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

|  |  |
| --- | --- |
| Demographic/Clinical variables | AgeSexEDSS scoreDisease durationBaseline DMTDMT changeMean ARR |
| Conventional MRI variables | T2-hyperintense LVT1-hypointense LVNBVNGMVNWMVNDGMV |
| RS FC variables | SMN I \_ decreased RS FC in the R paracentral lobuleSMN I – decreased RS FC in the R SMASMN I – increased RS FC in the R precentral gyrusSMN II – increased RS FC in the R precentral gyrusSMN II – increased RS FC in the R postcentral gyrusSMN II – increased RS FC in the L precentral gyrusBGN- decreased RS FC in the R cerebellumDMN I – decreased RS FC in the L PCCDMN II – increased RS FC in the R SFGDMN II – increased RS FC in the L ACCDMN III – decreased RS FC in the R caudate nucleusSN – decreased RS FC in the R insulaSN – decreased RS FC in the L caudate nucleusFPN – decreased RS FC in the R ACC |
| FNC variables | FNC SMN I – SMN IIFNC SMN I – BGNFNC SMN I – DMN IFNC SMN I – DMN IIFNC SMN I – DMN IIIFNC SMN I – SNFNC SMN I – FPNFNC SMN II – BGNFNC SMN II – DMN IFNC SMN II – DMN IIFNC SMN II – DMN IIIFNC SMN II – SNFNC SMN II – FPNFNC BGN – DMN IFNC BGN – DMN IIFNC BGN – DMN IIIFNC BGN – SNFNC BGN – FPNFNC DMN I – DMN IIFNC DMN I – DMN IIIFNC DMN I – SNFNC DMN I – FPNFNC DMN II – DMN IIIFNC DMN II – SNFNC DMN II – FPNFNC DMN III – SNFNC DMN III – FPNFNC SN - FPN |
| GM network atrophy | GM SMN IGM SMN IIGM BGNGM DMN IGM DMN IIGM SNGM 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 coordinatesx y z | Cluster extent |
| SMN I | HC > MSMS > HC | R paracentral lobule\*R SMAR precentral gyrus | 473 | 6 -28 588 -38 4648 -26 52 | 251010 |
| SMN II | MS > HC | R precentral gyrus\*R postcentral gyrus\*L precentral gyrus\* | 436 | 34 -22 6046 -22 34-34 -12 60 | 373335 |
| 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 | 3232 | 12 52 28-2 42 8 | 3012 |
| DMN III | HC > MS | R caudate nucleus | - | 14 0 20 | 10 |
| SN | HC > MS | R insulaL caudate nucleus | 47- | 38 26 6-8 10 2 | 1511 |
| 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.