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Identifying a system of predominant negative symptoms: Network analysis of three randomized clinical trials

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ABSTRACT

Background: Reasons for the recent mixed success of research into negative symptoms may be informed by conceptualizing negative symptoms as a system that is identifiable from network analysis. We aimed to identify: (I) negative symptom systems; (I) central negative symptoms within each system; and (III) differences between the systems, based on network analysis of negative symptoms for baseline, endpoint and change.
Methods: Patients with chronic schizophrenia and predominant negative symptoms participated in three clinical trials that compared placebo and amisulpride to 60 days (n = 487). Networks analyses were computed from the Scale for the Assessment of Negative Symptoms (SANS) scores for baseline and endpoint for severity, and estimated change based on mixed models. Central symptoms to each network were identified. The networks were contrasted for connectivity with permutation tests.
Results: Network analysis showed that the baseline and endpoint symptom severity systems formed symptom groups of Affect, Poor responsiveness, Lack of interest, and Apathy-inattentiveness. The baseline and endpoint networks did not significantly differ in terms of connectivity, but both significantly ($P < 0.05$) differed to the change network. In the change network the apathy-inattentiveness symptom group split into three other groups. The most central symptoms were Decreased Spontaneous Movements at baseline and endpoint, and Poverty of Speech for estimated change.
Conclusions: Results provide preliminary evidence for: (I) a replicable negative symptom severity system; and (II) symptoms with high centrality (e.g., Decreased Spontaneous Movement), that may be future treatment targets following replication to ensure the curent results generalize to other samples.

1. Introduction

Since Kraepelin's historic portrayal of the destruction of the personality (Kraepelin, 1971), negative symptoms have been considered as central to schizophrenia. Negative symptoms are associated with deficits in cognitive, social and real-world functioning (Bowie et al., 2006; Harvey et al., 2006; Kirkpatrick et al., 2006), and are more relevant to functioning than positive symptoms (Rabinowitz et al., 2012). Despite being relevant to functioning in schizophrenia, meta-analysis has established that second-generation antipsychotic medications have efficacy in the treatment of positive and not negative symptoms of schizophrenia disorder (Leucht et al., 2009). Furthermore, at present no treatment for negative symptoms has attained the clinically significant improvement threshold (Fusar-Poli et al., 2015). The inefficacy of medication to treat negative symptoms led to a NIMH-MATRICS expert consensus group statement on negative symptoms (Alphs, 2006; Kirkpatrick et al., 2006; Kirkpatrick and Fischer, 2006; Marder et al., 2011). That group has, for instance, highlighted methodological and assessment limitations in clinical trials of negative symptoms (Kirkpatrick et al., 2006). Despite consensus surrounding negative symptoms, subsequent treatment initiatives for negative symptoms have failed to demonstrate efficacy (e.g., biopertine, mGlu2/3). One reason for the mixed success of these initiatives may be the conceptualization, measurement and derivation of treatment targets for negative symptoms.

Generally to conceptualize and understand the nature of negative symptoms studies have used factor analysis. For instance, factor analytic studies have examined Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983) since it is the most widely used and approved negative symptom measure (Kirkpatrick et al., 2006). In theory, the SANS is comprised of five a priori symptom factors (i.e., symptom clusters) of affective flattening, alogia, avolition, anhedonia. However, factor analytic studies that examine the nature of negative symptoms provide inconsistent results. Studies have identified that the SANS comprises of two (Toomey et al., 1997), three (Keefe et al., 1992; Kelley et al., 1999; Levine and Leucht, 2013b; Mueser et al., 1994; Sayers et al., 1996), four (Rabany et al., 2011), and five (Peralta et al., 1995) different

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symptom factor structures (i.e., co-varying symptom clusters). Hence there appears to be a lack of consistent identification of the nature of negative symptoms.

Existing understanding and hence identification of treatment targets for negative symptoms may be elaborated on beyond factor analysis by using network analysis for several reasons. We summarize the key differences between network and factor analyses in Table 1. First, in factor analysis an unmeasured (i.e., implicit or technically 'latent') symptom factor 'causes' the associations among the observed symptom rating scores. Seen this way, for example, a proclivity to inattentiveness implicit symptom factor 'causes' the SANS symptoms of test and social inattentiveness. It is noted that the proclivity to inattentiveness is not measured per se, rather it is an explicit latent variable in factor analysis. Unlike factor analysis, network analysis considers negative symptoms as a system. Seen this way, for example, test and social disturbances group together. The association between two symptoms cannot be attributed to another symptom, but they may be legitimately associated with some of the remaining negative symptoms. Second, factor analysis cannot ascertain which of the negative symptoms are central. This is in contrast to network analysis where the extent to which a negative symptom connects with the remaining symptoms in the network varies both by the number and magnitude of connections with the other negative symptoms in the system. This conceptualization of negative symptoms as a network is reminiscent to current notions regarding connectivity between brain circuits in neuropsychiatry.

To understand the negative symptom system we apply network analysis to baseline, endpoint and change SANS items in three clinical trials of predominant negative symptoms. We aim to identify negative symptom networks, the most central negative symptoms within each symptom network, and differences between networks.

2. Materials and methods

2.1. Participants

Patients (n = 437) were participants in three double-blind randomized placebo-controlled clinical trials that compared amisulpride with placebo for the treatment of predominant negative symptoms (Boyer et al., 1995; Danion et al., 1999; Loo et al., 1997). The trials: used similar symptom selection criteria, randomized participants to placebo or amisulpride, had similar diagnostic groups (i.e., absence of early onset), used the Scale for the Assessment of Negative Symptoms (SANS) to assess negative symptoms (Andreasen, 1983) and had similar visit schedules.

Across the three trials most participants were male (65.3% n = 318), and had a mean age of 34.04 (SD = 9.4). Each trial may be described as follows - (1) a multicenter trial, symptom inclusion thresholds of ≥75 SANS & ≤60 SAPS, diagnoses of disorganized, catatonic, undifferentiated and residual schizophrenia, and a 6-week washout phase (12-week if neuroleptics were received) followed by a six-week trial with randomization to placebo (n = 34) or amisulpride (n = 80) (Boyer et al., 1995); (ii) a multicenter multinational trial, symptom inclusion thresholds of > = 60 SANS & < = 50 SAPS, diagnoses of residual schizophrenia, and a 4-week washout period followed by randomization for 12 weeks to amisulpride (n = 159) or placebo (n = 83) (Danion et al., 1999); and (iii) a multicenter trial, symptom inclusion thresholds of ≥SANS & ≤50 SAPS, diagnoses of subchronic or chronic schizophrenia, and entering the trial directly for 24 weeks randomized to amisulpride (n = 69) or placebo (n = 72) (Loo et al., 1997). The trial protocols are documented in the primary efficacy studies (Boyer et al., 1995; Danion et al., 1999; Loo et al., 1997). Furthermore, the trials have been pooled and reanalyzed elsewhere (Levine and Leucht, 2012, 2013a, 2014).

2.2. Analytic approach

To prepare for network analysis the 20 SANS (items without global and subjective ratings like prior research) (Kelley et al., 1999) were extracted at baseline and endpoint. To examine change in clinical trials, prior studies of the PANSS (Marder et al., 1997; Marques et al., 2014) and SANS (Levine and Leucht, 2013b) have computed symptom change scores in various ways. These have included factor analysis of endpoint severity or change (i.e., improvement) scores. However, these approaches to change are dissimilar to how total change scores are analyzed during clinical trials. In clinical trials, estimated total change (i.e., improvement) is calculated with Mixed Models for Repeated Measures (MMRM) adjusted by baseline and treatment. To closely resemble the way change scores are computed in clinical trials, we computed estimated change scores (coded as improvement) for each SANS item from MMRM, adjusting for baseline and treatment (Furukawa et al., 2015). Next, network analyses were computed for baseline, endpoint and estimated change SANS items separately.

Standard guidelines (Costantini et al., 2015) were followed to compute network analysis with the qgraph package (Borsboom et al., 2011; van Borkulo et al., 2015a) in R (Core R Team, 2014). qgraph has been used in psychiatric research (Fried et al., 2015; Kossakowski et al., 2015; van Borkulo et al., 2015b) and to examine stress in schizophrenia (Clamor et al., 2015). The qgraph package has not been used longitudinally in clinical trials, or to examine the negative symptoms of schizophrenia. Negative symptom networks of the SANS items were derived from partial polychoric correlations with the glasso (i.e., lasso) procedure that adjusts for false positive 'edges' (i.e. symptom connections) (Epskamp et al., 2012). The use of partial correlations means any connection between two symptoms cannot be attributed to any other symptom.

The magnitudes of the contribution by each symptom to each network were assessed with centrality indices (Newman and Girvan, 2004). Although centrality indices are highly correlated, for comprehensiveness we reported the centrality indices of strength, betweenness and closeness. Closeness centrality indexes how near a focal symptom is to others and is computed as the inverse of the sum of the distances (i.e., length of the shortest paths between symptoms) of the focal symptom from all other symptoms in the network (i.e., the swiftness to arrive at a focal symptom). Betweenness centrality is the proportion of shortest paths between a two symptoms that transverse the focal symptom of interest. Betweenness values of zero mean that the given symptom is not found on the shortest pathway between two other symptoms; whereas values exceeding zero have short paths that

Table 1
Factor and network analysis contrasted.

Difference	Factor analysis	Network analysis
Formulation	Hierarchical symptom structure	System of interrelating symptoms
Symptom structure	A latent variable termed a 'factor' is at the apex. Observed symptoms are arranged below	By partial correlations between observed symptoms. Two symptoms are correlated, and that correlation cannot be due to a third symptom
Symptom level interpretation	Each symptom has a 'loading' ranging from −1 to 1. Loadings determine the extent that the factor effects the symptom	Each symptom has a degree of 'centrality'. Centrality indexes the extent that each symptom is fundamental to the symptom network
Symptom cluster interpretation	Imply *latent* factor name from how symptoms load on each factor	Examine how *observed* symptoms group in the network
Example	Hallucinations and delusions are correlated due to the latent positive factor that is not directly measured	Hallucinations and delusions are correlated irrespective of the manner in which they correlate with other symptoms

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