Cognitive heterogeneity in the offspring of patients with schizophrenia or bipolar disorder: a cluster analysis across family risk

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Abstract

Background: Neurocognitive impairment is considered to lie on a continuum of severity across schizophrenia (SZ) and bipolar disorder (BP), possibly reflecting a gradient of neurodevelopmental load. Cluster analyses have identified different levels of impairment across the two disorders, from none to widespread and severe. We for the first time used this approach to examine cognitive function pooling together children and adolescents at familial risk of SZ or BP.

Methods: 220 participants, 49 offspring of individuals with schizophrenia (SZO), 90 offspring of individuals with bipolar disorder (BPO) and 81 offspring of healthy control parents (HC), aged 6 to 17 years, underwent a comprehensive clinical and cognitive assessment. Cognitive measures were used to group SZO and BPO using K-means clustering. Cognitive performance within each of the clusters was compared to that of HC and clinical variables were compared between clusters.

Results: We identified three cognitive subgroups: a moderate impairment group, a mild impairment group, and a cognitively intact group. Both SZO and BPO were represented in each of the clusters, yet not evenly, with a larger proportion of the SZO in the moderately impaired cluster, but also a subgroup of BPO showing moderate cognitive dysfunction.

Limitations: Participants have yet to reach the age of onset for the examined disorders.

Conclusions: The findings point to a range of neurodevelopmental loadings across youth at familial risk of both SZ and BP. They have therefore important implications for the stratification of cognitive functioning and the possibility to tailor interventions to individual levels of impairment.

Background

Schizophrenia (SZ) and Bipolar Disorder (BP) are considered nosologically distinct but views are shifting from a categorical to a more dimensional and transdiagnostic conceptualisation (Owen & O'Donovan, 2017). The two disorders co-segregate in families and are characterised by extensive genetic sharing (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium., 2018; Lichtenstein et al., 2009). Yet differences also have a genetic basis (Lichtenstein et al., 2009; Ruderfer et al., 2014) and despite overlapping clinical features, the extent to which cognition is impaired appears to differ between the two disorders (Trotta, Murray, & MacCabe, 2015). In particular, severity and trajectories have been considered to diverge (Trotta et al., 2015).

In terms of severity, SZ is characterized by widespread cognitive impairment, with most severe deficits in verbal learning, executive function and processing speed (Bora & Pantelis, 2015). Cognitive impairment is also increasingly recognized as an important dimension of BP (Trotta et al., 2015), observed during periods of euthymia (Bourne et al., 2013) and worsened during symptomatic relapse (Kurtz & Gerraty, 2009). The same cognitive domains most affected in SZ show the largest impairments in BP (Bora & Pantelis, 2015), yet overall severity is milder, with performance reported as intermediate between that of patients with SZ and healthy controls (HC) (Bora & Pantelis, 2015). These quantitative but not qualitative differences between SZ and BP have been difficult to interpret due to the significant cognitive heterogeneity observed in both disorders. Recent studies have therefore examined cognitive function cross-diagnostically, using data-driven approaches to cluster patients based on performance rather than diagnostic group (Bora, Veznedaroglu, &

Vahip, 2016; Karantonis et al., 2020; Lee et al., 2017; Lewandowski, Sperry, Cohen, & Ongur, 2014; Van Rheenen et al., 2017). The findings across SZ and BP consistently revealed low and high performance profiles (Lee et al., 2017). Most studies identified a group characterized by severe and widespread impairment, a group with cognition comparable to that of HC, as well as one or more intermediate groups, displaying moderate or selective impairments (Bora et al., 2016; Karantonis et al., 2020; Lewandowski et al., 2014; Van Rheenen et al., 2017). Participants from both diagnostic groups were represented in each of the clusters, but in different proportions, with SZ more frequently characterised by severe impairments and BP participants more often cognitively spared. Results therefore allowed to dissect the known heterogeneity and described a higher proportion of severe deficits in SZ, but also confirmed that pronounced impairments can be observed in BP.

It is however still unclear whether SZ and BP also share the timeframe of emergence of cognitive impairment. Cognitive deficits were thought to develop during the course of the illness in BP, while dysfunction at illness onset was considered to be specific to SZ (Bora & Pantelis, 2015). A recent meta-analysis, however, reported impairments across all cognitive domains in first episode BP patients (Bora & Pantelis, 2015). First episode SZ patients significantly underperformed first episode BP patients, similarly to what is observed in the later course of the illness, yet differences were modest (Bora & Pantelis, 2015). What still remains debated is whether trajectories differ premorbidly. Several studies have reported that cognitive abnormalities in SZ predate illness onset, while the evidence for BP is mixed (Trotta et al., 2015). In SZ premorbid abnormalities have been demonstrated by retrospective scholastic achievement examination (Fuller et al., 2002; Reichenberg et al., 2010), as well as

both prospective and retrospective cognitive assessment (Trotta et al., 2015), while high school grades were identified as protective (MacCabe et al., 2008). Cognitive impairment has also been described in both clinical and familial SZ high-risk samples (Bora et al., 2014; Hemager et al., 2018). In contrast, scholastic achievement was reported to be poor but also excellent in children and adolescents who subsequently developed BP (MacCabe et al., 2010), with an almost two-fold increased risk in poor performers but also a nearly four-fold increased risk in those displaying excellent performance. A meta-analysis of premorbid intellectual function reported milder impairments in BP relative to SZ (Trotta et al., 2015). Deficits in BP, however, were only identified when examining retrospective studies, while no significant difference to HC was observed when restricting the analysis to studies employing a prospective design (Trotta et al., 2015). Cognitive deficits have also been described in BP offspring (de la Serna et al., 2016), but cognition has also been reported not to differ from HC (Hemager et al., 2018). Yet a recent meta-analysis in youth at familial risk for BP (Bora & Ozerdem, 2017b) identified significant deficits relative to HC in visual and verbal memory, attention and processing speed.

BP and SZ have been reconsidered as part of a broader neurodevelopmental continuum (Owen & O'Donovan, 2017) together with classic childhood onset neurodevelopmental disorders. They display an increasing level of neurodevelopmental load, with BP at one end of the spectrum followed by SZ, attention deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASD) and intellectual disability at the other end. Discrete syndromes along the continuum are considered to reflect the severity and timeframe of abnormal brain development (Owen & O'Donovan, 2017). However, evidence of neurodevelopmental mechanisms

is not univocal in BP and these mechanisms might either be less pronounced or only pertain to a subgroup of BP patients (Valli, Fabbri, & Young, 2019). To address such question a recent study employed a clustering approach to examine cognitive function in the offspring of patients with BP (Bora et al., 2019). Similarly to studies in adult BP patients (Burdick et al., 2014), the authors identified three performance clusters, one characterised by severe impairments, one with good performance and one intermediate between the other two. However, to date no study has jointly examined the offspring of patients with SZ and BP. We therefore decided to study children and adolescents at familial risk of SZ and BP and group participants based on cognitive performance rather than parental diagnosis. Such approach aimed at addressing questions related to cognitive heterogeneity within both SZ and BP offspring, employing a transdiagnostic perspective. We hypothesised that cognitive performance across the offspring of patients with schizophrenia (SZO) and the offspring of patients with bipolar disorder (BPO) would coalesce into different clusters, including a severe impairment group, one or more intermediate impairment groups and a cognitively spared group, similarly to what has been observed in adults after illness onset. We also hypothesised a non-homogeneous distribution of SZO and BPO between clusters, with a prominent presence of SZO in the most impaired group yet also a BPO representation.

Methods

Participants

90 BPO and 49 SZO participants were recruited via adult psychiatry services of the Hospital Clinic in Barcelona and the Hospital Gregorio Marañón in Madrid, liaising with affected parents for potential offspring participation. The 81 control participants

were recruited via parents responding to advertisement in primary health care centres and other community services in the same geographical area.

Participants were included if their age was between 6 and 17 years. Family high-risk participants were included if one of their parents was diagnosed with SZ or BP while HC were excluded if they had first or second degree family history of either disorder. Control participants were not included in the present study if they met criteria for any psychiatric diagnosis at the time of the assessment, including the presence of sub threshold psychotic symptoms meeting criteria for an At Risk Mental State for psychosis.

Additional exclusion criteria for the whole sample were intellectual disability, history of significant head injury or current medical or neurological condition.

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was obtained from one of the parents, having the other parent been informed, together with written assent from the participant if aged 12 and above.

Clinical and functioning assessment

Trained psychiatrists conducted the clinical assessment of both parents using the Spanish version of the Structured Clinical Interview for DSM-IV Disorders (SCID-I) (First, Spitzer, Gibbon, & Williams, 1997). Trained child psychiatrists, blind to parental diagnosis, conducted the children's assessment using the Spanish version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997; Ulloa et al., 2006), administered separately to children and parents. Children were also assessed using the

Clinical Global Impression (CGI) (Guy, 1976) and the Scale of Prodromal Symptoms (SOPS) (Miller et al., 2003). Functioning was assessed using the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983) and socioeconomic status with the Hollingshead-Redlich scale (Hollingshead & Redlich, 1958).

Neuropsychological assessment

The neuropsychological assessment was conducted blind of parental diagnosis and has been previously described in detail (de la Serna et al., 2016).

General intelligence was assessed using the Spanish version of the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV) (Wechsler, 2003). We employed the General Ability Index (GAI), which provides a measure of intellectual ability with reduced emphasis on working memory and processing speed.

Variables used for the clustering analysis were agreed by two of the authors (EDS, IV) and are detailed below.

- Attention was assessed with the Conners' Continuous Performance Test II (CPT II) (Conners & Staff, 2000). Omissions, Commissions and Hit Reaction Time were used for the clustering analysis.
- Working memory was measured with the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV) (Wechsler, 2003). Digit Span and Letter-Number Sequencing subtests were used for the clustering.
- Processing speed was measured with the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV) (Wechsler, 2003). Symbol Search and Coding subtests were used for the clustering.

- Verbal memory and learning were tested using the TOMAL-Memory and Learning test (Reynolds, Bigler, & Goikoetxea, 2001), a standardised memory assessment battery that evaluates general and specific memory functions and is validated for use between ages 5 and 19 years. Two subtests were selected for the clustering analysis: Word Selective Reminding (WSR) and Memory for Stories (MFS), both assessing immediate and delayed verbal memory.
- Visual memory, both immediate and delayed, was tested using the Visual Reproduction subtests of the Wechsler Memory Scale – R (WMS-R) (Wechsler, 1997). This test is only validated for individuals above 16 years of age. Data for the clustering analysis were therefore standardised using age matched HC participants. In addition, Rey Complex Figure test (RCF) (Rey, 1958) was used to assess perceptual organisation of complex visual stimuli. Copy and Delayed Recall were used for the clustering, scored based on the reproduction accuracy and relative position of 18 different elements from a complex figure as specified in the manual.
- Executive function was assessed using the Wisconsin Card Sorting Test (WCST), using for the clustering analysis Errors, Perseverations and Perseverative Errors, as well as the interference component of the Stroop Colour and Word test (SCWT) (Golden, 1978).

Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics version 25 and R 3.6.1 software. We also employed Profile-R version 0.3-5 (Desjardins & Bulut, 2020) to perform profile analysis in order to formally assess the shape of the profiles for different cognitive domains across clusters.

Cognitive measures listed above (except from Wechsler visual reproduction subtests) were adjusted for age using published normative data (de la Serna et al., 2016). Different tests employ different metrics, so in order for each measure to contribute equally to the cluster analysis, scores for each cognitive test were standardized to z-scores based upon the HC sample performance with mean of 0 and SD of 1. Missing values were imputed using principal component analysis (3.7% imputed). We then conducted a cluster analysis across the SZ and BP offspring sample using the K-means algorithm. K-means is an unsupervised method that enables the partition of *n* observations into *k* clusters, assigning each observation to the cluster with the nearest centroid. The method proceeds by iterative calculations, with an assignment step that allocates an observation to a certain cluster based on the distance to its centroid being the smallest, and a maximisation step that recalculates the position of the centroids for each assignment configuration, until no observation changes cluster membership. The number of clusters was defined using the elbow method which is considered an indicator of the optimal number of clusters based on the location of a bend in the plot that charts the percentage of variance explained for each cluster solution (Jain, 2010). Finally, cluster membership was saved as grouping variable.

Individual cognitive measures employed for the clustering analysis were subsequently grouped into the corresponding cognitive domains in order to describe the cognitive characteristics of each identified cluster compared to the other clusters and relative to HC. For visualisation purposes and ease of interpretation between-group differences were hence reported in terms of attention, working memory, processing speed, verbal memory, visual memory and executive function.

Finally, SZO and BPO grouped according to the newly identified clusters were compared with HC in terms of demographic, clinical and cognitive variables using χ^2 tests and ANOVA tests followed by Bonferroni corrected post-hoc pairwise comparisons.

Results

SZO, BPO and HC did not significantly differ in terms of age and gender (Tab 1 supplementary material).

Clustering analysis

Using the elbow method, visual inspection of the plot (Fig 1 supplementary material) suggested that SZ and BP family risk participants were best clustered into three groups (Fig 2 supplementary material). The three-cluster solution resulted in the identification of a group performing in the normal range (48 subjects, 34.53%), one characterised by modest impairments of about 0.5 SD below HC mean (64 subjects, 46.04%) and a group characterised by moderate impairments (27 subjects, 19.42%), between 1 and 2 SD below HC mean (Fig 1). Profile analysis revealed that profiles were not parallel ($F=11.53$, $p<0.0001$), they did not have equal levels ($F=127.10$, $p<0.0001$) and were not flat ($F=23.71$, $p<0.0001$). Indeed none of the clusters displayed deficits across all domains, hence the level of impairment reported refers to the domains affected despite others being spared. For simplicity clusters were labelled as 'intact', 'intermediate' and 'impaired' in order to convey severity of the impairment rather than array (Fig 1). The 'intermediate cluster' should therefore be understood as characterised by mild impairments while the 'impaired cluster' by moderate ones, yet neither was global.

Parental diagnosis by cluster

When examining the distribution of participants in each cluster based on parental diagnosis, both diagnoses were represented in each cluster (Fig 2c), yet not evenly (χ^2 (2,139)=8.08, p=0.018): 41.1% of BPO were in the cognitively intact group, 45.6% in the intermediate group and 13.3% in the cognitively impaired group, whereas 22.5% of SZO were in the cognitively intact group, 46.9% in the intermediate group and 30.6% in the cognitively impaired group (Table 1, Fig 2b).

Demographic and clinical characteristics by cluster (Table 1)

There was no significant difference between clusters in terms of recruitment centre (χ^2 (2, 139)=0.74, p=0.69). The three clusters did not significantly differ in terms of age or gender (Table 1), but there was a main effect of group for socioeconomic status ($p<0.001$) with significant post-hoc differences: higher in the intact vs the impaired cluster ($p<0.001$) and in the intermediate vs the impaired (p=0.023). They also differed in terms of ADHD prevalence, with a significant overrepresentation in the impaired cluster, but not in terms of lifetime prevalence of affective disorders (Table 1). Within SZO, ADHD diagnosis was equally represented in the three clusters, while in BPO, ADHD was significantly more frequent in the impaired cluster (Table 1). When evaluating the effect of cluster membership on clinical variables, there was a main effect of group in terms of the SOPS disorganised subscale. Post-hoc testing revealed significant differences, with lower severity in the intact vs the impaired cluster (p=0.047) and also in the intermediate vs the impaired cluster (p=0.029). No effect was observed for SOPS total and any of the other subscales. There was also a main effect of group for both CGAS and CGI, with post-hoc comparisons indicating

significantly higher scores in the intact vs the impaired cluster as well as the intermediate vs the impaired cluster.

Cognition by cluster (Table 2, Fig 1)

When examining cognitive domains, there was a main effect of group in terms of attention ($p=0.004$), with post-hoc testing revealing a significant difference between the intact and impaired cluster ($p=0.002$) and a trend-level difference between HC and the impaired cluster ($p=0.069$). There was also a main effect of group for all the other cognitive domains ($p<0.001$). For Working Memory, Visual Memory and Processing Speed there was no difference between HC and the intact cluster. Both significantly outperformed the intermediate and the impaired cluster and there was also a significant difference between the latter two. The same set of post-hoc differences was identified for Verbal Memory, except for no difference between intermediate and impaired clusters. Finally, for Executive Function, the intact cluster significantly outperformed the other three. There was no significant difference between HC and the impaired cluster, no significant difference between the intermediate and the impaired cluster, while HC significantly outperformed the intermediate one (Table 2).

As expected, the clusters significantly differed in terms of GAI (Table 1). Post-hoc tests indicated that there was no difference between the intact cluster and HC, while there was a significant difference between both the impaired and intermediate cluster and each of the former two. The impaired cluster also significantly underperformed the intermediate one.

Discussion

We examined cognitive function in a sample of children and adolescents at familial risk of SZ and BP, and clustered them using for the first time a data-driven cross-diagnostic approach. Consistent with our first hypothesis, the analysis identified distinct cognitive subgroups: a cognitively intact group, an intermediate impairment group and a moderate impairment group. The clustering pattern we identified overlaps with that previously observed after illness onset, both when the two disorders were examined independently (Burdick et al., 2014; Green, Girshkin, Kremerskothen, Watkeys, & Quide, 2019) and cross-diagnostically (Bora et al., 2016; Karantonis et al., 2020; Lewandowski et al., 2014; Van Rheenen et al., 2017), as well as with the only study examining BPO (Bora et al., 2019).

The intact cluster did not differ from HC on any domain, with the exception of executive function, where the family risk offspring significantly outperformed HC. The intermediate cluster was characterised by mild impairments relative to HC in all domains, except for attention. The moderately impaired cluster showed deficits across the same domains, but effect sizes were significantly larger, especially for visual and verbal memory, while executive function was not impaired. The latter finding differs from previous work in BPO (Bora et al., 2019), where executive function was also found to be impaired in the cluster displaying the most pronounced cognitive abnormalities. The transition from childhood to adolescence is a time of significant development for executive function (Best & Miller, 2010) and participants in the latter study were aged between 15 and 30 years. The age range of our participants might have hampered the possibility to identify differences, as for many of them executive function would still be under development.

In line with our second hypothesis, both SZO and BPO were represented in each of the clusters, yet not evenly. A larger proportion of BPO were cognitively spared, while SZO were more frequently clustered in the moderate impairment group. However, a subsample of BPO also displayed moderate deficits. Our findings hence confirm that cognitive function is highly heterogeneous in the offspring of patients with SZ and BP and that moderate impairments of a similar magnitude can be identified in both groups, as opposed to being specific to SZO. The relabeling of participants from parental diagnostic groups to more homogenous cross-diagnostic clusters can therefore help to interpret the quantitative but not qualitative differences in cognitive performance identified between SZO and BPO when examining group means. These differences appear to reflect the presence of different cognitive profiles in both family risk groups. More severe deficits in SZO are consistent with a larger proportion of participants displaying moderate impairments while milder overall deficits in BPO appear to reflect a smaller proportion of moderately impaired individuals and larger numbers of mildly impaired and cognitively intact.

Members of the most impaired cluster showed poorer functioning and CGI as well as higher scores on clinical measures of disorganization compared to the other two clusters. Follow-up assessment will clarify whether cluster membership is differently associated with transition rate. It will hence help to determine whether the stratification of cognitive heterogeneity within populations at familial risk of SZ and BP can elucidate the relative role of neurodevelopmental mechanisms. It will also contribute to clarify the timeframe of emergence of cognitive impairment in BP, which was thought to develop over the course of the illness (Trotta et al., 2015). It was also considered to be more severe in relation to age of onset, BP subtype and history of psychosis, worsening with number of prior episodes and duration of illness

(Lewandowski, Cohen, & Ongur, 2011). Cognitive ability is highly heritable in the general population (Davies et al., 2011) and several aspects of cognitive dysfunction have been found to be heritable both in SZ (Gur et al., 2007) and BP (Glahn et al., 2010). Our findings don't imply heritability of cluster membership but rather confirm that cognitive impairment can be observed with different levels of severity, from none to moderately severe, in both SZO and BPO and suggest that the causality proposed above might be reversed. As opposed to particular BP clinical phenotypes leading to more severe cognitive impairment, it could be hypothesized that individuals with premorbid cognitive deficits, hence a more significant neurodevelopmental load, might develop a more severe clinical picture. This would be consistent with a meta-analysis reporting no cognitive decline in BP follow-up studies (Bora & Ozerdem, 2017a) and also with findings regarding risk of BP at both ends of scholastic achievement (MacCabe et al., 2010). The latter have been interpreted as suggestive of different BP subgroups, the one with the poorest school performance likely characterised by a neurodevelopmental component to the disorder. A reversed causality is also supported by the results of a recent study (Chan, Shanahan, Ospina, Larsen, & Burdick, 2019) that retrospectively examined premorbid adjustment (PMA) across SZ and BP, and identified three cross-diagnostic clusters. One characterised by normal academic and social PMA, one with normal social but impaired academic PMA and a third cluster characterised by both social and academic impairments. The first cluster was characterised by the least severe clinical picture while the third showed the most pronounced negative symptoms.

SZ and BP offspring present higher rates of psychiatric disorders compared to offspring of control parents. (Rasic, Hajek, Alda, & Uher, 2014). In our study affective disorders were equally distributed across the three clusters, while ADHD

was significantly overrepresented in the impaired one. This difference, in the impaired cluster, was driven by the BPO. In general, prospective longitudinal studies in BP familial high-risk cohorts describe a non-specific set of premorbid features (Duffy, 2012). Among those at risk who later develop BP, the index manic or hypomanic episode is commonly preceded by anxiety and depressive symptoms as well as sleep disturbances. ADHD is not considered a reliable predictor of future illness in BP high-risk samples, despite a significantly higher prevalence in BPO (27%) relative to HC (9.6%) (Faraone, Biederman, & Wozniak, 2012). Higher rates of ADHD have been specifically described in the offspring of BP patients with a clinical picture characterized by early age of onset (Rasic et al., 2014), psychotic symptoms and poor response to treatment with lithium (Duffy, 2012). A younger age of onset in BP patients has also been correlated with polygenic loading for ADHD (Grigoroiu-Serbanescu et al., 2020). It has therefore been suggested that ADHD could be viewed as a neurodevelopmental childhood phenotype preceding the emergence of a specific subtype of BP with earlier age of onset (Faraone et al., 1997) more pronounced neurodevelopmental characteristics and potentially a greater degree of etiological proximity to SZ (Duffy, 2012).

Our study has a number of strengths, the main being the ability to examine cognitive function without the possible confounds of illness or medication. Studies in adult patients include non-remitted participants, making the role of variable symptom severity difficult to interpret, and have treatment as a further potential confound. We also acknowledge a number of limitations, the main being the lack of information about the relationship between cluster membership and future illness, as participants, for the most part, have not yet reached the age of onset for SZ and BP. This was not the focus of the current work but warrants being examined in due course. Further

limitations are the relative imbalance in size between the BPO and the SZO group, the potential effect of examining executive function across an array of developmental stages and the lack of measures of social cognition. It has in fact been suggested that social cognitive deficits might be more pronounced in SZO compared to BPO (Christiani et al., 2019), yet a recent meta-analysis did not suggest disease specificity (Bora, 2016). Also, as expected, the clusters we identified differed significantly in terms of GAI. It has been suggested that, when studying neurodevelopmental disorders, not matching for general intelligence can overestimate cognitive differences, yet matching can mask true deficits associated with IQ (Bora & Pantelis, 2015). Finally, the most impaired cluster was characterised by significantly lower SES compared to the other two. Low SES is known to have an impact on cognitive development (Hackman, Farah, & Meaney, 2010) hence it represents an important confounder to our results.

To conclude, we identified three cognitive clusters across the offspring of individuals with SZ and BP, similarly to what has been observed after illness onset. This suggests that cognitive impairment could potentially be observed premorbidly in both disorders and be characterised by a similar level of severity in SZ and in BP. This hypothesis warrants testing once participants will have reached adulthood and clinical follow-up will clarify the relationship between cognition and outcome. Longitudinal measures will also contribute to elucidate whether etiopathologically different subgroups exist in BP, with one characterised by a more significant neurodevelopmental component. Our findings have therefore important implications for the future understanding of possible stratified neurodevelopmental features in SZ and BP and potentially different clinical trajectories across and within each of the two disorders.

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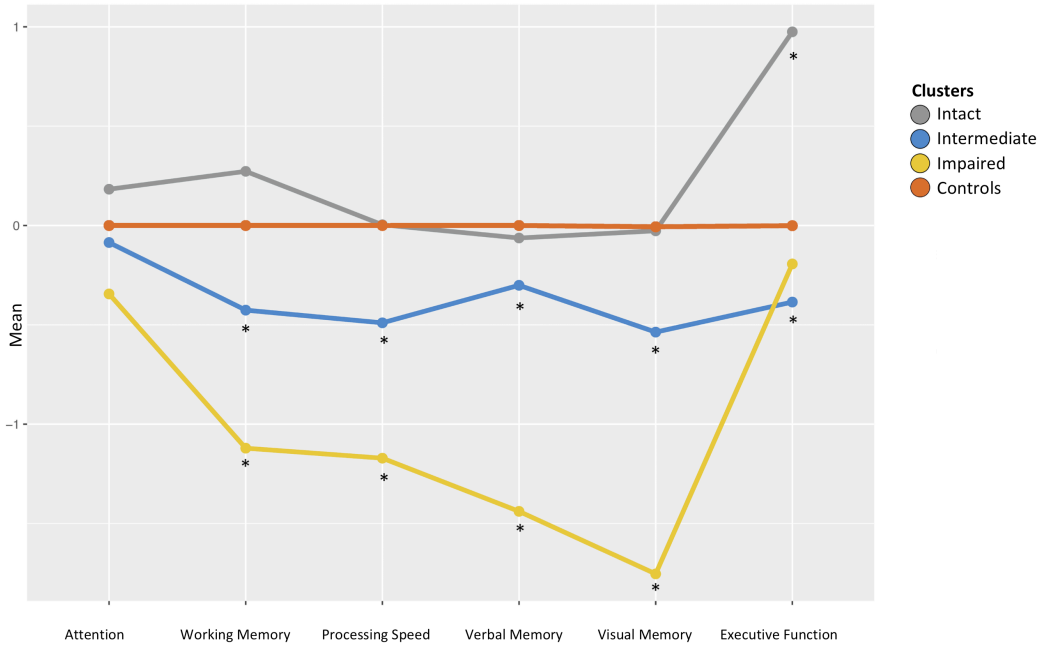
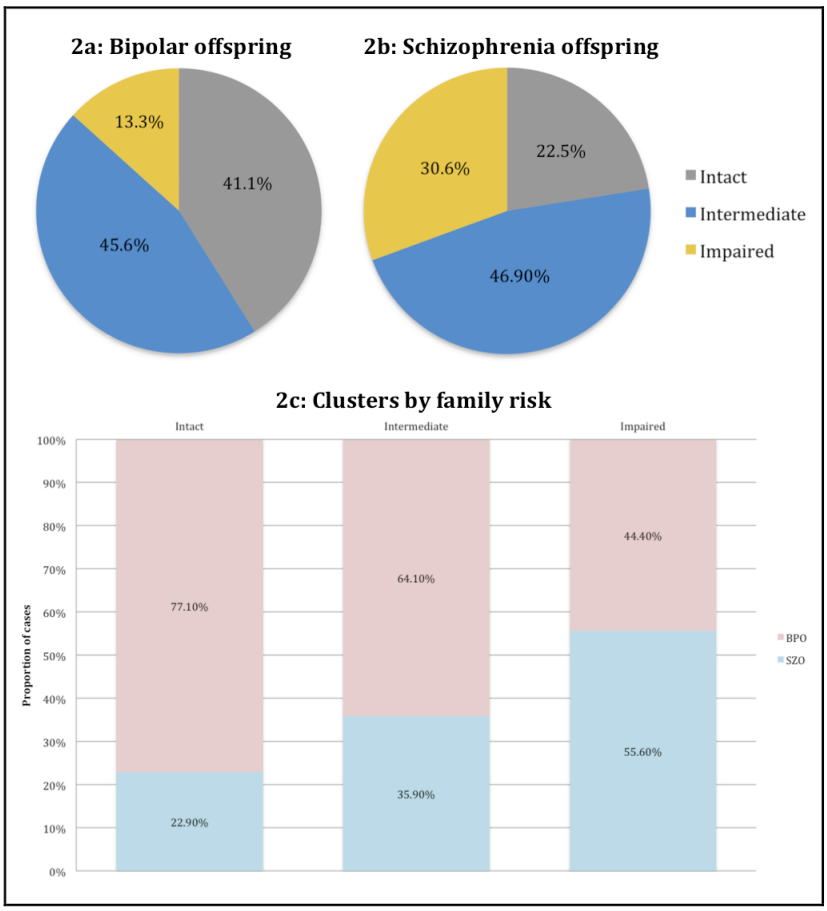
	Intact (1) Mean (S.D.)	Intermediate (2) Mean (S.D.)	Impaired (3) Mean (S.D.)	HC (4) Mean (S.D.)	Significance			
					df	F or χ^2	p value	Group comparison
Age (years)	12.39 (3.17)	11.14 (3.05)	11.81 (3.06)	11.43 (2.79)	3	1.774	0.153	
Gender n (%)								
Males	28 (58.3%)	32 (50.0%)	20 (74.1%)	40 (49.4%)	3	5.835	0.120	
Females	20 (41.7%)	32 (50.0%)	7 (25.9%)	41 (50.6%)				
GAI	109.98 (10.64)	101.00 (12.07)	89.52 (14.25)	109.35 (12.37)	216	21.822	<0.001	4 vs 2 p<0.001 4 vs 3 p<0.001 1 vs 2 p=0.001 1 vs 3 p<0.001 2 vs 3 p<0.001
Offspring n (%)								
SZO	11 (22.5%)	23 (46.9%)	15 (30.6%)		2	8.089	0.018	
BPO	37 (41.1%)	41 (45.6%)	12 (13.3%)					
SOPS positive	1.05 (1.76)	0.90 (1.89)	0.87 (1.63)		2	0.104	0.902	
SOPS negative	1.07 (2.86)	1.06 (1.90)	2.13 (2.67)		2	1.757	0.177	
SOPS disorganized	1.02 (1.68)	0.98 (1.53)	2.04 (1.64)		2	3.897	0.023	
SOPS total	4.28 (7.25)	3.39 (4.92)	6.39 (5.51)		2	1.991	0.141	
CGI	1.62 (0.99)	1.82 (1.12)	2.73 (1.37)		2	8.526	<0.001	1 vs 3 p<0.001 2 vs 3 p=0.001
CGAS	84.21 (10.63)	80.67 (12.09)	72.08 (15.63)		2	8.119	<0.001	1 vs 3 p<0.001 2 vs 3 p=0.003
ADHD n (%)	7 (14.6%)	17 (26.56%)	17 (62.96%)		2	19.940	<0.001	
SZO	4 (36.4%)	11 (47.8%)	15 (66.7%)		2	2.509	0.285	
BPO	3 (8.1%)	6 (14.6%)	7 (58.3%)		2	16.147	<0.001	
Affective disorders n (%)	7 (14.6%)	12 (18.8%)	2 (7.4%)		2	1.921	0.383	

Table 1: Demographic and clinical variables by cluster

	Intact Mean (S.D.)	Intermediate Mean (S.D.)	Impaired Mean (S.D.)	Controls Mean (S.D.)	Significance		Significant post-hoc comparisons
					F	p value	
Attention	0.18 (0.44)	-0.08 (0.50)	-0.34 (0.78)	0.00 (0.65)	$F_{3,216}$=4.596	0.004	4 vs 3 p=0.069 1 vs 3 p=0.002
Working memory	0.27 (0.81)	-0.42 (0.81)	-1.12 (0.89)	0.00 (0.85)	$F_{3,216}$=18.604	<0.001	4 vs 2 p=0.018 4 vs 3 p<0.001 1 vs 2 p<0.001 1 vs 3 p<0.001 2 vs 3 p=0.003
Processing speed	0.01 (0.86)	-0.49 (0.74)	-1.17 (0.95)	0.00 (0.86)	$F_{3,216}$=15.949	<0.001	4 vs 2 p=0.003 4 vs 3 p<0.001 1 vs 2 p=0.015 1 vs 3 p<0.001 2 vs 3 p=0.003
Verbal memory	-0.06 (0.57)	-0.30 (0.52)	-1.44 (0.54)	0.00 (0.71)	$F_{3,216}$=38.733	<0.001	4 vs 2 p=0.024 4 vs 3 p<0.001 1 vs 3 p<0.001 2 vs 3 p<0.001
Visual memory	-0.03 (0.64)	-0.54 (0.68)	-1.75 (0.61)	-0.01 (0.71)	$F_{3,216}$=45.861	<0.001	4 vs 2 p<0.001 4 vs 3 p<0.001 1 vs 2 p=0.002 1 vs 3 p<0.001 2 vs 3 p<0.001
Executive function	0.97 (0.41)	-0.38 (0.65)	-0.19 (0.99)	0.00 (0.75)	$F_{3,216}$=34.791	<0.001	4 vs 1 p<0.001 4 vs 2 p=0.014 1 vs 2 p<0.001 1 vs 3 p<0.001

Table 2: Comparison between the three HR clusters and HC across cognitive domains (z scores)


Clusters
Intact
Intermediate
Impaired
Controls
Mean
1
0
−1
Attention
Working Memory
Processing Speed
Verbal Memory
Visual Memory
Executive Function


2a: Bipolar offspring
13.3%
41.1%
45.6%
2b: Schizophrenia offspring
22.5%
30.6%
46.90%
Intact
Intermediate
Impaired
2c: Clusters by family risk
Intact
Intermediate
Impaired
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Proportion of cases
77.10%
22.90%
64.10%
35.90%
44.40%
55.60%
BPO
SZO