

## **Abstract**

**Background:** Thalamic atrophy is proposed to be a major predictor of disability progression in multiple sclerosis (MS), while thalamic function remains understudied.

**Objectives:** To study how thalamic functional connectivity (FC) is related to disability and thalamic or cortical network atrophy in two large MS cohorts.

**Methods:** Structural and resting-state functional MRI was obtained in 673 subjects from Amsterdam (MS: N=332, healthy controls (HC): N=96) and Graz (MS: N=180, HC: N=65) with comparable protocols, including disability measurements in MS (Expanded Disability Status Scale, EDSS). Atrophy was measured for the thalamus and seven well-recognised resting-state networks. Static and dynamic thalamic FC with these networks was correlated with disability. Significant correlates were included in a backward multivariate regression model.

**Results:** Disability was most strongly related (adjusted  $R^2=0.57$ ,  $p<0.001$ ) to higher age, a progressive phenotype, thalamic atrophy and increased static thalamic FC with the sensorimotor network (SMN). Static thalamus-SMN FC was significantly higher in patients with high disability ( $EDSS\geq 4$ ) and related to network atrophy but not thalamic atrophy or lesion volumes.

**Conclusions:** The severity of disability in MS was related to increased static thalamic FC with the SMN. Thalamic FC changes were only related to cortical network atrophy, but not to thalamic atrophy.

## Introduction

Thalamic atrophy is common in multiple sclerosis (MS) and has been consistently observed throughout the disease, from early disease stages onwards.<sup>1</sup> Strong relations of thalamic atrophy have been described with disease progression,<sup>2</sup> disability,<sup>3</sup> fatigue<sup>4</sup> and cognitive dysfunction.<sup>5</sup> Thalamic atrophy seems most strongly related to structural disconnection in cortico-thalamic tracts caused by white matter (WM) damage rather than intra-thalamic lesions, although this remains understudied.<sup>6-8</sup> As such, thalamic atrophy has been increasingly highlighted as a potential critical measure of the severity of neuro-axonal (network) damage in MS.<sup>1</sup>

The thalamus is connected to almost all motor, sensory, integrative and higher order areas and is a major brain hub<sup>9</sup>, with its degeneration likely to have major consequences for brain functioning. For instance, changes in default-mode<sup>10</sup> and sensorimotor networks<sup>11</sup> have been shown to relate to cognitive and sensorimotor impairment, respectively, although how these changes relate to the thalamus remains unclear. Thalamo-cortical FC changes have mostly been related to cognitive impairment,<sup>12, 13</sup> where the increased thalamic FC explained additional variance beyond thalamic damage.<sup>13</sup> Recent technological breakthroughs in the field of network neuroscience allow the evaluation of different types of connectivity, i.e. static FC (i.e. two regions are active at the same time) and dynamic FC (the stability of FC strength during the scan), all of which seem to have differential relations with cognition.<sup>14</sup> Such types of connectivity have not been explored separately for the thalamus, although it was shown that the thalamus loses its normal dynamic pattern of connectivity, again related to cognitive dysfunction.<sup>15</sup> In addition, thalamic FC

changes are related to the severity of cortical functional network disruption,<sup>16</sup> but relations with cortical damage (e.g. atrophy) and disability remain unclear.

Therefore, this study investigated how thalamic resting-state FC changes relate to disability. In addition, we explored possible underlying structural correlates, i.e. whether thalamic FC changes were related to thalamic atrophy, cortical network atrophy or WM damage, in two large MS cohorts.

## **Materials and Methods**

### **Participants**

This retrospective study investigated 673 subjects from the MS cohorts of Amsterdam,<sup>15</sup> The Netherlands (acquired 2008-2012, 332 persons with MS [pwMS] and 96 healthy controls [HC]) and Graz,<sup>17</sup> Austria (acquired 2014-2017, 180 pwMS and 65 HC; Figure 1).

Both cohorts were combined to include patients across the disease span, as the Amsterdam MS cohort does not include patients with a disease duration below six years, whereas the Graz cohort also contains CIS. Amsterdam patients all had a diagnosis of MS according to the 2010 revised McDonald criteria and a relapse-free period with no steroid treatment for at least two months prior to MRI. Similarly, Graz patients were considered CIS or MS according to the same criteria and experienced no relapse and no treatment with corticosteroids within two months prior to scanning. Exclusion criteria for both cohorts were the presence or history of psychiatric or neurologic disease (other than MS). All patients underwent Expanded Disability Status Scale (EDSS) score assessment within one week of MRI, with available functional system scores (FSS, thresholded at >2 or below), e.g. for pyramidal or cerebellar function. High disability (i.e. physical impairment) was defined as EDSS $\geq$ 4, i.e. impairment in walking.<sup>18</sup>

### **Standard protocol approvals, registrations, and patient consents**

The study was approved by the local ethics committee of the respective institutional ethics review boards of the VU University Medical Center and the Medical University of Graz. All participants gave written informed consent prior to participation.

## **MRI data acquisition**

In both centres MRI was performed on a 3-Tesla scanner (Amsterdam: Signa HDxt; GE, Milwaukee, Wis, 8-channel head coil; Graz: TimTrio, Siemens Healthcare, Erlangen, Germany, 12-channel head coil). The Amsterdam MRI protocol included a high-resolution 3D T1-weighted FSPGR sequence with 1mm isotropic resolution (TR=7.8ms, TE=3ms, TI=450ms), a 3D-FLAIR sequence (TR=8000ms, TE=125 ms; TI=2350 ms; in-plane resolution, 1.0x1.0mm<sup>2</sup>; slice thickness 1.2mm), and a resting-state fMRI sequence (echo-planar imaging; 202 volumes; TR=2200, TE=35; resolution 3.3x3.3x3mm, 42 slices). The Graz MRI protocol included a high-resolution structural 3D T1-weighted MPRAGE sequence with 1mm isotropic resolution (TR=1900 ms, TE=2.19 ms, TI=900 ms), a 2D FLAIR sequence (TR=9000ms; TE=69 ms, TI=2500 ms, in-plane resolution, 0.9x0.9 mm<sup>2</sup>; slice thickness 3mm) and a resting-state fMRI (rfMRI) sequence (echo planar imaging, 150 volumes, TR=3000ms; TE=30ms; resolution 3x3x3mm, 36 slices). Participants were asked to close their eyes during resting-state fMRI in both centres. For both centres, each resting-state session lasted for 7.5 minutes.

## **Structural MRI analyses**

### **Lesion segmentation**

Total T2-lesion load (T2-LL) was determined on FLAIR in pwMS. In Amsterdam, lesions were automatically segmented using k-nearest neighbour classification with tissue-type priors,<sup>15</sup> in Graz lesions were assessed by a semi-automated region growing algorithm<sup>17</sup> subsequent to lesion identification by a single experienced rater (CE). In Amsterdam lesion filling was performed using Lesion Automated Processing, in Graz using the FSL lesion filling toolbox.

## **Brain volume measurements**

Total brain, grey (GM), and WM volumes were calculated on the lesion-filled 3DT1 with SIENAX and deep GM volumes with FIRST (both part of FSL5, <https://www.fmrib.ox.ac.uk/fsl>). Thalamic volume was defined as the bilateral sum, cortical network volumes by the total volume, i.e. the sum of each segmented Brainnetome (<https://atlas.brainnetome.org>) region belonging to a specific network on the 3DT1 (see below). All volumes were normalized for head size with V-scaling.

## **Processing of rfMRI data**

Initial pre-processing of rfMRI data was performed using the MELODIC pipeline of FSL5 and included removal of non-brain tissue, motion correction and spatial smoothing with a 5mm Gaussian kernel. Registration parameters were calculated with the use of boundary-based registration (BBR) between the fMRI and 3DT1 sequences and nonlinear registration between 3DT1 and the 2mm MNI standard brain. Subsequently, to further correct for motion artefacts, ICA-AROMA was applied, after which the average signal of WM and CSF was regressed out, as described.<sup>15</sup> Finally, a high-pass temporal filter was applied, equivalent to 0.01Hz. A mask was made of each functional image (based on the robust range) which was used to exclude regions with significant distortion (see below).

## **Regions of interest**

The cortical Brainnetome atlas<sup>19</sup> was used to segment the cortex into regions of interest to extract time-series, which were allocated to seven meaningful literature-based functional networks<sup>20</sup> (after calculating connectivity) based on maximal overlap (Supplementary Table). For each subject, the atlas was co-registered to 3DT1 with inversed non-linear registration parameters and multiplied with GM masks from

SIENAX. FIRST-derived deep grey matter (DGM) areas were then added and this complete atlas was co-registered to fMRI images using inversed BBR parameters. Here, each individual atlas was multiplied with the aforementioned distortion mask, subsequently excluding all regions containing <30% of original voxels. This led to the exclusion of bilateral orbitofrontal, inferior temporal and nucleus accumbens areas, and the entire limbic network, which showed extensive distortion.

### **Functional connectivity**

Static FC: Pearson correlations were calculated between the thalamus and each other atlas region, negative values were set to zero. Scores were transformed to Z-scores using the Fisher r-to-z transformation; left and right thalamic connectivity values were averaged. These matrices were averaged into networks (default-mode, DMN; fronto-parietal, FPN; dorsal and ventral attention, DAN and VAN; visual, VN; sensorimotor, SMN and DGM). FC matrices were corrected for (i.e. divided by) whole-brain FC.

Dynamic FC was calculated based on a sliding window approach, as previously published.<sup>21</sup> For the dynamic FC calculation, each window was set at 60s (27 timepoints in Amsterdam, 20 in Graz due to differences in TR, no difference in total scan duration), using a step-size of 10s (5 and 4 volumes, respectively). For each window, FC between the thalamus and each Brainnetome region was calculated, again converted to Fisher Z-scores. These Z-scores were made absolute to quantify the variability between states of low and high synchronization, regardless of directionality. Subsequently, the coefficient of variation of each link was calculated by dividing the standard deviation over time by the mean over time. This measure was again averaged into networks and used as the dynamic thalamic FC measure.

## **Statistical Analysis**

Statistical analyses were performed using IBM SPSS 26. For data harmonization, volumetric and connectivity variables were converted to site-specific Z-scores based on means and standard deviations of within-site controls. Patients with high vs low disability and controls were compared using a general linear model (GLM), correcting for age, sex and MS phenotype (CIS, RRMS, SPMS or PPMS). To reduce the number of tests for FC analyses, correlation analyses were first performed between EDSS and FC variables using Spearman's correlation coefficients. Subsequently, after Bonferroni correction, significant FC correlates of disability were fed into a backward multivariate linear regression model using EDSS as an outcome measure, also including age, sex, MS phenotype, site and thalamic volume as predictors. The outcome of this model identified the cortical network whose thalamic FC best related to disability. To assess whether functional correlates would still remain significant after correcting for atrophy of the respective cortical network as well as lesion volumes, the aforementioned model was repeated with volumetric variables. All models were checked for collinearity constraints. Significant FC variables in the final model were also compared between disability groups and between FSS groups (>2 or below) using abovementioned GLM procedures and related to measures of damage. Bonferroni correction for multiple comparison was used where applicable, all reported p-values are corrected,  $p < 0.05$  was considered significant.



## Results

The combined sample (Table 1) had a mean age of  $39.9 \pm 12.3$  years for HC and  $43.8 \pm 12.1$  for patients and a mean disease duration based on first symptom onset of  $12.1 \pm 8.7$  years. 145 were classified with high disability ( $EDSS \geq 4 = 28\%$ ).

### Disability and Structural damage

Looking at all patients compared to controls, volumes were lower for thalamus ( $p=0.002$ ) and cortex ( $p<0.001$ ) and all networks except SMN, DAN and FPN (average  $p=0.01$ ). In patients with high disability, compared to HC, all volumes were significantly lower (average  $p<0.001$ ) and lowest for thalamus ( $Z=-2.7$ ), DGM ( $Z=-2.7$ ), DMN ( $Z=-1.3$ ), VAN ( $Z=-1.3$ ) and SMN ( $Z=-1.2$ ; Figure 2). In contrast, patients with low disability did not show significantly lower volumes for DAN, but differences in thalamus ( $Z=-1.2$ ), DGM ( $Z=-1.2$ ), VAN ( $Z=-0.45$ ) and DMN volume ( $Z=-0.44$ ) compared to HC. Patients with high disability also had higher lesion volumes (median 15.9ml) compared to patients with low disability (8.3ml,  $p<0.001$ ).

In the entire MS group, EDSS correlated with T2 lesion volume ( $\rho=0.29$ ,  $p<0.001$ ) and volumes of thalamus ( $\rho=-0.42$ ,  $p<0.001$ ), cortex ( $\rho=-0.21$ ,  $p<0.001$ ), and all networks (all Spearman's  $\rho$  and  $p<0.001$ ): DGM -0.42, SMN -0.39, FPN -0.35, DMN -0.34, DAN -0.34, VAN -0.32, visual -0.17. In addition, lesion load correlated with thalamic ( $\rho=-0.63$ ,  $p<0.001$ ) and cortical volume ( $\rho=-0.44$ ,  $p<0.001$ ).

### Disability and Functional connectivity

In the entire MS group, higher EDSS correlated with higher mean static thalamic connectivity (i.e. FC with the rest of the brain,  $\rho=0.13$ ,  $p=0.004$ ), as well as higher static thalamic FC with the visual network ( $\rho=0.15$ ,  $p=0.001$ ), SMN ( $\rho=0.13$ ,

$p < 0.005$ , Figure 3) and DAN ( $\rho = 0.12$ ,  $p = 0.01$ ). For dynamic FC, there was a significant positive correlation with mean dynamic FC ( $\rho = 0.09$ ,  $p = 0.04$ ), the DGM ( $\rho = 0.17$ ,  $p < 0.001$ ), VAN ( $\rho = -0.11$ ,  $p = 0.02$ ) and FPN ( $\rho = 0.09$ ,  $p = 0.04$ ), i.e. more severe dynamic fluctuations with the thalamus. Figures 2 and 3 depict group differences and correlations, respectively.

### Linear regression: EDSS

Based on the above, the backward selection linear regression model included age, sex, MS phenotype, thalamic volume and static FC between the thalamus and the visual, sensorimotor and dorsal attention networks, as well as dynamic thalamic FC with the DGM, VAN and FPN. The final model (adjusted  $R^2 = 0.57$ ,  $p < 0.001$ , see Table 2) indicated that worse disability was related to a more progressive phenotype ( $\beta = 0.49$ ,  $p < 0.001$ ), higher age ( $\beta = 0.25$ ,  $p < 0.001$ ), worse thalamic atrophy ( $\beta = -0.19$ ,  $p < 0.001$ ), and higher static thalamus-SMN FC ( $\beta = 0.08$ ,  $p = 0.02$ ) and a trend for higher dynamic thalamus-VAN FC ( $\beta = 0.07$ ,  $p = 0.07$ ). The final model was repeated after also adding SMN, VAN and lesion volumes (adjusted  $R^2 = 0.57$ ,  $p < 0.001$ ), which did not result in the loss of significance for any variable. In addition, there were no significant effects for SMN and lesion volumes, while VAN volume was significant ( $\beta = -0.15$ ,  $p = 0.005$ ). See Table 2 for more statistical information.

### Thalamic FC: Relations with disability and structural damage

Static thalamus-SMN FC was significantly higher in patients with high disability, compared to patients with low disability only ( $p = 0.05$ ), with no effects for dynamic thalamus-VAN FC, which was not explored further. Comparing all patients to controls showed no significant effects. In addition, within the entire MS group, increased static thalamus-SMN FC was only related to FSS scores ( $> 2$ ) on pyramidal ( $p = 0.02$ ) and

cerebellar ( $p=0.04$ ) subscores, Within phenotypes, only cerebellar FSS was significant, and only in CIS/RRMS ( $p=0.009$ ). Increased static thalamus-SMN FC was not related to thalamic ( $\rho=-0.03$ ,  $p=0.52$ ) or lesion volume ( $\rho=0.07$ ,  $p=0.13$ ), but was significantly correlated with SMN volume ( $\rho=-0.11$ ,  $p=0.016$ ) and VAN network volume ( $\rho=-0.11$ ,  $p=0.01$ ) .

## Discussion

Using a large multicentre sample, this study investigated in detail how disability in MS is related to thalamic atrophy, altered (static and dynamic) thalamic FC<sup>22</sup> and cortical network atrophy. Disability in MS was related to atrophy of the thalamus and all cortical networks, especially SMN, DMN and VAN, while relations with increased FC centred around the SMN, visual network, VAN and DAN. The primary correlates of disability explained almost 60% of variance, including higher static thalamus-SMN FC, age, phenotype and lower thalamic and VAN volume. Thalamic FC was related to cortical network volumes, but not thalamic volume.

Higher static and dynamic thalamic FC related to poorer clinical functioning. Changes in FC due to MS have been frequently observed,<sup>23, 24</sup> showing the clinical relevance of both increases and decreases in FC for physical disability<sup>16, 25, 26</sup> and cognitive impairment,<sup>12, 15, 27</sup> although relations between disability and dynamic FC remain understudied. Based on directionality alone (increased versus decreased), however, it is impossible to distinguish between adaptive (e.g. compensation for damage to major hubs in the brain) or maladaptive (e.g. exhaustion of compensation leading to an overload) mechanisms.<sup>10</sup> However, as connectivity changes were related to worse disability, beneficial mechanisms might seem less likely, possibly suggesting a maladaptive overload and/or disinhibition of the thalamo-sensorimotor loop.

Thalamic atrophy is common and early in MS and has high promise for clinical implementation.<sup>2</sup> Our results showed predictive value for thalamic FC even after correcting for thalamic atrophy, indicating that structural damage alone cannot explain all variance. This confirms previous FC studies identifying clinically relevant

information beyond tissue damage, important information for tracking and predicting the disease course.<sup>28</sup> The relatively low explained variance might limit value for clinical practice of functional measures, but could provide insight into structural and functional relations in MS. Increased thalamus-SMN FC was not related to the severity of thalamic atrophy, but to network atrophy. This finding was unexpected, as thalamic degeneration seems to precede cortical changes.<sup>29</sup> Recent work suggested that the main driving force behind increased thalamic FC could reside in progressive disconnection of relevant structural WM tracts,<sup>30</sup> which are also thought to underlie thalamic atrophy (i.e. secondary neurodegeneration).<sup>2, 31, 32</sup> This could also explain why lesion volumes were not significant in our regression, as they might explain the same variance as thalamic volume. The SMN has been previously identified as the primary cortical area where atrophy relates to disability, a region possibly more sensitive to intrinsic (lesional) damage.<sup>33</sup> Future longitudinal studies are now needed comprising diffusion measurements to study the interplay of GM and WM damage with FC in MS.

Our study also highlighted that cortical network atrophy is extensive in patients with high disability, not only limited to the SMN, but also the DMN and attention networks. By contrast, cortical network atrophy was less severe in the low disability group (Figure 2), indicating that neurodegeneration accelerates in later stages, as recently suggested in progressive MS.<sup>29</sup> Interestingly, the same phenomenon was also visible for thalamic connectivity with this atrophic network, which could indicate that this acceleration is related to a sudden change in functional network topology, for which additional longitudinal data is required. In healthy aging, it was shown that age-related atrophy occurs in a network-dependent manner with distinct effects of GM network alterations on behavioural performance.<sup>34</sup> Also in MS such a network

specific exploration of atrophy seems fruitful to improve our understanding of the structure-function relationship, identifying patterns beyond conventional segmentation patterns. The DMN, VAN and DAN are not typically related to motor functioning. This might indicate that these networks are also involved in motor function, perhaps through altered levels of focused attention, or that this might be an indication of an overall state of “impairment”, be it disability or cognitive impairment. Unfortunately, cognitive data was only available in a subset.

The results of our study cannot be interpreted without considering the following limitations. First, we did not assess FC of thalamic subregions (e.g. motor vs relay nuclei),<sup>35</sup> which might reveal more detailed information of how thalamo-cortical FC changes in pwMS is associated with different components of disability. However, our aim was to explore whether and how thalamic FC is related to disability and structural damage. Secondly, the EDSS is only a crude measure for disability, but nevertheless the most commonly used and clinically relevant outcome measure in MS. In addition, our analysis of functional subsystem scores underlines the clinical relevance of our findings. Thirdly, DTI assessment was unfortunately not comparable between sites, therefore we could not investigate whether microstructural damage of specific tracts (e.g. thalamic radiation) would improve prediction of disability beyond FC changes, which requires more coherent scanning protocols in future studies. Fourth, although total fMRI scan duration was comparable between sites, differences in volume number and lesion volumes could have affected results. Finally, data on cognition and handedness was not available for all subjects, but should be explored in future studies.

## **Conclusion:**

This study highlights that thalamic connectivity is related to disability in MS, showing specific patterns of increased static connectivity with the sensorimotor network. Notably, FC increases were only related to network atrophy. Future work is now required to study the order of events leading to thalamic and cortical network changes and atrophy.

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**Conflict of Interest:**

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JJG is an editor of Multiple Sclerosis Journal. He serves on the editorial boards of Neurology and Frontiers in Neurology and is president of the Netherlands



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## References

1. Kipp M, Wagenknecht N, Beyer C, et al. Thalamus pathology in multiple sclerosis: from biology to clinical application. *Cell Mol Life Sci* 2015; 72: 1127-1147. DOI: 10.1007/s00018-014-1787-9.
2. Azevedo CJ, Cen SY, Khadka S, et al. Thalamic atrophy in multiple sclerosis: A magnetic resonance imaging marker of neurodegeneration throughout disease. *Ann Neurol* 2018; 83: 223-234. DOI: 10.1002/ana.25150.
3. Eshaghi A, Prados F, Brownlee WJ, et al. Deep gray matter volume loss drives disability worsening in multiple sclerosis. *Ann Neurol* 2018; 83: 210-222. DOI: 10.1002/ana.25145.
4. Capone F, Collorone S, Cortese R, et al. Fatigue in multiple sclerosis: The role of thalamus. *Mult Scler* 2020; 26: 6-16. 2019/05/30. DOI: 10.1177/1352458519851247.
5. Houtchens MK, Benedict RH, Killiany R, et al. Thalamic atrophy and cognition in multiple sclerosis. *Neurology* 2007; 69: 1213-1223. DOI: 10.1212/01.wnl.0000276992.17011.b5.
6. van de Pavert SH, Muhlert N, Sethi V, et al. DIR-visible grey matter lesions and atrophy in multiple sclerosis: partners in crime? *J Neurol Neurosurg Psychiatry* 2016; 87: 461-467. DOI: 10.1136/jnnp-2014-310142.
7. Harrison DM, Oh J, Roy S, et al. Thalamic lesions in multiple sclerosis by 7T MRI: Clinical implications and relationship to cortical pathology. *Mult Scler* 2015; 21: 1139-1150. 2015/01/15. DOI: 10.1177/1352458514558134.
8. Mehndiratta A, Treaba CA, Barletta V, et al. Characterization of thalamic lesions and their correlates in multiple sclerosis by ultra-high-field MRI. *Mult Scler* 2020: 1352458520932804. 2020/06/26. DOI: 10.1177/1352458520932804.
9. Minagar A, Barnett MH, Benedict RH, et al. The thalamus and multiple sclerosis: modern views on pathologic, imaging, and clinical aspects. *Neurology* 2013; 80: 210-219. DOI: 10.1212/WNL.0b013e31827b910b.

10. Schoonheim MM, Meijer KA and Geurts JJ. Network collapse and cognitive impairment in multiple sclerosis. *Front Neurol* 2015; 6: 82. DOI: 10.3389/fneur.2015.00082.
11. Zhuang Y, Zhou F and Gong H. Intrinsic functional plasticity of the sensorimotor network in relapsing-remitting multiple sclerosis: evidence from a centrality analysis. *PLoS One* 2015; 10: e0130524. DOI: 10.1371/journal.pone.0130524.
12. Tona F, Petsas N, Sbardella E, et al. Multiple sclerosis: altered thalamic resting-state functional connectivity and its effect on cognitive function. *Radiology* 2014; 271: 814-821. DOI: 10.1148/radiol.14131688.
13. Schoonheim MM, Hulst HE, Brandt RB, et al. Thalamus structure and function determine severity of cognitive impairment in multiple sclerosis. *Neurology* 2015; 84: 776-783. DOI: 10.1212/WNL.0000000000001285.
14. Bassett DS and Sporns O. Network neuroscience. *Nat Neurosci* 2017; 20: 353-364. DOI: 10.1038/nn.4502.
15. Eijlers AJC, Wink AM, Meijer KA, et al. Reduced Network Dynamics on Functional MRI Signals Cognitive Impairment in Multiple Sclerosis. *Radiology* 2019; 292: 449-457. 2019/06/27. DOI: 10.1148/radiol.2019182623.
16. Tewarie P, Schoonheim MM, Schouten DI, et al. Functional brain networks: linking thalamic atrophy to clinical disability in multiple sclerosis, a multimodal fMRI and MEG study. *Hum Brain Mapp* 2015; 36: 603-618. DOI: 10.1002/hbm.22650.
17. Pinter D, Beckmann CF, Fazekas F, et al. Morphological MRI phenotypes of multiple sclerosis differ in resting-state brain function. *Sci Rep* 2019; 9: 16221. 2019/11/09. DOI: 10.1038/s41598-019-52757-7.
18. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444-1452.
19. Fan L, Li H, Zhuo J, et al. The Human Brainnetome Atlas: A New Brain Atlas Based on Connectional Architecture. *Cereb Cortex* 2016; 26: 3508-3526. DOI: 10.1093/cercor/bhw157.

20. Yeo BT, Krienen FM, Sepulcre J, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol* 2011; 106: 1125-1165. DOI: 10.1152/jn.00338.2011.
21. Douw L, Leveroni CL, Tanaka N, et al. Loss of resting-state posterior cingulate flexibility is associated with memory disturbance in left temporal lobe epilepsy. *PLoS One* 2015; 10: e0131209. DOI: 10.1371/journal.pone.0131209.
22. Ji B, Li Z, Li K, et al. Dynamic thalamus parcellation from resting-state fMRI data. *Hum Brain Mapp* 2016; 37: 954-967. 2015/12/27. DOI: 10.1002/hbm.23079.
23. Filippi M, Preziosa P and Rocca MA. Brain mapping in multiple sclerosis: Lessons learned about the human brain. *Neuroimage* 2019; 190: 32-45. 2017/09/18. DOI: 10.1016/j.neuroimage.2017.09.021.
24. Tahedl M, Levine SM, Greenlee MW, et al. Functional Connectivity in Multiple Sclerosis: Recent Findings and Future Directions. *Front Neurol* 2018; 9: 828. 2018/10/27. DOI: 10.3389/fneur.2018.00828.
25. Janssen AL, Boster A, Patterson BA, et al. Resting-state functional connectivity in multiple sclerosis: an examination of group differences and individual differences. *Neuropsychologia* 2013; 51: 2918-2929. 2013/08/27. DOI: 10.1016/j.neuropsychologia.2013.08.010.
26. Zhong J, Nantes JC, Holmes SA, et al. Abnormal functional connectivity and cortical integrity influence dominant hand motor disability in multiple sclerosis: a multimodal analysis. *Hum Brain Mapp* 2016; 37: 4262-4275. 2016/07/07. DOI: 10.1002/hbm.23307.
27. Rocca MA, Valsasina P, Absinta M, et al. Default-mode network dysfunction and cognitive impairment in progressive MS. *Neurology* 2010; 74: 1252-1259. DOI: 10.1212/WNL.0b013e3181d9ed91.
28. Fleischer V, Radetz A, Ciolac D, et al. Graph Theoretical Framework of Brain Networks in Multiple Sclerosis: A Review of Concepts. *Neuroscience* 2019; 403: 35-53. 2017/11/05. DOI: 10.1016/j.neuroscience.2017.10.033.

29. Eijlers AJC, Dekker I, Steenwijk MD, et al. Cortical atrophy accelerates as cognitive decline worsens in multiple sclerosis. *Neurology* 2019; 93: e1348-e1359. 2019/09/06. DOI: 10.1212/WNL.00000000000008198.
30. Tewarie P, Steenwijk MD, Brookes MJ, et al. Explaining the heterogeneity of functional connectivity findings in multiple sclerosis: An empirically informed modeling study. *Hum Brain Mapp* 2018; 39: 2541-2548. DOI: 10.1002/hbm.24020.
31. Magon S, Tsagkas C, Gaetano L, et al. Volume loss in the deep gray matter and thalamic subnuclei: a longitudinal study on disability progression in multiple sclerosis. *J Neurol* 2020 2020/02/11. DOI: 10.1007/s00415-020-09740-4.
32. Zhang J, Giorgio A, Vinciguerra C, et al. Gray matter atrophy cannot be fully explained by white matter damage in patients with MS. *Mult Scler* 2020: 1352458519900972. 2020/01/25. DOI: 10.1177/1352458519900972.
33. Steenwijk MD, Geurts JJ, Daams M, et al. Cortical atrophy patterns in multiple sclerosis are non-random and clinically relevant. *Brain* 2016; 139: 115-126. DOI: 10.1093/brain/awv337.
34. Koini M, Duering M, Gesierich BG, et al. Grey-matter network disintegration as predictor of cognitive and motor function with aging. *Brain Struct Funct* 2018; 223: 2475-2487. 2018/03/08. DOI: 10.1007/s00429-018-1642-0.
35. d'Ambrosio A, Hidalgo de la Cruz M, Valsasina P, et al. Structural connectivity-defined thalamic subregions have different functional connectivity abnormalities in multiple sclerosis patients: Implications for clinical correlations. *Hum Brain Mapp* 2017; 38: 6005-6018. 2017/09/08. DOI: 10.1002/hbm.23805.