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Rethinking "Aggression" and Impulsivity in Bipolar Disorder: Risk, Clinical and Brain Circuitry Features

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Abstract

Background: Elevated aggression and impulsivity are implicated in Bipolar Disorder (BD); however, relationships between these behavioral constructs have not been clarified, which can lead to misconceptions with negative consequences including stigma and adverse outcomes including suicide. The study aimed to clarify brain-based distinctions between the two constructs and their associations to risk factors, symptoms and suicide thoughts and behaviors.

Methods: Self-rated Brown-Goodwin Aggression (BGA) and Barratt Impulsiveness Scale (BIS) scores were compared between adults with BD (n=38, 74% female) and healthy controls (HC, n=29, 64% female). Relationships were examined between BGA and BIS with childhood trauma

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questionnaire (CTQ), mood, comorbidities, and magnetic resonance imaging gray matter volume (GMV) assessments.

Results: In BD, BGA and BIS total scores were both elevated and associated with childhood maltreatment (CM), particularly emotional CM, depression, substance use disorders (SUDs) and suicide attempts (SAs). BGA scores were increased by items corresponding to dysregulation of emotional and social behavior and associated with elevated mood states and suicide ideation and GMV decreases in bilateral orbitofrontal cortex and left posterior insula brain regions, previously associated with these behaviors and clinical features. BIS motor impulsiveness scores were associated with GMV decreases in anterior cingulate cortex implicated in mood and behavioral dyscontrol.

Limitations: modest sample size, self-reports

Conclusions: The findings suggest separable brain-based domains of dysfunction in BD of motor impulsiveness versus emotionally dysregulated feelings that are primarily self-directed. Both domains are associated with suicide behavior and modifiable risk factors of CM, depression and SUDs that could be targeted for prevention.

Keywords

bipolar disorder; aggression; impulsive behavior; MRI; prefrontal cortex; insula

Introduction

Elevated impulsivity and aggression have previously been implicated in Bipolar Disorder (BD). However, ambiguity surrounds the specific constructs measured by scales designed to assess aggression and how they relate to impulsivity. Misunderstanding of aggression and impulsivity can lead to misconceptions about persons with BD that can have negative consequences, including stigma and missed opportunities for reduction of adverse outcomes of BD including suicide. Studies reporting elevated aggression in BD have used varying measures and often have not distinguished self-directed aggression or have studied impulsive-aggression as a unitary construct. The scales used to measure aggression have assessed many subjective experiences and behaviors, not just violence towards others. Items included on many commonly used scales aimed to measure aggression assess subjective feelings related to emotion dysregulation, self-directed behavior and interpersonal impairment, in addition to outward aggression or violence; however, the contribution of these items, while having quite different implications, is often not identified, risking misattribution of elevated rating to tendency towards violence. When impulsiveness is studied separately, a commonly used measure is the Barratt Impulsiveness Scale (BIS), which instead provides measures of cognitive behavior domains of motor, non-planning, and cognitive-attentional impulsiveness. Relative to aggression, impulsiveness has been more widely studied with BIS elevations detected in adolescents and adults with BD, and independent of mood state, suggesting it may be an early trait feature of BD (Etain et al., 2013; Najt et al., 2007b; Nandagopal et al., 2011; Newman and Meyer, 2014; Peluso et al., 2005; Saddichha and Schuetz, 2014; Swann et al., 2009; Swann et al., 2003).

Potential distinctions between the constructs measured by scales aimed to study aggression and impulsiveness are further suggested by differences in reported brain associations in BD. Scores on scales designed to measure aggression, including the Lifetime History of Aggression (Coccaro et al., 1997) and the Brief Aggression Questionnaire (Webster et al., 2014), have been associated with decreased gray matter volume (GMV) in medial and lateral ventral prefrontal cortices in the general population, and particularly in orbitofrontal cortex (OFC) in psychiatric patients, including persons with BD (Chester et al., 2017; Coccaro et al., 2018; Gansler et al., 2009). The OFC subserves emotional and social behaviors, as well as inhibition of maladaptive responses especially in the context of changing reinforcement contingencies (Rolls, 2019). Decreased OFC GMV has also been associated with BIS scores among non-psychiatric populations by Matsuo and colleagues (Matsuo et al., 2009a). However, in studying persons with BD, they did not detect associations of BIS with decreased OFC GMV, but instead with dorsal and rostral anterior cingulate cortex (ACC) GMV (Cauda et al., 2011), particularly associated with the motor subscale (Matsuo et al., 2009b), suggesting the connection between ACC volume and cognitive motor control in BD. Both aggression and impulsiveness measures have shown associations with childhood maltreatment (CM) (Adigüzel et al., 2019; Garno et al., 2008; Richard-Lepouriel et al., 2019; Song et al., 2020; Tunc and Kose, 2019), mood symptoms (Garno et al., 2008; Strakowski et al., 2009; Swann et al., 2008), substance use disorders (SUDs) (Cassidy et al., 2001; Garno et al., 2008; Grunebaum et al., 2006a; Latalova, 2009; Swann et al., 2004) and suicide behavior in BD (Ekinci et al., 2011; Gilbert et al., 2011; Grunebaum et al., 2006b; Jiménez et al., 2012; Jiménez et al., 2016; Mahon et al., 2012; Michaelis et al., 2004; Oquendo et al., 2004; Oquendo et al., 2000; Reich et al., 2019). Thus, improved understanding of aggression and impulsivity in BD, and the relationship between them with factors, such as CM, SUD, and severe outcomes, could inform prevention strategies.

The current study is one of the first investigations in BD of associations of the self-reported Brown Goodwin Aggression (BGA) and BIS with CM, comorbidity, mood state and symptoms, suicide thoughts and behaviors (STBs), and brain regional GMV. We hypothesized that both BGA and BIS scores would be elevated in BD relative to HC, although BGA score elevations would not exclusively reflect aggression towards others or violent behavior. We anticipated that the BGA and BIS would show similar associations, as identified previously, to risk factors and adverse outcomes including CM, SUDs, mood symptoms and STBs. However, we hypothesized that the BGA and BIS would have different associations with regional GMV in BD, reflecting distinctions in the behavioral constructs they measure.

Methods and Materials

Subjects

Participants included 38 BD subjects (ages 18-58 years; mean age±standard deviation (SD): 35.7±11.5 years; 74% female) and 29 matched HCs (ages 18-57 years; mean±SD: 38.3±11.2 years; 66% female) without any DSM-IV Axis I disorder or first-degree family member with a major mood or psychotic disorder on the Family History Screen for

Epidemiological Studies (Lish et al., 1995). Diagnostic groups were matched for age, gender, and socioeconomic status (Hollingshead, 1957) (Table 1).

Psychiatric diagnosis, mood state, rapid cycling, and psychosis history were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1995). Thirteen (34%) BD subjects were euthymic, 10 (26%) depressed, and 15 (39%) in elevated mood states (manic/hypomanic/mixed). Mood symptom severity was assessed with the 29-item Hamilton Depression Rating Scale (Hamilton, 1960) and Young Mania Rating Scale (Young et al., 1978) and most severe lifetime suicide ideation with the Beck Scale for Suicide Ideation (Beck et al., 1979). Thirteen (34%) had an actual SA by the Columbia Suicide History Form (Oquendo et al., 2004). Table 2 lists clinical characteristics of the BD sample.

Participants were recruited from clinical programs affiliated with the Yale School of Medicine and greater Connecticut community and were without history of medical (except 1 BD with treated hypothyroidism) or neurological disorders/conditions that could affect the central nervous system, including loss of consciousness >5min, substance or alcohol abuse or dependence within 3 months, or positive toxicology screen. Subjects provided written informed consent in accordance with Yale Human Investigation Committee/Institutional Review Board.

Aggression, Impulsiveness and CM Self-Ratings

Lifetime aggression was measured on the BGA by semistructured interview in which subjects reported frequency of specified behaviors in adolescence and adulthood (Brown et al., 1979; Manuck et al., 1998). BGA total score is the sum of scores on ten items, each the maximum of adolescent and adult frequencies (never=1, rarely=2, occasionally=3, often=4) (Coccaro et al., 1996; Manuck et al., 1998). An 11^{th} item assesses non-suicidal self-injury (NSSI). Trait impulsivity was measured using the BIS-11 self-report (Patton et al., 1995) total and three subscale scores: motor, non-planning, and cognitive-attentional impulsiveness. Participants self-reported CM using the Childhood Trauma Questionnaire short form (CTQ) (Bernstein et al., 1994; Bernstein et al., 2003). Analyses were performed for CTQ total and five subscale scores: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect.

Imaging Acquisition

Structural magnetic resonance imaging (sMRI) data were acquired using a single 3-Tesla Siemens Trio MR scanner (Siemens, Erlangen, Germany). Sagittal sMRI images were obtained with a T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence using the following parameters: echo time (TE) = 2.83 ms, repetition time (TR) = 1500 ms, matrix = 256 x 256 matrix, field of view = 256 x 256 mm^2, 160 one-mm slices without gaps.

Statistical Analyses

Continuous variables were tested for normality using Kolmogorov-Smirnov tests and normal probability plots. Groups were compared using independent t-tests or Mann-Whitney U tests for continuous, and Chi-square tests for categorical, variables. Spearman correlation

coefficients were estimated to examine relationships between behavioral and clinical variables and BGA total and BIS total and subscale scores within HCs and BDs, separately. Mann-Whitney U or Kruskal-Wallis tests (BGA) and independent samples t-tests or ANOVA (BIS total) were used to examine relationships between the scores with categorical demographic and behavioral variables within each group. Comorbidities were analyzed if in ≥10 BD subjects. As these analyses were exploratory, results were considered significant at an uncorrected, two-tailed alpha threshold of 0.05.

Imaging Processing and Analyses

Statistical Parametric Mapping (SPM)-12 was used for image processing, as described previously (Lippard et al., 2019), and for group level analyses. General linear models were constructed to conduct whole-brain voxel-based analyses to assess relationships between GMV and BGA or BIS, within BD and HC groups, corrected for individual intracranial volume (ICV) (Pell et al., 2008). Results were considered significant at voxel threshold p<.005 and cluster k>=20, and if surviving cluster-based correction for multiple comparisons of p<.05 [family-wise error (FWE)-corrected; $p_{fwe\text{-}cluster}$<.05]. Exploratory analyses were performed using partial correlation tests between GMV extracted from significant clusters and each BIS subscale, controlling for the other subscales and corrected for ICV, and results were considered significant at $p_{uncorrected}$<.05. All significant results are reported.

Results

Compared to HC group, the BD group had higher BGA total scores (U=274.5, p<.001), with increases observed for items 1 (discipline), 3 (angry outbursts/temper tantrums), 4 (getting along with supervisor), 5 (severe arguments), 7 (destroyed property), 10 (tried to hurt other) and 11 (NSSI) (Table 2, p's<.05). Higher BIS total (U=77.0, p<.001) and all subscale (U≥104.0, p's<.001) scores were observed among BD compared to HCs.

BGA Score Associations Within BD

BGA scores were positively associated with CTQ emotional neglect subscale (r_s=.384, p=.025), HDRS (r_s=.363, p=.025) and YMRS (r_s=.389, p=.016) scores and mood state (H(2)=7.0, p=.030). BGA scores were higher in BD subjects in elevated than depressed states (p=.008); scores in euthymia were intermediate but did not differ significantly from the acute mood state groups. BGA scores were higher in past SAs than non-attempters (NSAs) (U=66.5, p=.003), and associated with most severe lifetime SI (r_s,=.497, p=.002) and with a history of alcohol/substance abuse/dependence (U=99.0, p=.021).

BGA scores correlated negatively with GMV in bilateral OFC (Brodman Areas, BAs, 11/47; peak Montreal Neurological Institute (MNI) coordinates x=12mm, y=28mm, z=−27mm; k=1819 voxels, $p_{fwe\text{-}cluster}$=.001) and left posterior insula (PIns; peak x=−38mm, y=−8mm, z=16mm; k=1066 voxels, $p_{fwe\text{-}cluster}$=.026) (Figure 1).

BIS Total and Subscore Associations Within BD

BIS total scores were positively associated with CTQ total (r_s=.340, p=.023), emotional abuse (r_s=.567, p<.001) and emotional neglect (r_s=.349, p=.043) and HDRS (r_s=.369, p=.023) scores. BIS scores were higher in past SAs than NSAs (t(36)=−2.98, p=.005) and among subjects with history of alcohol/substance abuse/dependence (t(36)=−2.73, p=.010). Cannabis and cocaine abuse/dependence were the only substances in sufficient numbers to explore; BIS total scores were higher in those with than without a history of cocaine abuse/dependence (t(36)=−2.96, p=.005).

BIS total scores correlated negatively with GMV in bilateral ACC regions (BAs 32/24; bilaterally the peaks were in dorsal ACC and the clusters extended to rostral ACC and on the left into ventral ACC (x=−16mm, y=34mm, z=22mm; x=14mm, y=33mm, z=12mm, k=3404 voxels; $p_{fwe\text{-}cluster}$<.001) (Figure 1). Controlling for other two subscales, the BIS motor subscale was negatively correlated with bilateral ACC GMV (r=−.476, p=.004).

Discussion

In adults with BD, both BGA and BIS scores were higher in the BD than in the HC group and associated with emotional subtypes of CM, depression, and history of SUDs and SAs. BGA, but not BIS, scores were associated with elevated mood states and lifetime SI severity. BIS, but not BGA, scores were associated with history of cocaine abuse/dependence. In BD, BGA scores were negatively associated with GMV in bilateral OFC and left Pins, while BIS scores were negatively associated with GMV in bilateral ACC.

Higher BGA scores in BD are consistent with prior literature (Ballester et al., 2012; Perroud et al., 2011). However, it is noteworthy that the BGA provides subject's self-report of a wide array of behaviors, with items ranging from benign outbursts to attempting to hurt others. Six of the ten items were significantly higher in BD. Several indicate dysregulated social interactions but not violent physical aggression, and these were the most frequently reported of the items; for example, being disciplined (item 1), having outbursts (item 3), difficulty getting along with supervisors (item 4), and severe arguments (item 5). While item 10, in which subjects reported having attacked another person with a weapon, was significantly higher in BD, only six participants endorsed this behavior and for two who provided the context it was as self-defense when under physical and sexual assault. Together with associations of BGA scores with SI, suicide attempts and NSSI, the findings are consistent with literature that individuals with psychiatric disorders are more likely to self-harm than harm others and be the victims rather than perpetrators of violence (Trevillion et al., 2012). Future research that carefully parses the specific behavioral domains within the wide range of behavior often subsumed under the term "aggression," and whether the behavior is directed to self or others, as well as the circumstances, may help to reduce misconceptions and societal stigmatization of those with BD.

The identification of associations of CM and adverse clinical factors in BD with BGA and BIS scores has potential to inform strategies to reduce and prevent aggression and impulsiveness. Consistent with previous reports, both were associated with emotional subtypes of CM (Garno et al., 2008; Tunc and Kose, 2019), suggesting the importance of

addressing prevention of not only physical but also emotional CM. Also in agreement with earlier studies, both BGA and BIS were higher in individuals with a history of comorbid SUDs (Grunebaum et al., 2006a; Latalova, 2009; Swann et al., 2004). Though a small subsample had history of cocaine dependence/abuse, the association with elevated BIS score in BD is consistent with prior reports (Moeller et al., 2002; Moeller et al., 2001). While CM and SUDs may be risk factors for aggression and impulsiveness, longitudinal studies are needed to clarify these relationships.

Both BGA and BIS scores were associated with HDRS scores suggesting associations of aggression and impulsiveness with negative affect. In line with prior reports on BGA scores, in addition to being associated with depressive symptoms, scores were also associated with manic symptoms as measured by YMRS (Garno et al., 2008), as well as elevated mood states in BD. These data further suggest the BGA measure's relation to emotion dysregulation and both depressed and elevated symptoms (Rey et al., 2016; Van Rheenen et al., 2015). While associations to mood symptoms may reflect contributions of emotion dysregulation to aggressive feelings and behavior, it is also possible that mood at time of assessment influenced subjects' self-reported ratings (Barnett et al., 2011; Vojta et al., 2001). In contrast to BGA, and in line with previous findings, BIS was only associated to depressive, but not manic, symptoms (Strakowski et al., 2010). For example, Strakowski and colleagues found that, in individuals with BD in manic/mixed states, impulsivity was correlated with depressive symptoms but not manic symptoms (Strakowski et al., 2009). Further research is required to elucidate the relationships between affective states with aggression and impulsive behavioral constructs.

In addition to clinical and behavioral manifestations, brain structural correlates were different for BGA and BIS, providing evidence that the two instruments measure different brain-based domains of behavior in BD. While some in the field have considered impulsivity and aggression a unitary construct, conceptualizing the two as distinct but related behavioral domains is supported by many others, who have identified complexity within each construct and in the relationship between the two, while still drawing distinctions between them (Bresin, 2019; Critchfield et al., 2004; Ende et al., 2016; Gokcay and Balcioglu, 2020; Soloff et al., 2017). Further, the findings are in line with a body of work that has identified distinct neurological correlates of the two constructs, both in BD and the general population (Antonucci et al., 2006; Chester et al., 2017; Coccaro et al., 2018; Gansler et al., 2009; Matsuo et al., 2009b). In the BD group, BGA scores were negatively associated with GMV in OFC and PIns. The OFC is involved in the regulation of behavioral responses to negative and positive emotional stimuli (Gyurak et al., 2011; Phillips et al., 2008; Rolls, 2004; Rolls, 2019; Roy et al., 2012), including the management of behavioral responses in the context of changing social reinforcement contingencies (Diekhof et al., 2011), and has shown decreased volume in BD (Dickstein et al., 2005; Najt et al., 2007a). In social situations, individuals with OFC deficits may not be able to inhibit maladaptive responses leading to negative social interactions (Berlin et al., 2004; Grafman et al., 1996; Hornak et al., 2003; Pietrini et al., 2000) that can be similar to ones measured on the BGA. Other research groups have reported reductions and asymmetries in OFC volume in psychiatric populations, including specifically in BD, in association with earlier BGA versions (Antonucci et al., 2006; Gansler et al., 2009). Prior studies by our and other research groups of individuals

with BD in elevated mood states have shown attenuated OFC resting state activity and responses during a Stroop task in which prepotent responses need to be inhibited to respond (Blond and Blumberg, 2010; Blumberg et al., 2003; Blumberg et al., 1999). As here we also observed elevated symptoms in association with the BGA, this suggests the OFC may be a common substrate for constructs measured by the BGA and for elevated mood states. Our finding that BGA scores were higher for those in manic states further supports this hypothesis. The PIns is involved in interoception, and sensorimotor and emotion processing and integration (Deen et al., 2010; Grecucci et al., 2015). The left PIns has been implicated as particularly important in the perception of interoceptive stimuli and pain (Duerden et al., 2013; Segerdahl et al., 2015; Tan et al., 2017). Reduced insular volume and connectivity are also increasingly implicated in BD by neuroimaging studies. Reduced GMV in the insula has been associated with BD in adolescents and adults (Lisy et al., 2011; Matsuo et al., 2012; Neves et al., 2015; Selvaraj et al., 2012; Shepherd et al., 2012; Wang et al., 2011; Wang et al., 2018), with some studies specifically reporting left insula (Lisy et al., 2011; Neves et al., 2015). In BD, decreased functional connectivity of the insula has been observed, including of left Pins (Yin et al., 2018). As research of the insula in BD advances, this study suggests consideration of the region's relationship to behavioral domains measured by the BGA.

BIS, on the other hand, consistent with the report of Matsuo and colleagues, was associated with reduction in GMV in the bilateral ACC in the BD participants. The peak was in the dorsal ACC (dACC), part of the cognitive division of the ACC (Bush et al., 2000) that modulates one's response in challenging scenarios via conflict detection and resolution; dACC deficits were previously associated with past suicidal behavior and disruptions in its conflict-related functions were postulated to be potential mechanisms contributing to STBs (Carter et al., 1999; Gasquoine, 2013; Heilbronner and Hayden, 2016; Hung et al., 2018; Minzenberg et al., 2016; Mohanty et al., 2007). The cluster of findings extended to the rostral ACC bilaterally and extended to the ventral ACC on the left, part of the affective division of the ACC (Bush et al., 2000; Kaufman et al., 2003). Rostral and ventral ACC structural and functional abnormalities have been repeatedly observed in BD (Blond et al., 2012; Blumberg et al., 2005; Liu et al., 2012; Lochhead et al., 2004; Sassi et al., 2004; Wang et al., 2009), although dorsal ACC findings have varied (Adler et al., 2005; López-Larson et al., 2002) which could relate at least in part to heterogeneity in the magnitude of impulsiveness (Matsuo et al., 2009b), as well as its associated clinical features. For example, cocaine-associated comorbid SUDs—associated here and in prior studies with greater impulsivity—have also been associated with dACC abnormalities (Minzenberg et al., 2016; Yip et al., 2018). Further, our exploratory analysis suggested that the motor subscale drove the correlation between ACC GMV and impulsivity, as also found by Matsuo et al (Matsuo et al., 2009b). The results of the present study, along with the literature, suggest that, in BD, ACC deficits are related to a tendency of acting upon impulses.

Aggression and impulsivity have both long been associated with SAs (Ekinci et al., 2011; Gilbert et al., 2011; Grunebaum et al., 2006b; Jiménez et al., 2012; Michaelis et al., 2004; Oquendo et al., 2004; Oquendo et al., 2000; Reich et al., 2019; Swann et al., 2005). Consistent with this, the findings of this study showed that both aggression and impulsivity were significantly higher in those with history of SAs than those without. Further, we found

that BGA, but not BIS, was significantly positively associated with most severe past SI. This finding reinforces our conceptualization of BGA, more so than BIS, reflecting internal emotional processes (Law et al., 2015) and suggests this may contribute to SI. Prior work showed elevated BIS, especially motor impulsivity, in attempters compared to individuals without prior suicide behavior even if they had ideation (Jiménez et al., 2012). Both scales may capture constructs important in the transition to suicide behavior, but the BGA may capture ones associated with the emergence of suicidal ideation. Given the distinct regions associated with BGA and BIS in those with BD, we propose that the two measures may reflect differing, though potentially interacting, brain-based behavioral pathways to SAs in BD: one in which emotional dysregulation, and the other behavioral dyscontrol, play a particularly predominant role (Figure 2).

Limitations

The findings of the present study should be interpreted in the context of the following limitations. Scores on the BGA and BIS were dependent on participants' self-reports which could be influenced by many factors. No causal conclusions can be drawn from our results; longitudinal experiments are needed in order to address causal links between aggression and impulsivity, with CM, clinical and brain factors in BD. The modest sample size may have limited our ability to identify relationships among the factors studied. Excluding participants with recent SUDs may have decreased generalizability, particularly to BD populations with SAs who often have high rates of SUDs. While previous studies have investigated psychotropic medications as potential treatments for aggressive (Aguglia et al., 2018; Barzman et al., 2006; Hafeman et al., 2020; Saxena et al., 2006; Swann, 1999) or impulsive behavior (Akingbala et al., 2006; Reddy et al., 2014) in BD with varying results, the present study is unable to draw conclusion on the effect of medication given the lack of systematic study. That GMV reductions associated with BGA or BIS were not detected in the HC group may be due to underlying differences in BD or to the smaller variance in HC groups. Finally, studies of BGA and BIS in other psychopathologies are needed to assess whether associations are transdiagnostic or specific to BD.

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Highlights

- "Aggression" in bipolar disorder is more likely to be directed to self than others
- Aggression and impulsivity reflect two pathways to suicide risk in bipolar disorder
- MRI shows distinct brain circuits in bipolar disorder aggression and impulsivity

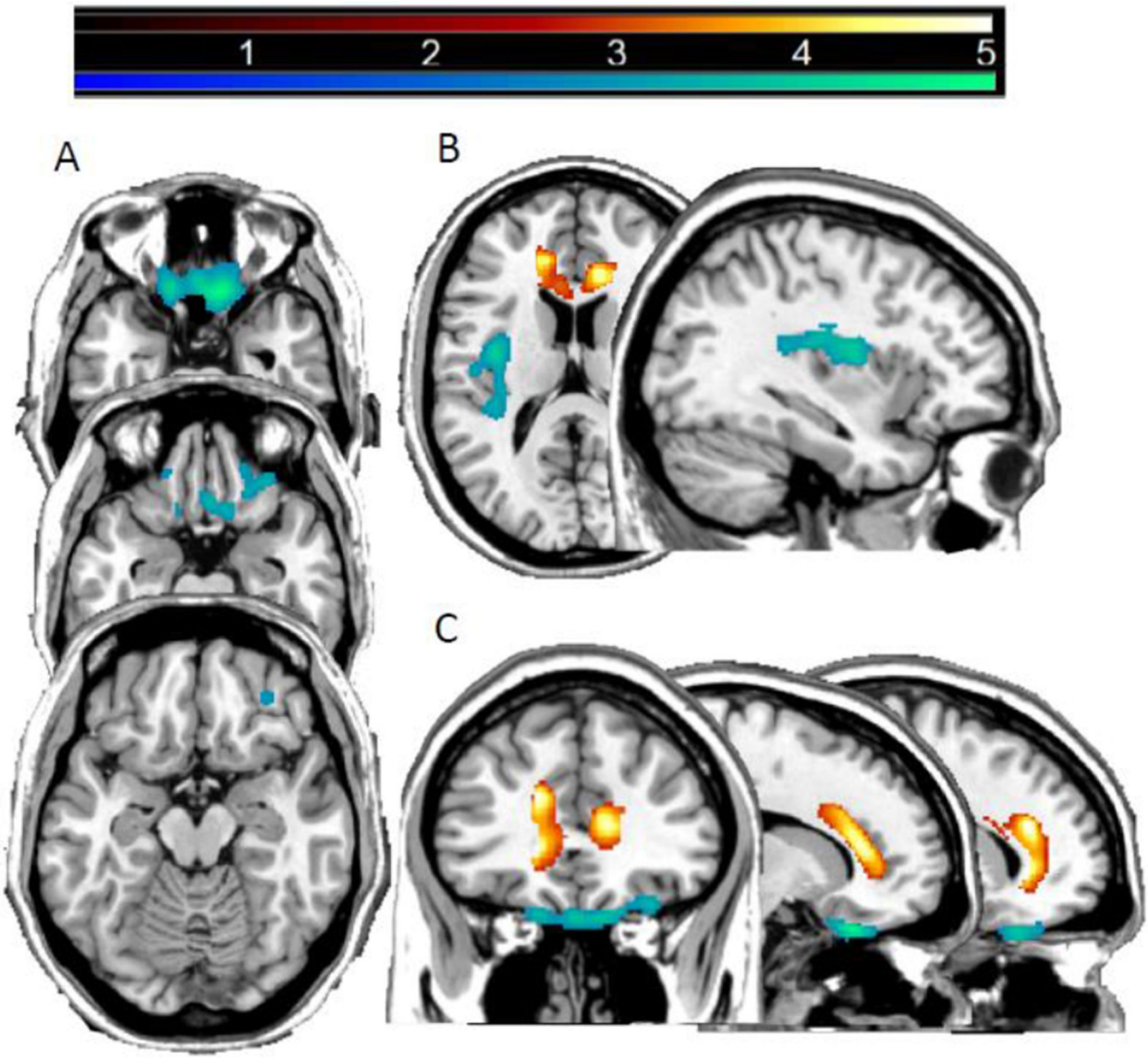

Figure 1: Regions of decreased gray matter volume associated with Brown-Goodwin Aggression and Barratt Impulsiveness Scale scores in bipolar disorder

The magnetic resonance imaging T1 images display the regions where gray matter volume showed a significant negatively correlation ($p_{fwe\text{-}cluster}<0.05$) with Brown-Goodwin Aggression (BGA) total scores (blue-green) or Barratt Impulsiveness Scale (BIS) total scores (red-yellow) among individuals with bipolar disorder. For BGA scores, associations were seen with bilateral orbitofrontal cortex and left posterior insula; for BIS scores, associations were seen with anterior cingulate cortex. Slices are shown at Montreal Neurological Institute (A) axial-oblique at z=−27mm, −22mm, −16mm and (B) z=16mm and sagittal at x=−36mm and (C) x=14mm, −16mm and coronal at y=34mm planes. The right sides of the axial-oblique images are the right side of the brain. The color bar shows the range of *F* values.

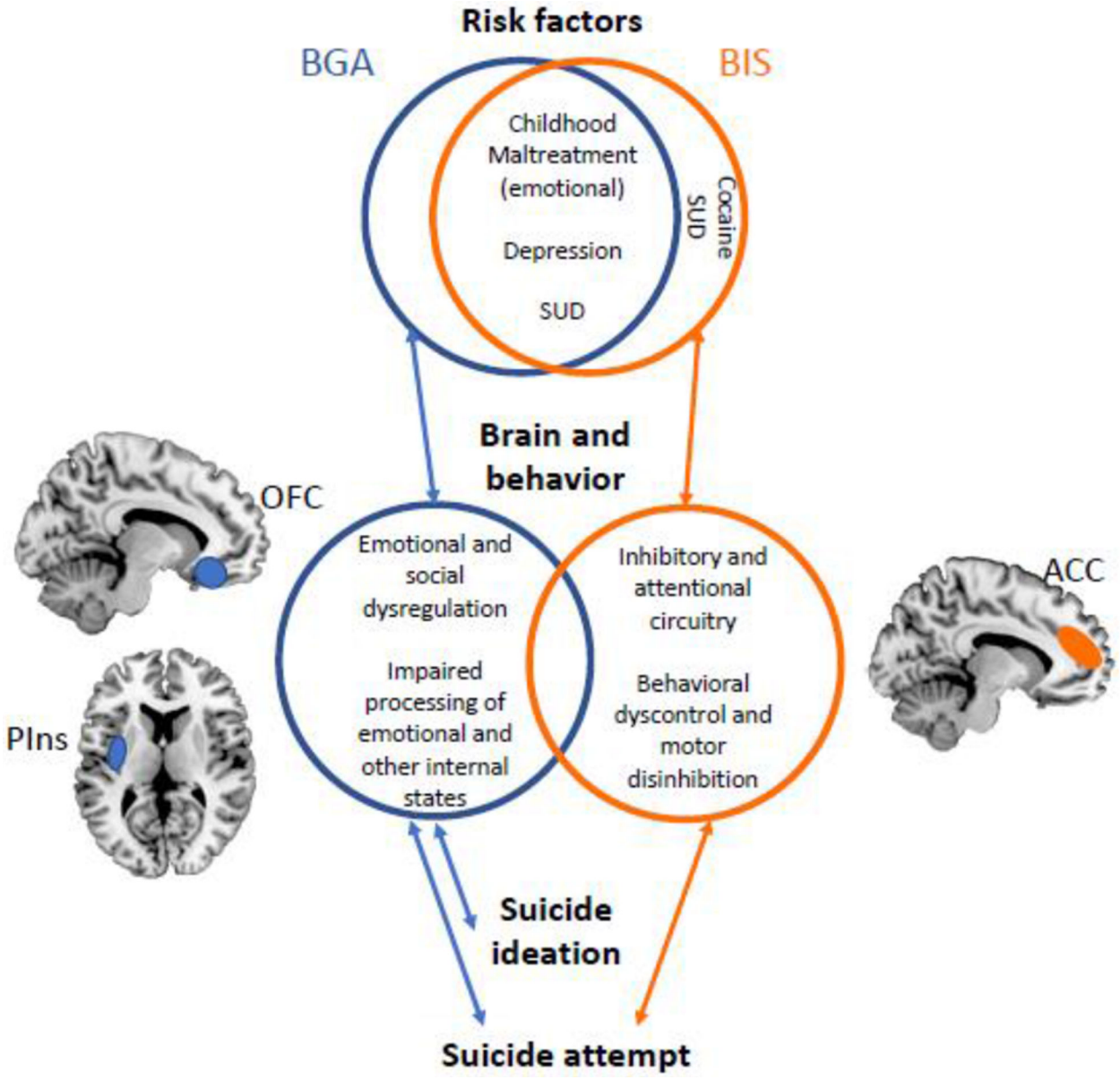

Figure 2: A proposed model of risk, clinical, and brain circuitry features of "aggression" and "impulsivity" in bipolar disorder

The figure illustrates common and differing risk, brain and clinical associations found to the Brown Goodwin Aggression (BGA) and Barratt Impulsiveness Scale (BIS) scores, and relationships observed among them. Abbreviations: SUD, substance abuse disorder; OFC, orbitofrontal cortex; Pins, posterior insula; ACC, anterior cingulate cortex.

Table 1.

Demographic, clinical, and behavioral variables by diagnosis

	Variable	BD (n=38)	HC (n=29)	*p* value
Demographic variables	Age (SD)	35.7 (11.5)	38.3 (11.2)	.35
	Number of females (%)	28 (74%)	19 (66%)	.47
	Socioeconomic status (SD)	40.8 (18.3)	39.6 (16.8)	.80
Clinical variables	Hamilton Depression Rating Scale, HDRS (SD)	12.3 (10.5)	0.2 (0.7)	**<.001**
	Young Mania Rating Scale, YMRS (SD)	5.6 (6.4)	0.3 (0.7)	**<.001**
	Lifetime suicide attempt (%)	13 (34%)	NA	NA
	Most severe suicide ideation (SD)	8.0 (9.2)	NA	NA
	Mood state (euthymic (%) / depressed (%) / elevated (%))	13 (34%) / 10 (26%) / 15 (39%)	NA	NA
	Rapid cycling (%)	12 (32%)	NA	NA
	Lifetime psychosis (%)	15 (40%)	NA	NA
	Unmedicated at time of scan (%)	15 (40%)	NA	NA
	Hospitalization (%)	29 (77%)	NA	NA
	Anxiety disorder lifetime (%)	19 (50%)	NA	NA
	Eating disorder lifetime (%)	3 (8%)	NA	NA
	History of alcohol/substance dependence/abuse (%)	16 (42%)	NA	NA
	History of alcohol dependence/abuse (%)	5 (13%)	NA	NA
	History of cocaine dependence/abuse (%)	6 (16%)	NA	NA
	History of cannabis dependence/abuse (%)	6 (16%)	NA	NA
	History of opioid dependence/abuse (%)	2 (5%)	NA	NA
	Total Childhood Trauma Questionnaire (CTQ) (SD)	**58.9 (22.9)**	**32.7 (10.1)**	**<.001**
	CTQ emotional abuse subscale (SD)	**14.2 (6.3)**	**6.7 (2.6)**	**<.001**
	CTQ physical abuse subscale (SD)	**10.8 (5.9)**	**6.5 (3.2)**	**.003**
	CTQ sexual abuse subscale (SD)	**9.6 (7.4)**	**5.1 (0.6)**	**<.001**
	CTQ emotional neglect subscale (SD)	**14.9 (7.1)**	**8.5 (4.6)**	**<.001**
	CTQ physical neglect subscale (SD)	**9.4 (4.4)**	**5.9 (1.5)**	**<.001**
Behavioral variables	Total Brown-Goodwin Lifetime History of Aggression (BGA) (SD)	**17.3 (7.5)**	**11.6 (3.0)**	**<.001**
	BGA item 1 (SD) – discipline problem	**1.7 (1.1)**	**1.2 (0.6)**	**.014**
	BGA item 2 (SD) – getting along with teachers	1.5 (1.1)	1.1 (0.6)	.066
	BGA item 3 (SD) – angry outbursts/temper tantrums	**1.9 (1.2)**	**1.0 (0.2)**	**<.001**
	BGA item 4 (SD) – getting along with work supervisor	**1.8 (1.1)**	**1.0 (0.0)**	**<.001**
	BGA item 5 (SD) – severe arguments	**2.5 (1.3)**	**1.3 (0.8)**	**<.001**
	BGA item 6 (SD) – physical fights	1.7 (1.1)	1.3 (0.8)	.11
	BGA item 7 (SD) – destroyed property	**1.6 (1.0)**	**1.0 (0.0)**	**.001**
	BGA item 8 (SD) – action against the law but not caught	1.9 (1.3)	1.4 (0.7)	.12
	BGA item 9 (SD) – any trouble with police	1.5 (0.8)	1.2 (0.5)	.10

	Variable	BD (n=38)	HC (n=29)	*p* value
	BGA item 10 (SD) – tried to hurt other	**1.3 (0.7)**	**1.0 (0.0)**	**.026**
	BGA item 11 (SD) – non suicidal self-harm	**1.5 (0.9)**	**1.0 (0.0)**	**.001**
	Total Barratt Impulsiveness Scale (BIS) (SD)	**75.4 (13.0)**	**54.6 (7.0)**	**<.001**
	BIS non-planning impulsiveness subscale (SD)	**29.2 (5.2)**	**21.1 (3.5)**	**<.001**
	BIS motor impulsiveness subscale (SD)	**26.1 (6.2)**	**20.6 (3.0)**	**<.001**
	BIS cognitive-attentional impulsiveness subscale (SD)	**20.1 (4.5)**	**13.0 (2.8)**	**<.001**

p-values correspond to Mann-Whitney U tests for all continuous variables (except for age, for which an independent-sample t-test was used) and to chi-squared tests for categorical variables. Socioeconomic status not available for 2 BD and 1 HC; CTQ not available for 4 BD and 1 HC; BG item 11 not available for 1 BD.

Table 2.

Correlations between and effects of demographic, clinical, and behavioral variables and comorbidities with Brown-Goodwin Aggression and Barratt Impulsivity Scale total scores within Bipolar Disorder

		BGA mean±SD or r	**p**	**BIS mean±SD or r**	**p**
Demographics	Age	−.11	.52	−.20	.22
	Sex (female/male)	18.1±8.1 / 15.0±5.1	.35	76.5±13.5 / 72.2±11.5	.37
	Socioeconomic status	−.26	.13	.06	.74
Behavioral	BIS	**.40**	**.012**	NA	NA
	BIS non-planning subscale	.18	.28		
	BIS motor impulsiveness subscale	**.44**	**.006**		
	BIS cognitive-attentional subscale	**.36**	**.025**		
	BGA	NA	NA	**.40**	**.012**
Clinical	Lifetime suicide attempt (yes/no)	**22.5±8.8 / 14.6±4.9**	**.003**	**83.3±13.1 / 71.2±11.1**	**.005**
	Most severe suicide ideation	**.50**	**.002**	.20	.24
	Mood state (euthymic / depressed / elevated)	**16.9 ± 8.4 / 13.4 ± 3.9 / 20.3 ± 7.5**	**.030**	73.2±10.4 / 74.8±10.6 / 77.7±16.5	.65
	Rapid cycling (yes/no)	17.9 ± 5.5 / 17.0 ± 8.3	.30	80.8±10.9 / 72.9±13.3	.08
	Lifetime psychosis (yes/no)	15.1±5.9 / 18.7±8.1	.16	76.4±8.6 / 74.7±15.4	.71
	Unmedicated at time of scan (yes/no)	19.0±8.8 / 16.2±6.4	.28	72.8±14.5 / 77.1±12.0	.33
	Hospitalization (yes/no)	18.3±7.9 / 14.1±5.0	.13	76.9±13.0 / 70.7±12.6	.22
	HDRS	**.36**	**.025**	**.37**	**.023**
	YMRS	**.39**	**.016**	.21	.21
	CTQ	.31	.079	.34	**.049**
	CTQ emotional abuse subscale	.28	.11	.57	**<.001**
	CTQ physical abuse subscale	.20	.25	.32	.061
	CTQ sexual abuse subscale	.05	.78	.02	.91
	CTQ emotional neglect subscale	**.38**	**.025**	**.35**	**.043**
	CTQ physical neglect subscale	.21	.24	.15	.41
	Anxiety disorder lifetime (yes/no)	16.7±5.0 / 18.0±9.4	.77	75.6±13.8 / 75.2±12.5	.93
	Eating disorder lifetime	18.0±7.6 / 17.3±7.6	NA	74.0±10.6 / 75.5±13.3	NA
	History of alcohol/substance dependence/abuse (yes/no)	**20.8±8.8 / 14.8±5.3**	**.021**	**81.6±12.4 / 70.9±11.7**	**.010**
	History of alcohol dependence/abuse (yes/no)	19.6±3.5 / 17.0±7.9	.17	75.8±18.1 / 75.3±12.4	.94
	History of cocaine dependence/abuse (yes/no)	22.2±13.0 / 16.4±5.8	.42	88.5±7.8 / 72.9±12.3	**.005**
	History of cannabis dependence/abuse (yes/no)	19.5±10.3 / 16.9±6.9	.70	78.8±9.6 / 74.8±13.6	.49
	History of opioid dependence/abuse (yes/no)	27.5±2.1 / 16.8±7.2	NA	85.0±8.5 / 74.9±13.1	NA

p-values correspond to spearman correlations for all continuous variables (except for age, for which a Pearson correlation was used) and to Mann-Whitney U or Kruskal-Wallis H tests for categorical variables. Socioeconomic status not available for 7 BD; Most severe suicide ideation not available for 1 BD; CTQ not available for 4 BD.