The Interrelations between Symptoms and Cognitive Impairments in Schizophrenia: a network analysis

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Summary

Background: Psychiatric research investigating the neural correlations and causes of psychopathological symptoms have produced very limited results. Potential interrelations among symptoms and other factors, such as cognition, might aid to unravel the complex nature of symptoms. Employing a psychometric network model, the current paper has three exploratory aims; 1) to explore the difference in interconnections of cognitive functions between healthy control subjects and first-episode schizophrenic patients, 2) to inspect the interconnections of symptoms in patients, and 3) to investigate the interrelations between symptoms and cognitive impairment in schizophrenic patients.

Methods: The analyses applied psychiatric data from patients at the Danish OPUS-clinic, diagnosed with first-episode schizophrenia (ICD-10), and matched healthy control subjects. Four weighted partial correlation networks were estimated using GGM graphical LASSO implementing EBIC selection. Network structures were assessed according to global properties of connectedness and local properties of individual nodes and edges. Stability and robustness of network estimates were evaluated.

Results: Results revealed a cluster formation of the cognitive domains *Verbal memory, Verbal fluency, Working memory,* and *Processing speed* in the network of schizophrenic patients, which was not present in the control network. Aim 2 suggested that most symptoms were related to each other, while no symptoms formed clusters of particularly strong correlations. Results of aim 3 indicated that symptoms exhibited strong correlations to each other, as did cognitive functions, while correlations across the two domains were weaker, but frequent.

Conclusion: The results suggested that symptoms and cognitive impairments convey information on distinct aspects of schizophrenia. The two domains were not embedded in clusters of close interrelations, rather, they were spatially separate with many relatively weak correlations between specific symptoms and cognitive functions. Thus, while cognitive impairments seem to be able to explain some aspects of the symptoms (or vice versa), they cannot alone account for the complexity of symptoms. Cognitive impairments seem to provide additional information on the pathological nature of mental disorders, not inherent in the symptoms.

Keywords: *psychometric networks, network analyses, psychopathology, schizophrenia, symptoms, cognitive impairment*

GitHub Repository:
https://github.com/Solvej94/The-interrelations-between-symtoms-and-cognitive-impairment-in-scizophrenia-a-network-analysis.git

Introduction

The traditional approach in psychiatric assessment of mental disorders is grounded in the idea that psychological symptoms reflect the existence of a particular underlying pathology. Because a mental disorder is associated with particular symptoms, all assumed to be caused by one latent variable, it is rationalized that these can be employed in the identification of the disorder. This implies, that removing the common cause will result in total symptom remission (Micoulaud-Franchi et al., 2018). However, decades of research attempting to identify the neural biomarkers causing the symptoms of mental disorders, have resulted in very limited results. While biological and genetic correlates of several symptoms have been implicated (e.g., Kim et al., 2011), these findings have not yet been able to explain the occurrence of mental disorders through neuropsychological pathways (Borsboom et al., 2018). The lack of knowledge regarding psychopathological symptoms is evident in the prevalent discrepancy across rating scales of a given disorder (Fried et al., 2017; Fried, 2017). Further, the manifestation of mental disorders are commonly found to vary both across patients and according to the sociocultural context (Boschloo, 2015; Berrios, 2013; Wakefield, 1992). Such variation might be an effect of the use of sum-scores as the standard method of diagnostics; severals scholars argue, that aggregated symptom scores lead to massive loss of information, because each individual symptom play a unique role in the disorder (Fried & Nesse, 2015; Boschloo, 2015). Thus, in such approach, two patients displaying different symptoms might be diagnosed with the same disorder, causing conceptual heterogeneity in disorder manifestations. Opposite, the symptoms displayed by one patient can lead to the identification and diagnosis of several disorders too. This phenomenon, termed comorbidity, is a highly common finding in psychiatric practice, and has been described as the rule rather than the exception (Borsboom et al., 2011). The phenomenon clarifies the challenges of identifying a particular disorder based on symptoms. Further, the latent variable model struggles to explain the commonly found downstream effects among symptoms, in which changes in one symptom can alter another (Beard et al., 2016). If symptoms of a particular disorder were caused by a common cause, only the removal of this cause would lead to symptom remission. Hence, the lack of empirical evidence on the biological correlates of disorder categories, as well as the challenges posed by common clinical findings, suggest that the nature of symptoms might be more complex than what can be explained by a common underlying pathology. Investigations beyond the identification of neural substrates seem necessary to understand the nature of psychopathological symptoms.

Conceptualizing mental disorders as networks

An alternative approach has been suggested to provide solutions for some of the core problems in the latent variable model. Daniel Borsboom (2008) introduced the Network model to psychopathology. Taking a holistic approach, it understands mental disorders as complex systems of interacting symptoms. According to the network approach, symptoms are not reflective of one underlying pathological cause, rather, the interactions between symptoms causes the emergence of the disorder, and are thus constitutive of it (McNally, 2016; Borsboom et al., 2018). The general idea is that activation of one symptom will spread to others through a symptom network, and such propagating activation causes symptom co-occurrence. This does not indicate that the model neglects the existence of neural correlates (which underlie all human behaviour), just that several neural substrates might be implicated in a disorder rather than just one (Epskamp et al., 2016). Take cancer as an analogy; while cancer is identified with a tumour, which does not necessarily cause symptoms, one can hardly imagine depression without symptoms (Borsboom et al., 2018). According to the network approach, symptoms as *sad mood*, *insomnia* and *anhedonia* are not caused by one entity of "depression", analogous to the tumour, but rather have each their underpinnings, and influence each other causing what we know as depression.

The model has been applied across a wide scope of mental disorders. Major Depressive Disorder (MDD) has been the main target of investigations (e.g. Bringmann et al., 2015; van Borkulo et al., 2015; Cramer et al., 2016; Beard et al., 2016; Fried et al., 2016; Boschloo et al., 2016; van de Leemput et al., 2014), but exploratory investigations have been carried out in other disorders as well, including General Anxiety Disorder (Beard et al., 2016), Social Anxiety Disorder (SAD) (Heeren & McNally, 2016), Bipolar Disorder (Koenders et al., 2015), Obsessive Compulsive Disorder (OCD) (McNally et al., 2017), Autism Spectrum Disorder (ASD) (Ruzzano et al., 2015), Post Traumatic Stress Disorder (PTSD) (McNally et al., 2015; Mitchell et al., 2017) and Schizophrenia (van Kampen, 2014). Additionally, a few studies have made cross diagnostic investigations (e.g. Cramer et al., 2010; Boschloo et al., 2015), concerned with identifiers of comorbidity. Applying network models have revealed important insights about the relations of symptoms in mental disorders (for a review see: Fried et al., 2017).

Unfolding the implications of psychometric networks

The conceptualization of mental disorders as interconnected networks allows us to exploit insights from the interdisciplinary field of network science, aiming to reconstruct complex systems and consider the interrelations among the components (Borsboom, 2017). Networks have been applied in various contexts including neural connectivity, social relations and financial flow (Barabasi, 2016, p.24).

Network science has roots in physics and rely on graph theory (Barabasi, 2016, p.43). The method is based on the computation of correlation matrices, indicating whether there is a relation between two variables or not ("psychosystems project", 2014). These can further be weighted according to the strength of association. Next the matrix is visualized as a network graph, with a set of nodes (variables) and edges connecting them (associations). In psychometric networks, symptoms are represented as nodes, and edges between them represent causal connections, weighted according to their relative strength . Lastly, one derives descriptive parameters to unravel the complex structure of all interrelated variables, described in detail below.

Psychometric networks are theorized to be scale-free networks. These are governed by a series of principle laws that determine and limit the behaviour of a system, largely resulting from its distribution of node connections, called the degree distribution (Barabasi & Albert, 1999). The degree distribution displays the probability that a randomly selected node in the network has a given number of connections. In a scale-free network the degree-distribution conform to a power law. It follows from the power law that few nodes are highly connected, and the vast majority have a smaller degree than average. Networks with this property are in effect held together by a few highly connected nodes. Contrary, a random network follows a poisson distribution, since the probability of two nodes being connected is constant. Thus, in a random network the degree of most nodes are in the narrow vicinity of the mean, while few are highly connected or hardly connected at all. In effect of the scale-free structure, any two nodes are likely to be connected by a relatively short path of other nodes, seeing the central nodes strengthen the overall connectedness of the system. This is termed the small-world property, and is characteristic of scale free networks differentiating it from the random network (Barabasi, 2016, p.113). Hence, given psychometric networks are scale-free, activity will spread fast from one symptom to another.

Further, the scale free networks have high clustering of nodes (i.e. how many of the neighbours to a node are interconnected themselves), compared to random networks, as consequence of the organizing principles (Barabasi, 2013). This entails that scale-free networks become resilient to random decay of nodes, which will not affect the overall network structure. The network structure will only change significantly, if a highly connected node is attacked deliberately. In random networks on the other hand, no matter which nodes are attacked, the network may fragmentize rather fast. In psychometric networks this means, one must target specific and highly central symptoms in order to disrupt the activation flow. A symptom is central if it: has strong connections to other symptoms

(strength); is closely connected to all other symptoms (closeness); and/or if it mediates other symptoms (betweenness). Last, we may inspect clusters of the network, in order to gain information on which symptoms are most dependent on each other. A symptom with high clustering has well connected neighbours, meaning it can have great influence, while it is also redundant and unimportant to the overall flow of the network. Descriptive measures will inform us of the network flow and functioning in different prospects. Initial activation of a highly central symptom will lead to more efficient spread than activation of peripheral symptoms (Fried et al., 2016. A highly connected network will spread activity more rapidly than a loosely connected one. High clustering in the network, will result in self-sustaining loops, causing prolonged symptom activation (Borsboom, 2017). In effect of these structural aspects, a stable state will form, wherein the patient is stuck. This signifies the difference between a mental health state and a disorder state, rather than absence of symptoms.

The network approach seek to explain common findings in clinical psychology including heterogeneity of patients, high comorbidity rates and downstream effects. Heterogeneity could arise due to differences in individual symptom networks (Fried et al., 2017). It may be under dispositional influence, expressed through neurobiological dysfunction causing networks to activate and sustain more easily; similar effects can emerge from the temporal influence of factors such as stress. Comorbidity emerges because symptoms associated with different disorders function as bridging-nodes which activate several disorder categories (Borsboom et al., 2011). Downstream effects occur in consequence of the interrelations amongst symptoms. Breaking the self-sustaining loop effect by exploiting such downstream, may lead to symptom remission (Borsboom, 2017). Generally, we must understand the intricate network behind the symptom system, to best interpret and alter the behavior of it.

Cognition in schizophrenia

The structure of psychometric networks may allow investigation of complex interactions beyond symptoms. This is highly interesting as psychopathological research pay increasing attention to the relationship between symptoms and other factors. Several scholars have suggested that symptoms are highly correlated with genetical, environmental, emotional, and neurocognitive domains (e.g., Fried and Cramer, 2017; Hoorelbeke et al., 2016; Boschloo et al., 2015; Isvorano et al., 2016). Particularly the influence and role of cognitive functioning in psychopathology has been studied. Cognitive dysfunction has been found to be a core feature of various mental disorders, including Major Depression Disorder (MDD) (Ladegaard et al., 2016; Lam et al., 2014), Schizophrenia (Bliksted et al., 2018; Medalia & Lim, 2004; Nuechterlein et al., 2004), Bipolar Disorder (Dere et al., 2010; Wolf et al., 2010; Kurtz and Gerraty, 2009), Autism Spectrum Disorder (ASD) (Robinson et al., 2009; Baron-Cohen

and Belmonte, 2005; Hill and Frith, 2003), Attentional Deficit Hyperactivity Disorder (ADHD) (Uekermann et al., 2010; Vaidya and Stollstorff, 2008), Obsessive-Compulsive Disorder (OCD) (Sayin et al., 2010; Burdick et al., 2008), and Post Traumatic Stress Disorder (PTSD) (Liberzon & Sripada, 2008; Castaneda et al., 2008). Particularly interesting findings have been reported on the relationship between cognitive impairment and symptoms in schizophrenia. Schizophrenia is characterized by psychotic symptoms causing disturbances in thought, perception and behaviour (American Psychiatric Association, 2013). The symptoms are divided into negative symptoms, composing decreased functionality in the given domain (e.g., alogia, anhedonia, and apathy), and positive symptoms, reflecting psychological features which were not present in the premorbid mental stage (e.g., hallucinations and delusions). Further, seven major domains of cognitive impairments implicated in schizophrenia, have been identified by the MATRICS (Treatment Research to Improve Cognition in Schizophrenia) initiative, including 1) *speed of processing*, 2) *attention/vigilance,* 3) *working memory*, 4) *verbal learning and memory*, 5) *visual learning and memory*, 6) *reasoning and problem solving*, and 7) *social cognition* (for details see: Nuechterlein, 2004; Green et al., 2004). A large body of research has identified a correlation between these cognitive domains and both positive symptoms (Frith & Corcoran, 1996; Moritz & Woodward, 2007; Penn et al., 2008) and negative symptoms (Strassnig et al., 2015; August et al., 2012) of schizophrenia. Negative symptoms have been found to correlate particularly with social cognitive abilities, and social cognitive impairment has subsequently been suggested to mediate the relationship between negative symptoms and functional outcomes in schizophrenic patients (Bowie and Harvey, 2006). Positive symptoms have been suggested to be mediated by dysfunctions in the prefrontal cortex (PFC), including cognitive functions as attention, working memory, and executive function (Thompson et al., 2004; Corcoran et al., 2003). This relationship has been explained through the dopamine hypothesis, stating that abnormalities in the dopamine (DA) response system cause disruptions in the crucial selection of relevant stimuli. Such disruptions are theorized to cause dysfunction of information processing abilities in the PFC, contributing to positive symptoms as hallucinations and delusions. Thus, the suggested causal relationship between the positive symptoms and the DA response system, might be mediated through cognitive dysfunctions in the PFC. Such interactions may profitably be investigated utilizing the structure of psychometric networks.

The current study

The current study explored the network structure of symptoms and cognitive impairments of schizophrenia, in terms of interconnection of nodes and potential cluster formations. The analysis had three aims; 1) to explore the differences in interrelations among the cognitive domains in patients compared to controls, 2) to establish the structural organization of symptoms in first-episode

schizophrenic patients, and 3) to investigate the extent and organization of relations between symptoms and cognitive impairments. Aim 1 was assessed computing two weighted networks of cognitive functioning; one for schizophrenic patients and one for healthy control subjects. Comparison of network structures and centrality indices across the two networks, allowed inspection of the most apparent differences in correlations of cognitive domains, between control subjects and patients. Strong differences might reveal which cognitive domains best reflect general impairments in schizophrenia. The organization of cognitive domains provided a baseline for aim 3. To assess aim 2, a weighted network of symptoms observed in the patient group was computed. This allowed for the establishment of intercorrelations among symptoms, and provided a baseline for aim 3. Aim 3 was assessed by the estimation of a weighted network integrating nodes of both symptoms and cognitive domains. Based on the network structures of aim 1 and 2, it is possible to inspect the way in which structures in the cognition network integrates with structures of the symptom network. The emergence of strongly interrelated clusters of symptoms and cognitive domains could either indicate a general impairment domain of schizophrenia exploiting both psychological and cognitive mechanisms, or that nodes of one domain mediate connections within the other (Borsboom et al., 2011). Contrary, if symptoms and cognitive domains are mostly separated in the emergent network structure, it would indicate that the two constructs convey rather different information and are less likely to be influenced by each other, i.e., they constitute two, at least partially, independent dimensions of schizophrenia . In this case, cross-domain connections between the two dimensions, would indicate that while symptoms and cognition are related to each other, one domain (e.g., cognition) does not mediate the connections within the other (e.g., between two symptoms).

Symptoms and cognitive domains were represented as nodes in the networks, while correlations among two nodes are represented by edges connecting them. Small-world property (smallworldness index) and degree distribution was measured to assess the structural type of the network. Smallworldness measures the ratio between global clustering coefficient and average shortest path length. A value above 3 indicates a small-world property, while a value between 1 and 3 suggest a borderline small-world property (Constantini et al., 2015). Degree-distribution describes the probability that a randomly selected node in the network has a given number of connections.

For exploration of the general structure and connectedness of the network, three global properties were measured; 1) mean edge weight, 2) global clustering coefficient, and 3) mean shortest path length. Mean edge weight is defined as the mean correlation weight across all edges, and provides information about the general connection strength of the network, i.e., the global tendency of nodes

to be correlated with each other (Barabasi, 2016, p. 43). The global clustering coefficient, often termed transitivity, is defined as the total number of closed triplets, i.e., three nodes which are all interconnected, divided by the possible amount of triplets in the network. Thus, it measures the probability that two nodes who share a neighbour are connected themselves for the entire network (Constantini et al., 2015). Mean shortest path length is defined as the average of the shortest path between each pair of nodes in the network. In a weighted network, the shortest paths are quantified by the sum of the inverse weights of edges on the path. Thus, it serves as an indication of the speed with which activation will spread through the network (Barabasi, 2016, p. 43).

To assess the influence and role of individual nodes in the general information flow, three centrality indices were implemented; strength, closeness, and betweenness (Constantini et al., 2015). For all three centrality measures, a larger index indicates more importance of the target node. Strength centrality is a generalization of degree centrality, employed in weighted networks. Degree centrality describes the number of connections a given node has, while strength is computed as the absolute sum of a node's connection weights. Hence, strength centrality informs about the extent to which a node can influence, or be influenced by, other nodes in the network directly. Closeness centrality measures the tendency of one node, to be influenced by, or influence, any other node in the network, either directly through its connections, or indirectly through the connections of other nodes. When the shortest distance between the node of interest and any other node in the network is calculated, closeness is defined as the inverse sum of these distances. Betweenness centrality defines the number of times the shortest path between any pair of nodes in the network, passes through the target node. Thus, the removal of a betweenness central node is will generally increase path lengths between other nodes in the network, leading to reduced efficiency of information flow.

Psychiatric networks are estimated directly from the data and often include many variables, which increase the risk of overfitting. In effect the network become error prone to sampling variation, and psychometric networks should thus be estimated from large sample sizes (Epskamp et al., 2018). However, psychiatric data is often limited and network analysis is therefore conducted on smaller datasets than desirable. This is particularly true in the current study. Therefore, the applied model takes a conversative approach in network selection, attempting to reduce the risk of false positives. Further, thorough assessment of network accuracy and stability was conducted prior to interpretation.

Methods

Data collection

Data was obtained from three different studies, each assessing cognitive function and symptom severity of schizophrenic patients and healthy controls subjects (Bliksted et al., 2014; Bliksted et al., 2018; unpublished). All patients were diagnosed with first-episode schizophrenia according to ICD-10, and had received antipsychotic medication for less than three months prior to the diagnostic interview. Healthy control subjects were matched one-to-one with patients according to age, gender, ethnicity, handedness, educational level, community of residence and parental socio-economic status. Exclusion criteria for patients and control subjects were identical in all three studies.

Data preparation

Since data was collected from three independent studies, different measures were obtained for different subjects. In order to compare networks, we included only patients who were tested on all cognitive measures and clinical symptoms. Likewise, only control subjects assessed on all cognitive measures were included. This reduced the total number of observations from 264 to 175. Four cognitive measures assessed general IQ, and were excluded due to topological content overlap with the remaining cognition variables. The clinical symptoms included 47 different questions, divided into 8 subdomains each associated with a global score. To keep the number of variables at a minimum and maintain statistical power, we included only the global scores of each symptom domain. Further, three cognitive measures were excluded, as they were obtained on only a fourth of the data, and the inclusion of these variables would eliminate 75% of the observations. Lastly, since network models rely on correlation matrices, variables must contain a certain amount of variation in order to reliably inform network estimations. Therefore, we included only variables having more than 10 non-zero values. All variables met this criteria.

Participants

Following data cleanup, the dataset contained 175 subjects, of which 88 were patients and 87 were control subjects. Patients had a mean age of 23.5 (SD = 3.6) ranging from 18 to 33 years of age. The mean age of controls was 23.5 (SD = 3.9) ranging from 18 to 34 years of age. The patient group consisted of 35 females, while control subjects consisted of 36 females. Patients had a mean length of education of 12.9 years (SD = 2.7) ranging from 11 to 19 years, while the average length of education for controls were 14.6 years (SD = 2.5) ranging from 9 to 23 years.

Measurements

The resulting data included 16 variables, of which 8 constituted clinical symptoms, while 8 concerned cognitive assessment.

Symptom scores were assessed using the PSE-Interview (Present State Examination, ICD-10) and included 1) *affective flattening,* 2) *alogia*, 3) *avolition-apathy*, 4) *anhedonia-asociality*, 5) *hallucinations*, 6) *delusions*, 7) *bizarre behaviour,* and 8) *formal thought disorder* (World Health Organization, 2014). The first four symptoms are categorized as negative symptoms, while the last four are categorized as positive symptoms. All variables are measured on a scale from 0-5, with 0 indicating absence of the symptom and 5 indicating severe symptoms. *Affective flattening* is a global score of 7 questions assessing the level of appropriate affection manifested in facial expressions, social interaction and gestures. *Alogia* reflects the global score of 4 questions assessing poverty of speech, speech content, blocking and latency of response in conversations. *Avolition-Apathy* constitute the aggregated score of 3 questions concerning hygiene, impersistence at work or school and lack of physical energy. *Anhedonia-Asociality* measures the global score of 4 questions, assessing the ability to feel intimacy and maintain close relationships, sexual activity and general interest in recreational activities. *Hallucinations* compose the global score of 6 questions concerning both auditory, visual, olfactory, somatic and tactile hallucinations. *Delusions* assesses 12 questions regarding delusions of different character, such as emotional delusions (e.g., of guilt or jealousy), religious delusions, delusions of being controlled or of mind reading, and somatic delusions. *Bizarre behaviour* combines the score of 4 questions assessing clothing and appearance, social and sexual behaviour, and aggressive, repetitive, or stereotyped behaviour. *Formal thought disorder* express the global score of 7 questions concerning aspects of abnormal thought processes, such as incoherence, tangentiality, derailment, illogicality and circumstantiality.

Cognitive measurements included 1) *verbal memory*, 2) *working memory*, 3) *motor function*, 4) *verbal fluency*, 5) *processing speed,* 6) *executive functions*, 7) *intentionality*, and 8) *appropriateness* scores. The first six measurements were obtained from the Brief Assessment of Cognition (BACS) test; a newly developed tool for assessment of cognitive dysfunction in schizophrenia, yielding high reliability and validity (Keefe et al., 2004). Higher scores are associated with better function. *Verbal memory* is based on a list learning task, in which participants are presented with 15 words and asked to recall as many as possible. *Working memory* is assessed through a digit sequencing task, measuring the ability of subjects to recall clusters of numbers in the correct order of which they are presented. The clusters presented varies in length. *Motor function* measures motor speed, and is based on a token motor task,

in which subjects are to place 100 plastic tokens, two at a time, into a container as fast a possible. *Verbal fluency* is based on two tasks. One is a category instances task in which participants are to name as many words as possible of a given category within 60 seconds. The second task is a controlled oral word association test, measuring the number of words subjects produce beginning with a specific letter, within 60 seconds. *Processing speed* assess attention and speed of information processing through a symbol coding task. Subjects are to match the numerals 1-9 to symbols on a response sheet, as quickly as possible for 90 seconds. *Executive functions* is assessed with the Tower of London task, in which subjects are presented with two images showing three balls of different colours placed differently on three pegs. The task is to name the number of times the balls in the first image have to be moved in order to obtain the arrangement on the second image. The last two measures were obtained from the Moving Shapes Paradigm, which is a generally accepted measure of Theory of Mind abilities (Abell et al., 2000). *Intentionality* score was obtained from the Animated Triangles Task, and measures the amount of mental state attributions to moving triangles in the video, through the use of emotional words, mental states and length of phrases. *Appropriateness* score was assessed employing the same task, and measures how accurately the overarching storyline was captured and described in the videos (Bliksted et al., 2014).

Network estimation and selection

Using the R-packages *bootnet* (Epskamp, Borsboom & Fried, 2018) and *qgraph* (Epskamp et al., 2012), we estimated regularized partial correlations implementing glasso with EBIC model selection based on polychoric and pearson correlations. All cognitive variables were numerical, while all symptoms were ordinal variables. This was accounted for by using the function *cor_auto* (qgraph) based on the *Lavaan* function *lavCor* (Rosseel et al., 2018), relying on polychoric correlations of the ordinal variables, and Pearson correlations of numerical variables (Epskamp & Fried, 2018; Epskamp et al., 2018). We estimated networks by applying a Gaussian Graphical Model (GGM), which take the correlation matrix as input (Epskamp et al., 2018). In such a network edges represent partial correlations, as each relationship between two nodes is estimated after controlling for the correlation of all other nodes. The correlations ranged from -1 to 1. As this model estimates a large number of parameters, both for the individual variables and each of their association, it inflates the risk of false positives. Therefore, we implemented a regularizing graphical LASSO (least absolute shrinkage and selection operator), which applies a penalty to each parameter, shrinking them and setting small parameters to exactly zero (Tibshirani, 1996). Thus, the estimation is conservative returning a sparse network. However, controlling for false edges induces the risk of omitting true edges. Therefore, the regularizing lasso is controlled by a tuning parameter, λ (lambda), which decide the penalty degree, and a hyperparameter, γ (gamma), controlling the preference for simple versus complex models

(Epskamp & Fried, 2018). Gamma influences the model selection by minimizing Extended Bayesian Information Criteria (EBIC) in sparse models compared to complex ones. EBIC is a measure of out of sample error, estimating how error prone the model is if applied to new data (Epskamp & Fried, 2018). The higher the gamma value, the more sparse networks are preferred in model selection. The model estimated a collection of 100 networks, with different λ tunings. The network with the lowest EBIC score (corrected by the gamma tuning) was selected. We ran such model estimation with three different γ tunings (0.1; 0.25; 0.5) and chose the tuning that most conservatively returned a connected network.

For visualization we implemented a multi-dimensional scaling (MDS) of networks as suggested by Jones and colleagues (2018), available in the *smacof* package (De Leeuw & Mair, 2011). MDS represent proximities between variables, such that closely related nodes are placed in near distance of each other, while weakly related ones appear further apart. Thereby, the distances between nodes become conceptually interpretable. MDS uses a configuration matrix determining the spatial placement of nodes in a low dimensional space (in our case a two-dimensional space). The configuration matrix is fit on a transformation of the dissimilarity matrix of the network. The method of transformation is chosen from a data driven perspective, where different distributions are fit to the data. Here, data was fitted to ordinal MDS, interval MDS, ratio MDS and spline MDS. The fit of the distribution need to be both parsimonious to avoid overfitting and provide a good fit to the data, avoiding underfitting. To guide the choice of transformation, the MDS distributions are visualized together with data from the dissimilarity matrix. A stress value (ranging from 0-1) is computed, for each distribution, indicating how well the data can be represented in two dimensions; higher values suggest worse fit. In all four networks of the current analysis, ordinal MDS provided the best fit, and this transformation was implemented in the network visualization. The stress value is printed in each plot, indicating how well the data is represented by a two-dimensional space, and thus how interpretable the spatial organization of nodes is.

The global network properties of mean weight, number of nodes, number of edges, and degree distributions were obtained from the *bootnet* package. Global clustering coefficient and average shortest path length were estimated using the *igraph* package (Csárdi & Nepusz, 2006). The smallworldness-index was obtained from the *qgraph* package. Before calculation of the smallworldness value, the function standardizes the global clustering coefficients and average shortest path length, by comparing them to the corresponding values obtained in 100 equivalent random networks, estimated on the same number of observations and degree distribution

(Constantini et al., 2015). The estimates of the target network should be significantly different from those of the sampled networks, in order to reflect a smallworld property. Local node properties of strength-, betweenness-, and closeness centrality were estimated from the *qgraph* package. Clustering coefficients of nodes were obtained from the *igraph* package. Both global and local clustering coefficients were estimated according to the Watts-Strogatz model. Degree distributions of 2500 samples of each network were obtained.

Network accuracy and stability

We investigated sampling variability, to establish the accuracy of edge weights, by estimating the confidence intervals (CI) for each edge. This was done by non-parametric bootstrapping, which sample new data from the multivariate normal distributions of the data. The bootstrap was carried out utilizing the *bootnet* package and computed 2500 samples. Confidence intervals indicate that if the analysis was re-run an infinite number of times, and the data is representative of the true population, then the true value will be within the interval estimates in 95% of all cases (Field, 2012, p. 45). While confidence intervals are usually not enough to interpret whether an edge is significantly different from zero, in this case, the glasso estimation has already shrunk weak edges to exactly zero. Hence, we can cautiously infer that they are different from zero.

To assess the stability of centrality indices we performed a case-dropping subset bootstrap (Epskamp et al., 2018), in which centrality indices are found for subsets of the data. Again, *bootnet* was used to run the analysis on 2500 subsets. For each re-estimate, the bootstrap drops an increasing number of observations. The correlation between the original centrality estimates and the average of those obtained from the bootstrap is estimated. A correlation stability coefficient (CS-coefficients) is calculated for each centrality measure, and express the maximum number of participants that can be dropped while retaining a correlation of estimates of 0.7 with a probability of 95%. CS-coefficients inform about the stability of centrality indices when estimated on less observations, indicating how stable the indices would be when estimated on new datasets. The larger amount of participants that can be dropped while maintaining a high correlation of estimates, the more stable the centrality indices are, and the higher their estimated generalizability to new datasets. Epskamp, Boorsboom and Fried (2018) recommend to only consider centrality indices as stable if the CS-coefficients are above 0.25, and preferably above 0.5.

Lastly, within network comparison of edge-weights and node-centralities, were computed using the above mentioned non-parametric bootstrap. This comparison investigated whether edge weights and node centralities of each node differed significantly from one another. The difference between

measures of two edges or nodes is calculated and the bootstrapped CI of this difference is estimated. Next the differences are tested as a null-hypothesis in which differences are significant if the boostrapped CI does not overlap with zero. If two estimates do not differ significantly from each other, it does not necessarily imply that they are similar. Rather, it indicates that we cannot know whether they are different, and should be cautious when interpreting the results. The difference test is slightly conservative, keeping false positives rates low (type I error), and is thus more prone to underestimating differences than the opposite (Epskamp et al., 2018). Additionally, confidence intervals of node centrality indices were visualized using these bootstrapped results.

Network Comparison

For comparison of the networks of cognition in schizophrenic patients and control subjects, the Network Comparison Test (NCT) was implemented. NCT is a non-parametric permutation-based hypothesis test of the difference of two networks (Van Borkulo et al., 2017). It applies to independent networks, and gaussian data. NCT include three steps; First, it estimates networks and their underlying matrices from each dataset using EBICglasso. Next, participants are randomly rearranged in two groups and networks including matrices are re-estimated. This procedure is repeated 100 times, and the outcome constitute a reference distribution. Lastly, the reference distribution and observed data is evaluated and p-values are obtained.

NCT investigates the invariance of network structure in terms of individual edge weights and global network strength. First, it hypothesizes that the overall network structure is identical across the two populations, i.e., that edge-weight matrices are similar. To test the hypothesis, NCT computes a matrix with absolute differences of edge weights. From this, the maximum norm (M) is measured as the largest difference of the matrix. Finally, random permutation of subgroups leads to a reference distribution of M, which is a baseline of how big the difference would be, if the nodes were randomly reshuffled across networks. The second hypothesis concerns specific edges, and assumes similar edges to be equally strong across networks. To test this, the difference of specific edges (E) are found, and through random permutation we obtain a reference distribution. The third hypothesis test the variance of global strength by assessing the absolute sum of all edges (S) across networks. Again, random permutation across groups is performed, and the reference distribution allows evaluation of the null-hypothesis. Additionally, we plotted a network of the difference matrix visualizing which edges exhibited the largest difference (Bringmann et al., 2013).

Lastly, we report CI overlap of the specific edge weights as well as node strength-centrality indices of each network, implementing the non-parametric bootstrap.

Results

Three aims were assessed, analysing four different networks. Partial correlation networks were estimated using GGM graphical LASSO implementing EBIC selection. All networks were assessed according to their global properties of structure and connectedness, as well as the local indices of correlation strength and centrality. Finally, the accuracy and stability of each network and its associated properties were assessed.

Aim 1: Cognitive functioning in first-episode schizophrenic patients compared to a healthy control group

Control group (Network 1)

Network 1 represents the network structure of cognitive functions in healthy control subjects. It was estimated with a hyperparameter of 0.25. The resulting network (figure 1.a) consisted of 8 nodes and 20 non-zero edges of 28 possible. Degree distribution is plotted in appendix (appendix: figure 1). The mean absolute weight of edges was 0.084. The network had a smallworldness value of 0.98. The global clustering coefficient was 0.68, and the average shortest path length was 1.29. These values were not different from those emerged from a similar random network (0.69 and 1.29, respectively). The stress value is very low indicating that the correlation weight of edges is well represented by the visual distances of the nodes, and can be interpreted with confidence.

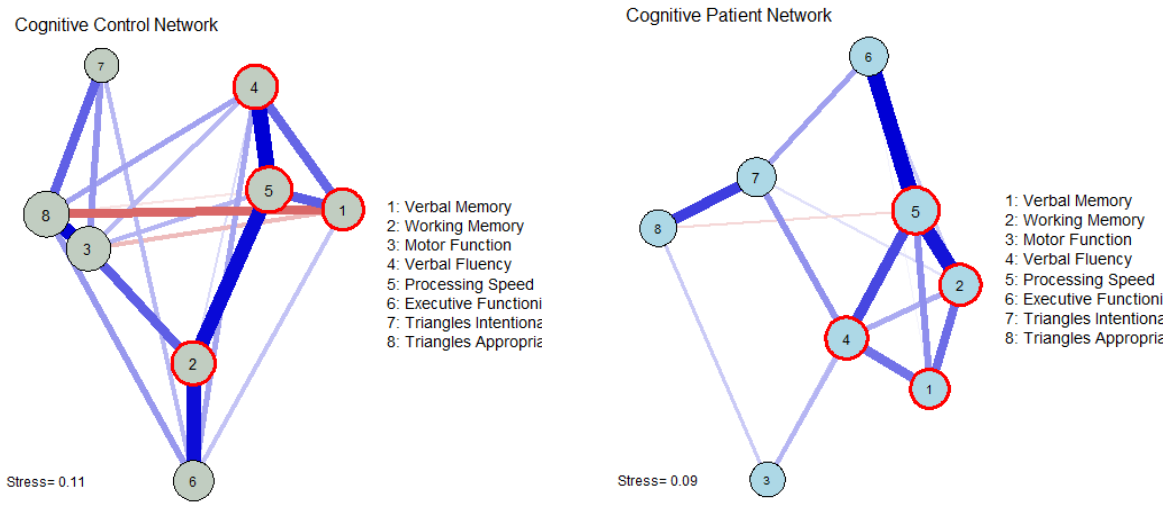

Figure 1: Network of cognitive measures in healthy control subjects (a:left) and first-episode schizophrenic patients (b:right). Nodes represent variables of cognitive function domains. Blue edges represent positive correlations, and red edges represent negative correlations. Larger node sizes represent higher node strength-centrality. Wider edges represent stronger correlations. Nodes marked in red constitute the most prominent difference between the networks.

Inspection of the visual structure of network 1 reveals a rather even distribution of connections among the eight nodes. As indicated by the global clustering coefficient, it seems that most of the nodes are interconnected with each other. Node 1 (Verbal Memory), 4 (Verbal Fluency), and 5 (Processing Speed) appear to form a cluster in which all nodes are interconnected and show high spatial proximity. Further, node 3 (Motor Functioning) and 8 (Triangles Appropriateness) seems to be closely related, as well as node 2 (Working Memory) and 6 (Executive Function). However, connections across these clusters appear equally strong as connections within clusters, and with no clear differences in importance across nodes, immediately apparent. The network contains three negative edges, constituting the connections between node 1 (Verbal Memory) and node 3 (Motor Function), between node 1 and node 8 (Triangles Appropriateness), and between node 5 (Processing Speed) and node 8 (Triangles Appropriateness).

Estimated edge strengths show similar results. The four strongest edges concern the connections between 1) *Verbal fluency* and *Processing speed,* 2) *Motor function* and *Appropriateness,* 3) *Working memory* and *Processing Speed,* and 4) *Working memory* and *Executive function.* Thus, the strongest edges emerge across the entire network. The stability check of edge estimates (figure 2), indicates that sampled edge-weights are very similar to those of the estimated network. However, the CIs of all edges share great overlap, and the bootstrapped difference test showed no significant differences among any of the edges (appendix: figure 2). Hence, weight differences among them cannot be interpreted reliably.

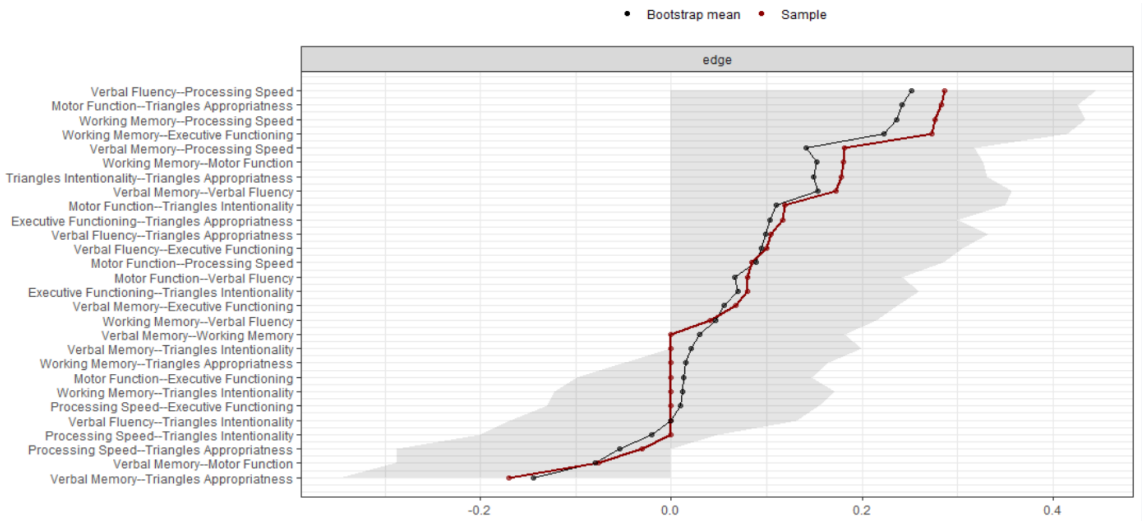

Figure 2: Bootstrapped 95% CIs for edge weights. x-axis represents edge weight values and the associated 95% CI. y-axis represent each edge, and are ordered such that stronger edges are in the top. The black line represents the estimated edge weights of the target network. The red line express edge weights estimated from the 2500 bootstrapped samples.

Node centrality indices are plotted in figure 3a, (appendix: table 1) and indicate that *Processing Speed* is among the most central nodes, revealing the largest betweenness and strength centrality, and the second largest closeness centrality. *Verbal fluency* further appear as highly central being the most closeness-central, and the second most strength-central node. Further, *Intentionality* appears to be the second most betweenness-central while it is not among the most central on other indices. Across all centrality indices *Motor function* and *Appropriateness* consistently appear as the least central. The difference test of centrality indices reveal that none of the nodes are significantly different from each other regarding any of the measures (appendix: 4,5,6). Further, the stability check (figure 4) reveal that all three indices have a CS-coefficient of 0, indicating very poor stability. Confidence intervals of node centrality estimates are plotted in appendix (appendix: figure 12). The nodes of *Intentionality* and *Verbal Fluency* are associated with the largest clustering coefficient, while *Executive function* and *Appropriateness* possess the smallest clustering coefficients (figure 3b; appendix: table 2).

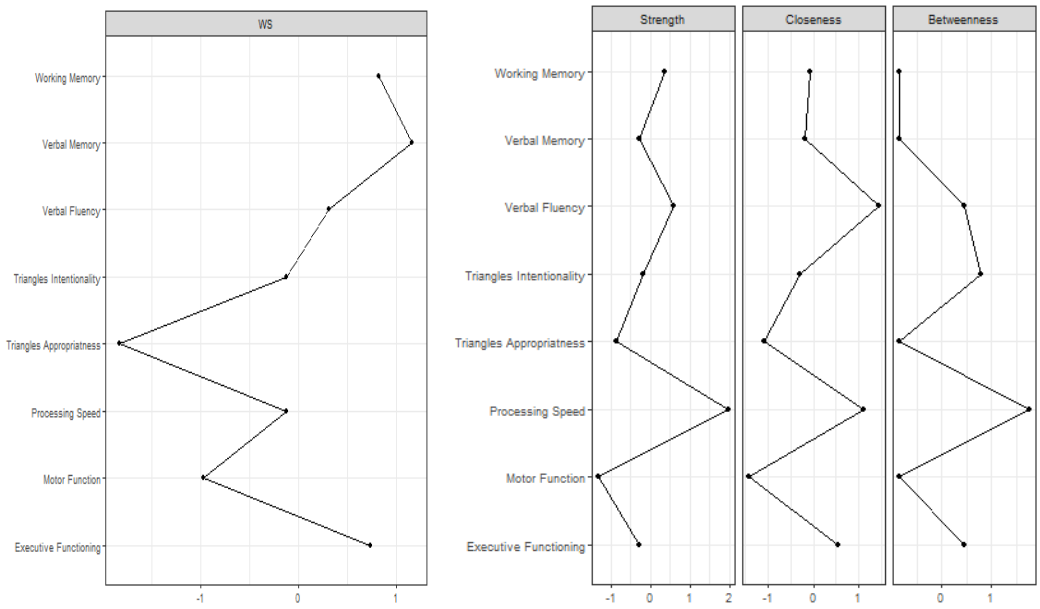

Figure 3: Figure A (left): Node centrality indices for each node. Values are standardized and 0 represents the mean. Figure B (right): Watts-Strogatz clustering coefficient for each node. Values are standardized and 0 represents the mean.

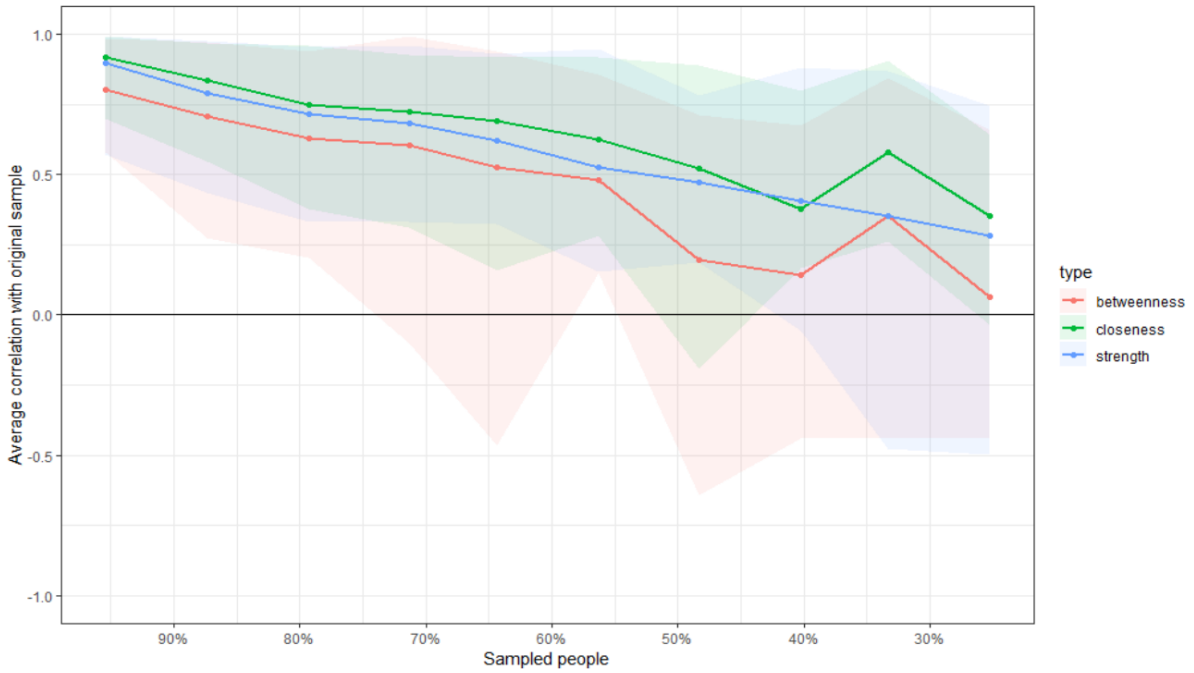

Figure 4: Case-dropping sampled bootstrap assessing robustness of node centrality indices. The x-axis represent the proportion of samples employed in the estimation. The y-axis express the correlation between the bootstrapped centrality values and the original values of the estimated network.

Patient group (Network 2)

Network 2 represents the network structure of cognitive functions in first-episode schizophrenic patients. It was likewise estimated with a hyperparameter value of 0.25. The resulting network (figure 1b) is composed of 8 nodes and 17 non-zero edges of 28 potential edges. Degree distribution is plotted in appendix (appendix: figure 7). The mean absolute weight of edges is 0.095. The network has a smallworldness value of 1.02. The global clustering coefficient is 0.56, and the average shortest path length is 1.39, which are not different from those emerging in a similar random network (0.55 and 1.40, respectively). The stress value is very low indicating that the correlation weight of edges is well represented by the visual distances of the nodes, and can be interpreted with confidence.

The visual organization of network 2 reveal a more differentiated structure than that of network 1. Generally, each node appear to have fewer connections. Further, as indicated by the global clustering coefficient, network 2 is generally less connected than network 1. A clear cluster emerges consisting of node 1 (Verbal Memory), node 2 (Working Memory), node 4 (Verbal Fluency), and node 5 (Processing Speed). Albeit most of these nodes are connected to nodes outside of the cluster, they seem to be particularly interrelated, due to the fact that they are all strongly correlated, and each node has more connections to other symptoms within the cluster than outside the cluster. Further, they show particularly high spatial proximity, compared to the distance from the remaining nodes in the network. Node 6 (Executive Function) appear to be strongly related to this cluster, mediated by

Processing Speed. One negative edge is present, comprising the connection between node 5 (Processing Speed) and node 8 (Triangles Appropriateness).

The accuracy check of edge strength estimates indicate that six edges are particularly strong in the network (figure 5). This concerns the connections between 1) *Processing Speed* and *Executive Function,* and 2) *Working Memory* and *Processing Speed,* 3) *Intentionality* and *Appropriateness,* 4) *Verbal Fluency* and *Processing speed,* 5) *Verbal memory* and *Working memory,* and 6*) Verbal memory* and *verbal fluency*. The bootstrapped CIs of these edges overlap the least with the remaining nodes, hence, they can cautiously be interpreted as stronger than the majority of edges. However, they overlap greatly with each other and weight differences between them cannot be interpreted. The difference test of edge weights showed, that only the first two of these edges differed significantly from most of the remaining edges in weight (appendix: figure 8).

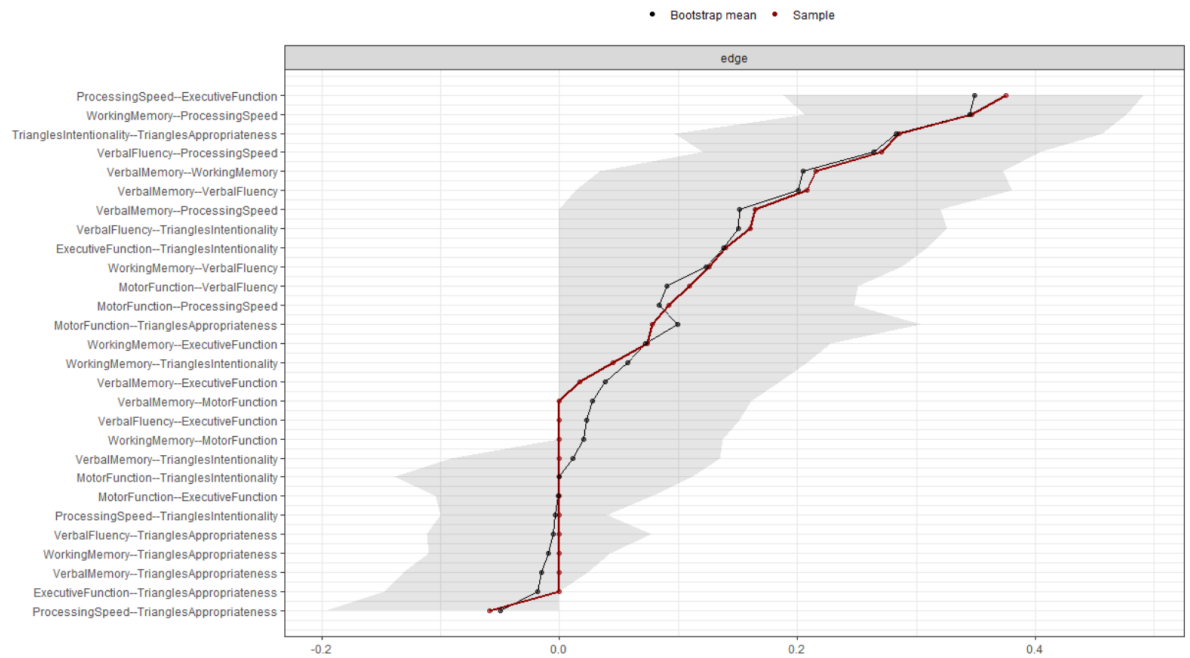

Figure 5: Bootstrapped 95% CIs for edge weights. x-axis represents edge weight values and the associated 95% CI. y-axis represent each edge, and are ordered such that stronger edges are in the top. The black line represents the estimated edge weights of the target network. The red line express edge weights estimated from the 2500 bootstrapped samples.

The stability check of centrality indices revealed a CS-coefficient for betweenness of 0.045. For closeness, the CS-coefficient is 0.205, while it is 0.443 for the strength index (figure 7). Thus, betweenness and closeness have relatively poor stability, while strength indices are stable. *Processing speed* appear to be most central across all three centrality indices (figure 6a; appendix: table 3),

possessing the largest betweenness centrality and strength centrality, and the second largest closeness centrality. Further, *Verbal fluency* appear to be highly central, constituting the largest closeness centrality and the second largest strength centrality. Contrary, *Motor function* and *Appropriateness* consistently appear the least central across all three centrality indices. The difference test of centrality indices for each node, reveal that *Processing speed* and *Verbal fluency* are not significantly different from each other on any of the three centrality indices (appendix: figure 9,10,11). The strength centrality of *Processing speed* is significantly different from that of all other nodes, except for *Working memory. Verbal fluency* is only significantly different in strength from *Motor function,* indicating that *Processing speed* is likely to be the most strength central. On closeness and betweenness indices, *Processing speed* is only significantly different from two other nodes, while *verbal fluency* does not differ significantly from any other nodes. Confidence intervals of node centrality estimates are plotted in appendix (appendix: figure 12). The nodes of *Verbal Memory* and *Working memory* are associated with the largest clustering coefficients (figure 6b; appendix: table 4), while the smallest clustering coefficients are those of *Intentionality* and *Appropriateness.*

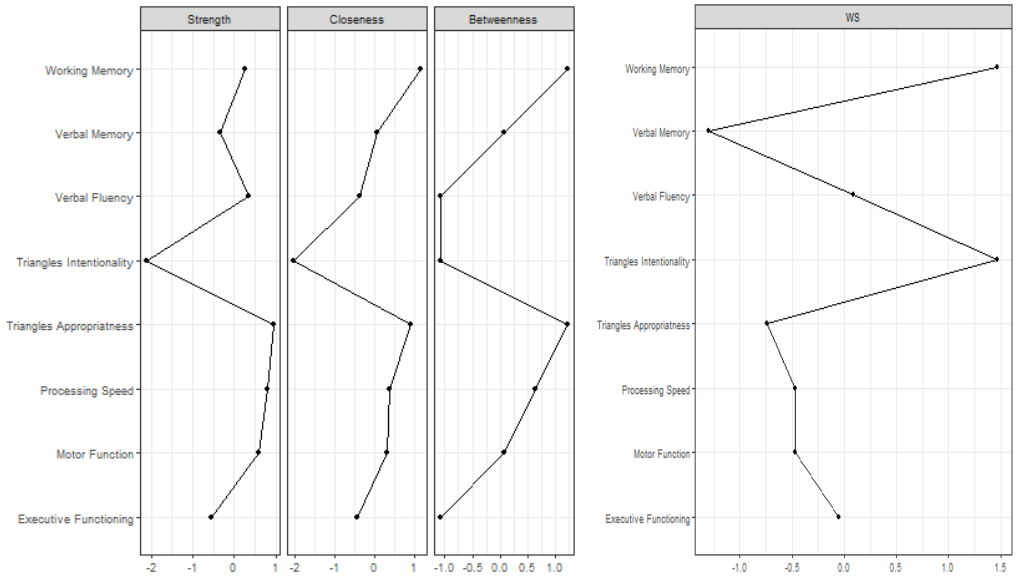

Figure 6: Figure A (left): Node centrality indices for each node. Values are standardized and 0 represents the mean. Figure B (right): Watts-Strogatz clustering coefficient for each node. Values are standardized and 0 represents the mean.

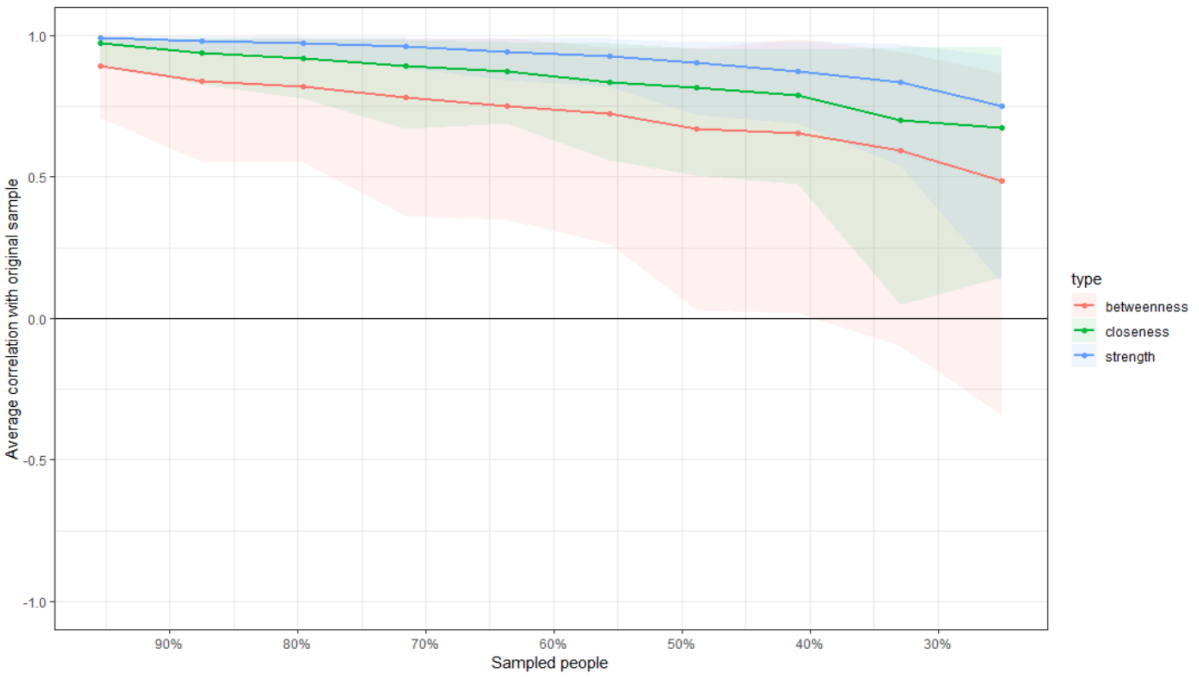

Figure 7: Case-dropping sampled bootstrap assessing robustness of node centrality indices. The x-axis represent the proportion of samples employed in the estimation. The y-axis express the correlation between the bootstrapped centrality values and the original values of the estimated network.

Network comparison of cognitive functioning between a healthy control group and first-episode schizophrenic patients

Figure 8.a visualizes the differences in edges between the networks based on correlation differences. The Network Comparison Test (NCT) yielded no significant difference in the global strength (S) of the two networks ($p > 0.05$). Strength difference (S) estimated by NCT are plotted in appendix (appendix: figure 13). The NCT maximum difference in edge weight (M) showed that one edge changes significantly in weight between the two networks (appendix: figure 14), representing the correlation between *Processing Speed* and *Executive Function.* This edge is significantly stronger in the network of patients than of controls (difference = 0.38, $p < 0.05$). The difference test on this edge (E) is visualized with reference distribution in appendix (appendix: figure 15). The overlap of edge weight CIs between the two networks (figure 8.b), visualizes these differences and similarly yields that only the CIs of the edge between *Processing Speed* and *Executive Function* did not overlap across networks. Contrary, the CIs of the remaining edges overlap, hence, and differences in these connections between networks, cannot be interpreted. The plot further indicates, that estimates of the control network were associated with more uncertainty than those of network 2, given the larger CIs. CI overlap of node strength centrality is presented in appendix (appendix: figure 12), and similarly yields extensive overlap across networks. Thus, we cannot be sure that any of the nodes differ in centrality between networks. Concludingly, the global connectedness of the two networks appear to be highly similar, as do centrality of the nodes across networks. Likewise it seems that edge weights are highly similar, with

only the edge connecting *Processing Speed* and *Executive Function* yielding a significantly stronger correlation in the patient network compared to that of control subjects.

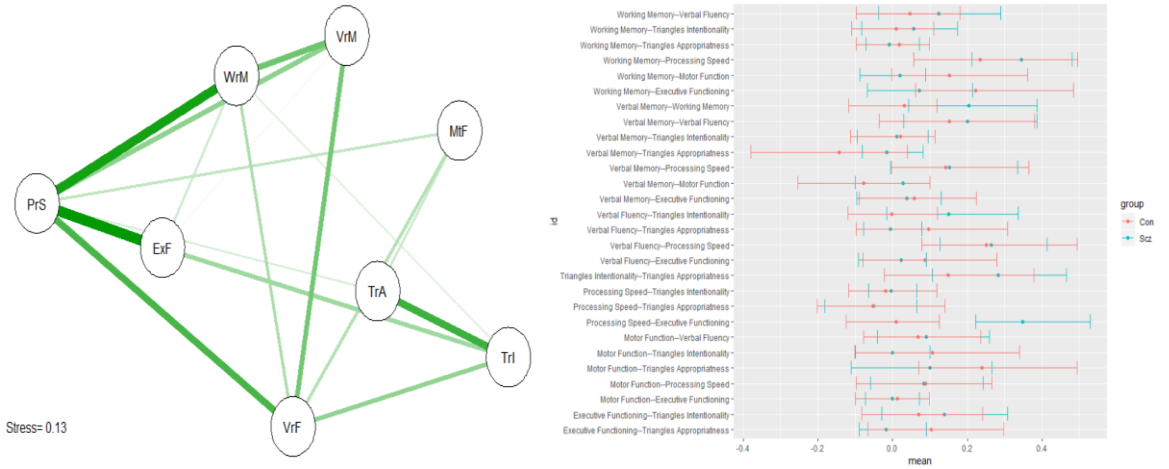

Figure 8: A (left) Correlation network of edge differences (qgraph). Stronger edges represent larger differences between edge weights in network 1 and network 2. B (Right) bootstrapped CI overlap of edge strength between networks

Aim 2: Network structure of symptomatology in first-episode schizophrenic patients

Network 3

Network 3 was estimated employing a hyperparameter of 0.5.[1] The resulting network (figure 9) was composed of 8 nodes and 20 non-zero edges of 28 potential edges. Degree distribution is plotted in appendix (appendix: figure 16). The network had a mean absolute edge weight of 0.092. The smallworldness value of the network was 0.97. The global clustering coefficient was 0.7, and the average shortest path length was 1.29. These estimates were not different from those of similar random networks (0.72 and 1.29, respectively). The stress value is very low indicating that the correlation weight of edges is well represented by the visual distances of the nodes, and can be interpreted with confidence.

[1] The network was also estimated with a hyperparameter of 0.25, as the previous networks, which yielded identical results.

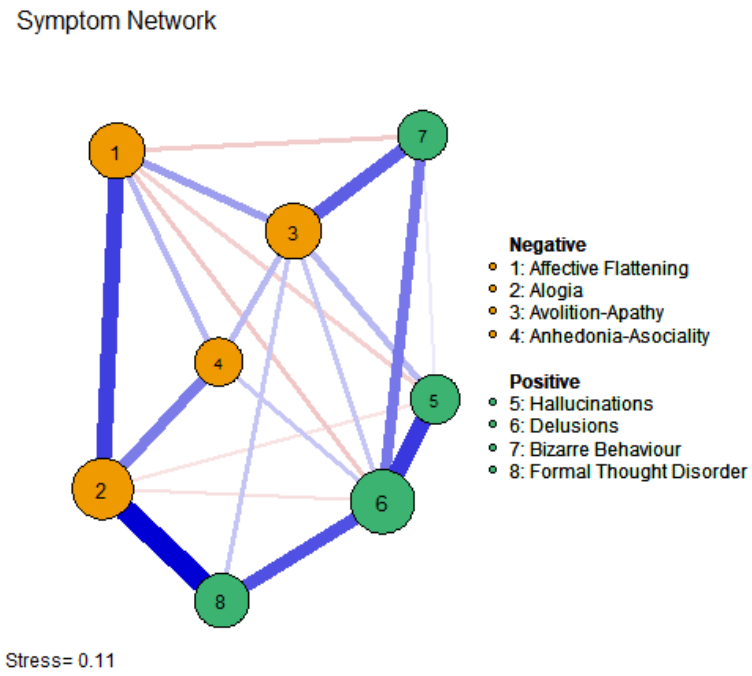

Figure 9: Network of symptoms in first-episode schizophrenia patients. Blue nodes represent positive symptoms. Yellow nodes represent negative symptoms. Blue edges express positive correlations. Red edges express negative correlations. Larger node sizes indicate higher node centrality. Wider edges represent stronger correlations.

Generally, each node in network 3 appears to be connected to most of the remaining nodes in the network, in line with the relatively high global clustering coefficient. The visual organization of the nodes reveal no clear tendency for nodes to form clusters. Nodes appear to be evenly distributed throughout the network, as does the edges between them. However, symptoms are spatially organized according to the symptom category, such that negative symptoms are positioned at the left side, while positive nodes are positioned at the right side. Network 3 contains five negative edges, which all constitute connections between negative and positive symptoms.

The bootstrapped 95% CIs reveal that the estimated edge weights are relatively stable, as they align nicely with those of the samples (figure 10). Confidence intervals of one edge does not include 0, and represents the connection between *Alogia* and *Formal thought disorder.* This edge further appears to be the strongest in the network. However, the CIs of this edge overlap with the majority of the remaining edges in the network, and can only cautiously be interpreted as stronger. The difference test (appendix: figure 17) similarly reveals that this edge is the only one differing significantly from other edges in the network. This edge appear to be reliably stronger than at least six other edges, while we cannot interpret the weight differences concerning the remaining edges reliably.

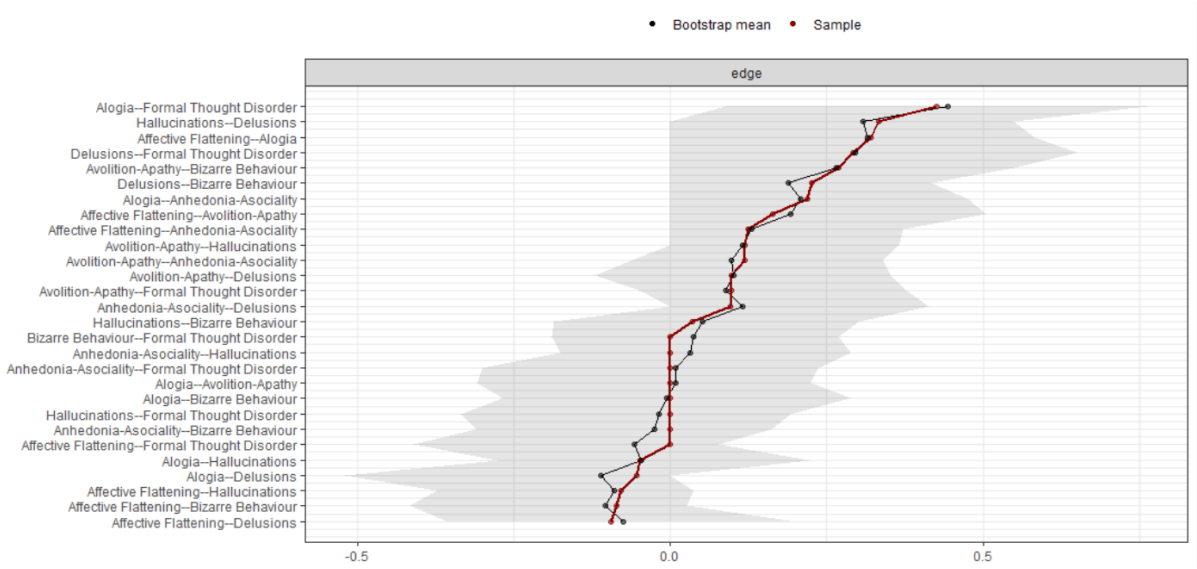

Figure 10: Bootstrapped 95% CIs for edge weights. x-axis represents edge weight values and the associated 95% CI. y-axis represent each edge, and are ordered such that stronger edges are in the top. The black line represents the estimated edge weights of the target network. The red line express edge weights estimated from the 2500 bootstrapped samples.

Across all three node centrality indices, the nodes of *Alogia* and *Delusions* are most central, with *Delusions* being slightly more strength-central (figure 11a; appendix: table 5). Further, *Formal thought disorder* appears to be the most closeness-central and is equally betweenness-central as the two above, while it is not among the most strength-central. *Avolition-Apathy* is among the three most strength-central, while it is weakly closeness- and betweenness central. *Hallucinations* is among the least central across all three indices, while *Anhedonia-Asociality* is the least betweenness- and closeness-central, and *Affective flattening* is the least strength-central. The difference test of centrality indices reveal that none of the nodes differ significantly from each other on neither of the indices (appendix: figure 19,20,21). CIs of node centrality estimates are plotted in appendix (appendix: figure 18). According to the stability check, both betweenness and strength indices has a CS-coefficient of 0, while it is 0.045 for closeness (figure 12). Thus, all centrality indices show poor stability. The nodes possessing the largest clustering coefficient are *Anhedonia-Asociality* and *Hallucinations*, while *Alogia* and *Formal thought disorder* show the smallest clustering coefficients (figure 11b; appendix: table 6).

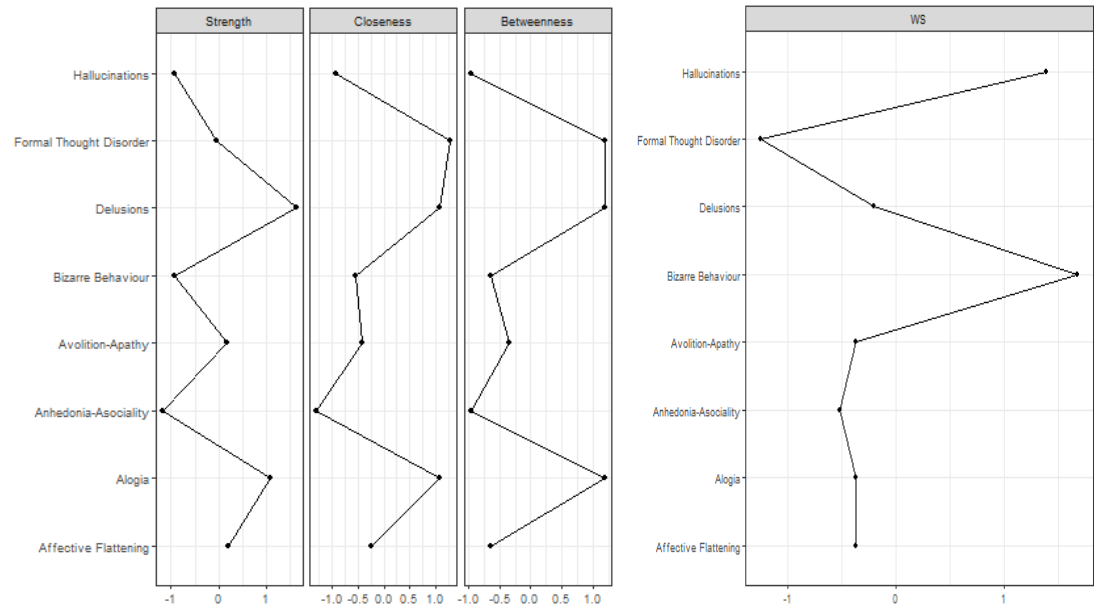

Figure 11: Figure A (left): Node centrality indices for each node. Values are standardized and 0 represents the mean. Figure B (right): Watts-Strogatz clustering coefficient for each node. Values are standardized and 0 represents the mean.

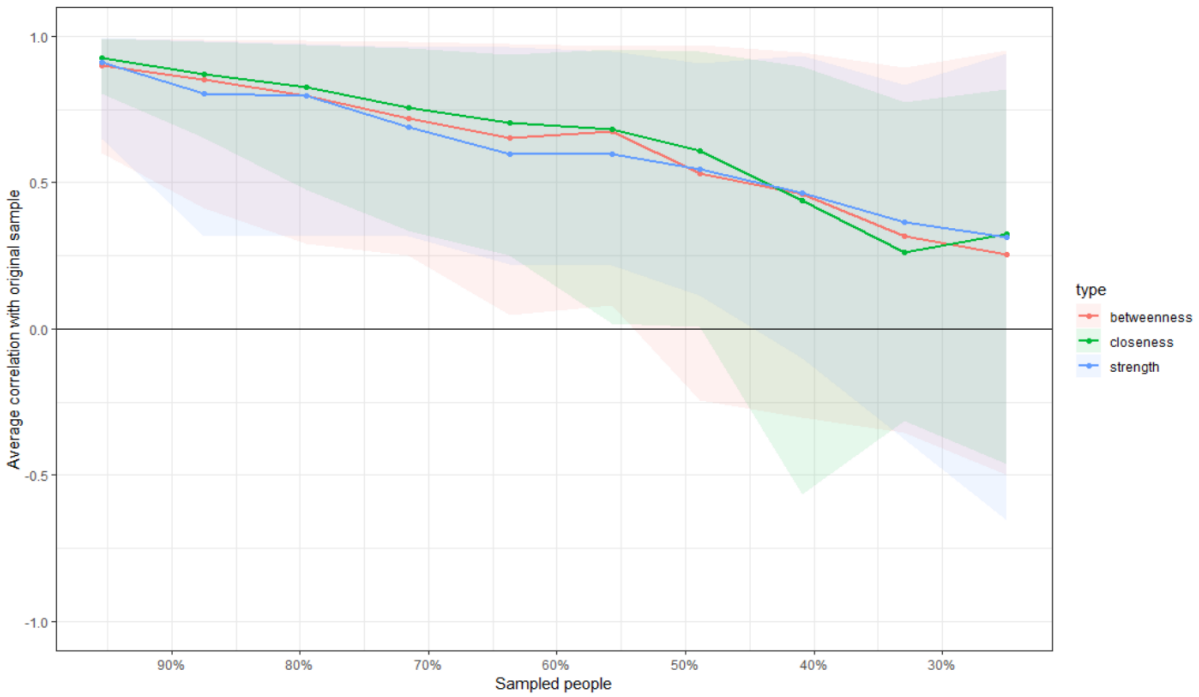

Figure 12: Case-dropping sampled bootstrap assessing robustness of node centrality indices. The x-axis represent the proportion of samples employed in the estimation. The y-axis express the correlation between the bootstrapped centrality values and the original values of the estimated network.

Network 4

Network 4 was estimated with a hyperparameter of 0.25. The resulting network (figure 13) consisted of 16 nodes. It was composed of 49 non-zero edges of 120 possible. Degree distribution is plotted in appendix (appendix: figure 22). The mean absolute weight of edges was 0.035. The network had a smallworldness value of 1.03. The global clustering coefficient was 0.41, while the average shortest path length was 1.63. These values were not different from those emerging from a similar random network (0.39 and 1.62, respectively). The stress value is very low indicating that the correlation weight of edges is well represented by the visual distances of the nodes, and can be interpreted with confidence.

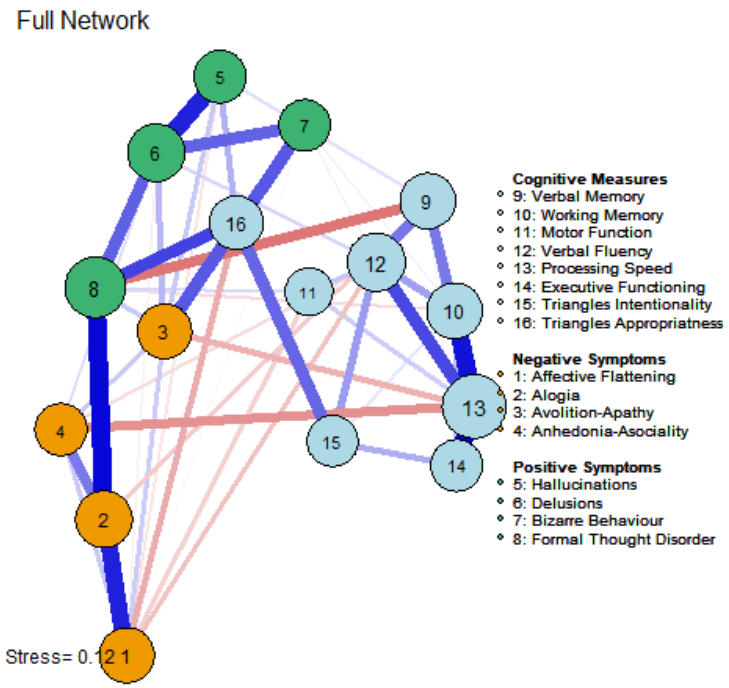

Figure 13: Network of cognitive measures and symptoms in first-episode schizophrenia patients. Blue nodes represent negative symptoms. Green nodes represent positive symptoms. Yellow nodes represent cognitive measures. Blue edges express positive correlations. Red edges express negative correlations. Larger node sizes indicate higher node centrality. Wider edges indicate stronger correlations.

Generally, the network appear to be highly interrelated and both strong and weak edges are evenly distributed among the nodes. The nodes seem to organize according to their category; cognitive functions are positioned at the right side, negative symptoms at the bottom left, and positive symptoms at the top left. Each group is highly interconnected, while several edges connect nodes across groups. Additionally, the positive edges of the network generally constitute connections within

either symptom-nodes or cognition-nodes, while negative edges represent connections across these two domains. The only exception of this, is node 16 (Triangles Appropriateness) which is correlated positively to most of the symptoms, while it is only related to other cognitive functions through node 15 (Triangles intentionality).

The stability check of edge strengths indicate that the estimated edge weights are relatively stable (figure 14) compared to those of the samples. The seven strongest edges have CIs that do not contain 0, and these do not overlap with a majority of the remaining edges. Of these edges, three connections are among two cognitive variables, three are among two symptom variables, and one is between one cognitive and one symptom variable. The strongest edges among two cognitive variables are those connecting 1) *Processing Speed* and *Executive Function,* 2) *Working Memory* and *Processing Speed,* and 3) *Verbal fluency* and *Processing speed.* The difference test of edge weights indicate that the first two of these differ significantly from the majority of the remaining edges in the network (appendix: figure 23). The strongest edges among two symptoms are those connecting 1) *Alogia* and *Formal thought disorder,* 2) *Affective flattening* and *Alogia,* and 3) *Hallucinations* and *Delusions.* According to the difference test only the first of these edges differ significantly from the majority of other edges. The strongest edge connecting a cognitive variable and a symptom variable is the connection between *Formal thought disorder* and *Appropriateness.* However, this edge only differs significantly from the weakest third of all edges. Neither of the seven strongest edges differ significantly from each other in strength. Edges connecting cognitive and symptom variables generally appear to be the weakest in the network. Further, except for the one mentioned above, all strong cross-domain edges only differ significantly from one other edge In summary, the general tendency is for within-domain edges to appear strongest, however, they are only significantly stronger than the weakest third of the edges, composing cross-domain edges.

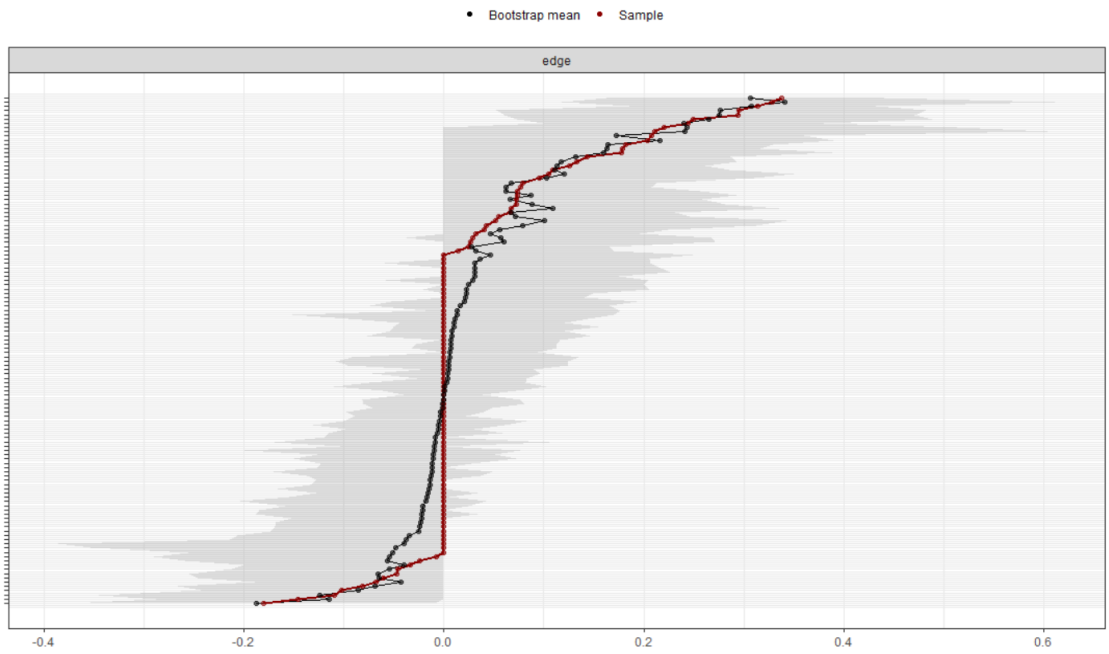

Figure 14: Bootstrapped 95% CIs for edge weights. x-axis represents edge weight values and the associated 95% CI. y-axis represent each edge, and are ordered such that stronger edges are in the top. The black line represents the estimated edge weights of the target network. The red line express edge weights estimated from the 2500 bootstrapped samples.

Inspecting node centrality indices, *Formal thought disorder* appears to be the most central in general, constituting the most betweenness- and closeness-central and the second most strength-central (figure 15a; appendix: table 7). The most strength-central node is *Processing speed,* which is also the second most betweenness-central, while it is only moderately closeness-central. Further, *Alogia* and *Verbal memory* are among the most closeness-central while less central on other indices. *Motor function* is consistently the least central across all three indices. Also among the least central appear *Hallucinations* regarding betweenness and closeness, and *Bizarre behaviour* on closeness- and strength centrality.

Inspecting the difference test on centrality indices reveal that neither of the nodes differ significantly from each other on closeness-centrality (appendix: figure 25,26,27). The two most central nodes, *Formal thought disorder* and *Processing speed,* are not significantly different from each other on neither strength nor betweenness centrality. However, they are both significantly more central than 4 other nodes regarding strength. Concerning betweenness-centrality, *Formal thought disorder* differs significantly from four other nodes, while *Processing speed* only differs significantly from one other node. *Alogia* differs only significantly from one node on strength, while *Verbal memory* does not differ from any other nodes. On closeness, neither of the two differ significantly from any other nodes. In

summary, it appears that only *Formal thought disorder* reliably can be interpreted as more central than at least some of the other nodes, on both betweenness- and strength centrality, while *Processing speed* additionally appear significantly more strength-central than other nodes. Further, only *Motor function* appear to be reliably interpreted as the least central node. Confidence intervals of node centrality estimates are plotted in appendix (figure 24). The stability check of the centrality indices revealed that the betweenness index has a CS-coefficient of 0.125. Closeness has a CS-coefficient of 0, while it is 0.125 for strength (figure 16). Thus, all three centrality measures are associated with poor stability. The three nodes associated with largest clustering coefficients are *Working memory, Executive function,* and *Verbal memory.* The lowest clustering coefficients are those associated with *Appropriateness, Intentionality* and *Formal thought disorder* (figure 15b, appendix: table 8).

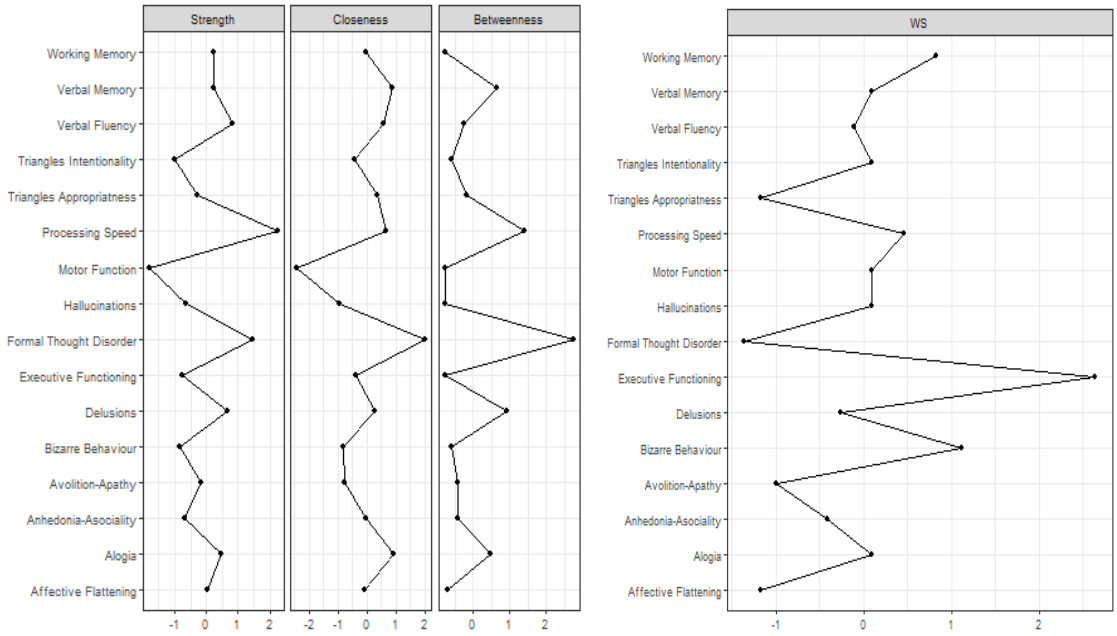

Figure 15: Figure A (left): Node centrality indices for each node. Values are standardized and 0 represents the mean. Figure B (right): Watts-Strogatz clustering coefficient for each node. Values are standardized and 0 represents the mean.

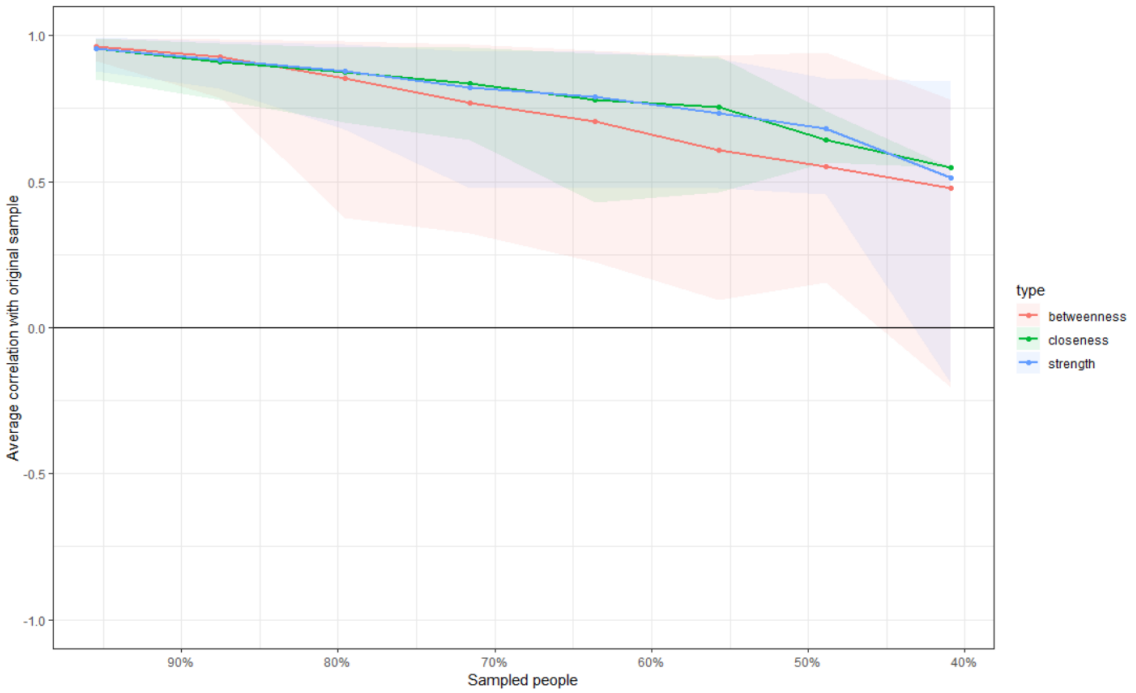

Figure 16: Case-dropping sampled bootstrap assessing robustness of node centrality indices. The x-axis represent the proportion of samples employed in the estimation. The y-axis express the correlation between the bootstrapped centrality values and the original values of the estimated network.

Discussion

The current study aimed to investigate the relationship between symptoms and cognitive functions in schizophrenia, using a network approach. According to psychometric network theory, the network structures should align with that of scale-free networks, which was examined through smallworldness and degree distribution. The smallworldness values of all networks were between 0.97 and 1.03, suggesting a structure on the border of a small-world topology. This is supported by the degree distribution of the networks, which all conformed to a poisson distribution, but had long right-hand tails, indicating a network structure in between scale-free and random. The borderline random structure would imply that all nodes have equal relevance to the network, however a careful look at the results indicated some differences in node centralities and edge strength, revealing some nodes to be more important than others. Thus, since the networks were not characterized by a clear random structure, it seems likely that the networks merely contained too few variables to allow for detection of a clear scale-free structure.

All networks were assessed in terms of their global properties of connectedness and tendency to form clusters, as well as local properties of individual nodes and connections between them. Network estimation was data-driven, and thus highly sensitive to the particular data exploited. To assess the

generalizability of the network estimates, accuracy- and stability checks were computed for both edge strength estimates and node centrality measures. The results generally indicated poor accuracy of network estimates. Edge strengths were associated with large CIs in all networks, and revealed that only few edges reliably could be distinguished from each other in terms of strength. This was the general tendency for node centrality estimates as well, in which only a few nodes were significantly different from each other. Further, stability checks of centrality indices revealed that estimates were highly dependent on the particular data, and hence cannot be generalized beyond the currently estimated networks. These results are most likely caused by insufficient sample sizes. The networks were estimated on significantly less observations, than what is suggested in the literature for network models. Therefore, small variations in the data would strongly inflate correlation estimates among variables, such that the removal of one particular observation would alter the results noticeably. This could further explain the wide confidence intervals of edge strengths. The networks obtained here provide indications of the general organization of symptoms and cognitive impairments, in terms of emerging interconnections, and allow inferences regarding the existence of relationships among them. However, the importance of particular nodes and edges in the general information flow of the network, should be inferred from these results with caution; only nodes and edges that could be distinguished from others in terms of importance, can be interpreted reliably. Further, while the results do provide some information on the interrelations of variables in the particular subject group employed here, the poor stability and accuracy indicate that generalization of results beyond the current study is unfeasible. With such caution in mind, accepting the results at face value do reveal interesting findings in the three aims explored here.

Comparison of cognitive function in healthy control group and schizophrenic patients

Network 1 and network 2 aimed to compare the structural relationships among cognitive functions in healthy control subjects and first-episode schizophrenic patients. The two networks exhibited quite different global structures. Network 1 (healthy control subjects) was characterized by high connectedness, with 71,4 % of all possible edges being present and a global clustering coefficient of 0.68. Meanwhile, network 2 (schizophrenic patients) showed less connectedness, containing 60,7% of the possible edges, and a global clustering coefficient of 0.56. Hence, more cognitive features were connected to each other in network 1, and the tendency for three features to all be correlated to each other, was higher for network 1 than network 2. Interestingly, the mean weight of edges, was smaller for network 1 (0.048) than network 2 (0.095), despite the globally stronger connectedness of network 1. This suggest, that while features were generally less connected in network 2, some cognitive aspects portrayed very strong correlations, driving the mean weight to be higher for network 2. Contrary, the lower mean weight in network 1 suggest, that although all features are generally more connected, the

weight of connections are more evenly distributed. Inspecting the visual organization we find these properties to be explained by a strongly connected cluster in network 2. Network 2 contains one cluster, in which all nodes are interconnected to each other, while the remaining nodes are positioned with greater distance from each other, and are only minimally connected to the rest of the network. The cluster encompasses the nodes of *Verbal memory, Working memory, Verbal fluency,* and *Processing speed*. Three of these also form a closed cluster in network 1, however, they are equally related to nodes within and without the cluster. Further, network 1 is composed of several closed node triplets, in which the three nodes appear multiple times. Thus, the interconnections among these nodes in network 1 appear to be an expression of the large global clustering coefficient and general connectedness, rather than of a distinct cluster, while the cluster in network 2 clearly distinguishes itself from the general tendency of the network.

In network 2, six edges appear to be stronger than the remaining edges. Interestingly, four of these are part of the above mentioned cluster, supporting the notion that these four nodes are particularly strongly connected, compared to the rest of the network. Further, the connection between *Processing speed* and *Executive function* appeared among the strongest edges in network 2, while this edge is absent in network 1. No edge weights differed from each other in network 1, which could either indicate that they are highly similar, or that network estimation was highly uncertain. The large CI overlap among edge weights (figure 2) indicate the latter to be the case here. However, the particular edge between *Processing speed* and *Executive function* can reliably be interpreted as being different between the two networks, as shown by the maximum difference in edge weight test of the NCT (appendix: figure 14,15), as well as the non-overlapping CI of its weight across the two networks (figure 8.b). While node centrality indices were indistinguishable in network 1, and associated with very poor stability, strength-centrality was relatively robust in network 2. The results suggest, that *Processing speed* and *Verbal fluency* are the most strength-central nodes in network 2. While they were not significantly different from each other, *Processing speed* was significantly stronger than almost of all the remaining nodes. *Verbal fluency* was only different from one other node. Hence, *Processing speed* appear to be the most central node in network 2. As this node constitute the connection between the cluster and the node of *Executive function,* it seems that, in addition to the cluster itself, its connection to *Executive function,* is highly relevant for the information flow of the network. In line with these results, the difference network of edge weights (figure 8.a) show that the two networks differ most in the particular edges of the cluster present in network 2.

The emerging cluster hence seems to constitute the largest difference between healthy control subjects and schizophrenic patients. The fact that some cognitive functions are more strongly correlated in schizophrenic patients, than in healthy control subjects, might be a reflection of greater variation in cognitive abilities in the patient group. Since correlations are estimated from standard deviations (SD) in the data distribution, greater variation in scores on the cognitive tasks would cause one SD to be larger. Larger SDs leads to the calculation of stronger correlations between two variables, i.e., extreme values in the tails of the score distribution, drive the correlation to be stronger. Inspection of the score distributions in the cognitive tasks for both patients and control subjects (appendix: figure 28), support this interpretation. Across all four cognitive abilities of the cluster, as well as for *Executive function,* the score distributions for schizophrenic patients showed a lower peak than that of controls and longer tails, indicating more heterogeneity among patients. The control subject generally had close to normal distributions with a peak further to the right, indicating a tendency for higher scores. Thus, the variation in cognitive abilities were greater in the patient group, causing the correlations among cognitive abilities to be stronger. This could further explain why the network estimates of the control group were associated with much more uncertainty than that of patients (figure 8.b; appendix: figure 12).

However, the formation of a cluster in network 2, consisting of stronger intercorrelations than in network 1, is not simply a statistical artefact. The main difference between control subjects and patients, the cluster, seem to concern a general cognitive domain of fluid intelligence; i.e., the combined abilities of novel problem solving through logic thinking. The strong correlations among *Verbal memory, Working memory, Verbal fluency* and *Processing speed,* indicate that these features are highly influenced by each other, and information is effectively shared among them. This suggest, that knowing one of these features would facilitate more accurate inferences about the impairment of the remaining features in the cluster. The presence of this cluster, as well as the high centrality associated with it, is in line with the findings of other studies. Roca and colleagues (2014) argue, that the strong correlations between a large set of cognitive tasks can be accounted for by a measure of general fluid intelligence. Once they controlled for fluid intelligence, no differences in executive cognition impairments were found between control subjects and schizophrenic patients. The notion that fluid intelligence mainly contributes to executive tasks, is further supported by the current study. The strongest connection in network 2, also representing the largest difference from network 1, was the correlation between *Executive function* and *Processing speed,* connecting the cluster of fluid intelligence to executive functions. Such findings have important clinical implications. Given the large variation found in the cognitive abilities of patients, as well as the important relationship between the

cluster of fluid intelligence and executive functions, the evaluation of a patient's general cognitive ability, would benefit from assessing at least one of the fluid intelligence variables. These account for a substantial part of cognitive deficits, and would particularly allow inferences about individual executive impairments in the patient.

Symptoms in schizophrenic patients

The second aim concerned the structure and interrelations of symptoms, with the intention of evaluating how these might organize with cognitive measures. We investigated the general connectivity of network 3, expecting it to reflect a strong self-sustaining symptom network. We found that approximately 71% of the possible edges appeared in the network, the average shortest path length was 1.29, and the global clustering was 0.7 (where 1 indicate a fully connected network). These measures all indicate that the network is strongly connected, supporting the main assumption of the psychometric network theory.

Next, the network structuring was examined. The global clustering is relatively high, indicating that the network generally is highly connected. However, as evident in the network visualization, all nodes seem to conform to one cluster rather than separated ones and generally organize in positive and negative symptoms. The nodes of *Anhedonia-Asociality* and *Hallucinations* cluster the most (figure 11.b; appendix: table 5), suggesting that they are somewhat redundant to the overall network flow, seeing their neighbours are highly interconnected. The nodes *Alogia, Formal Thought Disorder* and *Delusions* have the lowest clustering, indicating they are non-redundant.

Inspecting edges, we found the strongest edge was between *Alogia* and *Formal Thought Disorder,* which is the only one that differs significantly from the remaining edges. This confirm the importance of *Formal Thought Disorder* and *Alogia* in the network. The connection is intuitive, given one is associated with disorganized thinking and speech, and the other with general speech deficit. The fact that all other edges do not differ, could indicate that all edges simply are equal in strength. This would further underline the conclusion, that no distinct sub clusters emerge. Contrary, it could be a result of great uncertainty of the estimates. The wide confidence intervals of edge weights, support this interpretation (figure 10).

Looking at node centralities we found that *Alogia, Formal Thought Disorder* and *Delusions* are among the strongest across all measures. They contribute to the network flow seeing they often lie on the shortest path between other nodes. In addition, they have short distances to all other nodes and strong connections to their immediate neighbours, resulting in rapid activity spread throughout the

network. Among the weakest nodes are *Hallucinations* and *Anhedonia-Asociality.* Relative to other nodes, they are distanced far from their neighbours, and never operate as intermediate nodes on the shortest paths. Thus, they generally have little influence on the network flow. The accuracy check revealed none of the nodes differ on any centrality measures though (appendix: figure 19,20,21). This could mean they are very similar in strength, and thus distinct entities which are all important to the network. However, the great uncertainty of the network, could also explain that no nodes differ significantly. A look at CI intervals of the strength centrality support this (appendix: figure 18), as does the stability check (figure 12).

Overall the accuracy and generalizability is poor, however, taking the measures at face value, both clustering, edge centrality and node centrality suggest *Alogia, Formal Thought Disorder* and *Delusions* are important to the network structure and flow, whereas *Hallucinations* and *Anhedonia-Asociality* are of less importance. Interpreting the visual network and the measures we do not find separate sub clusters, which suggest all symptoms to be distinct entities. Previous studies have suggested negative symptoms may be captured by two dimensions: diminished motivation (*anhedonia, avolition, asociality*) and diminished expression (*blunted affect, alogia*) (Blanchard & Cohen, 2005; Marder & Galderisi, 2017). Our results find *Affective flattening* and *Alogia* are quite strongly connected, supporting a dimension of diminished expression. However, *Anhedonia-Asociality* and *Avolition-apathy* are only weakly connected, and thus hardly representative of the same dimension. Further, none of the variables cluster, and all are rather similar in importance; neither edges nor nodes differ significantly in centrality (appendix: figure 17,19,20,21). Overall, our results suggest that all measures are separate from each other, thus, the symptomatology and their interrelations are too complex to be expressed by two dimensions. These findings align with a network analysis by Strauss and colleagues (2018), who found negative symptoms of schizophrenia to represent five distinct entities (*anhedonia, avolition, asociality, blunted affect and alogia*). In sum, the results indicate that all global scores are informative and mostly non-redundant. Hence, if symptoms of schizophrenia integrate closely with cognitive impairments in a network structure, they should do so in a very specific manner of one-to-one relationships, rather than forming clusters of strong relations.

Symptoms and cognitive impairments in schizophrenic patients

In aim 3 the interrelations among cognitive variables and symptoms were investigated. The global properties of network 4 generally revealed a less connected network compared to network 1, 2, and 3. 40,8% of the possible connections were present, hence, less than half of all node pairs were connected. Similarly, the clustering coefficient suggested a low tendency for closed clusters to emerge in the network (C=0.41). These results reflect that symptoms and cognitive abilities are less connected

across domains than within each domain. This notion is further indicated by edge strengths. The strongest edges are generally found within domains, while the weakest correlations represent cross-domain connections. Further, the nodes are spatially organized by domain, maintaining the network structure found in aim 1 and 2. Thus, no cognitive nodes are positioned on the shortest path between two symptoms, as well as no symptoms are positioned on the shortest path between two cognitive functions. Hence, these findings suggest, that symptoms and cognitive abilities convey different types of information. Interestingly, both the strongest edges as well as the most central nodes constitute both symptoms and cognitive abilities. Hence, it seems that both domains are equally important for the information flow in the patient network, and that the removal of either symptoms or cognitive measures will cause loss of information. Although, the cross-domain edges appear to be the weakest in the network, they are very prevalent in the network. About half of the edges constitute cross-domain correlations, suggesting that while symptoms and cognitive abilities do represent distinct aspects of the disorder, they are nevertheless correlated with each other. Further, the waste majority of cross-domain connections are correlated in a negative fashion, indicating that the more severe symptoms are, the greater the cognitive impairment tend to be. While these findings are in line with the extensive literature (see introduction) suggesting a relationship between symptoms and cognitive impairments, the structure of these connections reveal an interesting finding; the network reveal no tendencies for symptoms and cognition to form clusters of general impairment domains, such that particular groups of one map onto a cluster of the other. The cluster found in network 2, representing a general impairment in fluid intelligence, does not seem to overlap with a set of symptoms. Contrary, the two domains seem related to each other through single connections, such that one particular symptom is related to one particular cognitive ability. Among the strongest cross-domain edges are the connection between the positive symptom of *Formal thought disorder* and *Verbal memory,* and the connection between the negative symptom of *Anhedonia-Asociality* and *Processing speed.* Both *Verbal memory* and *Processing speed* are part of the cognitive cluster, indicating that *Formal thought disorder* and *Anhedonia-Asociality* are related to the impairment of fluid intelligence. Further, *Formal thought disorder* was consistently the strongest node in the network. Since this symptom is strongly related to fluid intelligence, it supports the notion, that this general impairment is highly central to the pathology of schizophrenia.

The network structure of symptoms and cognitive abilities support the suggestion that the two domains are related to each other in psychopathological disorders. However, it does not support the notion that particular sets of symptoms (e.g., negative symptoms) are more related to particular sets of cognitive impairments (e.g., social cognition) than others. In terms of network structure, this would

require a cluster of symptoms to be integrated in a cluster of cognitive abilities (or vice versa). Such overlap could indicate that they represent similar pathological information, and maybe even that one domain (e.g., cognition) mediate the influence between elements of the other domain (e.g., symptoms). Since symptoms and cognitive functions were organized spatially independent from each other, as well as the finding that correlations within domains were strongest, and cross-domain correlations weakest, the study suggest that the symptoms and cognition convey distinct information, and that neither of them mediate the intern relationships of the other. Further, the weak cross-domain correlations suggest a simple causal relationship between symptoms and cognition to be unlikely. Instead, the very specific interrelations among particular symptoms and cognitive abilities found in the current study, suggest that information of cognitive impairment can explain some aspects of the psychopathological symptoms, however, the nature of the symptoms is too complex to be completely accounted for by cognition. While cognition cannot account for all the information conveyed by symptoms, they themselves seem to provide additional information about the nature of schizophrenia, not inherent in the symptoms.

Methodological discussion

The current study was highly exploratory, and networks were estimated directly from the data, which inflates the risk of overfitting and make the network sensitive to change. Generally, we found the networks to be highly unstable indicating a need for more data, in order to retain proper power. This is a general problem of psychometric networks which are highly exploratory and thus involve a large number of parameters, increasing the amount of data necessary to retain power. Exactly how much data is needed in order to have adequate power is currently unanswered, and a matter of future research. Despite reducing the variables of interest, the current sample only allowed network estimation with a gamma value of 0.25, which is below the suggested gamma value of 0.5 (Epskamp & Fried, 2018). Hence, the model estimation might not have been cautious enough, causing the low accuracy and stability. Larger sample sizes would allow us to increase the gamma parameter, which might increase the stability of the results. Further, the obtained networks should be simpler and thus easier to interpret. Therefore, the current study should be viewed as an initial exploratoration, and future studies including more data is therefore encouraged.

The networks are estimated using a Graphical EBIC LASSO model relying on polychoric correlations of the ordinal variables, and Pearson correlations of numerical variables. The polychoric correlations rely on the assumption that a normally distributed phenomena underlies the observed ordinal variables. It is currently unknown whether this assumption is justified, and up to future research to determine whether this is an appropriate method to obtain correlations (Fried & Cramer, 2017). The Pearson

correlations assume absence of outliers, linearity and homoscedasticity. We did not find any substantial outliers, however, the assumption of linearity and homoscedasticity may be violated, seeing that particularly the schizophrenic data was relatively skewed. This may be due to insufficient sample sizes, since linearity of data on small samples are harder to detect. Alternatively, this could be explained by the schizophrenic group reflecting different subgroups of a population, rather than one homogenous group. If this is the case, assigning sub-groups, according to the disorder profile, may solve the problem of homoscedasticity (Fried & Cramer, 2017).

Another point worth mentioning is the choices we made regarding exclusion of variables. In any network one must decide which nodes are to be included, considering the tradeoff between including to few or to many. We included only the global symptom scores in the network for two reasons. First, including all questionnaire elements would lead to severe power problems. Secondly, the sub-questions of each symptom exhibited at least partial topological overlap, seeing they belong to the same overall categories. This would affect the estimation of network structure and its connections, causing them to be less informative. However, this procedure might have caused the exclusion of important nodes in the network, violating the assumption that all relevant variables are included (Fried & Cramer, 2017). Thus, there is a risk that including another set of nodes, would result in complete alteration of the network structure. The same trade-off is evident for cognitive measures. The current study prioritized interpretability and power, however, the tradeoff is difficult and thus debatable.

Theoretical discussion

Though the two groups did not map directly onto each other, interrelations among them where prevalent. Such cross-domain connections can indicate that one causes the other. Commonly, causality between nodes is assumed in psychometric networks, seeing the theory relies on nodes affecting each other. Yet, we cannot confirm causality through the network estimation employed in this study, since the network only represent partial correlations. Partial correlations estimate the association between two variables controlling for confounding variables. Thus, they tell us there is a relation between two variables not caused by common neighbors, however, this does not confirm causality as the connection may be confounded by variables outside the network. This is a general challenge to psychometric networks. To gain more knowledge of the causality between the nodes of our network, and particularly about the direction of causation, longitudinal data is needed. Data collected over a longer period might provide significant information about the causal interrelations of symptoms and cognitive dysfunction. Several studies have attempted to estimate directed networks

based on longitudinal data (Bringmann et al., 2015; Beard et al., 2016) and may provide guides for investigations of the causal nature in relations between cognitive impairments and symptoms.

While a directed network could inform us of the direction of causation, it cannot explain the nature of the connections. Whereas edges in most networks represent physical entities, the edges of psychometric networks are highly theoretical. Take the example of power grid networks; here, the edges among nodes represent power lines. However, in a psychiatric network, the edges correspond to a theoretical relation between symptoms, of which we have no clear physical correlate. One suggestion is that edges correspond to cognitive domains, mediating relations between symptoms (Borsboom et al., 2011). If that was the case, we would expect cognitive measures and symptoms to distribute evenly in the network, and to form strong connections. This is not in line with the current analysis, which only result in weak relations among symptoms and cognition and show low spatial proximity of the two domains. Symptoms seem too complex to be described by one factor and does more likely reflect a complex interplay between a variety of factors. To unravel the complexity of symptoms it may be necessary to include both genetical, emotion and environmental aspects as suggested previously (e.g. Boschloo et al., 2015). To better assess how different domains relate, future studies might model them as distinct explanatory layers with direct links in between, employing multilayer network analysis.

Generally, one must consider the consequences of the constituent elements of a network. Besides the methodological challenges discussed, the choice of variables also pose conceptual challenges. In regard to symptoms, only those categorized under schizophrenia in ICD were represented. However, since diagnostic scales are highly heterogeneous, they may not accurately reflect the disorder, imposing a clear problem of utility. Though the inclusion of additional aspects in psychometric networks provides more information, continuously increasing the complexity of such networks will reduce the utility of them. The possibilities of associated factors are endless, so how do we define the boundaries of the networks? The relevance of different factors should be determined according to the aim of investigation. If the aim is to explore what constitute symptoms and might replace them as more objective measures, the elements overlapping with symptoms in close clusters, are most informative. Contrary, if the goal is to nuance the disorder image, the elements that are most distinct may be more appropriate, seeing they convey information not inherent in symptoms. A focus on elements which are comparable to healthy individuals (in this case cognitive measures) will be informative about the distinct dysfunctions in the disorder that differentiate it from a healthy state.

A key goal of psychometric networks is to improve the diagnostic practice of mental disorders. However, generalizing disorder networks has proven to be extremely difficult given that mental disorders are highly idiosyncratic. A general network may fail to account for heterogeneity of patients: if two patients show different clusters, the overall network may fail to reflect the true population, in its attempt to account and generalize across both profiles (Fried & Cramer, 2017). Much research and massive amounts of data are needed to generalize a network at population level, if even possible. Therefore, the ideal is to identify individual disorder networks and structure interventions accordingly. The current study indicates that including cognitive measures in a symptom network, will contribute vastly in this prospect for three reasons. Firstly, because these measures are highly heterogeneous and may better account for patient variations than symptoms. Secondly, because assessing one function of the fluid intelligence cluster will, to a great extend, be indicative of general cognitive impairment in the individual patient. Lastly, because cognitive impairments seem to provide additional information on the disorder, not inherent in the symptoms.

The area of psychometric networks is still in an exploratory state, and though there are challenges, much new information may be gained from this approach. The field is highly important giving how widespread mental disorders are, and how little they are understood. Given the complex nature of mental disorders, network models seem to be a more adequate representation, and is further grounded by common clinical findings. The prospects of gaining new information from psychometric networks are optimistic, however, more studies are needed that explicitly evaluate the discussed issues and consider how to overcome them.

Conclusion

The current paper had three aims. First, it aimed to explore the difference in interconnections of cognitive functions between healthy control subjects and first-episode schizophrenic patients. Results revealed that a cluster representing fluid intelligence in the patient network, strongly related to executive functioning, constituted the main difference from healthy control subjects. This suggest, that fluid intelligence and executive function deficits best represent cognitive impairments in schizophrenia. The second aim assessed interconnections of symptoms in the patient group. Results indicated that all symptoms contributed to the disorder, and that none clustered in sub dimensions. However, *Formal Thought Disorder*, *Delusions* and *Alogia* appear to be slightly more central in the symptom network, and might thus be important to address in treatment. Third, we aimed to investigate the interrelations between symptoms and cognitive impairment in schizophrenic patients. Although we found symptoms and cognitive functioning to be more connected within domain, cross-

domain connections were highly prevalent, implying they are influenced by each other. These connections may be candidates for future research unfolding the nature of relation between cognitive impairments and symptomatology in schizophrenia. In conclusion the results suggest both symptoms and cognitive functioning provide distinct information on the pathology of schizophrenia, which stress the point of investigating measures beyond symptoms when attempting to understand the causes of mental disorders and how to treat these.

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Appendix

Network 1

Figure 1: Degree Distribution

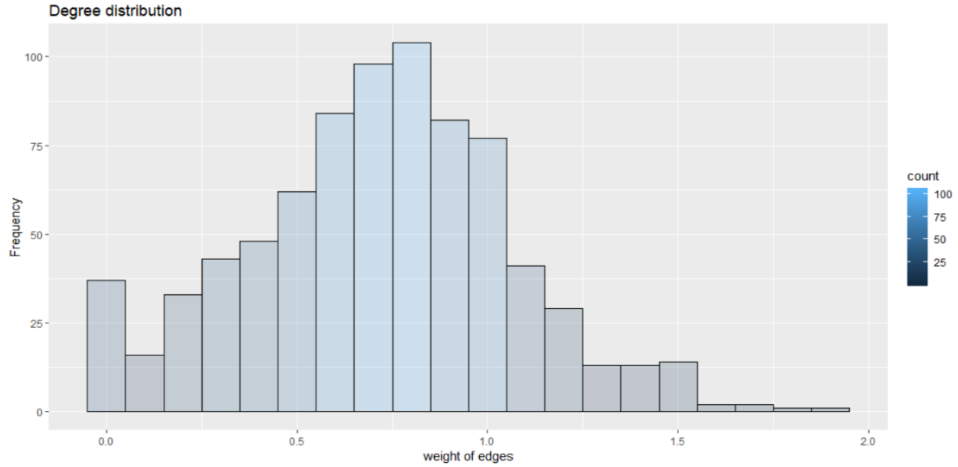

Figure 1: Sampled degree distribution of edge weights, based on 100 networks from bootstrapping.

Figure 2: Difference test of edge strengths

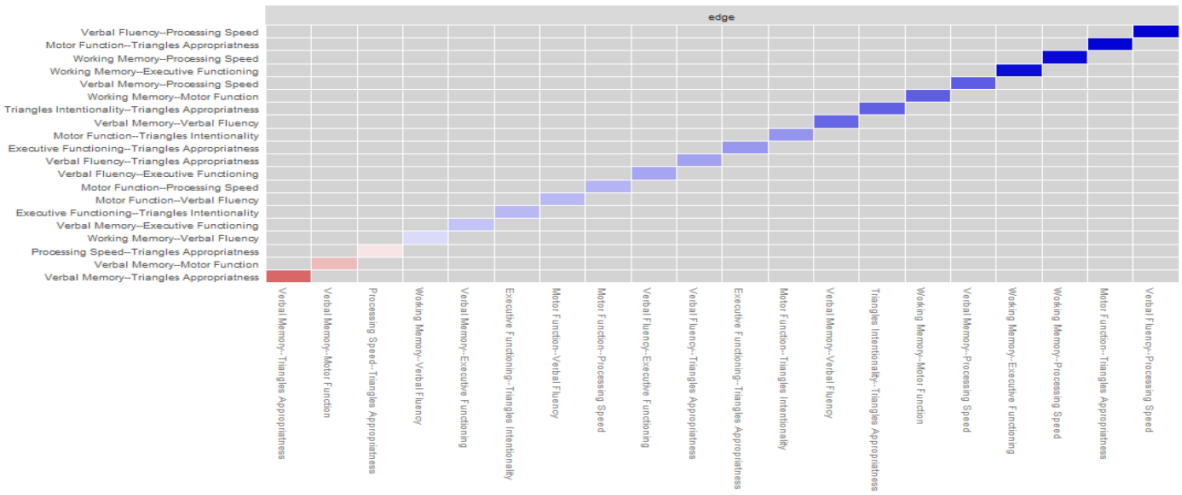

Figure 2: Bootstrapped difference test for edge weights, alpha level = 0.05. Each edge is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the weight of the edge, such that stronger colour yields larger weight. Grey boxes express no significant difference between edge weights. Black boxes represent significantly different edges weights.

Table 1: Node centrality

	Betweenness	Closeness (x 100)	Strength (x 100)
Verbal Memory	0	1.57	60.4
Working Memory	0	1.60	80.6
Motor Function	0	1.12	27.9
Verbal Fluency	4	**2.15**	**87.4**
Processing Speed	**8**	**2.02**	**130.7**
Executive Function	4	1.83	60.5
Triangles Intentionality	**5**	1.52	63.1
TrianglesAppropriateness	0	1.24	42.2

Table 1: Node centrality indices

Difference test of node centrality indices

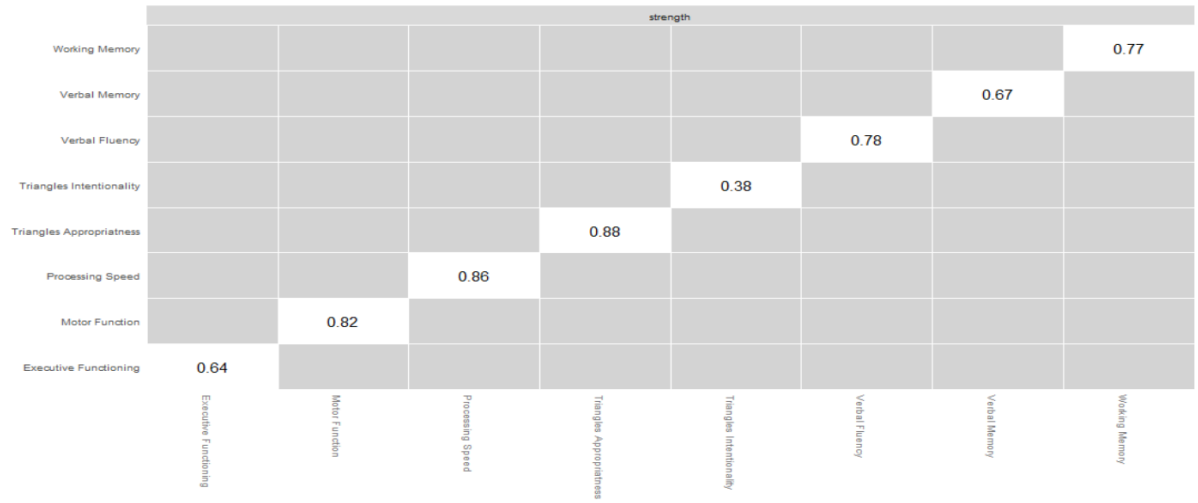

Figure 4: Bootstrapped difference test for node strength centrality, alpha level = 0.05. Each node is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the strength centrality of the node, such that stronger colour yields higher values. Grey boxes express no significant difference between nodes centrality. Black boxes represent significantly different node centrality.

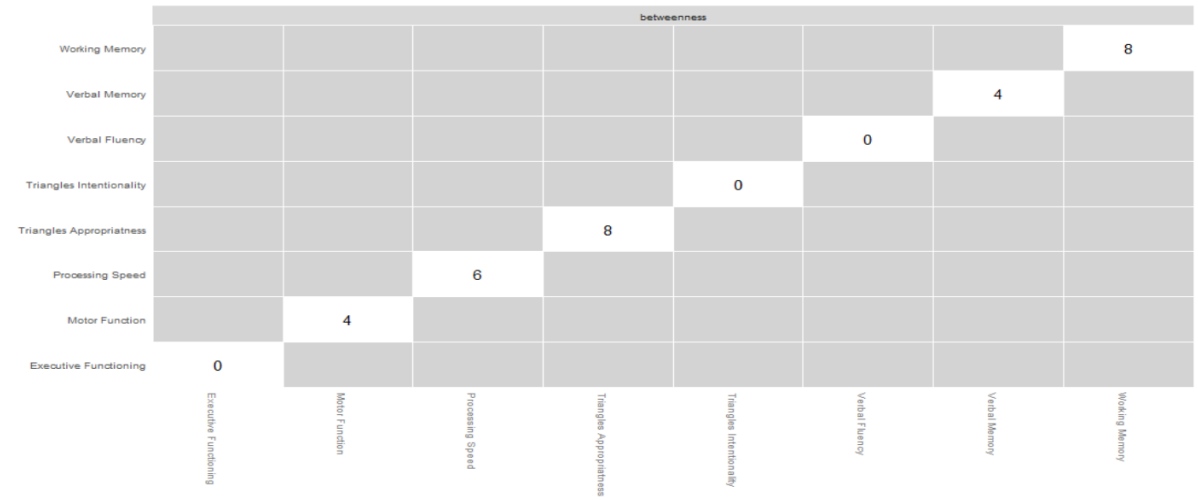

Figure 5: Bootstrapped difference test for node betweenness centrality, alpha level = 0.05. Each node is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the betweenness centrality of the node, such that stronger colour yields higher values. Grey boxes express no significant difference between nodes centrality. Black boxes represent significantly different node centrality.

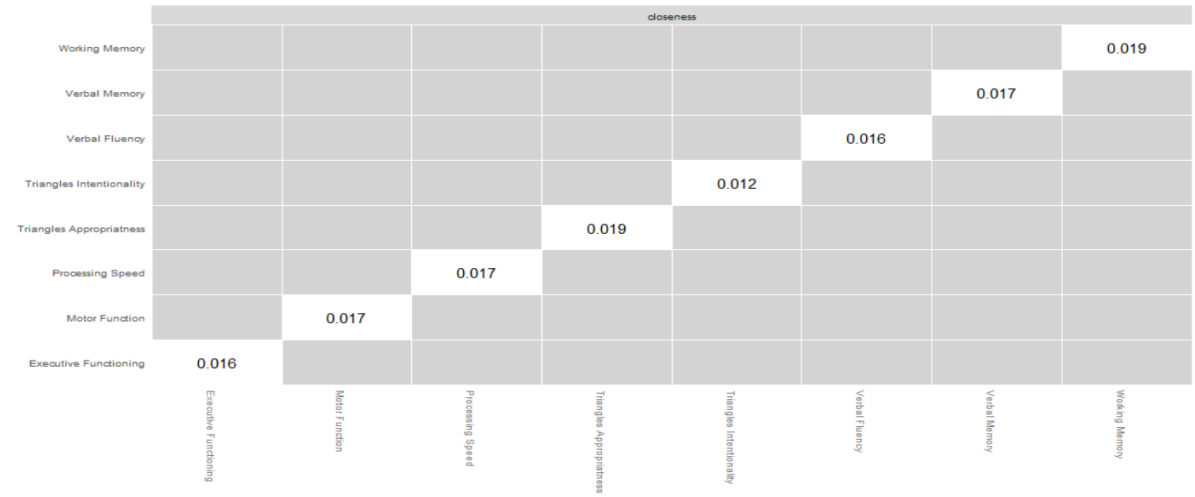

Figure 6: Bootstrapped difference test for node closeness centrality, alpha level = 0.05. Each node is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the closeness centrality of the node, such that stronger colour yields higher values. Grey boxes express no significant difference between nodes centrality. Black boxes represent significantly different node centrality.

Table 2: WS clustering coefficients of nodes

Verbal Memory	*Working Memory*	*Motor Function*	*Verbal Fluency*	*Processing Speed*	*Executive Functioning*	*Triangles Intentionality*	*Triangles Appropriateness*
0.80	*0.67*	*0.60*	*0.73*	*0.80*	*0.50*	*0.67*	*0.67*

Table 2: Clustering coefficient table.

Network 2

Figure 7: Degree Distribution

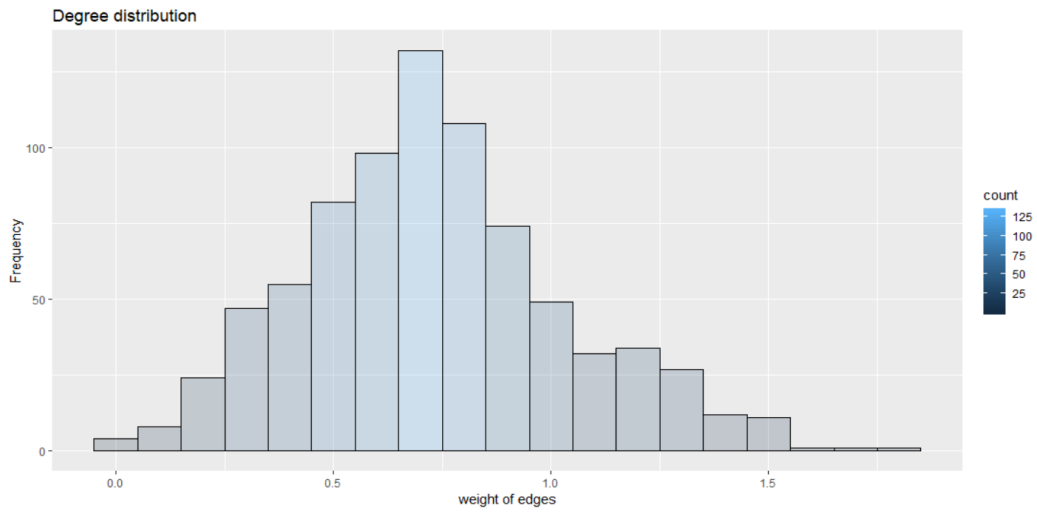

Figure 7: Sampled degree distribution of edge weights, based on 100 networks from bootstrapping.

Figure 8: Difference test of edge strength

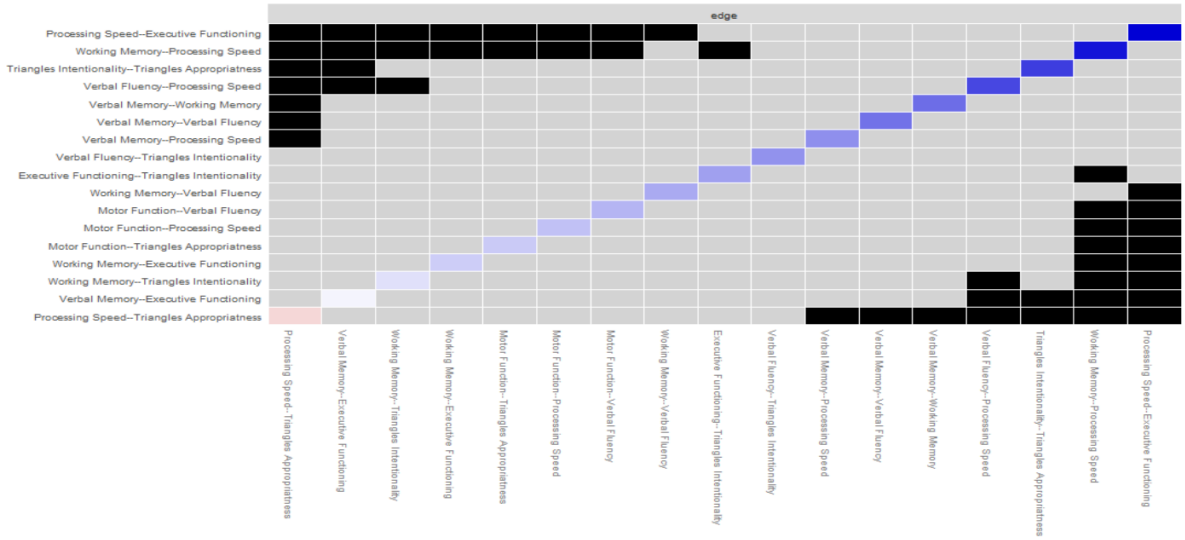

Figure 8: Bootstrapped difference test for edge weights, alpha level = 0.05. Each edge is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the weight of the edge, such that stronger colour yielding larger weight. Grey boxes express no significant difference between edge weights. Black boxes represent significantly different edges weights.

Table 3: Node centrality

	Betweenness	Closeness (x 100)	Strength (x 100)
Verbal Memory	0	1.57	60.4
Working Memory	0	1.60	80.6
Motor Function	0	1.12	27.9
Verbal Fluency	4	**2.15**	**87.4**
Processing Speed	**8**	**2.02**	**119.0**
Executive Function	4	1.83	60.5
Triangles Intentionality	**5**	1.52	63.1
Triangles Appropriateness	0	1.24	30.5

Table 3: Node centrality indices

Difference test of node centrality indices

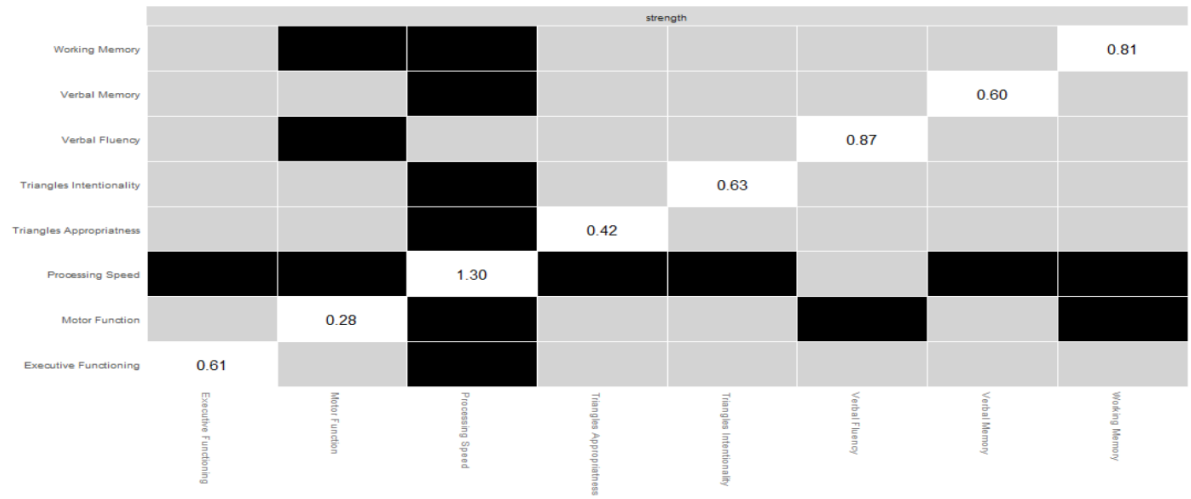

Figure 9: Bootstrapped difference test for node strength centrality, alpha level = 0.05. Each node is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the strength centrality of the node, such that stronger colour yields higher values. Grey boxes express no significant difference between nodes centrality. Black boxes represent significantly different node centrality.

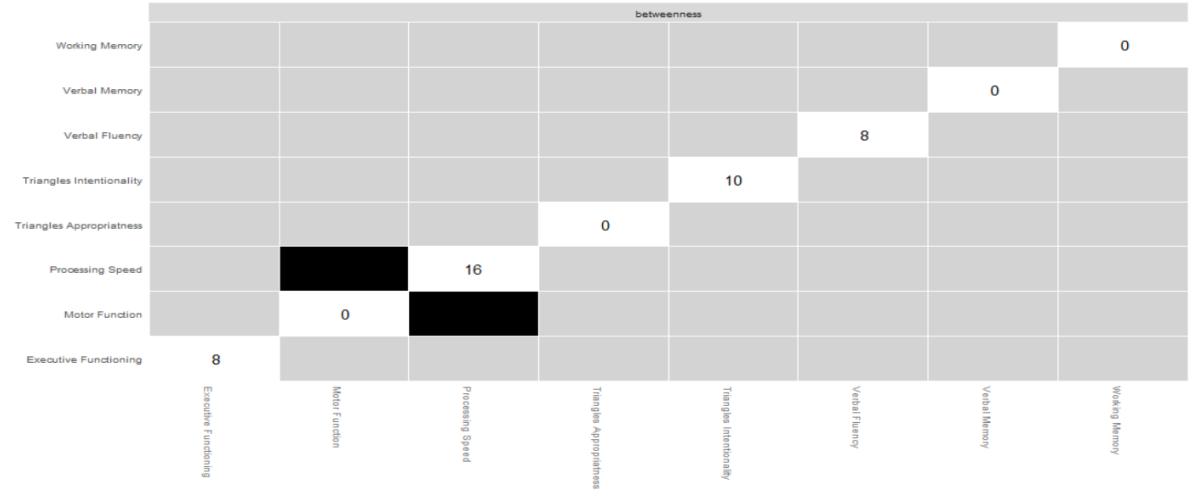

Figure 10: Bootstrapped difference test for node betweenness centrality, alpha level = 0.05. Each node is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the betweenness centrality of the node, such that stronger colour yields higher values. Grey boxes express no significant difference between nodes centrality. Black boxes represent significantly different node centrality.

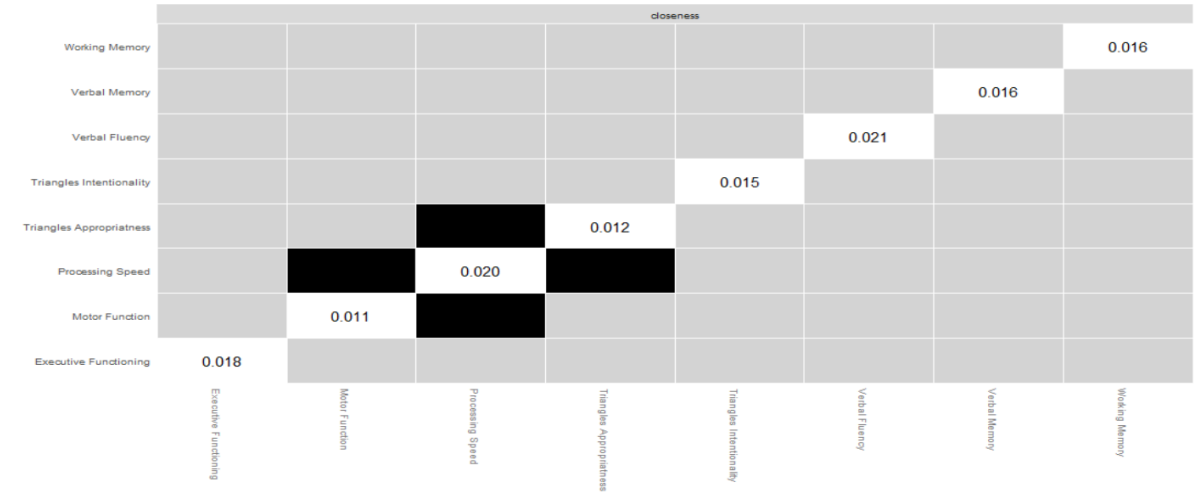

Figure 11: Bootstrapped difference test for node closeness centrality, alpha level = 0.05. Each node is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the closeness centrality of the node, such that stronger colour yields higher values. Grey boxes express no significant difference between nodes centrality. Black boxes represent significantly different node centrality.

Table 4: WS clustering coefficients of nodes

Verbal Memory	Working Memory	Motor Function	Verbal Fluency	Processing Speed	Executive Functioning	Triangles Intentionality	Triangles Appropriateness
0.83	0.70	0.67	0.50	0.47	0.67	0.33	0.33

Table 4: Clustering coefficient table.

Comparison of network 1 and 2

Figure 12: Difference in node strength between network 1 and network 2

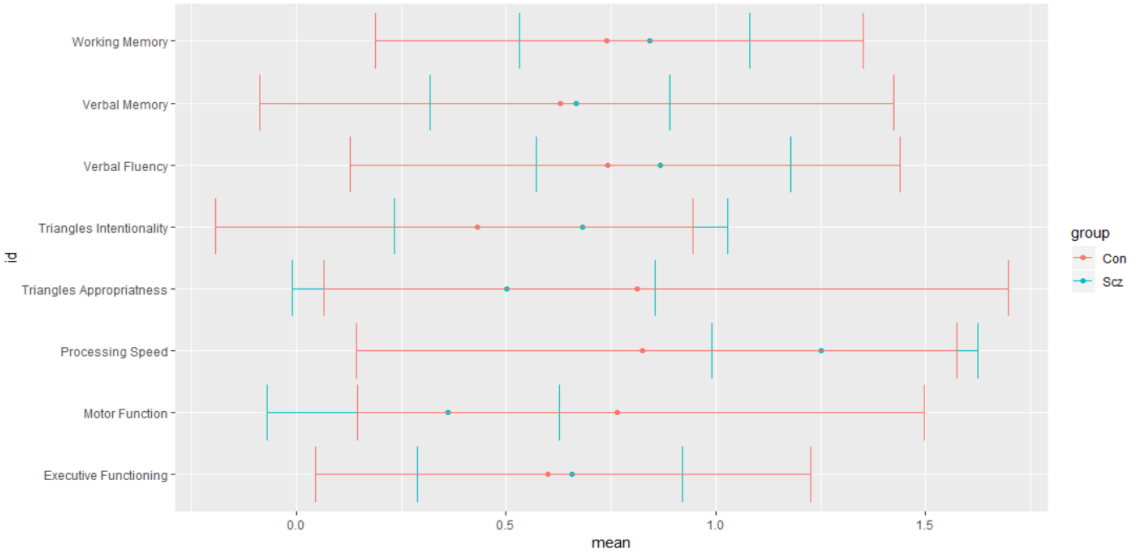

Figure 12: CI overlap of node strength (included because it yielded best stability)

Figure 13: NCT difference in global strength

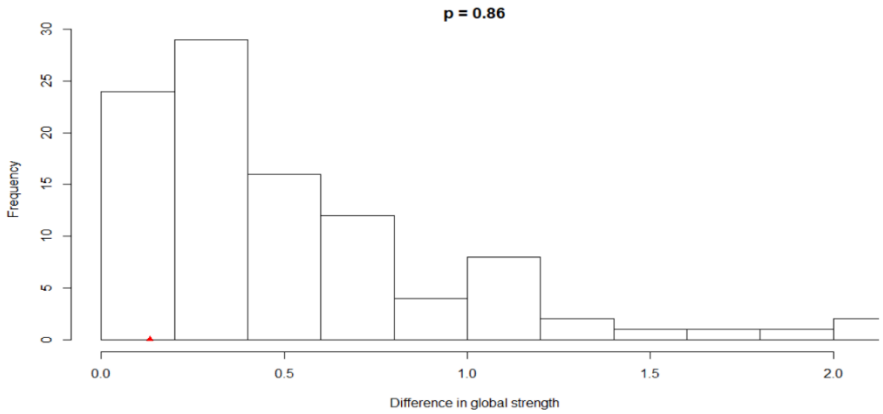

Figure 13: Between networks difference test on global strength. The distribution is based on 100 iterations. The red triangle indicate our value. P-value of difference test is included, and indicate no difference.

Figure 14: NCT maximum difference in edge weight

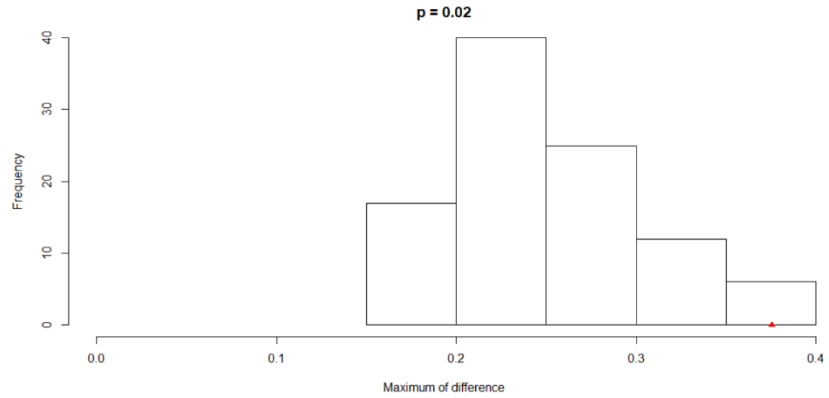

Figure 14: Between networks difference test on maximum edge difference. The distribution is based on 100 iterations. The red triangle indicate our value. P-value of difference test is included, indicating a significant difference.

Figure 15: NCT difference in edge between processing speed and executive functioning

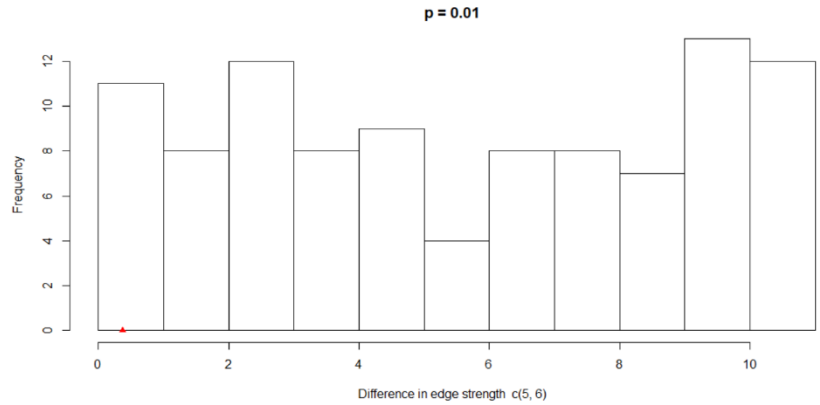

Figure 15: Between networks difference test on edge between executive functioning and processing speed. The distribution is based on 100 iterations. The red triangle indicate our value. P-value of difference test is included, indicating a significant difference.

Network 3

Figure 16: Degree Distribution

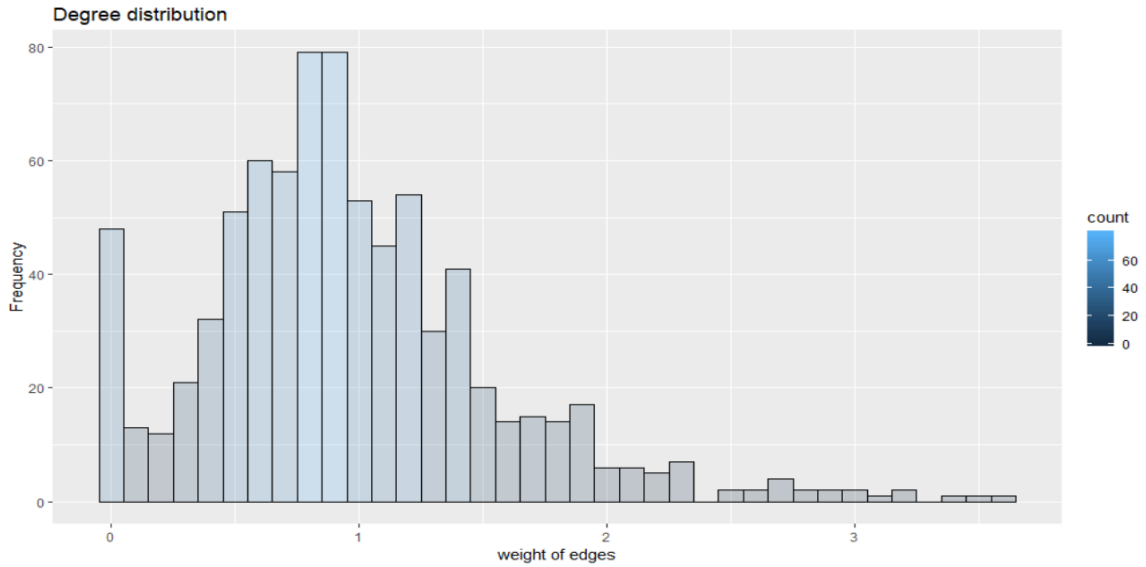

Figure 16: Sampled degree distribution of edge weights, based on 100 networks from the bootstrapping.

Figure 17: Difference test for edge weights

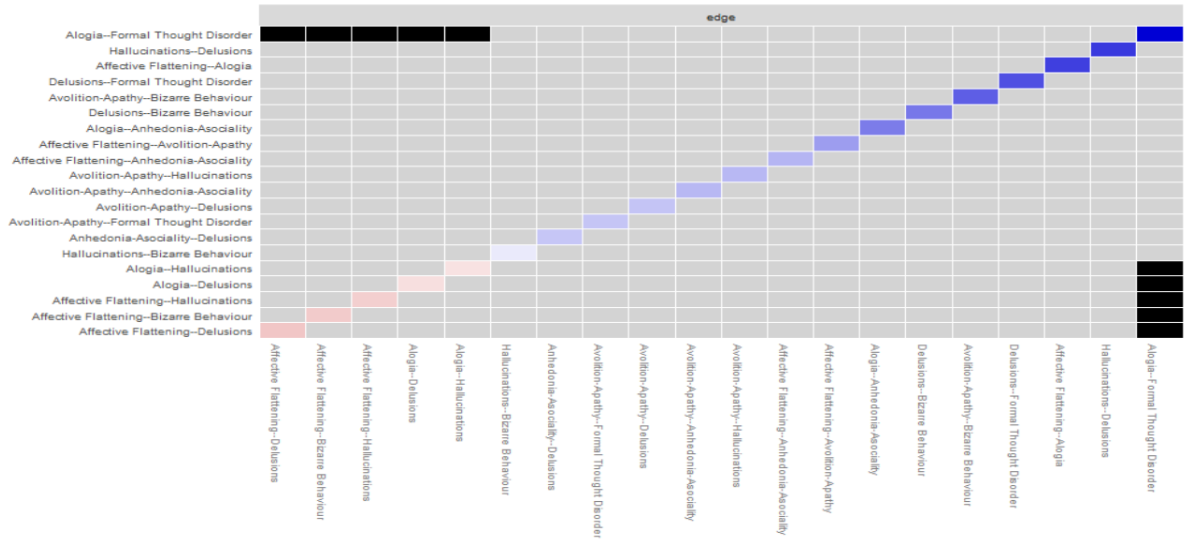

Figure 17: Bootstrapped difference test for edge weights, alpha level = 0.05. Each edge is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the weight of the edge, such that stronger colour yielding larger weight. Grey boxes express no significant difference between edge weights. Black boxes represent significantly different edges weights.

Table 5: Node centrality

	Betweenness	Closeness (x 100)	Strength (x 100)
Affective Flattening	1	1.89	34.7

Alogia	**7**	**2.28**	**86.5**
Avolition-Apathy	2	1.84	**86.5**
Anhedonia-Asociality	0	1.58	55.8
Hallucinations	0	1.69	36.0
Delusions	**7**	**2.28**	**89.6**
Bizarre behaviour	1	1.80	44.4
Formal thought disorder	**7**	**2.34**	81.5

Table 5: Node centrality indices

Figure 18: Confidence intervals on node strength

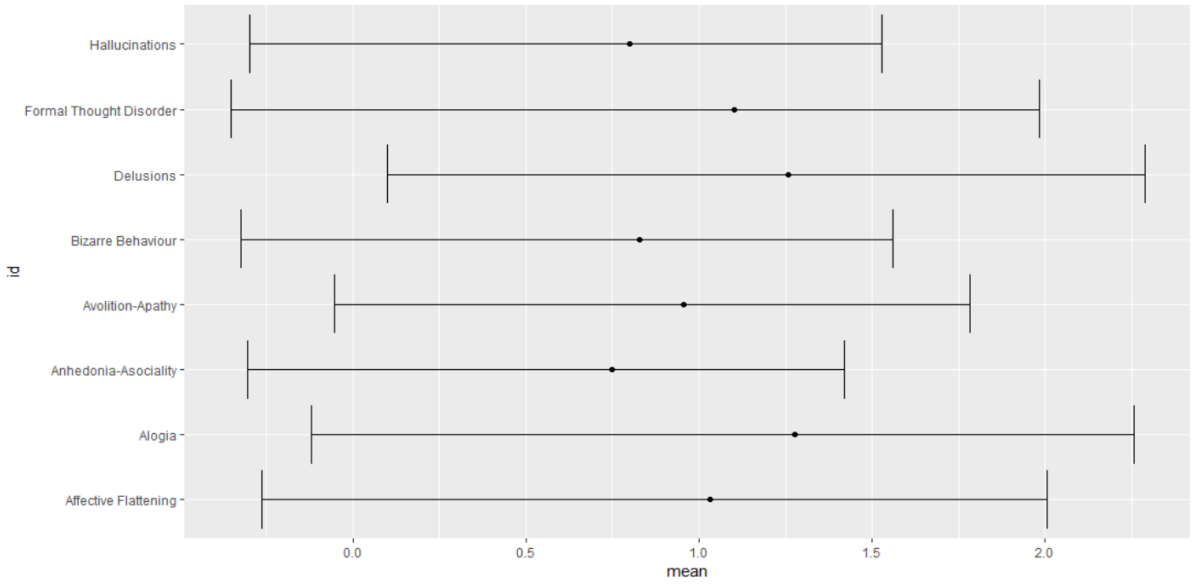

Figure 18: Confidence intervals on node centrality, strength.

Difference test for node centrality indices

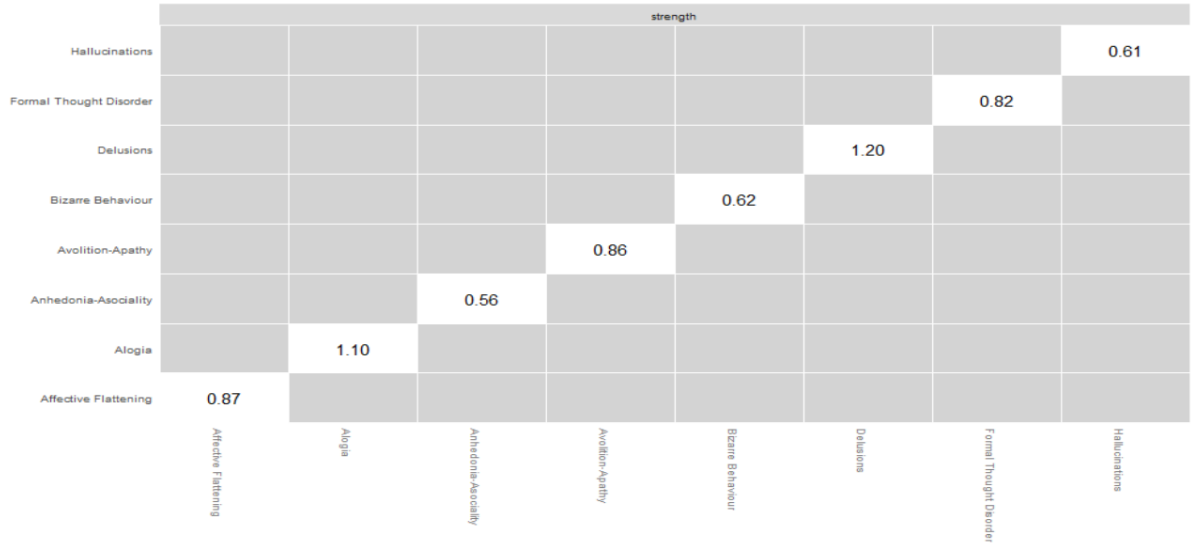

Figure 19: Bootstrapped difference test for node strength centrality, alpha level = 0.05. Each node is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the strength centrality of the node, such that stronger colour yields higher values. Grey boxes express no significant difference between nodes centrality. Black boxes represent significantly different node centrality.

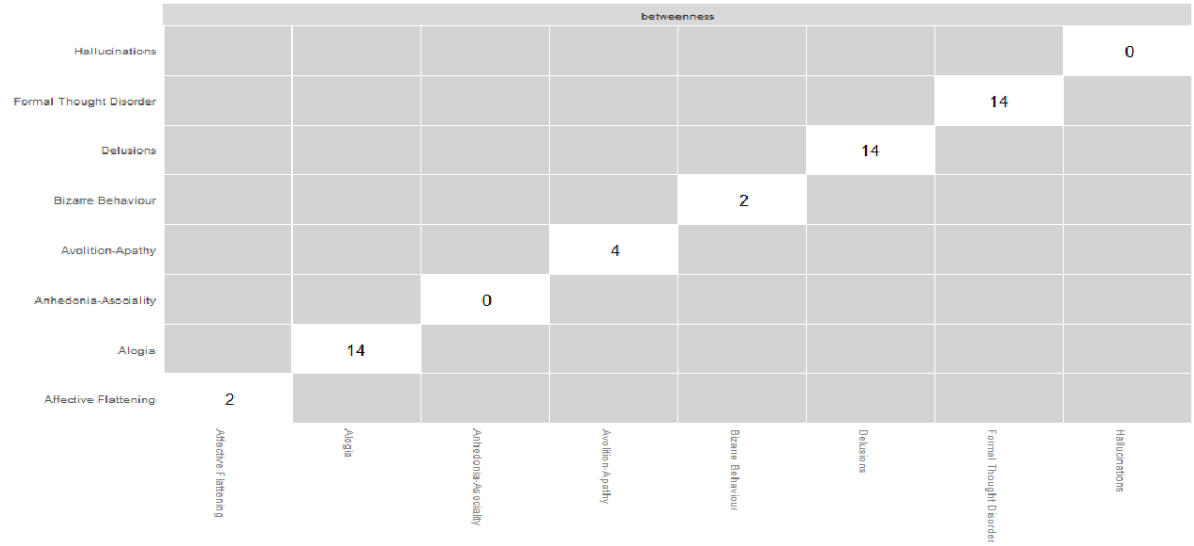

Figure 20: Bootstrapped difference test for node betweenness centrality, alpha level = 0.05. Each node is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the betweenness centrality of the node, such that stronger colour yields higher values. Grey boxes express no significant difference between nodes centrality. Black boxes represent significantly different node centrality.

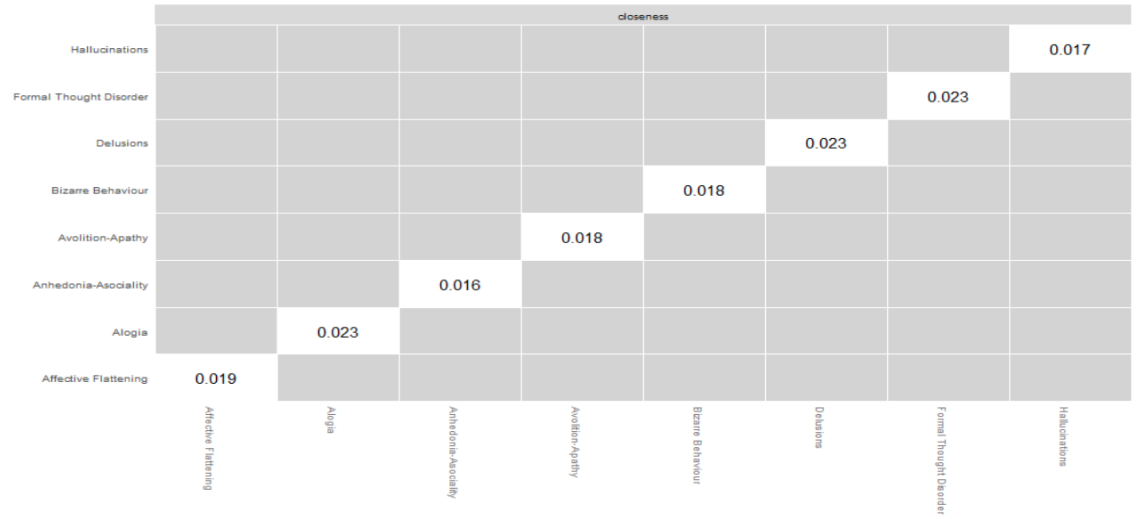

Figure 21: Bootstrapped difference test for node closeness centrality, alpha level = 0.05. Each node is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the closeness centrality of the node, such that stronger colour yields higher values. Grey boxes express no significant difference between nodes centrality. Black boxes represent significantly different node centrality.

Table 6: WS Clustering coefficients

Affective Flattening	Alogia	Avolition-Apathy	Anhedonia-Asociality	Hallucinations	Delusions	Bizzare Behaviour	Formal Thought Disorder
0.73	0.60	0.60	0.83	0.80	0.62	1.00	0.67

Table 6: Clustering coefficient table.

Network 4

Figure 22: Degree Distribution

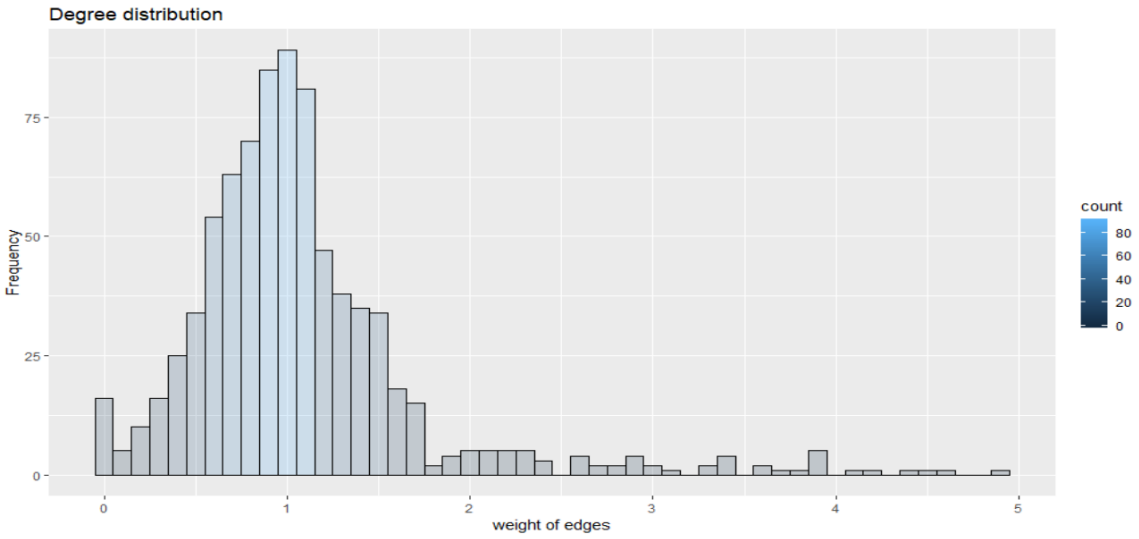

Figure 22: Sampled degree distribution of edge weights, based on 100 networks from the bootstrapping.

Figure x: Difference test for edge weights

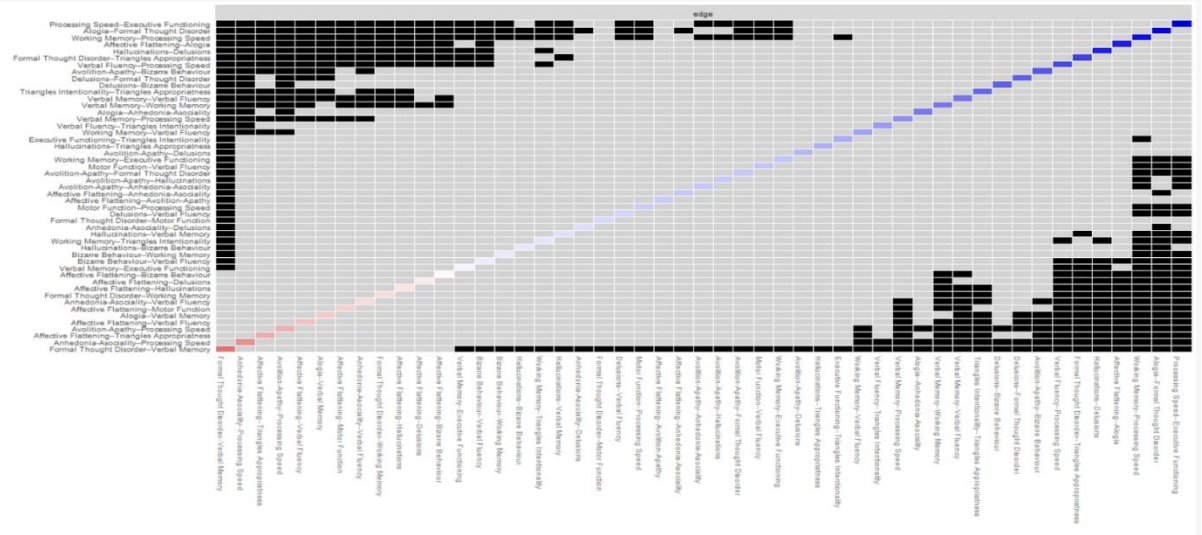

Figure 23: Bootstrapped difference test for edge weights, alpha level = 0.05. Each edge is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the weight of the edge, such that stronger colour yielding larger weight. Grey boxes express no significant difference between edge weights. Black boxes represent significantly different edges weights.

Table 7: Node centrality

	Betweenness	Closeness (x 100)	Strength (x 100)
Affective flattening	1	0.52	75.2
Alogia	15	**0.61**	86.8
Avolition-Apathy	4	0.46	70.5
Anhedonia-Asociality	4	0.53	55.7
Hallucinations	0	0.45	57.5
Delusions	**20**	0.55	93.0
Bizarre behaviour	2	0.46	51.7
Formal thought disorder	**42**	**0.70**	**114.1**
Verbal Memory	17	**0.61**	80.6
Working Memory	0	0.53	80.2
Motor Function	0	0.32	25.6

Verbal Fluency	6	0.58	**96.8**
Processing Speed	**26**	0.59	**135.2**
Executive Function	0	0.50	53.9
Triangles Intentionality	2	0.49	47.7
Triangles Appropriateness	7	0.56	66.8

Table 7: Node centrality indices

Figure 24: Confidence intervals on node strength

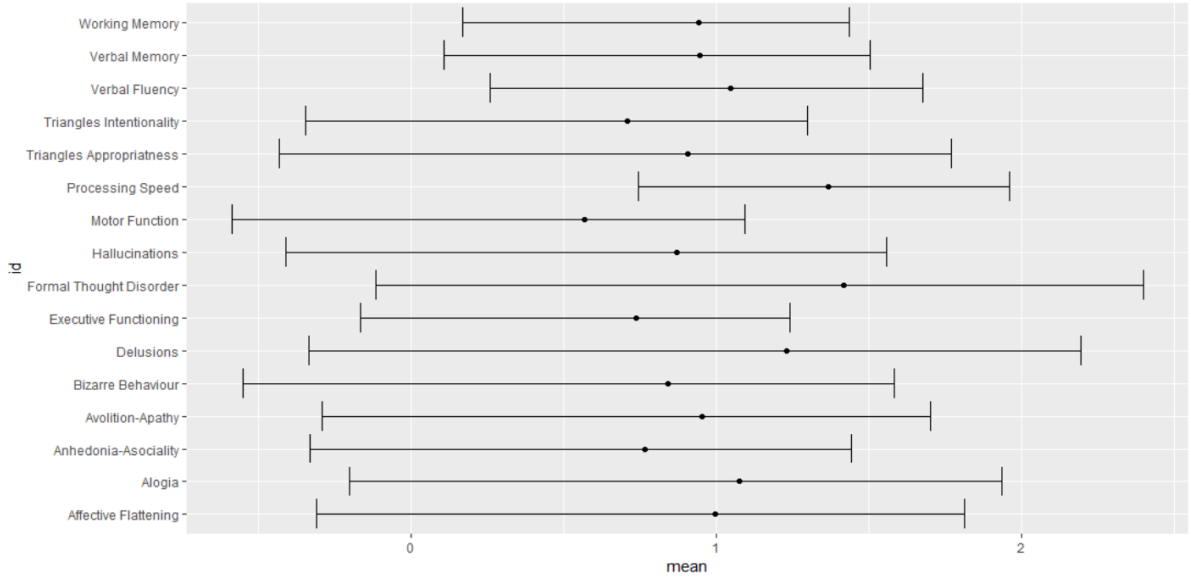

Figure 24: Confidence intervals on node centrality, strength.

Difference test for node centrality

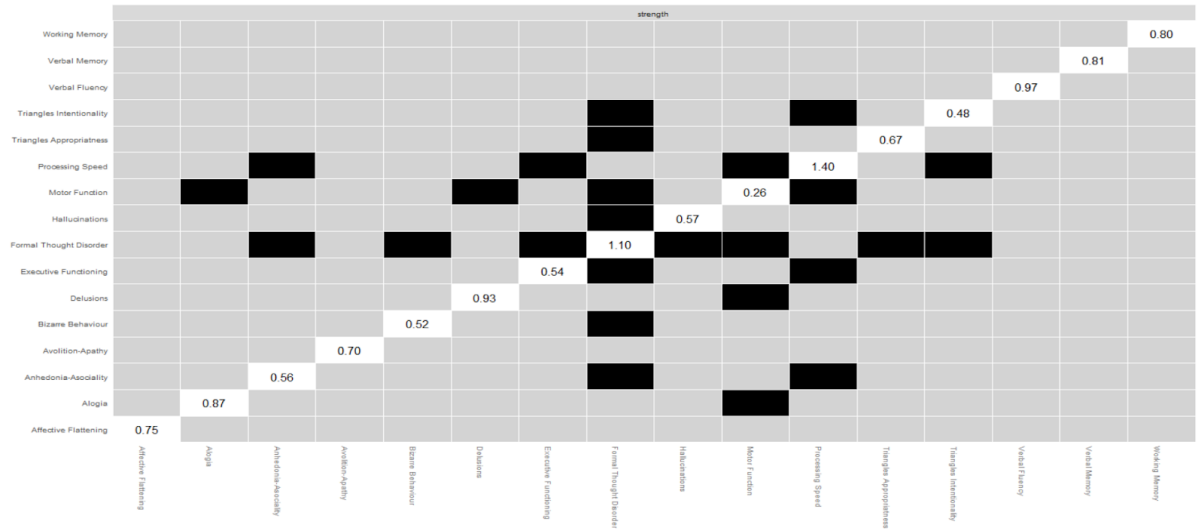

Figure 25: Bootstrapped difference test for node strength centrality, alpha level = 0.05. Each node is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the strength centrality of the node, such that stronger colour yields higher values. Grey boxes express no significant difference between nodes centrality. Black boxes represent significantly different node centrality.

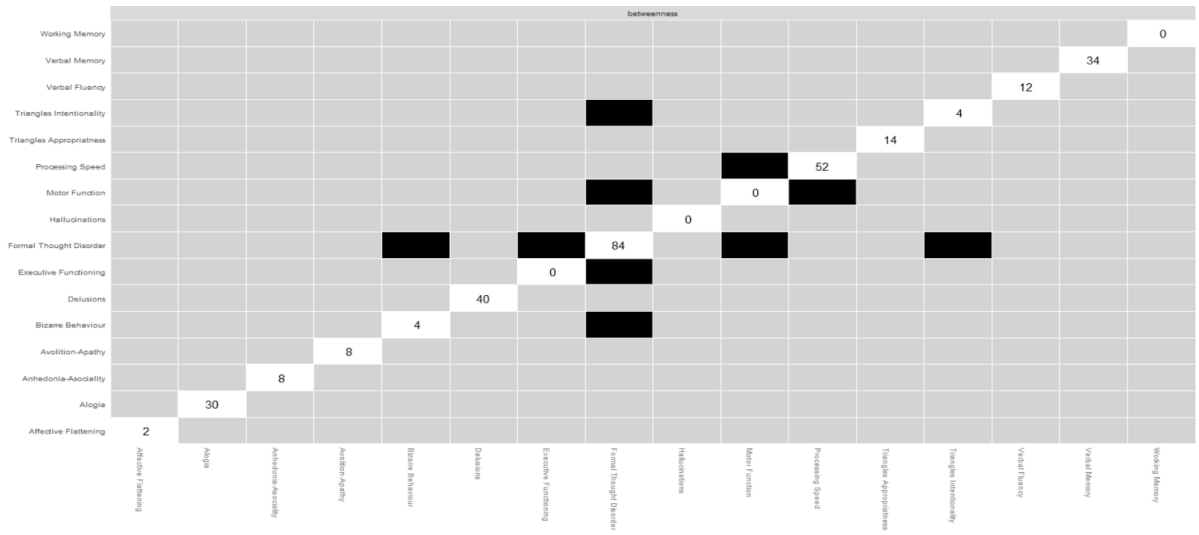

Figure 26: Bootstrapped difference test for node betweenness centrality, alpha level = 0.05. Each node is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the betweenness centrality of the node, such that stronger colour yields higher values. Grey boxes express no significant difference between nodes centrality. Black boxes represent significantly different node centrality.

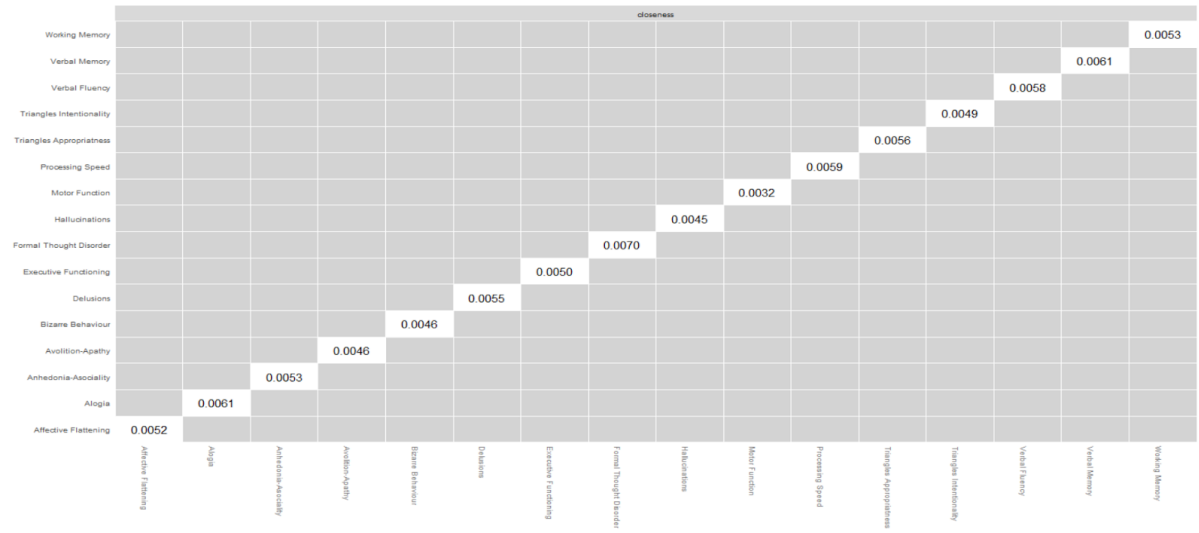

Figure 27: Bootstrapped difference test for node closeness centrality, alpha level = 0.05. Each node is represented horizontally and vertically in the matrix. The pink-blue boxes constitute the diagonal, and the colour saturation represent the closeness centrality of the node, such that stronger colour yields higher values. Grey boxes express no significant difference between nodes centrality. Black boxes represent significantly different node centrality.

Table 8: Clustering coefficients

Verbal Memory	Working Memory	Motor Function	Verbal Fluency	Processing Speed	Executive Functioning	Triangles Intentionality	Triangles Appropriatness
0.33	0.43	0.33	0.36	0.38	0.67	0.33	0.17

Affective Flattening	Alogia	Avolition-Apathy	Anhedonia-Asociality	Hallucinations	Delusions	Bizzare Behaviour	Formal Thought Disorder
0.39	0.33	0.48	0.53	0.47	0.57	0.60	0.14

Table 8: WS Clustering coefficient table.

Score distributions on cognitive tasks

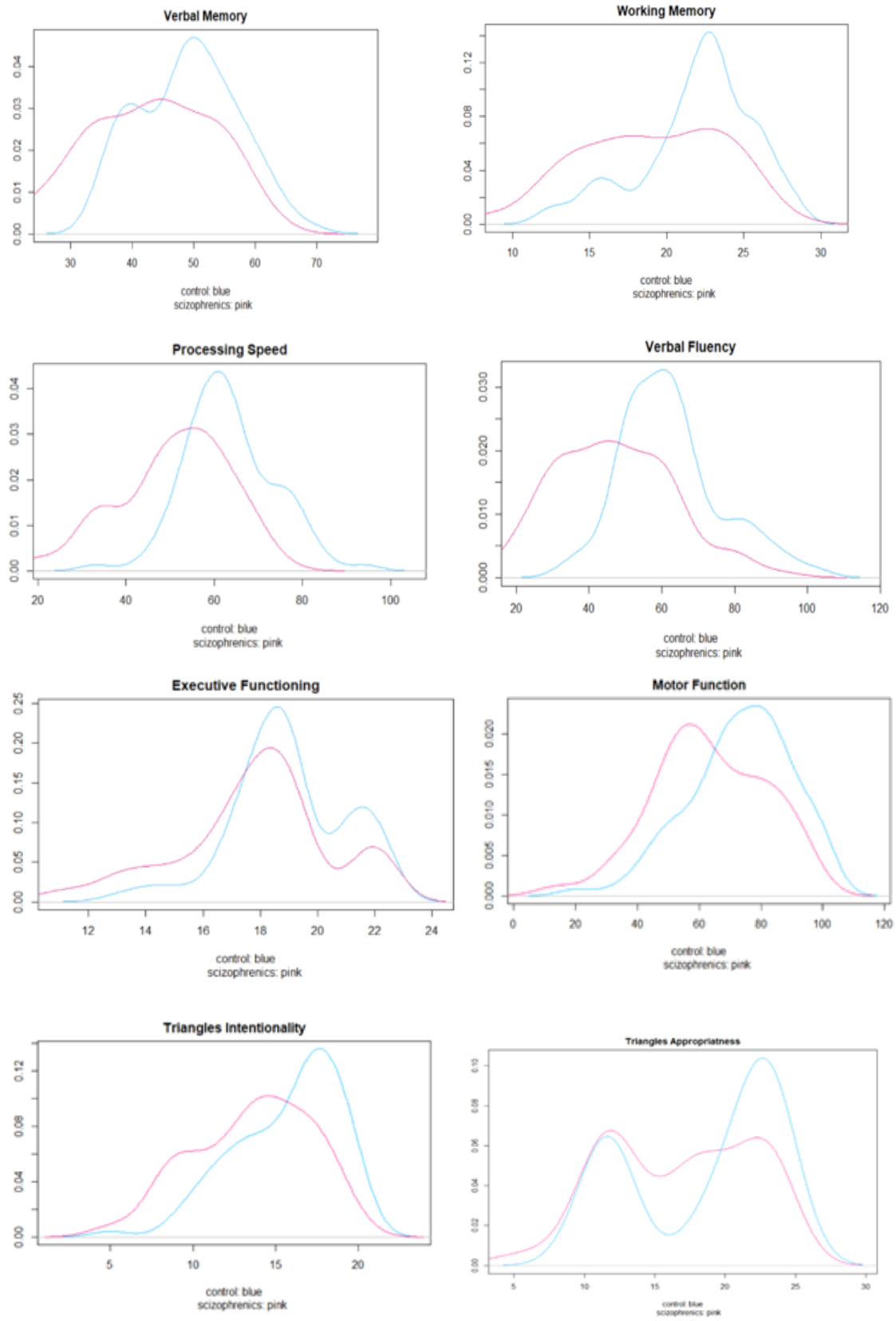

Figure 28: Density plots of cognitive measures in controls and schizophrenic patients