Motor network efficiency and disability in multiple sclerosis

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ABSTRACT

Objective: To develop a composite MRI-based measure of motor network integrity, and determine if it explains disability better than conventional MRI measures in patients with multiple sclerosis (MS).

Methods: Tract density imaging and constrained spherical deconvolution tractography were used to identify motor network connections in 22 controls. Fractional anisotropy (FA), magnetization transfer ratio (MTR), and normalized volume were computed in each tract in 71 people with relapse onset MS. Principal component analysis was used to distill the FA, MTR, and tract volume data into a single metric for each tract, which in turn was used to compute a composite measure of motor network efficiency (composite NE) using graph theory. Associations were investigated between the Expanded Disability Status Scale (EDSS) and the following MRI measures: composite motor NE, NE calculated using FA alone, FA averaged in the combined motor network tracts, brain T2 lesion volume, brain parenchymal fraction, normal-appearing white matter MTR, and cervical cord cross-sectional area.

Results: In univariable analysis, composite motor NE explained 58% of the variation in EDSS in the whole MS group, more than twice that of the other MRI measures investigated. In a multivariable regression model, only composite NE and disease duration were independently associated with EDSS.

Conclusions: A composite MRI measure of motor NE was able to predict disability substantially better than conventional non-network-based MRI measures. **Neurology® 2015;85:1115–1122**

GLOSSARY

AC-PC = anterior commissure–posterior commissure; **BPF** = brain parenchymal fraction; **EDSS** = Expanded Disability Status Scale; **FA** = fractional anisotropy; **GM** = gray matter; **GT** = graph theory; **MS** = multiple sclerosis; **MTI** = magnetization transfer imaging; **MTR** = magnetization transfer ratio; **NAWM** = normal-appearing white matter; **NE** = network efficiency; **PASAT** = Paced Auditory Serial Addition Test; **PCA** = principal component analysis; **PD** = proton density; **ROI** = region of interest; **RRMS** = relapsing-remitting multiple sclerosis; **SPMS** = secondary progressive multiple sclerosis; **TE** = echo time; **TOI** = tract of interest; **TR** = repetition time; **WM** = white matter.

In multiple sclerosis (MS), the most widely used clinical score is the Expanded Disability Status Scale (EDSS).[1,2] However, while accepted as a primary outcome in treatment trials, its reliability[3] and sensitivity to change are limited, requiring large cohorts and lengthy follow-up to reliably identify treatment effects. MRI measures, such as white matter (WM) lesion load,[4] enable treatment effects to be detected in smaller cohorts but are not accepted primary outcomes as their correlation with disability is modest.[5,6] MRI measures are usually of the whole brain or anatomical regions of interest (ROIs), potentially including functionally irrelevant, or overlooking relevant, areas.[7] An alternative is to evaluate networks underlying functions.[8] A network can be assessed as a single ROI, but information about connectivity is lost. In structural connectomics studies, graph theory (GT)[9,10] enables a single measure, such as network efficiency (NE), to encapsulate network-wide damage while weighting the effects of pathology dependent

on where it occurs. Such studies are usually based on diffusion MRI measures,[11] but in MS, combining them with other measures, such as magnetization transfer ratio (MTR), could provide a more comprehensive assessment of pathology.

The aims of this work were to determine whether (1) motor network compared with non-network-based MRI measures correlate more closely with EDSS scores; (2) EDSS scores correlate more with NE than WM fractional anisotropy (FA) in the motor network; and (3) EDSS scores correlate more with NE computed using FA or FA and MTR.

METHODS **Patients.** Seventy-one patients with relapse-onset MS (mean age 46.2 ± 10.3 years; mean disease duration 15.4 ± 10.0 years; 44 female, 27 male; 27 secondary progressive MS [SPMS] and 44 relapsing-remitting MS [RRMS]) were included in this study. Clinical and MRI assessments were not undertaken in those who had had a relapse or received corticosteroids within the preceding 4 weeks. The primary clinical measure of this study was the EDSS.[1] Clinical and demographic data for the whole MS group and the SPMS and RRMS subgroups are shown in table 1.

A group of 22 age- and sex-matched healthy controls (age 44.4 ± 2.4 years; 13 female, 9 male), with no known neurologic or psychiatric conditions, were also enrolled in the study.

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from all patients. This study was approved by the local institutional ethics committee.

MRI protocol and analysis. An outline of the analysis pipeline is shown in figure 1.

MRI protocol and preprocessing. Brain MRI was performed on a Philips Achieva 3T system (Philips Healthcare, Best, Netherlands) using a 32-channel head coil. The high angular resolution diffusion imaging scan consisted of a cardiac-gated spin-echo echoplanar imaging sequence, with slices acquired in the axial-oblique orientation aligned with the anterior commissure–posterior commissure (AC-PC) line (2 × 2 × 2 mm³, 61 isotropically distributed diffusion-weighted directions with b = 1,200 seconds/mm², 7 b = 0 volumes, echo time [TE] = 68 ms, repetition time [TR] = 24 seconds [depending on the cardiac rate], sensitivity encoding factor = 3.1, field of view 112 × 112, number of slices 72). In each subject we also acquired the following: (1) dual-echo proton density (PD)/T2-weighted axial-oblique scans aligned with the AC-PC line (1 × 1 × 3 mm³, TR = 3,500 ms, TE = 19/85 ms, field of view 240 × 240), (2) 3D sagittal T1-weighted fast field echo scan (1 × 1 × 1 mm³, TR = 6.9 ms, TE = 3.1 ms), and (3) magnetization transfer imaging (MTI) scans (1 × 1 × 1 mm³, TR = 6.4 ms, TE = 2.7/4.3 ms, field of view 256 × 256, number of slices 180).

Preprocessing steps included (1) removal of non-brain tissue using FSL,[12] (2) eddy-current correction of diffusion images and vector realignment using FSL,[12] and (3) fitting of the diffusion tensor using Camino.[13]

Network-based analysis: Identification of the motor network components and quantification of tract FA, MTR, and volume. The pipeline for the identification of the motor network components is reported in the e-Methods on the *Neurology*® Web site at Neurology.org and summarized in figure 1. Briefly, the cortical and subcortical gray matter (GM) structures of the motor network were identified based on published models of motor function[14] using the Harvard-Oxford cortical and subcortical structural atlas, included in FSL.[12] Using these as seed points, constrained spherical
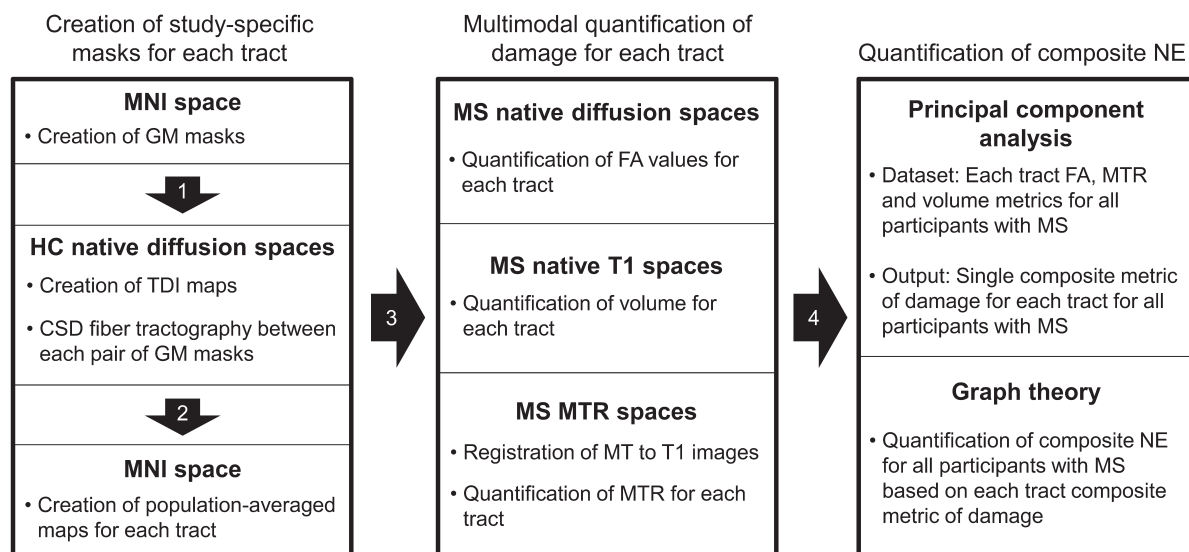
Table 1	Demographic, MRI, and clinical data of patients with multiple sclerosis and healthy controls enrolled in the study			
	Whole MS group	RRMS	SPMS	HC
Age, y	46.2 ± 10.3	42.4 ± 10.0	52.4 ± 7.6	44.4 ± 2.4
Sex, F/M	44/27	29/15	15/12	13/9
Disease duration, y	15.4 ± 10.0	11.4 ± 8.1	21.9 ± 9.3	NA
Median EDSS (range)	4.5 (1–8.5)	2.0 (1–7)	6.5 (4–8.5)	NA
Composite NE	0.57 ± 0.05	0.59 ± 0.04	0.54 ± 0.04	0.66 ± 0.03
FA NE	0.40 ± 0.04	0.41 ± 0.04	0.37 ± 0.04	0.46 ± 0.03
NAWM MTR, %	38.1 ± 1.4	38.4 ± 1.1	37.5 ± 1.6	39.9 ± 0.8
BPF	0.80 ± 0.02	0.80 ± 0.02	0.79 ± 0.02	0.84 ± 0.02
Whole network FA	0.45 ± 0.06	0.47 ± 0.06	0.43 ± 0.06	0.49 ± 0.04
WM PD/T2 LL vol, mL	8.50 ± 10.28	7.60 ± 10.92	9.97 ± 9.13	NA
Cervical cord area, mm²	74.1 ± 11.1	77.2 ± 10.8	69.0 ± 10.0	82.5 ± 10.9

Abbreviations: BPF = brain parenchymal fraction; composite NE = multiparameter principal component–derived network efficiency; EDSS = Expanded Disability Status Scale; FA = fractional anisotropy; FA NE = unimodal network efficiency (based on fractional anisotropy values only); HC = healthy controls; MS = multiple sclerosis; MTR = magnetization transfer ratio; NA = not applicable; NAWM = normal-appearing white matter; NE = network efficiency; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; WM PD/T2 LL = white matter lesion load quantified on proton density/T2 scans.
Values are mean ± SD unless otherwise noted.

Figure 1 MRI analysis pipeline

Creation of study-specific masks for each tract

1

MNI space
- Creation of GM masks

HC native diffusion spaces
- Creation of TDI maps
- CSD fiber tractography between each pair of GM masks

2

MNI space
- Creation of population-averaged maps for each tract

3

Multimodal quantification of damage for each tract

MS native diffusion spaces
- Quantification of FA values for each tract

MS native T1 spaces
- Quantification of volume for each tract

MS MTR spaces
- Registration of MT to T1 images
- Quantification of MTR for each tract

4

Quantification of composite NE

Principal component analysis
- Dataset: Each tract FA, MTR and volume metrics for all participants with MS
- Output: Single composite metric of damage for each tract for all participants with MS

Graph theory
- Quantification of composite NE for all participants with MS based on each tract composite metric of damage

CSD = constrained spherical deconvolution; FA = fractional anisotropy; GM = gray matter; HC = healthy controls; MNI = Montreal Neurologic Institute (atlas); MTR = magnetization transfer ratio; MS = multiple sclerosis; NE = network efficiency; TDI = track density imaging.

deconvolution tractography[15] was used to create in healthy controls the population-weighted masks of all the WM tracts connecting the motor network GM structures (i.e., masks for all tracts of interest [TOIs]). FA, MTR, and normalized volume were then computed for each TOI for all participants with MS as described in the e-Methods.

Network-based analysis: Principal component analysis of multiparameter MRI data. Principal component analysis (PCA) is a data reduction technique that extracts the main components that explain observed variation in multiple different measurements. Practically, it can be used to distill multiple MRI measures[16,17] into fewer variables, so enabling multimodal MRI data to be used where only unimodal data could otherwise be used. GT network analysis works with single measurements for each WM tract, and so in this work we used PCA to condense multimodal MRI data from the WM tracts. To achieve this, FA, MTR, and normalized volume data from all tracts in all patients were included in a single PCA analysis. Each tract in each subject represented a separate data point. The analysis revealed a single factor that explained ~80% of the variance in these 3 measures (in this order of association), i.e., 80% of the unique information in the tracts' FA, MTR, and normalized volume measures. This value of this PCA factor was then calculated in all tracts, rescaled between 0 and 1 across all tracts, and then used in the subsequent GT network analysis.

Network-based analysis: Computation of multiparameter and FA NE. NE, normalized to the maximum theoretical efficiency of the network, was computed using the MATLAB Connectivity Toolbox (www.brain-connectivity-toolbox.net). NE was computed separately (1) based on the WM tract FA (as per previous studies)[11] to generate an FA-based NE measure (FA NE) and (2) using the PCA main factor to generate a composite NE measure incorporating effects of FA, MTR, and tissue volume. In this analysis, higher NE values represent the potential for more efficient information exchange.[9,10]

Other MRI metrics. All the tracts of the motor network were merged to form a single mask of motor network WM. Mean FA was then measured inside this mask (whole network FA).

Whole brain PD/T2-weighted lesion volumes, normal-appearing WM (NAWM) MTR, brain parenchymal fraction (BPF), and cervical cord area were measured. WM PD/T2 lesion load was measured using PD/T2 images and JIM (Xinpase Systems; www.xinapse.com). NAWM MTR values were computed from the WM mask (generated as above) excluding PD/T2 WM lesions. BPF was computed using the GM, WM, and CSF masks.[18] Cervical spinal cord area was measured using the T1-weighted volumetric images as previously described.[19]

Statistical analysis. Log-transformed volume was used to normalize the PD/T2 WM lesion load data. In the whole MS group, associations between EDSS and MRI metrics were examined with Spearman and Pearson correlations. Multivariable associations with EDSS were examined using multiple linear regression, with the MRI and demographic variables as predictors. There was no evidence of residual non-normality, but as a precaution the results assuming normality were confirmed using a nonparametric bias-corrected and accelerated bootstrap with 1,000 replicates. There was evidence of heteroscedasticity, but robust standard error[20] regressions accommodating heteroscedasticity did not materially alter results, therefore standard least squares results are reported. Although the regression p values, confidence intervals, and R^2 are valid after the residual checks above, regression coefficients must be interpreted with caution: the EDSS scale does not have a uniform linear interpretation. For this reason, the potentially different association between EDSS and composite NE in SPMS and RRMS was examined not with a conventional interaction test, which compares slopes in the 2 groups, but by comparing residual variance between the groups using an F test, with smaller variance indicating better model fit. The same analysis was performed dividing the whole MS group into EDSS >3.5 or EDSS ≤3.5 subgroups. Statistical analyses were performed in Stata 13.1 (Stata Corporation, College Station, TX), and statistical significance reported at $p < 0.05$. Data are reported as mean ± SD, unless stated otherwise.

Figure 2   Gray and white matter components of the motor network

A

Region of interest	WFU atlas labels	Region of interest	WFU atlas labels	Identification
Left primary sensory motor cortex	Left B.A. 1,2,3,4	Right primary sensory motor cortex	Right B.A. 1,2,3,4	S-M1
Left secondary motor cortex	Left B.A. 6	Right secondary motor cortex	Right B.A. 6	M2
Left secondary sensory cortex	Left B.A. 40	Right secondary sensory cortex	Right B.A. 5,7	S2
Left posterior associative sensory cortex	Left B.A. 5,7	Right posterior associative sensory cortex	Right B.A. 5,7	AS Sens C
Left prefrontal cortex	Left B.A. 9,10,11,46	Right prefrontal cortex	Right B.A. 9,10,11,46	PFC
Left deep gray matter	Left thalamus, caudate nucleus, putamen, pallidum	Right deep gray matter	Right thalamus, caudate nucleus, putamen, pallidum	Deep GM
Left cerebellar cortex	Left cerebellar cortex	Right cerebellar cortex	Right cerebellar cortex	Cerebellum

B

(A) Gray matter (GM) regions included in the motor network. (B) Connectivity matrix of the tracts included in the motor network based on the tractography results. Included tracts are shown in light blue; tracts not identified by fiber tractography are shown in dark blue. As Sens C = associative parietal sensory cortex; BA = Brodmann area; deep GM = deep gray matter; M2 = secondary motor area; PFC = prefrontal cortex; S-M1 = primary sensory motor cortex; S2 = secondary sensory area.

RESULTS **MRI and EDSS associations in the whole MS group.** The connectivity matrix of the motor network is shown in figure 2 (lower panel). The MRI measurement values are given in table 1. Table 2 shows pairwise correlations and R^2 values among EDSS, MRI, and demographic variables. While all correlations were significant (table 2), composite NE had the highest R^2, explaining 58% of variance in EDSS scores compared with 21% for FA NE (figure 3) and with 18% for cervical cord area (the second and third best performing metrics).

In a multivariable regression analysis including composite NE and other MRI or demographic variables, disease duration was the only significant predictor of EDSS independent from the composite NE (model R^2 0.64, composite NE $p < 0.001$, disease duration $p = 0.003$). While none of the MRI parameters were independent predictors of EDSS in models with composite NE, the logarithmic transformation of T2 lesion load approached significance ($p = 0.081$), despite having the smallest univariable R^2 (0.09). However, log T2 lesion load lost significance in a model with disease duration as a covariate.

MRI and EDSS association in RRMS and SPMS subgroups. The composite NE was also significantly associated with EDSS in the RRMS (R^2 0.46) and SPMS (R^2 0.50) groups. The reduced R^2 value

Table 2 Correlations and univariable R^2 of the MRI measures with EDSS in the whole multiple sclerosis group

Demographic measures	Spearman correlations	Pearson correlations	Univariable R^2
Age	rho = 0.45, $p < 0.001$	$r = 0.49$, $p < 0.001$	0.24
Disease duration	rho = 0.57, $p < 0.001$	$r = 0.55$, $p < 0.001$	0.30
MRI measures			
Composite NE	rho = −0.77, $p < 0.001$	$r = -0.77$, $p < 0.001$	0.58
FA NE	rho = −0.52, $p < 0.001$	$r = -0.52$, $p < 0.001$	0.28
NAWM MTR	rho = −0.37, $p = 0.002$	$r = -0.34$, $p = 0.004$	0.12
BPF	rho = −0.30, $p = 0.011$	$r = -0.31$, $p = 0.009$	0.10
Whole network FA	rho = −0.39, $p < 0.001$	$r = -0.43$, $p < 0.001$	0.18
WM PD/T2 LL	rho = 0.27, $p = 0.026$	$r = 0.08$, $p = 0.486$ (NS)	0.01 (NS)
log WM PD/T2 LL	rho = 0.27, $p = 0.026$	$r = 0.30$, $p = 0.012$	0.09
Cervical cord area	rho = −0.41, $p < 0.001$	$r = -0.43$, $p < 0.001$	0.18

Abbreviations: BPF = brain parenchymal fraction; composite NE = multiparameter principal component–derived network efficiency; EDSS = Expanded Disability Status Scale; FA = fractional anisotropy; FA NE = unimodal network efficiency (based on fractional anisotropy values only); MTR = magnetization transfer ratio; NAWM = normal-appearing white matter; WM PD/T2 LL = white matter lesion load quantified on proton density/T2 scans.

observed in either subgroup compared to that in the whole MS cohort is consistent with the smaller range of values in the MRI and EDSS measures seen in the subgroups when compared with the whole MS group. A comparison of the residual variance in the 2 subgroups confirmed a higher variance in RRMS than in SPMS ($p < 0.001$), providing evidence that composite NE prediction of EDSS is better in the SPMS than in the RRMS group. Neither disease duration nor any other variable predicted EDSS independently of composite NE in separate models for SPMS and RRMS. As reported in the supplementary data on the *Neurology*® Web site at Neurology.org, the association between composite NE and EDSS remained significant when considering separately patients with MS with EDSS ≤3.5 (27 patients) or EDSS >3.5 (44 patients).

DISCUSSION The results of this study suggest that a network-based multiparameter MRI measure (composite NE) correlates significantly better with EDSS scores than either conventional brain or spinal cord MRI measures or NE calculated using FA alone. Composite NE explained ~58% of the variability in EDSS scores, with the next best measure (FA NE) explaining about half of this variability. No MRI variable predicted EDSS independently of composite NE in the whole MS group or in the SPMS and RRMS subgroups, indicating that the network multiparameter MRI approach used in this study improves the prediction of clinical disability from MRI data.

Developing MRI markers of clinical outcomes has proven difficult in MS. One major issue is the spatial variability of MS pathology, which can have very different effects on clinical outcomes dependent on its location. As such, it is not surprising that the correlations between whole brain MRI measures of MS pathology and neurologic and cognitive disability[5,6] are only modest, and ROI-based studies have not clearly found a single region that consistently correlates with motor outcomes.[7] Network-based metrics avoid these pitfalls by incorporating data from all the functionally relevant components of a network.

Assessing performance across a neural network can be undertaken in different ways, but in connectomics GT has proven useful as it enables network-wide characteristics to be summarized in a single metric.[9,10] In MS, GT has been applied at a whole brain level using functional MRI,[21,22] diffusion,[23,24] and volumetric MRI data,[25] showing that MS pathology has detectable effects on the function of networks. At a single network level, we have previously found that for Paced Auditory Serial Addition Test (PASAT) scores, FA NE was better able to predict test performance than the raw PASAT network WM tract FA measures used to calculate NE.[26] The results of the present study confirm that this approach is applicable to other brain networks in MS.

NE is calculated using a single measure only, and previous structural GT studies have relied exclusively on FA measures to calculate NE in MS[23,24] and other neurologic conditions.[11] However, no single MRI measure fully captures the spectrum of MS pathology, and so using several different MRI measures may provide a more comprehensive assessment. Previous multiparameter MRI studies in MS, however, have looked at each MRI measure independently.[27,28] We found that multiparameter MRI data combined using PCA, when compared with FA alone, further

Figure 3 Correlation between multiparameter motor NE (composite NE) and EDSS scores
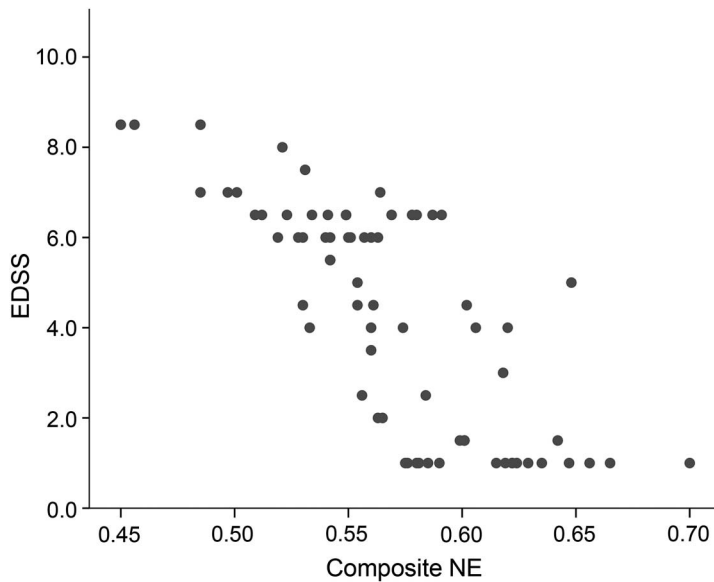
EDSS = Expanded Disability Status Scale; NE = network efficiency.

improved the association between network-based MRI measures and EDSS scores, increasing the explained variance in EDSS scores from 21% using a FA NE measure (based on FA alone) to 58% with a composite NE that used MTR, FA, and normalized tract volume measures. These 3 measures provide complementary information on the underlying pathology. MTR is reduced with demyelination,[29] FA in WM tracts is reduced both with demyelination and when axonal integrity is disrupted,[30] and a decrease in tissue volumes is thought to reflect axonal loss and neurodegenerative changes.[31] This may account for the stronger correlation of the composite NE measure with disability than NE computed using FA alone. Associations between the composite NE measure and EDSS were similar in RRMS (R^2 0.46) and SPMS (0.50), suggesting that this measure may be equally useful across different disease subtypes.

A limitation of the study is the difficulty in identifying relevant GM areas to prime motor network tractography. While we included all the main areas described in published models of motor function,[14] in people with MS, additional cortical areas are recruited during the execution of motor tasks as disability increases.[32] However, the majority of studies localize these additional areas in contralateral motor or prefrontal territories, i.e., all areas already included in our network.[32] In addition, our GM masks are larger than those usually used in whole-brain connectomics studies, potentially incorporating functionally independent areas in some masks. This will tend to reduce the apparent associations between network measures and clinical scores. However, larger GM

regions, and consequently larger WM tract masks, will reduce the impact of interindividual anatomical variability. As this study sought to determine whether a GT-based approach was worth pursuing in MS, we focused on NE, the most commonly used GT metric. As NE quantifies a physiologically relevant property, i.e., the structural capacity for information transfer between parts of a network, it was a suitable choice for this proof-of-concept study. Other network properties that can be characterized using GT, such as nodal degree (which represents the strength with which a given GM region is connected to the rest of the network),[9,10] should be explored in future studies to determine which parameters best encapsulate the effects of MS pathology on a network. Similarly, the MRI parameters included in this study were based on those most often used in MS clinical studies, but again future work could determine whether or not other parameters contribute further.

In this study, the generation of composite measures has been optimized for this dataset. While including people with a wide range of EDSS scores (1–8.5), a substantial proportion had EDSS scores ≤3.5 (27 out of 71), and people who were in, or had recently had, a relapse were not included. Further studies in cohorts with a greater proportion of people with higher EDSS scores, and in people during and after relapses, are required to more fully assess the performance of multiparameter motor network efficiency measures throughout the EDSS scale, and to determine whether or not associations between NE and disability are disrupted by acute inflammatory activity. This study used cross-sectional data from a single center; however, treatment trials are often multisite and require serial measurements. Further work is also needed to determine the reliability of motor NE measures, and whether or not they need to be tuned for MRI scanners individually in multicenter studies. Finally, while the clinical outcome measure used in this work was EDSS, future studies are warranted to assess associations of MRI-based motor network measures with more specific measures of upper and lower limb function.

The results of this study suggest that multiparameter MRI-based measures of motor network efficiency may have a useful role in the assessment of clinically relevant pathology. They were able to explain about 58% of the variation in EDSS scores in a diverse group of people with MS, substantially and significantly outperforming a series of conventional and non-network-based MRI measures.

AUTHOR CONTRIBUTIONS

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Section Co-Editors Johan A. Aarli, MD, and Oded Abramsky, MD, PhD, FRCP, encourage submissions to the Global Perspectives section that provides a platform in *Neurology* for news about scientific findings or academic issues. News may include international research content, spotlights on specific neurologic practice concerns within a country, or important information about international educational or scientific collaborative efforts.

Submissions must be 1,250 words or less with five or less references. A maximum of two figures or two tables (or combination) can be incorporated if necessary. For complete submission requirements, please go to *Neurology.org* and click on "Information for Authors." The submissions will be reviewed by the editors and may be edited for clarity.

Interested submitters can register and upload manuscripts under the section "Global Perspectives" at *http://submit.neurology.org*. Please send inquiries to Kathy Pieper, Managing Editor, *Neurology; kpieper@neurology.org*.