Title: Autistic and Schizotypal Traits and Global Functioning in Bipolar I Disorder

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Abstract

Objective: To determine the expression of autistic and positive schizotypal traits in a large sample of adults with bipolar I disorder (BD-I), and the effect of co-occurring autistic and positive schizotypal traits on global functioning in BD-I. **Method:** Autistic and positive schizotypal traits were self-assessed in 797 individuals with BD-I recruited by the Bipolar Disorder Research Network. Differences in global functioning (rated using the Global Assessment Scale) during lifetime worst depressive and manic episodes (GASD and GASM respectively) were calculated in groups with high/low autistic and positive schizotypal traits. Regression analyses assessed the interactive effect of autistic and positive schizotypal traits on global functioning. **Results:** 47.2% (CI=43.7-50.7%) showed clinically significant levels of autistic traits, and 23.22% (95% CI=20.29-26.14) showed clinically significant levels of positive schizotypal traits. In the worst episode of mania, the high autistic, high positive schizotypal group had better global functioning compared to the other groups. Individual differences analyses showed that high levels of co-occurring traits were associated with better global functioning in both mood states. **Limitations**: Autistic and schizotypal traits were assessed using self-rated questionnaires. **Conclusions:** Expression of autistic and schizotypal traits in adults with BD-I is prevalent, and may be important to predict illness aetiology, prognosis, and diagnostic practices in this population. Future work should focus on replicating these findings in independent samples, and on the biological and/or psychosocial mechanisms underlying better global functioning in those who have high levels of both autistic and positive schizotypal traits.

Key words: Autism, Global functioning, Psychosis, Schizophrenia, Schizotypy

Introduction

Bipolar disorder (BD) is a major affective disorder characterised by chronically recurring episodes of mania (or hypomania) and depression, which in their severe forms may present with psychotic symptoms, such as hallucinations or delusions (Weissman et al., 1996). This complex condition is often exacerbated by the presence of one or more comorbid conditions, in addition to a number of clinical factors such long duration of illness (Altamura et al., 2015; Altamura et al., 2010). While BD, schizophrenia spectrum disorders (SSD) and autism spectrum disorders (ASD) are considered distinct conditions, there is evidence for an overlap between BD and SSD (Altamura, Buoli, & Pozzoli, 2014; Carroll & Owen, 2009; Moller, 2003), as well as between ASD and BD (Carroll & Owen, 2009; Stahlberg, Soderstrom, Rastam, & Gillberg, 2004). Indeed, BD has a number of genetic, symptomatological and epidemiological overlaps with SSD (Laursen, Agerbo, & Pedersen, 2009; Lichtenstein et al., 2009; Murray et al., 2004), and psychosis has been recognised as an important dimension in the psychopathology of BD (van Os & Kapur, 2009). In addition, schizotypy, which encompasses a set of personality traits that reflect subclinical expression of schizophrenia (Ettinger et al., 2015), is recognised as genetically related to SSD and is considered an endophenotype common to both SSD and BD (Ettinger, Meyhofer, Steffens, Wagner, & Koutsouleris, 2014; Mahon, Perez-Rodriguez, Gunawardane, & Burdick, 2013; Schurhoff, Laguerre, Szoke, Meary, & Leboyer, 2005). Schizotypy has been reported at elevated rates in individuals with BD compared to healthy controls, although this was conducted in a relatively small BD sample (N=92) (Heron et al., 2003).

Furthermore, there is growing evidence of an association between ASD and BD (Cross-Disorder Group of the Psychiatric Genomics, 2013; Vannucchi et al., 2014). ASD is defined by

its cardinal impairments in social interaction, language and communication, and restricted behaviour and interests. To date, the majority of reports of ASD-BD comorbidity are in ASD samples, with prevalences ranging from 6% to 21.4% (Vannucchi et al., 2014). Only two studies have assessed ASD in BD samples: in youths (aged 7-17 years, N=157), 30% met diagnostic criteria for ASD (Joshi et al., 2013); and in a small sample of adults (N=56), 50% had high levels of autistic traits as measured with the Social Responsiveness Scale (Matsuo et al., 2015). Thus the extant literature reporting the expression of autistic or schizotypal traits in BD has been limited by small samples, and requires replication in large, well-characterised, adult samples of BD.

The interplay between BD, SSD and ASD or expression of their traits may have significant consequences on global functioning in patients with BD. Global functioning, a measure of illness severity, provides an overall picture of an individual's combined psychological, social and occupational functioning, such as how adaptive the patient is in dealing with social and interpersonal problems (Endicott, Spitzer, Fleiss, & Cohen, 1976). Poor functioning has been reported in individuals with schizotypal personality disorder (Henry, Bailey, & Rendell, 2008; Skodol et al., 2002), schizophrenia (Robertson et al., 2013) and ASD (Engstrom, Ekstrom, & Emilsson, 2003; Kastner et al., 2015). Hence a combined worsening effect may be expected in BD patients with high levels of co-occurring autistic and schizotypal traits. A recent study evaluated the effect of co-occurring autistic and positive schizotypal (i.e. relating to psychotic-like experiences) traits on the ability to appreciate the perspective of others (or *mentalising*) in the general population (N=201) (Abu-Akel, Wood, Hansen, & Apperly, 2015). It showed that while autistic and positive schizotypal traits independently induced perspective-taking errors, their interaction was associated with fewer errors, reflecting an

improvement in mentalising abilities. The authors proposed that this unexpected finding may be explained by the diametric model (Crespi & Badcock, 2008), which postulates that ASD and SSD have opposing effects on mentalising abilities, whereby autism is associated with reduced or no mentalising, and schizophrenia with dysfunctional overmentalising. While global functioning is not a test of mentalising per se, it has been shown to be associated with socio-cognitive abilities (Bo, Kongerslev, Dimaggio, Lysaker, & Abu-Akel, 2015) and improve following mentalising-based treatments (Bateman & Fonagy, 2008). To-date, no study has investigated the effect of co-occurring autistic and schizotypal traits on an outcome of clinical value in a psychiatric population.

Thus the present study has two main objectives: (1) to determine the expression of autistic and positive schizotypal traits in a large sample of adults with BD, and (2) to examine whether co-occurring autistic and positive schizotypal traits interact to affect global functioning in this population. The assessment of positive schizotypy only, rather than the general construct of schizotypy (comprising both positive and negative traits), is based on evidence that autistic and schizotypal traits cannot be distinguished by the presence or absence of negative traits, due to similarities in impaired social and communicative functioning (Spek & Wouters, 2010). Moreover, given that ASD is more prevalent in males compared to females (Lehnhardt et al., 2016), the expression of autism traits in our sample were analysed for male and female patients separately.

Investigating the prevalence of autistic and schizotypal traits in BD has management implications for individuals with BD, and may contribute to understanding the aetiology of BD. Moreover, isolating and characterising the expression of autistic and schizotypal traits is

important to understanding the nature of their effect on the course, outcome and treatment of the index condition (i.e. BD).

Methods

Participants

Participants were recruited by the Bipolar Disorder Research Network (BDRN) to an on-going programme of research into the genetic and non-genetic causes of BD. The study has UK National Health Service (NHS) Research Ethics Committee approval and local Research and Development approval in all participating NHS Trusts/Health Boards. Participants were recruited systematically via NHS mental health services, and non-systematically via advertisements on the BDRN website, in general practitioner surgeries and local media, and patient support organisations (such as Bipolar UK). Participants are included in the BDRN study if they meet the following criteria: i) capable of providing written informed consent; ii) aged at least 18 years; iii) meet DSM-IV criteria for a major affective disorder; and, iv) due to the study's genetic focus, UK/Ireland White ethnicity. The exclusion criteria are individuals who: i) have only experienced affective illness secondary to alcohol or substance abuse, medical illness or medication; ii) have a cognitive impairment that affects their ability to complete the measures; and, iii) are biologically related to another BDRN participant. After complete description of the study to the participants, written informed consent was obtained. The present analysis was performed on a subset of BDRN participants with DSM-IV bipolar I disorder who completed measures of both autistic spectrum and schizotypal traits (N=797).

Assessments

Lifetime clinical data were compiled by trained research psychologists and psychiatrists using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) semi-structured interview (Wing et al., 1990), and available psychiatric case notes. Data were combined for each participant, and lifetime best-estimate diagnostic and key clinical ratings (such as age of illness onset and lifetime presence of psychosis) were made based on pre-specified guidelines. Specifically, following SCAN guidelines, the worse episode ('peak of the disorder' or most severe episode) of each of depression and mania was decided in consultation with the participant. In very rare cases where there was discrepancy between the participant's chosen episode and their medical case-notes, a consensus decision was made with the clinical team about the worst episode.

Global functioning

The Global Assessment Scale (GAS) (Endicott et al., 1976) was used to rate global functioning during lifetime worst depressive and manic episode separately (GASD and GASM, respectively). Scores range 1-100, with higher scores reflecting higher functioning. All ratings, including GASD and GASM, were made independently by at least two members of the research team and consensus reached. Inter-rater reliability was formally assessed using 20 random cases. Mean kappa statistics were 0.85 for DSM–IV diagnoses, and between 0.81 and 0.99 for other key clinical categorical variables. Mean intra-class correlation coefficients were between 0.91 and 0.97 for key clinical continuous variables, including GASD and GASM.

Autism and schizotypal traits

Autism and schizotypal traits were self-rated using the Autism-Spectrum Quotient (AQ-

Short) (Hoekstra et al., 2011) and Kings Schizotypy Questionnaire (KSQ) (Jones et al., 2000). Participants were administered the KSQ at the end of the clinical interview, and AQ-Short was subsequently administered via a questionnaire mail-out.

Autism-Spectrum Quotient (AQ-Short)

Autistic traits were assessed using an abridged version of the Autism-Spectrum Quotient (AQ-Short) (Hoekstra et al., 2011), a 28-item questionnaire that generates a total AQ score (range 28-112). Higher scores reflect higher levels of autistic traits. Hoekstra et al have suggested an AQ-Short score >65 as a cut-off for clinically significant levels of autistic traits, and ≥70 as a further stringent cut-off (Hoekstra et al., 2011). The AQ-Short consisted of five subscales as follows: Social skills, routine, switching, imagination, and numbers and patterns. The internal consistency in this study is good (Cronbach's $\alpha = 0.80$) and is comparable to the values reported by Hoekstra et al. (2011), which ranged from .78-.86 across 4 different samples.

Kings Schizotypy Questionnaire (KSQ)

Positive schizotypal traits were evaluated using the positive subscale (range 0-45) of the Kings Schizotypy Questionnaire (KSQ-Positive) (Jones et al., 2000). A clinical cut-off is not available for this scale, but previous research showed that, on average, healthy controls score 7, schizophrenia patients score 17, and BD patient score intermediately at about 11 (Heron et al., 2003). The questionnaire is reliable (Cronbach's $\alpha = 0.81$) and valid, correlating at .63 with the Schizotypy Traits Questionnaire (Claridge & Broks, 1984). Higher scores reflect higher levels of positive schizotypal traits. The KSQ-positive consisted of 5 subscales

as follows: Recurrent illusions 1, recurrent illusions 2, magical thinking, paranoid ideation, and ideas of reference. The internal consistency of this questionnaire in this study is high (Cronbach's $\alpha = 0.903$).

Data analysis

To achieve the first objective, the proportions of participants scoring above the clinically significant and stringent AQ-Short thresholds were calculated, with 95% confidence intervals (95% CI). The mean KSQ-Positive score in the sample, with 95% CI, was calculated for comparison with previous samples reported in the literature.

To address the second objective, we first conducted an individual differences analysis using backward linear regression to examine the best predictors of global functioning during lifetime worst depressive and manic episode (GASD and GASM, respectively), with AQ-Short score, KSQ-Positive score, the AQ-Short x KSQ-Positive interaction term, and all demographic and clinical variables included in the model. The backward linear regression was constrained such that the AQ-Short score, KSQ-Positive score, and the AQ-Short x KSQ-Positive interaction term were retained in the final model. However, collinearity diagnostics showed multicollinearity violations for KSQ-positive (Variance Inflation Factor =39.97) and the interaction term (Variance Inflation Factor =44.59). To remedy this violation, we conducted a Principle Component Analysis (PCA) with varimax rotation on the scores obtained on the individual subscales of the AQ-short and KSQ-Positive. The analysis produced two components: an autism factor (AQ-PC) and a positive schizotypy factor (KSQ-

Positive-PC; see Supplementary Material for details). The components' regression coefficient scores and their interaction were used in the regression model.

Significant interactions were probed with the Johnson-Neyman method using MODPROBE for SPSS (Hayes & Matthes, 2009). This method provides a 'high-resolution picture' of the interaction by estimating the value(s) of AQ-PC at which KSQ-Positive-PC (or vice versa) has a significant effect on global functioning. This is established by identifying the precise value(s) along the continuum of one variable for which the regression slopes of the other variable are estimated to be significantly different from zero.

Next, K-means cluster analysis was performed to classify participants by level of autistic and positive schizotypal traits based on the two components' regression scores from the PCA analysis. This analysis produced four groups: low autistic, low positive schizotypal (LALP); low autistic, high positive schizotypal (LAHP); high autistic, low positive schizotypal (HALP); and high autistic, high positive schizotypal (HAHP). The group analysis aimed to investigate if specific autism-schizotypy trait clustering is associated with different levels of functioning.

Differences in demographic and lifetime clinical characteristics between these four groups were examined using analysis of variance (ANOVA), with *post-hoc* Bonferroni correction, for continuous variables; Kruskal-Wallis tests (with *post-hoc* Bonferroni-corrected pairwise comparisons) for non-normally distributed continuous variables; and chi-squared tests for categorical variables.

Two separate ANOVAs, with *post-hoc* Bonferroni corrections, were conducted to examine differences between the four groups in global functioning during lifetime worst depressive and manic episodes (GASD and GASM, respectively). All demographic and lifetime clinical variables were subsequently included as covariates in two separate analyses of covariance (ANCOVA) to control for the effect of potential confounders on group differences in GASD and GASM scores.

All analyses were undertaken using SPSS (version 22.0), with two-sided p values considered significant at $p<0.05$.

Results

Expression of Autistic and Positive Schizotypal Traits

On the AQ-Short, the sample scored a mean of 65.02 (SD=11.51; 95% CI 64.22-65.82). When comparing males and females, the males (Mean ± SD= 68.66±10.76) scored significantly higher than the females (Mean ± SD=63.79±11.50) ($t_{df=795} = 5.28$, $p<.001$, Cohen's d=.44). Using the AQ-Short cut-off of >65, 47.2% (95% CI=43.7-50.7%) of the entire sample scored positive for clinically significant levels of autistic traits, 60.20% (95% CI=53.43-66.97%) in males, and 42.79% (95% CI=38.82-46.75%) in females. When using the more stringent cut-off (AQ-Short≥70), 36.1% (95% CI=32.8-39.5%) of the entire sample scored at or above this cut-off, 50.75% (95% CI=43.83-57.66%) in males, and 31.21% (95% CI=24.80-37.6%) in females.

On the KSQ-Positive scale, the sample scored a mean of 11.98 (SD=9.33; 95% CI 11.33-12.62). There was no significant difference between the males (Mean ± SD=11.37±8.60) and

the females (Mean ± SD=12.18±9.56) ($t_{df=795}$ = -1.06, p=.290). As noted above, a clinical cut-off is not available for this scale. However, as a potential cut-off, we used the mean score of 17 reported for schizophrenia patients (Heron et al., 2003). Using that score, 23.22% (95% CI=20.29-26.14) of our sample scored above this cut-off.

Individual differences analysis: Global Functioning in Depression and Mania

As shown in Table 1, the overall final models of the backward regressions were significant in each mood state. In the worst episode of depression (GASD), the final model contained seven variables explaining 44.9% of the variance. Four variables were significantly associated with poorer global functioning as follows: females, history of psychosis in depression, longer illness duration and higher mean number of depressive episodes per illness year. In contrast, global functioning was positively associated with the interaction term of the autism and positive schizotypy components (i.e., AQ-PC x KSQ-Positive-PC). In the worst episode of mania (GASM), the final model contained six variables, explaining 44.2% of the variance. Poorer global functioning was associated with being older at the time of interview and having a history of psychosis in mania. In contrast, better global functioning was associated with individuals who attended higher education, and higher scores on the autism and positive schizotypy components. The interaction term between the autism and positive schizotypy components was non-significant.

Table 1 about here

In probing the interactive effect of autism and positive schizotypal traits on GASD, the Johnson-Neyman analysis revealed that increasing positive schizotypal traits was associated with significantly poorer global functioning in individuals scoring more than .93 SD below mean on the AQ factor. This trend was reversed such that positive schizotypal traits were

significantly associated with better global functioning in individuals scoring 1.57 SD above the mean on the AQ factor. Conversely, increasing autism traits were significantly associated with poorer global functioning in individuals scoring .33 SD below the mean on the positive schizotypy factor. This trend was reversed such autism traits were associated with better global functioning in individuals scoring 2.68 SD above the mean the positive schizotypy factor (see Figure 1).

Figure 1 about here

Classification into Groups, and Group Characteristics

Based on participants' levels of autistic and positive schizotypal traits, K means cluster analysis identified the following four groups: low autistic, low positive schizotypal (LALP; N=282, 35.38%), low autistic, high positive schizotypal (LAHP; N=118, 14.81%), high autistic, low positive schizotypal (HALP; (N=286, 35.88%), and high autistic, high positive schizotypal (HAHP; N=111, 13.93%). Comparisons of demographic and lifetime clinical characteristics between these groups are summarised in Table 2. There were significant differences between the groups for age at interview, gender distribution, lifetime highest level of education, mean number of depressive and manic episodes, and history of psychosis in depression.

Table 2 about here

Comparison of Global Functioning Between Groups

There were significant differences between the groups in global functioning in both mood states (GASD: $F(3,715)=4.35$, $p=0.005$, $R^2=0.018$; GASM: $F(3,776)=5.43$, $p=0.001$, $R^2=0.021$). In the worst episode of depression, the LAHP group had worse functioning than the LALP group (GASD mean difference=3.81, p=0.007, Cohen's *d*= .36) (see Figure 2A). In the worst episode of mania, the HAHP group had better functioning than the LALP group (GASM mean

difference=4.66, p=0.001, Cohen's *d*= .43), the LAHP group (GASM mean difference=4.15, p=0.031, Cohen's *d*= .37), and the HALP group (GASM mean difference=4.69, p=0.001, Cohen's *d*= .43) (see Figure 2B). When adjusting for demographic and lifetime clinical variables (see Table 2) the differences among the groups became non-significant ($F(3,597)=1.88$, p=.131) in the GASD model (N=611), but remained significant ($F(3,627)=6.71$, p<0.001, $R^2=0.031$) in the GASM model (N=641). In the adjusted GASM model, the functioning of the HAHP group was significantly better than the LALP group (mean difference=4.82, p<0.001, Cohen's *d*= .52), LAHP group (mean difference=4.83, p=0.001, Cohen's *d*= .46) and HALP group (mean difference=3.72, p=0.006, Cohen's *d*= .39). Note, the sample sizes of the adjusted models are smaller due to missing data.

Figure 2 about here

Discussion

This study sought to assess the expression of autistic and positive schizotypal traits in a large, well-characterised, adult sample of BD (N=797), and their concurrent effect on global functioning. Approximately, half of the sample exhibited clinically significant levels of autistic traits, and over a third on applying a more conservative cut-off. This is consistent with the single previous study of autistic-like traits conducted in an adult BD sample, in which half of the participants demonstrated high levels of autistic-like traits (Matsuo et al., 2015). These results also support phenomenological commonalities reported between ASD and BD (Vannucchi et al., 2014), and speculatively genetic overlaps (Cross-Disorder Group of the Psychiatric Genomics, 2013; Ellis, Panitch, West, & Arking, 2016). However, interpretive caution is required, as these overlaps do not confirm shared aetiology.

It is worth noting that the mean scores of the autistic traits of the males and females in our sample were intermediate to the mean scores reported by Hoekstra et al (2015) for their English controls and Asperger Syndrome cohorts. Specifically, the mean scores of the males and females in our sample were respectively higher than the means of the males (N=737; Mean difference = 8.93; Cohen's d=.90) and females (N= 1,101; Mean difference = 7.79; Cohen's d=.76) of their English controls cohort, and lower than the means of the males (N=56; Mean difference = -19.10; Cohen's d=-1.67) and females (N=117; Mean difference = 27.70; Cohen's d=-2.40) of their English Asperger Syndrome cohort.

The observed mean KSQ-Positive score in the overall sample (mean=11.98) was consistent with findings previously reported in BD (Heron et al., 2003). Heron et al further described that the expression of positive schizotypal traits in BD (mean=11.48) is less than that observed in a similarly ascertained schizophrenia group (mean=17.37), yet greater than in healthy controls (mean=7.05). Similarly, Mahon et al showed that individuals with BD (N=55) had elevated rates of schizotypy compared to healthy controls, as measured by the Schizotypal Personality Questionnaire (Mahon et al., 2013). Participants' unaffected siblings scored intermediately, suggesting that schizotypy is a dimensional trait that contributes to the genetic risk for BD (Mahon et al., 2013).

This study's second objective was to examine the effect of co-occurring autistic and positive schizotypal traits on global functioning in BD. Generally, both the individual differences (i.e., regressions) and group analyses provided evidence that both autistic and positive schizotypal traits were associated with better global functioning, such that their effects were greatest when both traits were high rather when both were low. Specifically, during

the worst episode of mania, the individual differences analysis showed that both autism traits and positive schizotypal traits independently contributed to increased global functioning. This was consistent with the results from the group analysis, which showed that the functioning of the high autism, high positive schizotypal group were significantly better than the other groups during the worst episode of mania even after controlling for potential confounders. During the worst episode of depression, individual differences analysis showed that autistic and positive schizotypal traits were interactively associated with increased global functioning. However, the group analysis revealed no differences among the groups after adjusting for confounders. It is possible that the individual differences analysis is a more sensitive approach than group-based analysis, particularly as it allows us to explore interactions across the entire rage of the autism and positive schizotypal traits. Collectively, these findings suggest that high levels of co-occurring autistic and positive schizotypal traits may be associated with a normalising effect on global functioning, and are consistent with the improvement effect of these co-occurring traits in the general population on tasks tapping perspective-taking (Abu-Akel et al., 2015) and attentional abilities (Abu-Akel, Apperly, Wood, Hansen, & Mevorach, 2016).

However, the mechanism by which this takes place is currently unknown, and thus should be the focus of future research. It is worth noting however that the pattern of the interactive effect of autistic and schizotypal traits on global functioning during the worst depressive episode suggests that the effect of the expression of one condition depends on the relative expression of the other condition, and that these dimension traits may be interacting in a compensatory manner to improve global functioning. We conjecture that this interactive effect on global functioning is likely driven by more basic functions/abilities

such as attention and mentalising abilities where autism and positive symptoms tend to exert opposite effect on naturally interacting genetic/biological systems subserving these abilities (Abu-Akel, Apperly, Wood, & Hansen, 2016). If verified, this would be consistent with recent genetic evidence suggesting either shared aetiology or compensatory changes across these neuropsychiatric conditions (Ellis et al., 2016), and with the apparent susceptibility of global functioning to gene-dosage effects of shared autism and schizophrenia risk loci (Abu-Akel, Wood, Hansen, & Apperly, 2016; Stefansson et al., 2014). Yet, the precise genetic mechanisms underlying these effects remain elusive that need to be addressed in future work.

Taken together, there appears to be a pattern whereby co-occurring high levels of both traits are associated with better global functioning. However, the large sample size allowed the detection of small but statistically significant differences in global functioning between groups that are of only marginal clinical significance. The difference observed in global functioning in the worst episode of mania between the high autistic, high positive schizotypal group compared to the other three groups translates to a one decile change on the GAS, such that the average global functioning observed in the high autistic, high positive schizotypal trait group equates to 'major impairment in several areas', compared to being 'unable to function in almost all areas'. Therefore, although the association between high levels of both traits and better global functioning is robust – withstanding a large number of covariates – the level of global functioning observed in the high autistic, high positive schizotypal group remains markedly impaired.

Nonetheless, as the relative expression of both traits appears to have measurable consequences on functioning and illness outcomes, screening for both autistic and schizotypal traits in BD patients, may be of significant value to understanding the heterogeneity of BD. In addition, the robustness of the expression of both autistic and schizotypal traits suggest that screening for both traits may be of theoretical and clinical importance. Specifically, the high level of expressions of autistic traits in over a third of the sample underscores the importance of routinely assessing autism in BD patients, which may contribute to improved diagnostic practices in this population. To this end, the administration of standard diagnostic schedules is required. Finally, further investigations of the co-expression of autism and schizotypy/schizophrenia in BD may yield important insights about the inter-relationship of these neuropsychiatric conditions. This is warranted given recent evidence for this inter-relationship from genetic (Ellis et al., 2016; Goes et al., 2016), neurodevelopmental (O'Shea & McInnis, 2016), neurobiological as well as psychopathological studies (Abdolmaleky, Zhou, & Thiagalingam, 2015; Panaccione et al., 2013; Sani et al., 2012; Skokauskas & Frodl, 2015). This also can help explain performance in other domains relevant to global functioning such as mentalising, which has been shown to be affected in all three conditions (Bora, Bartholomeusz, & Pantelis, 2016).

The findings must be interpreted in light of several limitations. The findings are likely to be affected by volunteer bias as the majority of the sample was recruited non-systematically. Individuals who volunteered to participate in research may systematically differ in their level of functioning, and other characteristics, compared to the overall BD population. For example, with a male to female ratio of 1:3, the sample does not reflect the gender distribution in the BD population whereby lifetime rates of BD I are higher in males

(Merikangas et al., 2011). The sample was further restricted to UK White adults, therefore the results may not be generalizable to other ethnicities. Furthermore, the study used two self-rated questionnaires to measure autistic and schizotypal traits; due to the subjective nature of these measures, the levels of traits reported were open to response bias and therefore may be inaccurate. In addition, the GAS has widely acknowledged limitations such as raters' subjective bias and conflation of symptom severity (Gold, 2014). Clinical data were also collected retrospectively by interview, hence vulnerable to recall bias, although the interview data were supported by contemporaneous psychiatric case-note data where possible. Finally, determining the peak of the disorder might entail some uncertainties, as some individuals might have not yet experienced their worst lifetime episode. Therefore, assessing the effects of these traits during euthymia is an important next step for future research, which would enable us to assess how these trait dimensions affect functioning outside mood episodes. This is particularly important in light of recent research reporting cognitive (Buoli, Caldiroli, Caletti, Zugno, & Altamura, 2014) and socio-cognitive (Bora et al., 2016) impairment during euthymia.

In conclusion, this study is the first to assess the expression of autistic and schizotypal traits in a large sample of adults with BD. The high frequency of autistic traits observed emphasises that a significant proportion of BD patients may benefit from screening for these traits, and potentially more individualised management. Furthermore, this is the first study to concurrently assess both autistic and schizotypal traits in BD I, hence the first to report that the interaction between these traits is associated with an outcome of clinical value, i.e., better global functioning. These findings require replication in independent samples, including samples with primary psychotic disorders (e.g. schizophrenia). Moreover,

the association of the interaction of autistic and schizotypal traits with improved functioning may have potential implications for investigating compensatory changes or mechanisms in BD I. Future work should focus on investigating the biological and/or psychosocial mechanisms underlying better global functioning in those with high levels of both autistic and schizotypal traits.

Contributors

A.A. and J.K. analyzed the data and wrote the study. A.A., L.J., K.G.S. and J.K. designed the study. All authors contributed to and have approved the final manuscript.

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Table 1. Variables associated with global functioning during lifetime worst depressive episode (GASD) and manic episode (GASM) in adults with bipolar I disorder.

Outcome	Variables	β	SE	t	p	Model[c]	
						p	R^2
GASD[a]	Female	-2.09	.727	-2.87	**0.004**	<0.001	0.449
	History of psychosis in depression	-14.39	.718	-20.05	**<0.001**		
	Longer illness duration	-0.17	.026	-6.35	**<0.001**		
	Higher mean number of depressive episodes/illness year	-1.12	.530	-2.11	**0.035**		
	AQ-PC [d]	-0.307	.305	-1.01	0.314		
	KSQ-Positive-PC [d]	0.049	.324	0.15	0.880		
	AQ-PC x KSQ-Positive-PC	0.771	.330	2.33	**0.020**		
GASM[b]	Older age at interview	-0.09	.031	-2.97	**0.003**	<0.001	0.422
	History of psychosis in mania	-15.17	.739	-20.52	**<0.001**		
	Higher education	1.73	.683	2.53	**0.012**		
	AQ-PC [d]	1.100	.335	3.28	**0.001**		
	KSQ-Positive-PC [d]	1.22	.358	3.42	**0.001**		
	AQ-PC x KSQ-Positive-PC	0.130	.336	0.35	0.724		

[a] GASD, Global Assessment Scale score during lifetime worst *Depressive* episode.
[b] GASM, Global Assessment Scale score during lifetime worst *Manic* episode.
[c] Final models are the results of backward regressions. Initial models included all demographic (age at interview, gender, marital history, lifetime highest level of education, recruitment method) and clinical variables (illness duration, history of psychosis in depression and mania, and mean number of depressive and manic episodes per illness year) as predictors, in addition to scores on the AQ-PC, the KSQ-Positive-PC, and their interaction (i.e., AQ-PC x KSQ-Positive-PC).
[d] AQ-PC and KSQ-Positive-PC are respectively the autism and positive schizotypy components' regression scores per the Principle Component Analysis (see Supplementary Material).

Table 2. Demographic and clinical characteristics of groups with high/low levels of autistic and positive schizotypal traits, in an adult sample of bipolar disorder.

Characteristic	Overall sample (N=797)		Group								Group Differences		
			LALP (N=282)		LAHP (N=118)		HALP (N=286)		HAHP (N=111)				
Demographic variables [a]	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F**	**df**	**p**
Age at interview (years) [b]	49.09	11.30	50.16	11.95	45.92	10.83	50.63	10.90	45.80	9.75	9.13	3	**<0.001**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**χ^2**	**df**	**p**
Female [c]	596	74.80	220	78.00	100	84.70	199	69.6	77	69.4	13.60	3	**0.004**
Married/lived as married [d]	673	85.20	239	85.4	100	84.70	239	84.5	95	87.20	0.48	3	0.92
Undergraduate degree or higher [e]	365	47.70	148	54.80	54	47.80	120	43.20	43	41.00	9.69	3	0.021
Non-systematically recruited [f]	615	77.8	224	80.30	89	76.10	209	73.60	93	84.50	7.02	3	0.071
Clinical variables [a]	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F**	**df**	**p**
Illness duration (years) [g]	25.34	12.14	24.61	13.05	24.38	11.15	26.35	12.02	25.52	10.97	1.20	3	0.31
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**KW χ^2**	**df**	**p**
Mean number of depressive episodes per illness year [h]	0.35	0.48	0.26	0.42	0.40	0.47	0.33	0.48	0.54	0.58	19.92	3	**<0.001**
Mean number of manic episodes per illness year [i]	0.29	0.37	0.23	0.34	0.33	0.42	0.28	0.33	0.43	0.50	18.96	3	**<0.001**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**χ^2**	**df**	**p**
History of psychosis in depression [j]	184	25.10	50	18.90	38	35.50	58	22.30	38	38.00	21.56	3	**<0.001**
History of psychosis in mania [k]	535	68.90	189	68.70	81	72.30	191	68.00	74	68.50	0.74	3	0.83

LA, Low Autistic traits; HA, High Autistic traits; LP, Low Positive schizotypal traits; HP, High Positive schizotypal traits.

SD= Standard Deviation; IQR= Interquartile Range; KW χ^2= Kruskal Wallis χ^2; MD= Mean Difference.

[a] Ns vary due to missing data: [d] (N=790); [e] (N=766); [f] (N=790); [g] (N=765); [h] (N=708); [i] (N=740); [j] (N=732); [k] (N=776).

[b] LALP>LAHP, MD=4.25, p=0.003; LALP>HAHP, MD=4.36, p=0.003; HALP>LAHP, MD=4.17, p=0.001; HALP>HAHP, MD=4.83, p=0.001. It is worth noting that previous research reported no significant association in the expression of autism traits and age of participants (Hoekstra, Bartels, Cath, & Boomsma, 2008)

[c] LAHP>HALP, χ^2=9.96, p=0.002; LAHP>HAHP, χ^2=7.67, p=0.006.

[e] None of the pairwise comparisons survived Bonferroni correction.

[h] LALP<LAHP, χ^2=10.08, p=0.009; LALP<HAHP, χ^2=18.30, p<0.001; HALP<HAHP, χ^2=9.18, p=0.015.

[i] LALP<HAHP, χ^2=19.89, p<0.001; LALP<LAHP, χ^2=10.53, p=0.007.

[j] LALP<LAHP, χ^2=11.66, p<0.001; LALP<HAHP, χ^2=14.49, p<0.001; HALP<HAHP, χ^2=6.83, p=0.009; LAHP>HALP, χ^2=9.07, p=0.003.

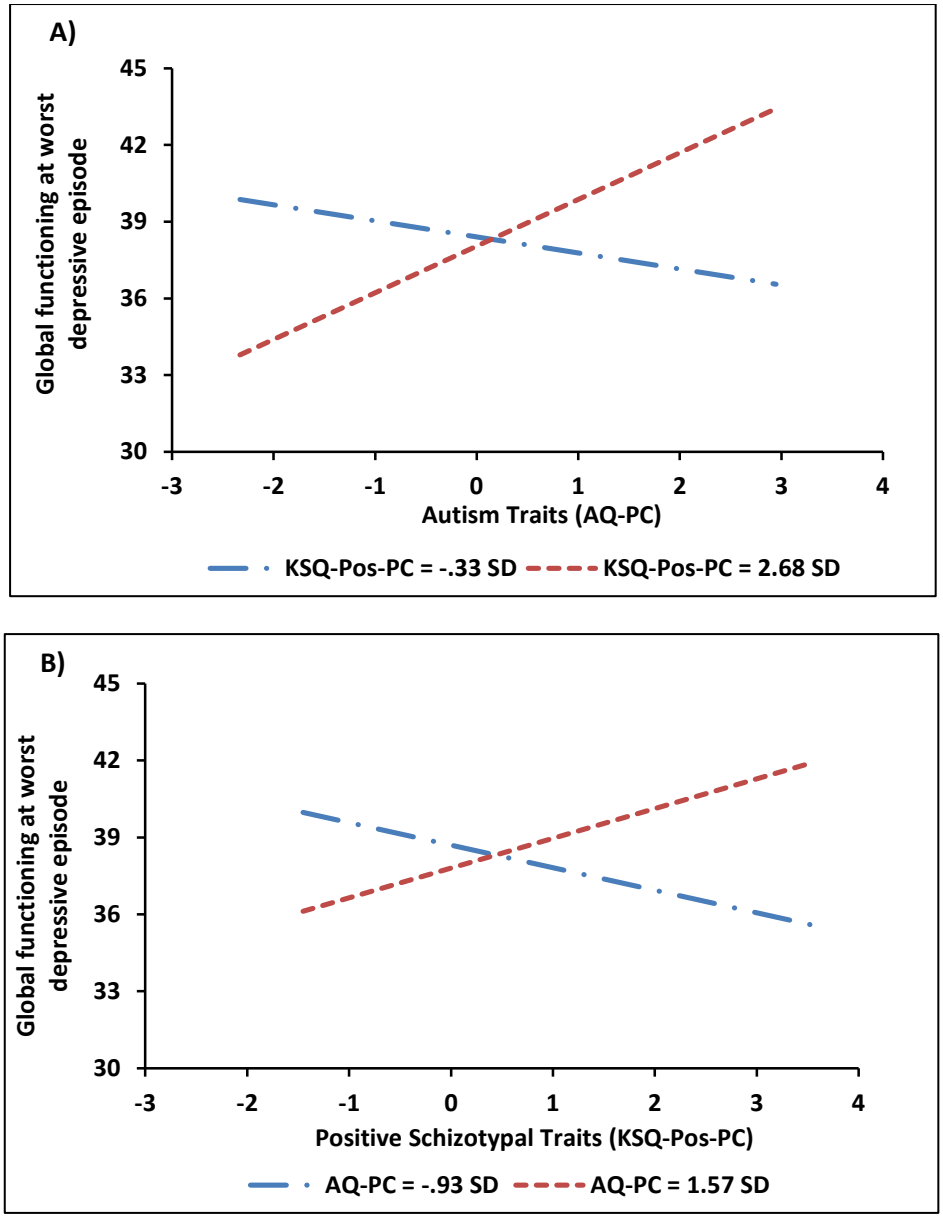
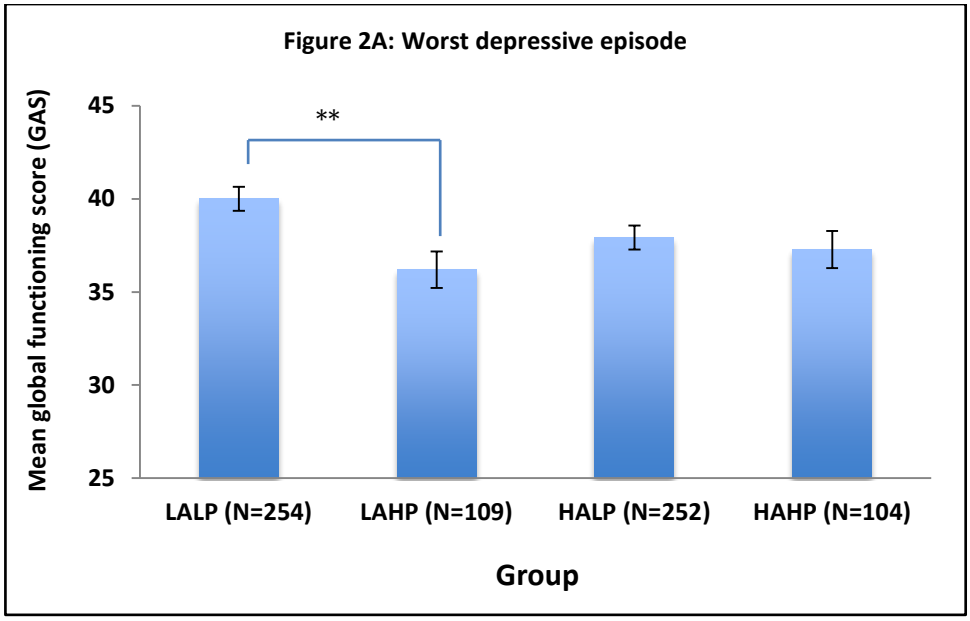


Figure 1. Visualisation of the interacitve effect of autism and positive schizotypal traits on global functioning during worst depressive episode. **Figure 1A** shows that AQ traits are significantly associated with poorer global functioning when positive schizotypal traits scores are .33 SD or more below the mean (at SD= -.33; β(se)=-.63(.32), t=-1.96, p=.05), and significantly associated with better global functioning at 2.68 SD or more above the mean (at SD=2.68; β(se)=1.83(.93), t=1.96, p=.05). **Figure 1B** shows that positive schizotypal traits are significantly associated with poorer global functioning when autism traits scores are .93 SD or more below the mean (at SD=-.93; β(se)=-.88(.45), t=-1.96, p=.05), and significantly associated with better global functioning at 1.57 SD or more above the mean (at SD=1.57; β(se)=1.16(.59), t=1.96, p=.05).



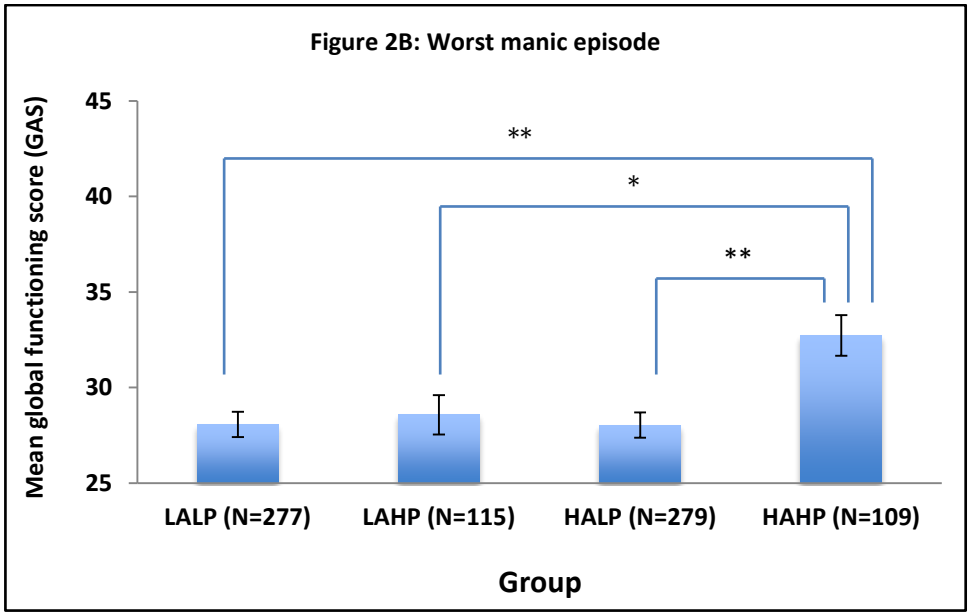


Figure 2. Global functioning as a function of autistic and positive schizotypal traits in adults with bipolar I disorder. **Figure 2A** displays the global functioning scores of the groups in the worst depressive episode. Analysis is based on data from 719 participants due to missing data. **Figure 2B** displays the global functioning scores of the groups in the worst manic episode. Analysis is based on data from 780 participants due to missing data. **LALP**=low autistic, low positive schizotypal. **LAHP**=low autistic, high positive schizotypal. **HALP**=high autistic, low positive schizotypal. **HAHP**=high autistic, high positive schizotypal. Error bars denote standard error of the mean. ***=**$p<0.05$; **=$p<.01$.

Supplementary Material

Principle Component Analysis

Constraining the backward elimination regression model by the concurrent inclusion of the AQ-Short, KSQ-Positive and their interaction term in the final model resulted in a multicolinearity violation. To remedy this situation, we conducted a Principle Component Analysis (PCA) on the scores of the five subscales of the AQ-Short (Hoekstra et al., 2011) (i.e., Social Skills, Routine, Switching, Imagination, and Numbers and Patterns) and the five subscales of the KSQ-Positive (Jones et al., 2000) (i.e., Recurrent Illusions 1, Recurrent Illusions 2, Magical Thinking, Paranoid Ideation, Ideas of Reference) following Dinsdale and colleagues (Dinsdale, Hurd, Wakabayashi, Elliot, & Crespi, 2013). Here, the PCA was conducted with a varimax rotation to maximize orthogonality and Kaiser Normalization. Moreover, variables with high (≥ 0.4) communalities (i.e., the proportion of each variable's variance that can be explained by the principal components) were retained. This resulted in the exclusion of the AQ Numbers and Patterns subscale, which had a communality score of only 0.190. The communalities of the remaining 9 subscales ranged from 0.438 – 0.768.

The PCA analysis produced two factors with eigenvalues ≥ 1, cumulatively explaining 58.18% of the variance. The first component was the positive schizotypy component (KSQ-Positive-PC), which explained 37.67% of the variance, and the second is the AQ component (AQ-PC), which explained 20.51%. Table 1S shows the loadings of the two principal components across the AQ-Short and KSQ-Positive subscales.

Table 1S. The principle components' loadings across the AQ-Short and the KSQ-positive subscales

Measure	**Subscale**	**KSQ-Positive-PC (eigenvalue = 3.77; variance = 37.67%;)**	**AQ-PC (eigenvalue = 2.05; variance = 20.51%)**
KSQ-Positive	Recurrent illusions 2	.870	
	Ideas of reference	.866	
	Recurrent illusions 1	.816	
	Magical thinking	.769	
	Paranoid ideation	.760	
AQ-Short	Routine		.768
	Switching		.760
	Social Skills		.750
	Imaginations		.618
PCA statistics			
Kaiser-Meyer-Olkin measure of sampling adequacy		.824	
Bartlett's test of sphericity		$\chi^2_{(df=45)} = 3141.03$, p<.001	

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