Title: Differential brain response between OPRM1 genotypes to reward feedback during early adolescence

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Adolescence is a developmental period characterized by greater risk-taking and reward-seeking behaviors, influenced by both environmental and genetic factors. The single nucleotide polymorphism (SNP) rs1799971 in the μ-opioid receptor (OPRM1) gene has been implicated in reward processing (Ray et al., 2014) and substance use disorders (Miranda et al., 2010), where the minor G-allele is implicated in higher risk. Few studies have investigated the effects of this SNP on adolescent reward processing, and no studies have examined a substance-naïve population. To assess the effect of this allelic variation on reward processing before exposure to drugs and alcohol, we analyzed blood oxygen level-dependent (BOLD) response during a Wheel of Fortune (WoF) functional MRI task, as well as moderation by family history of alcohol use/abuse and beliefs about substance use.

Participants were typically developing alcohol and drug naïve youth aged 11-13, N = 115 (25 AG; 63 F), enrolled in the Adolescent Development Study, a prospective longitudinal neuroimaging study of substance use in adolescents. BOLD signal was acquired during the WoF task on a Siemens 3T scanner. Image preprocessing and analysis were conducted in SPM8. Adolescents completed a survey querying beliefs about alcohol use. Parents reported on family history of alcohol use/abuse via the family tree questionnaire.

A whole brain analysis of activation patterns during feedback for winning versus losing trials in the WoF task revealed a significant cluster of activation (466 voxels, $p = 0.019$ FWE cluster-corrected) in the right middle frontal gyrus (MFG; peak 24, 28, 44) for AA homozygotes greater than AG heterozygotes. This region is involved in goal planning (Fincham et al., 2002) and attention to positive emotions (Kerestes et a., 2012), possibly implying greater reflection on the reward feedback in the AA homozygotes compared to G-allele carriers. The reduced MFG response to reward in the G-allele carriers suggests that they are less stimulated by natural reward.

No significant difference was found in family history of alcohol abuse. However, a significant difference ($p = 0.002$) was found in the adolescents' beliefs about parental consumption of alcohol, such that G-allele carriers believed their parents drank more alcohol than AA homozygotes believed of their parents. Taken together, results showing a heightened awareness of parental alcohol consumption and decreased brain response to reward, suggest G-allele carriers may be at increased risk for substance use disorders.