The dimensional structure of psychopathology in 22q11.2 Deletion Syndrome.

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Abstract

Background: 22q11.2 Deletion Syndrome (22q11.2DS) is one of the strongest known genetic risk factors for developing schizophrenia. Individuals with 22q11.2DS have high rates of neurodevelopmental disorders in childhood, while in adulthood ~25% develop schizophrenia. Similar to the general population, high rates of comorbidity are common in 22q11.2DS. Employing a dimensional approach where psychopathology is examined at the symptom-level as complementary to diagnostic categories in a population at such high genetic risk for schizophrenia can help gain a better understanding of how psychopathology is structured as well as its genetic underpinnings. This is the first study to examine the dimensional structure of a wide spectrum of psychopathology in the context of a homogeneous genetic etiology like 22q11.2DS. **Methods:** We evaluated 331 individuals with 22q11.2DS, mean age (SD)= 16.9(8.7); 51% males, who underwent prospective comprehensive phenotyping. We sought to replicate previous findings by examining a bi-factor model that derives a general factor of psychopathology in addition to more specific dimensions of psychopathology (i.e., internalizing, externalizing and thought disorder). **Results:** Psychopathology in 22q11.2DS was divided into one 'general psychopathology' factor and four specific dimensions (i.e., 'anxiety', 'mood', 'ADHD' and 'psychosis'). The 'psychosis' symptoms loaded strongly on the 'general psychopathology' factor. **Conclusions:** The similarity of the symptom structure of psychopathology between 22q11.2DS and community and clinical populations without the deletion indicate that 22q11.2DS can provide a model to explore alternative approaches to our current nosology. Our findings add to a growing literature indicating the need to reorganize current diagnostic classification systems.

Keywords: 22q11.2DS, psychopathology, schizophrenia, symptoms

Introduction

22q11.2 Deletion syndrome (22q11.2DS) is caused by a submicroscopic deletion in the long arm of chromosome 22 and has been associated with multiple diverse clinical manifestations (Shprintzen, 2008) including congenital immunodeficiency, heart defects, velopharyngeal insufficiency and cleft palate (Bassett et al., 2011). 22q11.2DS is among the strongest known genetic risk factors for developing schizophrenia. By adulthood, ~25% of patients with the deletion are diagnosed with schizophrenia, while elevated rates of neurodevelopmental disorders have been reported in childhood (Bearden et al., 2001; Hooper et al., 2013; Niarchou et al., 2014b; Tang, S.X. et al., 2014; Vorstman et al., 2006). Studies to date have indicated that the schizophrenia phenotype in individuals with 22q11.2DS is similar to non-deleted people with schizophrenia (Bassett et al., 2003; Niarchou et al., 2014a; Tang et al., 2016). Hence, examining this relatively homogenous group with the same genetic syndrome can provide clues on a potential pathway to schizophrenia that could be of relevance to the general population by disentangling the complexity of genotype-phenotype relationships and disease mechanisms (Owen et al., 2010).

Similar to clinical and community populations (Andrews et al., 2002; Kessler et al., 2005; Krueger and Markon, 2006), high rates of comorbidity are common for 22q11.2DS. For example, 37.5% of children with 22q11.2DS with Attention Deficit Hyperactivity Disorder (ADHD) also had at least one anxiety disorder, 37.5% also had Oppositional Defiant Disorder (ODD) and 41% screened positive for autism (Niarchou et al., 2014b). It is unknown whether the high overlap among psychiatric disorders is due to shared etiology or due to limitations of diagnostic nomenclature in describing disease processes (Bukstein et al., 1989). Examining disorders independently limits our capacity to understand the shared risk factors and etiological mechanisms that underlie these conditions in the general population. Factor-analytic approaches have been developed to better capture the common characteristics of these disorders.

Studies in clinical and community samples have examined the symptom-level structure of psychopathology and have provided conceptual insights into psychopathology

(Carragher et al., 2015). In general, they support the existence of two dimensions: the internalizing (including anxiety and depression symptoms) and externalizing (including antisocial, hyperactive and aggressive symptoms) dimensions of psychopathology. This finding has been replicated across different ages (Eaton et al., 2011), ethnicities (Eaton et al., 2013) and cultures (Calkins et al., 2015; Kessler et al., 2011; Krueger et al., 2003; Slade and Watson, 2006; Vollebergh et al., 2001). Studies that have also assessed psychosis have demonstrated an additional thought disorder dimension which is formed by schizophrenia-spectrum disorders or symptoms (Caspi et al., 2013; Kotov et al., 2011; Markon, 2010; Wright et al., 2013). Recently, a general psychopathology factor has been reported (Calkins et al., 2015; Caspi et al., 2013; Lahey et al., 2012), which explains the common variance across individual psychiatric disorder symptoms and represents individuals' general propensity to endorse such symptoms (Caspi et al., 2013).

Our aim was to employ a dimensional approach where psychopathology is examined at the symptom-level rather than in diagnostic categories in a population at high genetic risk for schizophrenia. This can improve understanding of how psychopathology is structured as well as its genetic underpinnings. Examining the extent to which the dimensions of psychopathology in 22q11.2DS resemble those seen in the general population can provide insight into the degree to which 22q11.2 can provide a model to explore alternative approaches to our current nosology. This is the first study to examine the dimensional structure of a broad range of psychopathology in 22q11.2DS. Findings are based on one of the world's largest samples of 22q11.2DS individuals who underwent prospective comprehensive phenotyping at a single site. We sought to replicate previous findings by examining a bi-factor model that derives a general factor of psychopathology in addition to more specific dimensions of psychopathology (i.e., internalizing, externalizing and thought disorder) (Calkins et al., 2015; Caspi et al., 2013; Lahey et al., 2012). We hypothesized that the symptom-level structure of psychopathology would be similar to that reported previously in samples without the deletion.

Materials and methods

Sample

Three hundred and thirty-one individuals with 22q11.2DS ((51% males, mean age (SD)= 16.9(8.7), age range=8 to 52 years) took part in the study. The majority of the sample were Caucasians (86%), there were also 9% African Americans, 1% Asian and 4% mixed ethnicities. The sample has been previously described (Gur et al., 2014; Tang, S et al., 2014). The rates of the endorsements of individual items are detailed in Table 1. Individuals with 22q11.2DS were referred mainly through the '22Q and You Center' at the Children's Hospital of Philadelphia as well as from social networks. Presence of the deletion was confirmed for all individuals using multiplex ligation-dependent probe amplification (Jalali et al., 2008). Exclusion criteria included inability to consent and moderate to severe intellectual disability based on clinical evaluation and IQ testing or estimated from the reading segment of the Wide Range Achievement Test 4 (WRAT4; estimated IQ<70) (Wilkinson and Robertson, 2006).

The study was approved by the Institutional Review Boards of the University of Pennsylvania and the Children's Hospital of Philadelphia. Informed consent/assent was obtained from adult participants and from caretakers of younger participants with their assent.

Measures

Psychopathology

For the current report, psychopathology was examined at the symptom-level rather than in diagnostic-categories, thus avoiding the common limitation of disease categorization and improving statistical power (Chmura Kraemer et al., 2004). Symptoms assessed were derived from interview schedules based on lifetime history of DSM-IV-TR criteria for ADHD, Major Depressive Disorder (MDD), Bipolar Disorder (BPD), Generalized Anxiety Disorder (GAD), Separation Anxiety Disorder (SAD) and Obsessive Compulsive Disorder (OCD) using a modified and locally computerized Schedule for Affective

Disorders and Schizophrenia for School-Age Children (K-SADS (Kaufman et al., 1997)). Psychosis spectrum symptoms during the preceding 6 months were assessed using the Structured Interview for Prodromal Syndromes (SIPS; (Miller et al., 2003)) while the Structured Clinical Interview for DSM-IV (SCID, modules C and D; (First and Gibbon, 2004)) was also applied for psychotic and mood differential diagnoses. Embedded questions assessed history of suicidal ideation/behavior and self-harm. Interviewers were experienced and trained clinical assessors who were supervised by clinical investigators. The primary caregiver was interviewed about the proband while proband interviews were also administered to participants ≥11 years. Participants and collaterals were also clinically interviewed by an experienced investigator.

As can be seen in Table 1, the K-SADS item pool covers many DSM-IV-TR symptoms of several of the disorders (e.g., ADHD), but comparably fewer for some disorders (e.g., MDD). We selected the 'stem questions' (i.e., screen-level questions) of these disorders. This was because administration of the K-SADS involved 'skip logic' – i.e., if someone did not endorse a sub-set of screening items about a disorder, s/he was not asked the remaining items about that disorder. This resulted in a substantial amount of missing data, and we therefore used only screening items in this analysis. However, although we kept only the screening items, these had good positive predictive values for clinical diagnosis. For example, of those screening positive for depression, 23% were diagnosed MDD, of those who screened positive for any anxiety disorder, 50% were diagnosed with an anxiety disorder. Similarly, of those screening positive for ADHD, 50% where diagnosed with ADHD. In contrast, among those screening positive for bipolar, 2% were diagnosed with bipolar disorder. The low positive predictive value for bipolar disorder may be explained in part by the rarity of bipolar disorder in this sample.

Some of the K-SADS questions were combined prior to analysis because they assessed the same symptom. In this case, if the subjects endorsed either/or in any of them, this was counted as a yes. For a list of symptoms assessed please see table 1. All study variables were dichotomous (0=no, 1=yes), where SIPS subscales were coded as 1 for clinically significant (rating of 3-6) or 0 for non-significant levels of endorsement (rating of 0-2).

Data analysis

We first conducted exploratory factor analyses (EFAs) on the symptom-level data. Unidimensional, 2-, 3-, and 4-factor solutions were extracted using the Bayes estimator (Muthén and Asparouhov, 2012) in Mplus (Muthén and Muthén, 1998-2011) and rotated using oblimin. The Bayes estimator was chosen due to several advantages over conventional estimators (Depaoli and van de Schoot, 2015; van de Schoot and Depaoli, 2014), such as substantially reduced vulnerability to Heywood cases (Heywood, 1931) and non-positive-definite residual correlation matrices.

Of the four EFAs described above, the four-factor solution was determined to be optimal based on examination of the scree plot (Cattell, 1966), model fit and interpretability of the solution. The item-factor assignments from the four-factor solution were then used to build and perform a confirmatory factor analysis (CFA) bifactor model. Bifactor modeling (Reise, 2012; Reise et al., 2010) involves allowing each item to load on exactly two factors, one specific factor (e.g., psychosis) and one general factor comprising all items. A key benefit of bifactor modeling is that accounting for the general factor allows one to model the specific factors orthogonally, because the correlations among the sub-factors (e.g., between psychosis and depression) are accounted for by the general factor and therefore do not need to be modeled. See (Reise et al., 2010): Figure 1 for conceptual visualization of the bifactor model compared to other models.

To assess the concurrent validity of the latent dimensions in the measurement model described above, age and sex were included in the model. That is, it was a multiple-indicators multiple-causes (MIMIC) model (Jöreskog and Goldberger, 1975) in which the latent variables were indicated by their respective items, and individual differences on the latent variables were "caused" by age and sex. A benefit of estimating the measurement model and the effects of interest (age and sex) simultaneously is that it obviates the need to calculate factor scores and therefore avoids potential problems therein (e.g., indeterminacy; see (Grice, 2001)). Bayes estimation was used (as in the EFA), and model fit was judged via posterior predictive checking (Gelman et al., 1996).

Results

Exploratory factor analysis (EFA)

The fit of the unidimensional, 2- and 3-factor models was poor (posterior predictive value for the model p<0.001, p<0.01 and p<0.05 respectively, 95% Confidence Interval for the difference between the observed and the replicated chi-squared values 479.69 to 858.91; 93.61 to 479.30 and 13067 to 408.448 respectively). The 4-factor solution fit was good (p=0.09, 95% CI: 63.81 to 326.91).

It should be noted that in an EFA the null hypothesis is that the model has good fit (i.e., there is no difference between the observed data and our hypothesized model). Consequently, a significant p-value suggests that the null hypothesis should be rejected because the hypothesized model does not adequately explain the covariances among items in the sample. This is why the 4-factor solution was selected.

The 4-factor solution extracted the following items (Table 1). The 1st factor (anxiety), included all the items from the GAD and SAD sections, as well as one symptom from the OCD section (OCD3- feel the need to do things just right), and the SIPS 'impaired tolerance to normal stress' general symptom item (G4). The 2nd factor (ADHD), included all the ADHD items, plus the 'trouble with focus and attention' disorganization symptom (D3) and 'motor disturbances' general symptom from the SIPS (G3). The 3rd factor (mood) included all the items from the OCD, MDD and BPD and suicide sections as well as the 'dysphoric mood' general symptom from the SIPS (G2). Finally, the 4th factor (psychosis), included the remaining SIPS positive, negative, disorganized and general symptoms.

We selected the 4- factor solution for our confirmatory analyses because the fit of the 4-factor solution was better, the scree plot identified 4 factors and the interpretation of the factors was more plausible. For the unidimensional, 2- and 3- factor solutions see Supplementary table 1.

Confirmatory Bifactor Analysis

Table 2 and Figure 1 show the 4- factor bifactor solution including sex and age as covariates. The fit of the model was good (posterior predictive p-value=0.06; 95%

confidence interval for the difference between the observed and the replicated chi-squared values -29.59 to 332.23).

The general psychopathology factor was strong (mean loading=0.49). The items loading highest on the general factor were BPD1 (increased motor activity, loading=0.89), BPD2 (increased energy, loading=0.76) and BPD5 (elevated mood, loading=0.75) while the items with the lowest loadings were SAD2 (wanting to avoid being away from attachment figures, loading= 0.19), ADHD14 (difficulty with quiet activities, loading=0.22) and MDD1 (sad or depressed most of the time, mean loading=0.25). The items that composed the psychosis factor had the highest mean loading (0.58) on the general factor compared to the items of the other factors (ADHD – mean loading=0.42; anxiety=0.45; mood=0.50).

After controlling for the general factor, the mean loading of the items on the psychosis factor was reduced from 0.66 to 0.48, indicating that they are essential to the general psychopathology factor. No other differences were noted for the other factors.

There were also strong associations with the sex and age of the participants. Being male was associated with higher symptoms of 'ADHD.' 'Anxiety' and 'ADHD' were reduced with age, while 'mood' symptoms were associated with increased age.

Discussion

Overall summary

This is the first study to examine the dimensional structure of a wide spectrum of psychopathology in the context of a homogeneous genetic etiology like 22q11.2DS. Our findings indicate that psychopathology in 22q11.2DS is divided into a strong 'general psychopathology' factor and four additional factors; 'mood', 'anxiety', 'psychosis' and 'ADHD'. The strongest loadings on the 'general psychopathology' factor were from the psychosis symptoms, indicating that psychosis plays a major role in the propensity for psychopathology in 22q11.2DS. When controlling for the 'general psychopathology' factor the loadings of the symptoms remained high. Males were more likely to experience 'ADHD' symptoms while younger age was associated with 'ADHD' and 'anxiety' and older age was associated with 'mood'.

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Our hypothesis was supported. In accordance with previous studies in the general population, the dimensions of internalizing ('anxiety' and 'mood'), externalizing ('ADHD') and thought disorder ('psychosis') emerged, as well as the dimension of 'general psychopathology' (Carragher et al., 2014; Krueger et al., 2003; Lahey et al., 2015; Markon, 2010; Slade and Watson, 2006; Stochl et al., 2015; Vollebergh et al., 2001). The internalizing dimension was further divided into 'anxiety' and 'mood'. The 'anxiety' dimension included symptoms related to stress (i.e., symptoms of GAD, SAD, OCD and the 'impaired tolerance to normal stress' symptom from the SIPS) while the 'mood' dimension included symptoms related to mood (i.e., symptoms of MDD, BPD, Suicide, OCD and the 'dysphoric mood' symptoms from the SIPS). These results are consistent with previous studies (Krueger, 1999; Krueger and Markon, 2006; Slade and Watson, 2006). However, MDD in previous studies was clustered with anxiety rather than with bipolar. Our study does not provide evidence for dissolving the class of mood disorders as has been previously suggested (Goldberg et al., 2009; Kotov et al., 2011). This difference could reflect our evaluation of symptoms rather than diagnoses, but it could also indicate a pathway that is more unique to individuals with the deletion. Interestingly, the 'increased motor activity' symptom had the highest loading on the general

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psychopathology factor. Indeed, motor deficits are common in 22q11.2DS and there is also evidence suggesting that 22q11.2DS is a risk factor for early-onset Parkinson disease (Butcher et al., 2013). Further studies to examine potential associations of motor deficits with psychopathology are warranted.

Consistent with previous reports (Calkins et al., 2015; Caspi et al., 2013; Lahey et al., 2012), our findings indicate the existence of a strong 'general psychopathology' factor. This factor has been interpreted as the individuals' propensity to experience psychopathology (Caspi et al., 2013). Previous studies examining the symptom structure of the SIPS have demonstrated that positive and negative symptoms load on two different factors in both people with schizophrenia (Blanchard and Cohen, 2006) and individuals with 22q11.2DS (Tang, Sunny et al., 2014). However, these studies did not examine the SIPS together with other psychopathology domains to understand how and whether SIPS symptoms load on a 'general psychopathology' factor. Our study indicates that positive symptoms and negative symptoms loaded on both the 'general psychopathology' and the 'psychosis' factor in 22q11.2DS. It remains to be seen whether these results are replicated in other genetic syndromes and in other populations at high-risk for schizophrenia.

Theoretical and clinical implications

Our findings indicate that current diagnostic classification systems are not adequately capturing the highly correlated nature of psychopathology in 22q11.2DS. The lack of associations between biomarkers and specific risk factors with independent psychiatric disorders in 22q11.2DS as well as in the non-22q11.2DS populations (Caspi et al., 2013) might partly stem from the effect of the 'general psychopathology' factor. Updating psychiatric nosology to also reflect the underlying dimensional structure of psychopathology may help advance our mechanistic understanding of psychiatric disorders (Stochl et al., 2015).

Research on the clinical utility of dimensions is still in its early phases (Carragher et al., 2015). However, our findings support a growing body of evidence indicating that obtaining a better understanding of the underlying liabilities of psychiatric disorders using these dimensional approaches can help direct treatment options (Carragher et al.,

2015). Moreover, our findings are further evidence that psychiatric assessments of individuals with 22q11.2DS should not be limited to a single disorder.

Strengths and limitations

The rarity of 22q11.2DS hinders recruitment of large samples with detailed phenotyping. This is therefore the first study sufficiently powered to examine the dimensional structure of a broad range of psychopathology in 22q11.2DS. Our findings can inform future genetic studies in 22q11.2DS. Examining the genetic underpinnings of the dimensions of psychopathology can provide insights on shared risk and etiological mechanisms that overlap across different psychiatric disorders. Moreover, demonstration of a dimensional structure of psychopathology in 22q11.2DS that is similar to the structures demonstrated in other populations provides evidence that clinical psychological measurement can be conducted in the 22q11.2DS population with minimal (if any) caveats about possible qualitative differences between the nature of psychopathology in 22q11.2DS and other populations. An additional strength is the use of Bayesian estimation that is advantageous over conventional estimators (Depaoli and van de Schoot, 2015; van de Schoot and Depaoli, 2014). Given that this study is the first in this population, replication in other datasets is needed before these associations are considered reliable. Due to time constraints, one limitation of the study is the lack of assessments for other disorders (e.g., Social Phobia, Specific Phobia, Autism Spectrum Disorder and antisocial behavior), which could potentially alter the structure. Another limitation of our analytical approach is that we only included stem questions and not all the symptoms that might reflect a disorder including associated symptoms and distress or impairment. Finally, we report cross-sectional data and the age range of our population is relatively wide. It is possible that the dimensional structure of psychopathology differs across age groups. Future studies are needed to examine dimensionally the longitudinal course of comprehensive psychopathology domains.

Conclusions

We examined the dimensional structure of psychopathology in individuals with 22q11.2DS. Psychopathology in 22q11.2DS was divided into one 'general psychopathology' factor and four specific dimensions (i.e., 'anxiety', 'mood', 'ADHD' and

'psychosis'). The 'psychosis' symptoms loaded strongly on the 'general psychopathology' factor. The similarity of the symptom structure of psychopathology between 22q11.2DS and community and clinical populations without the deletion indicate that 22q11.2DS can provide a model to explore alternative approaches to our current nosology. Our findings add to an expanding literature indicating the need to reorganize current diagnostic classification systems. Further studies in other high risk populations are needed to replicate and establish the generalizability of these findings.

Table 1. 4- factor solution using Bayes Estimation

Item description	Item	Proportions endorsed	4-factor			
			F1	F2	F3	F4
Worrier	GAD1	0.64	**0.87**	-0.01	0.13	0.06
Worrying more than most people	GAD2	0.57	**0.85**	-0.02	0.11	0.07
Worries about being away from attachment figures	SAD1	0.20	**0.81**	-0.12	-0.05	0.18
Wanting to avoid being away from attachment figures	SAD2	0.23	**0.91**	-0.05	-0.03	0.05
Upset/worried in anticipation of being away from attachment figures	SAD3	0.23	**0.88**	-0.04	0.03	0.08
Separation dreams	SAD4	0.09	**0.45**	0.26	0.24	0.22
Fear of being alone	SAD5	0.33	**0.69**	0.13	-0.17	0.03
Obsessions (i.e., bothersome, intrusive, and repetitive thoughts)	OCD1	0.45	0.05	-0.02	**0.44**	0.09
Compulsions (i.e., repetitive and intrusive behaviors)	OCD2	0.42	0.30	0.01	**0.30**	-0.04
Feel the need to do things just right	OCD3	0.16	**0.36**	0.12	0.35	-0.14
Frequent trouble paying attention to school/work/chores	ADHD1	0.68	-0.07	**0.96**	-0.10	0.07
Frequent trouble paying attention to enjoyable activities	ADHD2	0.30	-0.09	**0.78**	0.08	0.24
Difficulty paying attention to instructions	ADHD3	0.56	0.07	**0.83**	-0.14	0.22
Difficulty sustaining attention to activities requiring mental effort	ADHD4	0.59	-0.05	**0.83**	-0.10	0.24
Often losing things/ making careless mistakes	ADHD5	0.57	-0.10	**0.78**	0.01	0.04
Difficulty planning/organizing	ADHD6	0.63	-0.05	**0.83**	0.02	0.19
Daydreaming/trouble listening	ADHD7	0.55	-0.10	**0.78**	0.13	0.06

Often forgetting	ADHD8	0.48	0.06	**0.80**	0.06	0.08
Often distracted	ADHD9	0.62	-0.02	**0.92**	-0.09	0.07
Difficulty remaining still	ADHD10	0.41	0.25	**0.76**	0.19	-0.19
Fidgety	ADHD11	0.49	0.19	**0.81**	-0.07	-0.31
Always on the go	ADHD12	0.33	-0.05	**0.85**	0.24	-0.21
Climbing on things/ running around when it's not appropriate	ADHD13	0.28	-0.14	**0.92**	0.10	0.09
Difficulty with quiet activities	ADHD14	0.23	0.14	**0.83**	-0.03	-0.15
Extremely talkative	ADHD15	0.32	0.13	**0.77**	0.03	-0.18
Blurting out answers/interrupting people when they are talking	ADHD16	0.40	0.10	**0.70**	0.04	0.06
Trouble waiting for turn	ADHD17	0.46	0.04	**0.75**	-0.08	0.10
Sad or depressed most of the time	MDD1	0.30	-0.03	-0.16	**0.87**	0.11
Cried a lot, or felt like crying	MDD2	0.23	0.08	0.02	**0.76**	-0.04
Grouchy, irritable or in a bad mood most of the time	MDD3	0.34	-0.06	-0.07	**0.86**	0.07
Loss of interest	MDD4	0.21	-0.09	-0.14	**0.82**	0.21
Depressive mood change observable by others	MDD5	0.64	0.13	-0.13	**0.72**	0.04
Increased motor activity	BPD1	0.09	0.26	0.40	**0.58**	0.07
Increased energy	BPD2	0.08	0.13	0.36	**0.60**	0.02
Decreased need for sleep	BPD3	0.07	0.08	0.40	**0.55**	-0.03
Pressured speech/flight of ideas	BPD4	0.10	0.16	0.24	**0.66**	-0.02
Elevated mood	BPD5	0.04	0.24	0.31	**0.60**	0.14
Feeling like they could do almost anything	BPD6	0.05	0.30	0.26	**0.69**	-0.17
Irritable mood	BPD7	0.17	0.11	0.12	**0.71**	-0.02
Unusual thought content/delusional ideas	P1	0.21	0.13	0.00	0.17	**0.77**
Suspiciousness/persecutory ideas	P2	0.22	0.27	-0.02	0.24	**0.67**
Grandiose ideas	P3	0.07	0.29	-0.02	0.06	**0.65**

Perceptual abnormalities/hallucinations	P4	0.25	-0.02	-0.11	0.15	**0.71**
Disorganized communication	P5	0.18	0.16	0.19	-0.02	**0.64**
Social anhedonia	N1	0.21	0.11	0.06	0.03	**0.66**
Avolition	N2	0.32	0.08	0.16	-0.08	**0.72**
Expression of emotion	N3	0.19	-0.05	0.05	0.16	**0.64**
Experience of emotions and self	N4	0.05	-0.07	0.07	0.27	**0.62**
Ideational richness	N5	0.54	0.14	0.17	-0.23	**0.61**
Occupational functioning	N6	0.24	-0.06	0.20	0.12	**0.79**
Odd behavior or appearance	D1	0.13	0.31	0.11	0.05	**0.68**
Bizarre thinking	D2	0.09	0.08	0.09	0.12	**0.83**
Trouble with focus and attention	D3	0.43	0.07	**0.74**	-0.09	0.25
Impairment in personal hygiene	D4	0.13	0.17	0.27	0.04	**0.51**
Sleep disturbance	G1	0.28	0.21	0.02	0.24	**0.44**
Dysphoric mood	G2	0.22	-0.01	-0.04	**0.57**	0.42
Motor disturbances	G3	0.06	0.09	**0.36**	0.19	0.16
Impaired tolerance to normal stress	G4	0.32	**0.46**	0.16	0.06	0.43
Passive thoughts about death/dying	SUI1	0.19	0.10	-0.09	**0.69**	0.15
Suicidal thoughts	SUI2	0.10	-0.09	-0.03	**0.72**	0.34

Abbreviations: GAD– Generalized Anxiety Disorder, SAD- Separation Anxiety Disorder, OCD- Obsessive Compulsive Disorder, ADHD– Attention Deficit Hyperactivity Disorder, MDD- Major Depressive Disorder, BPD- Bipolar Disorder, P- Positive symptoms, N-Negative symptoms, D- Disorganization symptoms, G- General symptoms, SUI- Suicide

Table 2. Standardized coefficients and significance levels for confirmatory factor analysis including external effects of interest (MIMIC model)

Parameter estimate			
Latent variable	Item	Standardized Coefficients	P
ADHD measured by	ADHD1	0.75	<0.001
	ADHD2	0.60	<0.001
	ADHD3	0.53	<0.001
	ADHD4	0.57	<0.001
	ADHD5	0.56	<0.001
	ADHD6	0.57	<0.001
	ADHD7	0.58	<0.001
	ADHD8	0.57	<0.001
	ADHD9	0.70	<0.001
	ADHD10	0.94	<0.001
	ADHD11	0.87	<0.001
	ADHD12	0.90	<0.001
	ADHD13	0.92	<0.001
	ADHD14	0.87	<0.001
	ADHD15	0.62	<0.001
	ADHD16	0.57	<0.001
	ADHD17	0.63	<0.001
	D3	0.55	<0.001
	G3	0.26	0.02
Psychosis measured by	P1	0.83	<0.001
	P2	0.59	<0.001
	P3	0.53	<0.001
	P4	0.80	<0.001
	P5	0.31	<0.001
	N1	0.34	<0.001
	N2	0.26	0.002

	N3	0.44	<0.001
	N4	0.70	<0.001
	N5	0.38	<0.001
	N6	0.41	<0.001
	D1	0.46	<0.001
	D2	0.79	<0.001
	D4	0.13	0.11
	G1	0.21	0.02
Mood measured by	MDD1	0.86	<0.001
	MDD2	0.75	<0.001
	MDD3	0.77	<0.001
	MDD4	0.83	<0.001
	MDD5	0.69	<0.001
	BPD1	0.32	<0.001
	BPD2	0.37	<0.001
	BPD3	0.36	0.001
	BPD4	0.39	<0.001
	BPD5	0.55	<0.001
	BPD6	0.62	<0.001
	BPD7	0.53	<0.001
	SUI1	0.62	<0.001
	SUI2	0.71	<0.001
	OCD1	0.39	<0.001
	OCD2	0.27	0.001
	G2	0.48	<0.001
Anxiety measured by	GAD1	0.66	<0.001
	GAD2	0.65	<0.001
	SAD1	0.83	<0.001
	SAD2	0.94	<0.001
	SAD3	0.90	<0.001
	SAD4	0.32	<0.001

	SAD5	0.62	<0.001
	OCD3	0.19	0.06
	G4	0.26	<0.001
General psychopathology measured by	GAD1	0.59	<0.001
	GAD2	0.56	<0.001
	SAD1	0.27	0.01
	SAD2	0.19	0.03
	SAD3	0.28	0.004
	SAD4	0.74	<0.001
	SAD5	0.28	0.001
	OCD1	0.31	<0.001
	OCD2	0.31	0.001
	OCD3	0.39	0.002
	ADHD1	0.50	<0.001
	ADHD2	0.53	<0.001
	ADHD3	0.69	<0.001
	ADHD4	0.61	<0.001
	ADHD5	0.45	<0.001
	ADHD6	0.61	<0.001
	ADHD7	0.49	<0.001
	ADHD8	0.60	<0.001
	ADHD9	0.54	<0.001
	ADHD10	0.10	0.15
	ADHD11	0.11	0.13
	ADHD12	0.02	0.42
	ADHD13	0.11	0.15
	ADHD14	0.22	0.03
	ADHD15	0.48	<0.001
	ADHD16	0.47	<0.001
	ADHD17	0.44	<0.001
	MDD1	0.25	0.001
	MDD2	0.31	0.002

	MDD3	0.38	<0.001
	MDD4	0.30	0.001
	MDD5	0.32	0.02
	BPD1	0.89	<0.001
	BPD2	0.76	<0.001
	BPD3	0.59	<0.001
	BPD4	0.68	<0.001
	BPD5	0.75	<0.001
	BPD6	0.48	<0.001
	BPD7	0.54	<0.001
	P1	0.48	<0.001
	P2	0.63	<0.001
	P3	0.58	<0.001
	P4	0.28	0.001
	P5	0.71	<0.001
	N1	0.62	<0.001
	N2	0.71	<0.001
	N3	0.51	<0.001
	N4	0.37	<0.001
	N5	0.46	<0.001
	N6	0.74	<0.001
	D1	0.72	<0.001
	D2	0.53	<0.001
	D3	0.60	<0.001
	D4	0.74	<0.001
	G1	0.60	<0.001
	G2	0.62	<0.001
	G3	0.44	0.001
	G4	0.74	<0.001
	SUI1	0.47	<0.001
	SUI2	0.50	<0.001
General psychopathology regressed on	Sex	-0.08	0.08

	Age	-0.09	0.11
Anxiety regressed on	Sex	0.03	0.34
	Age	-0.13	0.05
Psychosis regressed on	Age	-0.07	0.21
	Sex	0.12	0.07
ADHD regressed on	Sex	-0.11	0.02
	Age	-0.31	<0.001
Depression regressed on	Sex	0.02	0.39
	Age	0.30	<0.001
Sex correlated with	Age	0.17	0.001

Abbreviations: MIMIC- multiple-indicators multiple-causes, GAD– Generalized Anxiety Disorder, SAD-Separation Anxiety Disorder, OCD-Obsessive Compulsive Disorder, ADHD– Attention Deficit Hyperactivity Disorder, MDD- Major Depressive Disorder, BPD- Bipolar Disorder, P- Positive symptoms, N-Negative symptoms, D- Disorganization symptoms, G- General symptoms, SUI- Suicide

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