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Behavioral impulsivity mediates the relationship between decreased frontal gray matter volume and harmful alcohol drinking: A voxel-based morphometry study

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ABSTRACT

Alcohol use disorder (AUD) with harmful drinking patterns is on the one hand characterized by impulsive behavior and is on the other hand known to involve structural brain alterations with lower gray matter volume (GMV), especially in the prefrontal cortex (PFC). So far it is unclear whether frontal brain volumes are associated to harmful alcohol drinking and impulsivity, while controlling simultaneously for a wide array of important confounding factors, which are related to alcohol consumption.

We used voxel-based morphometry in 99 adults ranging within a continuum of normal to harmful drinking behavior and alcohol dependence, measured by the 'Alcohol Use Disorders Identification Test', to examine whether the severity of harmful drinking is correlated with structural markers, in particular in the PFC and whether such markers are linked to self-reported impulsivity. We included alcohol and nicotine lifetime exposure, age, education, and BMI as covariates to control that GMV decreases were not related to those factors.

Harmful drinking was associated with lower GMV in the right frontal pole, left inferior frontal gyrus, and bilateral inferior parietal lobe. GMV loss in the PFC regions was correlated with increased impulsivity. Follow-up mediation analyses showed that the relationship between GMV in the frontal pole and harmful drinking was mediated by impulsivity.

Our findings show that PFC reductions are associated with harmful drinking and impulsivity. Our data suggest that reduced frontal pole GM, independent of a number of alcohol drinking associated covariates, e.g. lifetime alcohol consumption, is related to impaired top-down control of alcohol drinking behavior.

1. Introduction

Alcohol use disorder (AUD) is a complex, multifaceted condition, which is associated with severe medical comorbidities, psychosocial problems and marked cognitive deficiencies (Brooks et al., 2014; Grodin et al., 2013; Schuckit, 2009). AUD has consistently been associated with impaired response inhibition and detrimental executive functioning (Adólfsdóttir et al., 2014; Chanraud et al., 2007; Leeman et al., 2012), and poor impulse control is thought to be one of the characteristics of alcohol addiction (de Wit, 2009; Shin et al., 2012) which may impair treatment outcome (Tuithof et al., 2014). A hallmark diagnostic characteristic of alcoholism is the inability to refrain from drinking even in the face of severe consequences. It has been suggested that chronic alcohol consumption is related to reduced cognitive processes that critically rely on prefrontal cortex (PFC) functioning (Adams et al., 1993; Noël et al., 2001).

Brain imaging studies using voxel-based morphometry (VBM) have reliably shown lower cortical gray matter volumes (GMV) in alcohol dependent patients in a number of brain regions e.g. (Mechtcheriakov et al., 2007; Pfefferbaum et al., 1997). Notably, brain morphometry studies using other techniques such as

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diffusion tensor imaging (DTI) (Monnig et al., 2013) or surface-based morphometry (SBM) (Thayer et al., 2016) reported in AUD reduced axial diffusivity in bilateral frontal and temporal white matter (Monnig et al., 2013) and thinner frontal cortices as well as abnormalities in temporal and parietal cortices (Thayer et al., 2016). In VBM studies in particular the volume of the PFC (De Bellis et al., 2005; Medina et al., 2008; Xiao et al., 2015) was affected. Decreased GMV in the prefrontal cortex was furthermore related to impaired performance in an inhibitory control task in alcohol-dependent patients (Wiers et al., 2015).

Previous findings have suggested that AUD is characterized on the one hand by behavioral impulsivity and on the other hand involves structural brain alterations. So far it is unclear whether 'Alcohol Use Disorders Identification Test' (AUDIT) (Saunders et al., 1993a, 1993b) scores, assessing alcohol drinking behavior on a continuum from normal to dependent alcohol consumption, are associated with PFC decreases and if these GMV alterations are furthermore linked to deficient impulse control. Further, hitherto it is not clear, which role the large number of factors associated with alcohol consumption (e.g. neurotoxic side-effects, smoking) and their combinations play in GMV alterations.

On the one hand, there is ample evidence that the neurotoxic effect of alcohol leads to deleterious effects on the central nervous system, such as brain atrophy and cognitive dysfunction (Nicolás et al., 1997; Taki et al., 2006; Wiers et al., 2015). It has been suggested that there is a specific vulnerability to the neurotoxic effects of alcohol in the PFC (De Bellis et al., 2005; Medina et al., 2008) and in the hippocampus (De Bellis et al., 2000; Nagel et al., 2005; Welch et al., 2013), including long-term reduced neurogenesis in the hippocampus that has been shown in animal models (Paula-Barbosa et al., 1993). In a study of a Dutch group (de Bruin et al., 2005) in non-alcohol-dependent males, the lifetime alcohol intake was associated with focal gray matter decreases in the right frontal and right parietal brain regions. However, a previous study of our group (Wiers et al., 2015) investigated faster responses on go trials in a stop-signal task in of group of alcohol-dependent patients and related these to the lifetime alcohol intake (Life Time Drinking History, LTDH). In fact, when LTDH was added as a covariate in this exploratory analysis, the faster responses were independent of lifetime alcohol consumption. Additionally, it has been shown that other factors, which often accompany excessive alcohol consumption, such as higher BMI (Body Mass Index) (Bobb et al., 2014), advancing age (Raz et al., 2005), lower educational status (Foubert-Samier et al., 2012) and especially smoking (Pan et al., 2013) are also associated with structural brain decreases. Smokers have shown considerable regional GMV decreases compared to non-smokers (Peng et al., 2015), particularly in the PFC (Fritz et al., 2014) and smoking alcohol-dependent patients showed decreases in pre- and paracentral frontal cortical areas, as well as parahippocampal and temporal regions (Luhar et al., 2013). Furthermore de Wit (2009) reported that abstinence from cigarette smoking increased discounting for cigarette, and another group (Field et al., 2006) reported that nicotine deprivation increased impulsive choices for both cigarette and monetary rewards in a delay-discounting task.

On the other hand, it has been questioned (de Wit, 2009) whether volume loss, in particular in the PFC, is solely a consequence of excessive alcohol consumption, including neurotoxic effects on the brain and long-term plasticity, or whether GMV loss is a vulnerability marker and underlying risk factor that predisposes individuals to AUD (Dick et al., 2010; Verdejo-García and Pérez-García, 2008). Behavioral longitudinal studies strongly suggest an association between pre-existing deficits in frontal lobe functions during child-hood and adulthood, in particular disinhibited behavior, and the subsequent development of substance use disorders (Brooks et al., 2014).

Understanding how structural brain alterations and associated impulsive behavior are related to the harmful and uncontrollable use of alcohol, aside from purely neurotoxic exposure effects, is important for exploring the complex development of AUD. Previous structural neuroimaging studies in AUD have mostly investigated patients with severe long-term alcohol dependence (Mechtcheriakov et al., 2007; Pfefferbaum et al., 1997) (as opposed to harmful drinking behavior in general, see Asensio et al., Matsuo et al., 2009; Rando et al., 2011) and have in the majority of the cases not controlled for the amount of lifetime intake of alcohol (reflecting possible neurotoxic effects of alcohol, see de Bruin et al., 2005 and Wiers et al., 2015) and other AUD associated psychosocial and medical factors (smoking, age, education) and BMI. Importantly, only few studies have investigated whether the relationship between lower PFC volumes and AUD is mediated by impulsivity, namely if lower PFC volume are associated with higher behavioral impulsivity (Asensio et al., 2015; Matsuo et al., 2009; Rando et al., 2011), which is an important factor influencing harmful and uncontrolled drinking behavior. So far no study has investigated at the same time whether harmful drinking behavior as a continuum is related to morphometric changes in the PFC and its relationship with impulsivity, while controlling for important factors often associated with alcohol consumption.

To address this issue, we examined harmful drinking behavior, assessed with the AUDIT score, in a large sample consisting of participants with normal to moderate and severe harmful drinking behavior. The usage of AUDIT scores as a continuous measure of current harmful drinking, is in accordance with the new DSM-5 (Diagnostic and Statistical Manual of Mental Disorders - Version 5), which suggests that alcohol use occurs along a continuum with considerable variability in harmful drinking behavior among individuals. The association between AUDIT scores and GMV was tested in a multiple regression analysis controlling for a combination of potentially confounding variables often associated with alcohol consumption, namely BMI, education, age, as well as the (neurotoxic) amount of lifetime intake of alcohol and nicotine. Therefore, the present study addresses for the first time the association of frontal brain volumes to harmful alcohol drinking and the role of impulsivity, while at the same time carefully controlling for a wide array of important covariates. In the light of previous behavioral longitudinal studies that have demonstrated impaired frontal lobe functions already in adolescent AUD (Bava et al., 2013; Welch et al., 2013), we expected that lower GMV in the PFC would be related to severity of harmful drinking behavior, even if controlled for other AUD associated factors. We further hypothesized that prefrontal GMV would be negatively associated with deficient response inhibition and expected that the relationship between low prefrontal GMV and severity of drinking behavior would be mediated by increased impulsivity.

2. Methods

2.1. Participants

A total of 99 right-handed male subjects (mean age = 39.23 years ± 9.17 SD, range = 22–59) participated in the study. In the study sample, the average AUDIT score of all 99 subjects was 14.86 points (±11.11 SD, 1–40 points) (for further participant characteristics see Table 1).

DSM-5 criteria were assessed with the Mini-international neuropsychiatric interview, a structured diagnostic interview (M.I.N.I. plus (Sheehan et al., 1998)). 35 subjects fulfilled the DSM-5 criteria for severe AUD, 26 subjects for mild/moderate AUD. All participants were at least abstinent one day before scanning and participants with severe AUD were detoxified. Exclusion criteria for