**Supplementary Material**

**Connectivity Between Brain Networks Dynamically Reflects Cognitive Status of Parkinson’s Disease: A Longitudinal Study**

**Effect size calculation**

Effect size was calculated using nonparametric approach suggested by Grissom and Kim (2012) [1]. For estimating effect size in between-group measures the following formula was used: , where U is Mann-Whitney U statistic, na and nb are two sample sizes. U is sum of ranks in sample where greater values are present. then represents the probability that a number randomly drawn from this sample will be greater than a number randomly drawn from the other sample. For estimating effect size in paired between-time measures the same formula was used, but in this case U was calculated as , where W is absolute value of sum of signed ranks obtained from Wilcoxon signed-rank statistic in sample with same-signed differences (either positive or negative) where greater values are present, and nx is this sample size. then represents the probability that a number randomly drawn from this sample will be greater than the number randomly drawn from the other sample.

**Supplementary Table 1.**

**Coordinates of seeds of respective networks for calculation of BNC** **[2]**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **X** | **Y** | **Z** | **area** | **network** |
| -45 | -69 | -2 | IMT+ | DAN |
| 50 | -69 | -3 | rMT+ |
| -27 | -52 | 57 | lIPS |
| 24 | -56 | 55 | rIPS |
| -25 | -8 | 50 | lFEF |
| 27 | -8 | 50 | rFEF |
| -36 | 57 | 9 | laPFC | FPCN |
| 34 | 52 | 10 | RaPFC |
| 3 | 31 | 27 | ACC |
| -52 | -49 | 47 | laIPL |
| 52 | -46 | 46 | raIPL |
| -50 | 20 | 34 | ldlPFC |
| 46 | 14 | 43 | rdlPFC |
| -31 | 21 | -1 | lINS |
| 31 | 22 | -2 | rINS |
| -21 | -15 | -14 | lHF | DMN |
| 24 | -19 | -21 | rHF |
| 0 | 51 | -7 | vmPFC |
| 1 | -55 | 17 | PCC |
| -47 | -71 | 29 | lpIPL |
| 50 | -64 | 27 | rpIPL |
| -8 | -72 | 4 | lCal | VN |
| 16 | -67 | 5 | rCal |
| -5 | -96 | 12 | lCS |
| 18 | -96 | 12 | rCS |
| -23 | -89 | 12 | lLO |
| 37 | -85 | 13 | rLO |

MT+, middle temporal area; IPS, intra-parietal sulcus; FEF, frontal eye field; aPFC, anterior prefrontal cortex; ACC, anterior cingulate cortex; aIPL, anterior inferior parietal lobule; dlPFC, dorsal lateral prefrontal cortex; INS, insula; HF, hippocampus formation; vmPFC, ventromedial prefrontal cortex; PCC, posterior cingulate cortex; pIPL, posterior inferior parietal lobule; Cal, calcarine; CS, cuneus; LO, lateral occipital

**Supplementary Table 2**

**Allocation of AAL parcels to large-scale functional networks of interest**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***Network*** | **DAN** | **FPCN** | **DMN** | **VN** |
| ***AAL parcels*** | Parietal\_Sup\_L | Insula\_L | Angular\_L | Cuneus\_L |
| Parietal\_Sup\_R | Insula\_R | Angular\_R | Cuneus\_R |
| Precentral\_L | Cingulum\_Ant\_L | Precuneus\_L | Calcarine\_L |
| Precentral\_R | Cingulum\_Ant\_R | Precuneus\_R | Calcarine\_R |
| Temporal\_Mid\_L | Parietal\_Inf\_L | Cingulum\_Post\_L | Occipital\_Sup\_L |
| Temporal\_Mid\_R | Parietal\_Inf\_R | Cingulum\_Post\_R | Occipital\_Sup\_R |
|  | Frontal\_Mid\_L | Hippocampus\_L | Occipital\_Mid\_L |
|  | Frontal\_Mid\_R | Hippocampus\_R | Occipital\_Mid\_R |
|  |  |  | Occipital\_Inf\_L |
|  |  |  | Occipital\_Inf\_R |

**Supplementary Table 3**

**Differences in baseline GT measures among HC and PD subgroups and longitudinal changes in HC and PD-all groups**

**a) Global GT measures**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Measure** | **Baseline** | | | | | | | | | | **Follow-up** | | | | | | | |
| **Group** | | | **Kruskal-Wallis** | | **Post-hoc comparisons** | | | | | **HC** | | | **PD-all** | | | | |
| **HC** | **PD-NC** | **PD-MCI** | |  | | **HC versus PD-NC** | **HC versus PD-MCI** | **PD-NC versus PD-MCI** | **Before** | | **After** | **Wilcoxon test** | | **Before** | **After** | **Wilcoxon test** |
| clustering coefficient | 0.307 ± 0.071 | 0.252 ± 0.058 | 0.286 ± 0.076 | | **0.007 \*** | | **0.007 (**= 0.75**)** | 0.219  **(**= 0.62**)** | 0.384 **(**= 0.62**)** | 0.310 ± 0.078 | | 0.329 ± 0.099 | 0.354  **(**= 0.52**)** | | 0.275 ± 0.082 | 0.289 ± 0.071 | 0.506  **(**= 0.52**)** |
| path length | 2.991 ± 0.431 | 3.305 ± 0.413 | 3.131 ± 0.480 | | **0.042** | | **0.042 (**= 0.70**)** | 0.364  **(**= 0.60**)** | 0.565 **(**= 0.59**)** | 2.970 ± 0.458 | | 2.870 ± 0.493 | 0.274  **(**= 0.52**)** | | 3.205 ± 0.491 | 3.116 ± 0.472 | 0.390  **(**= 0.63**)** |
| gamma | 1.029 ± 0.036 | 1.040 ± 0.023 | 1.036 ± 0.038 | | 0.176 | | 0.150 **(**= 0.66**)** | 0.810  **(**= 0.54**)** | 0.499 **(**= 0.59**)** | 1.028 ± 0.040 | | 1.025 ± 0.029 | 0.827  **(**= 0.54**)** | | 1.040 ± 0.028 | 1.027 ± 0.019 | 0.050  **(**= 0.73**)** |
| lambda | 1.268 ± 0.090 | 1.305 ± 0.063 | 1.286 ± 0.074 | | 0.199 | | 0.187 **(**= 0.63**)** | 0.660  **(**= 0.57**)** | 0.683 **(**= 0.60**)** | 1.259 ± 0.094 | | 1.267 ± 0.090 | 0.541  **(**= 0.52**)** | | 1.292 ± 0.077 | 1.280 ± 0.072 | 0.211  **(**= 0.54**)** |
| node strength | 26.170 ± 5.655 | 21.737 ± 4.736 | 24.535 ± 6.263 | | **0.011 \*** | | **0.010 (**= 0.74**)** | 0.290  **(**= 0.61**)** | 0.377 **(**= 0.62**)** | 26.359 ± 6.265 | | 27.899 ± 7.735 | 0.248  **(**= 0.53**)** | | 23.457 ± 6.612 | 24.695 ± 5.610 | 0.372  **(**= 0.56**)** |
| global efficiency | 0.405 ± 0.057 | 0.361 ± 0.050 | 0.388 ± 0.064 | | **0.013 \*** | | **0.014 (**= 0.73**)** | 0.226  **(**= 0.62**)** | 0.493 **(**= 0.59**)** | 0.406 ± 0.064 | | 0.425 ± 0.081 | 0.197  **(**= 0.50**)** | | 0.379 ± 0.068 | 0.389 ± 0.058 | 0.570  **(**= 0.64**)** |
| modularity | 0.174 ± 0.057 | 0.202 ± 0.040 | 0.191 ± 0.053 | | 0.068 | | 0.082 **(**= 0.67**)** | 0.313  **(**= 0.61**)** | 0.760 **(**= 0.56**)** | 0.169 ± 0.061 | | 0.171 ± 0.059 | 0.780  **(**= 0.59**)** | | 0.198 ± 0.052 | 0.179 ± 0.050 | 0.082  **(**= 0.57**)** |

**bi) Local GT measures - DAN**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Measure** | **Baseline** | | | | | | | **Follow-up** | | | | | | |
| **Group** | | | **Kruskal-Wallis** | **Post-hoc comparisons** | | | **HC** | | | | **PD-all** | | |
| **HC** | **PD-NC** | **PD-MCI** |  | **HC versus PD-NC** | **HC versus PD-MCI** | **PD-NC versus PD-MCI** | **Before** | **After** | **Wilcoxon test** | **Before** | | **After** | **Wilcoxon test** |
| clustering coefficient | 0.334 ± 0.083 | 0.270 ± 0.066 | 0.309 ± 0.090 | **0.011 \*** | **0.010**  **(**= 0.73**)** | 0.280  **(**= 0.62**)** | 0.379  **(**= 0.63**)** | 0.338 ± 0.088 | 0.360 ± 0.106 | 0.248  **(**= 0.53**)** | 0.295 ± 0.097 | | 0.314 ± 0.087 | 0.527  **(**= 0.66**)** |
| path length | 2.750 ± 0.444 | 3.067 ± 0.393 | 2.893 ± 0.509 | 0.053 | 0.052  **(**= 0.70**)** | 0.406  **(**= 0.59**)** | 0.571  **(**= 0.58**)** | 2.715 ± 0.451 | 2.624 ± 0.493 | 0.274  **(**= 0.52**)** | 2.983 ± 0.512 | | 2.877 ± 0.486 | 0.527  **(**= 0.76**)** |
| node strength | 26.170 ± 5.655 | 21.737 ± 4.736 | 24.535 ± 6.263 | **0.011 \*** | **0.010**  **(**= 0.74**)** | 0.290  **(**= 0.61**)** | 0.377  **(**= 0.62**)** | 26.359 ± 6.265 | 27.899 ± 7.735 | 0.248  **(**= 0.53**)** | 23.457 ± 6.612 | | 24.695 ± 5.610 | 0.372  **(**= 0.56**)** |
| modularity | 1.972 ± 0.662 | 2.219 ± 0.535 | 2.181 ± 0.523 | 0.088 | 0.223  **(**= 0.64**)** | 0.153  **(**= 0.63**)** | 1.000  **(**= 0.51**)** | 1.932 ± 0.599 | 2.128 ± 0.696 | 0.182  **(**= 0.55**)** | 2.188 ± 0.478 | | 2.244 ± 0.602 | 0.653  **(**= 0.37**)** |
| eigenvector centrality | 0.125 ± 0.010 | 0.122 ± 0.015 | 0.125 ± 0.010 | 0.903 | 0.939  **(**= 0.53**)** | 0.979  **(**= 0.52**)** | 0.895  **(**= 0.54**)** | 0.126 ± 0.011 | 0.128 ± 0.014 | 0.192  **(**= 0.56**)** | 0.121 ± 0.017 | | 0.124 ± 0.015 | 0.506  **(**= 0.52**)** |
| betweeness centrality | 93.347 ± 35.168 | 92.053 ± 36.155 | 88.451 ± 34.268 | 0.947 | 1.000  **(**= 0.50**)** | 0.947  **(**= 0.53**)** | 0.965  **(**= 0.52**)** | 92.892 ± 36.399 | 80.676 ± 36.563 | 0.184  **(**= 0.62**)** | 91.057 ± 37.467 | | 82.989 ± 31.331 | 0.381  **(**= 0.67**)** |

**bii) Local GT measures - FPCN**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Measure** | **Baseline** | | | | | | | **Follow-up** | | | | | |
| **Group** | | | **Kruskal-Wallis** | **Post-hoc comparisons** | | | **HC** | | | **PD-all** | | |
| **HC** | **PD-NC** | **PD-MCI** |  | **HC versus PD-NC** | **HC versus PD-MCI** | **PD-NC versus PD-MCI** | **Before** | **After** | **Wilcoxon test** | **Before** | **After** | **Wilcoxon test** |
| clustering coefficient | 0.311 ± 0.071 | 0.249 ± 0.060 | 0.281 ± 0.077 | **0.003 \*** | **0.004**  (= 0.76**)** | 0.119  **(**= 0.65**)** | 0.457  **(**= 0.61**)** | 0.314 ± 0.078 | 0.331 ± 0.105 | 0.512  **(**= 0.54**)** | 0.270 ± 0.086 | 0.282 ± 0.071 | 0.426  **(**= 0.51**)** |
| path length | 2.908 ± 0.426 | 3.258 ± 0.399 | 3.099 ± 0.449 | **0.010 \*** | **0.013**  (= 0.73**)** | 0.150  **(**= 0.64**)** | 0.584  **(**= 0.59**)** | 2.882 ± 0.452 | 2.816 ± 0.514 | 0.455  **(**= 0.56**)** | 3.156 ± 0.483 | 3.074 ± 0.465 | 0.355  **(**= 0.55**)** |
| node strength | 26.170 ± 5.655 | 21.737 ± 4.736 | 24.535 ± 6.263 | **0.011 \*** | **0.010**  **(**= 0.74**)** | 0.290  **(**= 0.61**)** | 0.377  **(**= 0.62**)** | 26.359 ± 6.265 | 27.899 ± 7.735 | 0.248  **(**= 0.53**)** | 23.457 ± 6.612 | 24.695 ± 5.610 | 0.372  **(**= 0.56**)** |
| modularity | 2.004 ± 0.558 | 2.074 ± 0.679 | 2.276 ± 0.546 | 0.163 | 0.946  **(**= 0.52**)** | 0.141  **(**= 0.65**)** | 0.441  **(**= 0.60**)** | 1.959 ± 0.538 | 2.139 ± 0.553 | 0.184  **(**= 0.62**)** | 2.125 ± 0.562 | 2.216 ± 0.538 | 0.763  **(**= 0.53**)** |
| eigenvector centrality | 0.110 ± 0.013 | 0.105 ± 0.017 | 0.104 ± 0.013 | 0.248 | 0.466  **(**= 0.59**)** | 0.310  **(**= 0.61**)** | 0.991  **(**= 0.50**)** | 0.109 ± 0.014 | 0.108 ± 0.015 | 0.411  **(**= 0.54**)** | 0.104 ± 0.018 | 0.105 ± 0.012 | 0.808  **(**= 0.56**)** |
| betweeness centrality | 49.612 ± 26.227 | 57.897 ± 26.795 | 49.650 ± 26.230 | 0.546 | 0.555  **(**= 0.59**)** | 0.997  **(**= 0.51**)** | 0.603  **(**= 0.59**)** | 49.608 ± 24.722 | 49.257 ± 30.134 | 0.597  **(**= 0.52**)** | 54.682 ± 26.716 | 59.375 ± 18.432 | 0.101  **(**= 0.57**)** |

**biii) Local GT measures - DMN**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Measure** | **Baseline** | | | | | | | **Follow-up** | | | | | | |
| **Group** | | | **Kruskal-Wallis** | **Post-hoc comparisons** | | | **HC** | | | **PD-all** | | |
| **HC** | **PD-NC** | **PD-MCI** |  | **HC versus PD-NC** | **HC versus PD-MCI** | **PD-NC versus PD-MCI** | **Before** | **After** | **Wilcoxon test** | **Before** | **After** | **Wilcoxon test** |
| clustering coefficient | 0.294 ± 0.070 | 0.248 ± 0.053 | 0.278 ± 0.070 | **0.032** | **0.029**  **(**= 0.71**)** | 0.403  **(**= 0.60**)** | 0.457  **(**= 0.61**)** | 0.294 ± 0.077 | 0.309 ± 0.102 | 0.502  **(**= 0.60**)** | 0.269 ± 0.074 | 0.280 ± 0.069 | 0.527  **(**= 0.63**)** |
| path length | 3.037 ± 0.443 | 3.282 ± 0.368 | 3.093 ± 0.399 | 0.120 | 0.102  **(**= 0.67**)** | 0.695  **(**= 0.56**)** | 0.496  **(**= 0.60**)** | 3.024 ± 0.466 | 2.975 ± 0.526 | 0.572  **(**= 0.57**)** | 3.163 ± 0.415 | 3.134 ± 0.494 | 0.661  **(**= 0.66**)** |
| node strength | 26.170 ± 5.655 | 21.737 ± 4.736 | 24.535 ± 6.263 | **0.011 \*** | **0.010**  **(**= 0.74**)** | 0.290  **(**= 0.61**)** | 0.377  **(**= 0.62**)** | 26.359 ± 6.265 | 27.899 ± 7.735 | 0.248  **(**= 0.53**)** | 23.457 ± 6.612 | 24.695 ± 5.610 | 0.372  **(**= 0.56**)** |
| modularity | 2.067 ± 0.545 | 2.207 ± 0.543 | 1.970 ± 0.617 | 0.423 | 0.675  **(**= 0.56**)** | 0.743  **(**= 0.55**)** | 0.388  **(**= 0.64**)** | 2.027 ± 0.555 | 2.196 ± 0.554 | 0.184  **(**= 0.58**)** | 2.080 ± 0.598 | 2.119 ± 0.564 | 0.762  **(**= 0.59**)** |
| eigenvector centrality | 0.101 ± 0.013 | 0.104 ± 0.013 | 0.107 ± 0.014 | 0.239 | 0.751  **(**= 0.55**)** | 0.217  **(**= 0.63**)** | 0.767  **(**= 0.55**)** | 0.100 ± 0.014 | 0.098 ± 0.014 | 0.267  **(**= 0.58**)** | 0.106 ± 0.016 | 0.103 ± 0.018 | 0.685  **(**= 0.60**)** |
| betweeness centrality | 60.571 ± 29.800 | 82.626 ± 26.204 | 79.499 ± 27.436 | **0.001 \*** | **0.009**  **(**= 0.75**)** | **0.012**  **(**= 0.70**)** | 0.950  **(**= 0.50**)** | 57.865 ± 29.389 | 57.480 ± 26.147 | 0.718  **(**= 0.69**)** | 80.773 ± 31.328 | 72.023 ± 34.433 | 0.249  **(**= 0.60**)** |

**biv) Local GT measures - VN**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Measure** | **Baseline** | | | | | | | | **Follow-up** | | | | | | |
| **Group** | | | **Kruskal-Wallis** | | **Post-hoc comparisons** | | | **HC** | | | **PD-all** | | |
| **HC** | **PD-NC** | **PD-MCI** | |  | **HC versus PD-NC** | **HC versus PD-MCI** | **PD-NC versus PD-MCI** | **Before** | **After** | **Wilcoxon test** | **Before** | **After** | **Wilcoxon test** |
| clustering coefficient | 0.339 ± 0.086 | 0.274 ± 0.058 | 0.315 ± 0.078 | | **0.009 \*** | **0.007**  **(**= 0.74**)** | 0.348  **(**= 0.61**)** | 0.283  **(**= 0.66**)** | 0.345 ± 0.089 | 0.363 ± 0.109 | 0.377  **(**= 0.53**)** | 0.297 ± 0.086 | 0.322 ± 0.091 | 0.291  **(**= 0.68**)** |
| path length | 2.766 ± 0.487 | 3.164 ± 0.470 | 2.957 ± 0.499 | | **0.012 \*** | **0.013**  **(**= 0.73**)** | 0.211  **(**= 0.63**)** | 0.507  **(**= 0.61**)** | 2.723 ± 0.465 | 2.622 ± 0.514 | 0.274  **(**= 0.52**)** | 3.090 ± 0.566 | 2.913 ± 0.570 | 0.236  **(**= 0.71**)** |
| node strength | 26.170 ± 5.655 | 21.737 ± 4.736 | 24.535 ± 6.263 | | **0.011 \*** | **0.010**  **(**= 0.74**)** | 0.290  **(**= 0.61**)** | 0.377  **(**= 0.62**)** | 26.359 ± 6.265 | 27.899 ± 7.735 | 0.248  **(**= 0.53**)** | 23.457 ± 6.612 | 24.695 ± 5.610 | 0.372  **(**= 0.56**)** |
| modularity | 2.034 ± 0.864 | 2.137 ± 0.881 | 1.844 ± 0.824 | | 0.477 | 0.944  = 0.52**)** | 0.552  **(**= 0.57**)** | 0.513  **(**= 0.62**)** | 2.093 ± 0.846 | 2.132 ± 1.027 | 0.731  **(**= 0.60**)** | 1.909 ± 0.921 | 1.975 ± 0.933 | 0.806  **(**= 0.57**)** |
| eigenvector centrality | 0.133 ± 0.016 | 0.128 ± 0.028 | 0.135 ± 0.016 | | 0.731 | 0.944  **(**= 0.53**)** | 0.817  **(**= 0.55**)** | 0.728  **(**= 0.56**)** | 0.134 ± 0.017 | 0.133 ± 0.021 | 0.862  **(**= 0.56**)** | 0.129 ± 0.027 | 0.131 ± 0.022 | 0.961  **(**= 0.51**)** |
| betweeness centrality | 34.421 ± 22.045 | 41.615 ± 21.009 | 29.726 ± 17.905 | | 0.237 | 0.394  **(**= 0.60**)** | 0.769  **(**= 0.55**)** | 0.215  **(**= 0.67**)** | 34.967 ± 23.867 | 30.883 ± 23.200 | 0.342  **(**= 0.60**)** | 30.364 ± 19.336 | 33.657 ± 17.445 | 0.673  **(**= 0.70**)** |

Table 4a shows the baseline global GT measures, differences between groups, and baseline/follow-up GT measures in HC and PD-all groups, 4b shows the baseline local GT measures in large-scale functional networks of interest (bi – DAN, bii – FPCN, biii – DMN, biv - VN), differences between groups, and baseline/follow-up GT measures in HC and PD-all groups; mean ± standard deviation are displayed when group (baseline) and timepoints Before and After (follow-up) are presented, p-values are displayed when results of statistics are presented (Kruskal-Wallis, Post-hoc comparisons, Wilcoxon test), significant results at an alpha level of 0.05 displayed in bold, \* marks significant Kruskal-Wallis results after FDR correction, determines effect size, gamma is the normalized clustering coefficient, and lambda is the normalized path length

**REFERENCES**

[1] Grissom RJ, Kim JJ (2012) *Effect sizes for research: Univariate and multivariate applications, second edition*.

[2] Gao W, Lin W (2012) Frontal parietal control network regulates the anti-correlated default and dorsal attention networks. *Hum Brain Mapp* **33**, 192–202.