Supplementary Material

1.0 Supplementary methods

1.1. Centrality measures

To investigate the importance of individual symptoms we calculated the following three centrality measures: node strength, closeness and betweenness (Barrat et al., 2004; Boccaletti et al., 2006; Opsahl et al., 2010). 'Node strength' reflects the involvement of a node within the network and is calculated as the sum of the number and strength of all connections of one node to all other nodes. 'Closeness' is calculated as the inverse of the sum of all the shortest paths between the index symptom and all other symptoms and thereby gives an indication of how easy it is to reach all other nodes from the node of interest. The last centrality measure ('betweenness') is determined by counting how often a symptom of interest is placed on the shortest path between any combination of two nodes. Thus, a high betweenness indicates that a specific node is highly connected with other nodes in a network. Of note, centrality measures are highly correlated, however, for the completeness we calculated all three measures.

1.2 Network Comparison Test

In order to compare networks of psychotic remitted and non-remitted male patients we used a network comparison test (NCT; van Borkulo et al., 2017). The NCT is a permutation test (1000 iterations) in which the difference between networks of two groups (i.e., remitters and non-remitters) is calculated repeatedly for randomly regrouped individuals and is implemented in the *R* package 'NetworkComparisonTest'(R Core Team 2016; van Borkulo, 2016). By using the NCT it is possible to compare two (independent) networks based on i) network structure and ii) overall global strength. In the situation that the network structure shows a significant difference it is possible to test which specific edges differ significantly.

The NCT includes three steps: in the first step the networks of both groups are estimated. In the following steps, different networks are estimated based on randomly regrouped individuals (i.e., random permutation of group membership across cases) (van Borkulo et al., 2017) from these different networks. Thirdly, the test statistic of interest is calculated which generates a reference distribution and a *p*-value (which we determined to be significant at a threshold of p=. 05).

1.3. Stability check

The stability check was designed by Epskamp and colleagues and details of this test are published elsewhere (Epskamp et al., 2017) and also applied to our earlier performed network study (van Rooijen et al., 2017). Overall the results of the stability check give an indication of the robustness of

the network, by investigating how likely it is to find a comparable network when constructing the same network in another sample. More robust findings indicate that the degree of certainty of finding a comparable network in another sample is increased, which suggest generalizability of the generated network.

In order to apply stability tests, we make use of a technique known as 'bootstrapping resampling' (Efron, 1979). By using this procedure, a new cohort is created by multiplying the existing sample. From this cohort, a new sample is taken and analyzed: this process is repeated several times (i.e., 1000 iterations). The characteristics of the bootstrapped samples are plotted and analyzed (providing a sample with a normal distribution). The statistic measures of interest of the bootstrapped sample can be compared with the true values within the original data. For the stability checks the *R* package *'bootnet'* was used (Epskamp et al., 2016; R Core Team, 2016). The applied stability check consists of three parts: i) estimating bootstrapped confidence intervals (referred throughout the text below as CIs) on edge-weights for testing the accuracy of edge-weights and ii) a 'bootstrapped difference test' for edge-weights and iii) centrality measure 'node strength'.

1.3.1.Bootstrapped confidence intervals of edge-weights

In the generated network there are many edges connecting different symptoms with each other. Our network is an undirected, weighted network indicating that the edges connect different symptoms but, it is unclear whether symptom x influence symptom y, y influence symptom x, or causality goes both ways. Additionally, thicker lines represent stronger partial correlations between symptoms.

In this first part of the stability check, it is tested what the chance is of finding comparable strengths of the partial correlations between symptoms (i.e., edge-weights) when constructing the network in a different (but comparable) sample. For this, 95% bootstrapped CIs for edge-weights are constructed based on the normal variance in the bootstrapped sample. Based on the range of these CIs something can be said about the stability of the edge-weights (i.e., a wide interval represents low stability and a narrow interval represents high stability). Moreover, when a bootstrapped CI around a specific edge-weight contains 'zero' in it, this indicates that the weight of this edge does not differ significantly from other edge-weights. As a result, the applied ordering in the figure (indicating that the strength of the partial correlations between symptoms differ) might, however, not be the case. Hence, the stability check should not be interpreted as a significance test, but rather as a way to investigate the robustness of findings of a generated network.

1.3.2. Bootstrapped difference test for node strength and edge-weights

In this part of stability check, we investigate whether edge-weights and the centrality measure 'node strength' differ significantly from other edge-weights respectively other node strengths within the generated network. As mentioned earlier, node strength is a centrality measure, which is calculated by the sum of the weighted numbers of all associations of a specific node. As a result, a high node strength index indicates that a specific node is highly connected with other symptoms within the network.

For both counts (i.e., node strength and edge-weights), we calculated bootstrapped values of these measures for every symptom within the network. Next, difference scores between the bootstrapped values of every combination of two symptoms are calculated. Additionally, a difference score between the bootstrapped values of two symptoms is estimated and a CI around this difference score is constructed. Lastly, a null-hypothesis test is performed on the range of the CI. In the situation that the range of the constructed CIs contains 'zero' in it, the edge-weights (or node strength) of two different symptoms do not differ significantly from each other.

Of note, in the situation of performing multiple significant tests as done in the stability check described above, the problem of 'multiple testing' arises. This means that purely based on chance, a number of tests will test significantly while this might not be true. To get around this problem, one may use 'Bonferroni corrections' (Bland and Altman, 1995). Using Bonferroni corrections in the network approach will lead to very low significance levels, because when using Bonferroni correction one needs to divide α by the number of tests. Thus, as outlined by Epskamp and colleagues (2016), applying the Bonferroni correction to a "20-node network requires 17.955 tests, leading to a corrected significance level of 0.000003". Testing on this Bonferroni corrected significance level is not considered feasible. In other words, we recognize the limitations of the current stability tests, however, there are currently no other statistical techniques to investigate the stability of a network, nor methods to correct for multiple testing problem.

1.4 Exploratory Graph Analyses (EGA)

There are several methods to detect for the number of underlying dimensions in data. Here, we considered the Exploratory Graph Analysis (EGA) the most appropriate; as this technique allows not only to detect the number of underlying dimensions but also to assess which items belong to the same dimension. For the details of this approach we refer to Golino and Epskamp (2016) who in depth discusses the pros and cons of this approach. In short, the first steps of EGA resemble our approach of constructing a symptom network. At first, the correlation matrix of all variables is constructed, which is followed by LASSO regularization, which encompasses model selection with the Extended

Bayesian Information Criterion (EBIC). This is followed by the 'walktrap' algorithm, which defines the number of underlying communities within the partial correlation matrix. Based on random walks, this algorithm generates a "measure of similarities between vertices" (Golino and Epskamp, 2016) that determine the number of clusters within the symptom network.

2.0 Supplementary tables

Table S1. An overview of the items of the CDSS and the PANNS, their abbreviations, median and mean scores per item.

Iten	n description	Total s	ample (n=	470)	Males Re	emission	Males Non –					
					(n=150)			Remis	sion			
								(n= 31	6)			
Item†	Depressive	Mean	Median	IQR	Mean	Median	IQR	Mean	Median	IQR		
Label	symptoms	(SD)			(SD)							
	(CDSS, range											
	0 to 3)											
D1	Depressed	0.46	0	1	0.21	0	0	0.57	0	1		
	mood	(0.70)			(0.44)			(0.77)				
D2	Hopelessness	0.27	0	0	0.11	0	0	0.34	0	1		
		(0.60)			(0.35)			(0.67)				
D3	Self –	0.33	0	1	0.19	0	0	0.48	0	1		
	deprecation	(0.62)			(0.50)			(0.73)				
D4	Guilt ideas of	0.15	0	0	0.08	0	0	0.19	0	0		
	reference	(0.47)			(0.30)			(0.53)				
D5	Pathological	0.17	0	0	0.13	0	0	0.20	0	0		
	guilt	(0.49)				(0.41)		(0.53)				
D6	Morning	0.19	0	0	0.13	0	0	0.22	0	0		
	depression	(0.53)			(0.43)			(0.58)				
D7	Early wakening	0.11	0	0	0.07	0	0	0.13	0	0		
		(0.41)			(0.30)			(0.46)				
D8	Suicide	0.12	0	0	0.06	0	0	0.14	0	0		
		(0.41)			(0.24)		(0.44)					
D9	Observed	0.25	0	1	0.11	0	0	0.31	0	1		
	depression	(0.48)			(0.35)			(0.52)				
	Negative symp	toms (P	ANSS. rai	nge 1 to	o 7)							
N1	Blunted affect	2.12	2	2	1.61	1	1	2.37	3	3		
		(1.24)			(0.77)			(1.34)				
N2	Emotional	1.72	1	1	1.33	1	1	1.91	2	2		
	withdrawal	(1.00)			(0.60)			(1.09)				

N3	Poor rapport	1.54	1	1	1.20	1	0	1.71	1	1
		(0.96)			(0.52)			(1.07)		
N4	Passive social	2.00	1	2	1.42	1	1	2.27	2	2
	withdrawal	(1.28)			(0.74)			(1.40)		
N5	Difficulty in	1.73	1	1	1.47	1	0	1.86	1	2
	abstract	(1.15)			(0.92)			(1.23)		
	thinking									
N6	Lack of	1.68	1	1	1.35	1	1	1.85	1	2
	spontaneity	(1.10)			(0.65)			(1.23)		
N7	Stereotyped	1.45	1	1	1.22	1	0	1.56	1	1
	thinking	(0.90)			(0.54)			(1.01)		
	Positive symp	toms (PA	7)							
P1	Delusions	2.29	2	2	1.51	1	1	2.66	3	3
		(1.48)			(0.81)			(1.58)		
P2	Disorganization	1.60	1	1	1.23	1	0	1.77	1	1
		(1.05)			(0.55)			(1.19)		
P3	Hallucinatory	1.92	1	2	1.22	1	0	2.27	1	3
	behavior	(1.48)			(0.61)			(1.65)		
P4	Excitement	1.32	1	0	1.19	1	0	1.38	1	0
		(0.76)			(0.59)			(0.82)		
P5	Grandiosity	1.44	1	0	1.22	1	0	1.56	1	1
		(1.00)			(0.62)			(1.13)		
P6	Suspiciousness	1.99	1	2	1.49	1	1	2.22	2	2
		(1.30)			(0.84)			(1.42)		
P7	Hostility	1.20	1	0	1.07	1	0	1.27	1	0
		(0.58)			(0.35)			(0.65)		
	I									

[†]Item label corresponds to individual items (i.e., symptoms) as questioned in the Calgary Depression Scale for Schizophrenia (CDSS) and Positive and Negative Syndrome Scale (PANSS), IQR = interquartile range.

+	P1	P2	Р3	P4	P5	P6	P7	N1	N2	N3	N4	N5	N6	N7	D1	D2	D3	D4	D5	D6	D7	D8	D9
P1		.41	.42	.21	.39	.59	.20	.21	.23	.18	.25	.18	.08	.38	.26	.28	.25	.31	.16	.08	.05	.17	.22
Р2 Р3	.41		.27	.29	.20	.27	.24	.17	.29	.28	.28	.41	.17	.46	.14	.15	.12	.11	.08	.03	.03	.05	.15
P4	.42	.27		.08	.18	.33	.15	.15	.14	.13	.18	.16	.07	.15	.25	.22	.17	.18	.08	.05	.04	.12	.18
P5	.21	.29	.08		.22	.19	.34	.10 -	.02	.12	.00	.15	.08 -	.25	.01	.00	.02	.08	.04	.08	.10 -	.03	.04
P6	.39	.20	.18	.22		.31	.22	.09	.03	.06	.02	.01	.08	.24	.05	.08	.02	.17	.02	.03	.06	.08	.04
P7	.59	.27	.33	.19	.31		.28	.21	.22	.20	.22	.14	.08	.27	.27	.27	.23	.29	.14	.17	.02	.22	.21
N1	.20	.24	.15	.34	.22	.28	01	.01	.02	.12	.02	.12	.06	.13	.07	.14	.09	.03	.08	.09	.03	.10	.10
N2	.21 .23	.17 .29	.15	.10 .02	.09 .03	.21 .22	.01 .02	.54	.54	.43 .57	.49 .71	.23 .21	.51 .41	.20 .27	.26 .23	.20 .16	.20 .22	.13 .13	.12 .08	.08 .18	.15 .25	.09 .15	.31 .22
N3	.23	.29	.14 .13	.02	.03	.22	.02	.34	.57	.57	.71	.21	.41	.27	.25	.10	.22	.15	.08	.18	.25	.13	.22
N4	.10	.28	.15	.00	.00	.20	.02	.49	.71	.46	.10	.22	.36	.10	.13	.10	.12	.12	.01	.13	.10	.10	.20
N5	.18	.41	.16	.15	.01	.14	.12	.23	.21	.22	.29		.29	.34	.02	.11	.03	.04	- .05	- .03	.03	.03	.01
N6	.08	.17	.07	- .08	- .08	.08	.06	.51	.41	.57	.36	.29		.20	.20	.14	.15	.11	.03	.08	.09	.13	.18
N7	.38	.46	.15	.25	.24	.27	.13	.20	.27	.40	.25	.34	.20		.11	.07	.15	.17	.11	.01	.03	.09	.07
D1 D2	.26	.14	.25	.01	.05	.27	.07	.26	.23	.15	.22	.02	.20	.11		.48	.48	.26	.30	.42	.26	.39	.64
D2 D3	.28	.15	.22	.00	.08	.27	.14	.20	.16	.10	.26	.11	.14	.07	.48		.38	.20	.24	.18	.18	.50	.47
D4	.25	.12	.17	.02	.02	.23	.09	.20	.22	.12	.19	.03	.15	.15	.48	.38		.23	.33	.22	.16	.33	.40
D5	.31	.11	.18	.08 -	.17	.29	.03 -	.13	.13	.14	.12	.04 -	.11	.17	.26	.20	.23		.30	.14	.13	.14	.24
D6	.16	.08	.08	.04	.02	.14	.08	.12	.08	.01	.05	.05 -	.03	.11	.30	.24	.33	.30		.18	.08	.16	.24
D7	.08	.03	.05 -	.08	.03	.17	.09	.08	.18	.13	.12	.03	.08	.01	.42	.18	.22	.14	.18	. –	.27	.17	.27
D8	.05	.03	.04	.10	.06	.02	.03	.15	.25	.16	.15	.03	.09	.03	.26	.18	.16	.13	.08	.27	12	.13	.30
D9	.17 .22	.05	.12	.03	.08	.22	.10	.09	.15	.10	.10 20	.03	.13	.09	.39	.50 47	.33	.14	.16	.17	.13	12	.43
	.22	.15	.18	.04	.04	.21	.10	.31	.22	.14	.20	.01	.18	.07	.64	.47	.40	.24	.24	.27	.30	.43	

'Item label corresponds to individual items (i.e., symptoms) as questioned in the Calgary Depression Scale for Schizophrenia (CDSS) and the Positive and Negative Syndrome Scale (PANSS).

3.0 Supplementary Figures

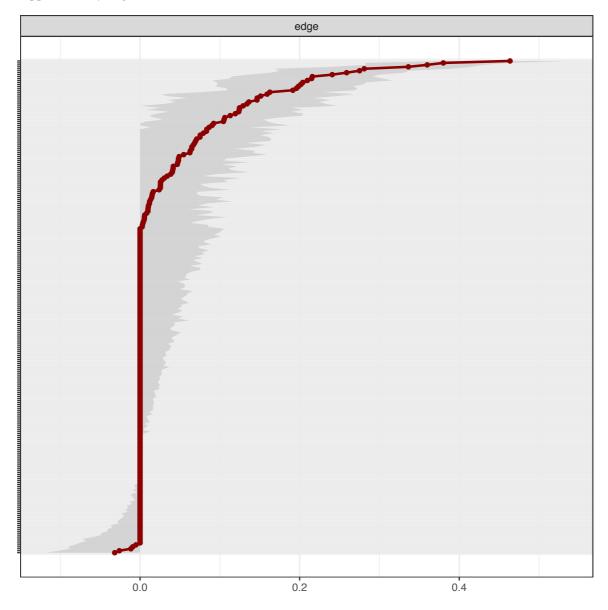


Figure S1. Bootstrapped Confidence intervals of all edges. Figure showing the bootstrapped 95% CIs around edge-weights. The X-axis represents the strength of the edge-weights. The y-axis lists all possible edges (i.e., $(n^*(n-1))/2) = 253$) between all 23 symptoms. Every horizontal line represents a certain edge-weights between two symptoms. But for the sake of clarity the labels are deleted. A top-down ordering is applied, so that the highest edge-weight is at the top (of the Y-axis) and the lowest edge-weights (i.e., negative correlations) are at the bottom. The red line indicates the value of the edge-weights in our network (Figure 1). The grey area around the red line indicates the bootstrapped 95% CIs. When CIs of different edge-weights show considerable overlap, the ordering of the edges could also be otherwise and the edge-weight might not significantly differ from each other (and the

top-down ordering could indeed be different). Likewise, when the range of the CIs contains zero, the edge-weights may also not differ from each other.

Based on this figure the following can be noticed: i) many CIs are larger then zero, for some of those there is considerable overlap with other CIs; ii) some edges are estimated as zero; iii) some CI are larger or smaller than zero but the bootstrapped CIs contain zero. The combination of overlap between CIs and the fact that many CIs include zero in their range implies that we should interpreted the network with caution regarding the differences between edge-weights. In other words, this figure indicates that differences edge-weights may not be significant, limiting us in the generalizability of the findings to other populations.

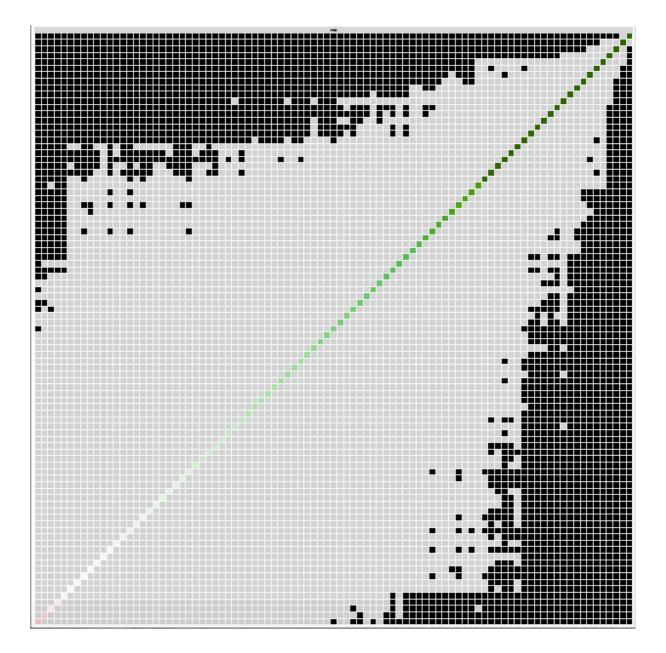


Figure S2. Bootstrapped stability test for edge-weight. Figure showing the results of the bootstrapped difference tests (α =0.05) for edge-weights. All possible edges (i.e., (n*(n-1))/2) = 253) between all 23 symptoms are shown at both axes. For the sake of clarity, the labels of the edges are deleted. The color of the boxes indicates whether edge-weights differ significantly from each other (i.e., black) or do not differ significantly (i.e., grey). The diagonal line indicates the strength of edge-weights, shifting from red (negative associations), to white (representing weaker edges) and ultimately dark green (representing stronger edge-weights).

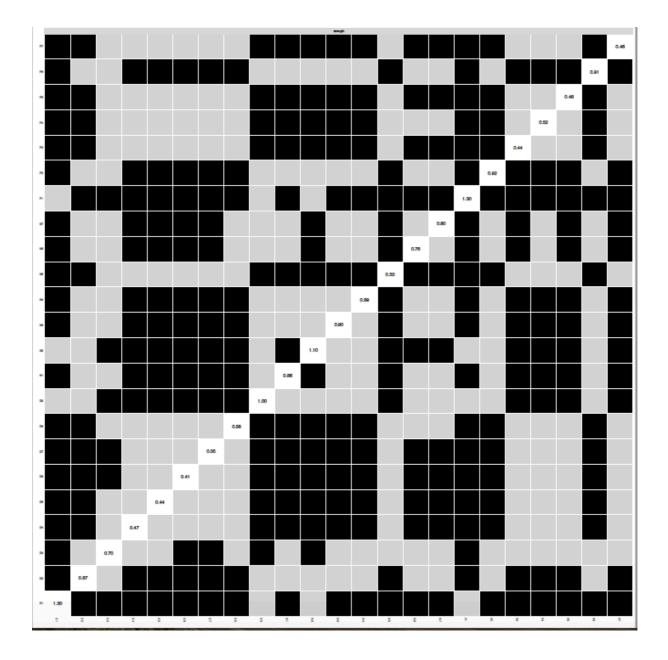


Figure S3. Bootstrapped stability test for centrality measure 'node strength'. Figure showing the results of the stability difference tests (α =0.05) for the centrality measure 'node strength'. Node strength reflects the involvement of a node within the network and is calculated as the sum of the

weighted number of all associations of a specific node. The applied stability test investigates whether node strengths of symptoms differ significantly from each other. For the sake of clarity, the labels of the symptoms (listed at both axes) are deleted. The color of the boxes indicates whether there is a significant difference between symptoms (i.e., grey boxes reflect no significant differences and black boxes reflect significant differences). The number in the white boxes (i.e., the diagonal line) denotes the value of node strength of a specific node. In this figure several black boxes can be noticed, indicating significant differences between symptoms regarding the centrality measure node strength.

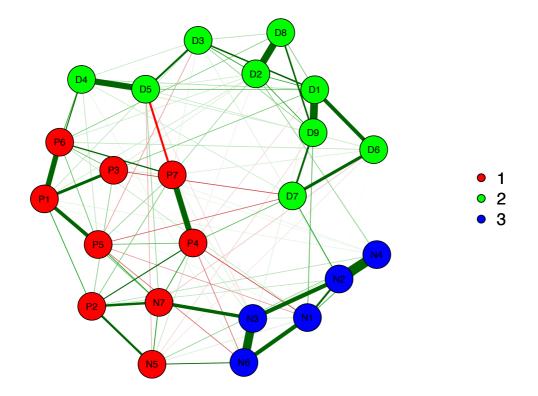


Figure S4. Network figure depicting the layout of the different dimensions derived from EGA

4.0 Supplementary R – Codes

##Required libraries library(qgraph) library(huge) library(NetworkComparisonTest) library(bootnet) library(EGA)

##Data Manipulation

#Total Sample - Men only
data_men <- read.csv("data.csv") ## Only men data</pre>

```
names(data_men) <- c("P1", "P2", "P3", "P4", "P5", "P6", "P7",
"N1", "N2", "N3", "N4", "N5", "N6", "N7",
"D1", "D2", "D3", "D4", "D5", "D6", "D7", "D8", "D9")
```

#Conduct nonparanormal transformation on the data & directly get back a correlation matrix datanpn_men <- huge.npn(data_men, npn.func='skeptic') # n = 470

```
#Compute network
network1 <- qgraph(datanpn_men, graph='glasso', sampleSize=nrow(data_men),
       layout='spring', color = c("red", "yellow", "green"),
       groups = list("Positive Symptoms" = 1:7,
              "Negative Symptoms" = 8:14,
              "Depressive Symptoms" = 15:23),
       vsize=3.5, legend.cex=.4, details=TRUE, cut=0, maximum=.5)
#Compute centrality indices
centralityPlot(network1)
# Save figures as pdf
# pdf("CDSS_men.pdf", width=(3.5/2.5)*5, height=5)
# network1 <- qgraph(datanpn_men, graph='glasso', sampleSize=nrow(data_men),</pre>
            layout='spring', color = c("red", "yellow", "green"),
#
#
            groups = list("Positive Symptoms" = 1:7,
#
                    "Negative Symptoms" = 8:14,
#
                    "Depressive Symptoms" = 15:23),
#
            vsize=4.5, legend.cex=.5, details=FALSE, cut=0, maximum=.5)
# dev.off()
#
# pdf("centralityCDSS_men.pdf")
# centralityPlot(network1)
# dev.off()
```

##Data Manipulation
datarem_long <- read.csv2("data2.remmission.csv", sep=",", header = TRUE) ## Data patients in
remission (n=150)
datanorem_long <- read.csv("data2.nonremission.csv", sep=",", header = TRUE) ## Data patients not
in remission (n=316)</pre>

names(datarem_long) <- c("P1", "P2", "P3", "P4", "P5", "P6", "P7", "N1", "N2", "N3", "N4", "N5", "N6", "N7", "D1", "D2", "D3", "D4", "D5", "D6", "D7", "D8", "D9") names(datanorem_long) <- c("P1", "P2", "P3", "P4", "P5", "P6", "P7", "N1", "N2", "N3", "N4", "N5", "N6", "N7", "D1", "D2", "D3", "D4", "D5", "D6", "D7", "D8", "D9")

```
#Conduct nonparanormal transformation on the data & directly get back a correlation matrix
dataremlong_npn <- huge.npn(datarem_long, npn.func='skeptic')
datanoremlong_npn <-huge.npn(datanorem_long, npn.func='skeptic')</pre>
```

```
#Compute networks
r <- qgraph(dataremlong npn, graph='glasso', sampleSize=nrow(datarem long),
      layout=network1$layout, groups = list("Positive Symptoms" = 1:7,
                          "Negative Symptoms" = 8:14,
                          "Depressive Symptoms" = 15:23),
      color=c("red", "yellow", "green"), vsize=4.5, legend.cex=.5,
      details=TRUE, cut=0, maximum=.5)
title("Remission Patients", line=1.4, adj=1)
nr <- qgraph(datanoremlong_npn, graph='glasso', sampleSize=nrow(datanorem_long),
       layout=network1$layout, groups = list("Positive Symptoms" = 1:7,
                           "Negative Symptoms" = 8:14,
                           "Depressive Symptoms" = 15:23),
       color=c("red", "yellow", "green"), vsize=4.5, legend.cex=.5,
       details=TRUE, cut=0, maximum=.5)
title("Non-Remission Patients", line=1.4, adj=1)
# Save Figures as pdf
# pdf("RemissionNoRemission_longitudinal.pdf", width=(3.5/2.5)*10, height=5)
# layout(t(1:2))
# r <- qgraph(dataremlong_npn, graph='glasso', sampleSize=nrow(datarem_long),</pre>
#
        layout=network1$layout, groups = list("Positive Symptoms" = 1:7,
#
                             "Negative Symptoms" = 8:14,
#
                             "Depressive Symptoms" = 15:23),
        color=c("red", "yellow", "green"), vsize=4.5, legend.cex=.5,
#
#
        details=TRUE, cut=0, maximum=.5)
# title("Remission Patients", line=1.4, adj=1)
#
# nr <- ggraph(datanoremlong npn, graph='glasso', sampleSize=nrow(datanorem long),</pre>
#
        layout=network1$layout, groups = list("Positive Symptoms" = 1:7,
#
                             "Negative Symptoms" = 8:14,
#
                             "Depressive Symptoms" = 15:23),
```

```
# color=c("red", "yellow", "green"), vsize=4.5, legend.cex=.5,
# details=TRUE, cut=0, maximum=.5)
# title("Non-Remission Patients", line=1.4, adj=1)
# dev.off()
```

##Network comparsion test to compare the network of patients in remission to ##the network of patients who were not in remission.

```
set.seed(1)
nct.res_long <- NCT(huge.npn(datarem_long), huge.npn(datanorem_long), gamma = 0, it = 1000,
weighted=TRUE, binary.data=FALSE, progressbar = TRUE, test.edges=TRUE, edges='all')</pre>
```

nct.res_long\$glstrinv.pval # 0.04 -> significant difference in global strength nct.res_long\$nwinv.pval # 0.4 -> no significant difference in terms of edge weights

##Write a function that uses the same estimation method as the one that has been used in the ##analysis (i.e., using the nonparanormal transformation)

```
estimator <- function(Data){

library("qgraph")

library("huge")

Network_cor <- huge.npn(Data, npn.func='skeptic')

Network <- qgraph(Network_cor, graph='glasso', sampleSize=nrow(Data), layout='spring')

return(getWmat(Network))

}
```

```
#Re-estimate Total sample network (men)
set.seed(1)
net_boot <- estimateNetwork(data_men, fun = estimator)</pre>
```

```
###Run stability check for the network
stability_men <- bootnet(net_boot, nBoots = 1000, nCores = 8)</pre>
```

```
plot(stability_men, order = "sample", labels=FALSE) # confidence intervals
plot(stability_men, "edge", plot = "difference", onlyNonZero = TRUE, order = "sample") # difference
of edges
plot(stability_men, "strength", plot = "difference") # node strenght
```

Save Figures as pdf

pdf("StabilityCDSSsample.pdf")
plot(stability_men, order = "sample", labels=FALSE)
dev.off()

```
# pdf("StabilityCDSSdiff.pdf", height=20, width=20)
# plot(stability_men, "edge", plot = "difference", onlyNonZero = TRUE, order = "sample")
# plot(stability_men, "strength", plot = "difference")
# dev.off()
```

#Run EGA EGA(data_men, plot.EGA = TRUE)

Save Figure as pdf
pdf("EGA.pdf", width=(3.5/2.5)*5, height=5)
EGA(data_men, plot.EGA = TRUE)
dev.off()

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