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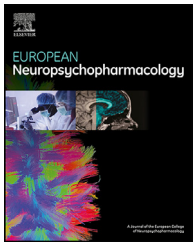

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Clinical and developmental characteristics of cognitive subgroups in a transdiagnostic sample of schizophrenia spectrum disorders and bipolar disorder

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Abstract
Evidence suggests that neurocognitive dysfunction is a transdiagnostic feature of individuals across the continuum between schizophrenia and bipolar disorder. However, there is significant heterogeneity of neuropsychological and social-cognitive abilities in schizophrenia, schizoaffective disorder, and bipolar disorder. The current study aimed to investigate the clinical and developmental characteristics of cognitive subgroups within the schizo-bipolar spectrum. 147 clinically stable patients with schizophrenia, schizoaffective or bipolar disorder were assessed using clinical rating scales for current psychotic and affective symptoms, and a comprehensive neuropsychological battery including measures of social cognition (Hinting and Reading the mind from the Eyes (RMET) task)). Developmental history and premorbid academic functioning

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were also evaluated. The study also included 36 healthy controls. Neurocognitive subgroups were investigated using latent class analysis (LCA). The optimal number of clusters was determined based on the Bayesian information criterion. A logistic regression analysis was conducted to investigate the predictors of membership to the globally impaired subgroup. LCA revealed two neurocognitive clusters including globally impaired ($n = 89$, 60.5%) and near-normal cognitive functioning ($n = 58$, 39.5%) subgroups. The near-normal cognitive functioning subgroup was not significantly different from healthy controls. The globally impaired subgroup had a higher score of developmental abnormalities ($p<0.001$), poorer premorbid academic functioning, mothers who were less educated and more severe disorganized speech ($p = 0.001$) and negative symptoms ($p = 0.004$) compared to the near-normal cognitive functioning group. History of developmental abnormalities and persistent disorganization rather than diagnosis are significant predictors of the subgroup of individuals with global cognitive impairment in the schizophrenia-bipolar disorder continuum.

1. Introduction

Schizophrenia and bipolar disorder (BD) have been traditionally considered to be distinct disorders but the validity of this categorical approach is a controversial issue (Craddock and Owen, 2010). Family and twin studies have shown that schizophrenia, schizoaffective disorder, and BD aggregate in families (Lichtenstein et al., 2009; Schürhoff et al., 2003). There is a considerable overlap of genetic susceptibility factors in schizophrenia and bipolar disorder in molecular genetic studies (Cardno et al., 2002; Cardno and Owen, 2014; Chang et al., 2013). The overlap of clinical features and genetic factors in schizophrenia and BD led to hypotheses of psychosis continuum/schizophrenia-BD continuum between schizophrenia and BD (Crow, 1986; Pearlson, 2015). According to these hypotheses, overlapping genetic susceptibility factors could lead to common symptoms (i.e. psychotic symptoms, subtle cognitive deficits), whereas severe cognitive impairment and developmental abnormality might be more specific to schizophrenia (Murray et al., 2004; Walker et al., 2002).

Previous studies have not supported the notion of specificity of severe cognitive impairment to schizophrenia. Cognitive deficits including social cognitive impairment are common features of schizophrenia, schizoaffective disorder, and bipolar disorder (Bora et al., 2009; Bora et al., 2015; Heinrichs and Zakzanis, 1998; Robinson and Ferrier, 2006; Lee et al., 2013). Cognitive impairment is evident both in schizophrenia and BD not only in chronic patients but also in first-episode patients and individuals with clinical and genetic risk of both disorders (Bora and Özerdem 2017; Bora and Pantelis, 2013, 2015; Fusar-Poli et al., 2012; Lee et al., 2014; Mesholam-Gately et al., 2009). Recent evidence suggests that there might be biological subtypes within the schizophrenia-BD continuum that do not respect traditional categorical boundaries (Clementz et al., 2016). Data-driven studies suggested that both BD and schizophrenia are associated with significant cognitive heterogeneity (Bora et al., 2016a; Burdick et al., 2014; Reser et al., 2015). Cluster analytical studies in both disorders consistently found several cognitive subgroups including a neuropsychologically normal subgroup and a few (1 to 4) subgroups with cognitive impairment (Bora, 2016a; Carruthers et al., 2022; Green et al., 2020).

Most of the studies investigating cognitive heterogeneity have focused on either schizophrenia or BD (Bora, 2016). To date, only a few studies have investigated cognitive heterogeneity in cross-diagnostic samples of the schizophrenia-BD continuum (Lewandowski et al., 2014; Van Rheenen et al. 2017; Lee et al., 2017; Bora et al., 2016b; Vaskinn et al. 2020). Cross-diagnostic data-driven studies investigating the relationship between cognitive heterogeneity and developmental/symptomatic features within the schizophrenia-BD continuum are particularly important to define the distinctive characteristics of the subgroup of patients with severe cognitive impairment. To date, only a limited number of characteristics of the severe cognitive impairment subgroup of patients have been investigated. Available evidence suggests that patients with severe cognitive impairment within the schizophrenia-bipolar spectrum might be less educated, had poorer community functioning, and were older than the other subtypes (Bora et al., 2016b; Lewandowski et al., 2014; Green et al., 2020).

In the current diagnostic systems, the distinction between schizophrenia and BD is heavily dependent on the pattern of psychotic (i.e. persistence beyond episodes) and affective symptoms (predominant or not). In all the available cross-diagnostic studies, the diagnosis had a limited utility in identifying cognitive group membership as all cognitive subgroups included individuals with schizophrenia and bipolar disorder. This might not be surprising as the severity of psychotic and affective symptoms might not be good predictors of cognitive functions in these disorders. Disorganized speech and negative symptoms are known to be associated with more severe cognitive deficits (Dibben et al., 2009) and they might be potentially better predictors of being a member of certain cognitive groups. The current evidence also suggests that the core of cognitive deficits in schizophrenia and BD might be related to neurodevelopmental factors (Bora, 2015; Melle, 2019). Early developmental abnormalities are associated with both disorders (Parelleda et al. 2017). Therefore, one may argue that developmental abnormalities might be potentially important predictors of cognitive group membership in schizophrenia and BD.

The primary aim of this study was to investigate the clinical and developmental predictors of cognitive subgroups based on a data-driven approach in a cross-diagnostic sam-

ple of BD and schizophrenia spectrum disorders. Our main hypothesis was that developmental abnormality and disorganized and negative symptoms, rather than clinical diagnosis, might be distinctive features of patients with severe cognitive impairment within the schizophrenia-BD spectrum.

2. Experimental procedures

The study was conducted at the Department of Neuroscience and Department of Psychiatry, Dokuz Eylul University. The participants included 147 patients (77 males, 52.4%) with schizophrenia-spectrum disorders (schizophrenia, schizoaffective disorder and bipolar disorders) and 36 healthy controls (13 males, 36.1%). The patients were recruited through the Mood Disorders and Psychotic Disorders Outpatient Units of the Department of Psychiatry. Healthy individuals without a personal history of psychiatric disorders and a family history (up to 2nd-degree relatives) of mood and psychotic disorders were recruited as controls through advertisements at the university hospital and on the medical school campus. Exclusion criteria for all participants were: (a) personal history of medical disorders, head injury or neurological disorders that can have e negative impact on neurocognition, vision and hearing; (b) current alcohol/substance abuse.

All participants (including healthy controls) were evaluated using the Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I) (First et al. 1997). Current mood symptoms were assessed using the Hamilton Depression Rating Scale (HAM-D-17) (Hamilton, 1960), and the Young Mania Rating Scale (YMRS) (Young et al., 1978). Clinician-Rated Dimensions of Psychosis Symptom Severity (CRDPSS) which assesses eight symptom dimensions including Hallucinations, Delusions, Disorganized speech, Abnormal psychomotor behavior, Negative Symptoms, Depression, and Mania was also used. This measure consists of items that are scored on a five-point scale ranging from “Not present” to “Present and Severe”. The academic achievement subscale of the Premorbid Adjustment Scale was also used.

A modified version of the general developmental scale (GDS) (Hollis, 2003) was used to record early childhood developmental delays and neurodevelopmental problems (See Supplement). It is a composite score based on motor milestones, language milestones, impaired social development, specific learning disabilities, neurodevelopmental problems, developmental coordination disorder, and enuresis. The total modified GDS score can range from 0 to 14. The relevant information for the scale was provided by family members and the participants.

The study protocol was approved by the Dokuz Eylul Hospital Ethics Committee and all participants provided written informed consent.

2.1. Neuropsychological measures

A comprehensive neuropsychological assessment including verbal memory, executive functions, processing speed, working memory, verbal fluency, and theory of mind (ToM) was administered to all participants. Cognitive assessment was conducted by postgraduate neuroscience students (Ö.A, B.V and A.I) who were blind to the clinical status of the participants.

Neuropsychological tests were administered to all participants in the same order. The Rey Verbal Learning Test (RVLT) was used to assess verbal memory (Learning (1–5), delayed recall, recognition) (Lezak et al., 2012). The Digit symbol substitution test (DSST) and the Trail Making Test-A (TMT-A) were used as measures of processing speed (Wechsler, 1981; Reitan, 1958). Executive functions were measured by Wisconsin Card Sorting Test (WCST), the Stroop Test and the Trail Making Test-B (TMT-B) (Heaton, 1981; Lezak et al., 2012; Reitan, 1958). The outcome variables considered were the number of categories completed and perseverative errors from the WCST, Stroop interference score and total time to complete TMT-B. The Digit Span task and the Auditory Consonant Trigrams Test (ACTT) were used to assess working memory (Lezak et al., 2012; Stuss et al., 1987). The outcome variables considered were the digits forwards and backwards raw scores for the digit span task and the total score for the ACTT (3, 9 and 18-second conditions). The phonetic (letters K, A, S) and semantic (Animals) category tasks indexed verbal fluency (Lezak et al., 2012). ToM measures included in this study were the Reading the Mind in the Eyes Test (RMET) and the Hinting Task (Baron-Cohen et al., 2001; Marjoram et al., 2005). Neuropsychological variables included, in addition to individual cognitive measures, cognitive domain scores (z-scores) for verbal memory, processing speed, executive functions, working memory, verbal fluency and social cognition.

2.2. Data analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 14 and R. Group differences for demographic, clinical and neuropsychological variables were tested with ANOVA and chi-square tests ($\chi 2$) (significance level of $p < 0.05$). For comparing neuropsychological variables between cognitive subgroups ANCOVA analyses correcting age, sex and antipsychotic use were also conducted.

In this study, latent class analysis (LCA) was used for investigating the clustering of neurocognitive data. All cognitive variables were used in the model. LCA was conducted with Mclust package in R (Fraley et al., 2012). Mclust is a software for model-based clustering, classification and density estimation and is based on finite Gaussian mixture modeling fitted via EM algorithm. In Mclust, the optimal model and number of clusters are automatically selected according to the Bayesian information criterion (BIC). In the current study, LCA is used to identify latent classes that group together individuals who were similar in cognitive functioning.

Logistic regression analysis was used to investigate predictors of cognitive group membership. Based on our hypothesis, a priori independent predictors were the GDS score, disorganized speech and negative symptoms scores of CRDPSS, diagnostic category of the patients, familial academic achievement (years of education for mother and father) and existence or absence of perinatal distress. We also planned to include other CRDPSS scores (such as depression or delusions) if we find significant group differences for these variables between cognitive variables.

3. Results

3.1. Cognitive clustering

BIC values for multiple models and shapes were compared. The best solution was provided by model “VEI” (diagonal, varying volume, equal shape) as the lowest BIC value was observed in this model. In this optimal model, a two-cluster solution had the lowest BIC value (log-likelihood=−9783.7, BIC=−19,861.8, ICL=−19,874.0) and provided the best fit as other cluster solutions had larger BIC values in this model (Fig. 1s in the supplement). Patients were optimally clustered into two discrete subgroups based on their neurocognitive profiles.

The first cluster included 58 (39.5%) patients with near-normal cognitive performance. There was no significant

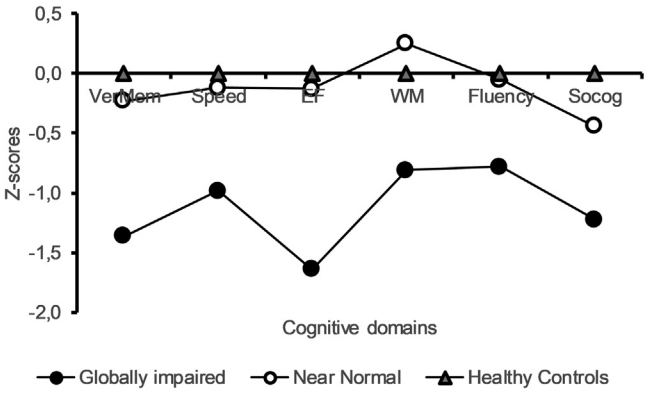

Fig. 1 Cognitive performances (Z-scores) of globally impaired and near-normal subgroups (in reference to healthy controls).

group difference in any cognitive domain or individual neuropsychological measure between the "*Near-Normal*" cluster and healthy controls (Table 3). A second cluster included 89 (60.5%) patients with global cognitive impairment. The patients in the "*Global Impairment*" class performed significantly less well than the *Near-Normal* subgroup and healthy controls in verbal memory, executive functions, processing speed, verbal fluency, working memory, and social cognition (Table 3). The *Global Impairment* subgroup performed poorer than the *Near-Normal* subgroup and healthy controls in each neuropsychological variable under 6 cognitive domains investigated. These findings did not change when corrected for age and sex ($F_{corrected}$ in Table 3). ANCOVA analyses using antipsychotic use as a categorical or dimensional (chlorpromazine equivalent) variable did not significantly change results either ($p<0.01$ for each of 6 domains).

3.2. Clinical and demographic characteristics

The *globally impaired* subgroup had significantly poorer premorbid academic success in childhood than the *near-normal* and *healthy control* groups ($p<0.001$). The duration of education of the "globally impaired" subgroup was also significantly shorter than the near-normal and "healthy control" groups. A significantly higher percentage of individuals in the globally impaired group were unemployed or not studying (Table 2). Compared to the *near-normal* subgroup, the *globally impaired* subgroup was significantly older ($p<0.001$) and had mothers who were less educated ($p = 0.02$). The *globally impaired* subgroup was also significantly older than the healthy control group (Table 1). While cognitive subgroups of patients tended to have a higher percentage of males, the difference between groups was not significant (Table 2).

While a relatively higher percentage of patients with bipolar disorder than schizophrenia were members of the *near-normal* subgroup (and opposite for the *generally impaired* subgroup), the between-group difference was not significant (Table 2, Chi square=5.07, $p = 0.08$). There was no significant difference for the history of psychosis and predominant polarity for BD patients within each cluster (Table 2). There was no significant difference between cognitive subgroups of patients for smoking and the history of alcohol and drug abuse (Table 2). A higher percentage of patients in the *globally impaired subgroup* (78.7%) than in the *near-normal* subgroup (58.6%) were using antipsychotics (Table 2). The chlorpromazine equivalent value was significantly higher in the *globally impaired* subgroup compared to the *near-normal* subgroup ($p = 0.03$) (Table 1). The age of onset did not differ significantly between cognitive groups but the *globally impaired* subgroup had a sig-

Table 1 Continous demographic and clinical characteristic of groups.

	Globally impaired	Near-Normal	Healthy controls	F	P	Post-hoc
Age	44.1 (11.3)	37.2 (8.9)	34.4 (10.3)	14.3	<0.001	NN=HC<GI
Education	10.7 (3.3)	13.1 (2.7)	12.4 (4.3)	10.3	<0.001	GI<NN=HC
Education (mother)	5.3 (3.6)	7.5 (5.1)	6.8 (4.6)	4.7	0.01	GI<NN
Education (father)	8.2 (4.0)	9.5 (4.7)	8.7 (5.0)	1.5	0.22	
BMI	29.7 (6.1)	28.3 (5.9)	24.2 (4.2)	10.7	<0.001	HC<NN=GI
PAS academic	0.41 (0.21)	0.25 (0.21)	0.22 (0.23)	15.7	<0.001	NN=HC<GI
GDS	2.03 (1.53)	1.10 (1.51)		13.0	<0.001	
Age of onset	25.5 (9.1)	24.2 (7.2)		0.8	0.38	
Illness duration	18.8 (10.1)	13.2 (7.0)		13.2	<0.001	
Admissions	2.8 (3.5)	1.8 (1.6)		3.9	0.05	
CPZ equivalents	311 (265)	217 (261)		4.6	0.03	
CRDPSS						
-Hallucinations	0.31 (0.67)	0.33 (0.71)		0.01	0.91	
-Delusions	0.72 (1.03)	0.53 (0.88)		1.23	0.27	
-Disorganized speech	0.49 (0.80)	0.12 (0.38)		11.0	0.001	
-Psychomotor	0.06 (0.27)	0.0		2.4	0.12	
-Negative symptoms	1.02 (1.20)	0.48 (0.94)		8.4	0.004	
-Depression	0.29 (0.55)	0.21 (0.45)		0.98	0.33	
-Mania	0.15 (0.41)	0.12 (0.42)		0.13	0.72	
YMRS	0.5 (1.1)	0.6 (1.5)		0.05	0.82	
Ham-D	1.8 (2.6)	1.4 (2.1)		0.94	0.33	

Table 2 Categorical demographic and clinical characteristic of groups.

	Globally impaired	Near-Normal	Healthy controls	$\chi 2$	P	Post-hoc
Sex (m/f)	42/47	35/23	13/23	5.5	0.06	
Unemployed/Not studying	51/30	24/28	4/31	26.1	<0.001	HC<NN<GI
Diagnosis (Sch/SA/BD)	29/12/48[a]	11/5/42[b]		5.07	0.08	
Predominant polarity (BD) (Mania/Depression/no PP)	10/11/27	12/6/24		1.44	0.49	
History of psychosis for BD						
Yes/No	29/19	27/15		0.15	0.71	
Perinatal (Yes/no)	20/66	11/47		0.38	0.54	
Smoking	42/47	29/29		0.07	0.79	
Past alcohol use (yes/no)	11/77	8/50		0.05	0.82	
Past drug (yes/no)	5/83	3/55		0.69	0.71	
Past cannabis (yes/no)	5/83	3/55		0.69	0.71	
Antipsychotics	70/19	34/24		8.8	0.009	
Lithium	30/59	22/36		0.18	0.67	
Valproate	29/60	25/33		1.99	0.16	

a = 44 BD type I/4 BD Type II, *b* = 41 BD Type I, 1 BD Type II,.

Table 3 Neurocognitive features of cognitive clusters and healthy controls.

	Globally impaired	Near-Normal	Healthy controls	F	$F_{corrected}$	P	Post-hoc
Verbal Memory	−1.36 (1.03)	−0.23 (1.14)	0 (1.0)	30.4	18.6	<0.001	GI<NN=HC
-RAVLT Learning	38.7 (9.6)	49.9 (10.1)	52.1 (0.95)	35.4		<0.001	GI<NN=HC
-RAVLT Delayed Recall	7.4 (2.6)	10.0 (3.4)	10.7 (2.5)	23.5		<0.001	GI<NN=HC
-RAVLT Recognition	11.0 (3.1)	12.8 (2.3)	13.1 (2.3)	11.8		<0.001	GI<NN=HC
Processing Speed	−0.98 (0.76)	−0.12 (0.80)	0 (1.0)	27.4	21.7	<0.001	GI<NN=HC
-TMT A	50.8 (18.2)	34.1 (15.5)	36.6 (20.2)	17.2		<0.001	GI>NN=HC
-Digit Symbol	36.1 (11.8)	49.9 (15.0)	55.5 (17.2)	31.2		<0.001	GI<NN=HC
Executive Function	−1.64 (1.29)	−0.13 (1.48)	0 (1.0)	32.1	19.4	<0.001	GI<NN=HC
-TMT B	135.9 (66.7)	79.1 (46.7)	83.7 (37.9)	21.5		<0.001	GI>NN=HC
-Stroop Interference	53.6 (25.1)	41.0 (21.7)	41.4 (13.6)	6.9		0.001	GI>NN=HC
-WCST Category	2.7 (2.2)	4.8 (2.1)	5.2 (1.6)	23.5		<0.001	GI<NN=HC
-WCST Per	32.7 (13.8)	18.7 (20.9)	12.0 (10.3)	20.5		<0.001	GI<NN=HC
Working Memory	−0.81 (0.68)	0.25 (0.98)	0 (1.0)	30.4	18.4	<0.001	GI<NN=HC
-Digit Span Forwards	5.8 (1.9)	8.0 (2.7)	6.7 (2.3)	15.4		<0.001	GI<NN=HC
-Digit Span Backwards	5.0 (1.6)	7.2 (2.9)	6.3 (2.8)	15.6		<0.001	GI<NN=HC
-ACT Total	25.1 (7.4)	33.7 (9.6)	33.5 (8.2)	23.9		<0.001	GI<NN=HC
Verbal Fluency	−0.78 (0.74)	−0.05 (0.94)	0 (1.0)	17.1	8.9	<0.001	GI<NN=HC
-Letter Fluency	28.3 (11.4)	36.9 (13.5)	35.1 (13.1)	9.6		<0.001	GI<NN=HC
-Semantic fluency	16.5 (5.0)	20.3 (5.1)	21.5 (5.4)	16.4		<0.001	GI<NN=HC
Social cognition	−1.22 (1.09)	−0.44 (1.38)	0 (1.0)	16.1	8.4	<0.001	GI<NN=HC
-RMET	19.1 (4.4)	21.1 (4.6)	23.5 (4.5)	12.5		<0.001	GI<NN=HC
-Hinting	15.6 (3.2)	17.9 (5.7)	18.5 (2.5)	8.5		<0.001	GI<NN=HC

$F_{corrected}$= ANCOVA analysis corrected for sex and age.

nificantly longer duration of illness and more hospital admissions (Table 1).

The *globally impaired* subgroup had significantly more severe negative symptoms ($F = 8.4$, $p = 0.004$) and disorganized speech ($F = 11.0$, $p = 0.001$) than the *near-normal* subgroup. There were no significant differences in other CRDPSS domains, YMRS and HAM-D scores between *globally impaired* and *near-normal* functioning patient groups.

3.3. Neurodevelopmental characteristics

The *globally impaired* subgroup had significantly higher ratings on the general developmental scale than the *near-normal* subgroup (Table 1, $F = 13.0$, $p<0.001$). In the specific items of the GDS, the *globally impaired* subgroup had a higher rate of specific learning disorders ($p = 0.008$), neurodevelopmental disorders ($p = 0.02$) and impaired social development ($p = 0.02$) than the *near-normal* subgroup. The

globally impaired subgroup had also a trend level increase in the history of enuresis ($p = 0.08$). There was no significant difference between cognitive subgroups for language and motor milestones, and developmental coordination disorder.

3.4. Logistic regression analysis

Logistic regression analysis was conducted with only a priori independent variables as there was no significant group difference for positive symptoms, mania and depression scores between the two cognitive subgroups. Logistic regression analysis suggested that neurodevelopmental abnormalities (Wald=3.95, $p = 0.04$) and disorganized speech (Wald=6.51, $p = 0.01$), and the duration of the mother's education (Wald=3.80, $p = 0.05$) were significant predictors of being included in the *globally impaired* subgroup (Chi square=32.7, $p<0.001$, Log likelihood=153.9, Nagelkerke R^2=0.284). The model correctly identified 84.5% of the members of the *globally impaired* subgroup. In contrast, the logistic regression model identified only 54.5% of the *near-normal* subgroup correctly.

Adding chlorpromazine equivalent as an independent predictor to the logistic regression equation did not significantly change the model (Chi square=33.2, $p<0.001$, Log likelihood=153.4, Nagelkerke R2=0.287). The chlorpromazine equivalent was not a significant predictor in this model (Wald=0.49, $p = 0.49$).

4. Discussion

The current study investigated the clinical and developmental characteristics of cognitive subgroups within the schizobipolar spectrum. LCA supported a two-class solution including a subgroup with global cognitive impairment and another subgroup with near-normal cognitive functioning. The globally impaired subgroup had more significant disorganized speech, negative symptoms, and a higher number of neurodevelopmental abnormalities.

The current study found two cognitive subgroups including a group with global cognitive impairment and another group with near-normal cognitive functioning. This finding was in line with the results of some of the previous data-driven studies on schizophrenia spectrum disorders (Carruthers et al., 2022; Cobia et al. 2011; Green et al., 2013). While other data-driven studies have reported different numbers of cognitive subgroups, a globally impaired and a normal or near-normal cognitive subgroups are common findings in all available studies (Bora, 2016; Carruthers et al., 2022; Green et al., 2020). Moreover, like the previous transdiagnostic studies, cognitive subgroups were not diagnosis-specific and each group included individuals with schizophrenia, BD and schizoaffective disorder. The *globally impaired* subgroup was associated with a poorer functional outcome as they had a higher unemployment rate, poorer premorbid academic success, and shorter duration of education.

In line with our hypothesis, a history of developmental abnormality was a significant predictor of being a member of the *globally impaired* subgroup. This finding is one of the original contributions of the current study. No previous studies have investigated developmental predictors of the data-driven cognitive subgroup of schizophrenia and BD. In one of the rare examples investigating the relationship between developmental markers and cognition in schizophrenia, a history of childhood enuresis was associated with more severe executive dysfunction and more pronounced brain imaging abnormalities (Hyde et al. 2008).

Consistent with our hypothesis, disorganized speech and negative symptoms were significantly increased in the *globally impaired* subgroup compared to the *near-normal* subgroup. Furthermore, disorganized speech was also a significant predictor of being a member of the *globally impaired* subgroup. The disorganization domain in psychotic disorders has been associated with more severe clinical course, chronicity and functional impairment (Andreasen and Grove, 1986; Norman et al., 1999; Roche et al., 2015; Wilcox et al., 2012; Yalincetin et al., 2017). Disorganized speech is also associated with more severe neurocognitive and social cognitive impairment in schizophrenia (Bora et al., 2019; Dibben et al., 2009; Ventura et al., 2013). Negative symptoms are also associated with more pronounced functional impairment and neurocognitive and social-cognitive deficits in schizophrenia (Bayrakçı et al., 2022; Bora et al., 2017; Dibben et al., 2009; Kirkpatrick et al., 2001; Ventura et al. 2014). There might be a close relationship between developmental abnormality and negative symptoms in schizophrenia. For example, deficit schizophrenia was reported to be associated with both developmental abnormalities and more severe cognitive deficits compared to non-deficit schizophrenia (Bora et al., 2017; Kirckpatrick et al. 2019; Takahashi et al., 2017).

It is important to consider the potential neurobiological mechanisms that may contribute to the differences in neurocognition between the cognitive subgroups, The association between cognitively impaired subgroup, developmental abnormalities and negative/disorganization symptoms might give some important clues about molecular level and macro-scale functional and structural level differences between cognitive subgroups.

Genetic factors are likely to differ between cognitively impaired and near-normal groups as many genetic risk loci for schizophrenia and BD have a role in brain development. In a combined large genome-wide association study data on schizophrenia, BD, and general intelligence, Smeland et al. (2020) reported that many schizophrenia and bipolar disorder risk alleles were associated with poorer cognition, albeit less strongly in BD. Evidence also suggests that there are both concordant and discordant associations between BD risk alleles and intelligence (Shang et al., 2022; Smeland et al., 2020). One might argue that concordant risk loci for schizophrenia/BD and intelligence might be genetic markers of the cognitively impaired subgroup of these disorders. Regarding symptoms dimensions, consistent with our findings, both disorganization symptoms and lower intelligence might be associated with schizophrenia polygenic risk scores (Legge et al., 2021). Another micro-level marker of the cognitively impaired subgroup might be decreased telomere length (Gurvich et al., 2022). Non-genetic developmental factors can also influence cognitive development

in schizophrenia and BD. For example, maternal viral infections are likely candidates for negative developmental impact on cognition in psychotic disorders as herpes viruses, cytomegaloviruses and toxoplasma gondii infections seem to be associated with both increased risk for psychotic disorders and more pronounced cognitive impairment in these disorders (Calkova et al., 2022; Cheslack-Postava and Brown, 2021; Hamdani et al., 2017). Obstetric complications (OC) is another nongenetic factor that might be overrepresented in the cognitively impaired group as OC is significantly associated with more severe cognitive deficits in schizophrenia (Amoretti et al., 2022). However, no study has investigated the potential association between history of maternal infections or OC and membership to the data-driven cognitively impaired subgroup in schizophrenia and BD.

At a macro-level, there is limited evidence of structural brain imaging markers of the cognitively impaired subgroup. For example, Geisler et al. (2015) reported that the cognitive subgroup characterized by general cognitive dysfunction had significantly more pronounced generalized cortical thinning than other cognitive subgroups. However, other studies have not found clear cortical thickness and volüme differences between cognitive subgroups (Karantonis et al., 2021). There is a need for further studies investigating neuroanatomical features of cognitive subgroups with other MRI methods such as diffusion tensor imaging.

A shorter duration of education in mothers was also a significant predictor of being a member of the *globally impaired* subgroup. In the Turkish context, the duration of education of mothers in our sample can be considered to be an indicator of better familial cognitive reserve. Also, more educated mothers can have a positive influence on the cognitive development of their offspring by providing a more stimulating environment. Educated mothers' better decision-making abilities can also help them to expose their children to better lifestyle factors (i.e. healthy diet). Another consideration is the potential effects of antipsychotics on cognitive functions. The individuals in the *globally impaired* subgroup were using a significantly higher amount of antipsychotics. However antipsychotic dose was not a significant predictor of cognitive group membership in the logistic regression model. Of further relevance, a significant difference in the illness duration was evident between the cognitive subgroups. The individuals in the *globally impaired* subgroup had a longer duration of illness than those in the *near-normal* subgroup. This finding might suggest that individuals who have developmental abnormalities and lower premorbid cognitive abilities might be more susceptible to the effects of aging. The interaction between low cognitive reserve and normal aging might lead to cognitive decline in a subgroup of individuals with psychotic disorders. Current findings might be potentially important for interventions that can make a positive impact on the trajectory of cognitive deficits in individuals who are at-risk for psychotic and bipolar disorders. Public health and social measures (inclusive access to education and access to a healthy diet and good quality medical care during the prenatal and postnatal period) and interventions such as case management of mothers at risk, specialist education and support for children with developmental problems can have some protective effects on cognitive functions in psychotic and bipolar spectrum disorders.

The current study has several limitations. The cross-sectional design of the study limits our ability to determine the stability of the resulting cognitive profiles over the illness course. Second, since our patients were recruited from two tertiary university outpatient programs, many of the participants may represent a more severely affected group of patients with BD and schizophrenia spectrum disorders. Also, we had no information about lifestyle factors that can have an impact on cognition such as dietary patterns, physical activity, and sedentary behavior (Van Rheenen and O'Neil, 2022). Therefore, one needs to be careful in generalizing our results.

Studies investigating neurobiological and genetic underpinnings of the relationship between cognitive impairment, neurodevelopmental abnormalities and persistent disorganized speech might be important to develop a more valid classification of disorders presenting with psychotic and mood symptoms. Further studies with larger samples that include individuals with first-episode patients and use longitudinal methodological designs are needed to investigate the validity and trajectory of cognitive subgroups in schizophrenia and bipolar spectrum disorders.

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Contributors

E.B designed the study and wrote the protocol. E.B, B.B.A, A.Ö, K.A contributed to planning stage of the study. E.B and D.C collected clinical data. B.V, Ö.A and A.I collected neuropsychological data. E.B conducted statistical analyses and wrote the first draft. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

All other authors declare that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2022.12.005.

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