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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 not only within their own cluster, but also between different clusters and that important information may be acquired by investigating interactions at a symptom level.

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, alogia, 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 γ, which is commonly set to 0.5. Details of the association between γ 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

Table 1
Abbreviations of a priori defined symptom domains and associated items (i.e., symptoms) as well as mean scores per item.

Item label	Item description	Male participants ($n = 408$) Mean (SD)
Manic syndrome (MS) (red)		
MS 1	Euphoric mood	0.10 (0.47)
MS 2	Increase in activity	0.11 (0.56)
MS 3	Increased talkativeness/pressure of speech	0.09 (0.49)
MS 4	Racing thoughts	0.23 (0.74)
MS 5	Inflated self esteem	0.13 (0.61)
MS 6	Decreased need for sleep	0.07 (0.49)
MS 7	Distractibility	0.29 (0.81)
MS 8	Reduced judgment	0.08 (0.46)
Major depressive syndrome (MD) (orange)		
MD 1	Depressive mood	0.74 (1.24)
MD 2	Change in appetite	0.36 (0.94)
MD 3	Weight gain	0.18 (0.67)
MD 4	Weight loss	0.15 (0.64)
MD 5	Sleep disturbances	0.47 (1.07)
MD 6	Insomnia	0.21 (0.71)
MD 7	Hypersomnia	0.38 (0.98)
MD 8	Psychomotor agitation	0.34 (0.88)
MD 9	Psychomotor retardation	0.33 (0.84)
MD 10	Loss of interest or pleasure	0.87 (1.34)
MD 11	Loss of energy	0.93 (1.33)
MD 12	Feelings of worthlessness	0.57 (1.10)
MD 13	Diminished ability to think or concentrate	0.89 (1.33)
MD 14	Recurrent thoughts of death/suicide	0.43 (0.98)
Delusions (DL) (yellow)		
DL 1	Persecutory delusions	1.15 (1.55)
DL 2	Delusions of jealousy	0.08 (0.42)
DL 3	Delusions of sin or guilt	0.25 (0.78)
DL 4	Grandiose delusions	0.52 (1.13)
DL 5	Religious delusions	0.38 (1.02)
DL 6	Somatic delusions	0.36 (0.98)
DL 7	Ideas and delusions of reference	1.10 (1.51)
DL 8	Delusions of being controlled	0.37 (1.01)
DL 9	Delusions of mind reading	0.57 (1.15)
DL 10	Thought broadcasting/Audible thoughts	0.44 (1.12)
DL 11	Thought insertion	0.39 (1.02)
DL 12	Thought withdrawal	0.31 (0.93)
Hallucinations (HA) (green)		
HA 1	Auditory hallucinations	1.02 (1.52)
HA 2	Voices commenting	0.68 (1.31)
HA 3	Voices conversing	0.50 (1.19)
HA 4	Somatic or tactile hallucinations	0.27 (0.82)
HA 5	Olfactory hallucinations	0.18 (0.67)
HA 6	Visual hallucinations	0.46 (1.10)
Bizarre behavior (BB) (dark green)		
BB 1	Received comments about clothing and appearance	0.18 (0.58)
BB 2	Received comments about (inappropriate) behavior	0.27 (0.76)
BB 3	Aggressive or agitated behavior	0.36 (0.92)
BB 4	Ritualistic or stereotype behavior	0.29 (0.82)
Formal thought disorder (FTD) (cyanogen)		
FTD 1	Disorganized speech	0.31 (0.88)
FTD 2	Pressured speech	0.46 (0.99)
FTD 3	Derailed speech	0.39 (0.93)
FTD 4	Chaotic speech	0.51 (1.11)
FTD 5	Incoherent speech	0.12 (0.50)
FTD 6	Illogical speech	0.22 (0.68)
FTD 7	Circumstantial speech	0.62 (1.11)
FTD 8	Distractible speech	0.21 (0.73)
FTD 9	Clanging	0.03 (0.33)
Avolition - Apathy (AP) (light grey)		
AP 1	Impersistence at work or school	1.15 (1.50)
AP 2	Physical anergia	1.32 (1.47)
AP 3	Less attention to grooming and hygiene	0.54 (1.04)
Anhedonia - Asociality (AS) (light blue)		
AS 1	Inability to enjoy recreational interest and activities	1.07 (1.49)
AS 2	Loss of sexual interest and activity	0.83 (1.38)
AS 3	Ability to feel intimacy and closeness	0.80 (1.34)
AS 4	Inability to form or maintain relationships with friends	1.24 (1.58)
Inatttention (AT) (dark blue)		
AT 1	Social inattentiveness	0.63 (1.08)
AT 2	Inattentiveness during mental status task	0.91 (1.34)
Catatonic motor behavior (CMB) (pink)		
CMB 1	Stupor	0.17 (0.46)
CMB 2	Rigidity	0.10 (0.37)
CMB 3	Waxy flexibility	0.01 (0.12)
CMB 4	Excitement	0.08 (0.31)
CMB 5	Posturing and mannerism	0.08 (0.33)
Alogia (AL) (purple)		
AL 1	Poverty of speech	0.71 (1.16)
AL 2	Poverty of content of speech	0.56 (1.01)
AL 3	Blocking of speech	0.18 (0.66)
AL 4	Increased latency when responding	0.60 (1.04)
AL 5	Perseveration	0.16 (0.57)
Affective flattening or blunting (AF) (soft red)		
AF 1	Monotone facial expression	1.26 (1.36)
AF 2	Reduced spontaneous movement	1.00 (1.23)
AF 3	Paucity of expressive gestures	1.09 (1.30)
AF 4	Poor eye contact	0.59 (1.06)
AF 5	Affective non-responsivity	0.58 (0.94)
AF 6	Lack of intonation	0.76 (1.16)
Inappropriate affect (IA) (dark grey)		
IA 1	Inadequate affect	0.28 (0.78)

indicating positive partial correlations or negative, colored red. The thickness of an edge represents the strength of the association, with thicker lines representing stronger associations (Costantini et al., 2015). Association with- and between-domains were described.

2.2.4. Network analyses

First, we analyzed our network by assessing three centrality measures for each node within the network, namely betweenness, node strength and closeness (Supplementary material Fig. S3) (Barrat et al., 2004; Boccaletti et al., 2006; Opsahl et al., 2010). 'Betweenness' is the proportion of the shortest paths of all possible empirical paths between two symptoms that have the node of interest in the path. It is measured by calculating how often a particular symptom lies on the shortest path between any combinations of two nodes. 'Node strength' is calculated as the sum of the weighted number and strength of all connections of a specific node relative to all other nodes. Lastly, 'closeness' is the average distance from the node of interest to all other nodes. Closeness is calculated as the inverse of the sum of all the shortest paths between the index symptom and all other symptoms. In other words, a high closeness index indicates a short average distance of a specific node to all other symptoms.

Second, we carried out a more in-depth, concentrated analysis by computing shortest pathways between depressive and delusional symptoms. Although there are several options to reach one node from other nodes, there is only one shortest route, which is highlighted in the shortest pathway figure (Brandes, 2008; Dijkstra, 1959; Isvoranu et al., 2017). This analysis allows for the identification of shortest pathways from delusional symptoms to depressive symptoms (or vice versa) and shows possible mediating symptoms between these domains.

2.2.5. Network stability

There is no clear consensus regarding the minimum number of participants per parameter needed to generate stable networks (Fried and Cramer, 2016). Therefore we performed a stability check as described by Epskamp et al. (2016). More specific, we estimated the accuracy of edge-weights, by drawing bootstrapped confidence intervals (CIs) and performed the 'bootstrapped difference test' for edge-weights and centrality measure 'node strength' (for more information regarding this procedure, see methods section in the Supplementary Material) (Epskamp et al., 2016).

3. Results

3.1. Study sample

Since the CASH was only assessed at three of the four centers, a total of 861 subjects completed the interview. From a total of 559 patients data was complete, with 408 male patients meeting the criteria for non–affective psychosis. In this sample, the mean age was 27.4 (SD = 7.5) years, with a mean age of onset of 22.3 (SD = 7.2). Of our sample, 306 participants (75%) were diagnosed with schizophrenia (Table 2).

3.2. Network analysis

3.2.1. Network structure and stability

The symptom network, based on the 79 symptoms, is presented in Fig. 1. As described above, the CASH contains thirteen a priori defined symptom domains that could be largely identified in the network structure. Symptoms within the same a priori defined symptom domains are shown in the same color. By applying a stability check (Epskamp et al., 2016, we demonstrated that our network can be interpreted as relatively stable. A detailed description of these additional analyses is presented in the Supplementary Material, figs. S1–S3.

3.2.2. Associations of symptoms within a priori defined symptom domains

An overview of the associations of symptoms between and within these domains is shown in Table 3. Within-domain associations between symptoms were in general stronger than between-domain associations. For example, the symptoms of affective flattening (AF) were associated to almost all symptoms within the affective flattening domain (i.e., 93.3% of all possible connections). This was comparable for symptoms of anhedonia (AS) (i.e., 83.3% of all possible connections), which means that the priori defined domains by the CASH correspond with distinguishable subnetworks of symptomatology. Symptoms within the domains bizarre behavior (BB) and avolition (AP) were however less strongly connected within clusters (i.e., 16.7% respectively 33.3% of all possible connections).

Interestingly, symptoms of the Schneider's First Rank Symptoms (FRS: Mellor, 1970; Schneider, 1959) were strongly associated, namely DL9 (delusions of mind reading), DL10 (thought broadcasting), DL11 (thought insertion), DL12 (thought withdrawal), and DL8 (delusions of being controlled). Other notable connections were between symptom MD14 (recurrent thoughts of dead/suicide) and MD12 (feelings of worthlessness) and between MD14 and MD1 (depressive mood), namely since connections from suicidal thoughts to other symptoms were missing.

3.2.3. Associations of symptoms between a priori defined symptom domains

Table 3 further presents the percentage of connections between the domains. This was highest for alogia (AL) and inappropriate affect (IA) (i.e., 60% of all possible connections), followed by anhedonia (AS) and avolition (AP) (i.e., 41.7% of all possible connections), meaning that symptoms of these domains tend to co-occur (or might influence each other). Besides the number of possible connections, the domain hallucinations (HA) was only connected to the domain delusions (DL) and not to other domains, while the domain delusion was connected to 8 other a priori defined domains (among others: formal thought disorder and anhedonia).

Several specific symptoms connected the different domains with each other. For example: DL3 (delusions of sin or guilt) was related with depressive symptom MD12 (feelings of worthlessness). Moreover, node MS5 (inflated self-esteem) was related to DL4 (grandiose delusions). DL2 (delusions of jealousy) was weakly associated with MS3 (increased talkativeness), but not with other delusion symptoms. In addition, there were several dense connections between items of the domains avolition (AP) and anhedonia (AS) and the depressive domain, suggesting that these domains cluster together more closely.

3.2.4. Centrality measures

MD10 (loss of interest and pleasure), FTD4 (chaotic speech), AS1 (inability to enjoy recreational interest in activities), AS4 (inability to form or maintain relationships with friends) and AL2 (poverty of content of speech) showed high centrality (Supplementary Material Fig. S4), indicating that these symptoms were central symptoms within the network.

3.2.5. Shortest pathways: delusional and depressive symptoms

We further constructed a network showing the shortest pathways between the depressive and delusional domains (Fig. 2). The shortest pathways from all delusional symptoms to depressive symptoms went through DL1 (persecutory delusions) and all passed through the domain anhedonia (AS) or vice versa. Notable, the shortest path from DL6 (somatic delusions) to depressive symptoms first went through symptoms of hallucinations.

Table 2
Demographics and clinical characteristics of (male) participants.

	Study group (n = 408)
Age, years (Mean, SD)	27.41 (7.5)
Age of onset, years (Mean, SD)	22.3 (7.2)
Episodes (n)	1.8 (1.3)
Diagnosis, n (%)	
• Schizophrenia	306 (75.0)
• Schizoaffective disorder	39 (9.6)
• Schizophreniform disorder	16 (3.9)
• Delusional disorder	4 (1.0)
• Brief Psychotic disorder	4 (1.0)
• Psychotic disorder NOS	39 (9.6)
Antipsychotics	
- *Atypical*	255 (62.5)
- *Typical*	44 (10.8)
Antidepressants (%)	130 (31.9%)

4. Discussion

The purpose of the current study was to determine the network structure of a broad range of symptoms within the psychosis spectrum (i.e., positive, negative, catatonia and affective symptom domains) based on the CASH, in a large sample of male patients with non–affective psychosis. To the best of our knowledge, this is the first report investigating a wide variety of symptoms in such a sample. Overall, the findings of this study lend support for the existence of the symptom domains as identified with the CASH, but also present evidence of multiple symptom-level associations not previously accounted for by factor analytical studies. Moreover, we identified specific symptoms with high centrality and specific associations both within-domains as well as between-domains, indicating that these symptoms may play an important role in the development and/or persistence of psychopathology. This report therefore is corroborative and additive to the existing literature

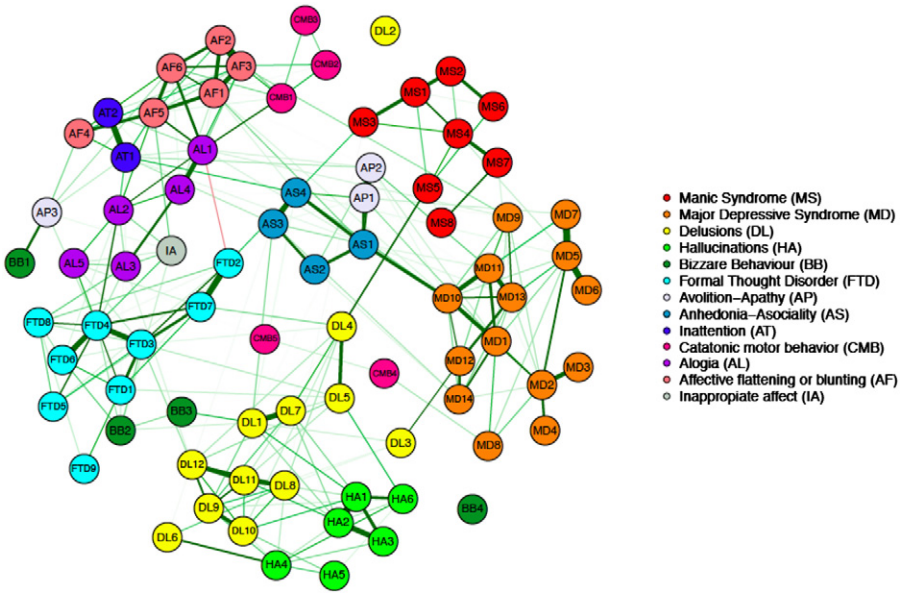

Fig. 1. Network model of (male) participants ($N = 408$). Network structure of 79 symptoms (based on symptomatology as assessed with the CASH) in male patients. Node colors refer to a priori symptom domains (see legend) and numbers refer to specific individual items (i.e. symptoms) (see Table 1). The associations are either positive (colored green) or negative (colored red), with thicker lines representing stronger associations.

(Levine and Leucht, 2016). In addition to knowledge about the clustering of symptoms, we add information on meaningful associations between individual symptoms, importance of certain symptoms to the network, as well as potential symptom pathways between-cluster domains. We herewith emphasize that important information might be lost when using only factor analytic methods.

4.1. Network clustering

The finding that, in general, network clusters correspond to results of factor analytic studies is in line with a previous study which compared principal component analysis with a network approach in 192 patients with 'unselected mental disorders' (Goekoop and Goekoop, 2014). They showed an 89% overlap between network clusters and components. In addition, an earlier factor-analytic study, which also included the present sample (Derks et al., 2012) found that the thirteen a priori defined symptom domains of the CASH in this study were reduced to the existence of five factors (mania, positive, depression, disorganization, and negative symptoms) to describe the psychosis spectrum. Especially the first three factors are also distinguished in our network model, within different symptom clusters.

4.2. Research relevance and implications

Thus, when these different psychometric approaches show overlap in findings, such as the findings described above, what is the added value of network analysis when investigating psychopathology? First, we consider the overlap in findings as a proof of stable and replicable research, which is relevant especially from the perspective of the recent replicability crisis (Open Science Collaboration, 2015). Second, despite certain overlap in findings, we argue that our network approach highlights novel results that could not have been identified otherwise when using a factor analytic approach. For instance, it is not possible within a factor analytic approach to investigate associations between individual symptoms of a disorder and to distill symptoms that connect distinct domains with each other while these symptoms might play an important role in the maintenance of psychopathology. Furthermore, the network approach allows for the identification of central (i.e., important) symptoms within a network, which could ultimately prove to be important targets for clinical intervention. Below we discuss in detail both findings also identified in previous literature, as well as novel findings and hypothesis generating results relevant for further research.

4.3. Within- and between-domains associations

We will first address the *within*-domain association identified in our study. We regard the clustering between the symptoms 'recurrent thoughts of death/suicide' and 'feelings of worthlessness' and 'depressive mood' relevant. As most important finding we found no other connections from 'recurrent thoughts of death/suicide' to other symptoms (and domains). This is particularly interesting since – although most studies revealed the contribution of depressive symptoms on suicidality (Karvonen et al., 2007; Schwartz and Cohen, 2001) – previous research has also described a correlation between positive symptoms and suicidality (i.e. command auditory hallucinations leading to suicidality; Kjelby et al., 2015). Recently, a study using Structural Equation Modeling (SEM) to investigate the influence of depressive and positive symptoms on suicidal ideation (Bornheimer, 2016), reported that symptoms of depression predicted suicidal ideation. In addition, positive symptoms were found to moderate the relationship between depression and suicidality (i.e., an increase in positive symptoms was leading to 'an increase in the estimated effect of symptoms of depression on suicidal ideation'). Our results support the important role of depressive symptoms on suicidal ideation, since there were no connections from 'recurrent thoughts of death/suicide' to other non-depressive symptoms. Furthermore, we showed that there was no direct relationship between delusional symptoms and recurrent thoughts of death/suicide', but instead, delusional symptoms seem to activate depressive symptoms and via this pathway influenced suicidal thoughts. Of note, based on our cross-sectional design, no clear causal relationship can be inferred (see limitations). Nevertheless, our findings underline the importance of interconnectedness between symptoms, which as hypothesis generating results can guide future research (e.g., interventions in these hypothesized pathways).

Regarding *between* domains associations, we found several symptoms connecting different domains. These associations are important as 'bridge symptoms' (Borsboom and Cramer, 2013) and are assumed to play an important role in maintaining and linking psychopathology. Of note, such bridge symptoms cannot be identified by studies using factor analytic approaches. Specifically, bridge symptoms connect

Table 3
The number of connections within and between a-priori defined symptom domains.

	Manic syndrome (MS)	Major depressive syndrome (MD)	Delusions (DL)	Hallu-cinations (HA)	Bizarre behavior (BB)	Formal thought disorder (FTD)	Avolition (AP)	Anhedonia (AS)	Inattention (AT)	Catatonic motor behavior (CMB)	Alogia (AL)	Affective flattening or blunting (AF)	Inappropiate affect (IA)
Manic Syndrome (MS) (%)	**14/28 (50)**												
Major depressive syndrome (MD) (%)	2/112 (1.8)	**38/91 (41.8)**											
Delusions (DL) (%)	1/96 (1)	1/168 (0.6)	**29/66 (43.9)**										
Hallu-cinations (HA) (%)	0/48 (0)	0/84 (0)	17/72 (23.6)	**10/15 (66.7)**									
Bizarre Behavior (BB) (%)	0/32 (0)	0/56 (0)	2/48 (4.2)	0/24 (0)	**1/6 (16.7)**								
Formal Thought Disorder (FTD) (%)	1/72 (1.4)	0/126 (0)	5/108 (4.6)	0/54 (0)	4/36 (11.1)	**24/36 (66.7)**							
Avolition (AP) (%)	0/24 (0)	7/42 (16.7)	1/36 (2.8)	0/18 (0)	1/12 (8.3)	1/27 (3.7)	**1/3 (33.3)**						
Anhedonia (AS) (%)	0/32 (0)	7/56 (12.5)	3/48 (6.2)	0/24 (0)	0/16 (0)	0/36 (0)	5/12 (41.7)	**5/6 (83.3)**					
Inattention (AT) (%)	0/16 (0)	1/28 (3.6)	0/24 (0)	0/12 (0)	0/8 (0)	1/18 (5.6)	2/6 (33.3)	2/8 (25)	**1/1 (100)**				
Catatonic motor behavior (CMB) (%)	1/40 (0)	1/70 (1.4)	0/60 (0)	0/30 (0)	0/20 (0)	0/45 (0)	0/15 (0)	0/20 (0)	0/10 (0)	**4/10 (40)**			
Alogia (AL) (%)	0/40 (0)	1/70 (1.4)	1/60 (1.7)	0/30 (0)	0/20 (0)	8/45 (17.8)	2/15 (13.3)	1/20 (5)	5/10 (50)	3/25 (12)	**7/10 (70)**		
Affective flattening or blunting (AF) (%)	0/48 (0)	2/84 (2.4)	0/72 (0)	0/36 (0)	0/24 (0)	0/54 (0)	3/18 (16.7)	2/24 (8.3)	3/12 (25)	8/30 (26.7)	8/30 (26.7)	**14/15 (93.3)**	
Inappropriate affect (IA) (%)	0/8 (0)	0/14 (0)	0/12 (0)	0/6 (0)	1/4 (25)	1/9 (11.1)	1/3 (33.3)	0/4 (0)	0/2 (0)	0/5 (0)	3/5 (60)	1/6 (16.7)	**0/0 (−)**

Overview of the number of connections between and within a priori defined symptom domains relative to the maximum number of possible connections. The maximum number of connections *within* domains can be computed as follows: suppose domain x has *Sx* number of symptoms, then the maximum number of connections within this domain equals *Sx* (*Sx*–1)/2. The maximum number of connections *between* domains can be calculated by multiplying the number of symptoms from one domain to the number of symptoms of the other domain. In bold the *within* - domain associations.

different domains within a network and thus, the activation of these bridge symptom might spread the activation towards other domains. For instance, in our network 'grandiose delusion' was associated with 'inflated self esteem', indicating that manic patients suffering from 'grandiose delusion' may be more likely to develop other delusional symptoms or vise versa (a patient who has 'grandiose delusions' may be 'at risk' to develop manic symptoms).

Furthermore, our centrality analyses revealed symptoms, which had more *within* and *between* connections compared to other symptoms and are therefore more *important* to the network. Central symptoms are for instance 'loss of interest and pleasure', 'inability to enjoy recreational interest in activities' and 'inability to form or maintain relationships with friends'. From a clinical perspective, these are recognizable, important symptoms since they determine the active social participation of patients. Symptoms with high centrality measures are known as 'hubs' and could be important for guiding treatment interventions. In the way that these symptoms are well connected to other symptoms, intervening on these hubs might have more "downstream consequences" in the network, e.g. reducing the co-occurrence of other symptoms. Nevertheless, we would like to stress that these findings are hypotheses generating, and the application of these ideas in clinical practice need to be demonstrated in well-designed trials.

4.4. From depressive to delusional symptoms

A recent developed technique of the network approach is the use of shortest pathway analysis. Shortest pathway analysis is a hypothesis generating technique that allows for the investigation of potential pathways and mediating items accounting for the associations between symptoms (Isvoranu et al., 2017). Here we investigated pathways between the depressive and delusional symptom domains, as previous research identified that depressive symptoms are a central part of a psychotic episode (An Der Heiden et al., 2005; Birchwood et al., 2000) and argued this association should be more thoroughly investigated. Our results indicate that the cluster 'anhedonia-asociality', together with the symptom 'persecutory delusions' plays a central role in this association between depressive and delusional symptoms. This might indicate that patients suffering from persecutory delusions are more likely to develop symptoms of anhedonia and as a result develop depressive symptoms or vice versa (i.e., depressed patients, probably those more vulnerable to psychosis, may first develop symptoms of anhedonia, which may then lead to persecutory delusions and trigger the activation of other delusional symptoms). Of note, the fact that the domain anhedonia is involved within the shortest paths from delusion to depressive symptoms might be due to a conceptual overlap between depression

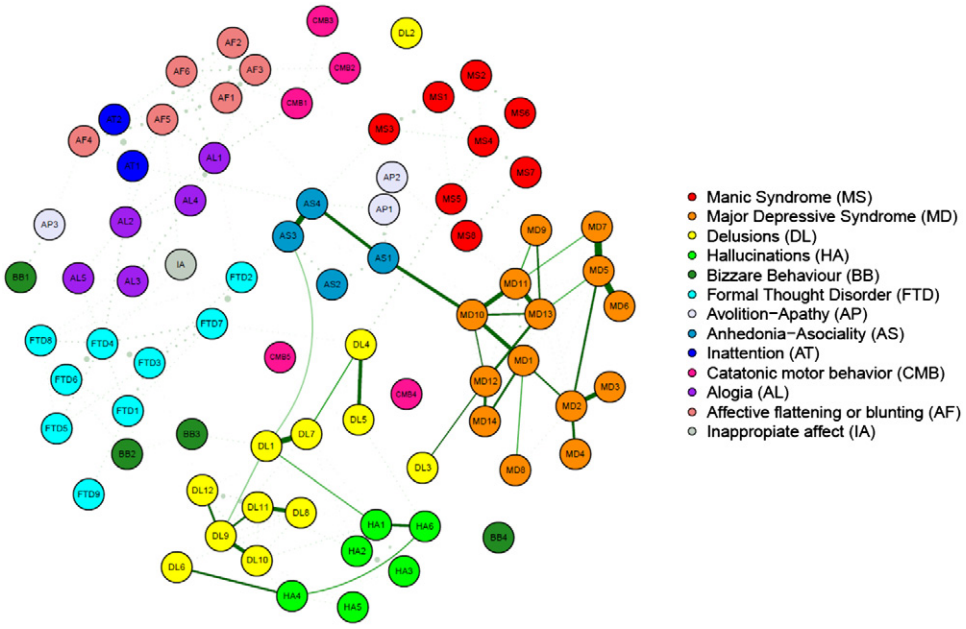

Fig. 2. Shortest pathways between depression and delusional symptoms. Network illustrating the shortest pathways between the depressive domain and delusional symptoms. Thicker lines represent stronger connections.

and anhedonia. Given the cross-sectional design of our study, which does not allow for causal inferences, these pathways are – as previously emphasized – hypothesis-generating pathways that should be investigated in future confirmatory research studies.

4.5. In light of previous (network) studies

We believe our study adds on to a recent network study, which was conducted within a more narrow perspective, with a focus on the negative symptoms domain rather than on a wider spectrum of symptoms (Levine and Leucht, 2016). The authors grouped symptoms assessed with the Scale for the Assessment of Negative Symptoms (SANS), in four 'symptom groups' namely: lack of interest, poor responsiveness, apathy-inattentiveness and affect. Of note, the negative items of the SANS are incorporated in the CASH. Broadly, the symptom groups 'affect' (including items 'inability to enjoy recreational interest and activities', 'loss of sexual interest and activity', 'ability to feel intimacy and closeness' and 'inability to form or maintain relationships with friends') and 'lack of interest' (including items 'monotone facial expression', 'paucity of expressive gestures', 'poor eye contact', 'affective non-responsivity' and 'lack of intonation') are also 'recognizable' in our network, but not the other two domains. We therefore argue that taking into consideration a wider range of symptoms may yield results otherwise not identified, as it allows for the interaction of between-domains items, which may themselves form new domain clusters. It may thus be beneficial to evaluate associations between domains rather than only at a single construct. Corroborative with this idea, Isvoranu et al. (2016) recently showed that there is no direct relation between childhood trauma and positive or negative psychotic symptoms, but that this relation is only mediated by general psychopathology symptoms when these are included within a network.

Our findings can also be interpreted within the earlier proposed concept of the 'transdiagnostic dimension of psychosis'(van Os, 2015). Van Os and colleagues stated that an absolute focus on distinguishing illness (i.e., between 'psychotic' versus 'non-psychotic') hinders clinical practice and research, since co-occurring symptoms are not taken into account. For example, a delusional patient might suffer from depressive symptoms while not meeting criteria for a depressive episode. However these co-occurring symptoms (e.g., depressive symptoms) might have important implications for treatment interventions and the persistence of psychopathology. Moreover, our findings also underline the results of the Bipolar and Schizophrenia Network for Intermediate Phenotypes (B-SNIP) study: a large cohort study that investigated patients with psychosis, family members of these patients and healthy controls (Tamminga et al., 2014). Three distinct 'biotypes' of psychosis were identified that did not respect traditional clinical diagnosis boundaries (Clementz et al., 2016). Thus, although in different domains, our findings are in line with this report, suggesting that new approaches towards diagnostic categories should be embraced and might be contributing to our understanding of schizophrenia. By using unconventional statistical approaches, we might be able to find more (data–driven) etiological models of mental disorders.

5. Limitations

With the relatively recent development and introduction of network analyses in psychiatry, many points of discussion remain, which are also applicable to this study. At first, a general criticism of networks concerns their replicability (Fried and Cramer, 2016). The first approach needed to improve network reproducibility is by estimating and publishing the stability of the networks. Although future studies are needed to prove generalizability of network models, the stability check of our network showed a relatively stable network (Supplementary material, Fig. S1–S3) (Epskamp et al., 2016). Second, we cannot rule out any bias due to the proportion of subjects who were excluded from analyses due to missing items. Nevertheless, imputation strategies are considered inappropriate for network analysis, since they are presumed to rely on associations between different symptoms. Therefore, imputation techniques will unquestionably bias the generated network model. Third, the naturalistic cross–sectional design does not permit to elucidate the possible effects of different pharmacological or other treatments on the symptomatology. Since 86% of the patients used different psychopharmacological agents, with highly variable duration and dosage the stratification of network-topology for treatment versus no treatment of different drugs was not feasible. Fourth, given the relatively low number of included female patients we were not able to construct a network for female patients, which would allow for gender comparison, as gender differences in symptomatology are now well established (Hill, 2016; Leung and Chue, 2000; Morgan et al., 2008). In line with this limitation we were unable to construct different subnetworks to assess the

influence of important clinical characteristics (e.g., (extrapyramidal) side effects, age at onset of psychosis and/or total illness duration). Further network studies in larger groups should evaluate potential interactions of symptoms networks with relevant clinical variables. Fifth, based on the included symptoms of the CASH we generated the present symptom network, however including different items from other assessment instruments may generate a different network (Fried and Cramer, 2016). Although the CASH is a widely used questionnaire including a wide variety of symptoms and validated in patients with psychotic disorders, the results should be interpreted with caution. Finally, as mentioned before, the cross-sectional design of the current study makes it impossible to investigate causal interactions between symptoms. Measuring symptoms within short time intervals as in Experience Sampling Method (ESM) studies are promising (Wigman et al., 2015). Future studies may add to our findings by investigating the individualized networks of symptoms and their (causal) changes over time within the psychosis spectrum.

6. Conclusion

In summary, the network structure we identified in the current study shows that individual psychotic symptoms are meaningfully related to each other. Our results support the overall structure indicated by previous factor-analysis based symptom domains, while in addition we described relations and interactions between the symptoms themselves. Investigating the network-topology may inform further research of etiology, course of illness and ultimately treatment selection.

Contributors

Geeske van Rooijen (GvR) and Carin Meijer (CM) performed the literature search. Adela–Maria Isvoranu and Claudia D. van Borkulo undertook the network analysis. GvR wrote the complete first draft of the manuscript. CM, Henricus G. Ruhé, Lieuwe de Haan revised the manuscript. All authors, including the GROUP investigators, approved the manuscript in its present form.

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Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.02.018.

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