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Alcohol misuse in emerging adulthood: Association of dopamine and serotonin receptor genes with impulsivity-related cognition

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HIGHLIGHTS

- Alcohol cognition mediates most of the association between impulsivity and drinking
- Dopamine and serotonin genes are implicated in alcohol misuse, but role is unclear
- Role of ANNK1 and HTR2A polymorphisms in alcohol-related cognition tested
- HTR2A directly associated with expectancies, refusal self-efficacy, alcohol misuse
- No polymorphism moderated links between impulsivity, cognition, and alcohol misuse

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ABSTRACT

Impulsivity predicts alcohol misuse and risk for alcohol use disorder. Cognition mediates much of this association. Genes also account for a large amount of variance in alcohol misuse, with dopamine and serotonin receptor genes of particular interest, because of their role in motivated behavior. The precise psychological mechanisms through which such genes confer risk is unclear. Trait impulsivity conveys risk for alcohol misuse by influencing two distinct domains of cognition: beliefs about the reinforcing effects of alcohol consumption (*positive alcohol expectancy*) and the perceived ability to resist it (*drinking refusal self-efficacy*). This study investigated the effect of the dopamine-related polymorphism in the *DRD2/ANKK1* gene (*rs1800497*) and a serotonin-related polymorphism in the *HTR2A* gene (*rs6313*) on associations between impulsivity, cognition, and alcohol misuse in 120 emerging adults (18–21 years). *HTR2A* predicted lower positive alcohol expectancy, higher refusal self-efficacy, and lower alcohol misuse. However, neither polymorphism moderated the linkages between impulsivity, cognition, and alcohol misuse. This is the first report of an association between *HTR2A* and alcohol-related cognition. Theoretically-driven biopsychosocial models have potential to elucidate the specific cognitive mechanisms through which distal risk factors like genes and temperament affect alcohol misuse in emerging adulthood.

1. Introduction

Alcohol outcome expectancies, refusal self-efficacy, and impulsivity have recently been highlighted as central psychological mechanisms in the initiation and maintenance of alcohol use disorders (Connor, Haber, & Hall, 2016). Social cognitive factors, such as an individual's beliefs about their ability to refuse alcohol (*refusal self-efficacy*) as well as the outcomes of consumption (*alcohol expectancy*), have been shown to mediate most of the risk conveyed by impulsivity (Gullo, Dawe, Kambouropoulos, Staiger, & Jackson, 2010; Harnett, Lynch, Gullo, Dawe, & Loxton, 2013; Kabbani & Kambouropoulos, 2013). The role of cognition in alcohol misuse may, in part, be affected by dopamine and serotonin receptor genes (Connor et al., 2008; Courtney, Ghahremani, & Ray, 2012; Meyers et al., 2013). However, there are few studies that have tested the specific effects of such genes on the combined role of impulsivity and social cognition in non-dependent alcohol misuse. A better understanding of the combined role of these factors may help inform prevention and early intervention programs.

Current evidence suggests impulsivity comprises two separate facets that uniquely contribute to the development of alcohol use problems (Gullo, Loxton, & Dawe, 2014; Gullo & Potenza, 2014). The first facet, *Reward Drive*, reflects the motivation to obtain, and sensitivity to, rewarding stimuli (Dawe & Loxton, 2004; Franken & Muris, 2006). The

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second facet, *Rash Impulsiveness*, reflects individual differences in the ability to inhibit approach behavior in light of negative outcomes. Individuals high in rash impulsiveness and reward drive are at greater risk of substance misuse (Dawe, Gullo, & Loxton, 2004; Kabbani & Kambouropoulos, 2013; Loxton et al., 2008). Gullo, Ward, Dawe, Powell, and Jackson (2011) found that both rash impulsiveness and reward drive directly and uniquely predicted hazardous drinking in young adults, with rash impulsiveness being the more robust predictor. A possible reason for this difference could be the role of social cognitive mediators of impulsivity's effect on alcohol use (Bandura, 1999). Two cognitive mechanisms proposed to mediate the relationship between impulsivity and alcohol use are drinking refusal self-efficacy (DRSE) and positive alcohol expectancy (PAE; Baldwin, Oei, & Young, 1993; Goldsmith, Thompson, Black, Tran, & Smith, 2012; Gullo et al., 2010).

Alcohol expectancy refers to an individual's belief about the predicted outcomes of alcohol consumption (Oei & Baldwin, 1994). Individuals with a greater number, and strength, of positive expectancies are more likely to engage in alcohol misuse (Connor, George, Gullo, Kelly, & Young, 2011; Greeley & Oei, 1999; Jones, Corbin, & Fromme, 2001). Positive alcohol expectancy develops through one's own experiences with alcohol, or through modelling. Children develop PAE before they have had any personal experience with alcohol consumption (Connor et al., 2011; Zucker, Donovan, Masten, Mattson, & Moss, 2008). According to the 2-Component Approach to Reinforcing Substances model (2-CARS; Gullo et al., 2010), individuals high in reward drive are more biased towards remembering the positive effects of alcohol and develop greater PAE. Several studies have supported this meditating role of PAE in the association between reward drive and hazardous alcohol consumption (Gullo et al., 2010; Harnett et al., 2013; Kabbani & Kambouropoulos, 2013).

Drinking refusal self-efficacy is an individual's belief about their ability to abstain from drinking in cued situations (Oei & Baldwin, 1994; Young, Oei, & Crook, 1991). Low DRSE is associated with a greater risk of hazardous alcohol consumption (Gullo, St. John, Young, Saunders, Noble and Connor, 2014; Oei & Morawska, 2004). Maisto, Connors, and Zywiak (2000) found that, for up to a period of one year, self-efficacy significantly predicted alcohol consumption. Self-efficacy is most influenced by past behavior, such that repeated instances of poor performance results in decreased self-efficacy (Bandura, 1977; Oei & Baldwin, 1994). According to 2-CARS, individuals high in rash impulsiveness have poorer inhibitory control, have an awareness of this, and therefore expect themselves to have greater difficulty resisting alcohol, just like any other reward (Gullo et al., 2010). Indeed, the rash impulsiveness-alcohol misuse relationship is mediated, to a large extent, by DRSE (Gullo, St. John et al., 2014; Harnett et al., 2013; Kabbani & Kambouropoulos, 2013; Patock-Peckham, Julie, Kevin, Antonio, & Emilio, 2011). Reward drive and rash impulsiveness are uniquely associated with PAE and DRSE, respectively (Gullo et al., 2010; Harnett et al., 2013; Kabbani & Kambouropoulos, 2013).

The temperamental and cognitive mechanisms leading to alcohol misuse may be influenced by genetics (Kendler, Prescott, Myers, & Neale, 2003; Leeman et al., 2014; Meyers et al., 2013). Twin studies suggest a substantial proportion of variance in PAE is genetic (Prescott, Cross, Kuhn, Horn, & Kendler, 2004; Vernon, Lee, Harris, & Jang, 1996). During adolescence, the influence of genetic factors on PAE increases with age, especially after drinking onset, with genetic influence nearly equaling that of shared environmental factors by age 18 (Young-Wolff et al., 2015). However, far less is known about the specific genes involved or how they affect alcohol use and related cognition.

Genetic polymorphisms affecting mesolimbic dopamine receptor functioning have been of particular interest, given that they are a common site of drug action. One of the most widely studied is the the *Taq1A* polymorphism, which was previously thought to be located on the dopamine D2 receptor gene (*DRD2*), but actually resides in the neighboring ankyrin repeat and kinase domain containing 1 (*ANKK1*) gene (Neville, Johnstone, & Walton, 2004). A recent study by Meyers et al. (2013) found an association between the *DRD2/ANKK1* gene and alcohol use, consistent with several previous studies reporting a link between *DRD2/ANNK1*, alcohol use, and cognition (Connor et al., 2008; Gullo, St. John et al., 2014; Leeman et al., 2014; Munafò, Matheson, & Flint, 2007). However, the strength of the association may differ according to the severity of dependence within the population studied (Dick et al., 2007; Munafò et al., 2007).

The inconsistency in associations between *ANKK1* and alcohol misuse may also be due to a possible indirect and complex role in drinking behavior. Gullo, St. John et al. (2014) investigated the moderating effect of the *ANKK1* on the association between rash impulsiveness, DRSE and alcohol dependence severity in a sample of alcohol dependent inpatients. While they replicated the mediating role of DRSE in rash impulsiveness and severity of drinking, this was not moderated by *ANKK1*. *ANKK1* was associated with DRSE directly, and it is possible that *ANKK1* has a stronger moderating role on cognition in early-stage drinking and, therefore, not observed in alcohol-dependent inpatients. Another important consideration is that Gullo, St. John et al. (2014) did not investigate the PAE-mediated pathway between reward drive and misuse. The present study aimed to extend this research to look at the role of *ANKK1* on both mediation pathways in a young sample of non-alcohol dependent individuals.

Serotonin receptor genes that indirectly affect mesolimbic dopamine neurons have also been linked to alcohol use disorders. A recent meta-analysis by Cao et al. (2014) reported that *rs6313* (102T/C at exon 1) on the 5-hydroxytryptamine (serotonin) 2A receptor gene (*HTR2A*) is associated with substance misuse and, more prominently, alcohol dependence. Presynaptic *HTR2A* receptors have been localized on dopaminergic neurons in the ventral tegmental area, suggesting possible involvement in reward processing (Cao et al., 2014). No research has been conducted on this gene and its relation to cognition, despite a clear role for serotonin in impulsivity (Cools, Roberts, & Robbins, 2008).

The aim of the current study was to investigate whether the relationship between rash impulsiveness, reward drive and alcohol misuse is mediated by two different cognitive mechanisms: DRSE and PAE. In addition, it aimed to determine the extent to which the *ANKK1* and *HTR2A* genes moderate these relationships (see Fig. 1). Consistent with previous studies, it was hypothesized that DRSE would mediate the association between rash impulsiveness and alcohol misuse, and that PAE would mediate the association between reward drive and alcohol misuse. It was also hypothesized that both mediational pathways would be moderated by the *HTR2A* gene and the *ANKK1* gene. The moderating effect of *HTR2A* and *ANKK1* would strengthen the mediational relationship between reward drive, PAE and alcohol misuse as well as rash impulsiveness, DRSE and alcohol misuse.

2. Methods

2.1. Participants

A total of 120 participants (50% female) were recruited through advertisements placed on local university and technical college campuses. Mean age was 19.47 years ($SD = 1.12$, range: 18–21). The majority were White/Caucasian (86.6%), with 12 (10.1%) Asian, and 4 (3.4%) 'Other'. Findings did not differ when only White/Caucasian cases were analysed, so results for the full sample are reported. Participants were recruited as part of a larger experimental study involving alcohol consumption and had to be of legal drinking age (18+ years). Additional inclusion criteria were: recent alcohol consumption (i.e., within the last 2 weeks), never been diagnosed with an alcohol use disorder, and not currently suffering from a medical condition or taking medication where alcohol consumption is contraindicated. Participants were reimbursed with a AUD$40 gift voucher for vendors that do not sell alcohol. The study was approved by the relevant university human research ethics committee.