

## Supplementary Material

**Supplementary Table S1.** region of interest included in the atlas and their affiliation to the investigated brain areas (merged region) in the current study.

| Brain region and atlas                                                                   | sub brain areas                                                                                                                                                                                                                                                                                                                                                                           |
|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cerebellum<br>(cerebellar atlas<br>with nonlinear<br>normalization in FSL <sup>1</sup> ) | Left Crus I<br>Left Crus II<br>Left I-IV<br>Left IX<br>Left V<br>Left VI<br>Left VIIb<br>Left VIIa<br>Left VIIIb<br>Left X<br>Right Crus I<br>Right Crus II<br>Right I-IV<br>Right IX<br>Right V<br>Right VI<br>Right VIIb<br>Right VIIa<br>Right VIIIb<br>Right X<br>Vermis Crus I<br>Vermis Crus II<br>Vermis IX<br>Vermis VI<br>Vermis VIIb<br>Vermis VIIa<br>Vermis VIIIb<br>Vermis X |
| Prefrontal cortex<br>(Harvard-Oxford atlas <sup>2</sup> )                                | Frontal Medial Cortex Left<br>Frontal Medial Cortex Right<br>Frontal Orbital Cortex Left<br>Frontal Orbital Cortex Right<br>Frontal Pole Left<br>Frontal Pole Right<br>Inferior Frontal Gyrus, pars opercularis Left<br>Inferior Frontal Gyrus, pars opercularis Right<br>Inferior Frontal Gyrus, pars triangularis Left<br>Inferior Frontal Gyrus, pars triangularis Right               |

|                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                      | Middle Frontal Gyrus Left<br>Middle Frontal Gyrus Right<br>Superior Frontal Gyrus Left<br>Superior Frontal Gyrus Right                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Motor cortex<br>(Jülich atlas <sup>3</sup> )         | Juxtapositional Lobule Cortex (formerly Supplementary Motor Cortex) L<br>Juxtapositional Lobule Cortex (formerly Supplementary Motor Cortex) R<br>Postcentral Gyrus L<br>Postcentral Gyrus R<br>Premotor cortex BA6 L<br>Premotor cortex BA6 R<br>Primary motor cortex BA4a L<br>Primary motor cortex BA4a R<br>Primary motor cortex BA4p L<br>Primary motor cortex BA4p R<br>Primary somatosensory cortex BA1 L<br>Primary somatosensory cortex BA1 R<br>Primary somatosensory cortex BA2 L<br>Primary somatosensory cortex BA2 R<br>Primary somatosensory cortex BA3a L<br>Primary somatosensory cortex BA3a R<br>Primary somatosensory cortex BA3b L<br>Primary somatosensory cortex BA3b R<br>Secondary somatosensory cortex Parietal operculum OP1 L<br>Secondary somatosensory cortex Parietal operculum OP1 R<br>Secondary somatosensory cortex Parietal operculum OP2 L<br>Secondary somatosensory cortex Parietal operculum OP2 R<br>Secondary somatosensory cortex Parietal operculum OP3 L<br>Secondary somatosensory cortex Parietal operculum OP3 R<br>Secondary somatosensory cortex Parietal operculum OP4 L<br>Secondary somatosensory cortex Parietal operculum OP4 R |
| Subcortical structures<br>(PD25 atlas <sup>4</sup> ) | Left caudate<br>Left globus pallidus externa<br>Left globus pallidus interna<br>Left putamen<br>Left substantia nigra<br>Left subthalamic nucleus<br>Left thalamus<br>Right caudate<br>Right globus pallidus externa<br>Right globus pallidus interna<br>Right putamen<br>Right Substantia nigra                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

|                                                   |                                             |
|---------------------------------------------------|---------------------------------------------|
|                                                   | Right subthalamic nucleus<br>Right thalamus |
| Brainstem<br>(Harvard-Oxford atlas <sup>2</sup> ) | Brainstem                                   |

**Supplementary Table S2.** Resting-state effective connectivity summary and group comparison with Wilcoxon signed-rank test/Mann-Whitney-Test.

| Connectivity                           | Mean(Median)           |                         |              | P-value                      |                             |                              |
|----------------------------------------|------------------------|-------------------------|--------------|------------------------------|-----------------------------|------------------------------|
|                                        | Baseline<br>(patients) | Follow-up<br>(patients) | Controls     | Baseline<br>v.s<br>Follow-up | Baseline<br>v.s<br>Controls | Follow-up<br>v.s<br>Controls |
| Cerebellum → Brainstem                 | 0.359(0.264)           | 0.339(0.366)            | 0.331(0.304) | 0.407                        | 1                           | 0.62                         |
| Prefrontal cortex → Brainstem          | 0.383(0.335)           | 0.327(0.292)            | 0.354(0.37)  | 0.084                        | 0.839                       | 0.342                        |
| Motor cortex → Brainstem               | 0.367(0.332)           | 0.331(0.288)            | 0.357(0.346) | 0.434                        | 0.369                       | 0.374                        |
| Subcortical region → Brainstem         | 0.348(0.371)           | 0.289(0.266)            | 0.348(0.337) | 0.123                        | 0.434                       | 0.221                        |
| Brainstem → Cerebellum                 | 0.065(0.048)           | 0.058(0.042)            | 0.054(0.045) | 0.722                        | 0.772                       | 0.729                        |
| Prefrontal cortex → Cerebellum         | 0.105(0.102)           | 0.097(0.09)             | 0.101(0.072) | 0.522                        | 0.506                       | 0.557                        |
| Motor cortex → Cerebellum              | 0.098(0.097)           | 0.104(0.082)            | 0.095(0.073) | 0.758                        | 0.487                       | 0.599                        |
| Subcortical region → Cerebellum        | 0.082(0.072)           | 0.107(0.083)            | 0.088(0.081) | 0.162                        | 0.603                       | 0.94                         |
| Brainstem → Prefrontal cortex          | 0.029(0.026)           | 0.026(0.024)            | 0.034(0.024) | 0.554                        | 0.729                       | 0.407                        |
| Cerebellum → Prefrontal cortex         | 0.057(0.046)           | 0.058(0.052)            | 0.068(0.044) | 0.492                        | 0.795                       | 0.845                        |
| Motor cortex → Prefrontal cortex       | 0.051(0.043)           | 0.08(0.056)             | 0.084(0.076) | 0.135                        | 0.065                       | 0.845                        |
| Subcortical region → Prefrontal cortex | 0.051(0.052)           | 0.06(0.058)             | 0.056(0.041) | 0.308                        | 0.544                       | 0.537                        |
| Brainstem → Motor cortex               | 0.049(0.043)           | 0.031(0.027)            | 0.05(0.029)  | <b>0.044</b>                 | 0.296                       | 0.358                        |
| Cerebellum → Motor cortex              | 0.067(0.045)           | 0.079(0.078)            | 0.075(0.066) | 0.434                        | 0.839                       | 0.599                        |
| Prefrontal cortex → Motor cortex       | 0.093(0.08)            | 0.076(0.078)            | 0.082(0.073) | 0.407                        | 0.469                       | 0.729                        |
| Subcortical region → Motor cortex      | 0.085(0.089)           | 0.06(0.058)             | 0.076(0.066) | <b>0.044</b>                 | 0.09                        | 0.407                        |
| Brainstem → Subcortical region         | 0.036(0.027)           | 0.053(0.034)            | 0.049(0.044) | 0.943                        | 0.154                       | 0.133                        |
| Cerebellum → Subcortical region        | 0.053(0.046)           | 0.072(0.045)            | 0.079(0.067) | 0.522                        | <b>0.023</b>                | 0.257                        |
| Prefrontal cortex → Subcortical region | 0.071(0.065)           | 0.084(0.068)            | 0.083(0.079) | 0.286                        | 0.283                       | 1                            |
| Motor cortex → Subcortical region      | 0.061(0.056)           | 0.072(0.06)             | 0.086(0.069) | 0.619                        | <b>0.049</b>                | 0.342                        |

**Supplementary Table S3.** Correlation analysis between UPDRS and resting-state effective connectivity

| Connectivity                           | UPDRS-III |                 | UPDRS-Total |                 |
|----------------------------------------|-----------|-----------------|-------------|-----------------|
|                                        | <i>r</i>  | <i>p</i>        | <i>r</i>    | <i>p</i>        |
| Brainstem → Cerebellum                 | 0.330735  | 0.166646        | 0.311919    | 0.193586        |
| Brainstem → Prefrontal cortex          | -0.06882  | 0.779518        | 0.087366    | 0.722106        |
| Brainstem → Motor cortex               | -0.08027  | 0.743912        | 0.179651    | 0.461768        |
| Brainstem → Subcortical region         | 0.40906   | 0.082029        | 0.577496    | <b>0.009618</b> |
| Cerebellum → Brainstem                 | 0.014114  | 0.954268        | -0.06107    | 0.803851        |
| Cerebellum → Prefrontal cortex         | 0.169495  | 0.48787         | 0.173017    | 0.478739        |
| Cerebellum → Motor cortex              | -0.14683  | 0.548618        | 0.067092    | 0.784929        |
| Cerebellum → Subcortical region        | 0.239566  | 0.323234        | 0.429807    | 0.066263        |
| Prefrontal cortex → Brainstem          | -0.12579  | 0.607853        | -0.19167    | 0.431815        |
| Prefrontal cortex → Cerebellum         | 0.180637  | 0.459274        | 0.269571    | 0.264388        |
| Prefrontal cortex → Motor cortex       | -0.45718  | <b>0.049074</b> | -0.12915    | 0.598241        |
| Prefrontal cortex → Subcortical region | 0.26011   | 0.282165        | 0.149887    | 0.540232        |
| Motor cortex → Brainstem               | 0.020028  | 0.935139        | -0.05711    | 0.816371        |
| Motor cortex → Cerebellum              | 0.193135  | 0.428241        | 0.194936    | 0.423862        |
| Motor cortex → Prefrontal cortex       | 0.299633  | 0.212661        | 0.342145    | 0.151621        |
| Motor cortex → Subcortical region      | 0.279781  | 0.246009        | 0.100878    | 0.681135        |
| Subcortical region → Brainstem         | 0.110094  | 0.653665        | -0.08675    | 0.723987        |
| Subcortical region → Cerebellum        | -0.09996  | 0.683893        | 0.035655    | 0.884781        |
| Subcortical region → Prefrontal cortex | -0.24674  | 0.308509        | -0.06947    | 0.777497        |
| Subcortical region → Motor cortex      | -0.08124  | 0.740922        | -0.15048    | 0.538598        |

## References

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