Supplementary document

Image acquisition

Brain images were acquired using a 3T Siemens Prisma scanner (Siemens, Erlangen, Germany) with a standard 64-channel head coil. First, a gradient echo field map sequence was measured for B_0-correction with the following image geometry: echo time (TE) = 10.00 ms / 12.46 ms; 90° flip angle; duration = 3:44 minutes. For the purpose of normalization of functional data, structural images were acquired using a T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence: 176 sagittal slices; slice thickness = 0.94 mm; voxel size = 0.94 mm x 0.94 mm; repetition time (TR) = 1580 ms; inversion time (TI) = 900 ms; TE = 2.30 ms; field of view (FOV) = 240 mm x 240 mm; 8° flip angle; acceleration factor = 3 (GRAPPA); duration = 4:29 minutes, and a T2-weighted (SPACE, dark fluid) sequence: 192 sagittal slices; slice thickness = 0.9; voxel size = 0.45 mm x 0.45 mm; TR = 5000 ms; TI = 1800 ms; TE = 387 ms; FOV = 230 mm x 230 mm; 120° flip angle; acceleration factor = 2 (GRAPPA). Functional images were produced with a T2*-weighted echo-planar imaging (EPI) sequence: 40 slices; slice thickness = 3.0 mm; distance factor = 25%; voxel size = 2.0 x 2.0 mm; TR = 2500 ms; acceleration factor = 2 (GRAPPA); TE = 30 ms; FOV = 220 mm × 220 mm; 85° flip angle; fat suppression; descending acquisition; duration = 24:43 minutes.

Functional image analyses

Image preprocessing and analyses were performed using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL 5.0.9, Feat 6.00). All EPIs were cut 30 seconds after the last stimulation. Preprocessing included motion correction using McFLIRT [1], B_0-unwarping, slice time correction using Fourier-space

time-series phase-shifting, non-brain removal using BET [2], spatial smoothing using a 5 mm full-width half-maximum Gaussian kernel and high pass temporal filtering with a 100 s cut-off. For outlier detection of functional scans, we used the minimum sum of squared differences to adjacent scans thresholded with the method of Hubert and van der Veeken. [3] Functional images were registered to individual anatomical images using FLIRT by boundary based registration. [4,5] Registration from high resolution structural to standard space of the Montreal Neurological Institute brain (MNI-152) was performed using a 12 parameter linear transformation (FLIRT) followed by a nonlinear registration (FNIRT). [6,7] One subject was registered only linearly because of a failure of FNIRT. Registration was applied to the contrast images of session-level models.
Subject level analyses included the regressors HIT and MISS for each correctly or incorrectly answered task (congruent, incongruent, or neutral), their first derivative, and a modulated regressor of HIT by congruent, incongruent, or neutral. The reaction time was used as a modulator to indicate cognitive load. Regressors of no interest were six motion parameters from motion correction and a binary regressor for each outlier volume.

We hypothesized that task complexity and longer reaction times are associated with increased brain activity. To study functional changes, we created two contrasts. The contrast TASK was defined as the difference between HIT (incongruent task), and the mean of HIT (congruent task) and HIT (neutral task). The contrast TIME considered reaction time regardless of the type of task. The session-level analysis, according to the general linear model with prewhitening, used the above-mentioned regressors. [8]
We defined the hippocampus, nucleus caudate, anterior cingulate gyrus, thalamus, pallidum, and putamen as regions of interest (ROI). Masks for ROI come from the

Harvard-Oxford Atlas delivered with FSL 5.0.9. The probability of a voxel belonging to a brain structure had to be at least 0.5 for assigning the voxel to that structure.

Areas of activation due to cognitive load / attentional performance were identified by a group-level design modelling the means of the groups. The contrasts give the means of the healthy controls and MS patients and were tested by permutation tests using a threshold-free-cluster-enhancement statistic with familywise error correction in each ROI using the software PALM (Version alpha 102 running in Octave 3.8.1) [9] with tail approximation [10]. Group comparison was restricted to voxel, showing activation due to mental load to at least one group. Each ROI was considered separately. The same design used to analyze areas of activation was used to test the difference between controls and patients (two-sided test).

Lesion analyses

To estimate the individual lesion load from the structural images, we used the legion segmentation tool (LST) toolbox version 2.0.15 [11] for SPM 12 [12]. The lesion growth algorithm (LGA) from the LST was started with an initial threshold of 0.3 (chosen after visual inspection) using T1- and T2-weighted structural images. For two subjects T2-weighted images were not available, so LGA could not be used. The corresponding values are missing in Table 1.

In addition to the lesion load from the LST, we select the extend of the white matter hyperintensities estimated from Freesurfer version 6.0 [13,14], run on a Linux Cluster with RedHat 6.9. For this analysis, we used the T1- and T2-weighted images where available and for the previously mentioned two subjects only the T1-weighted images. The recon-all pipeline was called with the parameters -mprage, -3T and all segmentations and surface reconstructions were visually checked for errors. Statistics

were calculated with PSPP (GNU PSPP, Version 1.2.0 https://www.gnu.org/software/pspp).

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