Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

A state-independent network of depressive, negative and positive symptoms in male patients with schizophrenia spectrum disorders

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ARTICLE INFO

Article history:
Received 30 May 2017
Received in revised form 14 July 2017
Accepted 15 July 2017
Available online xxxx

Keywords:
Depressive symptoms
Positive symptoms
Negative symptoms
Schizophrenia
Network comparison testNetwork analysis

ABSTRACT

Depressive symptoms occur frequently in patients with schizophrenia. Several factor analytical studies investigated the associations between positive, negative and depressive symptoms and reported difficulties differentiating between these symptom domains. Here, we argue that a network approach may offer insights into these associations, by exploring interrelations between symptoms. The aims of current study were to I) construct a network of positive, negative and depressive symptoms in male patients with schizophrenia to investigate interactions between individual symptoms; II) identify the most central symptoms within this network and III) examine group-level differences in network connectivity between remitted and non–remitted patients.

We computed a network of depressive, positive and negative symptoms in a sample of 470 male patients diagnosed with a psychotic disorder. Depressive symptoms were assessed with the Calgary Depression Rating Scale for Schizophrenia, while psychotic symptoms were assessed with the Positive and Negative Syndrome Scale. Networks of male patients who fulfilled remission criteria (Andreasen et al., 2005) and non–remitters for psychosis were compared.

Our results indicate that depressive symptoms are mostly associated with suicidality and may act as moderator between psychotic symptoms and suicidality. In addition, 'depressed mood', 'observed depression', 'poor rapport', 'stereotyped thinking' and 'delusions' were central symptoms within the network. Finally, although remitted male patients had a similar network structure compared to non-remitters the networks differed significantly in terms of global strength. In conclusion, clinical symptoms of schizophrenia were linked in a stable way, independent of symptomatic remission while the number of connections appears to be dependent on remission status.

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http://dx.doi.org/10.1016/j.schres.2017.07.035
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Please cite this article as: van Rooijen, G., et al., A state-independent network of depressive, negative and positive symptoms in male patients with schizophrenia spectrum disorders, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.07.035

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1. Introduction

Patients with schizophrenia may present with a wide variety of symptoms: positive and negative symptoms are considered core features of schizophrenia, but depressive symptoms are also common, with a modal prevalence rate of 25% (Buckley et al., 2009; Siris, 2000). In order to study the associations between symptoms, a network approach might be advantageous - in comparison to traditional factor-analytic approaches, network models offer the possibility to study potential interactions between individual symptoms (Borsboom, 2017; Borsboom and Cramer, 2013). Specifically, within a network perspective, it is presumed that mental health problems result from complex interactions between individual symptoms, which influence and reinforce each other, instead of originating from an underlying latent disorder (Borsboom and Cramer, 2013).

In the past years the network approach has been increasingly applied to study psychopathology ((Isvoranu et al., 2016; Isvoranu et al., 2017; van Rooijen et al., 2017); for a review see (Fried et al., 2016)). For instance, Wigman and colleagues (2015) showed that the networks of individuals with a psychiatric diagnosis contained positive feedback loops, which may explain a 'downward spiral of negative mental states', which are clinically recognizable in the way symptoms of psychosis can enhance each other. Isvoranu et al. (2017) have moved beyond symptom-symptom associations, integrating environmental risk factors into network models; they found that childhood trauma was associated with symptoms of general psychopathology and not directly to positive or negative symptoms. The network approach is therefore not bound to 'traditional' diagnostic categories – psychopathology is conceptualized as a complex system and the 'overlap' between symptoms and risk factors of different disorders is a source of valuable information rather than a problem to overcome.

Notably, a recent network paper using the baseline symptoms of the 'Genetic Risk and Outcome of Psychosis' (GROUP) study (Korver-Nieberg et al., 2012) showed that in male patients with schizophrenia the symptoms assessed by the Comprehensive Assessment of Symptoms and History (CASH; (Andreasen et al., 1992)) displayed strong within-and between- cluster interactions and formed a network with central symptoms such as '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' (van Rooijen et al., 2017). Central symptoms have been argued to be relevant as targets for treatment interventions, as these symptoms are most likely to influence the other symptoms in the network. In addition, relations between suicidality, depressive and positive symptoms were investigated and based on the strong associations between depressive symptoms and suicidality and between delusional and depressive symptoms, but in the absence of a direct relationship between delusional symptoms and suicidality, it was hypothesized that delusional symptoms may activate depressive symptoms and influence suicidal thoughts via this pathway.

However, the CASH is limited in addressing current depressive symptoms, since within the CASH the DSM-IV criteria are investigated; these are known to show overlap with other symptoms in patients with schizophrenia (i.e., negative and extrapyramidal side effects; (Siris, 2000)). We therefore aimed to expand on the previous study and investigate the association between positive, negative and depressive symptoms further by constructing a network model that includes the Calgary Depression Rating Scale for Schizophrenia (CDSS; (Addington et al., 1990)), which is a validated instrument for assessing depression in patients diagnosed with schizophrenia (Lako et al., 2012). The CDSS was administered at first follow-up. We combined data from the CDSS and the Positive and Negative Syndrome Scale (PANSS; (Kay et al., 1987)) assessed at follow-up. In addition, the latter questionnaire was used to assess psychotic remission status. A previous study in depression showed that different severity symptom networks in depressed patients (at baseline) were associated with varying illness courses (van Borkulo et al., 2015). In order to apply this type of profiling, first the stability (i.e., state-independence) of a network structure is required. However, this has not been investigated in patients with schizophrenia and was therefore the secondary aim of this study.

In summary, network analysis has been shown to help disentangle the interactions between individual symptoms of a disorder and as such we have employed this methodology in the current study in order to investigate the association between psychosis and depressive symptoms. The aims of current study were as follows: I) to construct a network of symptoms in male patients with a schizophrenia spectrum disorder in order to investigate how negative, positive and depressive symptoms interact, by using a validated questionnaires to asses depressive symptoms; II) to identify the most central symptoms within this network and III) to examine potential group-level differences in network connectivity between remitted and non–remitted patients. This might reveal important profiling information for prognosis.

2. Methods

2.1. Subjects

Data was collected as part of the longitudinal multicentre GROUP study, described in detail elsewhere (Korver-Nieberg et al., 2012). Here we used data from a GROUP subsample, consisting of male patients with non-affective psychotic disorders, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; (American Psychiatric Association, 2000)). Of note, we chose to include *only* male patients, given the known gender differences in symptomatology and the relatively small number of included female patients in GROUP (Hill, 2016; Morgan et al., 2008). Measurements of the GROUP study were collected at baseline, at 3 and 6-year follow-up. Because the CDSS was obtained in a large subsample at 3-year follow-up, we used data from this wave only.

2.2. Symptom assessment

The CDSS (Addington et al., 1990) was used to assess depressive symptoms. The CDSS is a nine-item structured interview, in which every item is rated on a scale ranging from 0 (absent) to 3 (severe) (Supplementary Table S1). The PANSS (Kay et al., 1987) was used to measure the severity of positive and negative symptoms. The PANSS consists of 30 items (Supplementary Table S1) in which each item is scored on a scale ranging from 1 (absent) to 7 (extreme) and it is divided into three subscales: positive, negative and general psychopathology (e.g., depression, anxiety and somatic concern) symptoms. The general psychopathology subscale was not included in our network, since inclusion of this subscale would have created a substantial overlap between with the items of the CDSS. In addition, we used the Andreasen et al. remission criteria (Andreasen et al., 2005) to assess whether a patient was in symptomatic remission at the time of assessment (i.e., during the second assessment of the GROUP-cohort). The Andreasen criteria constitute a symptom severity and a time criterion. The symptom severity criterion was determined by a score of 3 or lower on all of the following items: P1 (delusions), P2 (disorganization), P3 (hallucinatory behavior), G5 (mannerisms/posturing), G9 (unusual thought content), N1 (blunted affect), N4 (passive social withdrawal), and N6 (lack of spontaneity). For the time criterion we assessed whether a symptomatic remission had been maintained for 6 months or longer prior to the time of assessment (i.e., 6 months before the assessment).

2.3. Statistical analysis

2.3.1. Network construction

We constructed a symptom network as previously described (Borsboom and Cramer, 2013; Epskamp et al., 2017; van Rooijen et al., 2017) of positive, negative and depressive symptoms. In the generated

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