The Thesis Committee for Valeria Tretyak
Certifies that this is the approved version of the following Thesis:

Subjective Response to Alcohol in Typically Developing Emerging Adults and Those with Bipolar Disorder, Associated Alcohol Use, and Orbitofrontal Gray Matter Volume

APPROVED BY
SUPERVISING COMMITTEE:

Kim Fromme, Supervisor

Elizabeth Lippard, Co-supervisor

Subjective Response to Alcohol in Typically Developing Emerging Adults and Those with Bipolar Disorder, Associated Alcohol Use, and Orbitofrontal Gray Matter Volume

By

Valeria Tretyak

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Abstract

Subjective Response to Alcohol in Typically Developing Emerging Adults and Those with Bipolar Disorder, Associated Alcohol Use, and Orbitofrontal Gray Matter Volume

Valeria Tretyak, MA

The University of Texas at Austin, 2019

Supervisors: Kim Fromme & Elizabeth Lippard

Co-occurring alcohol use disorders (AUDs) are highly prevalent in bipolar disorder, though the developmental etiology of this comorbidity remains unknown. A decreased subjective response (SR) to alcohol and differential structure and function of the orbitofrontal cortex (OFC) have been implicated in problematic alcohol consumption in typically developing populations. Differential structure of the OFC has been linked to alcohol use problems in bipolar disorder, yet the underlying mechanisms of this relation are unknown. In this preliminary investigation, SR to alcohol, recent alcohol use, and variation in OFC gray matter volume (GMV)—and associations among these factors—were investigated in 48 emerging adults (24 typically developing, mean age=21, 67% female; 24 bipolar disorder, mean age=21, 75% female). Clinical, behavioral, and structural magnetic resonance imaging data was collected, including Self-Rating of the Effects of Alcohol scale, recent alcohol use, and drinking motives. No significant between-group differences in SR or alcohol use were observed, but a decreased SR to alcohol was associated with greater recent alcohol consumption in both groups ($p<.05$).

Decreased SR to alcohol was associated with lower GMV in OFC in typically developing emerging adults, and greater GMV in OFC in those with bipolar disorder (group by SR interaction $p<.001$, uncorrected). In both groups, variation in OFC GMV was also differentially related to drinking motives ($p<.05$). Findings suggest a transdiagnostic association between SR to alcohol and increased alcohol consumption, with differences in OFC structure contributing to this relation. Longitudinal studies are needed to examine how these associations relate to risk/development of AUDs.

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Introduction

Although estimates vary (Di Florio et al., 2014) lifetime prevalence rates of alcohol use disorders (AUDs) as high as 60% have been reported in bipolar disorder; a rate that is 3-5 times higher than in the general population (Regier et al., 1990). Co-occurring AUDs in bipolar disorder have been associated with a phenomenological change in symptomatology (Cassidy et al., 2001; Strakowski et al., 2005; Frye & Salloum, 2006) contributing to increased severity and frequency of mood symptoms (Salloum et al., 2001; Salloum et al., 2002) risk-taking behaviors (Kathleen Holmes et al., 2009), suicide attempts (Oquendo et al., 2010; McGrady et al., 2017), and decreased treatment response (Strakowski et al., 2000). Yet, few studies have investigated etiological mechanisms that may underlie the development of comorbid AUDs in bipolar disorder (Strakowski et al., 2000; Le Strat & Gorwood, 2008; Yip et al., 2012; Balanzá-Martínez et al., 2015).

Neuroimaging evidence suggests an overlap in brain systems implicated in bipolar disorder and alcohol/substance use disorders (A/SUDs). Abnormalities in the structure and function of the prefrontal cortex (PFC), particularly within ventral PFC (vPFC) systems, are central to bipolar disorder (Kronhaus et al., 2006; Langan & McDonald, 2009; Strakowski et al., 2012). Abnormalities in the vPFC are also strongly implicated in AUDs (Adinoff, 2004; Sullivan & Pfefferbaum, 2005; Koob & Volkow, 2010; Goldstein & Volkow, 2011; Goodkind et al., 2015). This overlap in neuroanatomical regions may therefore represent a risk factor contributing to increased vulnerability for co-occurring AUDs in bipolar disorder.

Few studies have investigated the neural correlates of co-occurring AUDs in bipolar disorder. The few that have investigated comorbidity suggest it is associated with glutamergic system deficits (Nery et al., 2010) and disruptions in the function (Hassel et al., 2009) and structure (Nery et al., 2011) of the PFC. Whether these differences contribute to development of comorbidity or represent a consequence of problematic drinking remains unknown. Problematic drinking in individuals with bipolar disorder has been shown to exacerbate oxidative stress and neurotoxicity within the frontotemporal cortices (Chitty et al., 2013, 2014), suggesting some differences may result from problematic drinking. However, data from a longitudinal study in adolescents with bipolar disorder suggested lower gray matter volume (GMV) in vPFC systems, including the orbitofrontal cortex (OFC), may predate—and be associated with risk for—the development of A/SUDs (Lippard et al., 2017).

Lower GMV in the OFC has been reported in heavy drinkers (no AUD diagnosis (Heikkinen et al., 2017) and in abstinent individuals with a history of AUDs (Tanabe et al., 2009). Lower GMV in the PFC, including the OFC, in healthy adolescents has been prospectively associated with increased risk for the initiation of future alcohol/substance use (Cheetham et al., 2012; Cheetham et al., 2014) similar to prospective findings of variation in OFC within individuals with bipolar disorder who proceed to develop alcohol/marijuana use problems (Lippard et al., 2017). Longitudinal studies have also shown that reduced amygdala-OFC connectivity may predict increased alcohol use in adolescents and emerging adults (Peters et al., 2017).

How neuroanatomical variation in the OFC contributes to risk for AUDs, in both typically developing and psychiatric populations remains unknown. The OFC plays a prominent role in affect/emotion regulation (Bechara et al., 2000; Golkar et al., 2012), reward (Rolls, 2000) and stress-related processing (Pruessner et al., 2008), as well as impulse/behavioral control (Berlin et al., 2004; Lejuez et al., 2010). A role of the OFC in these processes/traits has been observed in both typically developing populations and in those with bipolar disorder (Altshuler et al., 2005; Bermpohl et al., 2010; Nusslock et al., 2012; Townsend & Altshuler, 2012). Additionally, changes in affect, reward, and stress-related processes (Park et al., 2004; Birch et al., 2008; Mohr et al., 2013)—behaviors subserved by the OFC—have been associated with differences in drinking motives, further suggesting variation in the OFC, and associated differences in behavior, may represent a risk factor for heavy alcohol use and development of addiction (Schoenbaum et al., 2006).

An alternative mechanism through which variations in the OFC may contribute to risk for developing AUDs is via an altered subjective response (SR) to alcohol (Le Strat & Gorwood, 2008). The OFC represents both a neuroanatomical target for the effects of drugs, and a central hub for integrating information from, and modulating reactivity to, drug administration in its connecting limbic brain regions (Volkow & Fowler, 2000). Variation in OFC may, therefore, contribute to differences in SR to alcohol. Decreased SR to alcohol, or needing more drinks to feel intoxication, is an established phenotypic risk factor for problematic drinking and the long-term development of AUDs (Schuckit, 1994; Schuckit et al., 2004; Trim et al., 2009; Quinn & Fromme, 2011). A decreased SR

to alcohol has been linked to future alcohol-related problems in adolescents with limited prior alcohol exposure (Schuckit et al., 2005) and in light drinkers (Schuckit & Smith, 2000), as well as when controlling for family history of AUDs, age of alcohol initiation, and baseline drinking patterns (Trim et al., 2009). In the OFC, changes in endogenous opioid ligand release have been associated with differential SR and problematic alcohol consumption in healthy adults (Mitchell et al., 2012), whilst baseline differences in OFC dopamine release and mGluR5 availability before acute alcohol intake have also been associated with variations in SR (Leurquin-Sterk et al., 2018). No studies have examined the relation between SR and its associations with alcohol use and OFC structure in typically developing emerging adults compared to those with bipolar disorder. To our knowledge, only one study has investigated SR to alcohol in the context of bipolar disorder, reporting a decreased SR to alcohol in a sample of young adult males with a broad bipolar phenotype defined by hypomanic experiences not a bipolar disorder diagnosis (Yip et al., 2012). Additionally, greater impulsivity—a trait observed in bipolar disorder (Najt et al., 2007) and behavior associated with variation in OFC structure (Berlin et al., 2004; Lejuez et al., 2010)—has been associated with differences in SR to alcohol (Leeman et al., 2014; Stangl et al., 2016; Westman et al., 2016; Berey et al., 2017). These results converge to support differences in SR to alcohol as a potential mechanism of risk for the development of problematic drinking in typically developing emerging adults and those with bipolar disorder.

The Current Study

This preliminary study investigated self-reported SR to alcohol and associated alcohol use in typically developing emerging adults and those with bipolar disorder type 1. Based on previous findings highlighting 1) variation in OFC GMV as a risk factor for future alcohol use in emerging adults and those with bipolar disorder, 2) linking variation in OFC with altered SR to alcohol in typically developing populations, and 3) implicating altered development of the OFC in bipolar disorder, we hypothesized that an interaction between bipolar disorder, OFC development, and SR to alcohol may increase risk for the development of co-occurring AUDs in bipolar disorder. Associations between SR to alcohol and variation in OFC GMV were modeled. Additionally, relations among SR to alcohol and OFC GMV with impulsivity and drinking motives respectively, were explored across both groups. We predicted that emerging adults with bipolar disorder would exhibit decreased SR to alcohol compared to typically developing emerging adults, and that decreased SR to alcohol would be associated with greater recent alcohol use and lower OFC GMV in both groups.

Method

Participants

Participants included 48 emerging adults (24 typically developing [age_{mean} ±standard deviation (SD)= 21±2; 67% female], 24 with bipolar disorder type I [age_{mean} ±SD= 21±2; 75% female]; see table 1). Diagnoses of bipolar disorder, A/SUDs, and anxiety disorders were confirmed using the Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV; First et al., 2015). Within the bipolar group, 11 participants (46%) were euthymic at the time of the scan, nine (38%) were depressed, and four (17%) were in an elevated (i.e., manic, hypomanic, or mixed) mood state. In the typically developing group, all participants were euthymic. Current mood symptoms at the time of assessment were determined using the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) and Young Mania Rating Scale (YMRS) (Young et al., 1978). Verbal comprehension and matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II; Wechsler, 2011) were used as a measure of full-scale intelligence quotient (FSIQ-2). All study procedures were approved by the Institutional Review Board and written consent was obtained from all participants.

Exclusion criteria included history of any major medical illness with possible neurological or central nervous system outcomes, history of moderate/severe AUDs, IQ<85, being pregnant, or having a medical condition/previous surgery preventing participation in an MRI scan. Outside of a moderate or severe AUD, participants were not excluded for SUDs/anxiety disorders to avoid recruitment of a *super healthy* group, and to increase generalizability of findings (Greene et al., 2016). Urinalysis was conducted on

neuroimaging day to assess for pregnancy and substance use. Participants were asked to abstain from any alcohol or drug use for 24-hours preceding the structural magnetic resonance imaging (sMRI) scan. On the day of scan, within the typically developing group, four tested positive for tetrahydrocannabinol (17%), one for amphetamines (4%), and one for benzodiazepines (4%). Within the bipolar disorder group nine tested positive for tetrahydrocannabinol (43%), one for phencyclidines (5%), one for methamphetamines (5%), and one for benzodiazepines (5%).

Measures

All participants completed the Self-Rating of the Effects of Alcohol scale (SRE; Schuckit et al., 1997a), a 12-item self-report retrospective measure of SR to alcohol that asks the number of drinks required to feel different alcohol effects (i.e. feel any different, feel a bit dizzy or begin to slur your speech, begin stumbling or walking in an uncoordinated manner, and pass out or fall asleep). The SRE is an established measure of SR to alcohol that has been prospectively associated with alcohol-related problems, quantity and frequency of alcohol consumption, and AUDs (Schuckit et al., 1997). Past month alcohol use was assessed using a modified version of the Daily Drinking Questionnaire (DDQ; Collins et al., 1985) to assess the heaviest drinking week (DDQ-H) over the past month (i.e. total drinking days for frequency; total drinks consumed for quantity). Additionally, participants were asked a standalone question assessing the maximum number of drinks consumed in 24-hours over the past three months, and at what age they initiated alcohol use (i.e. age of first drink, not just a sip from an adult's

glass, and not including drinking as part of religious ceremonies). Drinking motives were assessed using the Drinking Motives Questionnaire-Revised (DMQ-R: Cooper, 1994), a 20-item self-report questionnaire assessing social, coping, enhancement, and conformity drinking motives. Impulsivity was measured with the 30-item Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995), which provides a measure of total impulsivity and cognitive-attention, motor, and non-planning impulsivity subscores.

MRI Acquisition and Processing

High-resolution sagittal structural MRI images were acquired with a three-dimensional gradient echo (MPRAGE) T_1-weighted sequence on a 3-Tesla Siemens Skyra (Seimens, Erlangen, Germany) using a 32-channel head coil, and the following parameters: repetition time (TR)=1900ms, echo time (TE)=2.42ms, matrix=224x224, field of view=220x220mm^2, 192 one-mm slices without gap and one average. Statistical Parametric Mapping-12 (SPM12; http://www.fil.ion.ucl.ac.uk/spm) was used to pre-process MPRAGE images with the DARTEL toolbox as previously described (Lippard et al., 2017). Three participants in the bipolar disorder group did not complete a sMRI scan and were not included in the neuroimaging analyses.

Analyses

Demographic and Clinical Factors

All analyses were performed in R version 3.4.2 (R Core Team, 2017). *T*-tests, Chi-square, and Fisher's exact were used to assess between-group differences (bipolar

disorder vs. typically developing) in age, IQ, sex (female/male), race, mood symptoms over the last week (HAM-D, YMRS), and history of an AUD/SUD as appropriate.

Between-group Differences in Subjective Response, Alcohol Use, Drinking Motives, and Impulsivity

For the SRE, each participant's individual item responses were converted to z-scores and averaged to produce an SRE_{mean} z-score. Standardized person-mean imputations were used to avoid assumptions that all items have a comparable distribution and prevent items with higher means from disproportionately influencing summary scores (Lee et al., 2015). Two-sample *t*-tests were conducted to assess between-group differences in SRE_{mean} z-scores, impulsivity scores, total drinking days, and total drinks consumed during heaviest drinking week. Mann-Whitney U tests were conducted to assess between-group differences on all non-normally distributed variables (Shapiro Wilke test, $p<.05$), including maximum drinks consumed during 24-hours over the past three months and drinking motives.

Associations Between Subjective Response to Alcohol and Recent Alcohol Consumption

Multiple linear regression was performed across groups with group (bipolar disorder vs. typically developing), SRE_{mean} z-scores, and their interaction as predictor variables, with biological sex and age of alcohol initiation as covariates. Parallel multiple linear regression models were performed within each group, to confirm within group associations. In all of our analyses, we controlled for biological sex in line with evidence that men continue to consume more alcohol and engage in binge drinking at higher rates

than women (Kanny et al., 2018) and that sex-differences may contribute to alcohol problems in bipolar disorder (Lippard et al., 2017). We controlled for age of alcohol initiation in light of evidence that earlier alcohol initiation negatively impacts brain structure and function, including the PFC (Luciana et al., 2013; Nguyen-Louie et al., 2018), and contributes to subsequent alcohol-related problems and AUDs (Grant, 1998; Hingson et al., 2000).

SRE Relations to OFC GMV

SPM12 was used to model the relation between SRE_{mean} z-scores and GMV in the OFC across all participants, with group, sex, and age of alcohol initiation as covariates. A separate model investigating group by SRE_{mean} z-score interaction was also conducted, alongside parallel models assessing the relation between SRE_{mean} z-scores and OFC GMV within each group. Findings within the OFC, our *a priori* region of interest (ROI), were considered significant at $p<.001$ (uncorrected) and clusters$\geq$20 voxels. Findings outside of the OFC were considered significant at $p<.05$ family-wise error corrected, and a threshold of 10 voxels for multiple comparisons. Mean GMV in OFC clusters showing a significant relation with SRE_{mean} z-scores in each model, was calculated and extracted for use in subsequent post-hoc analyses. The relation between SRE_{mean} z-scores and OFC GMV (extracted GMV from clusters showing a significant group by SRE_{mean} z-score interaction) was examined within each group, to explore group differences underlying a significant group by SRE_{mean} z-score interaction. Post-hoc sensitivity analyses investigating group by SRE_{mean} z-score interactions, and within group SRE_{mean} z-score relations to OFC GMV, were conducted—using extracted GMV from clusters showing a

significant relation to SRE_{mean} z-score as the dependent variable—after excluding 1) individuals with current/past mild AUD and 2) positive urinalysis toxicology screen.

SRE Relations with Impulsivity and OFC GMV Relations to Drinking Motives, Drinking Patterns, and Clinical Characteristics

Within each group, exploratory multiple linear regression was conducted to examine the relation between SRE and impulsivity scores. Parallel exploratory analyses were performed to examine relations between OFC GMV and drinking motives and recent drinking patterns. As this is the first study investigating SR to alcohol and associated OFC GMV in bipolar disorder, relations among OFC GMV and SRE_{mean} z-scores with clinical characteristics and medication classes that were present/absent in $N \geq 5$ participants were explored within the bipolar disorder group. Clinical characteristics included mood state (depressed vs. euthymic), past week depression and manic mood symptoms (HAM-D and YMRS), past-year rapid cycling (yes/no), lifetime psychosis (yes/no), history of suicide attempt(s) (yes/no), comorbid anxiety disorder (yes/no), current comorbid cannabis use disorder (yes/no), and if medicated (yes/no), or taking an antipsychotic, anticonvulsant, lithium, or a sedative/antihistamine (yes/no).

Results

Demographic and Clinical Factors Analyses

Current depressive symptoms (HAM-D scores) were higher in the bipolar disorder, compared to the typically developing group ($U=489$, $p<.001$). No other factors differed between groups (see Table 1).

Between-group Differences in Subjective Response, Alcohol Use, Drinking Motives, and Impulsivity

Emerging adults with bipolar disorder had significantly higher total BIS-11 ($t_{(46)}=4.17$, $p<.001$), non-planning ($t_{(46)}=3.81$, $p<.001$), and cognitive-attentional ($t_{(46)}=4.43$, $p<.001$) impulsivity scores. No other significant between-group differences were observed (see table 2).

Associations Between Subjective Response to Alcohol and Recent Alcohol Consumption

Across all participants, higher SRE_{mean} z-score ($\beta=3.201$, $p<.001$) was associated with greater maximum drinks consumed in 24-hours over the past three months ($\beta=3.201$, $p<.001$; $F_{(4,43)}=10.12$, $p<.001$, $R^2=.48$) and greater total drinks consumed during the past-month heaviest drinking week ($\beta=5.389$, $p<.001$; $F_{(4,43)}=6.54$, $p<.001$, $R^2=.38$). There were no significant group by SRE_{mean} z-score interactions on either of these drinking variables. Within both groups, higher SRE_{mean} z-score was associated with greater maximum drinks consumed in 24-hours over the past three months (Typically Developing: $\beta=2.682$, $p<.01$; $F_{(3,20)}=4.691$, $p<.05$, $R^2=.41$; Bipolar: $\beta=2.908$, $p<.01$; $F_{(3,20)}=17.77$, $p<.001$, $R^2=.73$) and greater total drinks consumed during the past-month

heaviest drinking week (Typically Developing: β=4.479, p<.05; $F_{(3,20)}$= 2.819, p=.065, R^2=.30; Bipolar: β=6.304, p<.01; $F_{(3,20)}$=6.202, p<.01, R^2=.48; see figure 1). Findings remained significant in post-hoc sensitivity analyses after excluding individuals with current/past mild AUD and positive urinalysis toxicology screen.

SRE Relations to OFC GMV

Across all participants, SRE_{mean} z-score was not related to GMV in the OFC. However, a significant group by SRE_{mean} z-score interaction on GMV in right OFC was observed (Brodmann area [BA] 11, MNI coordinates: x=15mm, y=41mm, z=-20mm, cluster=20 voxels). Post hoc within group analysis revealed, higher SRE_{mean} z-score was associated with lower GMV in this OFC cluster in typically developing emerging adults (β=-.025, p<.05; $F_{(3,20)}$=3.179, p=.05, R^2=.32), and conversely with greater GMV in this OFC cluster in the bipolar disorder group (β=.058, p=.001; $F_{(3,17)}$=8.577, p=.001, R^2=.60). In SPM12, higher SRE_{mean} z-score within the typically developing group was associated with lower GMV in the right vPFC (x=20mm, y=32mm, z=-3mm, cluster=61 voxels) extending into the right OFC (BA47/11; with a secondary cluster peak at x=23mm, y=27mm, z=-12mm). Higher SRE_{mean} z-score within the bipolar disorder group was associated with greater GMV in bilateral OFC (left BA11, x=-15mm, y=41mm, z=-18mm, cluster=68 voxels; right BA11, x=17mm, y=41mm, z=-18mm, cluster=20 voxels). No areas of significance were observed outside of our *a priori* ROI. Findings remained significant in post-hoc sensitivity analyses after excluding individuals with current/past mild AUD and positive urinalysis toxicology screen.

SRE Relation to Impulsivity and OFC GMV Relations to Drinking Motives, Drinking Patterns, and Clinical Characteristics

SRE: Relation to Impulsivity

In typically developing participants, SRE_{mean} z-score was not related to impulsivity scores. In those with bipolar disorder, higher SRE_{mean} z-score was associated with greater total (β=.032, $p<.05$; $F_{(3,20)}$=5.549, p=.01, R^2=.45), non-planning (β=.101, p=.01; $F_{(3,20)}$=6.75, $p<.01$, R^2=.50), and motor (β=.078, $p<.05$; $F_{(3,20)}$=5.57, p=.01, R^2=.46) impulsivity scores.

OFC GMV: Relations to Drinking Motives, Drinking Patterns, and Clinical Characteristics

For typically developing participants, lower GMV in right vPFC (extracted from within-group analysis) was associated with greater number of maximum drinks consumed in 24-hours over the past three months (β=-.005, $p<.05$; $F_{(3,20)}$=4.436, $p<.05$, R^2=.40) and greater total drinks consumed during the past-month heaviest drinking week (β=-.002, $p<.05$; $F_{(3,20)}$=3.718, $p<.05$, R^2=.36). Additionally, lower GMV in this vPFC cluster was associated with increased social drinking motives (β=-.002, $p<.05$; $F_{(3,20)}$=3.592, $p<.05$, R^2=.35).

For those with bipolar disorder, lower GMV in the OFC (extracted from cluster showing significant group by SRE_{mean} z-score interaction) was associated with decreased social (β=.005, $p<.001$; $F_{(3,17)}$=10.76, $p<.001$, R^2=.66), enhancement (β=.005, p=.01; $F_{(3,17)}$=4.844, p=.01, R^2=.46), and conformity drinking motives (β=.004, p=.045;

$F_{(3,17)}$=3.419, p<.05, R^2=.38). Lower GMV in this cluster was also associated with being unmedicated (β=-.060, p<.05; $F_{(3,17)}$=3.62, p<.05, R^2=.39). Lower GMV (extracted from within-group analysis) in bilateral OFC was associated with decreased social (right OFC: β=.004, p<.01; $F_{(3,17)}$=4.906, p=.01, R^2=.46; left OFC: β=.003, p<.05; $F_{(3,17)}$=3.906, p<.05, R^2=.41) and decreased enhancement drinking motives in the left OFC: β=.004, p<.05; $F_{(3,17)}$=3.909, p<.05, R^2=.42). Additionally, lower GMV in the left OFC cluster was associated with fewer maximum drinks consumed in 24-hours over the past three months (β=.011, p=.01; $F_{(3,17)}$=5.069, p=.01, R^2=.47).

Discussion

To our knowledge, this is the first study examining SR to alcohol, drinking patterns, and variation in OFC GMV in an emerging adult sample with a bipolar disorder type I diagnosis. We predicted that emerging adults with bipolar disorder would exhibit decreased SR to alcohol compared to typically developing emerging adults, and that decreased SR to alcohol would be associated with greater recent alcohol use and lower OFC GMV in both groups. Though no between-group differences in SRE_{mean} z-scores or recent drinking patterns were observed, a decreased SR to alcohol was transdiagnostically associated with recent quantity, but not frequency, of drinking (total drinks during past-month heaviest drinking week and maximum drinks in 24-hours during past three months) in both groups. Decreased SR to alcohol was associated with lower OFC GMV in typically developing emerging adults, and conversely greater OFC GMV in those with bipolar disorder. Results support that the OFC—and possibly developmental differences in the OFC—may contribute to altered SR to alcohol and increased alcohol consumption in both typically developing emerging adults and those with bipolar disorder.

A decreased SR to alcohol, or needing more drinks to experience intoxication, is a well-known phenotypic risk factor for heavy drinking and the development of future AUDs (Schuckit, 1994; Schuckit et al., 2004; Trim et al., 2009; Quinn & Fromme, 2011). While Yip and colleagues (2012) previously reported a decreased SR to alcohol in a group of young adult males with a broad bipolar phenotype following a within-subject alcohol challenge, we did not find a significant between-group difference in SR to

alcohol. However, greater SRE_{mean} z-scores (or a decreased SR to alcohol) was associated with greater quantity of recent alcohol use in both the typically developing and bipolar disorder groups. Findings therefore suggest a transdiagnostic relation between decreased SR to alcohol and greater quantity of alcohol use. Combined with prior evidence (Yip et al., 2012), findings also suggest variability in SR to alcohol within the context of bipolar disorder—as previously reported in typically developing populations—which may in turn relate to differential alcohol consumption and, while speculative, prospective risk for development of comorbid AUDs.

Though the developmental mechanisms contributing to differences in sensitivity to alcohol are unknown, our findings suggest that variation in OFC structure is associated with differences in SR to alcohol in both groups. Within the typically developing group, decreased SR to alcohol was associated with lower OFC GMV, with lower OFC GMV also associated with greater alcohol consumption and social drinking motives. These findings support prior evidence linking differential alcohol-induced reactivity in the PFC with decreased levels of subjective intoxication (Tolentino et al., 2011; Paulus et al., 2012; Schuckit et al., 2012), changes in endogenous opioid ligand release in the OFC with alterations in SR and heavy drinking patterns (Mitchell et al., 2012), and increased social drinking motives with greater alcohol consumption (Van Damme et al., 2013). While some individuals presented with a current/history of mild AUD, results remained significant after excluding these participants in post-hoc sensitivity analyses.

In bipolar disorder, decreased SR to alcohol was associated with greater OFC GMV. Exploratory analyses in this group indicated that lower OFC GMV was further

associated with decreased social and enhancement drinking motives and decreased alcohol consumption. While speculative, factors relating to illness heterogeneity may have influenced the relation between OFC GMV and SR to alcohol. Continued investigation is needed to better understand how clinical, psychosocial, and environmental factors may impact these relations. Though the current sample represents a generalizable group of emerging adults with bipolar disorder—presenting with a history of suicide attempt(s), lifetime psychosis, comorbid A/SUDs and anxiety disorders, similar to other comparable age study samples—many were recently diagnosed after experiencing their first manic episode. Some of those individuals—including those with greater illness severity—may have reduced their drinking in adherence to their pharmacotherapeutic regiments, and therefore exhibited decreased social and enhancement drinking motives. Longitudinal studies with larger and more diverse samples with bipolar disorder are crucial for capturing developmental/clinical changes that may occur over time, and may in turn, prospectively contribute to differences in SR, drinking patterns, and the structure and function of the OFC. A recent six-year longitudinal study found that lower GMV in OFC prospectively distinguished those with bipolar disorder who subsequently developed alcohol use problems (Lippard et al., 2017). Thus, while those with lower OFC GMV in this study may not currently exhibit heavy drinking patterns, they may still be at-risk for developing future problematic drinking.

We hypothesize that altered development of the OFC may have contributed to these results—with additional clinical/psychosocial factors moderating these relations in bipolar disorder. In typically developing populations, the adolescent/emerging adulthood

epoch represents a critical window of development in the vPFC, including the OFC (Gogtay et al., 2004; Hooper et al., 2004; Nelson & Guyer, 2011). Maturation in these neural systems coincides with changes in impulsivity (Chambers & Potenza, 2003). Greater impulsivity is an established risk factor for the initiation of problematic drinking (Dick et al., 2010), and has also been associated with differential SR to alcohol (Stangl et al., 2016; Westman et al., 2016; Berey et al., 2017). In bipolar disorder, abnormalities in the PFC, including the OFC, are believed to be progressive (Strakowski et al., 2012; Najt et al., 2016; Weathers et al., 2018), with greater abnormalities evolving during the adolescent/emerging adult period. Genes implicated in SR to alcohol and alcohol consumption (Ray et al., 2013; Otto et al., 2017; Leurquin-Sterk et al., 2018) have also been implicated in impulsivity (Isherwood et al., 2015; Pfeifer et al., 2015) and brain development (Drouin-Ouellet et al., 2011; Ballester-Rosado et al., 2016), with some of these genes such as OPRM1 showing differential expression in the OFC in bipolar disorder (Ryan et al., 2006). It is possible that prospective investigation of this bipolar disorder sample may reveal differences in SR to alcohol and alcohol use patterns over time.

Prior evidence suggests that disorder-related impulsivity may increase risk for problematic alcohol consumption in bipolar disorder (Najt et al., 2007). While those with bipolar disorder in our study exhibited greater impulsivity scores than the typically developing group, they did not differ in their recent alcohol use patterns. Similarly, Lippard and colleagues (2017) did not observe differences in impulsivity in youth with bipolar disorder who prospectively developed alcohol use problems, compared to those

who did not. We did, however, observe associations between impulsivity scores and variation in SR to alcohol in bipolar disorder. While speculative, impulsivity may also impact maintenance/escalation of risky drinking behavior and be associated with development of AUDs overtime.

Caution should be taken in interpreting results from this preliminary cross-sectional study due to the sample size and heterogeneous characteristics in the bipolar disorder group. Lower OFC GMV was observed in participants with bipolar disorder who were unmedicated at the time of the scan, compared to those who were taking medication. Exploratory analyses did not indicate any other significant effects of psychotropic medications, past-year rapid cycling, lifetime psychosis, history of suicide attempt, anxiety disorders, history/current AUD, or current cannabis use disorder comorbidity, on either SR to alcohol or OFC GMV. Future longitudinal studies with larger sample sizes—capable of controlling for, and investigating, clinical factors—are needed to better understand mechanisms that may contribute to risk, and directly relate to the development of AUDs over time. This includes investigations of genes that may moderate/mediate relations between SR to alcohol and OFC structure, alongside longitudinal designs directly investigating differential development of the OFC. Future investigations should aim to include non-retrospective measures of SR to alcohol, through the use of alcohol administration challenges. Despite this, however, the measure of SR used in this study (SRE) has been shown to correlate with SR reported during an alcohol administration paradigm in the same group of individuals up to 15 years prior (Schuckit et al., 1997). Alcohol administration challenges, utilizing functional imaging

protocols, may be used to better examine SR to alcohol and its relation to the structure/function of the OFC in bipolar disorder. Measures designed to assess more stimulating responses to alcohol—in contrast to the SRE which is designed to capture a decreased SR to alcohol—may reveal greater between-group differences in SR in bipolar disorder. For example, findings in adults with schizophrenia (D'Souza et al., 2006) support the differentiator model (Newlin & Thomson, 1990) of SR to alcohol. This model proposes increased risk for AUDs develops as a result of a biphasic response to alcohol, characterized by increased sensitivity to the stimulating effects of alcohol at the ascending limb of the blood alcohol concentration (BAC) curve and decreased sensitivity to the sedative effects at the descending limb of the BAC curve. While the low level of SR model has been extensively studied (Morean & Corbin, 2010), it may fail to account for the underlying mechanisms of the motivational aspects of drug-seeking behaviors, such as their addictive and rewarding properties (King et al., 2002). In light of these findings and the high genetic overlap between schizophrenia and bipolar disorder (Consortium, 2013) further research investigating a differential SR to alcohol and its relation to alcohol use patterns in bipolar disorder is needed.

Conclusion

This study indicates that differences in SR to alcohol may represent a transdiagnostic risk factor for increased alcohol use, and that variation in OFC GMV may contribute to differences in SR to alcohol in both typically developing emerging adults and those with bipolar disorder. The relation between alcohol use and bipolar disorder is

a multifaceted phenomenon (Strakowski & DelBello, 2000; Goldberg, 2001), that is significantly more complex than the commonly held self-medicating hypothesis. Continued efforts are needed to build a greater understanding of the development of this comorbidity as it relates to neural development and its influence on SR to alcohol, in search of novel biomarkers as targets for early intervention initiatives and identification of risk.

Figures

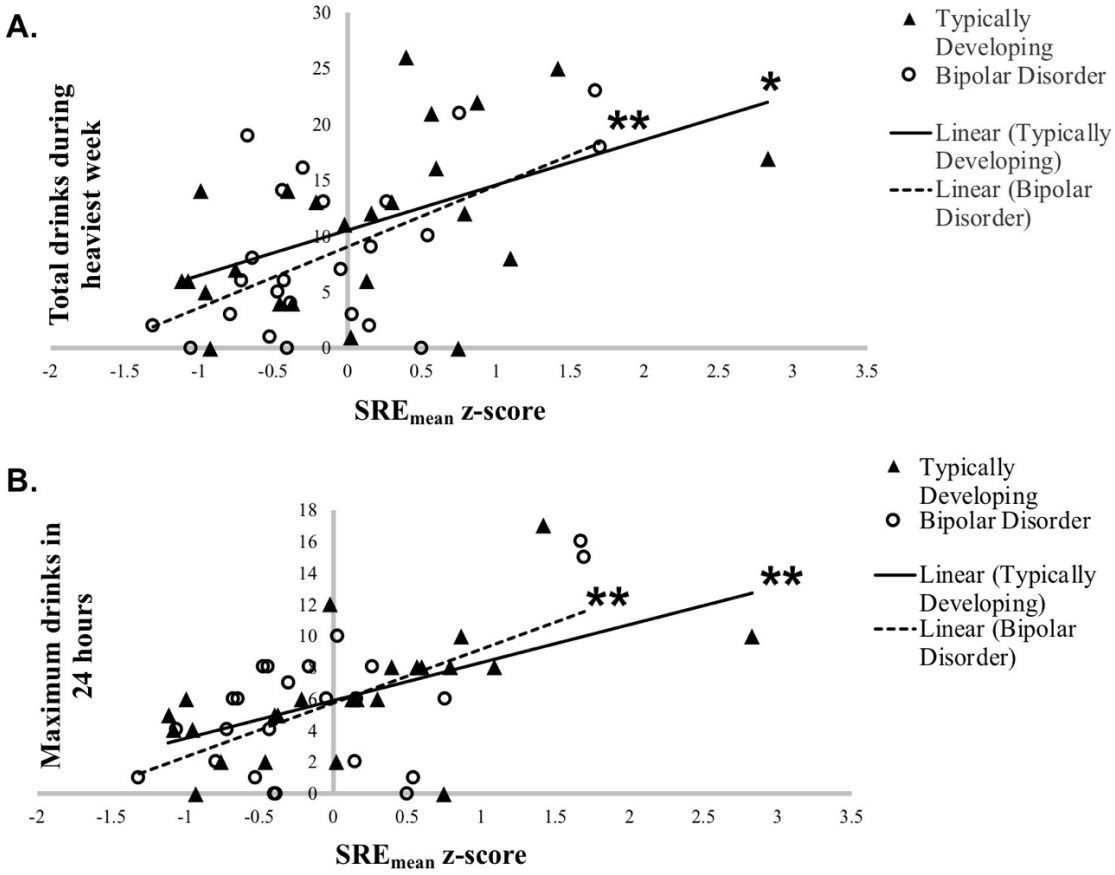

Figure 1. Relations between subjective response to alcohol and recent alcohol use

A. Relation between mean Self-Rating of the Effects of Alcohol Scale $(SRE)_{mean}$ z-scores and total drinks consumed during the past-month heaviest drinking week stratified by group (Typically Developing: N=24; Bipolar Disorder type I: N=24). ** p<.01, * p<.05.

B. Relation between mean SRE_{mean} z-score and maximum drinks consumed in 24-hours over the past three months stratified by group. ** p<.01, * p<.05

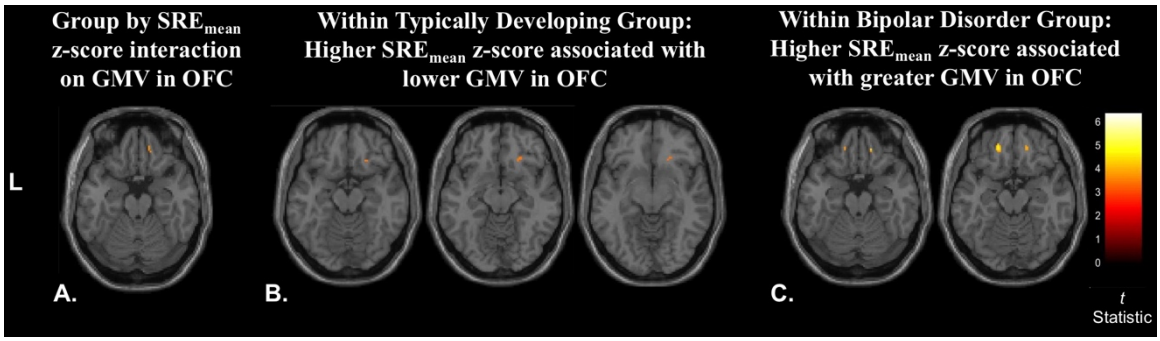

Figure 2. Areas of gray matter volume (GMV) that related to subjective response to alcohol

A. The axial-oblique images show the OFC region that showed a significant group (Bipolar: N=21, Typically Developing N=24) by SRE_{mean} z-score interaction. Higher SRE_{mean} z-score was associated with lower GMV in this OFC cluster in typically developing emerging adults, and conversely greater GMV in this OFC cluster in the bipolar disorder group. B. Axial-oblique images show within typically developing group negative relations between SRE_{mean} z-score and right ventral prefrontal cortex GMV, with this cluster extending into the right OFC. C. Axial-oblique images show within bipolar disorder group positive relation between SRE_{mean} z-score and GMV in bilateral OFC. Significance threshold is $p<.001$, uncorrected; clusters>20 voxels. Left of figure denotes left side of brain. The color bar represents the range of T values.

Tables

Table 1. Demographic and clinical factors stratified by group

		Typically developing (N=24)	*Bipolar disorder (N=24)*	*p value*
Demographics	Mean Age (SD)	21.0 (2)	21.4 (2)	*0.547*
	Number of Females (%)	16 (67)	18 (75)	*0.525*
	Mean WASI-II FSIQ-2[1] (SD)	119.6 (12)	116.5 (11)	*0.347*
	Caucasian/White (%)	12 (50)	13 (51)	*0.773*
	Hispanic/Latino (%)	7 (29)	5 (21)	*0.505*
	African/African American/Black (%)	0	2 (8)	*0.489* [F]
	Asian (%)	3 (13)	2 (8)	*1.000* [F]
	Mixed Race (%)	2 (8)	2 (8)	*1.000* [F]
Clinical Factors	**Mood State:**			
	Euthymic (%)	24 (100)	11 (46)	***< 0.001***
	Depressed (%)	0	9 (38)	***0.002*** [F]
	Elevated (%)[2]	0	4 (17)	*0.109* [F]
	Mood Symptoms:			
	Mean HAM-D Score (SE)	2.6 (1)	9.3 (1)	***< 0.001*** [U]
	Mean YMRS Score (SE)	0.6 (0.3)	1.6 (0.8)	*0.8071* [U]
	Rapid Cycling (%)[3]	-	6 (25)	***0.022*** [F]
	Lifetime Psychosis (%)	-	13 (54)	***< 0.001*** [F]
	Lifetime suicide attempt (%)	-	8 (33)	***0.004*** [F]
Comorbidities	**Current Alcohol Use Disorders (AUDs):**			
	AUD (mild)	0	2 (8)	*0.489* [F]
	Past Alcohol Use Disorders (AUDs):			
	AUD (mild)	2 (8)	4 (17)	*0.666* [F]
	Current Substance Use Disorder (SUDs):			
	Cannabis Use Disorder (mild)	1 (4)	4 (17)	*0.348* [F]
	Cannabis Use Disorder (moderate)	1 (4)	1 (4)	*1.000* [F]
	Cannabis Use Disorder (severe)	1 (4)	2 (8)	*1.000* [F]
	Sedative Use Disorder (severe)	0	1 (4)	*1.000* [F]
	Past Substance Use Disorder (SUDs):			
	Cannabis Use Disorder (mild)	1 (4)	0	*1.000* [F]
	Cannabis Use Disorder (severe)	0	1 (4)	*1.000* [F]
	Stimulant Use Disorder (severe)	0	1 (4)	*1.000* [F]
	Anxiolytic Use Disorder (moderate)	0	1 (4)	*1.000* [F]
	Sedative Use Disorder (mild)	0	1 (4)	*1.000* [F]

Table 1 (continued)

	Anxiety Disorders[4]	-	8 (33)	***0.004*** [F]
Medications	Unmedicated at scan (%)	-	5 (21)	-
	Antipsychotic (%)	-	10 (42)	-
	Anticonvulsant (%)	-	8 (33)	-
	Antidepressant / SSRIs (%)	-	3 (13)	-
	Stimulant (%)	-	4 (17)	-
	Lithium (%)	-	8 (33)	-
	Anxiolytics (%)	-	3 (13)	-
	Antihypertensives (%)	-	2 (8)	-
	Sedatives/Antihistamines (%)	-	7 (29)	-

Between-group (bipolar disorder vs. typically developing) differences in age and FSIQ-2 were compared using a two-sample t-test. All other factors were examined with a Mann-Whitney-Wilcoxon Test, Chi-square or Fisher Exact tests where appropriate. [F] represents p-value calculated with Fisher exact test. [U] represents p-value calculated with a Mann-Whitney-Wilcoxon Test. [1] FSIQ-2 represents the composite score for the full-scale intelligence quotient comprising verbal comprehension and matrix reasoning subtests on the Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II). [2] Elevated mood includes participants in hypomanic, mixed, and manic mood states. [3] Rapid Cycling reflects past-year rapid cycling in BD participants. [4] Anxiety disorders included generalized anxiety disorder and panic disorder.

Table 2. Subjective response to alcohol, recent alcohol use patterns, drinking motives, and impulsivity stratified by group

		Typically developing (N=24)	*Bipolar disorder (N=24)*	
		Mean (SE)	***Mean (SE)***	***p value***
Subjective Response to Alcohol (SRE) [1]	Average SRE z-scores	0.1 (0.2)	- 0.1 (0.2)	*0.384*
Recent Alcohol Use (DDQ-H [2] & individual question)	Total Drinking Days During Heaviest Drinking Week (past 30 days)	2.7 (0.3)	2.8 (0.4)	*0.877*
	Total Drinks Consumed During Heaviest Drinking Week (past 30 days)	11.0 (1.5)	8.5 (1.5)	*0.243*
	Maximum Drinks Consumed During 24-Hour Period (past three months)	6.2 (0.8)	5.4 (0.9)	*0.417* [U]
Drinking Motives (DMQ-R) [3]	Social Drinking Motives	18.2 (1.5)	16.2 (1.7)	*0.323* [U]
	Coping Drinking Motives	7.0 (0.8)	9.8 (1.7)	*0.361* [U]
	Enhancement Drinking Motives	14.7 (1.5)	14.2 (1.5)	*0.833* [U]
	Social Pressure and Conformity Drinking Motives	6.5 (0.8)	8.2 (1.2)	*0.293* [U]
Impulsivity (BIS-11) [4]	BIS-11 TOTAL	55.7 (1.5)	66.3 (2.1)	***< 0.001***
	BIS-11 Non-planning Impulsivity	21.2 (0.7)	25 (0.7)	***< 0.001***
	BIS-11 Motor Impulsivity	19.9 (0.6)	22.0 (0.9)	*0.050*
	BIS-11 Cognitive Impulsivity	14.6 (0.6)	19.4 (0.9)	***< 0.001***

Between group (bipolar vs. typically developing) differences were assessed with two sample t-tests and Mann-Whitney-Wilcoxon Test. [U] represents p-value calculated with Mann-Whitney-Wilcoxon Test. [1] Subjective response to alcohol was measured with the Self-Rating of the Effects of Alcohol (SRE) form. Participant's SRE scores were

standardized by converting to z-scores and averaged to provide an $(SRE)_{mean}$ z-scores for each participant. [2] Recent alcohol use was measured with the Daily Drinking Questionnaire adapted for heaviest drinking week over the past 30 days (DDQ-H) and a stand-alone question assessing the maximum number of drinks consumed in 24-hours over the past three months. [3] Drinking Motives Questionnaire – Revised (DMQ-R) was used to assess drinking motives. The DMQ-R consists of 20 items that are rated on a 5-point Likert scale ranging from 1-never/almost never to 5-almost always/always. [4] Barratt Impulsiveness Scale (BIS-11) was used to assess impulsivity. The BIS-11 consists of 30 items that are rated on a 4-point Likert scale ranging from 1-rarely/never to 4-almost always/always.

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