

THE DYNAMIC INTERACTION BETWEEN SYMPTOMS AND PHARMACOLOGICAL TREATMENT IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: THE ROLE OF NETWORK INTERVENTION ANALYSIS

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```
load(file = "Environment.RData")
```

In this document will be is provided the Source Code used to do the Network Analysis (models, predictability, and centrality measures) and Network Representations; as well as the code that generated the images of the Manuscript.

```
MDD_T0 <- as.matrix(MDD_T0)
MDD_T1 <- as.matrix(MDD_T1)

Groups_MDDT0 <- c(rep("Depression",2), rep("Neurocognitive",8),
                  rep("Psychosocial", 4))

Groups_MDDT1 <- c(rep("Depression",2), rep("Neurocognitive",8),
                  rep("Psychosocial", 4), rep("Treatment",2))
```

Creating groups for variable representation of Major Depression

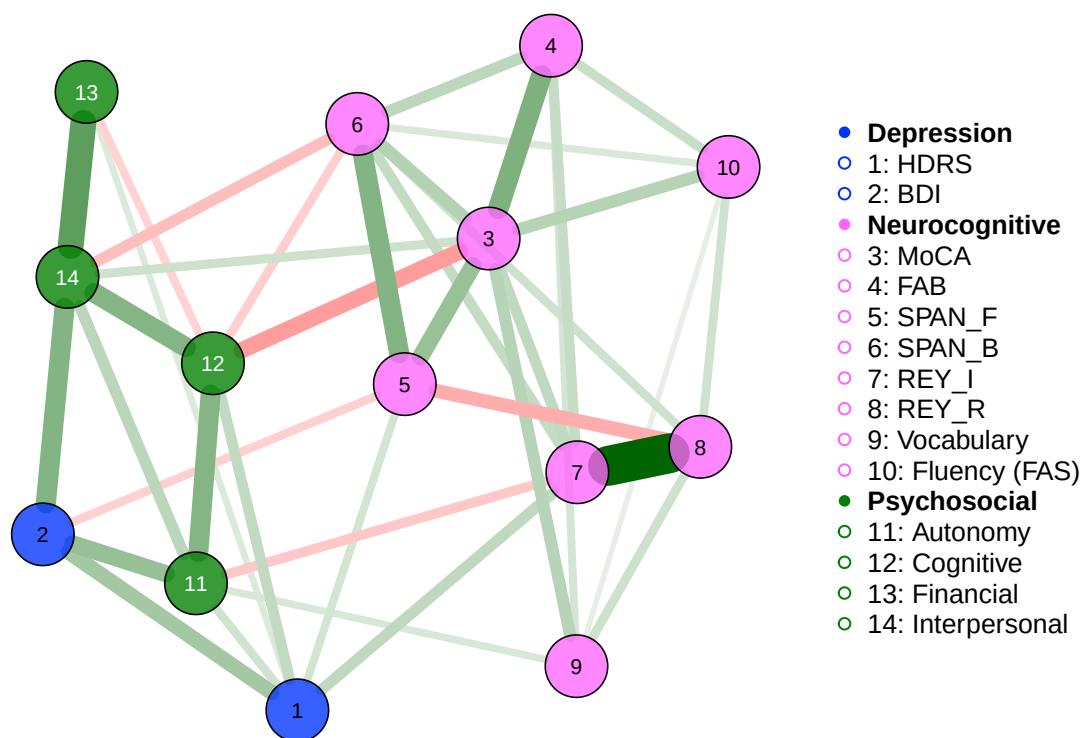
```
net_MDDT0 <- mgm(data = MDD_T0, alphaSel = "CV", alphaFolds = 10,
                 type = c("g","g","g","g","g","g","g","g","g","g",
                           "g","g","g","g","g"),
                 level = c("1","1","1","1","1","1","1","1","1","1",
                           "1","1","1","1","1"),
                 k = 2, ruleReg = "AND", alphaSeq = 0, scale = TRUE,
                 method = "glm", warnings = FALSE)
```

Mixed graphical Model for Time0 - MDD T0

```
## |
## Note that the sign of parameter estimates is stored separately; see ?mgm

qgraph_MDDT0 <- qgraph(net_MDDT0$pairwise$wadj, layout = "spring",
                      edge.color = net_MDDT0$pairwise$edgecolor,
                      groups = Groups_MDDT0, palette = "colorblind",
                      color = c("#0033FF", "#FF66FF", "#008000"),
                      nodeNames = colnames(MDD_T0), legend.mode = "style2",
                      legend.cex = 0.4, vTrans = 200,
                      vsizex = 5.5, esize = 25)

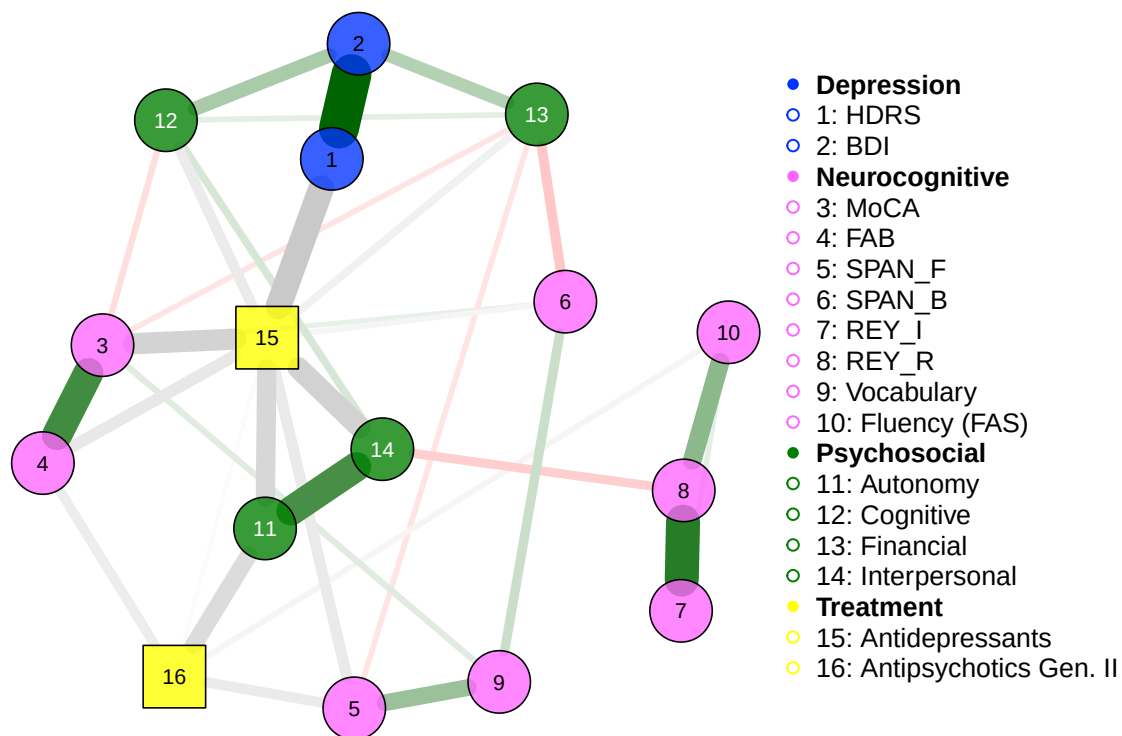
plot(qgraph_MDDT0)
```



```
net_MDDT1<- mgm(data = MDD_T1, alphaSel = "CV", alphaFolds = 10,
  type = c("g","g","g","g","g","g","g","g","g",
    "g","g","g","g","g","c","c"),
  level = c("1","1","1","1","1","1","1","1","1",
    "1","1","1","1","1","2","2"),
  k = 2, ruleReg = "OR", alphaSeq = 0, scale = TRUE,
  method = "glm", warnings = FALSE)
```

Mixed Graphical Model for Time1 - MDD T1

```
## |
## Note that the sign of parameter estimates is stored separately; see ?mgm
qgraph_MDDT1 <- qgraph(net_MDDT1$pairwise$wadj, layout = "spring",
  edge.color = net_MDDT1$pairwise$edgecolor,
  groups = Groups_MDDT1, palette = "colorblind",
  color = c("#0033FF", "#FF66FF", "#008000", "#FFFF00"),
  shape = c("circle","circle","circle","circle",
    "circle","circle","circle","circle",
    "circle","circle","circle","circle",
    "circle","circle","square","square"),
  nodeNames = colnames(MDD_T1), legend.mode = "style2",
  legend.cex = 0.4, vTrans = 200,
  vsiz = 5.5, esize = 25)
plot(qgraph_MDDT1)
```



```
A <- ncol(MDD_T0)

pred_objA <- predict(object = net_MDDT0, data = MDD_T0,
  errorCat = c("CC", "nCC", "CCmarg"),
  errorCon = c("R2"))

errorsA <- list()
for(i in 1:14) errorsA[[i]] <- pred_objA$errors[i,2]

color_listA <- list()
for(i in 1:14) color_listA[[i]] <- "#000000"
```

Predictability of the Nodes MDD_T0

```
B <- ncol(MDD_T1)

pred_objB <- predict(object = net_MDDT1, data = MDD_T1,
  errorCat = c("CC", "nCC", "CCmarg"),
  errorCon = c("R2"))

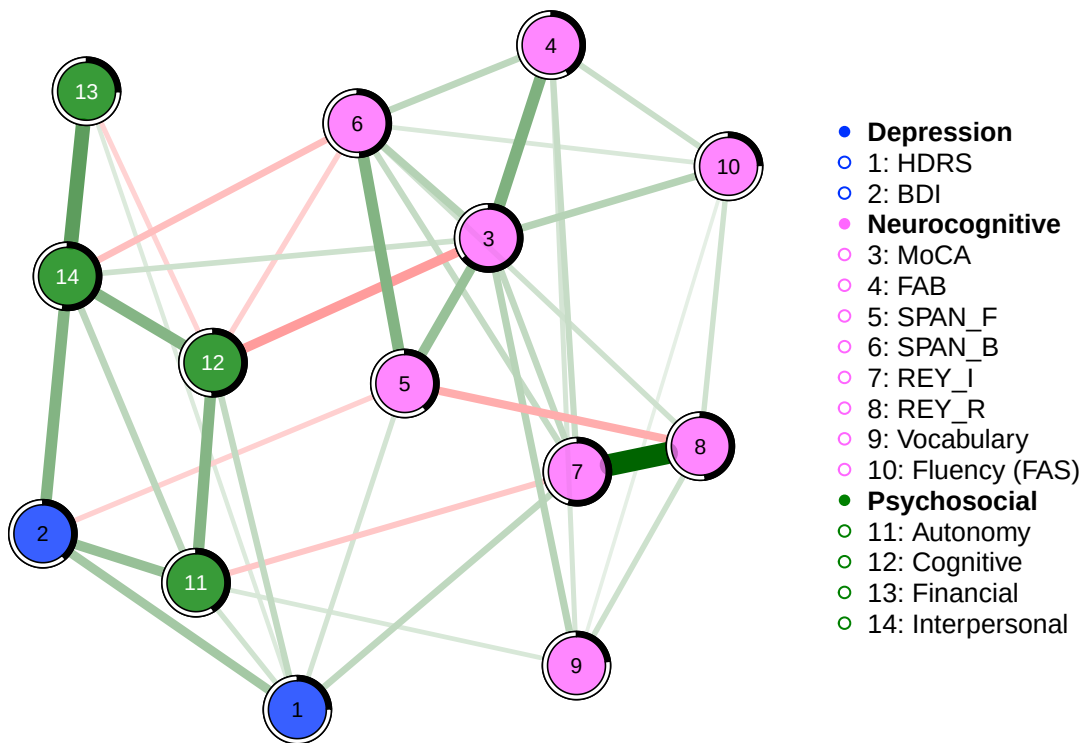
errorsB <- list()
for(i in 1:14) errorsB[[i]] <- pred_objB$errors[i,2]
for(i in 15:16) errorsB[[i]] <- pred_objB$errors[i,4]

color_listB <- list()
for(i in 1:16) color_listB[[i]] <- "#000000"
```

Predictability of the Nodes MDD_T1

```
NET_MDD_T0 <- qgraph(net_MDDT0$pairwise$wadj,
  layout = "spring", groups = Groups_MDDT0,
  vsize = 6, vTrans = 200, theme = "colorblind",
  edge.color = net_MDDT0$pairwise$edgecolor,
  nodeNames = colnames(MDD_T0), legend.mode = "style2",
  legend.mode = "style2", legend.cex = 0.4,
  color = c("#0033FF", "#FF66FF", "#008000"),
  pie = errorsA, pieColor = color_listA,
  title = "MDD T0")
```

Representation of the final network of MDD T0 & T1 with predictability rings
MDD T0



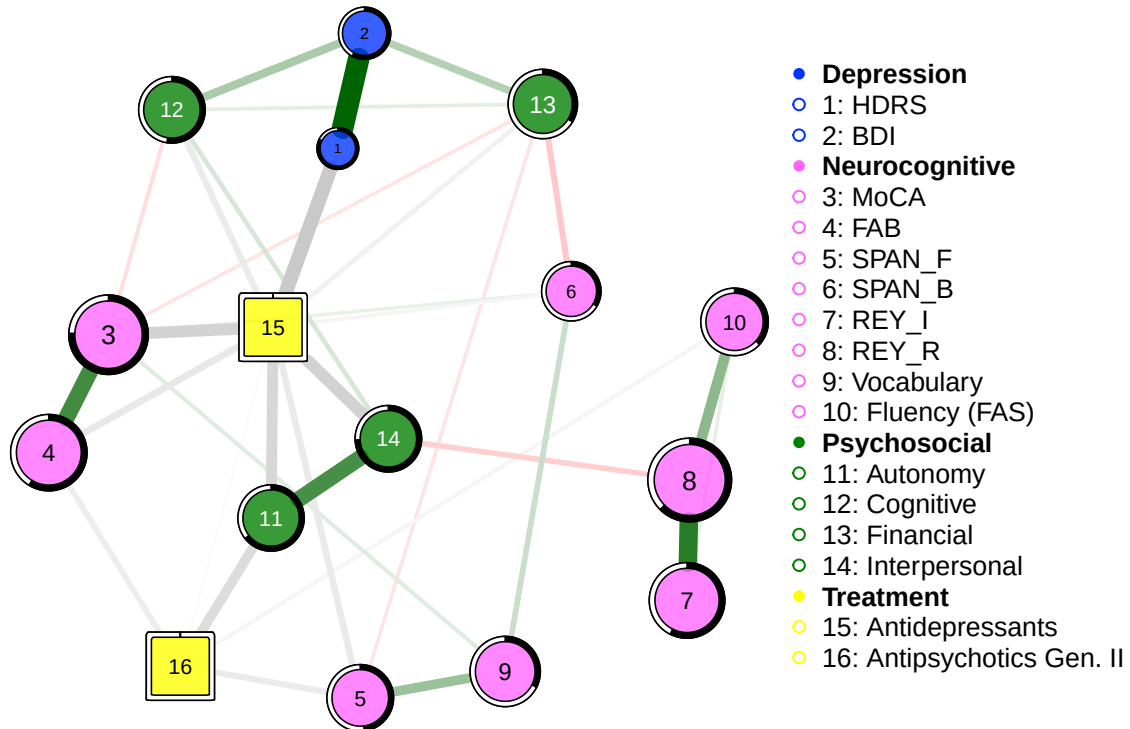
```
NET_MDD_T1 <- qgraph(net_MDDT1$pairwise$wadj,
  layout = "spring", groups = Groups_MDDT1,
  vsize = c(3.67,4.59,6.99,6.72,5.86,5.22,6.65,7.36,6.18,
    5.93,5.83,5.85,6.10,5.85, 6,6),
  vTrans = 200, theme = "colorblind",
  edge.color = net_MDDT1$pairwise$edgecolor,
  nodeNames = colnames(MDD_T1), legend.mode = "style2",
  legend.mode = "style2", legend.cex = 0.4,
  color = c("#0033FF", "#FF66FF", "#008000", "#FFFF00"),
  shape = c("circle","circle","circle","circle",
    "circle","circle","circle","circle",
    "circle","circle","circle","circle",
    "circle","circle","circle","circle"),
```

```

      "circle", "circle", "square", "square"),
    pie = errorsB, pieColor = color_listB,
    title = "MDD T1")

```

MDD T1



< ##### Transformation from qgraph to igraph object to do cluster analysis ##### <

```

MDDT0_igraph <- as.igraph(NET_MDD_T0)
MDDT1_igraph <- as.igraph(NET_MDD_T1)

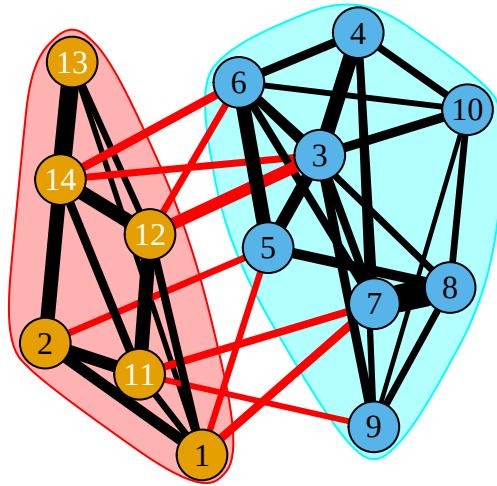
```

< ##### Cluster MDD with walktrap algorithm for MDD T0 and MDD T1 in order to see where there is a specific area where drugs take action ##### <

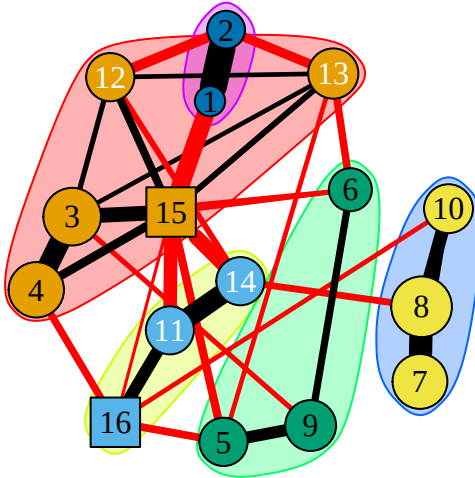
```

walktrap_MDDT0 <- cluster_walktrap(MDDT0_igraph)
plot(walktrap_MDDT0, MDDT0_igraph, layout = NET_MDD_T0$layout)

```



```
walktrap_MDDT1 <- cluster_walktrap(MDDT1_igraph)
plot(walktrap_MDDT1, MDDT1_igraph, layout = NET_MDD_T1$layout)
```



```
ecount(MDDT0_igraph)
```

Network Density and edge count

```
## [1] 39
```

```
edge_density(MDDT0_igraph, loops = FALSE)
```

```
## [1] 0.4285714
```

```
ecount(MDDT1_igraph)
```

```
## [1] 33
```

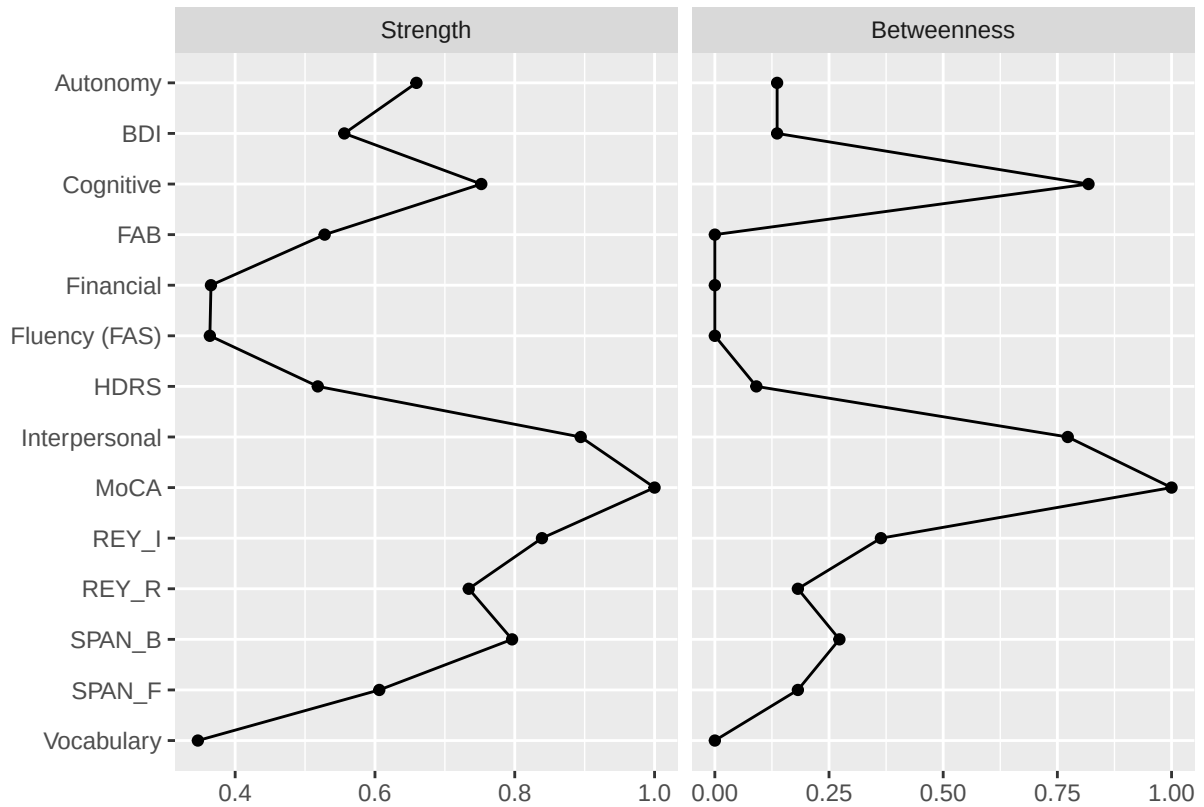
```
edge_density(MDDT1_igraph, loops = FALSE)
```

```
## [1] 0.275
```

```
CentralityPlot <- centralityPlot(NET_MDD_TO,
                                include = c("Strength", "Betweenness"),
                                scale = "relative", decreasing = TRUE,
                                theme_bw = FALSE, weighted = TRUE,
                                labels = colnames(MDD_TO))
```

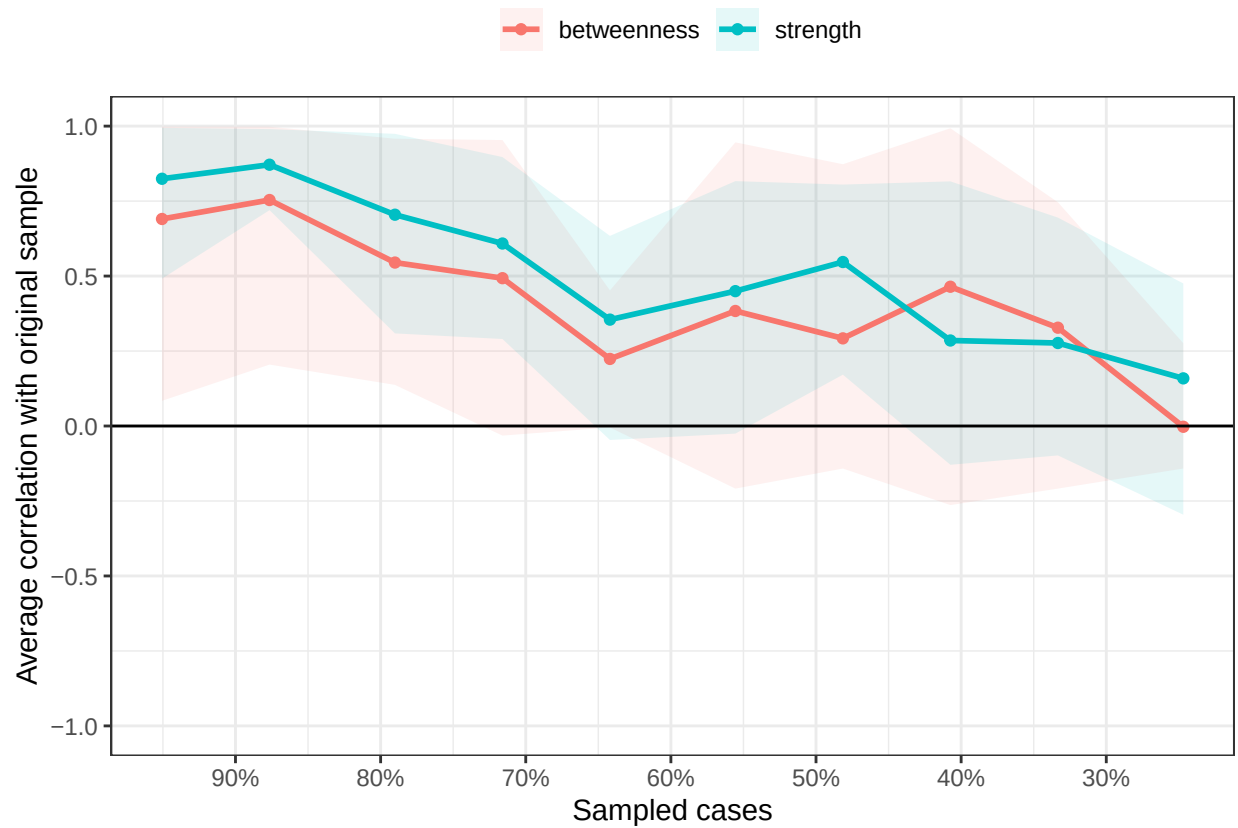
CENTRALITY ANALISYS

Note: relative centrality indices are shown on x-axis rather than raw centrality indices.



```
Bootstrap centrality Major Depressive Disorder boot_MDD_T0 <- bootnet(MDD_T0, nBoots =
100, nCores = 4, default = "mgm", type = "case", statistics = c("strength", "betweenness", "closeness"))
plot(boot_MDD_T0, statistics = c("strength", "betweenness", "closeness"))
```

```
## Warning in plot.bootnet(boot_MDD_T0, statistics = c("strength", "betweenness",
## : Statistic closeness does not contain any variance and is therefore not shown.
```

```
boot_MDD_T1 <- bootnet(MDD_T1, nBoots = 100, nCores = 4, default = "mgm", type = "case", statistics = c("strength", "betweenness", "closeness"))
```

```
plot(boot_MDD_T1, statistics = c("strength", "betweenness", "closeness"))
```

```
## Warning in plot.bootnet(boot_MDD_T1, statistics = c("strength", "betweenness",  
## : Statistic closeness does not contain any variance and is therefore not shown.
```



```
cenMDD_T0 <- centralityTable(NET_MDD_T0, standardized = FALSE, relative = TRUE)
cenMDD_T1 <- centralityTable(NET_MDD_T1, standardized = FALSE, relative = TRUE)

cenMDD_T0
```

CUSTOM MADE CENTRALITY PLOT

##	graph	type	node	measure	value
## 1	graph 1	NA	1	Betweenness	0.09090909
## 2	graph 1	NA	2	Betweenness	0.13636364
## 3	graph 1	NA	3	Betweenness	1.00000000
## 4	graph 1	NA	4	Betweenness	0.00000000
## 5	graph 1	NA	5	Betweenness	0.18181818
## 6	graph 1	NA	6	Betweenness	0.27272727
## 7	graph 1	NA	7	Betweenness	0.36363636
## 8	graph 1	NA	8	Betweenness	0.18181818
## 9	graph 1	NA	9	Betweenness	0.00000000
## 10	graph 1	NA	10	Betweenness	0.00000000
## 11	graph 1	NA	11	Betweenness	0.13636364
## 12	graph 1	NA	12	Betweenness	0.81818182
## 13	graph 1	NA	13	Betweenness	0.00000000
## 14	graph 1	NA	14	Betweenness	0.77272727
## 15	graph 1	NA	1	Closeness	0.68467243
## 16	graph 1	NA	2	Closeness	0.73844121
## 17	graph 1	NA	3	Closeness	1.00000000

```

## 18 graph 1 NA 4 Closeness 0.75691285
## 19 graph 1 NA 5 Closeness 0.85746847
## 20 graph 1 NA 6 Closeness 0.81931316
## 21 graph 1 NA 7 Closeness 0.79430924
## 22 graph 1 NA 8 Closeness 0.73581575
## 23 graph 1 NA 9 Closeness 0.61757337
## 24 graph 1 NA 10 Closeness 0.60658203
## 25 graph 1 NA 11 Closeness 0.80238607
## 26 graph 1 NA 12 Closeness 0.92800168
## 27 graph 1 NA 13 Closeness 0.63403337
## 28 graph 1 NA 14 Closeness 0.80665358
## 29 graph 1 NA 1 Strength 0.51822035
## 30 graph 1 NA 2 Strength 0.55614186
## 31 graph 1 NA 3 Strength 1.00000000
## 32 graph 1 NA 4 Strength 0.52805484
## 33 graph 1 NA 5 Strength 0.60617965
## 34 graph 1 NA 6 Strength 0.79616162
## 35 graph 1 NA 7 Strength 0.83891893
## 36 graph 1 NA 8 Strength 0.73420235
## 37 graph 1 NA 9 Strength 0.34663214
## 38 graph 1 NA 10 Strength 0.36381765
## 39 graph 1 NA 11 Strength 0.65934275
## 40 graph 1 NA 12 Strength 0.75212558
## 41 graph 1 NA 13 Strength 0.36538777
## 42 graph 1 NA 14 Strength 0.89434855
## 43 graph 1 NA 1 ExpectedInfluence 0.51822035
## 44 graph 1 NA 2 ExpectedInfluence 0.55614186
## 45 graph 1 NA 3 ExpectedInfluence 1.00000000
## 46 graph 1 NA 4 ExpectedInfluence 0.52805484
## 47 graph 1 NA 5 ExpectedInfluence 0.60617965
## 48 graph 1 NA 6 ExpectedInfluence 0.79616162
## 49 graph 1 NA 7 ExpectedInfluence 0.83891893
## 50 graph 1 NA 8 ExpectedInfluence 0.73420235
## 51 graph 1 NA 9 ExpectedInfluence 0.34663214
## 52 graph 1 NA 10 ExpectedInfluence 0.36381765
## 53 graph 1 NA 11 ExpectedInfluence 0.65934275
## 54 graph 1 NA 12 ExpectedInfluence 0.75212558
## 55 graph 1 NA 13 ExpectedInfluence 0.36538777
## 56 graph 1 NA 14 ExpectedInfluence 0.89434855

```

cenMDD_T1

```

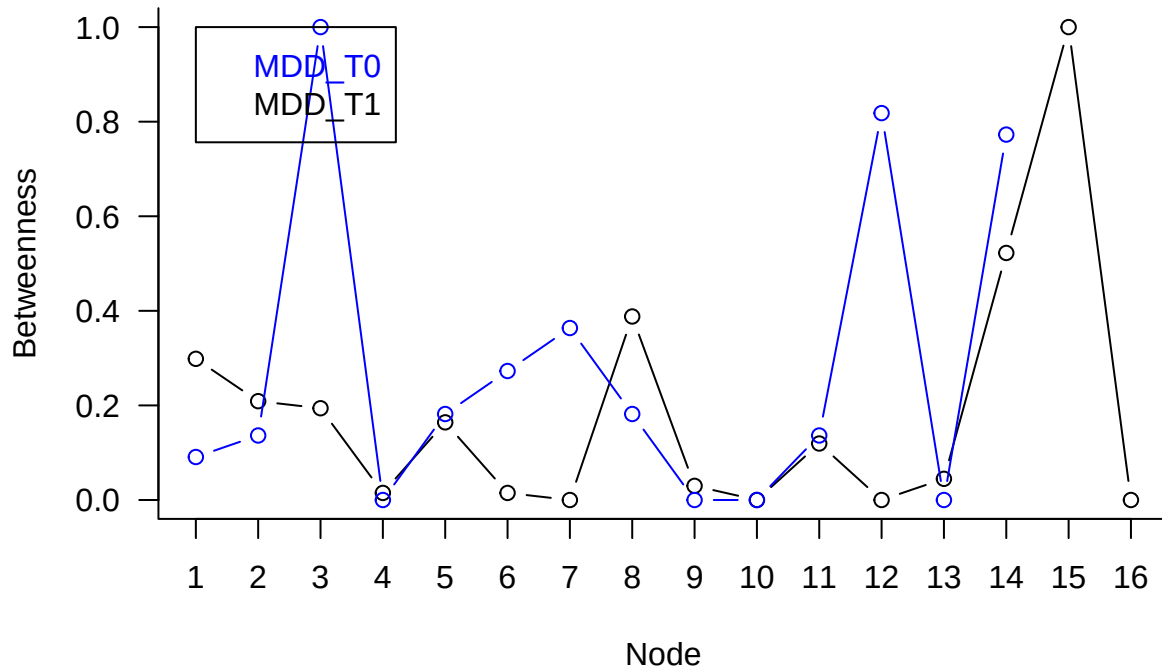
##      graph type node      measure      value
## 1 graph 1 NA 1 Betweenness 0.29850746
## 2 graph 1 NA 2 Betweenness 0.20895522
## 3 graph 1 NA 3 Betweenness 0.19402985
## 4 graph 1 NA 4 Betweenness 0.01492537
## 5 graph 1 NA 5 Betweenness 0.16417910
## 6 graph 1 NA 6 Betweenness 0.01492537
## 7 graph 1 NA 7 Betweenness 0.00000000
## 8 graph 1 NA 8 Betweenness 0.38805970
## 9 graph 1 NA 9 Betweenness 0.02985075
## 10 graph 1 NA 10 Betweenness 0.00000000
## 11 graph 1 NA 11 Betweenness 0.11940299
## 12 graph 1 NA 12 Betweenness 0.00000000

```

##	13	graph	1	NA	13	Betweenness	0.04477612
##	14	graph	1	NA	14	Betweenness	0.52238806
##	15	graph	1	NA	15	Betweenness	1.00000000
##	16	graph	1	NA	16	Betweenness	0.00000000
##	17	graph	1	NA	1	Closeness	0.85443577
##	18	graph	1	NA	2	Closeness	0.78093551
##	19	graph	1	NA	3	Closeness	0.76389986
##	20	graph	1	NA	4	Closeness	0.65281576
##	21	graph	1	NA	5	Closeness	0.65855102
##	22	graph	1	NA	6	Closeness	0.44667176
##	23	graph	1	NA	7	Closeness	0.48100814
##	24	graph	1	NA	8	Closeness	0.54012449
##	25	graph	1	NA	9	Closeness	0.53025901
##	26	graph	1	NA	10	Closeness	0.44439972
##	27	graph	1	NA	11	Closeness	0.82746094
##	28	graph	1	NA	12	Closeness	0.60428164
##	29	graph	1	NA	13	Closeness	0.55801238
##	30	graph	1	NA	14	Closeness	0.87941539
##	31	graph	1	NA	15	Closeness	1.00000000
##	32	graph	1	NA	16	Closeness	0.68757112
##	33	graph	1	NA	1	Strength	0.51001430
##	34	graph	1	NA	2	Strength	0.50920724
##	35	graph	1	NA	3	Strength	0.53217758
##	36	graph	1	NA	4	Strength	0.38319922
##	37	graph	1	NA	5	Strength	0.30679318
##	38	graph	1	NA	6	Strength	0.19645120
##	39	graph	1	NA	7	Strength	0.29721390
##	40	graph	1	NA	8	Strength	0.46590143
##	41	graph	1	NA	9	Strength	0.22818190
##	42	graph	1	NA	10	Strength	0.20732068
##	43	graph	1	NA	11	Strength	0.49906056
##	44	graph	1	NA	12	Strength	0.30086994
##	45	graph	1	NA	13	Strength	0.30977658
##	46	graph	1	NA	14	Strength	0.49886905
##	47	graph	1	NA	15	Strength	1.00000000
##	48	graph	1	NA	16	Strength	0.31573258
##	49	graph	1	NA	1	ExpectedInfluence	0.51001430
##	50	graph	1	NA	2	ExpectedInfluence	0.50920724
##	51	graph	1	NA	3	ExpectedInfluence	0.53217758
##	52	graph	1	NA	4	ExpectedInfluence	0.38319922
##	53	graph	1	NA	5	ExpectedInfluence	0.30679318
##	54	graph	1	NA	6	ExpectedInfluence	0.19645120
##	55	graph	1	NA	7	ExpectedInfluence	0.29721390
##	56	graph	1	NA	8	ExpectedInfluence	0.46590143
##	57	graph	1	NA	9	ExpectedInfluence	0.22818190
##	58	graph	1	NA	10	ExpectedInfluence	0.20732068
##	59	graph	1	NA	11	ExpectedInfluence	0.49906056
##	60	graph	1	NA	12	ExpectedInfluence	0.30086994
##	61	graph	1	NA	13	ExpectedInfluence	0.30977658
##	62	graph	1	NA	14	ExpectedInfluence	0.49886905
##	63	graph	1	NA	15	ExpectedInfluence	1.00000000
##	64	graph	1	NA	16	ExpectedInfluence	0.31573258

FIGURE 2 - Betweenness Centrality MDD-T0 and MDD-T1 pdf("CustomBetweenness_MDDNetwork.pdf", width = 20, height = 5)

```
plot(x <- cenMDD_T1$value[1:16],
     type = "b",
     bty = "n",
     family = "sans",
     las = 1, lwd = 1,
     xaxt = "n",
     xlab = "Node",
     ylab = "Betweenness")
axis(side = 1, labels = c(1:16), at = c(1:16))
lines(cenMDD_T0$value[1:16], type = "b", col = "#0000FF")
legend(x = 1, legend = c("MDD_T0", "MDD_T1"),
      text.col = c("#0000FF", "#000000"))
```



dev.off()

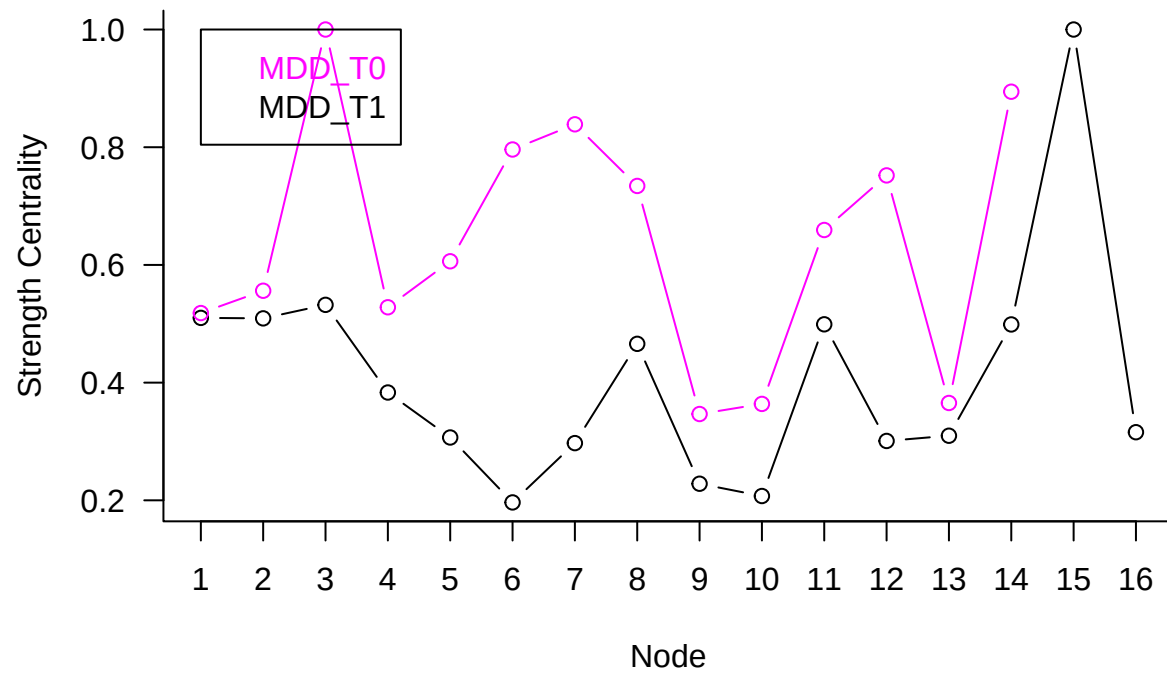
FIGURE 3 - Strength Centrality MDD pdf("CustomStrength_MDDNetwork.pdf", width = 40, height = 15)

```
plot(cenMDD_T1$value[33:48],
     type = "b",
     bty = "n",
     family = "sans",
     las = 1, lwd = 1,
     xaxt = "n",
```

```

xlab = "Node",
ylab = "Strength Centrality")
axis(side = 1, labels = c(1:16), at = c(1:16))
lines(cenMDD_T0$value[29:42], type = "b", col = "#FF00FF")
legend(x = 1, legend = c("MDD_T0", "MDD_T1"),
      text.col = c("#FF00FF", "#000000"))

```



dev.off()