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Prediction of alcohol drinking in adolescents: Personality-traits, behavior, brain responses, and genetic variations in the context of reward sensitivity

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ABSTRACT

Adolescence is a time that can set the course of alcohol abuse later in life. Sensitivity to reward on multiple levels is a major factor in this development. We examined 736 adolescents from the IMAGEN longitudinal study for alcohol drinking during early (mean age = 14.37) and again later (mean age = 16.45) adolescence. Conducting structural equation modeling we evaluated the contribution of reward-related personality traits, behavior, brain responses and candidate genes. Personality seems to be most important in explaining alcohol drinking in early adolescence. However, genetic variations in *ANKK1* (rs1800497) and *HOMER1* (rs7713917) play an equal role in predicting alcohol drinking two years later and are most important in predicting the increase in alcohol consumption. We hypothesize that the initiation of alcohol

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Longitudinal study
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Genetic variations

use may be driven more strongly by personality while the transition to increased alcohol use is more genetically influenced.

1. Introduction

Adolescence is a phase with a high risk for first alcohol consumption and the transition to future alcohol abuse (e.g. Kim, Zerwas, Trace, & Sullivan, 2011). The risk for prospective development of alcohol abuse increases the younger adolescents are when having their first drink (e.g. Behrendt, Wittchen, Hofler, Lieb, & Beesdo, 2009). This suggests that the early identification of risk factors and subsequent interventions could best prevent alcohol abuse. Several factors contribute to the initiation of alcohol use. One aspect is the social environment with family and peer factors strongly influencing substance use initiation (e.g. Oxford, Harachi, Catalano, & Abbott, 2001). Besides these external factors, several individual aspects have been identified. Among them sensitivity to reward has been assumed to play a major role. In a previous study (Nees et al., 2012), we showed that neural responses to reward, reward-related personality traits, and reward-related behavioral data are correlated with alcohol consumption in early adolescence. This study suggested that personality correlates are more strongly related to alcohol drinking behavior than neural activation or behavior (Nees et al., 2012). However, in this study, we neither tested genetic effects nor modeled the development of alcohol drinking behavior over time. In the present study we therefore extended our previous findings using follow-up data assessed two years after the first study and we also analyzed the effects of candidate genetic variations in a considerably enlarged sample compared to our first study.

Reward processing associated with alcohol use can be examined using several individual interrelated traits including the levels of personality, behavior, brain responses, and genetic variations. Reward sensitivity on all these connected levels has been shown to be related to the initiation of drinking or the development of alcohol abuse. To build up on the model of our first study and thus determine the additional influence of genetic factors and changes in alcohol consumption over time, we used all previously examined variables, i.e. the variables representing reward-related personality traits, reward-related behavior, and brain responses to reward were the same as in our first study (Nees et al., 2012). Likewise, we used the total score of the Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993) as outcome variable to account for the fact that even lower levels of alcohol consumption during adolescence might indicate hazardous drinking (e.g. Chung et al., 2000). For personality, sensation seeking, novelty seeking, impulsivity and extraversion are the most important components describing reward-related personality and have been found to be strongly associated with early initiation of hazardous alcohol use and as predictors for later alcohol abuse (e.g. Ayer et al., 2011; Cloninger, 1987; Hittner & Swickert, 2006). On a behavioral level, risk taking has been related to increased alcohol use as well as impaired control over alcohol use (Leeman, Patock-Peckham, & Potenza, 2012; MacPherson, Magidson, Reynolds, Kahler, & Lejuez, 2010). Here, the increased preference of a smaller immediate reward towards a larger delayed reward (de Wit, 2009) clearly shows its connection with reward sensitivity. An increased responsiveness in the brain reward system is also associated with reward sensitivity (Hahn et al., 2009) which makes the involved structures essential for the investigation of reward sensitivity in the context of alcohol consumption. The anterior cingulate cortex, the ventral pallidum, the ventral striatum, the orbitofrontal cortex, and the dopaminergic midbrain neurons are key structures of this network, and the amygdala, thalamus, orbital prefrontal cortex and the hippocampus are also involved in the regulation of reward (Haber & Knutson, 2010). We analyzed brain responses to a Monetary Incentive Delay (MID) task (Knutson, Adams, Fong, & Hommer, 2001). We included regions of interest in our analysis which have been shown to be associated with reward sensitivity during an MID task on the one hand and with alcohol consumption on the other hand. Hence, we included the striatum, amygdala, nucleus accumbens, nucleus caudatus, thalamus, insula, putamen, cerebellar vermis, and the prefrontal cortex which all met these criteria (Gilman, Smith, Ramchandani, Momenan, & Hommer, 2012; Haber & Knutson, 2010; Hahn et al., 2009; Nees et al., 2012; Oberlin et al., 2012) and have been shown to be valid predictors in our previous study (Nees et al., 2012).

Genetic factors play an important role in the development of alcohol abuse and several genetic risk factors for alcoholism have been identified (e.g. Morozova, Goldman, Mackay, & Anholt, 2012). Regarding our aim to establish a model on alcohol consumption specifically in the context of reward sensitivity, it has to be considered that reward sensitivity per se is also genetically influenced (Nees et al., 2013; Richter et al., 2013; Rietschel et al., 2010; Stacey et al., 2012). This suggests that the appropriate genetic factors might also contribute to alcohol drinking behavior via modifying reward sensitivity. To determine the effects of various domains including genetic variations on any mental symptom, specific hypotheses on single chosen variables are mandatory to exclude the risk of false positive results. Thus, one selection criterion was that the single nucleotide polymorphisms (SNPs) to be included in our analysis had to be associated with reward sensitivity. The second criterion for the selected SNPs was that they should be associated with alcohol use or addiction not only in our sample but in patient studies to ensure the clinical relevance of the selected SNPs. This led to the following candidate genes and specific SNPs: *ANKK1* (rs1800497), *RASGRF2* (rs26907), and a regulatory region of *HOMER1* (rs7713917) (Richter et al., 2013; Rietschel et al., 2010; Stacey et al., 2012). *ANKK1* encodes a protein belonging to a protein kinase family, which is involved in signal transduction and may influence dopaminergic signaling in the striatum (Klein et al., 2007; Neville, Johnstone, & Walton, 2004). As striatal dopamine responses to salient alcohol cues may be an inherited risk factor for alcoholism (Oberlin et al., 2013) this directly implies *ANKK1* in the formation of alcoholism. The TaqIA SNP (rs1800497) in *ANKK1* is one of the most widely examined genetic variations in mental disorders and its TaqIA A1 polymorphism is associated with alcoholism and other addiction disorders (Ponce et al., 2009). An imaging genetics study has shown that a variation in rs1800497 interacts with motivation in a reward flanker task (Richter et al., 2013), indicating a link between *ANKK1* and reward deficiency. Homer proteins regulate extracellular glutamate levels in cortical-limbic brain regions as well as signal transduction, synaptogenesis and receptor trafficking (Szumlinski, Kalivas, & Worley, 2006). Homer isoforms seem to influence the processing of reward anticipation; especially carriers of the A-allele of rs7713917 (located in a regulatory region of *HOMER1*) seem to be at a higher risk for a dysregulation of cognitive and motivational processes by influencing prefrontal activity during anticipation of reward (Rietschel