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## A symptom network structure of the psychosis spectrum

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### ABSTRACT

Current diagnostic systems mainly focus on symptoms needed to classify patients with a specific mental disorder and do not take into account the variation in co-occurring symptoms and the interaction between the symptoms themselves. The innovative *network approach* aims to further our understanding of mental disorders by focusing on meaningful connections between individual symptoms of a disorder and has thus far proven valuable insights to psychopathology. The aims of current study were to I) construct a symptom network and investigate interactions between a wide array of psychotic symptoms; II) identify the most important symptoms within this network and III) perform an explorative shortest pathway analysis between depressive and delusional symptoms. We analyzed interview data from  $n = 408$  male patients with non-affective psychosis using the Comprehensive Assessment of Symptoms and History (CASH). A network structure of 79 symptoms was computed to explore partial correlations between positive, negative, catatonia and affective symptoms.

The resulting network showed strong connectivity between individual symptoms of the CASH, both within- and between-domains. Most central symptoms included 'loss of interest', 'chaotic speech', 'inability to enjoy recreational interest in activities', 'inability to form or maintain relationships with friends' and 'poverty of content of speech'. The shortest pathway analysis between depressive and delusional symptoms displayed an important role for 'persecutory delusions'.

In conclusion, this study showed that individual psychotic symptoms are meaningfully related to each other only within their own cluster, but also between different clusters and that important information may be acquired by investigating interactions at a symptom level.

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### 1. Introduction

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM; American Psychiatric Association, 2013) classifies patients with a specific mental disorder based on pre-defined combinations of symptoms. A more fundamental problem of the current classification system may however be its categorical nature. Therefore, current classification systems have been criticized extensively (Goekoop and Goekoop, 2014; Kendell and Jablensky, 2003), mainly because strong empirical evidence for the

demarcations between symptoms is missing. Moreover, a slow progress in the identification of biomarkers (Weickert et al., 2013) and specific genes (Owen et al., 2016) for disorders or symptoms illustrate the caveats of the current diagnostic classification system and potentially the absence of an underlying disease model. Thus, although it cannot be refuted that the DSM has contributed to more uniformity in the diagnostic process, the phenotypic heterogeneity and complexity to link symptoms to underlying pathophysiology remain substantial and problematic.

Besides the well-known categorical diagnostic criteria of schizophrenia, the DSM-5 (American Psychiatric Association, 2013) incorporated a dimensional assessment to specify the severity of symptoms. The psychosis spectrum includes positive and negative symptoms as well as symptoms of disorganization and affective symptoms. Distinguishing between these symptoms is often difficult (e.g., negative symptoms are difficult to differentiate from depressive symptoms), which is partly due to the conceptual overlap between symptom

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domains. Nevertheless, this distinction is of great clinical relevance, since these symptom domains might require different treatments.

Previous factor analytic studies investigated this wide variety of symptoms within the psychosis spectrum by identifying factors underlying the symptomatology of schizophrenia. For example, a study by Derks et al. (2012), which included the present study sample, showed that variation in five dimensions (disorganization, positive, negative, mania, and depression) explained the largest portion of the variance within the psychosis spectrum. These results are in line with a review by Potuzak et al. (2012) who concluded that most factor (analytical) studies reported four or five of the aforementioned dimensions within the psychosis spectrum. However, they also pointed out that symptoms often loaded on more than one factor and those factors often showed considerable overlap. Differences in applied instruments and methodology may explain part of this variability in findings. Moreover, since significant differences in symptom profiles between genders have been described in schizophrenia (Hill, 2016; Leung and Chue, 2000), sample characteristics may also contribute to such variability. Overall, despite the relevance of factor studies in elucidating clusters of symptoms, their contribution to etiological research or valuable insights into psychopathology has been limited (Goekoop and Goekoop, 2014).

Factor analytical studies are conceptually based on the 'common cause model' (i.e., an underlying latent factor 'causes' the associations among symptoms; Borsboom and Cramer, 2013). Within this view, the association between, for example, insomnia and loss of energy is attributed by a common latent factor 'major depressive disorder'. However, the possibility that the symptom insomnia might itself cause a lack of energy is ignored. As an alternative to the latent factor model, a novel network framework recently emerged. The network framework adopts a different perspective on psychopathology, by assuming that disorders are the result of the interactions between (specific) symptoms, i.e., that symptoms are able to influence each other (Borsboom and Cramer, 2013).

To date, the network approach has been applied to a wide variety of psychiatric disorders, including research in depression, social anxiety disorder, personality disorder and more recently psychosis (Heeren and McNally, 2016; Isvoranu et al., 2016; Van Borkulo et al., 2015; Wright and Simms, 2016). For instance, a recent study investigated negative symptoms in patients with chronic schizophrenia at baseline and follow-up (i.e., 60-days later) and showed that (speech) symptoms remained strongly correlated, indicating that these symptoms were less influenced by treatment (Levine and Leucht, 2016). This study did not however include other symptoms (such as positive symptoms) to allow for the interpretation of negative symptoms in a wider spectrum of symptoms.

Here, we argue that exploring a network of a wide variety of symptoms is not only beneficial to identify interactions between an extensive range of symptoms, but also to explore the pathways and potential mediating items between symptoms and symptom domains. This can be done using shortest pathway analysis (Isvoranu et al., 2017), a recently developed hypotheses-generating technique. For the current paper, we chose to explore the shortest pathway between the depressive and delusional domains. Previous studies have identified that depressive symptoms are a central part of a psychotic episode (An Der Heiden et al., 2005; Birchwood et al., 2000) and argued that this association should be thoroughly investigated in further research. Thus, the aims of current study were to I) construct a symptom network and investigate interactions between a wide array of psychotic symptoms in a large cohort of male patients; II) identify the most important symptoms within this network and III) explore the pathway that connect depressive and delusional symptoms.

## 2. Methods

### 2.1. Subjects

The data in this study was part of the Dutch multicenter study 'Genetic Risk and Outcome of Psychosis' (GROUP). The details of this

study were described earlier (Korver-Nieberg et al., 2012). In short, the full GROUP sample consists of patients, between 16 and 50 years old, meeting criteria for a non-affective psychotic disorder (American Psychiatric Association, 2000). The patients were assessed at baseline and at three and six year follow-up. For the purpose of this study, baseline data was used. To avoid influences due to gender differences, we performed our analyses in only male participants. Due to the relatively low number of included women, we were not able to perform a network analysis in only female participants.

### 2.2. Measures

#### 2.2.1. Symptom assessment

All symptoms were assessed with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992) in three of the four participating centers. The CASH is a structured interview, in which every item is rated on a scale ranging from 0 (none) to 5 (severe). The CASH includes lifetime rated and present state symptoms. For this study, the present state symptoms were chosen since this is more suitable for a network approach in which symptoms are assumed to influence each other. Moreover, it prevents the risk of recall bias. A total of 79 items (i.e., symptoms) were included in the statistical analyses. Since items that indicate a specification of a particular symptom (e.g., in the case of mania, state 'euphoric' or 'agitated' and in the case of depression state 'depressed' or 'anxious') were missing in approximately 20% of these cases we did not include these items.

The CASH includes thirteen a priori defined symptom domains (i.e., manic syndrome, major depressive syndrome, delusions, hallucinations, bizarre behavior, formal thought disorder, avolition - apathy, anhedonia - asociality, catatonic motor behavior, alolia, affective flattening and inappropriate affect), each including a different number of symptoms (Table 1).

#### 2.2.2. Network construction

The details of the network approach and construction have been described earlier (Borsboom and Cramer, 2013; Epskamp et al., 2016). In brief, in our network, every item of the CASH (i.e., symptom) is represented as a *node*, whereas associations between nodes are represented as *edges*. Because, the current data were univariate not normally distributed, before performing analyses, we applied a non-paranormal transformation which is a tool for relaxing the normality assumption (Liu et al., 2009).

We expressed associations in our network between two nodes by partial correlations between those two symptoms. Partial correlations are preferred over zero-order correlations because the latter might be spurious, i.e., resulting from indirect (via other symptoms) interactions. Moreover, the partial correlations were L1-regularized (Friedman et al., 2008; Tibshirani, 1996). L1 regularization decreases the overall strength of some parameter estimates, while setting others to zero, thereby ensuring a more interpretable and sparse model. L1-regularization involves model selection with the Extend Bayesian Information Criterion (EBIC) to ensure accurate network estimations (Chen and Chen, 2008; Foygel and Drton, 2015, 2010; van Borkulo et al., 2014). Model selection with EBIC involves the hyperparameter  $\gamma$ , which is commonly set to 0.5. Details of the association between  $\gamma$  and network connectivity have been published previously (Van Borkulo et al., 2015). L1-regularization ensures an optimal balance between parsimony and goodness of fit of the network model. The network was estimated with R package *qgraph* (Epskamp et al., 2012; R Core Team, 2016).

#### 2.2.3. Network visualization

For the layout of the graph, the Fruchterman-Reingold algorithm was used, which calculates the optimal layout so that symptoms with less strength and less connections are placed further apart and those with more and/or stronger connections are placed closer to each other (Fruchterman and Reingold, 1991). The associations are either green

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