mean (SD)]	13.10 (2.51)	13.69 (3.67)	0.58, 0.56
Number of drinking days (in the 3 months prior to testing-T1) [Mean (SD)]	63.95 (18.22)	12.05 (10.37)	-11.21, 0.00
Cumulative amount of ethanol (gr) (in the 3 months prior to T1) [Mean (SD)]	9242.37 (4681.58)	459.90 (442.86)	-8.57, 0.00
Summary score *Alcohol Dependence Scale* (Skinner & Allen, 1982) [Mean (SD)]	15.32 (6.17)	1.57 (2.96)	9.12, 0.00
Duration of alcohol dependence (years) [Mean (SD)]	11.50 (8.46)	n/a	n/a
Number of previous detoxifications (prior to T1) [Mean (SD)]	2.89 (2.73)	n/a	n/a

3.2. Behavioural data

The behavioural data for response inhibition show that ADP as well as HC made more commission errors when alcohol-associated stimuli were presented compared to neutral stimuli (main effect *category*) [$F_{(1,38)}$=13.86, p=0.001], while the interaction *category by group* did not achieve significance [$F_{(1,38)}$=1.75, p=0.19]. Although ADP made more commission errors in general compared to HC, the *main effect group* was not significant [$F_{(1,38)}$ 2.09, p=0.16] (Table 2).

Table 2: Performance of alcohol-dependent patients and healthy controls in the AGN task (Alcohol go/no-nogo)

	Alcohol-dependent patients (n = 19)	Healthy control participants (n = 21)	Statistics (F, p-value)
AGN task			
Number of commission errors in response to alcohol-associated stimuli [Mean (SD)]	14.11 (9.47)	9.62 (7.34)	
Number of commission errors in response to neutral stimuli [Mean (SD)]	9.89 (8.97)	7.62 (5.09)	2.09, 0.16

3.3. Imaging data

In contrast (1) comparing correctly rejected no-go trials with alcoholic stimuli to correctly responded go trials with non-alcoholic stimuli, ADP showed significantly stronger BOLD activity in a right-hemispheric cluster in the occipital lobe composed of the lingual gyrus, right superior occipital gyrus and the right middle occipital gyrus (see Table 3 and Figure 1). Those brain areas are linked to processing vision, i.e. encoding of letters and complex images (Machielsen et al. 2000). The interaction contrast (3) revealed significantly stronger BOLD activation in ADP relative to HC in 3 clusters located in occipital brain areas (see Table 4 and Figure 2). The first cluster is composed of the right superior occipital gyrus, right middle occipital gyrus and right cuneus. The second cluster consists of the left middle occipital gyrus and left superior occipital gyrus and the third cluster of the right lingual gyrus, right cerebellum and right fusiform gyrus. For the main effect contrast (4) comparing all correct rejected no-go trials with correctly responded go trials, we observed significantly increased BOLD activity in ADP relative to HC in a left hemispheric cluster composed of the anterior cingulate gyrus, medial frontal gyrus and medial orbitofrontal cortex (see Table 5 and Figure 3). The anterior cingulate cortex (ACC) has been linked to decision making and impulse control (Luijten et al. 2014). HC only showed increased activity relative to ADP in one contrast (2) comparing correctly rejected neutral (geometrical) no-go stimuli with correctly

responded neutral go stimuli in a cluster consisting of the left postcentral gyrus and left inferior parietal lobule (see Table 6 and Figure 4). ADP did not show increased BOLD responses in this contrast. Additionally, all significant within-subject results can be found in the supplementary material. There were no significant within-subjects results for the contrast (3) interaction in both groups.

Table 3: Summary of fMRI peak activity for the contrast (1) Alcohol_nogo>Nonalcohol_go between ADP>HC

	MNI coordinates			Peak t-value
	x	y	z	
R Lingual Gyrus	27	-54	-8	4.02
R Fusiform Gyrus	33	-57	-4	3.99
R Superior Occipital Gyrus	21	-96	20	3.89
R Lingual Gyrus	24	-60	-4	3.84
R Middle Occipital Gyrus	39	-75	-12	3.52
R Lingual Gyrus	18	-60	-4	3.45
R Fusiform Gyrus	27	-78	-4	2.99
R Middle Occipital Gyrus	30	-84	20	2.93
R Calcarine Gyrus	18	-84	12	2.79

Cluster-level significance: $p < 0.05$ FWE corrected, regions were labeled using the Automatic Anatomical Labeling (AAL) software (Tzourio-Mazoyer, et al., 2002). MNI, Montreal Neurological Institute; L, left; R, right.
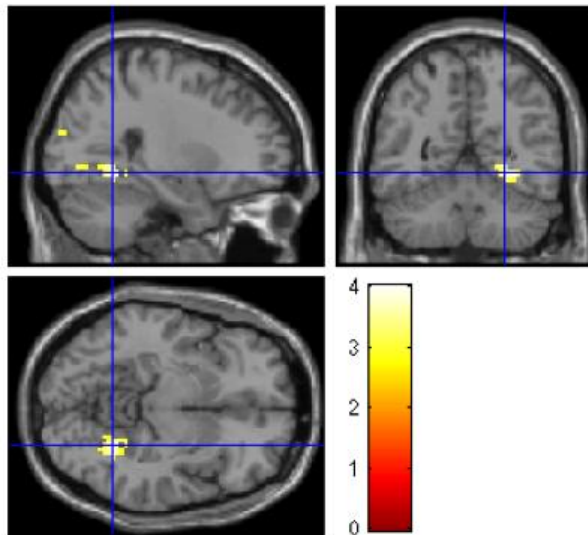
Figure 1: Significantly stronger activation in ADP relative to HC (k=129, t=2.71). Contrast images used for the group comparison were taken from the contrast (1) Alcohol nogo > Non-alcohol go. Results are significant at the cluster-level (p<0.05, FWE corrected). A list of all significant activations for this contrast can be found in Table 3.

Table 4: Summary of fMRI peak activity for the contrast (3) interaction (Alcohol_nogo > Nonalcohol_go) > (Geometric_nogo > Geometric_go) between ADP >HC

Cluster 1 (295 voxels)	MNI coordinates			Peak t-value
	x	y	z	
R Middle Occipital Gyrus	36	-75	20	4.59
R Middle Occipital Gyrus	42	-75	16	4.31
R Superior Occipital Gyrus	21	-93	20	4.07
R Superior Occipital Gyrus	27	-90	20	3.87
R Superior Occipital Gyrus	24	-69	20	3.75
R Superior Occipital Gyrus	18	-84	20	3.67
R Cuneus	12	-81	24	3.59
R Superior Occipital Gyrus	21	-78	20	3.56

	x	y	z	
R Superior Occipital Gyrus	18	-90	28	3.50
R Calcarine Gyrus	18	-78	4	3.39
R Cuneus	12	-87	20	3.38

Cluster 2 (284voxels)

	x	y	z	
L Middle Occipital Gyrus	24	-90	16	4.79
L Superior Occipital Gyrus	-18	-84	24	3.88
L Middle Occipital Gyrus	-39	-75	4	3.85
L Middle Occipital Gyrus	-36	-84	16	3.84
L Middle Occipital Gyrus	-42	-84	12	3.86
L Middle Occipital Gyrus	-45	-81	8	3.81
L Cuneus	-9	-90	24	3.44
L Middle Occipital Gyrus	-33	-78	20	3.44
L Middle Temporal Gyrus	-42	-66	8	2.99

Cluster 3 (168 voxels)

	x	y	z	
R Cerebelum (IV-V)	18	-39	-24	4.03
R Lingual Gyrus	24	-54	-4	3.76
R Fusiform Gyrus	24	-42	-12	3.60
R Lingual Gyrus	15	-78	-12	3.59
R Lingual Gyrus	18	-60	4	3.59
R Cerebelum (IV-V)	15	-57	-16	3.11
R Lingual Gyrus	21	-72	-12	3.10
R Lingual Gyrus	6	-63	0	3.06

Cluster-level significance: p<0.05 FWE corrected, regions were labeled using the Automatic Anatomical Labeling (AAL) software (Tzourio-Mazoyer, et al., 2002). MNI, Montreal Neurological Institute; L, left; R, right.

First Cluster:

Second Cluster:

Figure 2: Significantly stronger activation in two clusters in ADP relative to HC (k= 124, t=2.71). Contrast images used for the group comparison were taken from the contrast (3) interaction: [(Alcohol nogo > Non-alcohol go) > (Geometric nogo > Geometric go)]. Results are significant at the cluster-level ($p < 0.05$, FWE corrected). A list of all significant activations for this contrast can be found in Table 4.

Table 5: Summary of fMRI peak activity for the contrast (4) main effect (Alcohol_nogo & Geometric_nogo) > (Nonalcohol_go & Geometric_go) between ADP > HC

	MNI coordinates			Peak t-value
	x	y	z	
L Superior Medial Gyrus / L ACC	-9	48	16	3.83
R Mid Orbital Gyrus	6	48	-4	3.29
R Superior Medial Gyrus	9	51	0	3.23
R Mid Orbital Gyrus	12	42	-4	3.16
L Superior Orbital Gyrus	-18	51	-12	3.12
L Rectal Gyrus	-3	48	-16	2.98

Cluster-level significance: $p < 0.05$ FWE corrected, regions were labeled using the Automatic Anatomical Labeling (AAL) software (Tzourio-Mazoyer, et al., 2002). MNI, Montreal Neurological Institute; L, left; R, right.
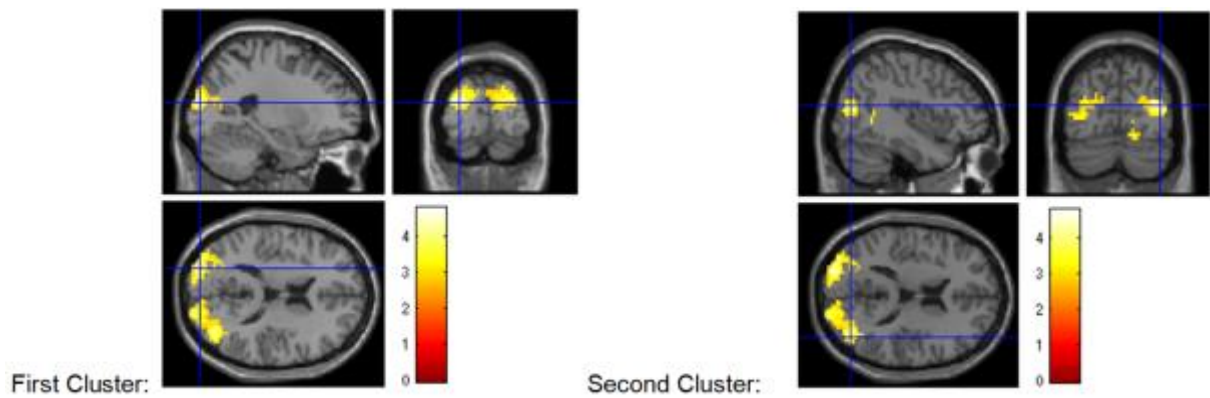
Figure 3: Significantly stronger activation in ADP relative to HC (k=137, t=2.71). Contrast images used for the group comparison were taken from the contrast (4) main effect: effect [(Alcohol nogo & Geometric nogo) > (Nonalcohol go & Geometric go)]. Results are significant at the cluster-level (p<0.05, FWE corrected). A list of all significant activations for this contrast can be found in Table 5.

Table 6: Summary of fMRI peak activity for the contrast (2) Geometric_nogo > Geometric_go between HC > ADP

	MNI coordinates			Peak t-value
	x	y	z	
L Postcentral Gyrus	-42	-24	48	4.31
L Postcentral Gyrus	-27	-33	44	3.86
L Inferior Parietal Lobule	-57	-27	44	3.22

Cluster-level significance: p<0.05 FWE corrected, regions were labeled using the Automatic Anatomical Labeling (AAL) software (Tzourio-Mazoyer, et al., 2002). MNI, Montreal Neurological Institute; L, left; R, right.
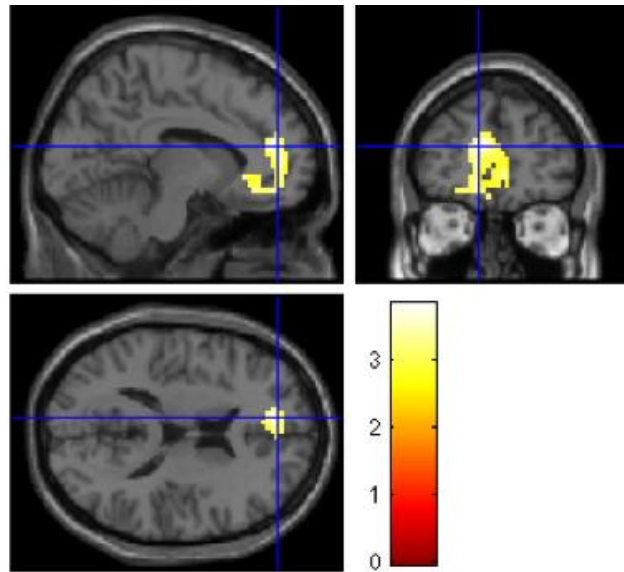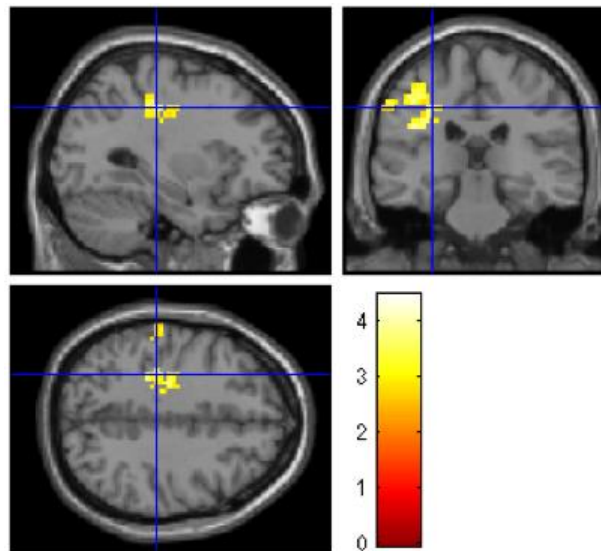
Figure 4: Significantly stronger activation in HC relative to ADP (k=132, t=2.71). Contrast images used for the group comparison were taken from the contrast (2) Geometric nogo > Geometric go. A list of all significant activations for this contrast can be found in Table 6.

4. Discussion

This study examined neural responses during response inhibition in a go/no-go task with alcohol-related stimuli in a sample of ADP and HC. To the best of our knowledge, this is the first study that investigated neural activity of response inhibition in ADP with a task using substance-related cues matching the subjects drinking preferences.

The major finding was that ADP showed significantly increased BOLD activity in occipital brain areas as well as in the anterior cingulate gyrus, medial frontal gyrus and medial orbitofrontal cortex compared to HC during successful inhibition. HC only showed increased activity in one contrast (comparing successful reactions towards geometrical no-go stimuli to successful reactions towards geometrical go stimuli) in a cluster consisting of the left postcentral gyrus and left inferior parietal lobule. Contrary to our initial hypothesis, we did not find any significant differences in BOLD response in the dlPFC and the IFG.

The comparison of all successful inhibition trials versus all go trials (main effect), revealed significantly higher BOLD activity in ADP compared to HC, but in a left hemispheric cluster comprised of the anterior cingulate gyrus, medial frontal gyrus and medial orbitofrontal cortex. These regions are also involved in cognitive control and executive processes. The left medial frontal gyrus has been linked to executive functions and decision-related processes, particularly in go/no-go tasks its' role has been described in converging information for decision aspects (Talati & Hirsch, 2005). The anterior cingulated gyrus is a part of the ACC, which repeatedly has been shown to be involved in cognitive control (Talati & Hirsch, 2005), error processing, decision making and impulse control (Ahmadi et al., 2013; Jasinska et al., 2014; Luijten et al., 2014). Though, neural deficits in the ACC are reportedly accompanied by hypoactivation in addicted patients (Luijten et al., 2014) as well as in heavy drinkers compared to light drinkers (Ahmadi et al., 2013). Hypoactivation in the ACC has been also linked to increased alcohol use severity (Claus et al., 2013). Activity in the medial orbitofrontal cortex however, is associated with monitoring and learning of reward values (Kringelbach, 2005).

ADP showed less activation in the left postcentral gyrus and left inferior parietal lobule than HC during successful inhibition of geometrical stimuli, but stronger activation in the lingual gyrus, the right middle occipital gyrus and the right superior occipital gyrus during inhibition of pictures of alcohol. The left postcentral gyrus is associated with somatosensory processing of the right side of the body. The lingual gyrus is a structure in the visual cortex which is involved in processing vision (Zeki et al., 1991), especially in the encoding of complex images (Machielsen et al., 2000) and recognition of words (Ghosh et al., 2010). The middle and the superior occipital gyri are also part of the visual cortex, thus playing a role in analysing the shape, colour and orientation of visual stimuli (Hermann et al., 2007). It might be the higher salience and visual complexity of

alcoholic stimuli that elicited greater activation in those areas in ADP relative to HC. Nevertheless, as features of the stimuli affect both groups, these results indicate that ADP needed more resources in visual areas to inhibit pictures of alcohol. There are studies reporting and discussing the role of occipital activation in ADP, albeit the activity reported in ADP is less compared to HC. In a study with detoxified ADP, Hermann et al. (2007) found significantly lower BOLD activity in an extended bilateral occipital area in ADP compared to HC during a visual acoustic and stimulation paradigm. As possible explanations they discussed a reduced arousal or a reduced attentional focus in ADP as well as the influence of inputs from higher brain regions (e.g. frontal cortex, thalamus) in terms of a top-down effect. Reduced grey matter volume in the visual cortex has also been linked with shorter time to relapse and heavy drinking in ADP (Rando et al., 2011).

A possible explanation for the increased BOLD signal in occipital areas in ADP in the present study could be that ADP need to activate this area stronger due to a deficit in attentional and inhibitory processes. Visual processing during watching alcoholic stimuli is clearly more complex than processing simple geometrical stimuli and therefore needs more resources in this area in general. However, it is interesting that ADP show significantly more neural activity in visual regions than HC, which could be a necessary compensation strategy. Correspondent with our finding, Li et al. (2009) also found more neural activity in bilateral visual cortices in ADP compared to HC during a stop signal task. Wetherill and colleagues (2013) regard greater activity in inhibition related neural networks in heavy drinkers as a necessary recruitment of neural resources in order to inhibition their responses successfully.

In line with this, in the interaction contrast, ADP showed more neural activity in three clusters covering bilateral occipital regions (middle and superior gyri), right-

hemispheric occipital areas (cuneus and lingual gyrus) as well as a structure in the cerebellum. This suggests that those areas play an important role during response inhibition processes with alcohol-related stimuli compared to neutral stimuli. The cuneus is of particular interest here, as its involvement in response inhibition and motor responses has been shown before (Booth et al., 2005; Matthews et al., 2005).

The differential activation patterns suggest that different brain areas are involved in the neural processing of response inhibition, dependent on the type of stimulus that is shown and processed. In the present study, general successful response inhibition (independent of the type of stimulus) elicited greater activation in left frontal regions, but response inhibition towards alcoholic stimuli was linked to greater activation in clusters of occipital regions. In this regard, the finding from a meta-analysis of fMRI studies using various go/no-go tasks (Simmonds et al., 2008) is crucial, showing that differences in neural activities among studies are task related. Dependent on the specific design and the stimuli used in a response inhibition paradigm, different underlying cognitive functions are needed and therefore different or additional brain areas are involved during task processing. This stresses the importance of conducting replication studies but also the need of more standardized paradigms to improve the comparability of research results.

The significantly greater neural activation in several brain areas in ADP indicates that ADP might need more neural resources for achieving the same performance in the go/no-go task as HC. This could be a compensatory mechanism accounting for the widely reported response inhibition deficit in ADP (Czapla et al., 2015; Naim-Feil et al., 2014; Noël et al., 2007, Salgado et al., 2009). As hypothesized by other researchers (Bauer & Ceballos, 2014; Rajah & D'Esposito, 2005; Wetherill et al., 2013), we regard enhanced neural activity in ADP as a compensation strategy for their deficits in

response inhibition. Whilst there are no comparable results for ADP, the findings of Tapert and colleagues (2007) at least support the compensation hypothesis for marihuana users, reporting significantly more BOLD activity during inhibition in a go/no-go task in right occipital gyri, right dlPFC, bilateral medial frontal and inferior and superior parietal lobules.

The behavioural data confirm our hypothesis of a pronounced response inhibition deficit towards alcohol-associated stimuli and replicates other research findings (Czapla et al., 2015; Kreusch et al., 2013; Noël et al., 2007; Weafer & Fillmore, 2012). All subjects made more commission errors when confronted with alcohol pictures compared to geometrical figures. This shows that alcohol-related stimuli have a higher salience and lead to a cognitive bias, which is also known from studies evaluating the cue-reactivity effect (Carter &Tiffany, 1999; Drummond, 2000). As proposed by Ames et al. (2014), alcohol related cues in the AGN task could have elicited an attentional or approach bias, resulting in more effort on a neuronal level to withhold a response, expressed by an enhanced BOLD response.

Though ADP made more commission errors than HC overall, the effect did not reach significance and there was no significant interaction effect observable as well. In line with this finding there are other fMRI studies reporting no differences in behavioural performance, despite significant differences on the neuronal level, between ADP and HC (Karch et al., 2008), between cocaine dependent patients and HC (Ma et al., 2015) as well as between marihuana users and HC in go/no-go tasks (Tapert et al., 2007) and between ADP and HC in a stop-signal task (Li et al., 2009). This suggests that compensation strategies might be effective and mask an actual impairment on the behavioural level by the activation of additional neural resources. Nevertheless, we

cannot exclude that the lack of significant group differences on the behavioural level is due to the small sample size or age differences between the two groups.

In summary, our results show increased neural activity in ADP compared to HC during response inhibition in several brain areas that are linked to visual processing, cognitive and impulse control. These results can be seen as a possible compensation strategy in ADP for impaired cognitive processes. Furthermore, the results show a pronounced inhibition deficit for alcohol-related stimuli in both groups and that brain activity during response inhibition is stimulus dependent. These findings help to increase the understanding of the neural basis of inhibition processes in addiction. However, more future research is needed with larger samples and prospective designs to investigate whether the proposed compensatory mechanism of increased neural activation is predictive for abstinence or relapse in ADP. In general, it can be concluded that interventions in ADP should also focus on strengthening inhibitory control and executive control processes.

5. Limitations

There are several limitations that should be acknowledged. First, alcohol related stimuli always served as no-go stimuli and non-alcoholic drinks always served as go stimuli. Although this can be seen as an advantage of the task as no approach bias is induced due to alcohol-related stimuli serving as go-stimuli, it only allows a limited number of comparisons. Second, geometrical stimuli served as control stimuli presented in neutral blocks and we cannot exclude that differences in picture complexity might have confounded our findings. Third, it remains uncertain whether the AGN task, or go/no-go tasks in general, can isolate the process of response inhibition. Related cognitive processes, such as attention and response selection are hardly distinguishable in this regard and therefore research findings have to be interpreted with caution. Fourth, we

had to exclude subjects from analysis due to excessive head movements and technical problems, resulting in a smaller sample size than initially planned, with a significant difference in age. Therefore, future research is needed with bigger samples and more balanced designs to account for confounding factors. Finally, due to the rather small sample size and the inevitable loss of patients during a follow-up period, no associations between neural activity and relapse could be analysed. This would be an interesting research question for future studies.

Acknowledgements

Authors Contribution

MC was responsible for recruitment of patients and healthy control participants, the collection of data and analysis of the results. JJS was responsible for adjusting and reprogramming the AGN task and assisted with data analysis. CB assisted with the data analysis. BR and MK provided access to the patient sample and supported the recruitment process. H-CF, KM, and SCH gave intellectual input. SL was responsible for the study concept and design and assisted with data analysis and interpretation of findings. MC drafted the manuscript. All authors critically reviewed content and approved the final version for publication.

Conflict of Interest: all authors declare that they have no conflict of interest.

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Supplementary material

Table 1: Summary of fMRI peak activity for the contrast (1) Alcohol_nogo > Nonalcohol_go within the group of ADP

	MNI coordinates			Peak t-value
	x	y	z	
R Superior Frontal Gyrus	18	42	36	8.48
L crus I of cerebellar hemisphere	-39	-69	-28	6.42
R Putamen	24	6	-12	5.76
L inferior frontal gyrus, pars orbitalis	-39	48	-12	5.71

Cluster-level significance: p<0.05 FWE corrected, regions were labeled using the Automatic Anatomical Labeling (AAL) software (Tzourio-Mazoyer, et al., 2002). MNI, Montreal Neurological Institute; L, left; R, right.

Table 2: Summary of fMRI peak activity for the contrast (2) Geometric_nogo > Geometric_go within the group of ADP

	MNI coordinates			Peak t-value
	x	y	z	
R superior parietal lobule	24	-69	60	5.43

Cluster-level significance: p<0.05 FWE corrected, regions were labeled using the Automatic Anatomical Labeling (AAL) software (Tzourio-Mazoyer, et al., 2002). MNI, Montreal Neurological Institute; L, left; R, right.

Table 3: Summary of fMRI peak activity for the contrast (4) main effect (Alcohol_nogo & Geometric_nogo) >

(Nonalcohol_go & Geometric_go) within the group of ADP

	MNI coordinates			Peak t-value
	x	y	z	
R inferior frontal gyrus, pars orbitalis	42	48	-12	7.22
R Amygdala	24	-3	-16	6.09

Cluster-level significance: p<0.05 FWE corrected, regions were labeled using the Automatic Anatomical Labeling (AAL) software (Tzourio-Mazoyer, et al., 2002). MNI, Montreal Neurological Institute; L, left; R, right.

Table 4: Summary of fMRI peak activity for the contrast (1) Alcohol_nogo > Nonalcohol_go within the group

of HC

	MNI coordinates			Peak t-value
	x	y	z	
R inferior parietal lobule	42	-39	52	5.62
R Cerebelum	-3	-51	-12	5.56
R crus I of cerebellar hemisphere	48	-63	-12	4.81
L angular gyrus	-33	-66	52	4.54

Cluster-level significance: p<0.05 FWE corrected, regions were labeled using the Automatic Anatomical Labeling (AAL) software (Tzourio-Mazoyer, et al., 2002). MNI, Montreal Neurological Institute; L, left; R, right.

Table 5: Summary of fMRI peak activity for the contrast (2) Geometric_nogo > Geometric_go within the group of HC

	MNI coordinates			Peak t-value
	x	y	z	
R postcentral gyrus	42	-36	56	5.43
L postcentral gyrus	-39	27	48	7.58
L middle frontal gyrus, orbital part	-33	48	-8	6.17

Cluster-level significance: p<0.05 FWE corrected, regions were labeled using the Automatic Anatomical Labeling (AAL) software (Tzourio-Mazoyer, et al., 2002). MNI, Montreal Neurological Institute; L, left; R, right.

Table 6: Summary of fMRI peak activity for the contrast (4) main effect (Alcohol_nogo & Geometric_nogo) > (Nonalcohol_go & Geometric_go) within the group of HC

	MNI coordinates			Peak t-value
	x	y	z	
R postcentral gyrus	42	-36	56	9.02
L middle frontal gyrus	-33	33	20	6.06

Cluster-level significance: p<0.05 FWE corrected, regions were labeled using the Automatic Anatomical Labeling (AAL) software (Tzourio-Mazoyer, et al., 2002). MNI, Montreal Neurological Institute; L, left; R, right.

3. General discussion

This work aimed to study cognitive control processes, with an emphasis on response inhibition and impulsivity, in subjects showing risky alcohol consumption patterns (binge drinkers) and subjects with a diagnosed alcohol dependence compared to healthy subjects (non-dependent and non-binge drinking subjects). The most critical question was whether there is a specific response inhibition deficit towards alcohol-related stimuli compared to neutral stimuli in subjects showing binge-drinking or alcohol dependence in relation to HC. In summary, the results show that binge drinkers, ADP but also HC showed an enhanced impairment in response inhibition towards alcohol-related stimuli compared to neutral stimuli. However, ADP generally showed a significantly greater deficit in response inhibition than HC and the alcohol-specific inhibition deficit together with the number of previous detoxifications, was a significant predictor for relapse in ADP. Concordantly, in binge drinkers the alcohol specific response inhibition deficit was the only significant predictor for binge drinking. Those results corroborate the hypotheses mentioned before, emphasizing the role of response inhibition in AUDs. Furthermore, this work aimed at assessing extensively different cognitive control processes with different paradigms and research methods in a sample of ADP and HC, to investigate which cognitive control processes might be impaired in ADP, if they are related to relapse behaviour in ADP and which differential neural activation patterns are involved in the cognitive process of response inhibition towards alcohol-related and neutral stimuli. The results will be discussed in further detail in the following section and the implications for future investigations and treatment options in AUDs will be addressed.

3.1. Study 1

In study 1 the objective was to investigate the alcohol-specific impairment of inhibitory control (as measured by a go/no-go task) in binge drinkers and non-binge drinkers. The hypothesis that binge-drinkers show a pronounced inhibition deficit towards alcohol-related stimuli was of particular interest, as only one study (Nederkoorn et al., 2009) so far has dealt with this question in binge-drinkers. Further, we investigated the predictive validity of trait-like impulsivity and impairment of response inhibition in regard to binge drinking with a multiple linear regression analysis.

The results of the study confirmed our main hypothesis, namely that binge-drinkers show significantly greater response inhibition deficits towards alcohol-related cues compared to neutral cues and non-binge drinkers do not show a similar pattern as they made about the same number of commission errors in both conditions. However, as there was no main effect of group, binge-drinkers and non-binge drinkers did not differ regarding the total number of commission errors including both neutral and alcohol-associated cues. As there were also no differences regarding trait impulsivity between the groups, these results suggest that this sample of binge-drinkers did not have a general inhibitory deficit, but a specific inhibitory deficit towards alcohol-related cues. This finding is in line with recent models of addiction, such as the I-RISA model (Goldstein & Volkow, 2002) meaning that drug-related cues have a particularly strong salience for people showing risky alcohol consumption and therefore inhibitory control would be more strongly impaired when confronted with drug-related cues. A study with ADP corroborated this hypothesis and reported a pronounced deficit in response inhibition towards alcohol-related stimuli in ADP (Noël et al., 2007) in comparison to HC. However, the method and the interpretation of the study by Noël and colleagues (2007) have been criticised (Field & Cole, 2007) and it suggested that the results are

more likely to reflect an impairment of cognitive processing of alcohol-associated words than a response inhibition deficit or that they rather indicate an over-preparedness to alcohol-related cues (Nederkoorn et al., 2009).

Furthermore, the findings of study 1 are in line with the results of Nederkoorn et al. (2009) that did not find any significant differences in overall response inhibition between binge and non-binge drinkers. On the other hand, the findings of study 1 also contrast previous findings (Henges & Marczinski, 2012; Townshend & Duka, 2005) as well as more recent findings (Morris et al., 2016; Poulton, Mackenzie, Harrington, Borg & Hester, 2016) that reported a general worse performance in response inhibition in binge drinkers compared to non-binge drinkers.

Regarding the predictive validity of binge drinking, only the number of alcohol-specific commission errors has turned out be a significant predictor. This suggests that once young adults have established a binge drinking alcohol consumption pattern, alcohol-specific inhibitory control is more crucial than a general inhibition deficit. In line with this finding, a prospective study with a 2-year-follow-up (Peeters et al., 2015) reported that poor response inhibition in 12-14 year-old adolescents predicted having a first drink. However, response inhibition was not a unique predictor for the binge drinking episode, but weak working memory function has been shown to predict both initiating of the first alcoholic drink and the first binge drinking episode. As Peeters et al. (2015) used a different paradigm for assessing response inhibition, the comparability of results is limited, but their study also emphasises the importance of assessing several domains of cognitive control processes, such as working memory.

Regarding the investigation of prediction factors for binge drinking, it has to be acknowledged that study 1 only concentrated on one domain of cognitive control processes, which could be viewed as a limitation. Moreover, there are a few other

limitations that have to be stated. The small sample size and the lack of assessment of the smoking status have been acknowledged already in the discussion of the article.

Another point that has to be stressed regarding the interpretation of the results is the cross-sectional design. In the context of young binge drinkers, it would be of special interest to follow-up on their drinking habits and to analyse whether some of the binge drinkers maintain or change their drinking habits and whether this is associated with inhibition performance. Impulsive behaviour and response inhibition deficits are risk factors for the development of problem-drinking and addiction (Verdejo-García et al., 2008), but another risk factor often reported in this context, is the family history of substance or alcohol dependence (Penick et al., 2010). Therefore, lack of assessment of the family history of SUDs in study 1 is another limitation. A positive family history of alcohol dependence has been linked to general cognitive deficits (Peterson et al., 1992) and impaired executive functions (Nigg et al., 2004). A positive family history of SUDs has also been associated with differences in neural structures and functions in adolescents before the initiation of heavy drinking and was therefore suggested as a phenotypic risk factor for substance use (Squeglia, Jacobus & Tapert, 2014). Neuroimaging studies comparing adolescents with a positive and negative history of substance use illustrated altered activation in frontal brain regions for subjects with a positive family history during response inhibitions tasks (Schweinsburg et al., 2004; Silveri, Rogowska, McCaffrey & Yurgelun-Todd, 2011) and working memory tasks (Cservenka, Herting & Nagel, 2012). Overall, there is evidence that a positive family history of substance dependence may be associated with an impairment of cognitive control functions in adolescents and may increase the risk of problematic substance use patterns in the future. However, future research is necessary.

3.2. Study 2

There is a large body of evidence for impaired cognitive functions in ADP (Bates et al., 2002; Wilcox et al., 2014) including findings from electrophysiological, neuroimaging and neuropsychological research. Among cognitive functions, cognitive control processes and especially inhibitory control have gained particular research interest in alcohol addiction research and it has been shown that ADP have deficits in inhibiting behavioural responses (Smith et al., 2014). Study 2 aimed at investigating the aspects of response inhibition and salience of alcohol-related pictures in ADP and HC. To the best of our knowledge, there has not been any study using alcohol-related pictures in a response-inhibition task with ADP before we conducted study 2. The study by Noël and colleagues (2007) has used alcohol-related words, but no pictures. Based on the results of study 1, we hypothesised that ADP would show a pronounced response inhibition deficit towards alcohol-related stimuli compared to neutral stimuli and that this pronounced inhibition deficit would be significantly greater in ADP compared to HC.

Previous studies with social drinkers investigating response inhibition with alcohol related cues showed mixed results (Kreusch et al., 2013; Kreusch et al., 2014; Nederkoorn et al., 2009; Weafer & Fillmore, 2012) and the only study with ADP using alcohol-related words in a response inhibition task, has pointed to a specific response inhibition deficit (Noël et al., 2007), however the results have been criticised and therefore the research findings for this particular question remain debatable.

Most reported studies investigating impairment of cognitive control processes in ADP focused on one to three cognitive domains. However, as cognitive control is a multidimensional construct (de Wit 2009; Fernández-Serrano, Pérez-García & Verdejo-García, 2011; Jones, Christiansen, Nederkoorn, Houben & Field, 2013), it is comprised of several different cognitive processes and there is a lack of studies that

aim at a more detailed assessment of cognitive control functions in ADP (de Wit, 2009). Against this background, the present study intended to extensively assess the following different cognitive control processes in ADP: attention, response initiation, response inhibition, delay discounting und reversal learning. The aim was to investigate in which domains of cognitive control processes ADP would show deficits compared to HC and further investigate whether deficits in cognitive control functions are predictive of relapse behaviour in a six-month follow-up period. As the number of detoxifications has been linked to cognitive impairment in ADP (Duka & Stephens 2014), we hypothesised that cognitive control deficits and the number of previous detoxifications would be associated with an increased risk for relapse in ADP. Finally, we wanted to investigate whether deficits in cognitive control functions are reversible after a period of a six-month abstinence.

One of the main findings is that, as expected, ADP generally performed worse on tasks assessing cognitive control functions compared to HC, thus corroborating previous research findings of a cognitive impairment in ADP. However, they did not show significant deficits in all measured domains of cognitive control, such as on the attention task (CRT) and regarding delay aversion as well as quality of decision making on the CGT. ADP showed significantly poorer performance in response initiation, complex sustained attention, response inhibition and executive functions. More precisely, ADP made more errors in the task measuring executive functions (IED), had less correct responses in the complex sustained attention task (RVP) as well as longer reaction times in the RVP and in the gambling task (CGT) and more commission errors (false alarms) in the RVP as well as in the specific response inhibition task (AGN). The results show that ADP often react slower in complex cognitive tasks and have problems with the precise and efficient processing of tasks. Those findings are in line with

previous studies that indicate cognitive deficits in ADP (e.g. see for an overview Moselhy et al., 2001). In regard to reversal learning ADP made more errors than HC, but differences only approached significance. With respect to response inhibition in the AGN, the results depict a pronounced specific inhibitory impairment for alcohol-related stimuli in ADP and in HC, as both groups made more commission errors during trials with alcohol pictures compared to trials with neutral pictures. Although ADP showed in general a worse performance in response inhibition related to HC with more commission errors in total. There was no interaction effect between category and group, meaning that ADP did not make more commission errors towards alcohol-related cues proportionately compared to neutral cues relative to the performance of HC. This suggests that the confrontation of alcohol associated stimuli triggers a certain approach bias even in non-addicted people, which is substantiated by research findings reporting a cognitive bias for alcohol associated stimuli, in both problem drinkers and people with normal alcohol consumption (Kreusch et al., 2013) as well as an attentional bias towards alcohol cues in both ADP and light social drinkers (Vollstädt-Klein, Loeber, von der Goltz, Mann & Kiefer, 2009). Very recent EEG studies investigating response inhibition towards neutral and alcohol-related stimuli (Petit et al., 2014; Matheus-Roth, Schenk, Wiltfang, Scherbaum & Müller, 2016), which have been published after study 2 was carried out, showed no context specific impairment for alcohol cues in detoxified ADP. Although the sample size was much smaller than in our study, the findings contribute to the ambivalence regarding the question of an alcohol-specific response inhibition deficit. Interestingly, in both studies (Petit et al., 2014; Matheus-Roth et al., 2016) differences between ADP and HC were observable on a neurophysiological level. Patients required more neural resources than HC during correct response inhibition (Petit et al., 2014) and patients relapsing in a 3-month follow-up time showed larger alcohol-cue related N170 ERP amplitudes (Matheus-

Roth et al., 2016). Recently, Noël and colleagues (2016) discussed two different hypotheses regarding response inhibition and presented results substantiating the automatic inhibition hypothesis. According to the automatic inhibition hypothesis, formerly proposed by Verbruggen and Logan (2008), "inhibitory control in go/no- go and stop-signal tasks can be triggered automatically via the retrieval of stimulus-stop associations from memory" (Noël et al., 2016, p. 85). The hypothesis is based on research findings showing that response inhibition or stop performance can become associatively mediated ('automatic') over practice (Noël et al., 2016; Verbruggen, Best, Bowditch, Stevens & McLaren, 2014) by coupling a stimulus with stopping in a task. Automaticity is understood as memory retrieval and it is suggested that through associative learning, a stop response can be activated, thereby suppressing an ongoing go process (Noël et al., 2016). The disinhibition hypothesis in contrast, reflects the idea of an inability to deliberately inhibit prepotent responses and has been substantiated by research findings reporting an impaired response inhibition in ADP (Noël et al., 2001, Smith et al., 2014). Noël et al. (2016) conducted a study with recently detoxified ADP performing a modified stop-signal task with neutral and alcohol related words which consisted of a training phase in which a subset of stimuli has been consistently associated with stopping or going. In a subsequent test phase the stimuli mapping for going or stopping was reversed. The performance regarding stimulus-stop learning effects in the training phase was similar in ADP and HC. However, in the test phase the probability of misses for stimuli that were associated with stopping before was higher in ADP compared to HC. The results (Noël et al., 2016) show that response inhibition can be improved over practice in ADP, which is a positive future outlook for the treatment of alcohol dependence.

The results in study 2 further indicated that the utilization of treatment after the detoxification in the six-month follow-up time had a strong effect on the course of abstinence, more specifically patients who attended regular treatment including psychotherapy, self-help groups or inpatient rehabilitation treatment showed a significantly lower rate of relapse and a longer duration of time until the first relapse. This is in line with other findings demonstrating that treatment drop-out is a significant relapse predictor (Bottlender & Soyka, 2005). Utilization of treatment and inhibitory deficits revealed to be significant predictors for relapse according to the logistic regression analysis, although utilization of treatment was the weakest predictor. In this context the results reported by Rupp and colleagues (2016) are very interesting, illustrating an association between treatment drop out and/or relapse in ADP and cognitive control deficits. Patients who relapsed during treatment or dropped out, showed significantly worse performance in response inhibition and delay discounting (Rupp et al., 2016), substantiating the theoretical framework of our study.

In study 2, cognitive deficits or deficits of inhibitory control processes did not directly predict relapse, but the deficits found in response inhibition in ADP significantly moderated the effect of classic relapse predictors. Thus, the number of previous detoxifications (corrected for the duration of addiction) turned out to be a significant relapse predictor, even when taking into account the use of follow-up treatment. However, this association depended on the presence of inhibitory control deficits: the number of previous detoxifications was a significant predictor of relapse only in patients with pronounced inhibitory control deficits, but not in patients with less impairment of inhibitory control. This suggests that those patients have problems to change pre-existing behavioural patterns and to inhibit automatic impulses during the confrontation with alcohol. As a consequence, the probability of relapse is increased. In this context

other studies are of interest (e.g. Loeber et al., 2009; Loeber et al., 2010) that indicate that a high number of previous detoxifications is associated with cognitive deficits (for an overview see Duka & Stephens, 2008). This seems to be affiliated with the excitotoxicity of high glutamate levels during acute withdrawal from alcohol and related harmful influences on the prefrontal cortex (Crews & Nixon, 2009). Thus, in predisposed patients, frequent detoxifications could lead to impairments in cognitive control- and regulation functions and therefore be associated with a poor prognosis for the future progress of the substance dependence. Thus, our findings suggest that patients with many detoxifications and inhibitory control deficits are in particular need of follow-up treatments that specifically address strengthening cognitive control processes. Previous studies indeed emphasize a possible regeneration of cognitive deficits under abstinence (Stavro et al., 2013). However, there is also evidence (Loeber et al., 2010) that, particularly in patients with a high number of detoxifications in comparison to patients with a small number of detoxifications, this reversibility is impaired, which again emphasizes the importance of specific trainings for this patient group. The results of study 2 showed that cognitive deficits in ADP generally did not improve after a period of a six-month long abstinence, thereby validating the findings of Stavro and colleagues (2013) who reported in their meta-analysis that reversibility of cognitive impairment takes up to one year. As the probability of having a relapse was highest in the group of ADP with many detoxifications and a pronounced response inhibition deficit, inhibitory control processes should be particularly addressed in future studies. In this context, it would be very interesting to investigate whether a specific training of inhibitory control functions can reverse observed deficits and reduce the relapse risk in the patient group with a high number of detoxifications and pronounced deficits in inhibition of control. For example, the AGN task could be modified to a response inhibition training and studied in regard to short and long-term effects on

inhibitory control and drinking outcomes.

There are a few limitations of study 2 which have to be addressed and some have been already stated in the discussion of the article. One of the limitations is the design of the go/no-go task in which alcohol-related pictures served as no-go stimuli but not as go stimuli. Therefore, we proposed to change the mapping of stimuli for future studies. In addition, the stimulus set for the neutral category could have been more complex and future studies should investigate stimulus material in regard to visual and attentional complexity in order to create a stimulus set that has more similar features. The pre-selection of the alcoholic stimuli is one of the strong points in our study as it provides a more personalised and ecologically valid content. Subjects had to choose their preferred eight pictures of alcoholic beverages out of a set of 85 pictures of different alcoholic beverages (different beers, wines, spirits). However, this approach poses problems with comparability to other designs and it would be interesting to compare task performance with personalised stimuli and with standardised stimuli in future studies.

Another point of criticism is the unbalanced distribution of males and females in the sample, although this reflects the higher prevalence rate of substance use disorders in males (Compton, Thomas, Stimson & Grant, 2007) and most samples in studies investigating inhibitory control in SUDs are predominantly male (Smith et al., 2014). However, there is evidence suggesting that women are more strongly affected by impairments in inhibitory control than men, thus supposedly leading to smaller effect sizes compared to the situation with an equal distribution of both sexes (Smith et al., 2014).

Taken together, the results of study 2 substantiate findings of previously reported deficits in cognitive control functions in ADP, but also demonstrate that not all domains of cognitive control are impaired in ADP. This emphasises the importance of specifying

measured cognitive functions in studies more precisely, as cognitive control is a multidimensional construct and our results suggest that some domains might not be affected as much as others. Moreover, paradigms that are described to measure the same or a very similar cognitive process can be very different and may measure different cognitive functions in the end. The wide range in the definition on impulsivity is an example, as described in this work before. Therefore, it is necessary to use standardised paradigms to increase comparability between studies, such as the tasks of the CANTAB which have been used in study 2.

Furthermore, the hypotheses of a response inhibition deficit in conjunction with elevated subjective impulsivity in ADP have been corroborated. Cognitive control functions allow for overriding automatized stimuli associated reactions and make self-regulated and goal-directed behaviour possible, involving processes such as attentional control or inhibition of inadequate behaviour. Therefore, the impairment of cognitive control functions plays a major role in the maintenance of addictive behaviour and our results contribute to a more elaborate understanding of those processes. The results of the present study also include some clues for the design of therapeutic add-on interventions: given the observed moderation effect, it seems reasonable to strengthen cognitive control processes by interventions such as inhibitory control training especially for high risk patients defined as patients with a high number of previous detoxifications.

3.3. Study 3

The aim of study 3 was to investigate neural activity patterns during response inhibition in general, and more specifically during response inhibition towards alcohol-related and neutral stimuli. Based on the results of study 2, which showed a significant general response inhibition deficit in ADP compared to HC and a pronounced response inhibition deficit towards alcoholic stimuli in ADP and HC, the main research question in study 3 was, whether there are also differences between both groups and between the stimulus categories on a neural level. Therefore, a subsample of the original sample (see study 2) underwent fMRI scans while conducting the AGN task. Neuroimaging studies showed that cognitive deficits in ADP are associated with significant changes in both brain function and brain structure (e.g. Bari & Robbins, 2013; Beck et al., 2012; Crews & Boettiger, 2009) and that those changes are associated with relapse risk. For example, Beck and colleagues (2012) reported pronounced atrophy in subsequent relapsers, in the bilateral orbitofrontal cortex and in the right medial prefrontal and anterior cingulate cortex, areas associated with error monitoring and behavioural control. This is in line with the findings of Rando et al. (2011), who showed that gray matter deficits in medial frontal and posterior parietal occipital regions were associated with a higher relapse risk and an earlier return to alcohol use. Furthermore, neural responses in brain areas associated with attentional bias towards alcohol related cues and with processing of salient stimuli, were enhanced in subsequent relapsers, emphasizing the meaning of impairment in cognitive control processes and approach behaviour for alcohol dependence (Beck et al., 2012; Grüsser at al., 2004). Neural processing during response inhibition has been mainly linked to the involvement of prefrontal brain areas, such as the dlPFC, ACC and IFG (Crews & Boettiger, 2009; Liddle et al., 2001; Lipszyc & Schachar, 2010).

The results of study 3 revealed that ADP showed significantly more neural activation in the left anterior cingulate gyrus, the left medial frontal gyrus and the left medial orbitofrontal cortex during successful inhibition (main effect). Studies with social drinkers support our findings: Ames et al. (2014) illustrated that, heavy drinkers in comparison to light drinkers, showed greater activity in the dlPFC during response inhibition with alcoholic stimuli. Petit and colleagues (2014) reported that ADP showed increased P3d amplitudes in an EEG recording compared to HC during correct response inhibition and thus required more neural resources than HC. On the behavioural level, both ADP and heavy drinkers showed a response inhibition deficit compared to the control groups of HC and light drinkers (Ames et al., 2014; Petit et al., 2014). Altogether, these findings and our results imply that cognitive deficits, such as an impairment in response inhibition, lead to a higher demand of neural resources. The need to recruit additional neural resources as a compensation strategy for deficits in cognitive processing in people with AUDs has been suggested by other authors as well (Bauer & Ceballos, 2014; Rajah & D'Esposito, 2005; Wetherill, Squeglia, Yang & Tapert, 2013). In accordance with the compensation hypothesis, Hu, Ide, Zhang, Sinha & Li (2015) recently reported greater neural activation in the pre-SMA and right IPL in ADP compared to HC in a stop signal paradigm. Along with an impairment in proactive control in ADP, enhanced activity in fronto-parietal areas has been suggested as a compensatory mechanism for cognitive control (Hu et al., 2015).

ADP in study 3 also showed greater activation compared to HC in other brain areas and in other contrasts. During successful inhibition of alcohol-related stimuli, more activation in the lingual gyrus, the right middle occipital gyrus and the right superior occipital gyrus was observable in ADP compared to HC. In the interaction contrast (comparing successful inhibition in relation to successful go reaction in alcohol-related versus geometrical stimuli), ADP also showed more neural activity in three occipital

clusters compared to HC. Although these brain areas do not match the typically reported response-inhibition network with prefrontal areas (Steele et al., 2014), the activity found in these brain areas matches the compensation hypothesis, showing that ADP had a stronger demand of neural resources during inhibition of alcohol-associated cues. Furthermore, Li and colleagues (2009) reported similar results with greater activity in bilateral visual cortices in ADP compared to HC in a response inhibition task.

Aside from the limitations which have already been mentioned in study 3, another limitation is that due to the small number of incorrect responses, especially in HC, a comparison between successful and failed response inhibition was not feasible.

3.4. Implications for clinical work and treatment

Relapse rates after alcohol withdrawal treatment are considerably high, ranging between 34.1% and 70.8% (2-year follow-up, Auswertung der Katamnesedaten, Bundesverband für Stationäre Suchtkrankenhilfe, 2012). For example, a longitudinal study by Moos and Moos (2006) reported that 62.4% of ADP who underwent treatment were remitted three years later, but by the 16-year follow-up 42.9% of the 3-year remitted patients had relapsed. However, ADP who were not seeking any help had much lower remission rates (43.4% by the 3-year follow-up) and much higher relapse rates (60.5% by the 16-year follow-up). Despite extensive research and development of new treatment options in the last decades, including both pharmacological and psychotherapeutic interventions, there is still more room for improvement. There is more evidence that cognitive functions could serve as a moderating or mediating variable (Bates et al., 2002; Bates et al., 2013; Worley, Tate, Granholm & Brown, 2014) and it is therefore of special interest to investigate how cognitive functions in ADP can be further strengthened. It has even been suggested that cognitive processes may be the most important factor for behavioural changes in a framework of emotions, affects, physiology, intention and social environment (Bates et al., 2013). Cognitive deficits evidently interfere with treatment success in SUDs. Working memory, attention and cognitive control processes are important functions that we need to change old behavioural patterns and to concentrate on therapeutic processes. However, the way in which cognitive deficits hamper treatment outcome in SUDs is not simple (Bates et al., 2013) and there are only very few studies reporting direct relationships. For example, neurocognitive performance (IQ, motor speed, attention) did not affect outcome in a computer assisted cognitive behavioural therapy, but higher risk taking in a behavioural risk task was related to lower treatment attendance and poorer substance use outcomes (Carroll et al., 2011). However, it has been hypothesized that

risk taking is rather associated with inhibitory deficits and is more directly linked with relapse than other aspects of cognitive control processes (Bates et al., 2013).

Cognitive deficits can serve as moderating variables for the treatment process by modifying the strength of other risk factors or predictors (for a review see Bates et al., 2002), e.g. by affecting psychosocial outcomes through changing the person's emotional and motivational responses (Bates et al., 2013) or interacting with self-efficacy (Bates et al., 2002). More precisely, the positive relationship between self-efficacy and drinking outcomes had been a strong prognostic factor for positive outcome in unimpaired patients, but this effect has been significantly diminished in patients with cognitive deficits (Bates, Pawlak, Tonigan & Buckman, 2006; Morgenstern & Bates 1999). Buckman, Bates and Cisler (2007) showed that a social network supporting abstinence was associated with a positive treatment outcome in ADP with cognitive deficits compared to cognitively unimpaired ADP and a social network supporting drinking was related to more negative drinking outcome in impaired ADP compared to unimpaired ADP. It has also been shown that deficits in executive function change the strength of the relations of self-efficacy, commitment to abstinence, affiliation to Alcoholics Anonymous and the motivations for behavioural change: the factors which have been robust predictors of a positive drinking outcome in cognitively unimpaired patients have only been weak predictors in the group of patients with significant executive deficits (Morgenstern & Bates, 1999). In a study with patients treated for alcohol or drug dependence and a comorbidity of major depression, cognitive impairment interacted with depression by moderating the effects of 12-step-affiliation and self-efficacy on future percent days of drinking. The positive predictive effect of 12-step-affiliation on future drinking outcome was greater for patients with cognitive deficits compared to patients with less deficits (Worley et al., 2014). Altogether these research findings support the idea that cognitive deficits can interfere

and change some significant mechanisms in the process of behavioural change. This should be taken in account when planning and deciding on individual treatment options for ADP.

Another way how cognitive deficits might influence the treatment process is by mediation. Thus, cognitive deficits can serve as mediators of other influences that contribute to the outcome or they can be mediated by other factors (Bates et al., 2002). For example, it is known that cognitive impairment can interfere with interpersonal relations and affective states (Loeber & Hay, 1997) and in turn low social support is associated with relapse likelihood (Marlatt & Gordon, 1985). Cognitive impairment also diminished the ability of learning treatment relevant information and is associated with more inattentiveness, lower motivation and greater denial, therefore interfering with the treatment process (for a review see Bates et al., 2013). Kiluk, Nich and Carroll (2011) reported that substance dependent patients with a higher IQ improved the quality of their coping skills from a cognitive behavioural therapy more than subjects with lower IQ. That in turn lead to reduced rates of substance use in the higher IQ group.

In summary, deficits of cognitive processes play an important role in treatment and therefore should be addressed, but it's an interesting question how exactly they can be implemented as there are many ways to do so. Most of the research in this field has concentrated on strengthening cognitive abilities of substance use dependent individuals, which is a logical conclusion of the above mentioned findings. In the following, an overview about different treatment approaches addressing cognitive functions in substance use dependence will be given.

3.4.1. Neuroscience based neuropsychological interventions

The most obvious approach of enhancing cognitive functioning is by cognitive remediation interventions, often accomplished with computerized neuropsychological training. Those interventions have shown good outcome for improvement of cognitive deficits in SUDs (for an overview see Brooks, 2016; Kiluk & Carroll, 2013). For example, Rupp, Kemmler, Kurz, Hinterhuber and Fleischhacker (2012) compared conventional treatment (CBT) and a computer-assisted cognitive remediation in addition to conventional treatment in a randomized controlled trial with ADP entering inpatient treatment. The additional cognitive remediation training addressed cognitive enhancement in several cognitive domains, such as attention, memory and executive functions. Patients in the cognitive training group showed significant improvement in their cognitive functions, especially in working memory, attention and delayed memory, as well as significant improvement in psychological well-being and craving. Houben, Nederkoorn, Wiers & Jansen (2011) showed that a go/no-go training with alcohol cues, aiming at strengthening response inhibition, reduced alcohol intake significantly in heavy drinking students. This indicates that cognitive training interventions may increase control over automatic processes, which would be of great interest for treatment of AUDs. Lawrence et al. (2015) used a similar paradigm and conducted a go/no-go training with obese subjects, in which they tested an active training (density snack foods as no-go signals) versus a control training (non-food stimuli as no-go signals). The active training group showed significant weight loss and reductions in daily energy intake compared to the control condition. Although the groups are not directly comparable, both studies show that a cognitive training of response inhibition has a significant impact on consumption patterns.

Another area that is promising and gained more attention recently consists of studying

and changing implicit cognitive processes, such as the approach bias, which has been associated with craving and relapse (Wiers, Eberl, Rinck, Becker & Lindenmeyer, 2011). In patients with alcohol dependence, the attentional bias is defined by an automatic tendency to approach alcohol cues faster than to avoid them, compared to neutral cues, a finding which was associated with craving and relapse (Wiers et al., 2011). Thus, Wiers et al. (2011) developed a task measuring the attentional bias towards alcohol, called the "Alcohol-Approach/Avoidance Task" (AAT), in which subjects view various pictures (alcohol associated, neutral, positive, negative) and have to push or pull a joystick to zoom in or out of the picture, thereby emulating an approach or avoidance. Wiers et al., 2011 used the task in a randomized controlled trial with ADP, allocating subjects to conditions where they either had to practice avoidance or approach towards alcoholic and non-alcoholic pictures. ADP trained to avoid alcohol pictures showed less bias towards alcohol and significantly improved drinking outcomes 1 year later in comparison to subjects in other conditions (Wiers et al., 2011). This method called cognitive-bias modification has been replicated in several studies (Eberl et al., 2013; Eberl et al., 2014) and appears to be a successful intervention in changing implicit and automatic processes related with alcohol use.

3.4.2. Neurofeedback and Neurostimulation

Besides pharmacological treatment, more direct methods of influencing brain functions in substance use disorders have been developed recently, such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), neurofeedback and a more invasive method of deep brain stimulation (for a review see Schulte et al., 2014; Wilcox et al., 2014). While fMRI neurofeedback has been shown to improve depression symptoms (Linden et al., 2012) and to reduce craving in

smokers (Li et al., 2012), there is evidence that in ADP (Karch et al., 2015) and in heavy drinking students (Kirsch, Gruber, Ruf, Kiefer & Kirsch, 2015) it can also help to modify neuronal activity and reduce craving (Karch et al., 2015).

3.4.3. Psychotherapy approaches

Besides neuropsychological training, psychotherapeutic interventions have the potential to strengthen cognitive processes as well. Especially response inhibition is a function which could be addressed by psychotherapy, e.g. by improving affect regulation or practicing mindfulness and becoming more aware of bodily and emotional processes. There is research supporting the effectiveness of mindfulness training in AUDs (Black, Semple, Pokhrel & Grenard 2011; Bowen et al., 2009). Mindfulness increases the patient's awareness of emotional triggers, potentially also triggers causing relapse, and strengthens the ability to tolerate and cope with stress and strain (Bowen et al., 2009; Witkiewitz, Lustyk & Bowen, 2013). There are studies which have shown an association between mindfulness training and improvement in executive function (Chiesa, Calati & Serretti, 2011), working memory tasks (Jha, Stanley, Kiyonaga, Wong & Gelfand, 2010; Zeidan, Johnson, Diamond, David & Goolkasian, 2010), response inhibition and decision making in subjects with drug and alcohol related problems (Alfonso, Caracuel, Delgado-Pastor & Verdejo-Garcia, 2011).

4. Summary

The present dissertation focused on cognitive control processes and impulsivity in the context of AUDs with an emphasis on response inhibition towards alcohol-related and neutral stimuli. Overall, different paradigms, methods and samples have been used in three studies including behavioural tasks, questionnaire data and fMRI recordings. For the assessment of specific response inhibition processes a go/no-go paradigm with pictures of the preferred alcoholic drinks and neutral stimuli has been further developed for this work to combine the aspects of behavioural inhibition and salience of drug-associated cues. Study 1 investigated the association between binge drinking, trait impulsivity and behavioural impulse control. The results revealed that only binge drinkers showed an alcohol-specific impairment of response inhibition and that the number of commission errors towards alcohol related stimuli was the only significant predictor for binge drinking. However, binge drinkers did not significantly differ from non-binge drinkers in regard to self-reported impulsivity and overall response inhibition performance. In study 2, a large sample of recently detoxified ADP and HC were compared with respect to their performance on five different behavioural tasks assessing different aspects of cognitive control processes and the association between cognitive control deficits in ADP and relapse behaviour in a six-month follow-up period has been investigated. Compared to HC, ADP showed an impairment in response inhibition, response initiation, complex sustained attention and executive functions. Both groups made more commission errors when they had to inhibit their reactions towards alcohol pictures compared to geometrical stimuli. This suggests a specific response inhibition deficit for alcoholic cues, however not specifically for the group of ADP. The strongest predictor for relapse has been the interaction between the number of previous detoxifications and response inhibition deficits, revealing that ADP with a

higher number of detoxifications and a pronounced impairment in response inhibition had the highest relapse risk. Study 3 focused on neuronal activity patterns, assessed with fMRI, in ADP and HC during a response inhibition task. During successful inhibition towards all stimuli, ADP showed enhanced neural activity compared to HC in brain areas linked to cognitive control, including the anterior cingulate gyrus, medial frontal gyrus and medial orbitofrontal cortex. These results are interpreted as an additional demand for neural resources, respectively a compensation due to a deficit in cognitive control processes in ADP.

In summary, it can be stated that ADP show a pronounced impairment in several cognitive control processes and that especially a deficit in response inhibition combined with many detoxifications in the past, is related to an enhanced relapse risk. Regarding the impact of alcoholic cues on response inhibition, the results suggest that alcohol-related stimuli interfere with response inhibition performance and are associated with more errors. Interventions for people with AUDs, including binge drinkers, should take those factors in account and clinicians should be particularly aware of patients with many detoxifications and poor response inhibition, as those factors comprise the high risk relapse group.

5. References (for the introduction and general discussion)

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