**e-Table 1.** List of study variables included in logistic regression models for the prediction analysis

|  |  |
| --- | --- |
| Demographic/Clinical variables | Age  Sex  EDSS score  Disease duration  Baseline DMT  DMT change  Mean ARR |
| Conventional MRI variables | T2-hyperintense LV  T1-hypointense LV  NBV  NGMV  NWMV  NDGMV |
| RS FC variables | SMN I \_ decreased RS FC in the R paracentral lobule  SMN I – decreased RS FC in the R SMA  SMN I – increased RS FC in the R precentral gyrus  SMN II – increased RS FC in the R precentral gyrus  SMN II – increased RS FC in the R postcentral gyrus  SMN II – increased RS FC in the L precentral gyrus  BGN- decreased RS FC in the R cerebellum  DMN I – decreased RS FC in the L PCC  DMN II – increased RS FC in the R SFG  DMN II – increased RS FC in the L ACC  DMN III – decreased RS FC in the R caudate nucleus  SN – decreased RS FC in the R insula  SN – decreased RS FC in the L caudate nucleus  FPN – decreased RS FC in the R ACC |
| FNC variables | FNC SMN I – SMN II  FNC SMN I – BGN  FNC SMN I – DMN I  FNC SMN I – DMN II  FNC SMN I – DMN III  FNC SMN I – SN  FNC SMN I – FPN  FNC SMN II – BGN  FNC SMN II – DMN I  FNC SMN II – DMN II  FNC SMN II – DMN III  FNC SMN II – SN  FNC SMN II – FPN  FNC BGN – DMN I  FNC BGN – DMN II  FNC BGN – DMN III  FNC BGN – SN  FNC BGN – FPN  FNC DMN I – DMN II  FNC DMN I – DMN III  FNC DMN I – SN  FNC DMN I – FPN  FNC DMN II – DMN III  FNC DMN II – SN  FNC DMN II – FPN  FNC DMN III – SN  FNC DMN III – FPN  FNC SN - FPN |
| GM network atrophy | GM SMN I  GM SMN II  GM BGN  GM DMN I  GM DMN II  GM SN  GM FPN |

Abbreviations: EDSS=expanded disability status change; DMT=disease-modifying treatment; ARR=annualized relapse rate; LV=lesion volume; NBV=normalized brain volume; NGMV=normalized grey matter volume; NWMV=normalized white matter volume; NDGMV=normalized deep grey matter volume; RS=resting state; FC=functional connectivity; SMN=sensorimotor network; R=right, L=left; SMA=supplementary motor area; BGN=basal ganglia network; DMN=default mode network; PCC=posterior cingulate cortex; SFG=superior frontal gyrus; ACC=anterior cingulate cortex; SN=salience network; FPN=fronto-parietal network; FNC=functional network connectivity; GM=grey matter.

**e-Table 2.** Brain regions showing significant differences of resting state (RS) functional connectivity (FC) between healthy controls (HC) and patients with multiple sclerosis (MS) within the eight functional networks examined (age- and sex-adjusted SPM12 voxel-wise linear models, p<0.001, uncorrected), and pairs of brain networks showing significantly abnormal functional network connectivity (FNC) in MS patients compared to HC (age- and sex-adjusted linear models on FNC strengths)

Results surviving at corrected threshold (p<0.05, clusterwise family-wise error corrected for voxel-wise RS FC and false discovery rate corrected for FNC, respectively), are marked with \*.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Voxel-wise RS FC analysis | | | | | |
| Functional network | Comparison | Brain region | Brodmann area | MNI space coordinates  x y z | Cluster extent |
| SMN I | HC > MS  MS > HC | R paracentral lobule\*  R SMA  R precentral gyrus | 4  7  3 | 6 -28 58  8 -38 46  48 -26 52 | 25  10  10 |
| SMN II | MS > HC | R precentral gyrus\*  R postcentral gyrus\*  L precentral gyrus\* | 4  3  6 | 34 -22 60  46 -22 34  -34 -12 60 | 37  33  35 |
| BGN | HC > MS | R cerebellum, anterior lobe (culmen)\* | - | 8 -52 -4 | 26 |
| DMN I | HC > MS | L PCC | 23 | -2 -52 30 | 10 |
| DMN II | MS > HC | R SFG\*  L ACC | 32  32 | 12 52 28  -2 42 8 | 30  12 |
| DMN III | HC > MS | R caudate nucleus | - | 14 0 20 | 10 |
| SN | HC > MS | R insula  L caudate nucleus | 47  - | 38 26 6  -8 10 2 | 15  11 |
| FPN | HC > MS | R ACC | 32 | 8 44 14 | 18 |
| FNC among networks | | | | | |
| Pair of functional networks | | Mean FNC in HC (r) | Mean FNC in MS patients (r) | | p value |
| BGN – SMN II | | -0.12 | -0.03 | | 0.02 |
| DMN I - FPN | | 0.02 | -0.08 | | 0.01 |
| DMN II – SMN II | | -0.28 | -0.17 | | 0.01 |
| SN - FPN | | 0.40 | 0.29 | | 0.002\* |

Abbreviations: L=left; R=right; MNI=Montreal Neurological Institute; SMN=sensorimotor network; BGN=basal ganglia network; DMN=default mode network; SN=salience network; FPN=fronto-parietal network; SMA=supplementary motor area; PCC=posterior cingulate cortex; ACC=anterior cingulate cortex; SFG=superior frontal gyrus.