Data-driven clustering reveals a link between symptoms and functional brain connectivity in depression

Supplemental Information

Supplemental Methods and Materials

Research Projects

The symptom data used in clustering was pooled across four research projects:

1: “Secondary prevention of depression applying an Attention Bias Modification Procedure” which was approved by the Regional Ethical Committee of South-Eastern Norway (REK South-East 2014/217). This is also the research project that the MRI-subsampl was drawn from. Here, the “Structured Clinical Interview for DSM-IV Axis I Disorders” (SCID-I) was used for screening.

2: “The effects of serotonin polymorphisms and gender on cognitive control and brain function in major depression and healthy control” which was approved by the Regional Ethical Committee of Northern Norway (REK North t6/2006)

3: “Cognitive control, genetics and emotion regulation” which was approved by the Regional Ethical Committee of South-Eastern Norway (REK South East 2011/1072).

4: “Executive functions in binge drinking young adults” which was conducted in compliance with the Helsinki Declaration and the Ethical principles for Nordic psychologists, as issued by the Norwegian Psychological Association.

Additional centrality measures

We computed three graph theoretical centrality measures using the R package qgraph (1). Node strength is the degree to which any given symptom is directly connected to other symptoms based on the sum of all edges. Closeness centrality is the extent to which a symptom is indirectly connected to other symptoms, based on the shortest path lengths. Betweenness centrality is the
extent to which a symptom lies on paths between other symptoms (2). The networks that these centrality measures are derived from are based on partial correlations in which false positive connections are controlled through the least absolute shrinkage and selection operator (LASSO) (3).

**MRI acquisition protocol**

For resting-state fMRI analysis a T2* weighted single-shot gradient echo EPI sequence was acquired with the following parameters: repetition time (TR)/echo time (TE)/flip angle (FA) = 2.500 ms/30 ms/80°; voxel size, 3.00 × 3.00 × 3.00 mm; 45 transverse slices, 200 volumes; scan time ≈ 8.5 min. Participants were instructed to have their eyes open, and refrain from falling asleep. Scanner noise and subject motion were reduced by using cushions and headphones. For co-registration, we collected a T1-weighted 3D turbo field echo (TFE) scan with SENSE using the following parameters: acceleration factor = 2; TR/TE/FA: 3000 ms/3.61 ms/8°; scan duration: 3 min 16 s, 1 mm isotropic voxels. Due to technical reasons during the time of acquisition, 64 of the individuals were scanned with the initial sagittal phase-encoding (PE) direction and the remaining 186 were scanned with an axial PE direction for the fMRI data.
Supplemental Results

Stability of symptom-based clustering

1: The number of times subjects were “placed” in the clusters was counted across 100 iterations of HDDC. The initial ordering of the resulting heatmap is based on the clustering solution used in all of the analyses in the current study. This test shows that many of the subjects end up in the same cluster, especially for subgroups 1 and 2 (Figure S7).

2: Cluster_similarity: the similarity between pairs of clustering solution is computed as the Jaccard index. A heatmap of the Jaccard index for 100 runs was created, and a histogram. The median Jaccard index coefficient is roughly 0.75 (Figure S8).

3: Clustomit: the subjects are clustered into the desired number of clusters (k), in this case 5. Then, one of the k clusters is left out, including all the subjects within. The rest of the subjects are then clustered into k-1 clusters. Finally, the similarity between the clustering of the original data and the left out clusters are computed using the Jaccard similarity coefficient. A Jaccardian index 0.58 was attained.

All in all, these tests suggest that the clustering solution used in the current study is quite robust/stable.
### Supplemental Tables

<table>
<thead>
<tr>
<th>Beck’s Depression Inventory Symptoms</th>
<th>Individuals with no history of depression</th>
<th>Individuals with a history of depression</th>
<th>M</th>
<th>SD</th>
<th>M</th>
<th>SD</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sadness (BDI_1)</td>
<td>0.137</td>
<td>0.382</td>
<td>0.475</td>
<td>0.650</td>
<td>94.452</td>
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<td>Pessimism (BDI_2)</td>
<td>0.227</td>
<td>0.504</td>
<td>0.652</td>
<td>0.789</td>
<td>98.355</td>
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<td>Past failure (BDI_3)</td>
<td>0.211</td>
<td>0.504</td>
<td>0.851</td>
<td>0.880</td>
<td>187.212</td>
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<td>Loss of pleasure (BDI_4)</td>
<td>0.227</td>
<td>0.446</td>
<td>0.728</td>
<td>0.774</td>
<td>148.134</td>
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<td>Feelings of guilt (BDI_5)</td>
<td>0.268</td>
<td>0.488</td>
<td>0.702</td>
<td>0.720</td>
<td>119.410</td>
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<td>Feelings of punishment (BDI_6)</td>
<td>0.114</td>
<td>0.440</td>
<td>0.391</td>
<td>0.755</td>
<td>46.986</td>
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<td>Feelings of dislike (BDI_7)</td>
<td>0.169</td>
<td>0.496</td>
<td>0.838</td>
<td>0.979</td>
<td>171.680</td>
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<td>Self-criticalness (BDI_8)</td>
<td>0.252</td>
<td>0.571</td>
<td>0.727</td>
<td>0.871</td>
<td>99.069</td>
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<td>Suicide (BDI_9)</td>
<td>0.048</td>
<td>0.214</td>
<td>0.230</td>
<td>0.480</td>
<td>54.928</td>
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<td>Crying (BDI_10)</td>
<td>0.128</td>
<td>0.471</td>
<td>0.553</td>
<td>0.880</td>
<td>84.284</td>
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<td>Agitation (BDI_11)</td>
<td>0.243</td>
<td>0.542</td>
<td>0.488</td>
<td>0.637</td>
<td>42.664</td>
<td>0.001</td>
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<tr>
<td>Loss of interest (BDI_12)</td>
<td>0.160</td>
<td>0.385</td>
<td>0.641</td>
<td>0.782</td>
<td>140.229</td>
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<td>Indecision (BDI_13)</td>
<td>0.176</td>
<td>0.496</td>
<td>0.722</td>
<td>0.871</td>
<td>138.898</td>
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<td>Worthlessness (BDI_14)</td>
<td>0.117</td>
<td>0.386</td>
<td>0.690</td>
<td>0.832</td>
<td>179.828</td>
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<td>Loss of energy (BDI_15)</td>
<td>0.323</td>
<td>0.519</td>
<td>0.907</td>
<td>0.771</td>
<td>189.040</td>
<td>0.001</td>
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<td>Change in sleeping pattern (BDI_16)</td>
<td>0.540</td>
<td>0.714</td>
<td>1.033</td>
<td>0.875</td>
<td>93.651</td>
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<td>Irritability (BDI_17)</td>
<td>0.151</td>
<td>0.406</td>
<td>0.528</td>
<td>0.708</td>
<td>100.027</td>
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<td>Change in appetite (BDI_18)</td>
<td>0.268</td>
<td>0.497</td>
<td>0.614</td>
<td>0.824</td>
<td>61.204</td>
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<td>Concentration difficulty (BDI_19)</td>
<td>0.236</td>
<td>0.499</td>
<td>0.762</td>
<td>0.766</td>
<td>157.567</td>
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<td>Tiredness or fatigue (BDI_20)</td>
<td>0.307</td>
<td>0.531</td>
<td>0.884</td>
<td>0.818</td>
<td>166.762</td>
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<td>Loss of interest in sex (BDI_21)</td>
<td>0.153</td>
<td>0.425</td>
<td>0.677</td>
<td>0.934</td>
<td>119.531</td>
<td>0.001</td>
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<td>Beck’s Anxiety Inventory Symptoms</td>
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<tr>
<td>Numbness or tingling (BAI_1)</td>
<td>0.142</td>
<td>0.421</td>
<td>0.392</td>
<td>0.649</td>
<td>49.914</td>
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<tr>
<td>Feeling hot (BAI_2)</td>
<td>0.126</td>
<td>0.407</td>
<td>0.392</td>
<td>0.657</td>
<td>56.353</td>
<td>0.001</td>
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<tr>
<td>Wobbliness in legs (BAI_3)</td>
<td>0.057</td>
<td>0.269</td>
<td>0.303</td>
<td>0.601</td>
<td>63.875</td>
<td>0.001</td>
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<tr>
<td>Unable to relax (BAI_4)</td>
<td>0.362</td>
<td>0.580</td>
<td>0.712</td>
<td>0.810</td>
<td>59.583</td>
<td>0.001</td>
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<td>Fear of worst happening (BAI_5)</td>
<td>0.199</td>
<td>0.524</td>
<td>0.738</td>
<td>0.845</td>
<td>139.235</td>
<td>0.001</td>
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<td>Dizzy or lightheaded (BAI_6)</td>
<td>0.137</td>
<td>0.358</td>
<td>0.515</td>
<td>0.716</td>
<td>103.015</td>
<td>0.001</td>
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<tr>
<td>Heart pounding/racing (BAI_7)</td>
<td>0.169</td>
<td>0.443</td>
<td>0.465</td>
<td>0.684</td>
<td>62.722</td>
<td>0.001</td>
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<tr>
<td>Unsteady (BAI_8)</td>
<td>0.078</td>
<td>0.330</td>
<td>0.311</td>
<td>0.555</td>
<td>61.665</td>
<td>0.001</td>
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<tr>
<td>Terrified or afraid (BAI_9)</td>
<td>0.041</td>
<td>0.259</td>
<td>0.197</td>
<td>0.514</td>
<td>33.881</td>
<td>0.001</td>
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<tr>
<td>Nervous (BAI_10)</td>
<td>0.437</td>
<td>0.616</td>
<td>0.679</td>
<td>0.812</td>
<td>27.334</td>
<td>0.001</td>
<td></td>
<td></td>
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<tr>
<td>Feeling of choking (BAI_11)</td>
<td>0.032</td>
<td>0.201</td>
<td>0.341</td>
<td>0.669</td>
<td>87.567</td>
<td>0.001</td>
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<tr>
<td>Hands trembling (BAI_12)</td>
<td>0.144</td>
<td>0.406</td>
<td>0.298</td>
<td>0.623</td>
<td>20.359</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Shaky/unsteady (BAI_13)</td>
<td>0.146</td>
<td>0.379</td>
<td>0.407</td>
<td>0.659</td>
<td>55.243</td>
<td>0.001</td>
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<tr>
<td>Fear of losing control (BAI_14)</td>
<td>0.162</td>
<td>0.443</td>
<td>0.538</td>
<td>0.760</td>
<td>85.719</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Difficulty in breathing (BAI_15)</td>
<td>0.043</td>
<td>0.226</td>
<td>0.318</td>
<td>0.622</td>
<td>77.746</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Fear of dying (BAI_16)</td>
<td>0.059</td>
<td>0.281</td>
<td>0.247</td>
<td>0.559</td>
<td>41.452</td>
<td>0.001</td>
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<tr>
<td>Scared (BAI_17)</td>
<td>0.094</td>
<td>0.315</td>
<td>0.290</td>
<td>0.602</td>
<td>38.674</td>
<td>0.001</td>
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<tr>
<td>Indigestion (BAI_18)</td>
<td>0.327</td>
<td>0.563</td>
<td>0.603</td>
<td>0.811</td>
<td>37.363</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Faint/lightheaded (BAI_19)</td>
<td>0.037</td>
<td>0.188</td>
<td>0.295</td>
<td>0.592</td>
<td>77.317</td>
<td>0.001</td>
<td></td>
<td></td>
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<tr>
<td>Face flushed (BAI_20)</td>
<td>0.151</td>
<td>0.383</td>
<td>0.240</td>
<td>0.537</td>
<td>8.767</td>
<td>0.003</td>
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<tr>
<td>Hot/cold sweats (BAI_21)</td>
<td>0.201</td>
<td>0.470</td>
<td>0.401</td>
<td>0.675</td>
<td>28.178</td>
<td>0.001</td>
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</tr>
</tbody>
</table>

**Table S1:** Case-control comparison on symptom scores.
<table>
<thead>
<tr>
<th>Subgroup 1 (n = 342)</th>
<th>Subgroup 2 (n = 272)</th>
<th>Subgroup 3 (n = 240)</th>
<th>Subgroup 4 (n = 106)</th>
<th>Subgroup 5 (n = 124)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female, %)</td>
<td>243 (71)</td>
<td>195 (72)</td>
<td>171 (71)</td>
<td>82 (77)</td>
<td>94 (76)</td>
</tr>
<tr>
<td>Age (mean, SD)</td>
<td>36.4 (13.2)</td>
<td>37.1 (13.6)</td>
<td>36.8 (13.1)</td>
<td>40.6 (13.4)</td>
<td>38.2 (13.7)</td>
</tr>
<tr>
<td>History of anxiety disorder (N, %)</td>
<td>50 (15)</td>
<td>87 (32)</td>
<td>21 (9)</td>
<td>6 (6)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>History of (hypo)mania (N, %)</td>
<td>27 (8)</td>
<td>30 (11)</td>
<td>6 (3)</td>
<td>4 (4)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>History of other Axis-I disorders (N, %)</td>
<td>15 (4)</td>
<td>23 (8)</td>
<td>6 (3)</td>
<td>3 (3)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>No. MDE (mean, SD)</td>
<td>2.26 (4.2)</td>
<td>4.3 (8.4)</td>
<td>1.4 (2.2)</td>
<td>0.7 (1.5)</td>
<td>0.7 (1.5)</td>
</tr>
<tr>
<td>Currently medicated (SSRI) (N, %)</td>
<td>57 (17)</td>
<td>87 (32)</td>
<td>21 (9)</td>
<td>6 (6)</td>
<td>6 (5)</td>
</tr>
</tbody>
</table>

Table S2: Key clinical and demographic factors of the subgroups for the total sample. P denotes the p-value assessing the main effect of subgroup using chi-square test for gender, history of additional disorders and current SSRI medication status while we used Kruskal-Wallis rank-sum tests for the rest.

<table>
<thead>
<tr>
<th>Overall</th>
<th>Subgroup 1</th>
<th>Subgroup 2</th>
<th>Subgroup 3</th>
<th>Subgroup 4</th>
<th>Subgroup 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.030</td>
<td>0.992</td>
<td>0.0783</td>
<td>0.887</td>
<td>0.030</td>
</tr>
<tr>
<td>Age</td>
<td>0.090</td>
<td>0.072</td>
<td>0.148</td>
<td>0.177</td>
<td>0.074</td>
</tr>
<tr>
<td>BDI-II</td>
<td>0.064</td>
<td>0.368</td>
<td>0.118</td>
<td>0.421</td>
<td>0.101</td>
</tr>
<tr>
<td>BAI</td>
<td>0.028</td>
<td>0.998</td>
<td>0.037</td>
<td>1</td>
<td>0.086</td>
</tr>
<tr>
<td>History of anxiety disorder</td>
<td>0.056</td>
<td>0.553</td>
<td>0.079</td>
<td>0.878</td>
<td>0.085</td>
</tr>
<tr>
<td>History of (hypo)mania</td>
<td>0.034</td>
<td>0.974</td>
<td>0.026</td>
<td>1</td>
<td>0.064</td>
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<tr>
<td>History of other Axis-I disorders</td>
<td>0.049</td>
<td>0.721</td>
<td>0.077</td>
<td>0.900</td>
<td>0.105</td>
</tr>
<tr>
<td>No. MDE</td>
<td>0.584</td>
<td>&lt;0.001</td>
<td>0.644</td>
<td>&lt;0.001</td>
<td>0.597</td>
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<td>Currently medicated (SSRI)</td>
<td>0.044</td>
<td>0.834</td>
<td>0.045</td>
<td>1</td>
<td>0.006</td>
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</table>

Table S3: Comparing the similarity between the total sample subgroups with the MRI subsample subgroups using Kolmogorov-Smirnov tests on key demographic and clinical features.
<table>
<thead>
<tr>
<th>Edges</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right FPN-Inferior and mid frontal (IC2-IC15)</td>
<td>2.6465</td>
<td>0.034</td>
</tr>
<tr>
<td>Right FPN- fronto-temporal (IC2-IC16)</td>
<td>2.7236</td>
<td>0.030</td>
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<tr>
<td>Right FPN-Thalamus (IC2-IC39)</td>
<td>2.8523</td>
<td>0.025</td>
</tr>
<tr>
<td>Left FPN-DMN (IC3-IC6)</td>
<td>2.8438</td>
<td>0.025</td>
</tr>
<tr>
<td>(posterior) DAN-Sensorimotor (IC4-IC12)</td>
<td>2.7223</td>
<td>0.030</td>
</tr>
<tr>
<td>(posterior) DAN-Cerebellum (IC4-IC31)</td>
<td>2.4873</td>
<td>0.044</td>
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<tr>
<td>(anterior) DMN- DMN (IC5-IC6)</td>
<td>3.0953</td>
<td>0.016</td>
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<tr>
<td>(anterior) DMN- fronto-temporal (IC5-IC16)</td>
<td>4.6049</td>
<td>0.001</td>
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<tr>
<td>(anterior) DMN- Cerebellum (IC5-IC31)</td>
<td>3.2454</td>
<td>0.013</td>
</tr>
<tr>
<td>DMN-Sensorimotor (IC6-IC12)</td>
<td>4.5060</td>
<td>0.002</td>
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<tr>
<td>Precuneus-Sensorimotor (IC7-IC12)</td>
<td>3.9858</td>
<td>0.004</td>
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<tr>
<td>Precuneus-Inferior and mid frontal (IC7-IC15)</td>
<td>2.5257</td>
<td>0.042</td>
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<tr>
<td>Precuneus fronto-temporal (IC7-IC16)</td>
<td>5.1689</td>
<td>&lt;0.001</td>
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<tr>
<td>Precuneus-Cerebellum (IC7-IC31)</td>
<td>3.0906</td>
<td>0.017</td>
</tr>
<tr>
<td>Precuneus-Thalamus (IC7-IC39)</td>
<td>2.7867</td>
<td>0.027</td>
</tr>
<tr>
<td>Visual- fronto-temporal (IC9-IC16)</td>
<td>3.4065</td>
<td>0.010</td>
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<tr>
<td>DAN-Thalamus (IC14-IC39)</td>
<td>3.0781</td>
<td>0.017</td>
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<tr>
<td>Inferior and mid frontal- fronto-temporal (IC15-IC16)</td>
<td>2.8763</td>
<td>0.024</td>
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<tr>
<td>fronoto-temporal - Supramarginal (IC16-IC18)</td>
<td>3.3498</td>
<td>0.011</td>
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<tr>
<td>Supramarginal-Cerebellum (IC18-IC31)</td>
<td>2.5231</td>
<td>0.042</td>
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<tr>
<td>Sensorimotor-Cerebellum (IC21-IC31)</td>
<td>2.6696</td>
<td>0.033</td>
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</tbody>
</table>

Table S4: Edge level statistics for subgroup main effect on sFC

```markdown
<table>
<thead>
<tr>
<th>Edges</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global efficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main effect of subgroup on global efficiency</td>
<td>0.688</td>
<td>0.601</td>
</tr>
<tr>
<td>Association between BDI-II sum score with global efficiency</td>
<td>0.407</td>
<td>0.524</td>
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<tr>
<td>Association between BAI sum score with global efficiency</td>
<td>0.075</td>
<td>0.787</td>
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<tr>
<td>Association between BDI-II somatic-affective subscale sum score with global efficiency</td>
<td>1.139</td>
<td>0.287</td>
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<tr>
<td>Association between BDI-II cognitive subscale sum score with global efficiency</td>
<td>0.001</td>
<td>0.979</td>
</tr>
<tr>
<td>Association between BAI somatic subscale sum score with global efficiency</td>
<td>0.282</td>
<td>0.596</td>
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<tr>
<td>Association between BAI cognitive subscale sum score with global efficiency</td>
<td>0.003</td>
<td>0.960</td>
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<tr>
<td>Metastability</td>
<td></td>
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<tr>
<td>Main effect of subgroup on metastability</td>
<td>0.254</td>
<td>0.907</td>
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<tr>
<td>Association between BDI-II sum score with metastability</td>
<td>0.538</td>
<td>0.464</td>
</tr>
<tr>
<td>Association between BAI sum score with metastability</td>
<td>0.580</td>
<td>0.447</td>
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<tr>
<td>Association between BDI-II somatic-affective subscale sum score with metastability</td>
<td>0.685</td>
<td>0.409</td>
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<tr>
<td>Association between BDI-II cognitive subscale sum score with metastability</td>
<td>0.283</td>
<td>0.595</td>
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<tr>
<td>Association between BAI somatic subscale sum score with metastability</td>
<td>0.447</td>
<td>0.505</td>
</tr>
<tr>
<td>Association between BAI cognitive subscale sum score with metastability</td>
<td>0.694</td>
<td>0.406</td>
</tr>
<tr>
<td>Main effect of subgroup on synchrony</td>
<td>1.156</td>
<td>0.331</td>
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<td>Synchrony</td>
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<tr>
<td>Association between BDI-II sum score with synchrony</td>
<td>1.045</td>
<td>0.308</td>
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<tr>
<td>Association between BAI sum score with synchrony</td>
<td>1.618</td>
<td>0.205</td>
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<tr>
<td>Association between BDI-II somatic-affective subscale sum score with synchrony</td>
<td>0.644</td>
<td>0.423</td>
</tr>
<tr>
<td>Association between BDI-II cognitive subscale sum score with synchrony</td>
<td>1.358</td>
<td>0.245</td>
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<tr>
<td>Association between BAI somatic subscale sum score with synchrony</td>
<td>0.677</td>
<td>0.412</td>
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<tr>
<td>Association between BAI cognitive subscale sum score with synchrony</td>
<td>2.869</td>
<td>0.092</td>
</tr>
</tbody>
</table>
```

Table S5: Null findings of global FC
Max. no. of edges | p
--- | ---
sFC
Association between BDI-II sum score with sFC | 1 | 0.9548
Association between BAI sum score with sFC | 0 | 1
Association between BDI-II somatic-affective subscale sum score with sFC | 5 | 0.5385
Association between BDI-II cognitive subscale sum score with sFC | 0 | 1
Association between BAI somatic subscale sum score with sFC | 2 | 0.8210
Association between BAI cognitive subscale sum score with sFC | 0 | 1
dFC
Main effect of subgroup on dFC | 5 | 0.5637
Association between BDI-II sum score with dFC | 4 | 0.7238
Association between BAI sum score with dFC | 3 | 0.8526
Association between BDI-II somatic-affective subscale sum score with dFC | 5 | 0.5977
Association between BDI-II cognitive subscale sum score with dFC | 3 | 0.8333
Association between BAI somatic subscale sum score with dFC | 3 | 0.8345
Association between BAI cognitive subscale sum score with dFC | 4 | 0.6805

**Table S6**: Null findings of local FC using permutations-based testing in NBS
Figure S1: Heatmap of the correlation between the BDI-II and BAI symptoms.

Symptoms are ordered in terms of hierarchical clustering as denoted by the dendrograms.
Figure S2: Density distributions of (A) BDI sum score by group and (B) BAI sum score by group.
Figure S3: Discarded noise ICAs
Figure S4: Sum scores of the BDI-II and BAI subscales.
Figure S5: Additional symptom centrality measures (standardized z-scores) characterizing subgroups 1, 2 and 3.
Figure S6: Distribution of patients and controls across the subgroups in the total sample.

Figure S7. Result of the robustness analysis. The X and Y axes represent the subject indexes.

Displayed is the number of times each subject gets clustered with every other subject. The order of subjects is based on the clustering from the main analysis.
**Figure S8.** Results from the stability analysis. (A) heatmap of the similarity between HDDC clustering iterations (100) using the Jaccard index. (B) Histogram of the Jaccard indices.

**Figure S9:** Mean score of each BDI-II and BAI item for each subgroup of the MRI-subsample.
References

