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**Title:**

Examining cognition across the bipolar / schizophrenia diagnostic spectrum

**Running Title:**

Cognition in schizophrenia and bipolar disorder

**Authors:**

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

**Affiliations:**

<sup>1</sup>MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, United Kingdom

<sup>2</sup>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 ( $OR=1.98, p=2.4 \times 10^{-16}$ ). 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.

## 1 **Introduction**

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

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

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

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

49 schizophrenia but did not consider the bipolar subtype <sup>14, 19</sup>. This suggests  
50 amalgamation of both subtype of schizoaffective disorder as a single group may  
51 obscure findings. To our knowledge, there have been no published studies that have  
52 compared the subtypes of schizoaffective disorder individually to schizophrenia and  
53 bipolar disorder.

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

## 66 **Methods**

67

### 68 Participants

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

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

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

#### 95 Neuropsychological Assessment

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



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

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

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

#### 117 Clinical and Demographic Variables

118 Lifetime mood and psychosis was rated using the Bipolar Affective Disorder  
119 Dimension Scale (BADDS<sup>28</sup>). The BADDS comprises of four dimensions, Mania,  
120 Depression, Psychosis and Incongruence. The first three dimensions were included  
121 and reflect the severity and frequency of these symptom domains. Current

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

### 130 Analysis

#### 131 *Comparing cognition between diagnostic groups*

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

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

147 *Examining cognition as a dimension across diagnostic groups*  
148 To test our hypothesis that cognition can be considered a dimensional phenotype  
149 showing increasing impairment from bipolar disorder to schizoaffective bipolar to  
150 schizophrenia and schizoaffective depressive combined, we conducted an ordinal  
151 regression using SPSSv.22 with diagnosis as the outcome, composite cognition score  
152 as the predictor and age and sex as covariates. Schizophrenia and schizoaffective  
153 depressive were combined given pre-existing data indicating that their degree of  
154 impairment is comparable <sup>10, 14, 19</sup>. Diagnosis was coded on an ordinal scale  
155 combining schizoaffective depressive and schizophrenia: 0 – schizoaffective  
156 depressive and schizophrenia, 1 – schizoaffective bipolar, 2 – bipolar disorder.

157 *Cross disorder symptom dimensions and cognitive performance*  
158 Finally, each BADDs dimension was entered into separate linear regressions as  
159 predictors with composite cognition as the outcome using R version 3.1.2. This was  
160 initially done across the whole sample and then separately for bipolar disorder /  
161 schizoaffective bipolar and schizophrenia / schizoaffective depressive.

## 162 **Results**

163

### 164 Demographic and clinical variables

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

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

#### 176 Comparing cognition between diagnostic groups

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

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

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

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

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

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

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

#### 246 Examining cognition as a dimension across diagnostic groups

247 We used ordinal regression to test whether cognition can be considered a  
248 dimensional phenotype across the diagnostic spectrum. This analysis indicated that  
249 higher cognitive scores were associated with higher scores on the diagnostic scale  
250 (0=schizoaffective depressive / schizophrenia, 1=schizoaffective bipolar and  
251 2=bipolar disorder, see supplementary table S12 for full model) supporting a  
252 spectrum of increasing impairment from bipolar disorder to schizoaffective bipolar  
253 to schizophrenia/schizoaffective depressive. An alternative way of interpreting this  
254 result is that among our clinical cases participants with a one standard deviation  
255 higher score in composite cognition were almost twice as likely to be diagnosed with  
256 schizoaffective bipolar or bipolar disorder compared to schizophrenia ( $OR = 1.98$ ,  $p =$   
257  $2.4 \times 10^{-16}$ ). Ordinal regression outputs a single odds ratio for the effect of the  
258 explanatory variable across all levels of the dependent variable because there is an  
259 assumption that the coefficients must be equal across all levels (assumption of  
260 proportional odds). This assumption was confirmed using the test of parallel lines in  
261 SPSS ( $\chi^2=4.97$ ,  $df=3$ ,  $p=0.17$ ) and by comparing the coefficients for binary regressions  
262 for each cut-off point in the scale. The results of the ordinal regression did not  
263 change after adjustment for olanzapine equivalent dose, antipsychotic exposure in  
264 months and current negative symptoms ( $OR = 1.63$ ,  $p = 4.9 \times 10^{-7}$ ), although we

265 interpret this result with caution given the proportional odds assumption was  
266 violated in this model ( $\chi^2=26.98$ ,  $p=1.5 \times 10^{-4}$ ).

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

#### 274 Cross disorder symptom dimensions and cognitive performance

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



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

## 291 **Discussion**

292 We set out to test the hypothesis that there is a spectrum of increasing cognitive  
293 impairment from bipolar disorder to schizophrenia and schizoaffective depressive.

294 We report that whilst cognitive profiles were similar across disorders, these  
295 impairments increased in severity from bipolar disorder to schizoaffective bipolar to  
296 schizophrenia and schizoaffective depressive. There were no differences between  
297 schizophrenia and schizoaffective depressive in severity of cognitive impairments.

298 Differences between the groups were not explained by differences in antipsychotic  
299 medication or current positive and negative symptoms. In accordance with our  
300 hypothesis, ordinal regression modelling provided support for a gradient of  
301 increasing cognitive impairment across disorders. Finally we found that higher scores  
302 on the BADDs psychosis dimension, a measure of the severity and frequency of  
303 lifetime psychosis, were associated with lower cognitive scores.

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

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

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

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

348 Lifetime history of psychosis, as measured by the BADDs psychosis dimension, was  
349 associated with cognitive performance in our cross-diagnostic analysis. The BADDs  
350 psychosis dimension measures the prominence of psychotic symptoms over the  
351 course of illness and considers both duration and number of psychotic episodes.  
352 Lifetime history of psychosis has been shown to be associated with poorer  
353 cognition<sup>17</sup>. Our results expand on these findings by using a dimensional approach to  
354 show that lifetime frequency and severity of psychosis predicts severity of cognitive  
355 impairments.

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

### 362 **Limitations**

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

380 deficits in theory of mind and emotion recognition suggesting that patients with  
381 bipolar disorder do have impairments in specific domains of social cognition<sup>48,49</sup>.

382 **Conclusion**

383 Using a large and well-characterised sample, we have demonstrated that there is a  
384 gradient of increasing cognitive impairment from bipolar disorder to schizoaffective  
385 bipolar to schizophrenia and schizoaffective depressive. Differences in cognitive  
386 profiles between the diagnoses were quantitative rather than qualitative. Our  
387 findings comparing cognition between diagnostic groups confirmed our a priori  
388 decision to combine participants with schizophrenia and schizoaffective depressive  
389 in the subsequent analyses. This argues against separating schizophrenia and  
390 schizoaffective depressive for such analyses. This study was also the first to use a  
391 regression model to demonstrate a gradient of cognitive impairment and show that  
392 a dimensional measure of lifetime psychotic episodes is linearly associated with  
393 cognition. These results provide support for a model of psychotic and affective  
394 disorders where diagnostic criteria focus on dimensional measures of symptoms  
395 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”).

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## Tables

Table 1 Demographic and Clinical Variables

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

<sup>†</sup>Medians and interquartile ranges are presented due to non-normal distribution.

<sup>§</sup>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  $p < 0.00625$