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The relationship of symptom dimensions with premorbid adjustment and cognitive characteristics at first episode psychosis: Findings from the EU-GEI study

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ABSTRACT

Premorbid functioning and cognitive measures may reflect gradients of developmental impairment across diagnostic categories in psychosis. In this study, we sought to examine the associations of current cognition and premorbid adjustment with symptom dimensions in a large first episode psychosis (FEP) sample.

We used data from the international EU-GEI study. Bifactor modelling of the Operational Criteria in Studies of Psychotic Illness (OPCRIT) ratings provided general and specific symptom dimension scores. Premorbid Adjustment Scale estimated premorbid social (PSF) and academic adjustment (PAF), and WAIS-brief version measured IQ. A MANCOVA model examined the relationship between symptom dimensions and PSF, PAF, and IQ, having age, sex, country, self-ascribed ethnicity and frequency of cannabis use as confounders.

In 785 patients, better PSF was associated with fewer negative ($B = -0.12$, 95% C.I. -0.18 , -0.06 , $p < 0.001$) and depressive ($B = -0.09$, 95% C.I. -0.15 , -0.03 , $p = 0.032$), and more manic ($B = 0.07$, 95% C.I. 0.01 , 0.14 , $p = 0.023$) symptoms. Patients with a lower IQ presented with slightly more negative and positive, and fewer manic, symptoms. Secondary analysis on IQ subdomains revealed associations between better perceptual reasoning and fewer negative ($B = -0.09$, 95% C.I. -0.17 , -0.01 , $p = 0.023$) and more manic ($B = 0.10$, 95% C.I. 0.02 , 0.18 , $p = 0.014$) symptoms. Fewer positive symptoms were associated with better processing speed ($B = -0.12$, 95% C.I. -0.02 , -0.004 , $p = 0.003$) and working memory ($B = -0.10$, 95% C.I. -0.18 , -0.01 , $p = 0.024$).

These findings suggest that the negative and manic symptom dimensions may serve as clinical proxies of different neurodevelopmental predisposition in psychosis.

1. Introduction

Premorbid and cognitive impairment at the first episode of psychosis (FEP) is associated with a worse psychosis outcome (Kravariti et al., 2019; Rabinowitz et al., 2006, 2005; Díaz-Caneja et al., 2015). However, such impairment is not diagnosis-specific (Arango et al., 2014; Cole et al., 2012; Horton et al., 2015; Larsen et al., 2004; Parellada et al., 2017; Sheffield et al., 2018). Although cognitive impairment in bipolar disorder seems to be generally more severe than in psychotic depression and less severe than in schizophrenia, cognitive function may also vary considerably among patients with the same diagnosis (Sheffield et al., 2018; Trotta et al., 2015; Zanelli et al., 2010).

The transdiagnostic and interindividual variability of premorbid and cognitive factors contributes to the well-known impossibility in setting neat boundaries between the categories of schizophrenia, schizoaffective, and bipolar and major depressive disorders with psychotic features (Laursen et al., 2009; Uptegrove et al., 2017).

Given that premorbid functioning and cognitive measures may reflect differential gradients of developmental impairment in psychosis (Demjaha et al., 2012a; Murray et al., 2004; Owen and O'Donovan, 2017), a model based on continuous symptom dimensions (Quattrone et al., 2019; Van Os et al., 1999) would be methodologically appropriate for examining how these features impact psychosis expression (Guerra et al., 2002; Kravariti et al., 2012; Linscott and van Os, 2010).

Previous studies using symptom dimensions have mostly focused on non-affective psychotic disorders. They showed an association between worse premorbid and cognitive factors with more negative and disorganised, but not positive and depressive symptoms (reviewed by de Gracia Domínguez et al., 2009; Ventura et al., 2010). Interestingly, one study including both non-affective and affective diagnosis at FEP confirmed that negative symptoms were associated with lower IQ and processing speed, while mania showed an inverted-U-shape relationship so that patients with intermediate levels of mania had better cognitive performance than those with low or high levels (Kravariti et al., 2012). Premorbid adjustment in schizophrenia has also been found to be worse in patients with more disorganised (Cohen et al., 2010) and negative symptoms (Bucci et al., 2018b), even when considering FEP samples

alone (Chang et al., 2016; Grau et al., 2016; Monte et al., 2008; Stouten et al., 2017); whereas there is mixed evidence on the association between poor premorbid adjustment and positive symptoms (Brill et al., 2009; Bucci et al., 2018b; Chang et al., 2016; Grau et al., 2016; Guerra et al., 2002; MacBeth and Gumley, 2008; Payá et al., 2013; Stouten et al., 2017).

Nevertheless, the paucity of data on premorbid and cognitive features by symptom dimensions in the whole psychosis spectrum (i.e. including both non-affective and affective psychotic disorders) is also caused by the absence of a systematic examination of manic symptoms in the literature (de Gracia Domínguez et al., 2009). Moreover, few studies have been based on large samples of patients at their first episode of psychosis (FEP), which minimise the confounding effect of the course of the disease on cognitive functioning and symptom presentation. In summary, to date, there are no studies that have used the same standardised methodology across multiple countries to evaluate psychopathology at FEP and its relationship with premorbid and cognitive domains.

In the present study, we used a large epidemiological multinational sample to investigate the relationship of both premorbid adjustment and current IQ on the one hand with a bifactor model of psychopathology at FEP on the other. Such a bifactor model comprises 1) a general psychosis factor, which accounts for the variance of all symptoms in the psychosis spectrum; and 2) specific symptom dimensions, that account for the variance due to specific subgroups of symptoms (i.e. positive, negative, disorganisation, manic, and depressive symptoms), independently from the general factor (Reininghaus et al., 2016; Reise et al., 2007). That is, while the general psychosis factor is a measure of the shared symptom presentation in this FEP sample, the specific symptom dimensions instead reflect its heterogeneity.

We expected that premorbid and cognitive measures would account for some heterogeneity in symptom presentation at FEP. Therefore, these measures would explain more variation in specific symptom dimensions than in the general psychosis factor.

More specifically, since the negative symptom dimension can be regarded as a clinical proxy of more neurodevelopmental impairment, we expected that worse premorbid adjustment and cognitive

functioning would be associated with more severe negative symptoms. Moreover, we examined if, as opposed to negative symptoms, the manic symptom dimension would indicate less neurodevelopmental impairment, and therefore associated with a better premorbid adjustment and current cognitive functioning.

2. Methods

2.1. Study design

Subjects were recruited between 01/05/2010 and 01/04/2015 across centres in five different European countries (UK, Italy, Spain, Netherlands, France) and Brazil, as part of *The European Network of National Schizophrenia Networks Studying Gene-Environment Interactions* (EU-GEI) study (<http://www.eu-gei.eu/>) (CORDIS, 2019; European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI) et al., 2014; Gayer-Anderson et al., 2020; Jongsma et al., 2018; van Os et al., 2008) with the overall aim to examine incidence rates and risk factors of psychotic disorders.

2.2. Subjects

Centrally trained researchers screened all potential FEP patients, presenting with a clinical diagnosis for an untreated FEP, even if long-standing, at the mental health services and residents in each catchment area. Since this was a sample of consenting patients derived from an incidence study, inclusion criteria were age 18–64 years and having received operationalised diagnosis of a psychotic disorder (ICD-10: F20–F33) from their clinicians, and confirmed by the researchers, through the Operational Criteria in Studies of Psychotic Illness (OPCRIT) system. Inter-rater reliability was regularly assessed throughout the study. Exclusion criteria were psychotic symptoms precipitated by acute intoxication (ICD10: F1X.5), psychosis due to another medical condition (ICD10: F09) (World Health Organization, 1992), and a previous anti-psychotic medication/prescription and/or previous contact with mental health services for psychosis. All local ethical committees approved the study (Gayer-Anderson et al., 2020; Jongsma et al., 2018).

2.3. Measures

We collected sociodemographic data using the Medical Research Council (MRC) sociodemographic schedule (Mallett et al., 2002). Psychopathology was rated using the OPCRIT system, a 90-item semi-structured interview, of which 59 items concern psychopathology (McGuffin et al., 1991; Williams et al., 1996). The estimation of general and specific symptom dimensions' scores was described in full in our previous study (Quattrone et al., 2019) and summarised in the supplementary material. Briefly, the general psychosis factor score measured the covariance due to all psychopathology items, with stronger factor loadings from manic and delusional items. In parallel, the specific symptom dimension scores measured the remainder of variance due to subgroups of positive, negative, disorganisation, manic and depressive items.

IQ was assessed by an abbreviation of the Wechsler Adult Intelligence Scale–III (WAIS-III, ref), including four subtests: Digit Symbol Substitution (Processing Speed), Arithmetic (Working Memory), Block Design (Perceptual Reasoning) and Information (Verbal Comprehension) (Velthorst et al., 2013).

Nine dimensions from the Premorbid Adjustment Scale (PAS) (Canon-Spoor et al., 1982; Rabinowitz et al., 2007) assessed premorbid social (PSF) and academic (PAF) adjustment in two distinct developmental age-periods: childhood to age 11 and early adolescence (i.e. 12 to age 16) (Rabinowitz et al., 2002; van Mastrigt and Addington, 2002). PSF included social withdrawal (<11 and 12–16 years), peer relationships (<11 and 12–16 years), and ability to form socio-sexual relationships (designed from 12 to age 16 only). PAF included scholastic

performance (<11 and 12–16 years), and adaptation to school (<11 and 12–16 years) (Ferraro et al., 2019). IQ calculation and the PAS reduction of dimensions (Ferraro et al., 2019) included in these analyses were described in our previous studies, also summarised in the supplementary material.

Date of onset and weeks of untreated psychosis (DUP) were recorded by the Nottingham Onset Scale (Singh et al., 2005). Thus, for retrospective interviews, we ensured that they referred to the pre-onset period (Gayer-Anderson et al., 2020). A medication list was recorded, including antipsychotic (AP) treatment, codified as AP free/ 1 AP /more than 1 AP. The Cannabis Experience Questionnaire (CEQ_{EU-GEI}) evaluated the frequency of cannabis use (Di Forti et al., 2019).

The core assessment (Gayer-Anderson et al., 2020) was administered as soon as the patient was compliant; psychopathology was rated by clinicians referring to any symptoms experienced within the first month of FEP; the WAIS and other retrospective measures (such as PAS) were proposed when the patient mental state was stable, as confirmed by his/her clinicians.

2.4. Statistical analysis

The analysis was performed following two steps in SPSS 25 (IBM Corporation, 2017).

First, we used multivariable analysis of the covariance (MANCOVA) to test the difference in symptom dimensions (the output), based on concomitant discrete and continuous independent variables (age, sex, self-reported ethnicity [white, black, or other ethnicities], study country, PSF, PAF, and IQ scores), so that the relationships found between one dimension and the predictors accounted (a) for those between the others, (b) and the intra-individual correlation of the dimensions in their severity. Given our previous reports in the EU-GEI study of an association between frequency of lifetime cannabis use with more positive and fewer negative symptoms (Quattrone et al., 2020), as well as better PSF and IQ (Ferraro et al., 2019, 2013), we added this variable as an additional ordinal predictor (i.e. never use = 0; occasional/less than daily use = 1; daily use = 2) (Ferraro et al., 2019). Box's M test examined the covariance matrix, and effect size estimates were evaluated by Pillai's trace and partial eta squared.

Second, we aimed to investigate if any specific cognitive function had a stronger relationship with the outcome than others. Thus, exploratory post hoc analyses were run by follow-up ANCOVAs with IQ subtests, PSF, PAF as the independent predictors, and age, sex, self-reported ethnicity, and study country as confounders, and those symptom dimensions where IQ had an effect as the dependent variables (inserted once at a time). Moreover, we were interested to test frequency of cannabis use role in those specific symptom dimensions where it had an effect, and its interactions with premorbid adjustment and current IQ scores if appropriate (i.e., if both terms were predictive per se). All comparisons in MANCOVA and ANCOVAs were Bonferroni-adjusted and further corrected using the Benjamini-Hochberg (B–H) procedure, pre-determining a 5% chance of a false discovery rate.

Following-up the Kravariti et al. (2012) study, we used a post hoc curve estimation regression to explore whether the association between manic symptoms and cognitive performance followed a U-shape (quadratic) better than a linear relationship, based on Akaike and Bayesian Information Criteria (AIC and BIC).

Finally, we wanted to repeat the MANCOVA by including DUP and AP treatment as covariates, to avoid any influence of long-lasting symptomatology and pharmacotherapy on the relationship between the variables of interest.

3. Results

3.1. Descriptive characteristics

785 out of 1130 FEP patients from the original sample (Di Forti et al.,

