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Brain Circuitry Associated with the Development of Substance Use in Bipolar Disorder and Preliminary Evidence for Sexual Dimorphism in Adolescents

Running Title: Bipolar Risk Circuitry for Substance Problems

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ABSTRACT

Substance use disorders (SUDs) and mood disorders are highly comorbid and confer a high risk for adverse outcomes. However, data are limited on the neurodevelopmental basis of this comorbidity. Substance use initiation typically occurs during adolescence and gender-specific developmental mechanisms are implicated. In this study we investigate the association of regional gray matter volume (GMV) with subsequent substance use problems in adolescents with bipolar disorder (BD) and examine these associations for females and males.

Thirty DSM-IV diagnosed BD adolescents with minimal alcohol/substance exposure (50% female) completed baseline structural magnetic resonance imaging scans. At follow-up (on average 6 years post-baseline), subjects were administered the CRAFFT interview and categorized into those scoring at high ($\geq$2: $\text{CRAFFT}_{\text{HIGH}}$) versus low (<2: $\text{CRAFFT}_{\text{LOW}}$) risk for alcohol/substance problems.

Lower GMV in prefrontal, insular, and temporopolar cortices were observed at baseline among adolescents with BD reporting subsequent alcohol and cannabis substance use compared to adolescents with BD who did not ($p<0.005$, clusters $\geq$20 voxels). Lower dorsolateral prefrontal GMV was associated with future substance use in both females and males. In females, lower orbitofrontal and insula GMV was associated with future substance use; while in males, lower rostral prefrontal GMV was associated with future use. Lower orbitofrontal, insular and temporopolar GMV was observed in those who transitioned to smoking tobacco. Findings indicate GMV development is associated with risk for future substance use problems in adolescents with BD, with results implicating GMV development in regions subserving emotional regulation in females and regions subserving executive processes and attention in males.

SIGNIFICANCE STATEMENT

Bipolar Disorder (BD) and substance use disorders (SUDs) are highly comorbid. This comorbidity often develops in adolescence and is associated with adverse outcomes. We prospectively investigated the relationship of gray matter volume (GMV) to subsequent substance use problems in adolescents with BD. Results indicate substance use problems in BD are associated with lower dorsolateral prefrontal GMV in females and males, lower orbitofrontal and insula GMV in females, and lower rostral prefrontal GMV in males. These common and gender-related findings point to regulatory brain systems that may underlie comorbid substance abuse and serve as targets for early detection and intervention strategies.

INTRODUCTION

Mood disorders and substance use disorders (SUDs) have most often been studied as distinct conditions, yet evidence suggests most individuals with a mood disorder or SUD develop comorbidity (Kessler et al. 1994). Bipolar Disorder (BD) is associated with an especially high rate of comorbid SUDs (DelBello et al. 1999; Goldberg 2001; Heffner et al. 2011; Krishnan 2005). An estimated 60% of individuals with BD present with lifetime prevalence of substance abuse (Cassidy et al. 2001). In adolescents/young adults with BD, especially high rates of alcohol, cannabis, and tobacco use are reported (Hermens et al. 2013; Leweke and Koethe 2008).

Comorbid SUD in BD is associated with more severe illness outcomes, including increased impulsivity (Heffner et al. 2012; Swann et al. 2004; Swann et al. 2008), more severe mood episodes (Nolen et al. 2004; Strakowski and DelBello 2000; Strakowski et al. 2007), cognitive deficits (Levy et al. 2008; Marshall et al. 2012), and an increase in the already high risk of suicide attempts (Dalton et al. 2003; Swann et al. 2005). Despite the importance of understanding this comorbidity, there has been a paucity of study on the neural mechanisms underlying its development.

Neuroimaging studies suggest abnormalities in prefrontal cortex (PFC) neural systems are central in BD. These systems subserve emotion and impulse regulation and include ventral, rostral and dorsal PFC regions, as well as PFC projection sites, including insular and temporopolar cortices and amygdala (Blond et al. 2012; Strakowski et al. 2012). Evidence also suggests abnormalities in PFC system developmental trajectories in adolescents/young adults with BD (Blond et al. 2012; Blumberg et al. 2004; Gogtay et al. 2007; Kalmar et al. 2009; Najt et al. 2015). The neural systems believed to be involved in BD have substantial overlap with the neural systems implicated in SUDs (Adinoff 2004; Goldstein and Volkow 2011; Koob and Volkow 2010; Sullivan and Pfefferbaum 2005), suggesting vulnerability for comorbidity may be related to anatomically overlapping brain regions.

Bipolar Disorder and Comorbid Substance Use Disorders

Few neuroimaging studies have examined SUD comorbidity in BD. Adults with BD and comorbid alcohol abuse/dependence compared to adults with BD without SUDs were found to have lower gray matter volume (GMV) (Nery et al. 2011), functional abnormalities (Hassel et al. 2009), and glutamatergic system deficits in dorsal PFC (Nery et al. 2010). However, tobacco use by these subjects was not reported and could have affected findings (Epstein 1990) as an association of reduced PFC and insula cortical thickness and tobacco use in adults with BD has been reported (Jorgensen et al. 2015). In young adults (18-30 years) with BD, oxidative stress in frontotemporal cortices is exacerbated by risky alcohol consumption and tobacco use (Chitty et al. 2013; Chitty et al. 2014), but it is unclear how pre-existing differences in frontotemporal cortices may contribute to this effect. To our knowledge, no studies have examined alcohol abuse/dependence or tobacco use during adolescence in BD with a focus on neuroanatomical factors involved in comorbidity development.

A pilot study of adolescents with BD, following subjects over two years, showed lower GMV in temporal cortex in those diagnosed with comorbid cannabis abuse/dependence before or after scan (n=7), compared to adolescents with BD without comorbid diagnoses (n=7) (Jarvis et al. 2008). In another study, adolescents/young adults (12-21 years) with BD and comorbid cannabis use disorders (n=25; 7 of whom also had comorbid alcohol abuse/dependence) were observed to have decreases in functional responses of the amygdala, shown to be excessive in adolescents with BD without comorbidity (Bitter et al. 2014). However, tobacco use was not examined in either of these studies and GMV was not assessed in the latter study. While the identification of altered GMV and functional responses in regions subserving emotional regulation in adolescents with BD and substance comorbidity may indicate regions involved in comorbidity development, the subjects were not studied exclusively prior to the development of comorbidity so a direct effect of drug exposure cannot be ruled out.

Gender Differences in Brain: Bipolar and Substance Use Disorders

It is well established that there are fundamental gender differences in brain, for example extending from *in utero* fetal hormone programming (Goldstein et al. 2014) through subsequent brain structure, function and chemistry (Cosgrove et al. 2007). Most brain-based diseases have gender differences in either prevalence, susceptibility, age of onset, presentation, course, prognosis, medication response, treatment outcome, and/or mortality (Institute of Medicine Forum on and Nervous System 2011). Gender differences also are reported in addiction processes (Becker and Hu 2008; Becker and Koob 2016; Fattore et al. 2008). For example, in females, greater internalizing symptoms, e.g. depression and anxiety, have been associated with tobacco, alcohol, and cannabis use (Bekman et al. 2013; Husky et al. 2008; McChargue et al. 2004; Moitra et al. 2015; Saraceno et al. 2012; Weinberger et al. 2009; Weinberger et al. 2013a); while in males, associations with externalizing behaviors, e.g. aggressive actions, and substance use have been found (Heron et al. 2013; Steinhausen et al. 2007; Tarter et al. 2009). Gender differences have also been demonstrated in prevalence, risk, and clinical correlates of alcoholism in adults with BD (Frye et al. 2003), including greater number of depressive episodes in females. It is unclear what neuroanatomical factors are associated with this sexual dimorphism.

Findings in groups at increased risk for BD and SUDs [e.g. with early life adversity and family history of SUDs (DeVito et al. 2013; Edmiston et al. 2011)] support gender distinctions in brain regions implicated in BD and in SUDs, e.g. greater abnormalities within ventral regions subserving emotional regulation in females versus dorsal regions subserving impulse control in males. Gender differences in neurochemical abnormalities in the dorsal PFC in adults with BD and comorbid alcohol abuse/dependence have also been found. Specifically, one study suggested that glutamatergic abnormalities in the dorsal PFC are associated with comorbidity in males, but not females; while myo-inositol abnormalities in dorsal PFC are associated with comorbidity in females, but not males (Nery et al. 2010). Although research suggests gender-specific mechanisms in the development of SUDs (Ceylan-Isik et al. 2010; Holmila and Raitasalo 2005; Kuhn 2015; Verplaetse et al. 2015), how sexual dimorphism may contribute to development of SUDs in BD is unknown.

The Purpose of the Current Study

The goal of this study was to identify regional GMV associated with future development of substance use problems. We assessed the relationships between GMV measures on high resolution structural magnetic resonance imaging (sMRI) scans of adolescents with BD who had minimal to no prior alcohol or other substance exposure at baseline, but reported substance use at follow-up on average 6 years later. Specific substances that were reported at follow-up were tobacco, alcohol and cannabis. We also explored patterns of regional GMV involvement in females and males. We hypothesized an inverse association between baseline GMV in PFC, insular and temporopolar cortices, and amygdala and severity of future substance use problems, with females showing more associations with future substance use in ventral system components subserving emotional regulation (Blond et al. 2012) and males in rostral and dorsal system components subserving impulse regulation (Bari and Robbins 2013).

MATERIALS AND METHODS

Participants

Participants included 30 adolescents/young adults diagnosed with BD [mean age at baseline ± standard deviation (SD)= 16±2 years, 50% female; mean age at follow-up= 22±3 years]. The presence and absence of psychiatric diagnoses and mood state at time of neuroimaging were confirmed with the Structured Clinical Interview for DSM-IV Diagnosis [SCID; (First 1995)] for participants ≥18 years and the Kiddie-Schedule for Affective Disorders and Schizophrenia [K-SADS; (Kaufman et al. 1997)] for participants <18 years. At baseline assessment, all participants completed sMRI. At the follow-up assessment, on average 6±2 years after the baseline assessment, subjects completed the CRAFFT interview to assess alcohol and substance use problems since baseline assessment.

As the aim of this study was to examine baseline GMV as a predictor of future alcohol and substance use problems, subjects were excluded if at baseline they self-reported more than minimal alcohol and/or cannabis exposure or ever having used cocaine, opioids, phencyclidine, hallucinogens, or solvents/inhalants. Sixty-three percent of subjects (11 males, 8 females) reported never trying alcohol or any other illicit substances or having tried a sip of alcohol once at a family gathering. Remaining subjects reported having tried alcohol or cannabis once or on a few occasions with peers. Subjects were not excluded for tobacco use. At baseline and follow-up assessment, tobacco use was assessed as smoking using the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al. 1991). At baseline, two subjects (7%) reported current smoking and one subject (3%) reported past history of, but not current, smoking. Transition to smoking was studied in the remaining subjects. In addition to the 3 subjects with a history of smoking tobacco at baseline (all 3 of whom smoked at follow-up), 11 individuals (41%; 7 of whom were female) with no tobacco use at baseline then reported smoking at follow-up (8 of whom were currently smoking at follow-up assessment; 4 current smokers at follow-up were female). Sixteen individuals (53%; 6 of whom were female) reported no history of smoking tobacco at either time point.

On the neuroimaging day, urine toxicology screens for substances of abuse (cannabis, cocaine, amphetamine, methamphetamine, methadone, opiates, phencyclidine, barbiturates, and benzodiazepines) were negative for all subjects. Exclusion criteria also included history of neurological illness, including head trauma with loss of consciousness for ≥5min, or major medical illness. After complete description of the study, written informed consent was obtained from subjects ≥18 years, and assent and parent/guardian permission from subjects <18, in accordance with the Yale School of Medicine human investigation committee.

At baseline assessment, 22 (73%) of participants were euthymic, 2 (7%) were in a depressed and 6 (20%) in an elevated (hypomanic/manic/mixed) mood state. Eleven (37%) met criteria for rapid cycling, 16 (53%) had a history of psychosis, 20 (67%) had previously been hospitalized, and 4 (13%) had a history of suicide attempt. The only comorbidity present of those assessed across all subjects was simple/specific phobia (N=3, 10%). Presence of disorders of childhood that were assessed by structured interview in subjects <18 years, included attention deficit hyperactivity disorder (ADHD, N=10, 33% of the overall sample), oppositional defiant disorder (ODD, N=3, 10%), conduct disorder (CD, N=1, 3%), and separation anxiety (N=1, 3%). Three participants (10%) were unmedicated at baseline. Psychotropic medications reported at baseline assessment by the other participants included antipsychotics (N=18, 58%), anticonvulsants (N=11, 37%), stimulants (N=10, 32%), lithium (N=9, 30%), antidepressants (N=5, 16%), benzodiazepines (N=5, 16%), ketamine (N=1, 3%), adrenergic agonist (N=1, 3%), and amantadine (N=1, 3%). Four participants (13%) had hypothyroidism treated with levothyroxine.

MRI Acquisition and Processing

High-resolution sMRI data were acquired for each subject with a 3-Tesla Siemens Trio MR scanner (Siemens, Erlangen, Germany). The sMRI sagittal images were acquired with a three-dimensional magnetization prepared rapid acquisition gradient echo (MPRAGE) T_1-weighted sequence with parameters: repetition time (TR) 1500ms, echo time (TE) = 2.83ms, matrix 256 x 256, field of view (FOV) = 256mm x 256mm, and 160 one-mm slices without gap and two averages. Images were processed with the DARTEL toolbox within Statistical and Parametric Mapping 12 (SPM12) (http://www.fil.ion.ucl.ac.uk/spm). The SPM segmentation function and SPM tissue probability maps for gray matter, white matter and cerebral spinal fluid were implemented for bias correction and segmentation and used to create DARTEL templates using the "Run Dartel (create Templates)" command under DARTEL tools (Henley et al. 2014; Malone et al. 2015). Data were normalized to Montreal Neurological Institute (MNI) space and smoothed with an 8mm full-width-at-half-maximum (FWHM) isotropic kernel.

Alcohol and Substance Use

Subjects were administered the CRAFFT interview (Knight et al. 1999), which consists of 6 yes/no questions inquiring about risk indicators or problems experienced from alcohol or drug use. CRAFFT is an acronym with each letter representing one of the 6 items. C relates to history of driving or riding in a Car driven by someone who had been using alcohol/drugs, R if used alcohol/drugs to Relax, A if used alcohol/drugs while Alone, F if Forgotten things that one did while using alcohol/drugs, F whether told by Family or Friends to cut down on alcohol/drug use, and T whether gotten into Trouble while using alcohol/drugs. The questions are equally weighted, i.e. one point for each yes answer. The CRAFFT has substantial empirical support as a substance use screening instrument for adolescents in multiple settings, including outpatient general medical and inpatient psychiatric settings (Cummins et al. 2003; Dhalla et al. 2011; Knight et al. 2003; Knight et al. 2002; Knight et al. 1999; Oesterle et al. 2015; Pilowsky and Wu 2013). A score of ≥2 has been used as threshold optimal for identifying alcohol/substance problems (Knight et al. 2002; Knight et al. 1999). At follow-up, 19 (63%) participants had a CRAFFT score of ≥2 ($CRAFFT_{mean}$±SD= 2.3±2.1; scores ranged from 0-6 and showed a normal distribution in both males and females).

Additional Assessments

At baseline assessment, 27 participants [14 female (51%)] completed the Child Depression Rating Scale (CDRS) (Emslie et al. 1990) and 25 participants [12 female (48%)] the Barratt Impulsiveness Scale (BIS)-11 or BIS-11a. The BIS is a self-reported measure of trait impulsivity. The total BIS score is the sum of three subscale scores: non-planning impulsivity (lack of sense of future), cognitive-attentional impulsivity (inability to focus or concentrate), and motor impulsivity (acting on the spur of the moment). BIS-11a scores were prorated to BIS-11 scores as previously described (Gilbert et al. 2011; Patton et al. 1995).

Statistical Analyses

Demographic and Clinical Feature Analysis

Subjects were categorized into those scoring at high (≥2: $CRAFFT_{HIGH}$) versus low (<2: $CRAFFT_{LOW}$) risk for alcohol and substance use problems. Independent t-tests were performed to assess group differences in age at baseline scans, age at follow-up, interval between baseline scan and follow-up, age of first mood episode, and baseline CDRS and BIS (total and subscale) scores. Chi-square (or Fisher's exact) tests were used to examine whether clinical factors differed by CRAFFT group at baseline (see Table 1). These included mood state (euthymic, depressed, elevated), history (yes/no) of hospitalization, rapid cycling, psychosis, suicide attempt, smoking tobacco, comorbid diagnosis (yes/no) of simple/specific phobia, ADHD, ODD, CD, or separation anxiety, and medication subclasses (on/off). Analyses were repeated stratified by gender. Additionally, a Chi-square test was used to assess if the number of individuals transitioning to smoking tobacco between baseline and follow-up assessment differed by CRAFFT group (excluding 3 individuals with baseline history of tobacco use). A Fisher's exact test was used to assess whether $CRAFFT_{HIGH}$ males and females differed in the number of individuals who transitioned to smoking tobacco between baseline and follow-up assessment. Results were considered significant at $p<0.05$.

SPM Voxel-Based Analysis

A two-sample t-test was conducted in SPM12 to assess $CRAFFT_{HIGH}$ versus $CRAFFT_{LOW}$ group differences in baseline GMV, including data from all subjects. For hypothesized regions, PFC, insular and temporopolar cortices and amygdala, results were considered significant at $p \leq 0.005$ (uncorrected) and clusters $\geq$20 voxels. This threshold was chosen based on a recommended balance for type I and type II errors in preliminary studies (Forman et al. 1995; Lieberman and Cunningham 2009). For remaining brain regions, findings were considered as significant with $p<0.05$ Family-Wise Error (FWE)-corrected and an extent threshold of 10 voxels for multiple comparisons. Mean GMV, extracted from clusters showing significant differences between CRAFFT groups, were calculated. Post hoc analysis was performed to assess effect of CRAFFT group after removing 3 subjects with a history of tobacco use at baseline, with GMV from extracted clusters as the dependent variable. To further confirm regional GMV association with CRAFFT outcome, the relationship between mean GMV in significant clusters with total CRAFFT score was assessed with Pearson correlations across all subjects. Correlations were repeated stratified by gender to explore gender-related patterns in volumetric features associated with the development of substance use problems. Correlation analyses were also performed across all subjects, and stratified by gender, to assess relationship between GMV and baseline CDRS or BIS (total and subscale) scores. Based on our *a priori* hypotheses, GMV from clusters within rostral PFC (rPFC) and dorsolateral PFC (dlPFC) showing a significant difference between CRAFFT groups were assessed for relationship with BIS (total and subscales) scores; GMV from clusters within orbitofrontal cortex (OFC) and insular and temporopolar cortices were assessed for relationship with baseline CDRS scores.

A t-test was used to explore differences in extracted GMV, from significant regions identified in the CRAFFT group analysis above, between individuals who never smoked tobacco at either assessment (N=16) and those who transitioned to smoking tobacco between baseline and follow-up assessment (N=11). Regional GMV identified as being associated with transitioning to smoking tobacco were explored across all subjects who transitioned and were currently smoking tobacco at follow-up using Pearson correlations to determine relationships with total FTND scores.

T-tests were performed to explore associations between mean GMV in significant clusters with clinical and medication subclass factors present and absent at baseline in N≥5 subjects, including mood state (euthymic versus elevated), history (yes/no) of hospitalizations, rapid cycling, lifetime psychosis, and if taking (off/on) an antipsychotic, anticonvulsant, stimulant, lithium, antidepressant, or benzodiazepine. Analyses were repeated stratified by gender for clinical factors present or absent at baseline in N≥5 female or male subjects, including history (yes/no) at baseline of rapid cycling, lifetime psychosis, and if taking (off/on) an antipsychotic at baseline. In females, we assessed effects of taking an anticonvulsant and differences between subjects transitioning to smoking tobacco between baseline and follow-up assessments (N=7 females), compared to those reporting no history of smoking at either assessment (N=6 females). In males, we assessed effects of comorbid ADHD and taking a stimulant or lithium at baseline assessment, but did not assess for smoking conversion as only 4 males converted. These post hoc analyses were considered significant at $p<0.05$. All significant results are reported below.

RESULTS

Demographic and Clinical Feature Analysis

In baseline analyses across all subjects, the $\text{CRAFFT}_{\text{HIGH}}$ group had higher CDRS scores ($\text{CRAFFT}_{\text{HIGH}}$: 28.1 ± 10.0; $\text{CRAFFT}_{\text{LOW}}$: 20.7 ± 4.8, t_{25}=2.11, p=0.045). Within females, the $\text{CRAFFT}_{\text{HIGH}}$ group had a trend towards higher CDRS scores ($\text{CRAFFT}_{\text{HIGH}}$ females: 30.8 ± 11.1; $\text{CRAFFT}_{\text{LOW}}$ females: 19.4 ± 4.8, t_{13}=2.14, p=0.054). No significant differences in BIS (total or subscales) scores were observed. More $\text{CRAFFT}_{\text{HIGH}}$ males, compared to $\text{CRAFFT}_{\text{LOW}}$

males, had comorbid diagnoses of ADHD (78% versus 17% respectively, p = 0.04, Fisher's exact test) and were taking a stimulant at baseline (78% versus 17% respectively, p = 0.04, Fisher's exact test). While not significant, more $CRAFFT_{HIGH}$ females, compared to $CRAFFT_{LOW}$ females, had a prior hospitalization (90% versus 40% respectively, p=0.08, Fisher's exact test). Overall, the $CRAFFT_{HIGH}$ group had more individuals transition to smoking tobacco at follow-up assessment (56% versus 18% respectively, χ^2=3.9, df=1, p=0.048). There was no difference between $CRAFFT_{HIGH}$ females and males in number of individuals who transitioned to smoking tobacco between baseline and follow-up assessment (63% $CRAFFT_{HIGH}$ females versus 50% $CRAFFT_{HIGH}$ males respectively, χ^2=0.25, df=1, p=0.61). There were no other differences in demographic/clinical factors between CRAFFT groups overall or within females or males (see Table 1).

SPM Voxel-Based Analysis

Within our *a priori* hypothesized regions, the $CRAFFT_{HIGH}$ group had lower GMV in left OFC [Brodmann area (BA) 11, MNI coordinates: x=-18mm, y=27mm, z=-20mm, cluster=45 voxels], right rPFC (BA10, x=18mm, y=60mm, z=3mm, cluster=35 voxels), left dlPFC (BA9, x=-28mm, y=27mm, z=38mm, cluster=79 voxels), and right insular (x=44mm, y=-8mm, z=-2mm, cluster= 175 voxels) and left temporopolar cortices (BA38, x=-48mm, y=20mm, z=-26mm, cluster=164 voxels) (Figure 1). The $CRAFFT_{HIGH}$ group did not show any areas of greater GMV in hypothesized regions. No significant differences in GMV were observed outside of hypothesized regions.

Significance remained in hypothesized regions when excluding 3 subjects with baseline history of tobacco use. Across all subjects, total CRAFFT scores were negatively correlated with extracted mean GMV of clusters within the OFC (r=-0.44, n=30, p=0.016), rPFC (r=-0.51, n=30, p=0.004), dlPFC (r=-0.63, n=30, p=0.0002), and insula (r=-0.45, n=30, p=0.013). Insula GMV was negatively correlated with baseline CDRS scores (r=-0.46, n=27, p=0.015). Both females and males showed a negative correlation between total CRAFFT scores and dlPFC GMV (females: r=-0.69, n=15, p=0.004; males: r=-0.67, n=15, p=0.008). Additionally, females, but not males, showed a negative correlation between total CRAFFT scores and OFC (r=-0.74, n=15, p=0.002) and insula (r=-0.69, n=15, p=0.004) GMV. Males, but not females, showed a negative correlation between total CRAFFT scores and rPFC GMV (r=-0.62, n=15, p=0.01). Within females, a trend for a negative correlation between insula GMV and baseline CDRS scores (r=-0.50, n=14, p=0.07) was observed.

Lower GMV within the OFC (t_{25}=2.98, p=0.006) and insular (t_{25}=2.46, p=0.021) and temporopolar (t_{25}=2.54, p=0.018) cortices was observed in individuals who transitioned to smoking tobacco between baseline and follow-up assessment, compared to individuals who reported no history of smoking tobacco at either assessment. Temporopolar GMV was negatively associated with follow-up FTND scores (r=-0.76, n=8, p=0.03) in individuals who transitioned to smoking tobacco after their baseline assessment and were currently smoking at follow-up. No other significant effects of clinical factors were observed on GMV when looking across all subjects or when investigating effects of clinical factors on GMV within females and males separately.

DISCUSSION

Lower baseline GMV in the PFC, including dorsolateral, orbitofrontal and rostral PFC, and insular and temporopolar cortices, were observed among adolescents with BD who subsequently reported substance use problems with alcohol and cannabis on the CRAFFT interview compared to adolescents with BD who did not. Exploratory analyses supported both common and different patterns of regional GMV associated with substance use development among females and males. Decreased baseline dlPFC GMV was associated with substance use problems in both females and males. Lower baseline OFC and insula GMV was associated with substance use problems in females; lower baseline rPFC GMV was associated with substance use problems in males. Greater depressive symptoms at baseline were associated with greater substance use problems at follow-up, with depressive symptoms related to lower insula GMV, with these associations driven by the female data. Additionally, lower OFC, insular and temporopolar GMV were observed in individuals who transitioned to smoking tobacco, with temporopolar GMV inversely associated with severity of nicotine dependence at follow-up.

Regions in which GMV abnormalities were associated with development of substance use problems in BD are consistent with previous findings in adolescents in the absence of BD with alcohol and substance abuse/dependence (Bava and Tapert 2010), and drug-related processes, including craving, motivational changes, withdrawal symptoms, and relapse/ treatment outcomes (Adinoff 2004; Goldstein and Volkow 2011; Koob and Volkow 2010; Naqvi et al. 2014; Sinha and Li 2007). Abnormalities in behaviors subserved by these regions may contribute to vulnerability/risk for substance use problems (Adinoff et al. 2007; Baker et al. 2004; Claus and Hutchison 2012; Li and Sinha 2008; Peeters et al. 2014). Dorsal system components, i.e. the dlPFC and rPFC, are associated with higher order executive functions and behavioral control (Aron et al. 2004; Burgess et al. 2007; Dumontheil et al. 2008; Gilbert et al. 2006; Koechlin and Hyafil 2007; Levy and Goldman-Rakic 2000; Petrides and Pandya 2007; Ramnani and Owen 2004). Ventral and paralimbic cortical regions implicated, i.e. OFC, insular and temporopolar cortices, are associated with affective processing and regulation, stimulus-reinforcement associations, behavioral control and risky decision making (Carr et al. 2003; Clark et al. 2008; Craig 2002; Crowley et al. 2015; Etkin et al. 2011; Fellows 2007; Kringelbach and Rolls 2004; Manes et al. 2002; Modinos et al. 2009; Muhlert and Lawrence 2015; Rolls 2004; Van Leijenhorst et al. 2010; Xue et al. 2010).

Circuitry Associated with Gender-Related Risk for Substance Problems

The findings in regions subserving affective and internal monitoring processes in females are consistent with literature supporting associations between disturbances in affective processing and internalizing symptoms and substance use problems. This has been found in the absence of BD (Boden and Fergusson 2011; Garfield et al. 2015; Hussong et al. 2011) and suggested to be especially salient in the development of substance use problems in females (Bekman et al. 2013; Moitra et al. 2015; Saraceno et al. 2012). The insula, in particular, has been previously associated with addictive behavior through involvement in interoceptive aspects of drug craving and seeking (Gaznick et al. 2014; Naqvi et al. 2014; Naqvi et al. 2007). However, the role of the insula in the development of substance use in females is not known. We observed associations between greater depression symptomology and lower insula GMV, largely due to data from females. Insula involvement in affective and internal monitoring processes are well established (Carr et al. 2003; Craig 2002; Meerwijk et al. 2013; Modinos et al. 2009) and insula structural and functional abnormalities are reported in affective disorders, including BD (Avery et al. 2014; Belden et al. 2015; Kim et al. 2009; Najt et al. 2015; Stein et al. 2007; Tang et al. 2014). An inverse association between insula GMV and number of depressive episodes in BD is reported (Takahashi et al. 2010). Results reported here suggest variation in insula GMV, and relationship with depression symptomology, may be associated with substance-related outcomes in females with BD.

Literature also supports associations between externalizing symptoms and substance use problems. This has been found in the absence of BD (Griffith-Lendering et al. 2011; Miettunen et al. 2014; Oshri et al. 2011; Rogosch et al. 2010) and suggested to be especially salient in the development of substance use problems in males (Heron et al. 2013; Steinhausen et al. 2007; Tarter et al. 2009). Impulsiveness has been suggested as a trait feature of BD that might increase vulnerability for substance use problems (Gilbert et al. 2011; Nery et al. 2013; Swann et al. 2004). We did not detect associations between BIS impulsivity scores and subsequent substance use problems. It is possible this is due to limited power to detect associations particularly in the small male subsample, or that differences in impulsiveness may not have emerged yet in this young sample and future studies examining behavioral trajectories associated with transitioning to substance use disorders may reveal differences. It is also possible that the BIS does not capture relevant impulsivity constructs. This is supported by work showing risk-taking and novelty seeking may distinguish adults with BD and comorbid SUDs better than BIS impulsiveness scores (Bauer et al. 2015; Haro et al. 2007; Kathleen Holmes et al. 2009).

More males with BD and prospective substance use problems were diagnosed with comorbid ADHD at baseline. Recent work suggests ADHD may increase risk for substance use problems in the absence of BD (Bidwell et al. 2014; Kolla et al. 2016; Urcelay and Dalley 2012) and when comorbid with BD (Perroud et al. 2014). The neuroanatomical factors underlying this association are unclear. Adults with BD and comorbid ADHD, compared to those without, showed greater rPFC dysfunction (Adler et al. 2005). While an association between comorbid ADHD and GMV findings were not detected in this study possibly owing to sample size, males but not females did show an inverse association between rPFC GMV and CRAFFT scores. More work is needed to identify if behavioral constructs associated with rPFC, e.g. executive functions, decision making and response processes (Burgess et al. 2007; Dumontheil et al. 2008;

Koechlin and Hyafil 2007), may be particularly salient in development of substance use problems in males with BD.

Lower baseline OFC, insular and temporopolar GMV in adolescents with BD were also associated with transitioning to smoking tobacco. As above, these regions are involved in affective processes, including depression symptomology (Arnsten and Rubia 2012; Hulvershorn et al. 2011; Pfeifer and Peake 2012; Wang et al. 2011). Findings in these regions are consistent with literature supporting associations between depression and tobacco use in the absence of BD (Cheetham et al. 2015; Graham et al. 2007; Kassel et al. 2003; Weinberger et al. 2013a; Weinberger et al. 2012; Weinberger et al. 2013b). It has been suggested that this relationship is especially salient for tobacco use in females (Husky et al. 2008; McChargue et al. 2004; Weinberger et al. 2009). We did not observe gender-related associations between GMV in these regions and transitioning to smoking tobacco; however, ability to detect associations was limited by sample size. While we did not detect an association between temporopolar GMV and follow-up CRAFFT scores, temporopolar GMV was inversely related to follow-up Fagerstrom scores for nicotine dependence severity suggesting its involvement in development of smoking. Future work should investigate neuroanatomical specificity for vulnerability/risk for certain drugs types in BD.

Neuroanatomical Factors Associated with Substance Use Problems in Other Populations

Studies of adolescents recruited from school systems, the majority of whom had no history of psychopathology at baseline, report lower dorsal PFC and OFC GMV and less OFC gyrification associated with subsequent alcohol-related problems and initiation of cannabis use (Cheetham et al. 2014; Cheetham et al. 2012; Kuhn et al. 2015). Functional MRI studies of adolescents having no history of psychopathology but genetic risk for substance use problems have shown associations between regional responses during response inhibition or working memory tasks in dorsal PFC, including dlPFC and rPFC, with subsequent substance use problems (Heitzeg et al. 2014; Norman et al. 2011; Squeglia et al. 2012; Wetherill et al. 2013). We are not aware of a study examining adolescents with minimal to no alcohol or substance use at baseline demonstrating associations between baseline insular and temporopolar GMV with prospective substance use problems. As above, a growing body of work suggests insula involvement in drug craving and seeking behavior (Naqvi et al. 2014). One report did show young adults with moderate alcohol use who then transitioned to heavy alcohol use had greater alcohol cue reactivity in the insula (Dager et al. 2014). However, as that study consisted of individuals with moderate alcohol use at baseline, brain effects of alcohol exposure cannot be ruled out.

We did not observe an association between amygdala GMV and subsequent substance use problems in BD. In previous studies examining adolescents who predominantly had no history of psychopathology, associations between amygdala volumes with prospective alcohol/cannabis use were also not detected (Cheetham et al. 2014; Cheetham et al. 2012). This suggests that previous observations of amygdala abnormalities as observed in adolescents/young adults without BD but with cannabis (Gilman et al. 2014; Padula et al. 2015) or alcohol use (Dager et al. 2013) as well as in adolescents with BD and comorbid cannabis use (Bitter et al. 2014) may be related to substance exposure. Additionally, altered amygdala morphology and function in association with substance use has shown genetic and gender-related associations (Benegal et al. 2007; Cacciaglia et al. 2013; Hill et al. 2001; Hill et al. 2013; McQueeny et al. 2011). It is therefore possible that genetic heterogeneity and limited power to detect gender-related associations may have confounded ability to detect findings.

To our knowledge, there have not been other reports demonstrating neuroanatomical predictors of subsequent transitions to smoking tobacco. Adolescents/young adult tobacco smokers in the absence of BD, compared to non-smokers, show cortical thinning in the OFC (Li et al. 2015) and a negative association between OFC and insula cortical thickness and magnitude of lifetime exposure to tobacco smoke (Li et al. 2015; Morales et al. 2014). Further study on OFC, insular and temporopolar cortices involvement in elevating risk for smoking tobacco is warranted.

Limitations and Future Directions

The size and heterogeneous clinical features of the subject sample could have limited power to detect associations with substance use. Future studies with larger sample sizes and greater power to identify gender-related circuitry while also systematically assessing clinical factors are needed. A strength of the present study is the minimal to no alcohol, cannabis, tobacco and other substance use at baseline; findings of lower GMV associated with prospective substance use problems are therefore unlikely to be due to brain effects of alcohol or other drug exposure. Although the toxicology screens aided determination of recent use, self-reports by subjects could have minimized substance use at baseline. We were not able to explore factors associated specifically with alcohol, cannabis or tobacco use as 89% of individuals meeting CRAFFT threshold at follow-up reported use of more than one of these substances. Type I errors are possible given the preliminary nature of this study, and we reported p-values uncorrected for multiple comparisons to minimize type II errors. Future studies are needed to confirm the current findings with sufficient power to detect regional differences in non-hypothesized regions.

Research incorporating longitudinal study, examining effects of genetic variations and behavioral constructs, and functional consequences of structural differences identified here are needed, including study to disentangle contributions of regions, and interactions between them contributing to development of substance use problems. Functions investigated should include emotional processing and regulation, in addition to executive functions, as these functions may be differently associated with substance use development in females and males. More work is needed investigating sexual dimorphism in mechanisms driving drug-seeking behavior and transitions to substance use problems in females and males with BD and commonalities and distinctions between BD and other psychiatric disorders. The current study did not include an at risk comparison group so diagnostic-associated neuroanatomical factors associated with risk cannot be determined. Future studies focused on mechanisms underlying resilience to developing substance use in psychiatric disorders and at risk populations could reveal novel therapeutic strategies.

In Conclusion

This study provides new preliminary evidence that GMV in brain regions with known roles in addiction are involved in risk for developing substance use problems in adolescents with BD. Work reported here in adolescents with BD, taken together with work examining predictors of future substance use in other non-psychiatric samples, suggests PFC abnormalities may be common to risk for developing substance use problems in females and males. Our preliminary findings suggest there may also be gender-related differences in the paths to developing substance use problems in BD with involvement of regions subserving emotional processes, such as the OFC and insula, in females, and regions subserving executive functioning or response processes, such as the rPFC, in males. Future work confirming underlying gender-specific mechanisms could improve detection of individuals at risk and intervention strategies.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ROLE OF AUTHORS

All authors had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: HPB, ETCL, CMM. Acquisition of data: HPB, ETCL, JAYJ. Analysis and interpretation of data: HPB, ETCL, CMM, JAYJ, LS, JW, BP, FW. Drafting of manuscript: HPB, ETCL, CMM. Critical revision of the manuscript: HPB, ETCL, CMM, JAYJ, LS, JW, BP, FW. Statistical analysis: HPB, ETCL, CMM, BP. Obtained funding: HPB, ETCL. Administrative, technical, and material support: JAYJ, LS. Study supervision: HPB, ETCL.

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REFERENCES

Adinoff B. 2004. Neurobiologic processes in drug reward and addiction. Harvard review of psychiatry 12(6):305-320.

Adinoff B, Rilling LM, Williams MJ, Schreffler E, Schepis TS, Rosvall T, Rao U. 2007. Impulsivity, neural deficits, and the addictions: the "oops" factor in relapse. Journal of addictive diseases 26 Suppl 1:25-39.

Adler CM, Delbello MP, Mills NP, Schmithorst V, Holland S, Strakowski SM. 2005. Comorbid ADHD is associated with altered patterns of neuronal activation in adolescents with bipolar disorder performing a simple attention task. Bipolar disorders 7(6):577-588.

Arnsten AF, Rubia K. 2012. Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders. Journal of the American Academy of Child and Adolescent Psychiatry 51(4):356-367.

Aron AR, Robbins TW, Poldrack RA. 2004. Inhibition and the right inferior frontal cortex. Trends in cognitive sciences 8(4):170-177.

Avery JA, Drevets WC, Moseman SE, Bodurka J, Barcalow JC, Simmons WK. 2014. Major depressive disorder is associated with abnormal interoceptive activity and functional connectivity in the insula. Biological psychiatry 76(3):258-266.

Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC. 2004. Addiction motivation reformulated: an affective processing model of negative reinforcement. Psychological review 111(1):33-51.

Bari A, Robbins TW. 2013. Inhibition and impulsivity: behavioral and neural basis of response control. Progress in neurobiology 108:44-79.

Bauer IE, Meyer TD, Sanches M, Zunta-Soares G, Soares JC. 2015. Does a history of substance abuse and illness chronicity predict increased impulsivity in bipolar disorder? Journal of affective disorders 179:142-147.

Bava S, Tapert SF. 2010. Adolescent brain development and the risk for alcohol and other drug problems. Neuropsychology review 20(4):398-413.

Becker JB, Hu M. 2008. Sex differences in drug abuse. Frontiers in neuroendocrinology 29(1):36-47.

Becker JB, Koob GF. 2016. Sex Differences in Animal Models: Focus on Addiction. Pharmacological reviews 68(2):242-263.

Bekman NM, Winward JL, Lau LL, Wagner CC, Brown SA. 2013. The impact of adolescent binge drinking and sustained abstinence on affective state. Alcoholism, clinical and experimental research 37(8):1432-1439.

Belden AC, Barch DM, Oakberg TJ, April LM, Harms MP, Botteron KN, Luby JL. 2015. Anterior insula volume and guilt: neurobehavioral markers of recurrence after early childhood major depressive disorder. JAMA psychiatry 72(1):40-48.

Benegal V, Antony G, Venkatasubramanian G, Jayakumar PN. 2007. Gray matter volume abnormalities and externalizing symptoms in subjects at high risk for alcohol dependence. Addiction biology 12(1):122-132.

Bidwell LC, Henry EA, Willcutt EG, Kinnear MK, Ito TA. 2014. Childhood and current ADHD symptom dimensions are associated with more severe cannabis outcomes in college students. Drug and alcohol dependence 135:88-94.

Bitter SM, Adler CM, Eliassen JC, Weber WA, Welge JA, Burciaga J, Shear PK, Strakowski SM, DelBello MP. 2014. Neurofunctional changes in adolescent cannabis users with and without bipolar disorder. Addiction (Abingdon, England) 109(11):1901-1909.

Blond BN, Fredericks CA, Blumberg HP. 2012. Functional neuroanatomy of bipolar disorder: structure, function, and connectivity in an amygdala-anterior paralimbic neural system. Bipolar disorders 14(4):340-355.

Blumberg HP, Kaufman J, Martin A, Charney DS, Krystal JH, Peterson BS. 2004. Significance of adolescent neurodevelopment for the neural circuitry of bipolar disorder. Annals of the New York Academy of Sciences 1021:376-383.

Boden JM, Fergusson DM. 2011. Alcohol and depression. Addiction (Abingdon, England) 106(5):906-914.

Burgess PW, Dumontheil I, Gilbert SJ. 2007. The gateway hypothesis of rostral prefrontal cortex (area 10) function. Trends in cognitive sciences 11(7):290-298.

Cacciaglia R, Nees F, Pohlack ST, Ruttorf M, Winkelmann T, Witt SH, Nieratschker V, Rietschel M, Flor H. 2013. A risk variant for alcoholism in the NMDA receptor affects amygdala activity during fear conditioning in humans. Biological psychology 94(1):74-81.

Carr L, Iacoboni M, Dubeau MC, Mazziotta JC, Lenzi GL. 2003. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proceedings of the National Academy of Sciences of the United States of America 100(9):5497-5502.

Cassidy F, Ahearn EP, Carroll BJ. 2001. Substance abuse in bipolar disorder. Bipolar disorders 3(4):181-188.

Ceylan-Isik AF, McBride SM, Ren J. 2010. Sex difference in alcoholism: who is at a greater risk for development of alcoholic complication? Life sciences 87(5-6):133-138.

Cheetham A, Allen NB, Schwartz O, Simmons JG, Whittle S, Byrne ML, Sheeber L, Lubman DI. 2015. Affective behavior and temperament predict the onset of smoking in adolescence. Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors 29(2):347-354.

Cheetham A, Allen NB, Whittle S, Simmons J, Yucel M, Lubman DI. 2014. Volumetric differences in the anterior cingulate cortex prospectively predict alcohol-related problems in adolescence. Psychopharmacology 231(8):1731-1742.

Cheetham A, Allen NB, Whittle S, Simmons JG, Yucel M, Lubman DI. 2012. Orbitofrontal volumes in early adolescence predict initiation of cannabis use: a 4-year longitudinal and prospective study. Biological psychiatry 71(8):684-692.

Chitty KM, Lagopoulos J, Hickie IB, Hermens DF. 2013. Risky alcohol use in young persons with emerging bipolar disorder is associated with increased oxidative stress. Journal of affective disorders 150(3):1238-1241.

Chitty KM, Lagopoulos J, Hickie IB, Hermens DF. 2014. The impact of alcohol and tobacco use on in vivo glutathione in youth with bipolar disorder: an exploratory study. Journal of psychiatric research 55:59-67.

Clark L, Bechara A, Damasio H, Aitken MR, Sahakian BJ, Robbins TW. 2008. Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. Brain : a journal of neurology 131(Pt 5):1311-1322.

Claus ED, Hutchison KE. 2012. Neural mechanisms of risk taking and relationships with hazardous drinking. Alcoholism, clinical and experimental research 36(6):932-940.

Cosgrove KP, Mazure CM, Staley JK. 2007. Evolving knowledge of sex differences in brain structure, function, and chemistry. Biological psychiatry 62(8):847-855.

Craig AD. 2002. How do you feel? Interoception: the sense of the physiological condition of the body. Nature reviews Neuroscience 3(8):655-666.

Crowley TJ, Dalwani MS, Mikulich-Gilbertson SK, Young SE, Sakai JT, Raymond KM, McWilliams SK, Roark MJ, Banich MT. 2015. Adolescents' Neural Processing of Risky Decisions: Effects of Sex and Behavioral Disinhibition. PloS one 10(7):e0132322.

Cummins LH, Chan KK, Burns KM, Blume AW, Larimer M, Marlatt GA. 2003. Validity of the CRAFFT in American-Indian and Alaska-Native adolescents: screening for drug and alcohol risk. Journal of studies on alcohol 64(5):727-732.

Dager AD, Anderson BM, Rosen R, Khadka S, Sawyer B, Jiantonio-Kelly RE, Austad CS, Raskin SA, Tennen H, Wood RM, Fallahi CR, Pearlson GD. 2014. Functional magnetic resonance imaging (fMRI) response to alcohol pictures predicts subsequent transition to heavy drinking in college students. Addiction (Abingdon, England) 109(4):585-595.

Dager AD, Anderson BM, Stevens MC, Pulido C, Rosen R, Jiantonio-Kelly RE, Sisante JF, Raskin SA, Tennen H, Austad CS, Wood RM, Fallahi CR, Pearlson GD. 2013. Influence of alcohol use and family history of alcoholism on neural response to alcohol cues in college drinkers. Alcoholism, clinical and experimental research 37 Suppl 1:E161-171.

Dalton EJ, Cate-Carter TD, Mundo E, Parikh SV, Kennedy JL. 2003. Suicide risk in bipolar patients: the role of co-morbid substance use disorders. Bipolar disorders 5(1):58-61.

DelBello MP, Strakowski SM, Sax KW, McElroy SL, Keck PE, Jr., West SA, Kmetz GF. 1999. Familial rates of affective and substance use disorders in patients with first-episode mania. Journal of affective disorders 56(1):55-60.

DeVito EE, Meda SA, Jiantonio R, Potenza MN, Krystal JH, Pearlson GD. 2013. Neural correlates of impulsivity in healthy males and females with family histories of alcoholism. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 38(10):1854-1863.

Dhalla S, Zumbo BD, Poole G. 2011. A review of the psychometric properties of the CRAFFT instrument: 1999-2010. Current drug abuse reviews 4(1):57-64.

Dumontheil I, Burgess PW, Blakemore SJ. 2008. Development of rostral prefrontal cortex and cognitive and behavioural disorders. Developmental medicine and child neurology 50(3):168-181.

Edmiston EE, Wang F, Mazure CM, Guiney J, Sinha R, Mayes LC, Blumberg HP. 2011. Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. Archives of pediatrics & adolescent medicine 165(12):1069-1077.

Emslie GJ, Weinberg WA, Rush AJ, Adams RM, Rintelmann JW. 1990. Depressive symptoms by self-report in adolescence: phase I of the development of a questionnaire for depression by self-report. Journal of child neurology 5(2):114-121.

Epstein RS. 1990. Nicotine use as a possible risk factor for subcortical abnormalities. Archives of general psychiatry 47(12):1172.

Etkin A, Egner T, Kalisch R. 2011. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends in cognitive sciences 15(2):85-93.

Fattore L, Altea S, Fratta W. 2008. Sex differences in drug addiction: a review of animal and human studies. Women's health (London, England) 4:51-65.

Fellows LK. 2007. The role of orbitofrontal cortex in decision making: a component process account. Annals of the New York Academy of Sciences 1121:421-430.

First MB, Spitzer, R.L., Gibbon, M., Williams, J.B.W. 1995. Structured Clinical Interview for DSM-IV Axis I & II Disorders (Version 2.0). New York: New York State Psychiatric Institute.

Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. 1995. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magnetic resonance in medicine 33(5):636-647.

Frye MA, Altshuler LL, McElroy SL, Suppes T, Keck PE, Denicoff K, Nolen WA, Kupka R, Leverich GS, Pollio C, Grunze H, Walden J, Post RM. 2003. Gender differences in prevalence, risk, and clinical correlates of alcoholism comorbidity in bipolar disorder. The American journal of psychiatry 160(5):883-889.

Garfield JB, Allen NB, Cheetham A, Simmons JG, Lubman DI. 2015. Attention to pleasant stimuli in early adolescence predicts alcohol-related problems in mid-adolescence. Biological psychology 108:43-50.

Gaznick N, Tranel D, McNutt A, Bechara A. 2014. Basal ganglia plus insula damage yields stronger disruption of smoking addiction than basal ganglia damage alone. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 16(4):445-453.

Gilbert KE, Kalmar JH, Womer FY, Markovich PJ, Pittman B, Nolen-Hoeksema S, Blumberg HP. 2011. Impulsivity in Adolescent Bipolar Disorder. Acta neuropsychiatrica 23(2):57-61.

Gilbert SJ, Spengler S, Simons JS, Steele JD, Lawrie SM, Frith CD, Burgess PW. 2006. Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. Journal of cognitive neuroscience 18(6):932-948.

Gilman JM, Kuster JK, Lee S, Lee MJ, Kim BW, Makris N, van der Kouwe A, Blood AJ, Breiter HC. 2014. Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. The Journal of neuroscience : the official journal of the Society for Neuroscience 34(16):5529-5538.

Gogtay N, Ordonez A, Herman DH, Hayashi KM, Greenstein D, Vaituzis C, Lenane M, Clasen L, Sharp W, Giedd JN, Jung D, Nugent TF, 3rd, Toga AW, Leibenluft E, Thompson PM, Rapoport JL. 2007. Dynamic mapping of cortical development before and after the onset of pediatric bipolar illness. Journal of child psychology and psychiatry, and allied disciplines 48(9):852-862.

Goldberg JF. 2001. Bipolar disorder with comorbid substance abuse: diagnosis, prognosis, and treatment. Journal of psychiatric practice 7(2):109-122.

Goldstein JM, Holsen L, Handa R, Tobet S. 2014. Fetal hormonal programming of sex differences in depression: linking women's mental health with sex differences in the brain across the lifespan. Frontiers in neuroscience 8:247.

Goldstein RZ, Volkow ND. 2011. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nature reviews Neuroscience 12(11):652-669.

Graham NA, Frost-Pineda K, Gold MS. 2007. Tobacco and psychiatric dual disorders. Journal of addictive diseases 26 Suppl 1:5-12.

Griffith-Lendering MF, Huijbregts SC, Mooijaart A, Vollebergh WA, Swaab H. 2011. Cannabis use and development of externalizing and internalizing behaviour problems in early adolescence: A TRAILS study. Drug and alcohol dependence 116(1-3):11-17.

Haro G, Calabrese JR, Larsson C, Shirley ER, Martin E, Leal C, Delgado PL. 2007. The relationship of personality traits to substance abuse in patients with bipolar disorder.

European psychiatry : the journal of the Association of European Psychiatrists 22(5):305-308.

Hassel S, Almeida JR, Frank E, Versace A, Nau SA, Klein CR, Kupfer DJ, Phillips ML. 2009. Prefrontal cortical and striatal activity to happy and fear faces in bipolar disorder is associated with comorbid substance abuse and eating disorder. Journal of affective disorders 118(1-3):19-27.

Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. 1991. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. British journal of addiction 86(9):1119-1127.

Heffner JL, Fleck DE, DelBello MP, Adler CM, Strakowski SM. 2012. Cigarette smoking and impulsivity in bipolar disorder. Bipolar disorders 14(7):735-742.

Heffner JL, Strawn JR, DelBello MP, Strakowski SM, Anthenelli RM. 2011. The co-occurrence of cigarette smoking and bipolar disorder: phenomenology and treatment considerations. Bipolar disorders 13(5-6):439-453.

Heitzeg MM, Nigg JT, Hardee JE, Soules M, Steinberg D, Zubieta JK, Zucker RA. 2014. Left middle frontal gyrus response to inhibitory errors in children prospectively predicts early problem substance use. Drug and alcohol dependence 141:51-57.

Henley SM, Downey LE, Nicholas JM, Kinnunen KM, Golden HL, Buckley A, Mahoney CJ, Crutch SJ. 2014. Degradation of cognitive timing mechanisms in behavioural variant frontotemporal dementia. Neuropsychologia 65:88-101.

Hermens DF, Scott EM, White D, Lynch M, Lagopoulos J, Whitwell BG, Naismith SL, Hickie IB. 2013. Frequent alcohol, nicotine or cannabis use is common in young persons presenting for mental healthcare: a cross-sectional study. BMJ open 3(2).

Heron J, Maughan B, Dick DM, Kendler KS, Lewis G, Macleod J, Munafo M, Hickman M. 2013. Conduct problem trajectories and alcohol use and misuse in mid to late adolescence. Drug and alcohol dependence 133(1):100-107.

Hill SY, De Bellis MD, Keshavan MS, Lowers L, Shen S, Hall J, Pitts T. 2001. Right amygdala volume in adolescent and young adult offspring from families at high risk for developing alcoholism. Biological psychiatry 49(11):894-905.

Hill SY, Wang S, Carter H, McDermott MD, Zezza N, Stiffler S. 2013. Amygdala Volume in Offspring from Multiplex for Alcohol Dependence Families: The Moderating Influence of Childhood Environment and 5-HTTLPR Variation. Journal of alcoholism and drug dependence Suppl 1.

Holmila M, Raitasalo K. 2005. Gender differences in drinking: why do they still exist? Addiction (Abingdon, England) 100(12):1763-1769.

Hulvershorn LA, Cullen K, Anand A. 2011. Toward dysfunctional connectivity: a review of neuroimaging findings in pediatric major depressive disorder. Brain imaging and behavior 5(4):307-328.

Husky MM, Mazure CM, Paliwal P, McKee SA. 2008. Gender differences in the comorbidity of smoking behavior and major depression. Drug and alcohol dependence 93(1-2):176-179.

Hussong AM, Jones DJ, Stein GL, Baucom DH, Boeding S. 2011. An internalizing pathway to alcohol use and disorder. Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors 25(3):390-404.

Institute of Medicine Forum on N, Nervous System D. 2011. The National Academies Collection: Reports funded by National Institutes of Health. Sex Differences and

Implications for Translational Neuroscience Research: Workshop Summary. Washington (DC): National Academies Press (US) National Academy of Sciences.

Jarvis K, DelBello MP, Mills N, Elman I, Strakowski SM, Adler CM. 2008. Neuroanatomic comparison of bipolar adolescents with and without cannabis use disorders. Journal of child and adolescent psychopharmacology 18(6):557-563.

Jorgensen KN, Skjaervo I, Morch-Johnsen L, Haukvik UK, Lange EH, Melle I, Andreassen OA, Agartz I. 2015. Cigarette smoking is associated with thinner cingulate and insular cortices in patients with severe mental illness. Journal of psychiatry & neuroscience : JPN 40(4):241-249.

Kalmar JH, Wang F, Spencer L, Edmiston E, Lacadie CM, Martin A, Constable RT, Duncan JS, Staib LH, Papademetris X, Blumberg HP. 2009. Preliminary evidence for progressive prefrontal abnormalities in adolescents and young adults with bipolar disorder. Journal of the International Neuropsychological Society : JINS 15(3):476-481.

Kassel JD, Stroud LR, Paronis CA. 2003. Smoking, stress, and negative affect: correlation, causation, and context across stages of smoking. Psychological bulletin 129(2):270-304.

Kathleen Holmes M, Bearden CE, Barguil M, Fonseca M, Serap Monkul E, Nery FG, Soares JC, Mintz J, Glahn DC. 2009. Conceptualizing impulsivity and risk taking in bipolar disorder: importance of history of alcohol abuse. Bipolar disorders 11(1):33-40.

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. 1997. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. Journal of the American Academy of Child and Adolescent Psychiatry 36(7):980-988.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. 1994. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Archives of general psychiatry 51(1):8-19.

Kim E, Jung YC, Ku J, Kim JJ, Lee H, Kim SY, Kim SI, Cho HS. 2009. Reduced activation in the mirror neuron system during a virtual social cognition task in euthymic bipolar disorder. Progress in neuro-psychopharmacology & biological psychiatry 33(8):1409-1416.

Knight JR, Sherritt L, Harris SK, Gates EC, Chang G. 2003. Validity of brief alcohol screening tests among adolescents: a comparison of the AUDIT, POSIT, CAGE, and CRAFFT. Alcoholism, clinical and experimental research 27(1):67-73.

Knight JR, Sherritt L, Shrier LA, Harris SK, Chang G. 2002. Validity of the CRAFFT substance abuse screening test among adolescent clinic patients. Archives of pediatrics & adolescent medicine 156(6):607-614.

Knight JR, Shrier LA, Bravender TD, Farrell M, Vander Bilt J, Shaffer HJ. 1999. A new brief screen for adolescent substance abuse. Archives of pediatrics & adolescent medicine 153(6):591-596.

Koechlin E, Hyafil A. 2007. Anterior prefrontal function and the limits of human decision-making. Science (New York, NY) 318(5850):594-598.

Kolla NJ, van der Maas M, Toplak ME, Erickson PG, Mann RE, Seeley J, Vingilis E. 2016. Adult attention deficit hyperactivity disorder symptom profiles and concurrent problems with alcohol and cannabis: sex differences in a representative, population survey. BMC psychiatry 16(1):50.

Koob GF, Volkow ND. 2010. Neurocircuitry of addiction. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 35(1):217-238.

Kringelbach ML, Rolls ET. 2004. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Progress in neurobiology 72(5):341-372.

Krishnan KR. 2005. Psychiatric and medical comorbidities of bipolar disorder. Psychosomatic medicine 67(1):1-8.

Kuhn C. 2015. Emergence of sex differences in the development of substance use and abuse during adolescence. Pharmacology & therapeutics 153:55-78.

Kuhn S, Witt C, Banaschewski T, Barbot A, Barker GJ, Buchel C, Conrod PJ, Flor H, Garavan H, Ittermann B, Mann K, Martinot JL, Paus T, Rietschel M, Smolka MN, Strohle A, Bruhl R, Schumann G, Heinz A, Gallinat J. 2015. From mother to child: orbitofrontal cortex gyrification and changes of drinking behaviour during adolescence. Addiction biology.

Levy B, Monzani BA, Stephansky MR, Weiss RD. 2008. Neurocognitive impairment in patients with co-occurring bipolar disorder and alcohol dependence upon discharge from inpatient care. Psychiatry research 161(1):28-35.

Levy R, Goldman-Rakic PS. 2000. Segregation of working memory functions within the dorsolateral prefrontal cortex. Experimental brain research 133(1):23-32.

Leweke FM, Koethe D. 2008. Cannabis and psychiatric disorders: it is not only addiction. Addiction biology 13(2):264-275.

Li CS, Sinha R. 2008. Inhibitory control and emotional stress regulation: neuroimaging evidence for frontal-limbic dysfunction in psycho-stimulant addiction. Neuroscience and biobehavioral reviews 32(3):581-597.

Li Y, Yuan K, Cai C, Feng D, Yin J, Bi Y, Shi S, Yu D, Jin C, von Deneen KM, Qin W, Tian J. 2015. Reduced frontal cortical thickness and increased caudate volume within fronto-striatal circuits in young adult smokers. Drug and alcohol dependence 151:211-219.

Lieberman MD, Cunningham WA. 2009. Type I and Type II error concerns in fMRI research: re-balancing the scale. Social cognitive and affective neuroscience 4(4):423-428.

Malone IB, Leung KK, Clegg S, Barnes J, Whitwell JL, Ashburner J, Fox NC, Ridgway GR. 2015. Accurate automatic estimation of total intracranial volume: a nuisance variable with less nuisance. NeuroImage 104:366-372.

Manes F, Sahakian B, Clark L, Rogers R, Antoun N, Aitken M, Robbins T. 2002. Decision-making processes following damage to the prefrontal cortex. Brain : a journal of neurology 125(Pt 3):624-639.

Marshall DF, Walker SJ, Ryan KA, Kamali M, Saunders EF, Weldon AL, Adams KM, McInnis MG, Langenecker SA. 2012. Greater executive and visual memory dysfunction in comorbid bipolar disorder and substance use disorder. Psychiatry research 200(2-3):252-257.

McChargue DE, Cohen LM, Cook JW. 2004. Attachment and depression differentially influence nicotine dependence among male and female undergraduates: a preliminary study. Journal of American college health : J of ACH 53(1):5-10.

McQueeny T, Padula CB, Price J, Medina KL, Logan P, Tapert SF. 2011. Gender effects on amygdala morphometry in adolescent marijuana users. Behavioural brain research 224(1):128-134.

Meerwijk EL, Ford JM, Weiss SJ. 2013. Brain regions associated with psychological pain: implications for a neural network and its relationship to physical pain. Brain imaging and behavior 7(1):1-14.

Miettunen J, Murray GK, Jones PB, Maki P, Ebeling H, Taanila A, Joukamaa M, Savolainen J, Tormanen S, Jarvelin MR, Veijola J, Moilanen I. 2014. Longitudinal associations between childhood and adulthood externalizing and internalizing psychopathology and adolescent substance use. Psychological medicine 44(8):1727-1738.

Modinos G, Ormel J, Aleman A. 2009. Activation of anterior insula during self-reflection. PloS one 4(2):e4618.

Moitra E, Anderson BJ, Stein MD. 2015. Reductions in cannabis use are associated with mood improvement in female emerging adults. Depression and anxiety.

Morales AM, Ghahremani D, Kohno M, Hellemann GS, London ED. 2014. Cigarette exposure, dependence, and craving are related to insula thickness in young adult smokers. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 39(8):1816-1822.

Muhlert N, Lawrence AD. 2015. Brain structure correlates of emotion-based rash impulsivity. NeuroImage 115:138-146.

Najt P, Wang F, Spencer L, Johnston JA, Cox Lippard ET, Pittman BP, Lacadie C, Staib LH, Papademetris X, Blumberg HP. 2015. Anterior Cortical Development During Adolescence in Bipolar Disorder. Biological psychiatry 79(4)303-310.

Naqvi NH, Gaznick N, Tranel D, Bechara A. 2014. The insula: a critical neural substrate for craving and drug seeking under conflict and risk. Annals of the New York Academy of Sciences 1316:53-70.

Naqvi NH, Rudrauf D, Damasio H, Bechara A. 2007. Damage to the insula disrupts addiction to cigarette smoking. Science (New York, NY) 315(5811):531-534.

Nery FG, Hatch JP, Monkul ES, Matsuo K, Zunta-Soares GB, Bowden CL, Soares JC. 2013. Trait impulsivity is increased in bipolar disorder patients with comorbid alcohol use disorders. Psychopathology 46(3):145-152.

Nery FG, Matsuo K, Nicoletti MA, Monkul ES, Zunta-Soares GB, Hatch JP, Lafer B, Soares JC. 2011. Association between prior alcohol use disorders and decreased prefrontal gray matter volumes in bipolar I disorder patients. Neuroscience letters 503(2):136-140.

Nery FG, Stanley JA, Chen HH, Hatch JP, Nicoletti MA, Monkul ES, Lafer B, Soares JC. 2010. Bipolar disorder comorbid with alcoholism: a 1H magnetic resonance spectroscopy study. Journal of psychiatric research 44(5):278-285.

Nolen WA, Luckenbaugh DA, Altshuler LL, Suppes T, McElroy SL, Frye MA, Kupka RW, Keck PE, Jr., Leverich GS, Post RM. 2004. Correlates of 1-year prospective outcome in bipolar disorder: results from the Stanley Foundation Bipolar Network. The American journal of psychiatry 161(8):1447-1454.

Norman AL, Pulido C, Squeglia LM, Spadoni AD, Paulus MP, Tapert SF. 2011. Neural activation during inhibition predicts initiation of substance use in adolescence. Drug and alcohol dependence 119(3):216-223.

Oesterle TS, Hitschfeld MJ, Lineberry TW, Schneekloth TD. 2015. CRAFFT as a Substance Use Screening Instrument for Adolescent Psychiatry Admissions. Journal of psychiatric practice 21(4):259-266.

Oshri A, Rogosch FA, Burnette ML, Cicchetti D. 2011. Developmental pathways to adolescent cannabis abuse and dependence: child maltreatment, emerging personality, and internalizing versus externalizing psychopathology. Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors 25(4):634-644.

Padula CB, McQueeny T, Lisdahl KM, Price JS, Tapert SF. 2015. Craving is associated with amygdala volumes in adolescent marijuana users during abstinence. The American journal of drug and alcohol abuse 41(2):127-132.

Patton JH, Stanford MS, Barratt ES. 1995. Factor structure of the Barratt impulsiveness scale. Journal of clinical psychology 51(6):768-774.

Peeters M, Vollebergh WA, Wiers RW, Field M. 2014. Psychological changes and cognitive impairments in adolescent heavy drinkers. Alcohol and alcoholism (Oxford, Oxfordshire) 49(2):182-186.

Perroud N, Cordera P, Zimmermann J, Michalopoulos G, Bancila V, Prada P, Dayer A, Aubry JM. 2014. Comorbidity between attention deficit hyperactivity disorder (ADHD) and bipolar disorder in a specialized mood disorders outpatient clinic. Journal of affective disorders 168:161-166.

Petrides M, Pandya DN. 2007. Efferent association pathways from the rostral prefrontal cortex in the macaque monkey. The Journal of neuroscience : the official journal of the Society for Neuroscience 27(43):11573-11586.

Pfeifer JH, Peake SJ. 2012. Self-development: integrating cognitive, socioemotional, and neuroimaging perspectives. Developmental cognitive neuroscience 2(1):55-69.

Pilowsky DJ, Wu LT. 2013. Screening instruments for substance use and brief interventions targeting adolescents in primary care: a literature review. Addictive behaviors 38(5):2146-2153.

Ramnani N, Owen AM. 2004. Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. Nature reviews Neuroscience 5(3):184-194.

Rogosch FA, Oshri A, Cicchetti D. 2010. From child maltreatment to adolescent cannabis abuse and dependence: a developmental cascade model. Development and psychopathology 22(4):883-897.

Rolls ET. 2004. The functions of the orbitofrontal cortex. Brain and cognition 55(1):11-29.

Saraceno L, Heron J, Munafo M, Craddock N, van den Bree MB. 2012. The relationship between childhood depressive symptoms and problem alcohol use in early adolescence: findings from a large longitudinal population-based study. Addiction (Abingdon, England) 107(3):567-577.

Sinha R, Li CS. 2007. Imaging stress- and cue-induced drug and alcohol craving: association with relapse and clinical implications. Drug and alcohol review 26(1):25-31.

Squeglia LM, Pulido C, Wetherill RR, Jacobus J, Brown GG, Tapert SF. 2012. Brain response to working memory over three years of adolescence: influence of initiating heavy drinking. Journal of studies on alcohol and drugs 73(5):749-760.

Stein MB, Simmons AN, Feinstein JS, Paulus MP. 2007. Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. The American journal of psychiatry 164(2):318-327.

Steinhausen HC, Eschmann S, Metzke CW. 2007. Continuity, psychosocial correlates, and outcome of problematic substance use from adolescence to young adulthood in a community sample. Child and adolescent psychiatry and mental health 1(1):12.

Strakowski SM, Adler CM, Almeida J, Altshuler LL, Blumberg HP, Chang KD, DelBello MP, Frangou S, McIntosh A, Phillips ML, Sussman JE, Townsend JD. 2012. The functional neuroanatomy of bipolar disorder: a consensus model. Bipolar disorders 14(4):313-325.

Strakowski SM, DelBello MP. 2000. The co-occurrence of bipolar and substance use disorders. Clinical psychology review 20(2):191-206.

Strakowski SM, DelBello MP, Fleck DE, Adler CM, Anthenelli RM, Keck PE, Jr., Arnold LM, Amicone J. 2007. Effects of co-occurring cannabis use disorders on the course of bipolar disorder after a first hospitalization for mania. Archives of general psychiatry 64(1):57-64.

Sullivan EV, Pfefferbaum A. 2005. Neurocircuitry in alcoholism: a substrate of disruption and repair. Psychopharmacology 180(4):583-594.

Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Moeller FG. 2004. Impulsivity: a link between bipolar disorder and substance abuse. Bipolar disorders 6(3):204-212.

Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Steinberg JL, Moeller FG. 2005. Increased impulsivity associated with severity of suicide attempt history in patients with bipolar disorder. The American journal of psychiatry 162(9):1680-1687.

Swann AC, Steinberg JL, Lijffijt M, Moeller FG. 2008. Impulsivity: differential relationship to depression and mania in bipolar disorder. Journal of affective disorders 106(3):241-248.

Takahashi T, Malhi GS, Wood SJ, Yucel M, Walterfang M, Tanino R, Suzuki M, Pantelis C. 2010. Insular cortex volume in established bipolar affective disorder: a preliminary MRI study. Psychiatry research 182(2):187-190.

Tang LR, Liu CH, Jing B, Ma X, Li HY, Zhang Y, Li F, Wang YP, Yang Z, Wang CY. 2014. Voxel-based morphometry study of the insular cortex in bipolar depression. Psychiatry research 224(2):89-95.

Tarter RE, Kirisci L, Gavaler JS, Reynolds M, Kirillova G, Clark DB, Wu J, Moss HB, Vanyukov M. 2009. Prospective study of the association between abandoned dwellings and testosterone level on the development of behaviors leading to cannabis use disorder in boys. Biological psychiatry 65(2):116-121.

Urcelay GP, Dalley JW. 2012. Linking ADHD, impulsivity, and drug abuse: a neuropsychological perspective. Current topics in behavioral neurosciences 9:173-197.

Van Leijenhorst L, Gunther Moor B, Op de Macks ZA, Rombouts SA, Westenberg PM, Crone EA. 2010. Adolescent risky decision-making: neurocognitive development of reward and control regions. NeuroImage 51(1):345-355.

Verplaetse TL, Weinberger AH, Smith PH, Cosgrove KP, Mineur YS, Picciotto MR, Mazure CM, McKee SA. 2015. Targeting the noradrenergic system for gender-sensitive medication development for tobacco dependence. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 17(4):486-495.

Wang F, Kalmar JH, Womer FY, Edmiston EE, Chepenik LG, Chen R, Spencer L, Blumberg HP. 2011. Olfactocentric paralimbic cortex morphology in adolescents with bipolar disorder. Brain : a journal of neurology 134(Pt 7):2005-2012.

Weinberger AH, Maciejewski PK, McKee SA, Reutenauer EL, Mazure CM. 2009. Gender differences in associations between lifetime alcohol, depression, panic disorder, and posttraumatic stress disorder and tobacco withdrawal. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions 18(2):140-147.

Weinberger AH, Mazure CM, Morlett A, McKee SA. 2013a. Two decades of smoking cessation treatment research on smokers with depression: 1990-2010. Nicotine & tobacco research: official journal of the Society for Research on Nicotine and Tobacco 15(6):1014-1031.

Weinberger AH, Pilver CE, Desai RA, Mazure CM, McKee SA. 2012. The relationship of major depressive disorder and gender to changes in smoking for current and former smokers: longitudinal evaluation in the US population. Addiction (Abingdon, England) 107(10):1847-1856.

Weinberger AH, Pilver CE, Desai RA, Mazure CM, McKee SA. 2013b. The relationship of dysthymia, minor depression, and gender to changes in smoking for current and former smokers: longitudinal evaluation in the U.S. population. Drug and alcohol dependence 127(1-3):170-176.

Wetherill RR, Squeglia LM, Yang TT, Tapert SF. 2013. A longitudinal examination of adolescent response inhibition: neural differences before and after the initiation of heavy drinking. Psychopharmacology 230(4):663-671.

Xue G, Lu Z, Levin IP, Bechara A. 2010. The impact of prior risk experiences on subsequent risky decision-making: the role of the insula. NeuroImage 50(2):709-716.

Table/Figure Legends

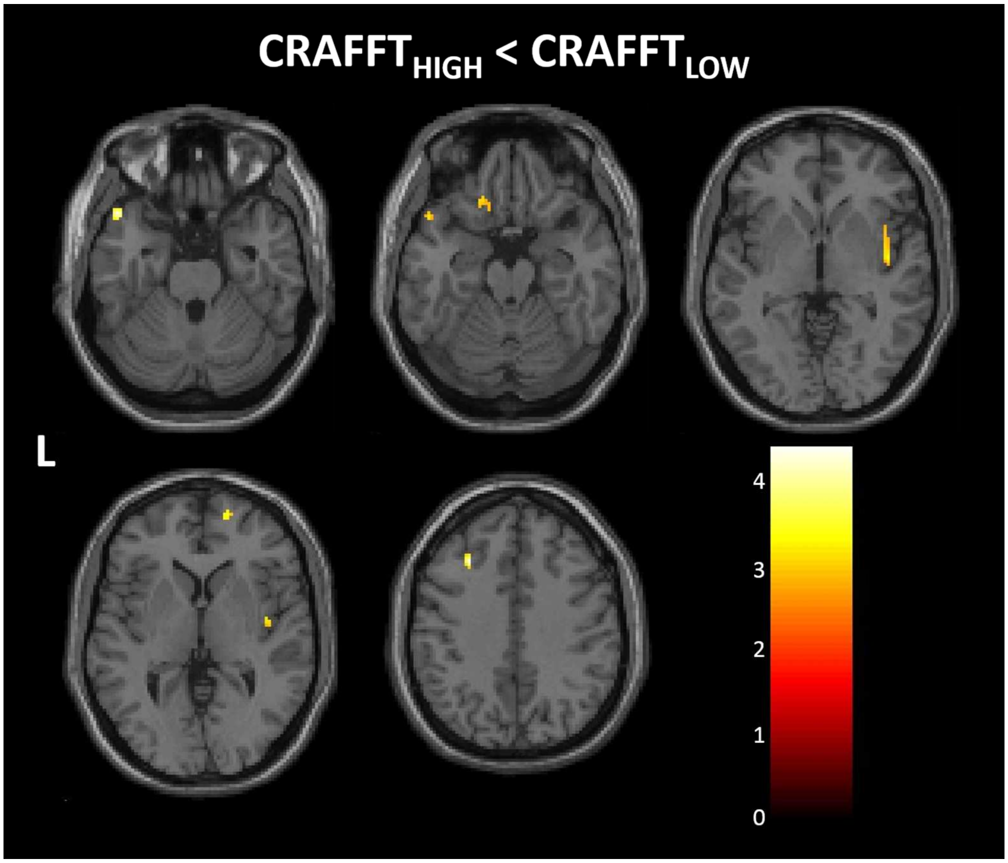
Table 1. Participant Characteristics Age at baseline scan, age at follow-up, interval between scan and follow-up, and age of first mood episode were examined by a t-test to assess effect of CRAFFT group (CRAFFT$_{HIGH}$ versus CRAFFT$_{LOW}$). All other factors were examined with Chi-square or Fisher's exact tests. [F]represents p-value calculated with Fisher's exact test. [1]Elevated mood includes subjects in hypomanic, manic, and mixed mood states. [2]Rapid-cycling reported is lifetime history of rapid cycling. [3]Presence of disorders of childhood were assessed by structured interview in subjects <18 years; percentage is based on the overall sample. [4]Individuals on levothyroxine had hypothyroidism. Results are shown across all subjects and when looking within males and within females separately.

Figure 1. Gray Matter Volume Decreases in Bipolar Disorder with Prospective Substance use Problems The images show the regions of gray matter volume decreases in the bipolar disorder (BD) group with prospective substance use problems (CRAFFT$_{HIGH}$), compared to the group with bipolar disorder without prospective substance use problems (CRAFFT$_{LOW}$). No regions of gray matter volume increases were observed in the BD CRAFFT$_{HIGH}$ group compared to BD CRAFFT$_{LOW}$ group. Significance threshold is $p<0.005$, cluster ≥ 20 voxels. 'L' on left of figure denotes left side of brain. The color bar represents the range of T values. BD CRAFFT$_{HIGH}$ N=19, BD CRAFFT$_{LOW}$ N=11.

		All Subjects			Male Subjects			Female Subjects		
		$CRAFFT_{LOW}$ (N=11)	$CRAFFT_{HIGH}$ (N=19)	p value	$CRAFFT_{LOW}$ (N=6)	$CRAFFT_{HIGH}$ (N=9)	p value	$CRAFFT_{LOW}$ (N=5)	$CRAFFT_{HIGH}$ (N=10)	p value
Demographics/ Clinical Factors	Age at Baseline Scan (SD)	17.1 (2.4)	16.1 (1.6)	0.199	17.5 (2.8)	16.0 (1.4)	0.204	16.6 (2.1)	16.2 (1.9)	0.691
	Age at Follow-up (SD)	23.5 (4.3)	22.1 (2.2)	0.226	23.8 (4.4)	23.1 (2.1)	0.656	23.2 (4.6)	21.2 (1.9)	0.251
	Interval Between Scan and Follow-up (SD)	6.5 (2.3)	6.0 (1.9)	0.560	6.4 (2.3)	7.0 (1.3)	0.561	6.6 (2.5)	5.0 (1.8)	0.197
	Age of First Mood Episode	9.5 (6.0)	9.7 (3.2)	0.934	9.8 (6.9)	8.6 (2.8)	0.624	9.2 (5.4)	10.7 (3.2)	0.510
	Mood State [Euthymic(%) / Depressed(%) / Elevated[1](%)]	9 (82) / 0 (0) / 2 (18)	13 (68) / 2 (11) / 4 (21)	0.824^{F}	4 (67) / 0 (0) / 2 (33)	7 (78) / 0 (0) / 2 (22)	1.000^{F}	5 (100) / 0 (0) / 0 (0)	6 (60) / 2 (20) / 2 (20)	0.341^{F}
	Prior Hospitalizations (%)	5 (45)	15 (79)	0.061	3 (50)	6 (67)	0.624^{F}	2 (40)	9 (90)	0.077^{F}
	Rapid Cycling (%)[2]	5 (45)	6 (32)	0.447	2 (33)	3 (33)	1.000^{F}	3 (60)	3 (30)	0.329^{F}
	Lifetime Psychosis (%)	6 (55)	10 (53)	0.919	5 (83)	4 (44)	0.287^{F}	1 (20)	6 (60)	0.282^{F}
	Suicide Attempt (%)	1 (9)	3 (16)	1.000^{F}	1 (17)	0 (0)	0.400^{F}	0 (0)	3 (30)	0.171^{F}
	Cigarette/Tobacco Use History at Baseline	0 (0)	3 (16)	0.279^{F}	0 (0)	1 (11)	1.000^{F}	0 (0)	2 (20)	0.524^{F}
Comorbidites	Simple/ Specific Phobia (%)	0 (0)	3 (16)	0.279^{F}	0 (0)	1 (11)	1.000^{F}	0 (0)	2 (20)	0.524^{F}
	Attention Deficit Hyperactivity Disorder[3]	2 (18)	8 (42)	0.247^{F}	1 (17)	7 (78)	0.041^{F}	1 (20)	1 (10)	1.000^{F}
	Oppositional Defiant Disorder[3]	1 (9)	2 (11)	1.000^{F}	1 (17)	2 (22)	1.000^{F}	0 (0)	0 (0)	-
	Conduct Disorder[3]	1 (9)	0 (0)	0.336^{F}	1 (17)	0 (0)	0.400^{F}	0 (0)	0 (0)	-
	Separation Anxiety[3]	1 (9)	0 (0)	0.336^{F}	1 (17)	0 (0)	0.400^{F}	0 (0)	0 (0)	-
Medications	Medicated at scan (%)	9 (82)	18 (95)	0.537^{F}	2 (33)	0 (0)	0.143^{F}	0 (0)	1 (10)	1.000^{F}
	Antipsychotic (%)	6 (55)	12 (63)	0.645	3 (50)	5 (56)	1.000^{F}	3 (60)	7 (70)	1.000^{F}
	Anticonvulsant (%)	5 (45)	6 (32)	0.447	2 (33)	2 (22)	1.000^{F}	3 (60)	4 (40)	0.608^{F}
	Stimulant (%)	2 (18)	8 (42)	0.247^{F}	1 (17)	7 (78)	0.041^{F}	1 (20)	1 (10)	1.000^{F}
	Lithium (%)	2 (18)	7 (37)	0.419^{F}	2 (33)	4 (44)	1.000^{F}	0 (0)	3 (30)	0.506^{F}
	Antidepressant (%)	2 (18)	3 (16)	1.000^{F}	0 (0)	1 (11)	1.000^{F}	2 (40)	2 (20)	0.560^{F}
	Benzodiazepine (%)	2 (18)	3 (16)	1.000^{F}	1 (17)	1 (11)	1.000^{F}	1 (20)	2 (20)	1.000^{F}
	Ketamine (%)	1 (9)	0 (0)	1.000^{F}	1 (17)	0 (0)	0.400^{F}	0 (0)	0 (0)	-
	Adrenergic Agonist (%)	0 (0)	1 (5)	1.000^{F}	0 (0)	1 (11)	1.000^{F}	0 (0)	0 (0)	-
	Amantadine (%)	0 (0)	1 (5)	1.000^{F}	0 (0)	1 (11)	1.000^{F}	0 (0)	0 (0)	-
	Levothyroxine (%)[4]	1 (9)	3 (16)	1.000^{F}	1 (17)	2 (22)	1.000^{F}	0 (0)	1 (10)	1.000^{F}

Participant Characteristics Age at baseline scan, age at follow-up, interval between scan and follow-up, and age of first mood episode were examined by a t-test to assess effect of CRAFFT group ($CRAFFT_{HIGH}$ versus $CRAFFT_{LOW}$). All other factors were examined with Chi-square or Fisher's exact tests. ^{F}represents p-value calculated with Fisher's exact test. [1]Elevated mood includes subjects in hypomanic, manic, and mixed mood states. [2]Rapid-cycling reported is lifetime history of rapid cycling. [3]Presence of disorders of childhood were assessed by structured interview in subjects <18 years; percentage is based on the overall sample. [4]Individuals on levothyroxine had hypothyroidism. Results are shown across all subjects and when looking within males and within females separately.

665x256mm (96 x 96 DPI)



Gray Matter Volume Decreases in Bipolar Disorder with Prospective Substance use Problems The images show the regions of gray matter volume decreases in the bipolar disorder (BD) group with prospective substance use problems (CRAFFT$_{HIGH}$), compared to the group with bipolar disorder without prospective substance use problems (CRAFFT$_{LOW}$). No regions of gray matter volume increases were observed in the BD CRAFFT$_{HIGH}$ group compared to BD CRAFFT$_{LOW}$ group. Significance threshold is $p<0.005$, cluster >20 voxels. 'L' on left of figure denotes left side of brain. The color bar represents the range of T values. BD CRAFFT$_{HIGH}$ N=19, BD CRAFFT$_{LOW}$ N=11.
256x219mm (150 x 150 DPI)