Supplementary Tables

Supplementary Table 1. Performance on neuropsychological tests of depressed and non-depressed patients with MS and healthy controls

	DMS (*n*=22)	nDMS (*n*=21)	HCs (*n*=12)	DMS vs. nDMS		DMS vs. HCs		nDMS vs. HCs	
				Difference [CI]	*P*	Difference [CI]	*P*	Difference [CI]	*P*
Verbal memory	-1.98 (1.67)[a]	-1.68 (2.11)	0.00 (1.00)	-0.57 [-1.53; 0.40]	0.24	-2.16 [-3.33; -1.00]	< 0.001	-1.60 [-2.72; -0.47]	< 0.01
Information processing speed	-0.66 (0.81)	-0.46 (0.81)	0.00 (1.00)	-0.37 [-0.85; 0.12]	0.14	-0.86 [-1.46; -0.27]	0.01	-0.50 [-1.07; 0.08]	0.09
Visuospatial memory	-0.23 (2.01)	-0.94 (3.03)	0.00 (1.00)	0.30 [-1.05; 1.65]	0.66	-0.69 [-2.33; 0.95]	0.40	-0.99 [-2.58; 0.60]	0.22
Short-term memory Digit span forward	 -0.42 (0.90)	 -0.65 (1.04)	 0.00 (1.00)	 0.21 [-0.41; 0.83]	 0.49	 -0.51 [-1.26; 0.24]	 0.18	 -0.72 [-1.45; 0.01]	 0.05
Working memory Digit span backward Letter-number sequencing	 -0.76 (1.28) -0.94 (1.16)	 -0.80 (1.35) -0.73 (1.25)	 0.00 (1.00) 0.00 (1.00)	 0.03 [-0.77; 0.83] -0.17 [-0.91; 0.57]	 0.95 0.65	 -0.81 [-1.78; 0.16] -0.92 [-1.82; -0.02]	 0.10 0.05	 -0.84 [-1.78; 0.10] -0.75 [-1.63; 0.12]	 0.08 0.09
Verbal fluency animals professions m-words	 -0.01 (0.73)[a] -0.32 (0.99)[a] -0.32 (0.77)[a]	 0.06 (1.01) 0.25 (1.04) -0.18 (0.81)	 0.00 (1.00) 0.00 (1.00) 0.00 (1.00)	 -0.02 [-0.60; 0.56] -0.41 [-1.02; 0.20] -0.22 [-0.71; 0.27]	 0.95 0.19 0.37	 0.11 [-0.59; 0.81] -0.02 [-0.76; 0.72] -0.35 [-0.94; 0.25]	 0.74 0.96 0.24	 0.13 [-0.54; 0.81] 0.39 [-0.33; 1.11] -0.13 [-0.70; 0.45]	 0.70 0.28 0.66

Displayed data are mean *Z*-score (standard deviation).

[a] n = 21

CI = confidence interval; DMS = depressed multiple sclerosis patients; HCs = healthy controls; nDMS = non-depressed multiple sclerosis patients.

Supplementary Table 2. Percentage of lesioned voxels for each white matter tract

	DMS (*n*=22)	nDMS (*n*=21)	DMS vs. nDMS		
			Difference [CI]	*P*	*P* corr.
Anterior thalamic radiation L	2.33 (2.89)	2.88 (3.37)	-0.80 [-2.74; 1.14]	0.41	0.61
Anterior thalamic radiation R	2.32 (3.07)	2.89 (2.55)	-0.79 [-2.61; 1.04]	0.39	0.67
Cingulum cingulate L	1.10 (1.65)	0.37 (0.64)	0.62 [-0.14; 0.38]	0.12	0.50
Cingulum cingulate R	0.55 (0.89)	0.24 (0.40)	0.28 [-0.17; 0.74]	0.21	0.63
Cingulum hippocampus L	0.16 (0.43)	0.44 (1.02)	-0.39 [-0.84; 0.06]	0.09	0.54
Cingulum hippocampus R	0.82 (1.57)	0.46 (0.79)	0.31 [-0.51; 1.12]	0.45	0.50
Superior longitudinal fasciculus L	1.16 (1.65)	1.48 (1.45)	-0.53 [-1.51; 0.45]	0.28	0.55
Superior longitudinal fasciculus R	1.47 (1.56)	2.27 (2.86)	-0.90 [-2.38; 0.59]	0.23	0.55
Uncinate fasciculus L	1.71 (1.90)	1.13 (1.58)	0.45 [-0.67; 1.57]	0.42	0.56
Uncinate fasciculus R	1.91 (2.32)	1.50 (1.09)	0.32 [-0.86; 1.50]	0.59	0.59
Corticospinal tract L	1.52 (1.72)	1.95 (1.92)	-0.39 [-1.45; 0.67]	0.46	0.50
Corticospinal tract R	1.23 (1.36)	3.55 (4.74)	-2.55 [-4.78; -0.33]	0.03	0.31

Displayed data are mean (standard deviation).

CI = confidence interval; corr. = FDR-corrected *P*-value; DMS = depressed multiple sclerosis patients; L = left; nDMS = non-depressed multiple sclerosis patients; R = right.

Supplementary Table 3. Group comparisons for structural MRI between DMS and nDMS patients with correction for disease duration and sex

	DMS (*n*=22)	nDMS (*n*=21)	Difference [CI]	*P*	*P* corr.
NWMV, ml	667.68 (34.89)	706.98 (47.90)	-54.86 [-79.98; -29.73]	<0.001	<0.001
NGMV, ml	745.76 (56.61)	715.45 (50.63)	0.67 [-23.79; 25.12]	0.956	0.956
T2LL, ml	5.69 (5.92)	7.45 (5.43)	-0.65 [-4.36; 3.07]	0.728	0.848
Hippocampus L, ml	4.74 (0.68)	4.66 (0.69)	-0.08 [-0.52; 0.35]	0.705	0.848
Hippocampus R, ml	4.80 (0.76)	4.51 (0.73)	0.07 [-0.38; 0.52]	0.754	0.848
Amygdala L, ml	1.55 (0.36)	1.59 (0.32)	-0.11 [-0.33; 0.11]	0.320	0.848
Amygdala R, ml	1.62 (0.41)	1.50 (0.29)	0.06 [-0.15; 0.27]	0.549	0.848
Thalamus L, ml	9.61 (1.00)	9.39 (1.39)	-0.28 [-0.96; 0.39]	0.399	0.848
Thalamus R, ml	9.33 (1.05)	9.06 (1.20)	-0.22 [-0.83; 0.40]	0.481	0.848

Displayed data are mean (standard deviation).

CI = confidence interval; corr. = FDR-corrected *P*-value; DMS = depressed multiple sclerosis patients; L = left; NGMV = normalized grey matter volume; nDMS = non-depressed multiple sclerosis patients; NWMV = normalized white matter volume; R = right; T2LL = T2-weighted lesion load.

Supplementary Table 4. Group comparisons for diffusivity parameters of each white matter tract between DMS and nDMS patients with correction for disease duration and sex

	DMS (*n*=22)	nDMS (*n*=21)	Difference [CI]	*P*	*P* corr.
FA					
Anterior thalamic radiation L	0.380 (0.021)	0.385 (0.018)	-0.009 [-0.022; 0.005]	0.208	0.646
Anterior thalamic radiation R	0.368 (0.020)	0.375 (0.014)	-0.011 [-0.023; 0.000]	0.052	0.383
Cingulum cingulate L	0.389 (0.024)	0.400 (0.022)	-0.018 [-0.033; -0.003]	0.018	0.218
Cingulum cingulate R	0.360 (0.025)	0.367 (0.023)	-0.014 [-0.030; 0.002]	0.080	0.383
Cingulum hippocampus L	0.351 (0.023)	0.342 (0.035)	0.004 [-0.016; 0.024]	0.678	0.814
Cingulum hippocampus R	0.357 (0.029)	0.352 (0.033)	0.001 [-0.021; 0.022]	0.949	0.972
Superior longitudinal fasciculus L	0374 (0.018)	0.374 (0.020)	-0.004 [-0.017; 0.008]	0.490	0.712
Superior longitudinal fasciculus R	0.378 (0.016)	0.370 (0.023)	0.003 [-0.010; 0.016]	0.658	0.814
Uncinate fasciculus L	0.360 (0.016)	0.373 (0.017)	-0.016 [-0.027; -0.004]	0.008	0.201
Uncinate fasciculus R	0.371 (0.017)	0.379 (0.016)	-0.011 [-0.022; 0.001]	0.068	0.383
Corticospinal tract L	0.494 (0.018)	0.496 (0.016)	-0.001 [-0.013; 0.011]	0.838	0.934
Corticospinal tract R	0.479 (0.018)	0.479 (0.022)	0.001 [-0.013; 0.015]	0.856	0.934
MD mm^2/s (*10^{-3})					
Anterior thalamic radiation L	0.869 (0.038)	0.856 (0.030)	0.013 [-0.010; 0.036]	0.269	0.646
Anterior thalamic radiation R	0.868 (0.038)	0.853 (0.031)	0.017 [-0.007; 0.041]	0.157	0.628
Cingulum cingulate L	0.824 (0.039)	0.814 (0.024)	0.007 [-0.015; 0.030]	0.504	0.712
Cingulum cingulate R	0.800 (0.032)	0.789 (0.025)	0.009 [-0.011; 0.029]	0.381	0.712
Cingulum hippocampus L	0.861 (0.041)	0.863 (0.039)	0.000 [-0.027; 0.026]	0.972	0.972
Cingulum hippocampus R	0.860 (0.043)	0.865 (0.040)	-0.010 [-0.038; 0.019]	0.495	0.712
Superior longitudinal fasciculus L	0.812 (0.034)	0.805 (0.026)	0.004 [-0.016; 0.025]	0.666	0.814
Superior longitudinal fasciculus R	0.806 (0.034)	0.813 (0.029)	-0.008 [-0.031; 0.014]	0.442	0.712
Uncinate fasciculus L	0.853 (0.035)	0.834 (0.028)	0.013 [-0.008; 0.035]	0.226	0.646

Uncinate fasciculus R	0.855 (0.037)	0.846 (0.025)	0.008 [-0.014; 0.030]	0.492	0.712
Corticospinal tract L	0.819 (0.027)	0.815 (0.022)	0.009 [-0.007; 0.026]	0.268	0.646
Corticospinal tract R	0.825 (0.026)	0.838 (0.036)	-0.010 [-0.032; 0.011]	0.347	0.712

Displayed data are mean (standard deviation).

CI = confidence interval; corr. = FDR-corrected *P*-value; DMS = depressed multiple sclerosis patients; FA = fractional anisotropy; L = left; MD = mean diffusivity; nDMS = non-depressed multiple sclerosis patients; R = right.

Supplementary Table 5. Group comparisons for functional connectivity of fronto-limbic structures between DMS and nDMS patients with correction for disease duration and sex

	DMS (*n*=22)	nDMS (*n*=21)	Difference [CI]	*P*	*P* corr.
Amygdala L – frontal FC	-1.066 (0.435)	-0.711 (0.678)	-0.308 [-0.699; 0.083]	0.119	0.357
Amygdala R – frontal FC	-1.094 (0.398)	-0.516 (0.655)	-0.507 [-0.873; -0.141]	0.008	0.047
Hippocampus L – frontal FC	-0.608 (0.535)	-0.535 (0.620)	-0.114 [-0.512; 0.285]	0.567	0.698
Hippocampus R – frontal FC	-0.681 (0.454)	-0.498 (0.517)	-0.210 [-0.549; 0.128]	0.217	0.433
Thalamus L – frontal FC	0.047 (0.482)	0.098 (0.580)	-0.098 [-0.452; 0.257]	0.581	0.698
Thalamus R – frontal FC	0.073 (0.514)	-0.047 (0.590)	0.072 [-0.307; 0.451]	0.702	0.702

Displayed data are mean (standard deviation).

CI = confidence interval; corr. = FDR-corrected *P*-value; DMS = depressed multiple sclerosis patients; FC = functional connectivity; L = left; nDMS = non-depressed multiple sclerosis patients; R = right.

Supplementary Table 6. Demographics and cognitive functioning of DMS^{MDD} and $nDMS^{lowHADS}$ patients

	DMS^{MDD} (*n*=14)	$nDMS^{lowHADS}$ (*n*=16)	*P*
Age	44.17 (11.57)	49.50 (7.95)	0.15
Sex (female/male)	11/3	13/3	0.86
Educational level*	6.00 (5.00 – 6.00)	6.00 (5.00 – 6.00)	0.89
MS type (RRMS/SPMS/PPMS/missing)	10/3/4/0	13/2/0/1	0.31
Disease duration	6.54 (6.69)	14.99 (8.68)	< 0.01
EDSS groups (percentage) 0 – 1.5 2 – 4 4.5 – 6 ≥ 6.5	 0 (0%) 11 (79%) 2 (14%) 1 (7%)	 0 (0%) 10 (63%) 6 (37%) 0 (0%)	0.23
HADS-A*	11.00 (7.75 – 11.25)	4.00 (2.25 – 6.75)	<0.001
HADS-D*	–	2.00 (1.25 – 2.75)	–
BDI-II	29.79 (7.94)	–	–

Displayed data are mean (standard deviation).

* Not normally distributed data for which median (interquartile range) are provided

BDI-II = Beck's Depression Inventory Second Edition; DMS^{MDD} = depressed multiple sclerosis patients with a current major depressive disorder; EDSS = Expanded Disability Status Scale; HADS = Hospital Anxiety and Depression Scale; A = Anxiety; D = Depression; $nDMS^{lowHADS}$ = non-depressed multiple sclerosis patients with a low hospital anxiety and depression – depression subscale score; PPMS = primary progressive multiple sclerosis; RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

Supplementary Table 7. Cognitive functioning of DMS^{MDD} and $nDMS^{lowHADS}$ patients

	DMS^{MDD} (*n*=14)	$nDMS^{lowHADS}$ (*n*=16)	Difference [CI]	*P*
Verbal memory and learning	-2.20 (1.08)[a]	-1.04 (2.02)	-1.68 [-3.00; -0.37]	0.01
Information processing speed	-0.60 (0.70)	-0.30 (0.83)	-0.57 [-1.19; 0.06]	0.07
Visuospatial memory	0.41 (0.87)	-0.49 (2.73)	0.18 [-1.46; 1.81]	0.83
Short-term memory Digit span forward	 -0.52 (0.85)	 -0.58 (1.00)	 0.05 [-0.79; 0.88]	 0.91
Working memory Digit span backward Letter-number sequencing	 -0.82 (1.28) -1.21 (1.15)	 -0.77 (1.41) -0.64 (1.37)	 -0.01 [-1.21; 1.19] -0.50 [-1.61; 0.61]	 0.98 0.37
Verbal fluency animals professions m-words	 0.16 (0.82)[a] -0.31 (1.40)[a] -0.38 (0.72)[a]	 0.19 (0.96) 0.26 (0.88) 0.04 (0.71)	 -0.15 [-0.93; 0.84] -0.63 [-1.46; 0.20] -0.33 [-0.92; 0.26]	 0.71 0.13 0.26

Displayed data are mean (standard deviation).

[a] n = 13

CI = confidence interval; DMS^{MDD} = depressed multiple sclerosis patients with a current major depressive disorder; $nDMS^{lowHADS}$ = non-depressed multiple sclerosis patients with a low hospital anxiety and depression – depression subscale score.

Supplementary Table 8. Structural MRI data from DMS^{MDD} and $nDMS^{lowHADS}$ patients

	DMS^{MDD} (*n*=14)	$nDMS^{lowHADS}$ (*n*=16)	Difference [CI]	*P*	*P* corr.
NWMV, ml	669.05 (31.20)	720.52 (45.14)	-75.84 [-104.00; -47.67]	< 0.001	< 0.001
NGMV, ml	749.33 (57.48)	731.43 (46.68)	-6.70 [-3.64; 23.00]	0.65	0.83
T2LL, ml	4.05 (3.69)	5.39 (3.41)	-0.14 [-0.43; 0.15]	0.35	0.63
Hippocampus L, ml	4.82 (0.71)	4.76 (0.67)	-0.04 [-0.60; 0.52]	0.88	0.88
Hippocampus R, ml	4.87 (0.79)	4.62 (0.68)	0.07 [-0.51; 0.66]	0.80	0.90
Amygdala L, ml	1.59 (0.36)	1.66 (0.31)	-0.08 [-0.38; 0.21]	0.58	0.87
Amygdala R, ml	1.73 (0.41)	1.54 (0.27)	0.16 [-0.11; 0.43]	0.23	0.51
Thalamus L, ml	9.66 (0.96)	9.84 (1.19)	-0.70 [-0.148; 0.08]	0.08	0.34
Thalamus R, ml	9.43 (0.96)	9.52 (0.87)	-0.48 [-1.10; 0.14]	0.13	0.38

Displayed data are mean (standard deviation).

CI = confidence interval; corr. = FDR-corrected *P*-value; DMS^{MDD} = depressed multiple sclerosis patients with a current major depressive disorder; L = left; NGMV = normalized grey matter volume; $nDMS^{lowHADS}$ = non-depressed multiple sclerosis patients with a low hospital anxiety and depression – depression subscale score; NWMV = normalized white matter volume; R = right; T2LL = T2-weighted lesion load.

Supplementary Table 9. Diffusivity parameters for each white matter tract of DMS^{MDD} and $nDMS^{lowHADS}$ patients

	DMS^{MDD} (*n*=14)	$nDMS^{lowHADS}$ (*n*=16)	Difference [CI]	*P*	*P* corr.
FA					
Anterior thalamic radiation L	0.384 (0.014)	0.390 (0.016)	-0.007 [-0.021; 0.006]	0.28	0.62
Anterior thalamic radiation R	0.371 (0.015)	0.377 (0.013)	-0.011 [-0.023; 0.000]	0.06	0.72
Cingulum cingulate L	0.396 (0.021)	0.404 (0.023)	-0.014 [-0.032; 0.004]	0.13	0.60
Cingulum cingulate R	0.369 (0.020)	0.371 (0.024)	-0.007 [-0.026; 0.012]	0.48	0.72
Cingulum hippocampus L	0.359 (0.021)	0.349 (0.036)	0.008 [-0.018; 0.035]	0.53	0.70
Cingulum hippocampus R	0.362 (0.029)	0.360 (0.032)	0.007 [-0.020; 0.034]	0.59	0.74
Superior longitudinal fasciculus L	0.378 (0.014)	0.377 (0.021)	-0.007 [-0.022; 0.009]	0.39	0.67
Superior longitudinal fasciculus R	0.381 (0.014)	0.375 (0.020)	-0.001 [-0.016; 0.014]	0.91	0.95
Uncinate fasciculus L	0.362 (0.011)	0.375 (0.016)	-0.014 [-0.027; -0.002]	0.03	0.64
Uncinate fasciculus R	0.373 (0.016)	0.381 (0.017)	-0.010 [-0.025; 0.005]	0.18	0.72
Corticospinal tract L	0.496 (0.020)	0.498 (0.017)	0.003 [-0.013; 0.019]	0.67	0.81
Corticospinal tract R	0.479 (0.018)	0.481 (0.024)	-0.002 [-0.021; 0.017]	0.82	0.90
MD mm^2/s (*10^{-3})					
Anterior thalamic radiation L	0.864 (0.025)	0.848 (0.028)	0.013 [-0.010; 0.037]	0.26	0.70
Anterior thalamic radiation R	0.862 (0.024)	0.845 (0.021)	0.019 [-0.001; 0.039]	0.06	0.49
Cingulum cingulate L	0.827 (0.038)	0.810 (0.024)	0.012 [-0.015; 0.039]	0.36	0.67
Cingulum cingulate R	0.799 (0.032)	0.789 (0.027)	0.008 [-0.017; 0.033]	0.53	0.74
Cingulum hippocampus L	0.864 (0.033)	0.865 (0.039)	0.006 [-0.025; 0.037]	0.69	0.79
Cingulum hippocampus R	0.860 (0.039)	0.865 (0.041)	-0.016 [-0.050; 0.019]	0.35	0.70
Superior longitudinal fasciculus L	0.816 (0.023)	0.803 (0.025)	0.013 [-0.009; 0.034]	0.23	0.68
Superior longitudinal fasciculus R	0.809 (0.029)	0.809 (0.025)	-0.001 [-0.025; 0.023]	0.91	0.91
Uncinate fasciculus L	0.858 (0.028)	0.831 (0.023)	0.019 [-0.003; 0.041]	0.08	0.51
Uncinate fasciculus R	0.853 (0.022)	0.840 (0.023)	0.011 [-0.009; 0.031]	0.28	0.68

Corticospinal tract L	0.819 (0.020)	0.809 (0.024)	0.012 [-0.007; 0.031]	0.22	0.76
Corticospinal tract R	0.822 (0.020)	0.830 (0.024)	-0.008 [-0.027; 0.012]	0.43	0.69

Displayed data are mean (standard deviation).

CI = confidence interval; corr. = FDR-corrected *P*-value; DMS^{MDD} = depressed multiple sclerosis patients with a current major depressive disorder; FA = fractional anisotropy; L = left; MD = mean diffusivity; $nDMS^{lowHADS}$ = non-depressed multiple sclerosis patients with a low hospital anxiety and depression – depression subscale score; R = right.

Supplementary Table 10. Functional connectivity between fronto-limbic structures of DMS^{MDD} and $nDMS^{lowHADS}$ patients

	DMS^{MDD} (*n*=14)	$nDMS^{lowHADS}$ (*n*=16)	Difference [CI]	*P*	*P* corr.
Amygdala L – frontal FC	-1.206 (0.453)	-0.695 (0.733)	-0.476 [-1.020; 0.068]	0.08	0.17
Amygdala R – frontal FC	-1.159 (0.426)	-0.514 (0.699)	-0.631 [-1.156; -0.106]	0.02	0.06
Hippocampus L – frontal FC	-0.505 (0.623)	-0.436 (0.646)	-0.145 [-0.711; 0.420]	0.60	0.72
Hippocampus R – frontal FC	-0.855 (0.386)	-0.429 (0.521)	-0.534 [-0.938; -0.129]	0.01	0.07
Thalamus L – frontal FC	0.179 (0.482)	0.185 (0.530)	0.031 [-0.395; 0.456]	0.88	0.88
Thalamus R – frontal FC	0.255 (0.482)	0.031 (0.533)	0.211 [-0.233; 0.655]	0.34	0.51

Displayed data are mean (standard deviation).

CI = confidence interval; corr. = FDR-corrected *P*-value; DMS^{MDD} = depressed multiple sclerosis patients with a current major depressive disorder; FC = functional connectivity; L = left; $nDMS^{lowHADS}$ = non-depressed multiple sclerosis patients with a low hospital anxiety and depression – depression subscale score; R = right.