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Examining cognition across the bipolar / schizophrenia diagnostic spectrum

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Cognition in schizophrenia and bipolar disorder

Authors:

Amy J. Lynham[1], BSc, Leon Hubbard[1], PhD, Katherine E. Tansey[2], PhD, Marian L. Hamshere[1], PhD, Sophie E. Legge[1], PhD, Michael J. Owen[1], FRCPsych, PhD, Ian R. Jones[1], MRCPsych, PhD, James T.R. Walters[1], MRCPsych, PhD

Affiliations:

[1]MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, United Kingdom

[2]College of Biomedical and Life Sciences, Cardiff University, Cardiff, United Kingdom

Corresponding Author:

James T.R. Walters

MRC Centre for Neuropsychiatric Genetics and Genomics

Division of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine

Hadyn Ellis Building

Maindy Road

Cardiff

CF24 4HQ

Email: WaltersJT@cardiff.ac.uk

Abstract

Background: Cognitive impairments are well-established features of schizophrenia whereas there is ongoing debate about nature and degree of cognitive performance in schizoaffective disorder and bipolar disorder. We hypothesised that there is a spectrum of increasing impairment from bipolar disorder to schizoaffective-bipolar type to schizoaffective-depressive type and schizophrenia.

Method: Performance on the MATRICS Consensus Cognitive Battery was compared between participants with schizophrenia (N=558), schizoaffective-depressive type (N=112), schizoaffective-bipolar type (N=76), bipolar disorder (N=78) and healthy participants (N=103) using analysis of covariance with post-hoc comparisons. An ordinal logistic regression was conducted to examine whether cognitive impairments followed the hypothesised spectrum from bipolar disorder (least severe) to schizophrenia (most severe). In addition to categorical diagnoses we addressed the influence of symptom domains, examining the association between cognition and mania, depression and psychosis.

Results: Cognitive impairments increased in severity from bipolar disorder to schizoaffective-bipolar to schizophrenia/schizoaffective-depressive. Participants with schizophrenia and schizoaffective-depressive displayed equivalent performance (d=0.07,p=0.90). The results of the ordinal logistic regression were consistent with a spectrum of deficits from bipolar disorder to schizoaffective-bipolar type to schizophrenia/schizoaffective-depressive type (OR=1.98, $p=2.4x10^{-16}$). In analyses of the associations between symptom dimensions and cognition, higher scores on the psychosis dimension were associated with poorer performance (B=0.015□□SE=0.002, $p=3.2 \times 10^{-16}$).

Limitations: There were fewer participants with schizoaffective disorder and bipolar disorder than schizophrenia. Despite this, our analyses were robust to differences in the group sizes and we were able to detect differences between groups.

Conclusion: Cognitive impairments represent a symptom dimension that cuts across traditional diagnostic boundaries.

Declaration of interest: None.

Introduction

Current diagnostic approaches view schizophrenia and bipolar disorder as distinct psychiatric conditions, despite emerging evidence of significant genetic and phenotypic overlap between the disorders [1]. One of the most obvious challenges to the simple dichotomous view is the existence of the intermediate condition, schizoaffective disorder [2]. The relationship between schizoaffective disorder and schizophrenia and bipolar disorder is uncertain and it has been variously suggested that schizoaffective disorder is a sub-type of either schizophrenia or bipolar disorder, that it reflects comorbidity of schizophrenia and mood disorder, that it is an independent disorder, and, finally, that it lies in the middle of a spectrum that ranges from a predominantly affective disorder to a predominantly psychotic disorder [3]. The latter hypothesis suggests that prototypical bipolar disorder and schizophrenia lie on the extreme ends of a diagnostic spectrum with schizoaffective disorder representing patients who have features of both disorders [4]. Support for this comes from evidence that symptomatic and functional outcomes for schizoaffective disorder are intermediate between schizophrenia and bipolar disorder [5, 6]. More recently it has been proposed that schizophrenia and bipolar disorder lie on a gradient of neurodevelopmental impairment indexed by the extent of cognitive dysfunction, with schizoaffective disorders occupying an intermediate position [1, 7, 8].

Neuropsychological studies that provide support for a diagnostic spectrum have demonstrated increasing severity of impairment from bipolar disorder to schizoaffective disorder to schizophrenia, although these differences were not always significant [9-11]. In one of the largest studies to date, Hill et al. [10] showed an association between ratings on the Schizo-Bipolar scale [12] and composite cognition

scores with more severe impairments amongst those with prominent psychosis and fewer affective symptoms. However, findings from neuropsychological studies of these three disorders have been inconsistent with some studies indicating that performance in schizoaffective disorder is similar to schizophrenia [13] and others indicating no differences between diagnostic groups [14-17].

There are a number of potential explanations for the conflicting findings between studies including differences in the use of covariates and the phase of illness of the study participants. Studies of symptomatic participants with schizophrenia, schizoaffective disorder and bipolar disorder have reported similar levels of impairment [15, 16]. It has been argued that cognitive impairments are state dependent in bipolar disorder and therefore improve during periods of remission. However, more recent research has demonstrated that cognitive impairments are present in euthymic bipolar disorder [18]. Lifetime history of psychosis in bipolar disorder has been identified as another important factor that may influence cognitive function. Studies do not consistently report the proportion of participants with bipolar disorder who have a lifetime history of psychosis despite evidence that the presence or absence of lifetime psychosis differentiates participants with cognitive impairments from those without impairments [17]. Finally, studies often consider schizoaffective disorder as a single group but there is little data to indicate whether differences exist between the subtypes of schizoaffective disorder (depressive or bipolar). The study by Hill et al. [10] showed greater overall impairment in participants with the depressive subtype of schizoaffective disorder than the bipolar subtype, although the differences were not significant. Two smaller studies found no differences between participants with the depressive subtype and participants with

schizophrenia but did not consider the bipolar subtype [14, 19]. This suggests amalgamation of both subtype of schizoaffective disorder as a single group may obscure findings. To our knowledge, there have been no published studies that have compared the subtypes of schizoaffective disorder individually to schizophrenia and bipolar disorder.

The aim of this study was to test the hypothesis that there is a spectrum of increasing cognitive impairment from bipolar disorder through schizoaffective bipolar to schizoaffective depressive and schizophrenia. We also hypothesised that lifetime frequency and severity of psychotic symptoms (across and within diagnostic boundaries) would be associated with cognitive impairment. These hypotheses were tested in three ways. Firstly, we compared cognitive performance between the diagnostic groups. Secondly, we examined whether cognition can be considered a continuous measure across disorders. For this analysis, the schizophrenia and schizoaffective depressive groups were combined into a single group based on pre-existing data suggesting that performance between these groups is equivalent[10, 14, 19]. Thirdly, we examined whether cognitive performance is associated with symptoms domains across diagnostic groups.

Methods

Participants

Participants were recruited as part of the Cognition in Mood, Psychosis and Schizophrenia Study (COMPASS), a UK based study that recruits from outpatient clinics. This sample includes participants previously referred to as the Cardiff Cognition in Schizophrenia (COGS) sample (described elsewhere in [20]). All patient groups were recruited as part of a single study and all aspects of recruitment,

response rates, phenotyping and determining diagnosis were equivalent across groups. Participants were interviewed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [21]. This interview was reviewed along with available clinical records by trained raters to determine a consensus lifetime DSM-IV diagnosis[22] (inter-rater reliability Kappa statistics: schizophrenia=0.83, schizoaffective depressive=0.63, schizoaffective bipolar=0.72, bipolar disorder=0.85). The final sample included 824 participants with a diagnosis of schizophrenia (N=558), schizoaffective depressive (N=112), schizoaffective bipolar (N=76) or bipolar disorder (N=78). The bipolar disorder group included all participants who met criteria for a diagnosis of bipolar disorder – type I (N=68) or type II (N=10), of which 59 had a lifetime history of psychosis. Participants were excluded if they suffered from a neurological condition that was likely to impact their ability to participate in the study or had a current substance dependence disorder.

One hundred and three control participants were recruited from the community and completed the Mini International Neuropsychiatric Interview (MINI) [23] as a screen for mental disorders. Controls were excluded if they met criteria for schizophrenia or bipolar disorder or there was a family history of these conditions. All participants provided written informed consent and were reimbursed for their participation. Participants were assessed for capacity to provide informed consent by their clinical team and an appropriately trained researcher. The study had UK multi-site NHS ethics approval.

Neuropsychological Assessment

Cognitive ability was assessed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery

(MCCB[24]). This battery was designed specifically for use in schizophrenia research but has been shown to be a valid and reliable cognitive measure in bipolar disorder [25-27]. The MCCB measures seven domains of cognition using ten tasks:

1. Speed of processing (Brief Assessment of Cognition in Schizophrenia: Symbol Coding; Category Fluency: Animal Naming; Trail Making Test: Part A)
2. Working memory (Wechsler Memory Scale III: Spatial Span; Letter-Number Span)
3. Attention / vigilance (Continuous Performance Test: Identical Pairs)
4. Verbal learning (Hopkins Verbal Learning Test-Revised)
5. Visual learning (Brief Visuospatial Memory Test-Revised)
6. Reasoning and problem solving (Neuropsychological Assessment Battery: Mazes)
7. Social cognition (Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions).

For each task, z scores were derived using the mean and standard deviation of the control group (50% males, mean age = 41.7 years). Domain and composite scores were calculated following the MCCB manual procedures. Composite scores were only calculated if a participant had completed 5 or more domains. It was possible to calculate composite scores for 926 of the 927 participants.

Clinical and Demographic Variables

Lifetime mood and psychosis was rated using the Bipolar Affective Disorder Dimension Scale (BADDS[28]). The BADDS comprises of four dimensions, Mania, Depression, Psychosis and Incongruence. The first three dimensions were included and reflect the severity and frequency of these symptom domains. Current

symptoms were rated as the total of the global scores for the Scale for the Assessment of Negative Symptoms (SANS[29]) and the Scale for the Assessment of Positive Symptoms (SAPS[30]). Global functioning was measured using the Global Assessment Scale (GAS[31]). Premorbid IQ was estimated using the National Adult Reading Test.[32] Doses of antipsychotic medication at time of assessment were calculated as olanzapine equivalents[33] and lifetime antipsychotic exposure was calculated from interview and notes data in number of months. Intraclass correlation coefficients for the clinical variables ranged from 0.71 to 0.95.

Analysis

Comparing cognition between diagnostic groups

Statistical analyses to compare the groups were performed using R version 3.1.2. For each cognitive domain and across diagnostic groups, performance was compared using analysis of covariance with age and sex as covariates and followed up with Tukey's HSD for pairwise comparisons. Bonferroni correction was used to adjust for multiple comparisons resulting in an alpha of 0.00625 (0.05/8, 7 domains and composite score). The alpha was not corrected further for the number of pairwise comparisons, as Tukey's HSD is already a conservative test that corrects for family-wise error rate. Cohen's d were calculated by dividing mean group difference by the pooled standard deviation and used as a measure of effect size.[34] Repeated measures analysis of variance was used to compare profiles of cognitive performance between groups. The within-subject factor was cognitive domain. The effects of medication and symptoms as potential confounding variables were investigated by including olanzapine equivalent dose, duration of antipsychotic

exposure, SAPS total scores, SANS total scores, BADDS lifetime depression, educational attainment and parental occupation as covariates.

Examining cognition as a dimension across diagnostic groups

To test our hypothesis that cognition can be considered a dimensional phenotype showing increasing impairment from bipolar disorder to schizoaffective bipolar to schizophrenia and schizoaffective depressive combined, we conducted an ordinal regression using SPSSv.22 with diagnosis as the outcome, composite cognition score as the predictor and age and sex as covariates. Schizophrenia and schizoaffective depressive were combined given pre-existing data indicating that their degree of impairment is comparable [10, 14, 19]. Diagnosis was coded on an ordinal scale combining schizoaffective depressive and schizophrenia: 0 – schizoaffective depressive and schizophrenia, 1 – schizoaffective bipolar, 2 – bipolar disorder.

Cross disorder symptom dimensions and cognitive performance

Finally, each BADDS dimension was entered into separate linear regressions as predictors with composite cognition as the outcome using R version 3.1.2. This was initially done across the whole sample and then separately for bipolar disorder / schizoaffective bipolar and schizophrenia / schizoaffective depressive.

Results

Demographic and clinical variables

Demographic and clinical variables are displayed for each diagnostic group in Table 1. Groups differed in proportion of males (χ^2=61.39, p<0.001) with more males observed in the schizophrenia group therefore sex was used as a covariate in all analyses. There were differences in estimated premorbid IQ (F=22.64, p<0.001) and years in education (F=14.19, p<0.001), which were lower for those with

schizophrenia and schizoaffective depressive compared to those with bipolar disorder and schizoaffective bipolar. Groups differed on current positive and negative symptoms (SAPS: $F=65.96$, $p=3.13 \times 10^{-14}$; SANS: $F=64.16$, $p=7.58 \times 10^{-14}$) with lower scores in those with bipolar disorder compared to all other groups. Measures of current global functioning (Global Assessment Scale) differed between groups ($F=4.99$, $p=0.002$) with higher scores observed in the bipolar disorder group.

Comparing cognition between diagnostic groups

There was a significant main effect of diagnosis for all domains of cognition in the analysis of covariance (for example, composite cognition: $F(4, 921) = 94.12$, $p<0.00625$, see supplementary table S1 for full results). Figure 1 displays the z scores (marginal means) observed for each group demonstrating an increasing severity of cognitive impairments from controls to bipolar disorder to schizoaffective bipolar to schizophrenia and schizoaffective depressive.

Effect sizes for each pairwise comparison between diagnoses for all domains are displayed in Figure 2. All diagnostic groups were impaired compared to controls across cognitive domains with the exception of social cognition in those with bipolar disorder. The bipolar disorder group was the least impaired of the diagnostic groups, performing 0.5 to 1.25 standard deviations below the mean of the control group across domains (composite cognition: $d=1.12$, $p<0.001$). Although the groups were small, we compared bipolar disorder – type I (N=68) and bipolar disorder – type II (N=10) and found no significant differences between these groups (composite cognition: $d=-0.07$, $p=0.83$, see supplementary table S2 for comparisons between domains). The results remained consistent when the analysis was restricted to bipolar disorder – type I (see supplementary table S3). We also compared bipolar

disorder with and without psychosis and found no significant differences between these groups (composite cognition: d=0.34, p=0.2, see supplementary table S4 for comparisons between domains). We note that caution should be applied in the interpretation of the results comparing subgroups of bipolar disorder given the small sample of participants without psychosis (N=19) and with bipolar disorder – type II (N=10). The schizoaffective bipolar group was more impaired than the bipolar disorder group although this does not withstand correction for multiple testing (composite cognition: d=0.44, p=0.02). The schizophrenia and schizoaffective depressive groups were the most cognitively impaired and did not differ on any cognitive variable (composite cognition: d=0.07, p=0.90) corroborating our a priori decision to amalgamate these groups for subsequent analyses. These participants were more impaired than those with schizoaffective bipolar (schizophrenia: d=0.52, p<0.001; schizoaffective depressive: d=0.45, p=0.01) and those with bipolar disorder (schizophrenia: d=0.90, p<0.001; schizoaffective depressive: d=0.83,p<0.001). In contrast to other domains, levels of impairment in social cognition between schizoaffective bipolar, schizoaffective depressive and schizophrenia did not differ (Cohen's d for pairwise comparisons between these groups ranged between 0.05 and 0.28). All three of these groups were more impaired than bipolar disorder on social cognition (Cohen's d ranged between 0.50 and 0.81).

In order to test whether between group differences were qualitative or merely quantitative we compared cognitive profiles between diagnostic groups using repeated measures analysis of variance, with cognitive domain included as the within-subject factor. Mauchly's test indicated that the assumption of sphericity had been violated ($\chi^2(20)=360.23$, $p=3.5 \times 10^{-64}$) therefore degrees of freedom were

corrected using Huynh-Feldt estimates of sphericity. The diagnosis-by-domain interaction was not significant ($F=1.62$, $df=15.50, 3051.33$, $p=0.06$). The analysis was repeated excluding social cognition (given the quantitative differences in this domain) and the diagnosis-by-domain interaction was not significant ($F=1.604$, $df=1.60, 2680.70$ $p=0.07$) indicating that patterns of cognitive ability did not differ by diagnostic group but rather differed quantitatively.

We went on to investigate the effects of the potential confounding variables: olanzapine equivalent dose, duration of antipsychotic exposure, total SANS scores and total SAPS scores. The main effect of diagnostic group on composite cognitive scores remained significant after controlling for duration of antipsychotic exposure ($F(3,765)=16.18$, $p=3.4 \times 10^{-10}$), olanzapine equivalent dose at time of testing ($F(3,773)=21.42$, $p=2.5 \times 10^{-13}$), total SAPS score ($F(3,807)=24.52$, $p=3.4 \times 10^{-15}$) and total SANS score ($F(3,805)=16.71$, $p=1.6 \times 10^{-10}$, see supplementary tables S5-S8 for full data). Olanzapine equivalent dose at time of testing, duration of antipsychotic exposure and negative symptoms were associated with cognitive performance on all domains. Current psychotic symptoms (SAPS score) were not associated with performance across domains, other than social cognition. The analyses were also repeated including educational attainment and parental occupations (as measures of socioeconomic status) and the effect of diagnosis on cognition remained significant (supplementary table S9). Finally, diagnosis, olanzapine equivalent dose, duration of antipsychotic exposure, total SANS scores, total SAPS scores and lifetime depression (as measured by the BADDS depression scale) were added as predictors into a single model. The main effect of diagnostic group on composite cognition remained significant ($F(3,694)=8.33$, $p=1.9 \times 10^{-5}$, see supplementary table S10 for individual

domains). After correction for multiple testing, there were significant differences in composite cognition scores between schizoaffective depressive and bipolar disorder (d=0.65, p<0.001) and schizophrenia and bipolar disorder (d=0.58, p<0.001). The relative contributions of each covariate can be found in supplementary table S11.

Examining cognition as a dimension across diagnostic groups

We used ordinal regression to test whether cognition can be considered a dimensional phenotype across the diagnostic spectrum. This analysis indicated that higher cognitive scores were associated with higher scores on the diagnostic scale (0=schizoaffective depressive / schizophrenia, 1=schizoaffective bipolar and 2=bipolar disorder, see supplementary table S12 for full model) supporting a spectrum of increasing impairment from bipolar disorder to schizoaffective bipolar to schizophrenia/schizoaffective depressive. An alternative way of interpreting this result is that among our clinical cases participants with a one standard deviation higher score in composite cognition were almost twice as likely to be diagnosed with schizoaffective bipolar or bipolar disorder compared to schizophrenia (OR = 1.98, $p = 2.4 \times 10^{-16}$). Ordinal regression outputs a single odds ratio for the effect of the explanatory variable across all levels of the dependent variable because there is an assumption that the coefficients must be equal across all levels (assumption of proportional odds). This assumption was confirmed using the test of parallel lines in SPSS (χ^2=4.97, df=3, p=0.17) and by comparing the coefficients for binary regressions for each cut-off point in the scale. The results of the ordinal regression did not change after adjustment for olanzapine equivalent dose, antipsychotic exposure in months and current negative symptoms (OR = 1.63, $p = 4.9 \times 10^{-7}$), although we

interpret this result with caution given the proportional odds assumption was violated in this model (χ^2=26.98, p=1.5 x 10^{-4}).

The analysis was followed up with binary regressions between the diagnostic groups (*model 1*: bipolar disorder and schizoaffective bipolar; *model 2*: schizoaffective bipolar and schizoaffective depressive/schizophrenia) to compare the gradients from one diagnosis to the next on the scale (see supplementary table S12). The resulting coefficients were equivalent for models 1 and 2. This confirmed that there is a gradient of increasing impairment from bipolar disorder to schizoaffective bipolar to schizophrenia / schizoaffective depressive.

Cross disorder symptom dimensions and cognitive performance

Median BADDS dimension scores for each diagnostic group are presented in supplementary table S13. Higher scores on the lifetime mania and depression dimensions were associated with better cognitive performance (mania: B=0.010, SE=0.001, p=6.4 x 10^{-13}; depression: B=0.004, SE=0.001, p=.012). Higher scores on the lifetime psychosis dimension predicted poorer cognitive performance (psychosis: B=-0.015, SE=0.002, p=3.2 x 10^{-16}). In the subgroup analyses (bipolar disorder and schizoaffective bipolar only, schizophrenia and schizoaffective depressive only), neither mania nor depression scores predicted performance but higher psychosis scores were associated with lower cognitive scores (schizoaffective bipolar / bipolar disorder: B=-0.010, SE=0.003, p=0.0006; schizoaffective depressive / schizophrenia: B=-0.011, SE=0.003, p=0.0009). All analyses were repeated adjusting for age, sex, antipsychotic exposure in months, olanzapine equivalent dose and current negative symptoms. This did not change the results (see supplementary table S14), although the association between BADDS psychosis scores and cognition in the schizoaffective

depressive and schizophrenia subgroup did not survive correction for multiple testing.

Discussion

We set out to test the hypothesis that there is a spectrum of increasing cognitive impairment from bipolar disorder to schizophrenia and schizoaffective depressive. We report that whilst cognitive profiles were similar across disorders, these impairments increased in severity from bipolar disorder to schizoaffective bipolar to schizophrenia and schizoaffective depressive. There were no differences between schizophrenia and schizoaffective depressive in severity of cognitive impairments. Differences between the groups were not explained by differences in antipsychotic medication or current positive and negative symptoms. In accordance with our hypothesis, ordinal regression modelling provided support for a gradient of increasing cognitive impairment across disorders. Finally we found that higher scores on the BADDS psychosis dimension, a measure of the severity and frequency of lifetime psychosis, were associated with lower cognitive scores.

Performance across the cognitive domains was equivalent in the schizophrenia and schizoaffective depressive groups. These results suggest that from a cognitive perspective, there is questionable validity in the nosological distinction between schizophrenia and schizoaffective depressive. Therapies developed to improve cognition in schizophrenia should also be targeted towards patients with schizoaffective depressive type. These findings also highlight the importance of considering the subtypes of schizoaffective disorder separately, as these groups differed in severity of cognitive impairments.

Differences in overall cognition between schizoaffective bipolar and bipolar disorder were not significant after correction for multiple testing. However, the effect size between these groups (d=0.44) was larger than that observed between schizophrenia and schizoaffective depressive (d=0.07). This may explain why a linear trend from bipolar disorder to schizoaffective bipolar to schizophrenia and schizoaffective depressive was still observed in the ordinal regression analysis. We used a conservative Bonferroni-corrected alpha value to control the type-I error rate but at the cost of loss of power, which could explain the lack of significant difference. However, it should be noted that there were smaller differences between schizoaffective bipolar and bipolar disorder on individual domains, which were not significant even at alpha=0.05.

Diagnostic groups were differentiated on the basis of severity of cognitive impairments but the overall pattern of impairment was similar between the groups (Fig. 1). This suggests cognitive impairment can be considered a dimensional phenotype that cuts across diagnostic boundaries. These results are consistent with the results of previous studies showing that multiple domains of cognition are affected and these impairments increase in severity from bipolar disorder to schizophrenia [9-12]. Similarities between the cognitive profiles of these disorders are consistent with a shared underlying neurobiology that differs quantitatively rather than qualitatively across the diagnostic groups [1, 7, 8]. Indeed, previous studies have indicated overlap in regions of grey matter reduction (though less consistently in bipolar disorder) [35-38] and genetic susceptibility [39-42].

Whilst neurocognitive impairments were evident across all diagnoses, impairments in social cognition were not present in bipolar disorder but were observed in schizophrenia and schizoaffective disorder. The largest difference between participants with schizoaffective bipolar and bipolar disorder was observed in social cognition suggesting there may be some distinction in the cognitive processes underlying these disorders despite similar neurocognitive profiles. Social cognition was the only domain associated with current positive symptoms. Previous studies have demonstrated associations between domains of social cognition, particularly theory of mind deficits, and psychotic symptoms in schizophrenia [43-45]. These results suggest that certain social cognitive tasks may differentiate bipolar disorder from other disorders within the bipolar disorder / schizophrenia spectrum. The association between social cognitive impairment and psychosis provides support for cognitive models of psychosis that posit a role for social interpretations in the development of psychotic thinking [46].

Lifetime history of psychosis, as measured by the BADDS psychosis dimension, was associated with cognitive performance in our cross-diagnostic analysis. The BADDS psychosis dimension measures the prominence of psychotic symptoms over the course of illness and considers both duration and number of psychotic episodes. Lifetime history of psychosis has been shown to be associated with poorer cognition[17]. Our results expand on these findings by using a dimensional approach to show that lifetime frequency and severity of psychosis predicts severity of cognitive impairments.

This study has several strengths. It is one of the largest samples to date and is of a sufficient size to allow us to separate the subtypes of schizoaffective disorder. The sample is well characterised with consensus lifetime diagnoses based on semi-structured interview and medical records. The clinical characterisation of the sample allowed us to adjust for the effects of current symptoms and antipsychotic medication, including both current and lifetime antipsychotic exposure.

Limitations

A number of limitations should be noted. The sizes of the diagnostic groups were uneven and there was a larger sample of participants with schizophrenia than the other disorders. Despite this, our analyses were robust to differences in the group sizes and we were able to detect differences between groups. Our bipolar disorder group consisted of a mixture of patients with and without a lifetime history of psychosis. Given the small number of participants without psychosis, it was not possible to separate the bipolar group into those with and without history of psychosis to examine differences between these groups and schizophrenia or schizoaffective disorder. The MCCB was designed for use with participants with schizophrenia. Previous studies of bipolar disorder have failed to find deficits in executive functioning using the NAB Mazes task [25, 27, 47]. The authors of these studies note that more complex measures of executive function, such as the Wisconsin Card Sorting Task, may be more sensitive to detecting deficits in bipolar disorder. Although our bipolar group was impaired on the NAB Mazes relative to controls, this task may not have been sufficiently complex to differentiate bipolar disorder and schizoaffective disorder – bipolar type. Furthermore, our bipolar group was not impaired on the social cognition task (MSCEIT) but previous studies have identified

deficits in theory of mind and emotion recognition suggesting that patients with bipolar disorder do have impairments in specific domains of social cognition [48, 49].

Conclusion

Using a large and well-characterised sample, we have demonstrated that there is a gradient of increasing cognitive impairment from bipolar disorder to schizoaffective bipolar to schizophrenia and schizoaffective depressive. Differences in cognitive profiles between the diagnoses were quantitative rather than qualitative. Our findings comparing cognition between diagnostic groups confirmed our a priori decision to combine participants with schizophrenia and schizoaffective depressive in the subsequent analyses. This argues against separating schizophrenia and schizoaffective depressive for such analyses. This study was also the first to use a regression model to demonstrate a gradient of cognitive impairment and show that a dimensional measure of lifetime psychotic episodes is linearly associated with cognition. These results provide support for a model of psychotic and affective disorders where diagnostic criteria focus on dimensional measures of symptoms rather than traditional diagnostic categories.

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Statement of Ethical Approval

All participants provided written informed consent. The study had UK multi-site NHS ethical approval granted by South East Wales Research Ethics Committee Panel (REC reference number: 07/WSE03/110; full study title: “Genetic susceptibility to cognitive deficits across the schizophrenia / bipolar disorder diagnostic divide”).

References

1. Craddock N, Owen MJ. The Kraepelinian dichotomy–going, going... but still not gone. *Br J Psychiatry* 2010;196(2):92-5.

2. Kasanin J. The acute schizoaffective psychoses. *Am J Psychiatry* 1933;90(1):97-126.

3. Cheniaux E, Landeira-Fernandez J, Lessa Telles L, et al. Does schizoaffective disorder really exist? A systematic review of the studies that compared schizoaffective disorder with schizophrenia or mood disorders. *J Affect Disord* 2008;106(3):209-17.

4. Crow TJ. Nature of the genetic contribution to psychotic illness - a continuum viewpoint. *Acta Psychiatr Scand* 1990;81(5):401-8.

5. Benabarre A, Vieta E, Colom F, et al. Bipolar disorder, schizoaffective disorder and schizophrenia: epidemiologic, clinical and prognostic differences. *Eur Psychiatry* 2001;16(3):167-72.

6. Harrow M, Grossman LS, Herbener ES, et al. Ten-year outcome: patients with schizoaffective disorders, schizophrenia, affective disorders and mood-incongruent psychotic symptoms. *Br J Psychiatry* 2000;177(5):421-6.

7. Owen MJ, O'Donovan MC, Thapar A, et al. Neurodevelopmental hypothesis of schizophrenia. *Br J Psychiatry* 2011;198(3):173-5.

8. Owen MJ. New Approaches to Psychiatric Diagnostic Classification. *Neuron* 2014;84(3):564-71.

9. Szoke A, Meary A, Trandafir A, et al. Executive deficits in psychotic and bipolar disorders – Implications for our understanding of schizoaffective disorder. *Eur Psychiatry* 2008;23(1):20-5.

10. Hill SK, Reilly JL, Keefe RSE, et al. Neuropsychological Impairments in Schizophrenia and Psychotic Bipolar Disorder: Findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Study. *Am J Psychiatry* 2013;170(11):1275-84.

11. Reichenberg A, Harvey PD, Bowie CR, et al. Neuropsychological Function and Dysfunction in Schizophrenia and Psychotic Affective Disorders. *Schizophr Bull* 2009;35(5):1022-9.

12. Keshavan MS, Morris DW, Sweeney JA, et al. A dimensional approach to the psychosis spectrum between bipolar disorder and schizophrenia: The Schizo-Bipolar Scale. *Schizophr Res* 2011;133(1-3):250-4.

13. Evans JD, Heaton RK, Paulsen JS, et al. Schizoaffective disorder: A form of schizophrenia or affective disorder? *J Clin Psychiatry* 1999;60(12):874-82.

14. Glahn DC, Bearden CE, Cakir S, et al. Differential working memory impairment in bipolar disorder and schizophrenia: effects of lifetime history of psychosis. *Bipolar Disord* 2006;8(2):117-23.

15. Amann B, Gomar JJ, Ortiz-Gil J, et al. Executive dysfunction and memory impairment in schizoaffective disorder: a comparison with bipolar disorder, schizophrenia and healthy controls. *Psychol Med* 2012;42(10):2127-35.

16. Lewandowski KE, Cohen BM, Keshavan MS, et al. Relationship of neurocognitive deficits to diagnosis and symptoms across affective and non-affective psychoses. *Schizophr Res* 2011;133(1-3):212-7.

17. Simonsen C, Sundet K, Vaskinn A, et al. Neurocognitive Dysfunction in Bipolar and Schizophrenia Spectrum Disorders Depends on History of Psychosis Rather Than Diagnostic Group. *Schizophr Bull* 2009;37(1):73-83.

18. Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: A meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord* 2009;113(1-2):1-20.

19. Maj M. Neuropsychological functioning in schizoaffective disorder, depressed type. *Acta Psychiatr Scand* 1986;74(5):524-528.

20. Rees E, Walters JT, Georgieva L, et al. Analysis of copy number variations at 15 schizophrenia-associated loci. *Br J Psychiatry* 2014;204(1-3):108-17.

21. Wing JK, Babor T, Brugha T, et al. SCAN: Schedules for Clinical Assessment in Neuropsychiatry. *Arch Gen Psychiatry* 1990;47(6):589-93.

22. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (4th ed., text rev.)*; 2000.

23. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59(Suppl 20):22-33.

24. Nuechterlein K, Green M, Kern R, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am J Psychiatry* 2008;165(2):203-13.

25. Burdick KE, Goldberg TE, Cornblatt BA, et al. The MATRICS Consensus Cognitive Battery in Patients with Bipolar I Disorder. *Neuropsychopharmacology* 2011;36(8):1587-92.

26. Sperry SH, O'Connor LK, Öngür D, et al. Measuring Cognition in Bipolar Disorder with Psychosis Using the MATRICS Consensus Cognitive Battery. *J Int Neuropsychol Soc* 2015;21(6):1-5.

27. Van Rheenen TE, Rossell SL. An empirical evaluation of the MATRICS Consensus Cognitive Battery in bipolar disorder. *Bipolar Disord* 2014;16(3):318-25.

28. Craddock N, Jones I, Kirov G, et al. The Bipolar Affective Disorder Dimension Scale (BADDS) - a dimensional scale for rating lifetime psychopathology in bipolar spectrum disorders. *BMC Psychiatry* 2004;4(1):19.

29. Andreasen NC. Scale for the assessment of negative symptoms. *Iowa City: University of Iowa* 1983.

30. Andreasen NC. Scale for the assessment of positive symptoms. *Iowa City: University of Iowa* 1984.

31. Endicott J, Spitzer RL, Fleiss JL, et al. The global assessment scale: A procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* 1976;33(6):766-71.

32. Nelson H, Willison J. NART: National Adult Reading Test. *NFER-Nelson* 1991.

33. Gardner DM, Murphy AL, O'Donnell H, et al. International consensus study of antipsychotic dosing. *Am J Psychiatry* 2010;167(6):686-93.

34. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edn. Hillsdale, New Jersey: L: Erlbaum; 1988.

35. Amann BL, Canales-Rodríguez EJ, Madre M, et al. Brain structural changes in schizoaffective disorder compared to schizophrenia and bipolar disorder. *Acta Psychiatr Scand* 2016;133(1):23-33.

36. Ivleva EI, Bidesi AS, Keshavan MS, et al. Gray matter volume as an intermediate phenotype for psychosis: Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). *Am J Psychiatry* 2013;170(11):1285-96.

37. Ivleva EI, Bidesi AS, Thomas BP, et al. Brain gray matter phenotypes across the psychosis dimension. *Psychiatry Res Neuroimaging* 2012;204(1):13-24.

38. Bora E, Fornito A, Yücel M, et al. The effects of gender on grey matter abnormalities in major psychoses: a comparative voxelwise meta-analysis of schizophrenia and bipolar disorder. *Psychol Med* 2012;42(2):295-307.

39. Owen MJ, Craddock N, Jablensky A. The genetic deconstruction of psychosis. *Schizophr Bull* 2007;33(4):905-11.

40. Lichtenstein P, Yip BH, Björk C, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* 2009;373(9659):234-39.
41. Consortium C-DGotPG. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* 2013;381(9875):1371-9.
42. Lee SH, Ripke S, Neale BM, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet* 2013;45(9):984-94.
43. Marjoram D, Gardner C, Burns J,et al. Symptomatology and social inference: A theory of mind study of schizophrenia and psychotic affective disorder. *Cogn Neuropsychiatry* 2005;10(5):347-59.
44. Doody GA, Götz M, Johnstone EC, et al. Theory of mind and psychoses. *Psychol Med* 1998;28(2):397-405.
45. Fett A-KJ, Maat A, GROUP Investigators. Social Cognitive Impairments and Psychotic Symptoms: What Is the Nature of Their Association? *Schizophr Bull* 2013;39(1):77-85.
46. Garety PA, Freeman D. The past and future of delusions research: from the inexplicable to the treatable. *Br J Psychiatry* 2013;203(5):327.
47. Yatham LN, Torres IJ, Malhi GS, et al. The International Society for Bipolar Disorders – Battery for Assessment of Neurocognition (ISBD-BANC). *Bipolar Disord* 2010;12(4):351-363.
48. Samamé C, Martino D, Strejilevich S. Social cognition in euthymic bipolar disorder: Systematic review and meta-analytic approach. *Acta Psychiatr Scand* 2012;125(4):266-280.
49. Bora E, Yücel M, Pantelis C. Theory of mind impairment: a distinct trait-marker for schizophrenia spectrum disorders and bipolar disorder? *Acta Psychiatr Scand* 2009;120(4):253-264.

Tables

Table 1 Demographic and Clinical Variables

DSM-IV Diagnosis	Bipolar Disorder	Schizoaffective Disorder – Bipolar Type	Schizoaffective Disorder – Depressive Type	Schizophrenia
N	78	76	112	558
Age*	45.8 (10.6)	43.8 (10.6)	44.1 (10.1)	43.3 (11.9)
Gender (% males)	40	46	40	69
Estimated Premorbid IQ*	97.5 (22.4)	94.0 (21.5)	85.3 (20.2)	81.7 (23.7)
Years in Education*	14.6 (3.3)	13.7 (3.0)	12.3 (2.3)	12.7 (2.7)
Taking Antipsychotic (%)	63.2	74.7	77.7	85.5
Olanzapine Equivalent Dose†	8 (12)	15 (10)	15 (13.5)	13.7 (13.7)
Antipsychotic exposure in months†	60 (102)	153 (181.5)	168 (164.5)	170 (168)
Current SAPS†§	0 (0)	2 (5)	2 (5)	3 (6)
Current SANS†§	0.5 (3)	4 (5)	6 (7)	5.5 (7)
GAS Past Week*	70.8 (14.2)	60.1 (16.8)	58.6 (15.8)	60.2 (15.1)

SAPS: Scale for the Assessment of Positive Symptoms; SANS: Scale for the Assessment of Negative Symptoms; GAS: Global Assessment Scale

*Means and standard deviations are presented.

†Medians and interquartile ranges are presented due to non-normal distribution.

§Current SAPS and SANS scores represent the sum of the global scores.

Figure Legends

Figure 1: Neuropsychological performance for participants with bipolar disorder, schizoaffective bipolar, schizoaffective depressive and schizophrenia

Figure 2: Pairwise comparisons. Footnote: Each 3x3 section displays the Cohen's d effect sizes for the difference between two diagnostic groups for each domain of cognition. Lighter shade $p<0.05$, darker shade $p<0.00625$