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Impulsivity across the psychosis spectrum: Correlates of cortical volume, suicidal history, and social and global function

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ABSTRACT

Patients with psychotic disorders appear to exhibit greater impulsivity-related behaviors relative to healthy controls. However, the neural underpinning of this impulsivity remains uncertain. Furthermore, it remains unclear how impulsivity might differ or be conserved between psychotic disorder diagnoses in mechanism and manifestation. In this study, self-reported impulsivity, measured by Barratt Impulsiveness Scale (BIS), was compared between 305 controls (HC), 139 patients with schizophrenia (SZ), 100 with schizoaffective disorder (SZA), and 125 with psychotic bipolar disorder (PBP). In each proband group, impulsivity was associated with regional cortical volumes (using FreeSurfer analysis of T1 MRI scans), suicide attempt history, Global Assessment of Functioning (GAF), and Social Functioning Scale (SFS). BIS scores were found to differ significantly between participant groups, with SZA and PBP exhibiting significantly higher impulsivity than SZ, which exhibited significantly higher impulsivity than HC. BIS scores were significantly related to suicide attempt history, and they were inversely associated with GAF, SFS, and bilateral orbitofrontal cortex (OFC) volume in both SZA and PBP, but not SZ. These findings indicate that psychotic disorders, particularly those with prominent affective symptoms, are characterized by elevated self-reported impulsivity measures. Impulsivity's correlations with suicide attempt history, GAF, and SFS suggest that impulsivity may be a mediator of clinical outcome. The observed impulsivity-OFC correlations corroborate the importance of OFC deficits in impulsivity. These correlations' presence in SZA and PBP but not in SZ suggests that impulsivity may have different underlying mechanisms in affective and non-affective psychotic disorders.

1. Introduction

Impulsivity is a multidimensional construct broadly described as a tendency towards reacting rapidly to internal or external stimuli without planning or concern for possible consequences (Moeller et al., 2001). Impulsivity-related behaviors can be measured in multiple ways including self-report inventories, measures of delay-discounting, and computer-tasks (Meda et al., 2009). Various forms of impulsivity have been found to be elevated in disorders across the psychosis spectrum, including bipolar disorder (Peluso et al., 2007; Strakowski et al., 2010; Swann et al., 2001), schizoaffective disorder, and schizophrenia (Enticott et al., 2008; Nolan et al., 2011; Premkumar et al., 2008). It appears to exacerbate morbidity in these disorders, as impulsivity has been associated with increases in the risks for violence (Quanbeck et al., 2007; Volavka and Citrome, 2008), substance abuse (Dervaux et al., 2001; Schiffer et al., 2010), more intensive hospital course (Bigelow et al., 1988; Bowers et al., 2008; Greenfield et al., 1989), and suicide attempts (Gut-Fayand et al., 2001; Swann et al., 2005, 2009). Impulsivity has also been used to guide treatment and it is an important factor to consider when selecting appropriate medication regimens (Chengappa et al., 2002; Dursun et al., 2000; Krakowski et al., 2006; Spivak et al., 2003; Volavka and Citrome, 2008).

Despite evidence indicating that impulsivity differentiates psychotic patients from healthy controls, it remains unclear how impulsivity might differ across psychotic disorders. In a relatively small-scale

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study comparing bipolar disorder (independent of psychosis) to schizophrenia, self-reported impulsivity was elevated in the bipolar group and risk averse behavior was elevated in the schizophrenia group (Reddy et al., 2014). However, to our knowledge, impulsivity-related measures have never been compared specifically across the psychosis spectrum. Inter-disorder comparisons are of interest as the nosology of psychotic disorders remains an open and active area of research given the heterogeneity within and overlap between diagnoses (Keshavan et al., 2013). Given that forms of impulsivity have been demonstrated to be heritable traits (Niv et al., 2012; Seroczynski et al., 1999) occurring in psychotic disorders, it may be a useful measure for addressing these nosological questions, as it may help clarify differences or similarities inherent to diagnoses.

Impulsivity's neural underpinnings are imperfectly understood. A series of fMRI studies to assess neural correlates of impulsivity in schizophrenia has yielded divergent findings, identifying association with dysfunction in a variety of brain regions including ventrolateral prefrontal cortex (Kaladjian et al., 2011), dorsolateral prefrontal cortex (Arce et al., 2006), anterior cingulate cortex (Rubia et al., 2001), posterior cingulate cortex (Laurens et al., 2003), caudate nucleus, and thalamus (Barkataki et al., 2008). Similarly, structural studies in bipolar disorder have pointed to several brain regions of impulsivity-associated abnormality, including anterior medial frontal regions (Matsuo et al., 2010) and anterior cingulate cortex (Matsuo et al., 2009). Moreover, neural correlates of impulsivity in different psychotic diagnoses have only been investigated in separate studies. Direct comparison within a single study is required to evaluate whether the neural correlates of impulsivity differ or are conserved between psychotic disorders.

In this study, we aimed to compare total level of impulsivity, its subdimensions, and its clinical and neural associations across the psychosis spectrum. We measured self-reported impulsivity-related behavior and correlated it with social and global functioning, suicidal history, and regional cortical volumes in healthy controls and in probands across the psychosis spectrum recruited as part of the six-site Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) research program.

2. Methods

2.1. Study participants

The study included 305 healthy controls (HC), 139 patients with schizophrenia (SZ), 100 with schizoaffective disorder (SZA), and 125 with bipolar disorder type I who endorsed psychotic symptoms (PBP) from the B-SNIP database (Table 1). Study participants underwent diagnostic interview using the Structured Clinical Interview for DSM-IV-TR (SCID-IV) (Spitzer et al., 1997) and were categorized by diagnosis. Diagnoses were made by a consensus process led by a senior clinician at each site involving reviews of results from clinical interviews, psychiatric and medical histories, and medical records. Inclusion criteria, diagnostic techniques, and recruitment strategies were identical across all sites, as described in previous B-SNIP studies, and institutional review boards at each site approved the project (Tamminga et al., 2013).

2.2. Procedures

Participants' impulsivity was assessed using Barratt Impulsiveness Scale (BIS) version 11, a 30-item self-report measure designed to assess the personality trait of impulsivity composed of three subscales: attentional (intolerance of complexity), motor (impetuous action), and nonplanning (lack of future orientation) impulsivity (Patton et al., 1995). Patient functioning was measured by Social Functioning Scale (SFS) (Birchwood et al., 1990) and Global Assessment of Functioning (GAF) (Jones et al., 1995). Patient symptomatology was quantified using Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987) and cognition was evaluated using Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe, 2004). Patient histories of suicide attempts were also recorded based on clinical interview and recorded by Beck Lethality Scale (Beck et al., 1979). Patients were also rated on Schizo-Bipolar Scale (SBS) (Keshavan et al., 2011), a descriptive measure capturing the type and relative proportions of psychotic and affective symptoms in psychotic disorder patients and thereby placing these patients on a spectrum of psychopathology. SBS is scored on a 10-point scale where 0 represents the most bipolar-like and 9 represents the most schizophrenia-like disorder.

Table 1
Demographics of included participants.

	Controls	Schizophrenia	Schizoaffective	Psychotic bipolar
n	305	139	100	125
Mean age (SD)	37.7 (12.2)	36.7 (13.0)	36.6 (11.4)	36.0 (13.0)
Race distribution	AA 81 (27%) CA 196 (64%) OT 28 (9%)	AA 67 (48%) CA 64 (46%) OT 8 (6%)	AA 45 (45%) CA 49 (49%) OT 6 (6%)	AA 30 (24%) CA 88 (70%) OT 7 (6%)
Gender distribution	F 159 (52%) M 146 (48%)	F 43 (31%) M 96 (69%)	F 56 (56%) M 44 (44%)	F 88 (65%) M 37 (27%)
GAF (SD)	N/A	42.5 (12.2)	40.7 (10.9)	51.3 (11.7)
SFS (SD)	N/A	107.8 (21.9)	104.3 (23.4)	115.9 (21.7)
SBS (SD)	N/A	7.9 (1.2)	5.1 (1.5)	1.1 (1.1)
CPZ equivalents (SD)	0.0 (0.0)	351.6 (376.1)	344.7 (472.9)	194.0 (337.0)

SD — standard deviation; AA — African American; CA — Caucasian; OT — other; F — female; M — male; GAF — Global Assessment of Functioning; SFS — Social Functioning Scale; SBS — Schizo-Bipolar Scale.

Structural data were acquired and underwent rigorous data quality control as described in previous work (Giakoumatos et al., 2015). Total cortical volume values were calculated in 64 anatomically defined cortical parcellations that covered the entire cortex (Desikan et al., 2006).

Outliers in impulsivity, clinical measures, and structure were handled by winsorizing all values to a level of three standard deviations from the mean.

2.3. Statistical analysis

Impulsivity measures were compared between participant groups (HC, SZ, SZA, and PBP) by performing analyses of covariance (ANCOVAs) and then Tukey's honest significant difference (HSD) tests on BIS total score and subscale scores for pairwise comparisons, controlling for age, sex, site, race, and chlorpromazine equivalents of antipsychotic dosages, which were included as covariates in all statistical analyses. Impulsivity was also directly compared across the psychosis spectrum by performing Pearson's correlations between BIS total score and SBS score. The relationships between impulsivity and clinical measures of functioning for each patient group were evaluated by conducting Pearson's correlations between BIS total score and both SFS and GAF scores, with Benjamini–Hochberg adjustment for the number of functioning scales. For scales with a trending association with BIS total score ($p < 0.10$), correlations with each of the impulsivity subscales were calculated, with Benjamini–Hochberg adjustment for the number of subscales. The normality of impulsivity distributions was evaluated by performing Shapiro–Wilk tests of normality on BIS total scores within each patient group.

The relationship between impulsivity and suicidality was assessed by performing a logistic regression associating a history of suicide attempt with BIS total score. Logistic regressions were also performed associating history of suicide attempt with each of the impulsivity

subscales, with Benjamini–Hochberg adjustment for the three subscales. For the suicide history analyses, impulsivity scores were scaled by HC z-scores for better interpretability of odds ratios (OR).

Regional cortical volumes were correlated with BIS total score for each participant group using a hierarchical approach designed to minimize Type I error risk via a two-step process: 1) a selection step and 2) a selective analysis (Nanda et al., 2014). In the selection step, BIS total score and cortical volume were correlated in twelve large functionally distinct regions of the brain, six in each hemisphere (frontal, temporal, parietal, occipital, sensorimotor, and cingulate cortex). When a large region exhibited a trending correlation ($p < 0.10$), it was retained for selective analysis. In this selective analysis, for each large region identified by the selection step, BIS total score and cortical volume were correlated in the large region's component sub-regions, with Benjamini–Hochberg adjustment for the number of sub-regions. To avoid circular analysis, the selection step was performed on a randomly chosen ¼ of the sample (maintaining participant group proportions) whereas the selective sub-region analysis was performed on the remainder (Kriegeskorte et al., 2009). The regional cortical volumes found to be significantly associated with BIS total score within a participant group by the above hierarchical analysis ($p < 0.05$) were tested for correlation with BIS subscale scores, with Benjamini–Hochberg adjustment for the number of subscales.

2.4. Post hoc OFC analysis

Because OFC sub-regional volumes were found to be significantly associated with impulsivity in SZA and PBP but not SZ, we directly tested for differences in the impulsivity-OFC relationship across diagnosis. Volumes were calculated for total left OFC (LOFC) and right OFC (ROFC). In the whole proband sample, ANCOVAs were employed to assess main effects of LOFC/ROFC and diagnosis as well as interaction effects of LOFC/ROFC by diagnosis on BIS total score.

3. Results

3.1. Group comparisons

BIS total score and all subscale scores were found to differ significantly between participant groups by ANCOVAs. Tukey's HSD test demonstrated that BIS total scores were significantly lower in HC than in SZ ($d = 1.2$, $p < 0.001$), SZA ($d = 2.1$, $p < 0.001$), and PBP ($d = 1.6$, $p < 0.001$) (Fig. 1a). Impulsivity was also found to be significantly lower in SZ than in SZA ($d = 0.7$, $p < 0.001$) and PBP ($d = 0.3$, $p < 0.001$). Similar patterns of differences between participant groups were observed for the impulsivity subscales (Fig. 1b–d). BIS total score was also found to be significantly inversely correlated with SBS score ($r = -0.15$, $p < 0.01$) (Fig. S1).

3.2. Function correlations

Results of function–impulsivity correlations can be found in Table 2. Shapiro–Wilk tests performed on BIS total scores were insignificant for all patient groups (SZ: $p > 0.80$; SZA: $p > 0.50$; PBP: $p > 0.15$), suggesting that impulsivity distributions were consistent with normal distribution.

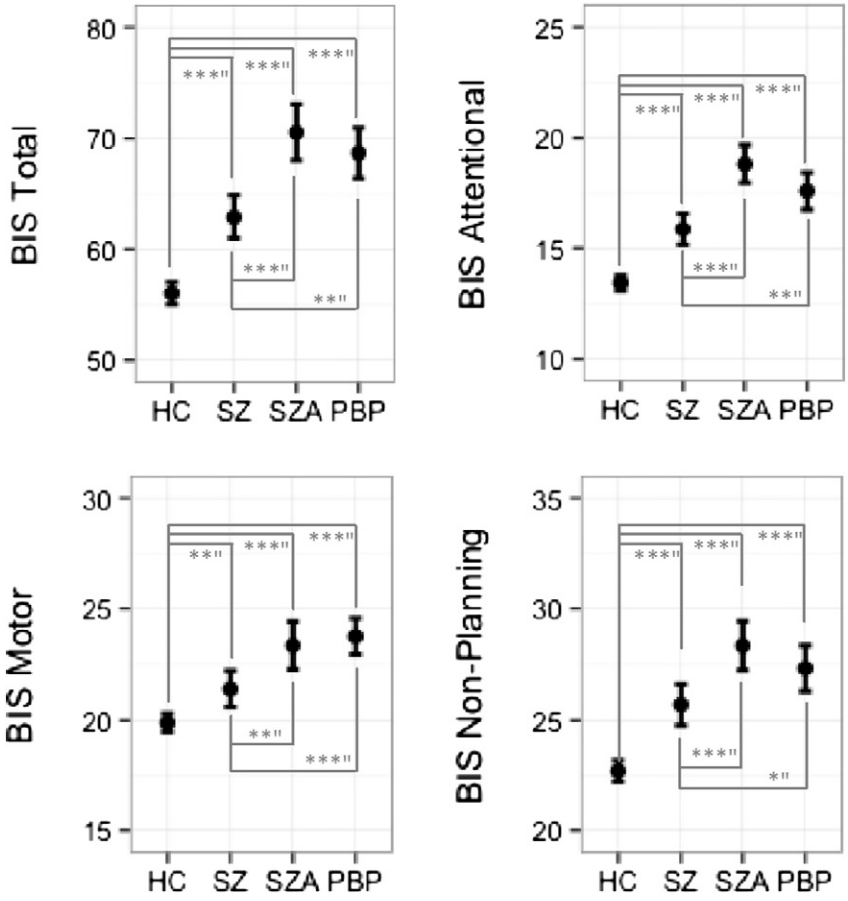

Fig. 1. Impulsivity scores compared between diagnoses and controls. Impulsivity is measured by (A) Barratt Impulsiveness Scale (BIS) version 11 total, (B) BIS attentional subscale, (C) BIS motor subscale, and (D) BIS non-planning subscale. Inter-group comparisons were performed using Tukey's honest significant difference tests. Error bars represent 95% confidence intervals. HC — healthy controls; SZ — schizophrenia; SZA — schizoaffective disorder; PBP — psychotic bipolar disorder; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 2
Correlations between impulsivity and functioning, stratified by diagnosis.

Group	Function scale	Pearson's r for overall impulsivity		Pearson's r for impulsivity subscales	
SZ	SFS	BIS total	−0.02	NA	
	GAF	BIS total	−0.03	NA	
SZA	SFS	BIS total	−0.35***	Attention	−0.34***
				Motor	−0.14
				Non-planning	−0.42***
	GAF	BIS total	−0.26**	Attention	−0.25*
				Motor	−0.25*
				Non-planning	−0.15
PBP	SFS	BIS total	−0.31***	Attention	−0.27**
				Motor	−0.07
				Non-planning	−0.42***
	GAF	BIS total	−0.18*	Attention	−0.26**
				Motor	−0.03
				Non-planning	−0.22*

SZ — schizophrenia; SZA — schizoaffective disorder; PBP — psychotic bipolar disorder; SFS — Social Functioning Scale; GAF — Global Assessment of Function; BIS — Barratt Impulsiveness Scale version 11.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

3.3. Suicide history logistic regressions

Of the 364 patients in the study, 122 reported previously attempting suicide. BIS total score was significantly associated with patients' past suicide attempts by logistic regression ($OR = 1.19$, $p < 0.05$) (Fig. S2). Of the BIS subscales, only the attentional subscale was found to be significantly associated with patients' past suicide attempts ($OR = 1.22$, $p < 0.01$).

3.4. Cortical volume correlations

No significant associations were found between regional cortical volumes and impulsivity for HC or SZ. In SZA, BIS total score was significantly associated with left lateral OFC volume ($r = -0.33$, $p < 0.05$) (Fig. 2a), which was also significantly associated with motor ($r = -0.29$, $p < 0.01$) and non-planning ($r = -0.23$, $p < 0.05$) BIS subscales. In PBP, BIS total score was significantly associated with right medial OFC volume ($r = -0.32$, $p < 0.05$) and right pars orbitalis volume ($r = -0.28$, $p < 0.05$). Right medial OFC volume was significantly associated with motor ($r = -0.33$, $p < 0.001$) and non-planning ($r = -0.32$, $p < 0.001$) BIS subscales whereas right pars orbitalis volume was significantly associated with attentional ($r = -0.20$, $p < 0.05$), motor ($r = -0.23$, $p < 0.05$), and non-planning ($r = -0.27$, $p < 0.01$) BIS subscales.

3.5. Post hoc OFC analysis

For both LOFC and ROFC, there were significant main effects of diagnosis ($F > 8$, $p < 0.01$) and significant interaction effects of cortical volume by diagnosis ($F > 2$, $p < 0.05$) on BIS total score (Fig. 2b). In both SZA and PBP, BIS total score was significantly associated with LOFC (SZA: $r = -0.20$, $p < 0.05$; PBP: $r = -0.18$, $p < 0.05$) and ROFC (SZA: $r = -0.22$, $p < 0.05$; PBP: $r = -0.22$, $p < 0.05$) volumes. However, no such significant associations were observed for SZ.

4. Discussion

The results corroborate prior research indicating that a self-reported measure of impulsivity-related behaviors appears substantially increased in psychotic disorders, as BIS total score differed between healthy controls and each proband group significantly and with large effect size (Cohen, 1992). Proband groups' substantially elevated impulsivity held true across all three BIS domains. The study is also significant for directly differentiating for the first time between proband groups' patterns of impulsivity across the psychosis spectrum. BIS scores were significantly higher in SZA and PBP than in SZ. A significant inverse correlation was also observed between impulsivity and score on SBS, which takes a dimensional approach in placing patients on a spectrum of psychopathology, further indicating that psychotic disorders with greater affective components consistently exhibit heightened impulsivity (Fig. S1).

BIS scores may be relatively muted in SZ because of the effect of negative symptoms, which are greatest in SZ (Fig. S3) and have been thought to potentially oppose impulsivity (Fanous et al., 2001). However, negative symptoms are also elevated in SZA, making this explanation less likely. Another possibility is that antipsychotic medications may dampen impulsivity in SZ (Reddy et al., 2014), although the proportion of patients taking antipsychotics in our sample was similar for SZ and SZA (71% in SZ and 68% in SZA). Alternatively, increases in BIS impulsivity may be rooted in different mechanisms impacting brain and behavioral aspects of emotion in psychotic disorders with and without prominent affective components, which may manifest as varying degrees of impulsivity elevation.

This possibility is further supported by the observation that BIS scores were associated with measures of functioning only in more affective psychotic disorders. Impulsivity, particularly of the attentional and non-planning varieties, was observed to be inversely correlated with both global and social functioning in SZA and PBP, which may be partially due to impulsivity's relationship with risky behaviors (Ryb et al., 2006), substance abuse (Moeller and Dougherty, 2002), and aggression (Seroczynski et al., 1999). The associations observed in this study between increased impulsivity and poorer functioning indicate the importance of impulsivity as a potential mediator of functional impairment in SZA and PBP. The relationship seen between impulsivity and suicidal history underscores the importance of impulsivity in affecting outcomes in psychotic disorders. Furthermore, these relationships support the contention that impulsivity may be a valuable target for treatment in these disorders (Moeller et al., 2001).

However, the impulsivity–functioning relationship was insignificant in SZ, with BIS score explaining less than 1% of the variance in GAF or SFS in SZ. The lack of association between functioning and impulsivity may also be explained by the accentuated negative symptomatology and cognitive deficit in SZ (Fig. S3). Functioning has long been observed to be associated with both negative symptoms (Addington et al., 1991; Couture et al., 2011; Fenton and McGlashan, 1991; Pogue-Geile and Harrow, 1985) and cognition (Green et al., 2000, 2004) in psychotic disorders, and so they may supersede and thereby mask the effects of impulsivity. Again, though, the high degree of negative symptoms and cognitive impairment in SZA, which exhibits no significant differences from SZ, diminishes the likelihood of this possibility.

The relationship between impulsivity and cortical volume followed a similar pattern, with significant correlations found in SZA and PBP but not in SZ. In both SZA and PBP, volumes of sub-regions within OFC were significantly and inversely related to BIS scores, particularly on the motor and non-planning subscales. Although the OFC sub-regions detected by the hierarchical analysis were inconsistent for SZA and PBP, post-hoc testing showed that both total left and total right OFC volumes were significantly inversely correlated with impulsivity in both groups. This finding matches prior research linking OFC structural abnormalities with increased impulsivity (Bechara et al., 2000; Berlin et al., 2004; Schilling et al., 2012). OFC appears to influence impulsivity by exerting "top-down" cognitive control over emotional reactivity (Joseph et al., 2009), decision making (Siever, 2008) by means including economic evaluation of options (Padoa-Schioppa and Assad, 2006), temporal discounting (McClure et al., 2004; Roesch et al., 2006), and calibration to social cues (Blair and Cipolotti, 2000). OFC volume deficits in SZA and PBP may lead to a partial failure of this inhibitory function, increasing affective intensity and persistence and also disrupting decision

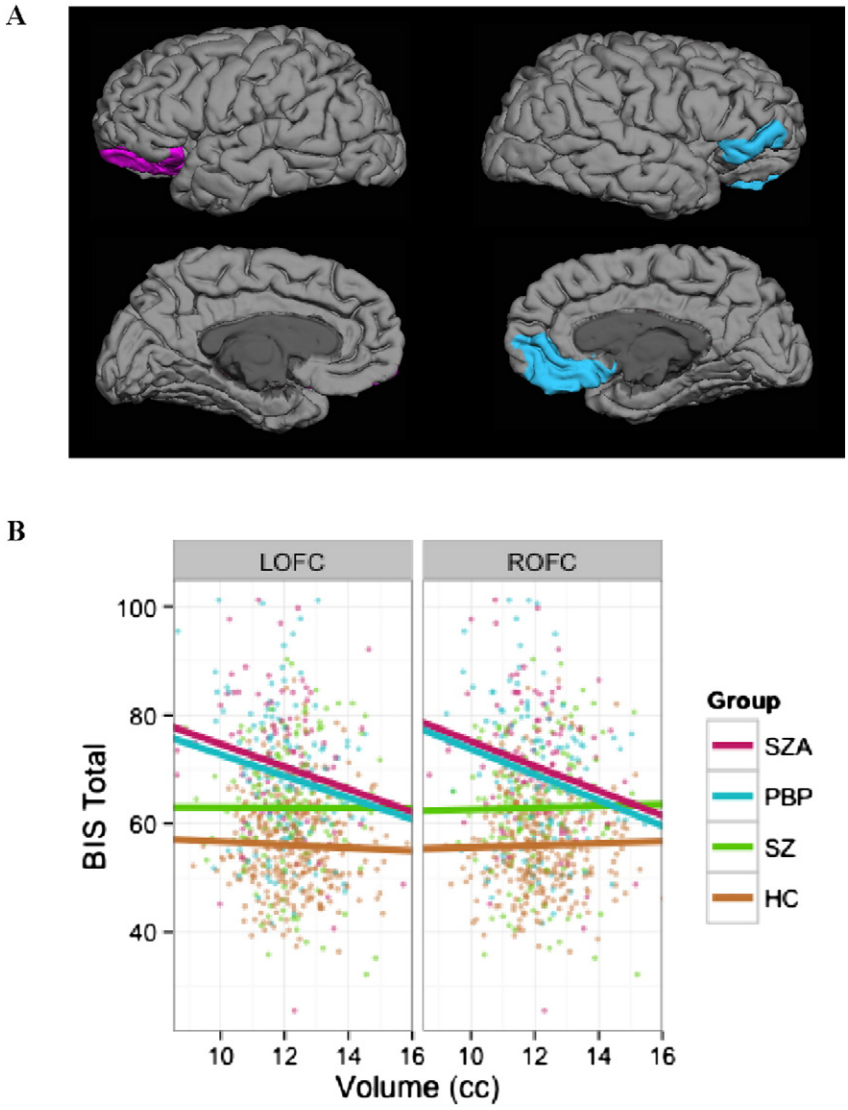

Fig. 2. Cortical volume associations with impulsivity. (A) Sub-regions of interest where cortical volume was significantly associated with Barratt Impulsiveness Scale (BIS) version 11 total score ($p < 0.05$) for the indicated participant group. In highlighted sub-regions, cortical volume and impulsivity were inversely correlated. (B) Impulsivity plotted by volume for left orbitofrontal cortex (LOFC) and right orbitofrontal cortex (ROFC) with linear trend lines for each participant group. The impulsivity-LOFC/ROFC correlations are significant ($p < 0.05$) for SZA and PBP only. HC — healthy controls; SZ — schizophrenia; SZA — schizoaffective disorder; PBP — psychotic bipolar disorder.

making during periods of heightened emotional arousal. These effects of OFC have been particularly implicated in bipolar disorder, with fMRI research demonstrating reduced OFC activity in bipolar patients during periods of mania, which is characterized by increased impulsivity, impaired attention, and increased motor activity (Altshuler et al., 2005). The impulsivity–OFC relationship may also underlie the high rates of suicidality and substance abuse in PBP and SZA, as orbitofrontal abnormalities and impulsivity have both been observed to be associated with past history of suicide attempts (Mahon et al., 2012; Matsuo et al., 2009) and substance use disorders (Dom et al., 2005; Jentsch and Taylor, 1999).

The impulsivity–OFC relationship was observed to differ significantly across diagnoses, and no significant associations were found between regional cortical volumes and impulsivity in SZ. The observation of significant associations between BIS scores and OFC volume in psychotic disorders with but not without affective components provides additional evidence for divergent mechanisms behind elevated impulsivity. The increased impulsivity found in SZ may involve different neural correlates, such as compromised frontal white matter integrity (Hoptman et al., 2004; Hoptman et al., 2002) or impaired efficiency of prefrontal cortex and decision making (Kaladjian et al., 2011). Alternatively, impulsivity may be characterized by orbitofrontal gray matter deficits only in a subset of SZ, as such impulsivity–structure associations have been observed in studies restricted to SZ patients with a history of serious physical violence (Kumari et al., 2009).

The results of this study may be limited by potential selection bias in the recruitment of the proband sample. The exclusion of patients with histories of substance abuse within the past month or substance dependence within the past 6 months may limit the generalizability of findings, particularly as impulsivity and gray matter volumes have previously been found to be associated in schizophrenia patients with comorbid substance abuse (Schiffer et al., 2010). The study may also be limited by the usage of only one scale to measure impulsivity, although it is a complex and multidimensional construct (Meda et al., 2009). Future studies using other measures for impulsivity may uncover more qualitative differences in the manifestation of impulsivity across the psychotic spectrum. Also, because the time frame of recruitment and assessment began before DSM 5 was available, DSM IV and not DSM 5 criteria were used to categorize participants. Furthermore, the hierarchical analysis may limit the sensitivity of the statistical analysis as the sample was split for the analysis's two steps. However, the rigor of this hierarchical analysis also enables us to report the structural

results with more confidence as it helps protect against the possibility of type I error.

The presence of significant impulsivity-OFC and impulsivity-functioning associations in SZA and PBP but not SZ suggests that increased impulsivity may have distinct mechanisms and manifestations in more and less affective psychotic disorders. Given the significant associations observed between functional outcomes and impulsivity in SZA and PBP, it may be worthwhile to leverage impulsivity as an important target of treatment in these disorders, for instance by considering selective serotonin reuptake inhibitors (SSRIs), which appear to dampen impulsivity by facilitating OFC inhibition of subcortical regions (New et al., 2004; Siever, 2008). Future studies should investigate the genetic bases of increased impulsivity in different psychotic disorder diagnoses in order to more conclusively establish potential differences in its pathophysiological roots.

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Sponsors had no involvement in study design; in the collection, analysis or interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Contributors

P. Nanda: Design and execution of statistical analysis, figure preparation, drafting of manuscript, critical revision of manuscript.

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I.T. Mathew: Image processing, figure preparation, critical revision of manuscript.

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G.D. Pearlson: Study supervision, acquisition of funding, critical revision of manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2015.11.030.

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