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

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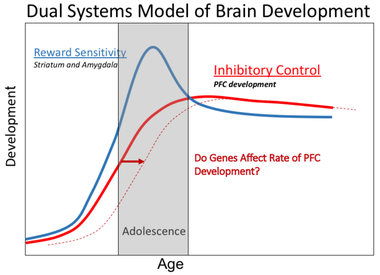
Introduction

Adolescent Development

- Adolescence is a period of development characterized by risk-taking and reward-seeking behaviors
- Brain development continues through adolescence into young adulthood, but rates of development vary in different parts of the brain
- **Dual Systems Model** – attributes high risk-taking during adolescence to slowed maturation of decision-making frontal cortex relative to reward-seeking striatal regions (Steinberg, 2010)

Dual Systems Model of Brain Development



Opioid Receptor Mu 1 (OPRM1)

The A118G (rs1799971) single nucleotide polymorphism (SNP) is relevant in:

- Alcohol use disorders (AUDs) in adolescents: G-carriers were 3x as likely to have an AUD, where 51.9% of those with an AUD had at least one G allele compared to 16.3% of adolescents without an AUD (Miranda et al., 2010)
- Pain management: G-carriers required greater doses (Chou et al., 2006a)
- Reward processing: in a study of participants with alcoholism, G-carriers had less frontal regulation when responding to reward stimuli (Ray et al., 2014)
- Treatment: Alcohol-dependent G-carriers had lower relapse rates after being treated with naltrexone (Chamorro et al., 2012)

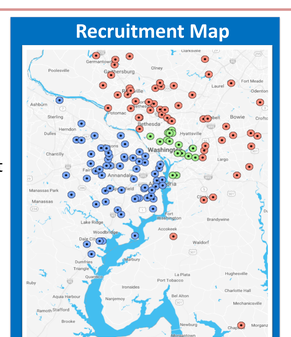
But opioid receptors respond to both exogenous (e.g. opiates) and endogenous (e.g. endorphins) opioids… No previous studies have examined effects of this SNP on adolescent brain development *prior to use initiation*

The Adolescent Development Study (ADS)

Study Sample

- The Adolescent Development Study (ADS) is a prospective longitudinal study of neurobehavioral development in the context of substance use
- Participants came in for 3 waves of data collection separated by ~18 months
- 147 participants recruited from in and around the District of Columbia

Recruitment Map



Inclusion Criteria: typically developing, drug and alcohol naïve, age 11-13

Exclusion Criteria: neurological disorder, substance users, left-handed, no genetics data, unusable imaging data

Current Analysis (*N* = 115):

	AA	AG
F	51	12
M	39	13
Total	90	25

Methods

Imaging and Wheel of Fortune (WoF) task

- Functional magnetic resonance imaging (fMRI) BOLD signal acquired with T2*-weighted gradient-echo planar imaging (EPI) on a Siemens 3T scanner
- Acquisition parameters: TR/TE 2500/30 ms, 90 ° flip angle, in-plane resolution 3.00 mm^2, 47 slices, slice resolution 3.00 mm
- Preprocessed and analyzed using SPM8 (Friston et al., 2007)

Wheel of Fortune
(Smith et al., 2009)

1. Participants were shown pie chart representing odds of winning specified amounts of money
2. They selected desired choice
3. They were shown whether they won or lost the amount

- Low risk choice: greater odds, less money
- High risk choice: lower odds, more money

Family History

- Family Tree Questionnaire (FTQ; Mann et al., 1985) - a brief pencil-and-paper questionnaire administered to participant's parent(s)
- Self-report of history of alcohol problems: first-degree (parents, siblings) and second-degree (grandparents, aunts/uncles)

Alcohol Expectancies

- Survey based on the expectancies scale by Grube et al. (1994); queried belief's about alcohol use
- Included beliefs about personal, peer and parental use, as well as peer and parental approval

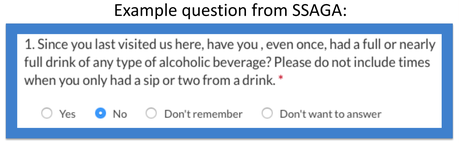
Genetics: OPRM1

- Analyzed the single nucleotide polymorphism A118G (rs1799971) in the OPRM1 gene
- Saliva collected through passive drool; DNA extracted from saliva via the methods of Freeman et al., 2003
- Taqman SNP Genotyping Assays were performed using an Allelic Discrimination Assay, in which samples were amplified by PCR, and a post-read was performed for analysis by automatic and manual clustering

Substance Use Survey

The alcohol and drug section of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA adolescent version; Bucholz et al., 1994) was used to obtain estimates of drug and alcohol consumption in the 2nd and 3rd waves of data collection

Example question from SSAGA:



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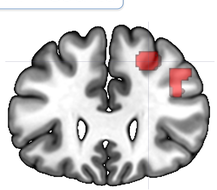
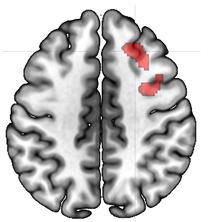
Results

fMRI Results



AA > AG for Wins > Losses in
Right Middle Frontal Gyrus



- Number of voxels: 466
- Peak coordinate: 24, 28, 44
- Peak t-Statistic: 4.106
- FWE-corrected p = 0.019*

Greater right middle frontal activation has been associated with attention to positive emotions by Kerestes et al. (2012) and goal planning by Fincham et al. (2002)

Reported Use at Follow-Up

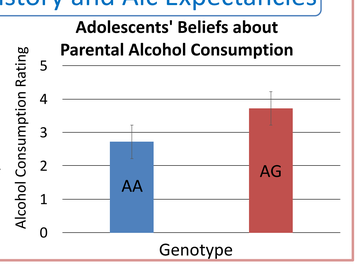
Reported Use in W2/W3	AA	AG
Use	26	10
No Use	64	15
OR [CI] = 1.6410 [0.6534 to 4.1215] p = 0.2918		

Family History and Alc Expectancies

Family History Density:
p = 0.506

Family History Parents:
p = 0.644

Alc Expectancy Result:
Adolescents' estimate of parental alcohol consumption
p = 0.002*



Conclusions

- Despite no difference in parents' reports of their own alcohol consumption between genotypes, adolescent G allele carriers believed that their parents consumed significantly more alcohol than did AA homozygotes
  - ➢ Suggests heightened awareness of parental alcohol consumption
- While the rates of substance use initiation reported at follow-up did not differ by OPRM1 genotype, the G allele carriers exhibit less prefrontal engagement to positive reward prior to initiation
  - ➢ Dampened response suggests they may need larger rewards to achieve the same level of gratification
  - ➢ We hypothesize that use may escalate more quickly in G-carriers, putting them at greater risk for addiction

Limitations

- ADS sample had no GG homozygotes
- Participants may have initiated substance after wave 3 of data collection

Future Analyses

- A future analysis will look at the fMRI data longitudinally and see whether this difference persists in waves 2 and 3: if it does not persist, that may suggest that this was a developmental delay in the G-carriers
- Analyze the *severity* of reported substance use between OPRM1 genotypes
- Follow up with ADS participants to record a fourth time point of substance use data, which may result in a greater difference between initiation rates and/or severity of substance use