Associations between corpus callosum damage, clinical disability, and surface-based homologous inter-hemispheric connectivity in multiple sclerosis

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Abstract
Axonal damage in the corpus callosum is prevalent in multiple sclerosis (MS). Although callosal damage is associated with disrupted functional connectivity between hemispheres, it is unclear how this relates to cognitive and physical disability. We investigated this phenomenon using advanced measures of microstructural integrity in the corpus callosum and surface-based homologous inter-hemispheric connectivity (sHIC) in the cortex. We found that sHIC was significantly decreased in primary motor, somatosensory, visual, and temporal cortical areas in a group of 36 participants with MS (29 relapsing–remitting, 4 secondary progressive MS, and 3 primary-progressive MS) compared with 42 healthy controls (cluster level, p < 0.05). In participants with MS, global sHIC correlated with fractional anisotropy and restricted volume fraction in the posterior segment of the corpus callosum (r = 0.426, p = 0.013; r = 0.399, p = 0.020, respectively). Lower sHIC, particularly in somatomotor and posterior cortical areas, was associated with cognitive impairment and higher disability scores on the Expanded Disability Status Scale (EDSS). We demonstrated that higher levels of sHIC attenuated the effects of posterior callosal damage on physical disability and cognitive dysfunction, as measured by the EDSS and Brief Visuospatial Memory Test-Revised (interaction effect, p < 0.05). We also observed a positive association between global sHIC and years of education (r = 0.402, p = 0.018), supporting the phenomenon of “brain reserve” in MS. Our data suggest that preserved sHIC helps prevent cognitive and physical decline in MS.

Keywords Inter-hemispheric functional connectivity · Resting state · Multiple sclerosis · Corpus callosum · Clinical

Introduction
The corpus callosum (CC) is a critical white matter tract in the pathophysiology of multiple sclerosis (MS). As the primary inter-hemispheric tract, the CC is particularly vulnerable to damage in MS (Barnard and Triggs 1974). This is likely the result of many factors, such as direct focal lesions and Wallerian degeneration from surrounding white and gray matter pathology (Evangelou et al. 2000; Ge et al. 2004; Klawiter et al. 2015). Structural disconnection of the CC is strongly associated with cognitive impairment (Bergandal et al. 2013; Bodini et al. 2013; Granberg et al. 2015; Huang et al. 2019) and physical disability (Kern et al. 2011; Llufriu et al. 2012; Ozturk et al. 2010).

Resting-state functional connectivity may help to elucidate the relationship between CC axonal damage and clinical disability in MS. The CC is essential for facilitating connections between bilateral, homotopic regions (Innocenti, 2009), which generally have high functional connectivity across hemispheres (Biswal et al. 1995). Various methods have been used to investigate how CC damage may influence inter-hemispheric homotopy in MS. Using EEG, Zito et al. (2014) found that CC atrophy was associated with less efficacious inter-hemispheric coherence in people with relapsing–remitting MS (RRMS) when performing a motor task. A task-based fMRI study found that CC atrophy in MS disrupted inter-hemispheric inhibition in the motor cortex...
Manson et al. 2006), and resting-state fMRI work showed that decreased functional connectivity between the bilateral primary sensorimotor cortices in MS was associated with damage in the corresponding transcallosal white matter tract (Lowe et al. 2008). Using the technique of voxel-mirrored homotopic connectivity (VMHC), Zhou et al. (2013) found a positive correlation between VMHC and fractional anisotropy (FA) of the CC. While these studies demonstrate a structure–function relationship, it is unclear how CC damage and homologous connectivity may interact and contribute to disability in MS. Work by Lin et al. (2020) found associations between altered functional inter-hemispheric connectivity and impaired information processing speed, while Zhou et al. (2013) found no correlation between global VMHC and Expanded Disability Status Scale (EDSS) scores.

Improvements in gradient hardware have allowed for the development of new diffusion MRI measures with useful applications in MS. Previous studies comparing diffusion tensor imaging (DTI) measures with MS histopathology have shown that conventional diffusion measures such as radial diffusivity, mean diffusivity (MD), and FA reflect demyelination more than axonal loss (Klawiter et al. 2011; Schniener et al. 2007). The use of high-gradient strengths up to 300 mT/m in the living human brain has enabled estimation of axonal size and density, providing measures for axonal integrity (Fan et al. 2020, 2021; Huang et al. 2015, 2020; Veraart et al. 2020). Using this technique, Huang et al. (2019) found that altered apparent axon diameter in the CC of participants with MS correlated with disability and cognitive dysfunction. These advanced measures may also provide a more sensitive biomarker for detecting the effects of CC damage on inter-hemispheric functional connectivity.

The purpose of this study is to investigate the interactions between CC damage, resting-state functional connectivity, and clinical disability using novel measures of microstructural integrity and inter-hemispheric connectivity. We evaluated functional connectivity between homologous regions using a technique known as surface-based Homologous Inter-hemispheric Connectivity (sHIC) (Tobyne et al. 2016). Surface-based analysis has proven to be more accurate and spatially specific than volumetric approaches (Anticevic et al. 2008; Jo et al. 2007, 2008; Tucholka et al. 2012), allowing for improved symmetry and mapping of homotopic connections. sHIC has been validated in a large healthy control (HC) dataset and shown to correlate negatively with CC atrophy in MS (Tobyne et al. 2016). Along with the conventional DTI measures of MD and FA, we investigated high-gradient diffusion MRI estimates of axon density, apparent axon diameter, and restricted volume fraction in the CC. First, we assessed differences in sHIC between MS and HC groups. We then examined how sHIC relates to CC damage and clinical disability in MS, both independently and combined in a multiple regression analysis. We hypothesized that microstructural alterations in the CC would disrupt homologous connectivity and contribute to clinical disability in tests dependent upon inter-hemispheric function.

### Materials and methods

#### Study population

Demographics for all participants are reported in Table 1. Patients were recruited from the Massachusetts General Hospital Multiple Sclerosis Clinic. This study was conducted on a group of 36 participants with MS (29 RRMS, 4 secondary progressive MS (SPMS), and 3 primary-progressive MS (PPMS)). Inclusion criteria for participants with MS were: a diagnosis of clinically definite MS, absence of clinical relapse within 3 months, and being on stable disease-modifying treatment or no treatment for at least 6 months. Exclusion criteria were: other major medical and/or psychiatric disorders, severe claustrophobia, and presence of MRI contraindications.

| Table 1 Demographics and clinical data |
|---------------------------------------|
| MS (n = 36)                           | HC (n = 42)                           | HCP (n = 59)                           |
| Age (years)                           | 43.9 ± 11.5 [23–60]                  | 37.3 ± 14.9 [20–63]                   | 31.5 ± 9.2 [20–60]                     |
| Sex (M/F)                             | 9/27                                  | 14/28                                 | 31/18                                 |
| Disease duration (years)              | 9.7 ± 6.7 [1–23]                     | –                                     | –                                     |
| Education (years)                     | 16.4 ± 2.4 [12–23]                   | –                                     | –                                     |
| EDSS (score)                          | 2.8 ± 1.8 [1–7.5]                    | –                                     | –                                     |
| 25-Ft walk (seconds)                  | 5.03 ± 2.3 [2–17]                    | –                                     | –                                     |
| 9-HPT (seconds)                       | 27.2 ± 14.3 [16–90]                  | –                                     | –                                     |
| SDMT (raw score)                      | 52.1 ± 12.4 [27–76]                  | –                                     | –                                     |
| PASAT (raw score)                     | 46.5 ± 12.8 [9–60]                   | –                                     | –                                     |
| BVMT (raw score)                      | 24.2 ± 8 [5–36]                      | –                                     | –                                     |

Mean value ± standard deviation [range]
The healthy control group used for the resting-state fMRI analysis consisted of 42 participants. The HC dataset was derived from the MGH-Harvard-USC Lifespan dataset (Fan et al. 2016) and from a separate technical development study using the same scanner. Additionally, a separate group of 59 healthy participants was taken from the MGH/UCLA Consortium Human Connectome Project (HCP, http://www.humanconnectomeproject.org). 59 of 60 participants were used with one excluded for technical reasons. This group (referred to as HCP) was used to construct a healthy structural connectome. Informed consent was obtained from all participants.

Neurological disability was measured for all patients with MS using clinical tests included in the Minimal Assessment of Cognitive Function in MS (MACFIMS) battery (Benedict et al. 2006) and Multiple Sclerosis Functional Composite (MSFC) (Cutter et al. 1999). Tests were administered by a trained examiner within 1 week of the MRI scan. We characterized cognitive performance using the neuropsychological tests BVMT (Brief Visuospatial Memory Test—Total Recall), PASAT (Paced-Auditory-Serial Addition Test—3 s), and SDMT (Symbol Digit Modalities Test). Physical disability was measured using timed 25-foot walk and timed 9-hole peg test (9-HPT). Five participants with MS were missing 9-HPT scores. A board-certified neurologist conducted a clinical examination and calculated EDSS scores. Z-scores were calculated for each test, except for EDSS. Raw scores are reported in Table 1.

MRI acquisition

All participants were scanned on the same 3 Tesla MRI scanner (MAGNETOM CONNECTOM, Siemens Healthcare, Erlangen, Germany) with a maximum gradient strength of 300 mT/m using a custom-designed 64-channel head coil (Keil et al. 2013). High-resolution three-dimensional T1-weighted (T1w) multi-echo magnetization prepared rapid gradient echo (MEMPRAGE) anatomical images (repetition time (TR)/echo time (TE)/inversion time (TI) = 2530/[1.15, 3.03, 4.89, 6.75]/1100 ms, field of view (FOV) = 256, flip angle (FA) = 60°, 2 × 2 × 2 mm³ voxel resolution, simultaneous multi-slice with a slice acceleration factor = 4) were acquired with one excluded for technical reasons. This group (referred to as HCP) was used to construct a healthy structural connectome. Informed consent was obtained from all participants.

Data preprocessing

Data were preprocessed using the pipeline established for the MGH-USC Human Connectome project (Fan et al. 2016) and tools from FreeSurfer (http://surfer.nmr.mgh.harvard.edu), FMRIB Software Library (FSL, https://fsl.fmrib.ox.ac.uk), MATLAB (version 9.5, Natick, Massachusetts: The MathWorks Inc., 2018b), and custom in-house software (Tian et al. 2022). The cortical surface was reconstructed from T1-weighted data using FreeSurfer (version 5.3). An experienced user manually reviewed and edited these reconstructions to correct for artifacts. White matter lesions disrupting the cortical boundary were manually filled in to prevent misclassification of grey matter (Govindarajan et al. 2015). The average of the interleaved b = 0 images after susceptibility distortion correction was registered to the T1-weighted data, and the FreeSurfer labels in native T1-weighted image space were transformed into diffusion image space using the inverse of the diffusion-to-native T1-weighted image transformation.

Functional preprocessing was conducted for each subject volume in native space before being resampled to a symmetric template. Resting-state and diffusion-weighted data were corrected for gradient nonlinearities, eddy currents, slice-timing, and motion artifacts, and visually inspected for quality assurance. Functional images were spatially smoothed with a 4 mm full width half maximum kernel and underwent grand mean intensity scaling and temporal bandpass filtering (0.001 < f < 0.08 Hz). Physiological noise was removed using multiple regression. Resting-state data had the following exclusion criteria: (1) functional SNR level < 150; (2) maximal absolute displacement > 1.5 mm; (3) average framewise displacement > 0.5 mm; (4) more than 5% of
timepoints with a framewise displacement $> 0.5$ mm; or (5) presence of significant image artifacts. Two resting-state runs were acquired for each subject. If both passed quality assurance, the run with less movement and noise was chosen for analysis.

**Surface-based homotopic inter-hemispheric connectivity**

Inter-hemispheric methods (surfer.nmr.mgh.harvard.edu/fswiki/Xhemi) were used to register each hemisphere to the “fsaverage_sym” symmetric surface template developed by FreeSurfer (Greve et al. 2013). sHIC was calculated using in-house MATLAB code and the techniques previously developed and validated by our group (Tobyne et al. 2016). Homologous vertices were defined as pairs of vertices that shared the same spatial location on the symmetric template. We calculated the pairwise Pearson’s correlation between the extracted time course for each member of each pair of vertices, generating a metric of sHIC per surface vertex. These resulting correlation values were normalized using Fisher’s $r$–Z transformation prior to group-level analysis. sHIC correlation maps were represented and analyzed on the left hemisphere.

**Corpus callosum diffusion analysis**

The three mid-sagittal slices of the corpus callosum were selected to ensure the mask included CC fibers with the greatest coherence. The CC mask was created using the FreeSurfer aparc + aseg atlas and was segmented into five sections (anterior, mid-anterior, central, mid-posterior, and posterior) using the FreeSurfer mri_cc command (Fischl et al. 2002). The five sub-sections were derived from evenly spaced partitions along the primary eigenaxis (Fig. 1a).

For all MS and HCP participants, each segment was manually edited by a trained research assistant to exclude voxels from the fornix and surrounding cerebrospinal fluid. Axonal integrity was measured in the CC using conventional DTI and multi-compartment modeling (Huang et al. 2019, 2020). Apparent axon diameter, restricted volume fraction, and axon density were calculated for each voxel. Apparent axon diameter reflects an MRI-volume weighted estimate of relative axonal size based on compartment models of diffusion MRI data and is not meant to be interpreted as the actual axon diameter. Axon density was calculated by weighting the restricted fraction by the cross-sectional area calculated using the mean apparent axon diameter. MD and FA were derived from the DTIFIT tool in FSL using an ordinary least-squares fit to the diffusion MRI data acquired at $b = 800$ s/mm$^2$ with a diffusion time of 19 ms and 32 diffusion-encoding gradient directions. Axon density, apparent axon diameter, restricted volume fraction, FA, and MD were estimated for each CC segment by averaging values over the segmented voxels.

**Structural connectome**

The HCP healthy control dataset was used to construct a generic structural connectome between the segments of the CC and defined cortical regions. This strategy has been employed in other neurological conditions to provide a more reliable model of connectivity that is not affected by disease pathology (Mandelli et al. 2016; Zhou et al. 2012). The cortical surface was reconstructed from T1-weighted data using FreeSurfer and parcellated into 31 regions per hemisphere using the FreeSurfer generated Desikan–Killiany atlas (Fig. 1b). Structural connectivity was measured in each subject using probabilistic streamline tractography. Given that the corpus callosum is widely connected to cortex, probabilistic tractography was used to explore the

![Fig. 1](a) Corpus callosum segmentation for a participant with MS (left to right: posterior, mid-posterior, central, mid-anterior, and anterior CC). Diffusion measures were extracted for each segment. **b** Desikan–Killiany atlas visualized using a left hemisphere symmetric surface template. Surface-based homologous inter-hemispheric connectivity (sHIC) was calculated for each cortical region. A structural connectivity matrix was generated using HCP data to define connections between the CC segments and cortical regions.
The greatest number of possible connections between regions. Although the probabilistic approach is potentially more vulnerable to false positives than deterministic tractography (Sarwar et al. 2019), it increases sensitivity to weaker connections (Rosen and Halgren 2021). Seed regions for each cortical parcel were defined as the white matter region adjacent to the given parcel. FSL’s probtrackx2 (Behrens et al. 2007) was used to perform tractography with 5000 streamlines generated per voxel in the seed ROI, 2000 steps per streamline, and step length of 0.5 mm. The number of samples connecting each pair of regions was entered into a structural connectivity matrix. To normalize for the different seed dimensions, the raw streamline values were divided by the number of streamlines generated per voxel multiplied by the number of voxels in the seed region (Rosen and Halgren 2021). Given a pair of regions A and B, matrices were made symmetric by taking the mean of the A-B and B-A normalized streamline counts. Each subject’s structural connectivity matrix was binarized at a density threshold of 30% to exclude spurious links (Rubinov and Sporns 2010). This was based off of matrix density thresholds used in other studies, which generally range from 10 to 35% (Kamagata et al. 2019; Zhang et al. 2011). Subject matrices were combined into a single aggregate matrix containing connections present in at least 50% of subjects. This resulted in a single binarized connectivity matrix that approximated a healthy structural connectome. This final matrix was used to determine the cortical regions connected to each CC segment. These connections are reported in Table 2.

### Statistical analysis

Statistical calculations were conducted using MATLAB and SPSS (version 27.0. Armonk, NY: IBM Corp). The Shapiro–Wilk test was used to assess normality of the data. Global sHIC was compared between MS and HC groups using a Student’s t test. sHIC was compared between MS and HC groups and associated with EDSS scores using vertex-wise general linear models from the FreeSurfer group analysis pipeline, controlling for age and gender. These analyses were run using the FreeSurfer mri_glmfit command. The cortical surface was smoothed with a 3 mm full width half maximum Gaussian kernel. Significant clusters were identified using the mri_glmfit-sim command, with a cluster-wise threshold of $p < 0.05$. Correction for multiple comparisons was performed at the cluster level using Monte Carlo simulation (Hagler et al. 2006).

sHIC was extracted from each cortical region and correlated with clinical test scores using Pearson or Spearman partial correlation, as appropriate depending on normality, adjusting for age and gender. Similarly, diffusion measures in each segment of the CC were correlated with sHIC values extracted from connected cortical regions, adjusting for age and gender. A partial regression plot was constructed to show the association.

### Table 2

| Anterior CC                      | Mid-anterior CC | Central CC                     | Mid-posterior CC | Posterior CC                      |
|---------------------------------|----------------|--------------------------------|------------------|----------------------------------|
| Caudal anterior cingulate       | Caudal anterior cingulate | Caudal anterior cingulate | Caudal anterior cingulate | Caudal anterior cingulate |
| Insula                          | Caudal middle frontal | Caudal middle frontal | Caudal middle frontal | Caudal anterior cingulate |
| Lateral orbitofrontal           | Insula          | Insula                        | Insula           | Cuneus                           |
| Medial orbitofrontal            | Isthmus cingulate | Isthmus cingulate             | Isthmus cingulate | Cuneus                           |
| Middle temporal                 | Pars opercularis | Pars opercularis              | Pars opercularis | Fusiform                          |
| Pars orbitalis                  | Pars orbitalis  | Pars orbitalis                | Postcentral      | Isometric                         |
| Pars triangularis               | Pars triangularis | Pars triangularis             | Posterior cingulate | Isometric                         |
| Posterior cingulate             | Posterior cingulate | Posterior cingulate           | Precentral       | Isometric                         |
| Rostral anterior cingulate      | Precentral      | Precentral                    | Superior frontal  | Superior frontal                  |
| Rostral middle frontal          | Rostral anterior cingulate | Rostral middle frontal | Superior temporal | Superior temporal |
| Superior frontal                | Superior frontal | Superior frontal              | Superior temporal | Superior temporal |
| Superior temporal               | Superior temporal | Superior temporal              | Superior temporal | Superior temporal |

These connections were determined using probabilistic tractography in a group of healthy control subjects.
between global sHIC and CC measures (restricted volume fraction and FA), adjusting for age and gender (Fig. 3). This is a plot of the residuals from regressing sHIC against age/gender and the residuals from regressing the CC measure against age/gender. The relationship between these residuals represents the partial correlation.

In addition, we sought to determine if sHIC moderates the effect of CC structural damage on clinical disability by applying multiple linear regression analysis. This was a post hoc analysis that focused on restricted volume fraction (RVF) and FA in the posterior CC and its interaction with the average sHIC extracted over all cortical regions connected to the posterior CC (posterior sHIC), due to the significance of these variables. Two regression models were applied to predict each clinical outcome (BVMT, SDMT, PASAT, EDSS, 25FT-Walk, 9-HPT). The first model predicting clinical outcome contained covariates for age, gender, years of education, RVF in the posterior CC, posterior sHIC, and an interaction term between posterior RVF and posterior sHIC. The other model predicting clinical outcome contained covariates for age, gender, years of education, FA in the posterior CC, posterior sHIC, and an interaction term between posterior FA and posterior sHIC. A statistically significant interaction term would suggest that the effect of posterior CC damage on clinical function depends on a subject’s sHIC.

Results

Group differences in sHIC

Participants with MS exhibited decreased sHIC in comparison to healthy controls. Average sHIC correlation maps for MS and HC groups show that inter-hemispheric connectivity was highest in primary motor, somatosensory, and visual cortices (Fig. 2). The vertex-wise group analysis showed that sHIC was decreased in several cortical areas in the MS group, based on vertex and cluster-wise significance thresholds of \( p < 0.01 \) and \( p < 0.05 \), respectively (Fig. 2). These alterations were most pronounced in primary motor, somatosensory, visual, cuneus, and temporal cortical areas (Table 3). There were no areas where sHIC was significantly higher in the MS group. Global sHIC, defined as a measure of the mean sHIC throughout the whole cortex, was also significantly reduced in the MS group (0.242 ± 0.065) compared to the HC group (0.284 ± 0.062) \( (p = 0.004) \).

sHIC and diffusion measures in the corpus callosum

These results were assessed for each segment of the corpus callosum and its corresponding cortical connections. The strongest associations between sHIC and CC diffusion measures were found in the posterior segment of the CC (Table 4). Average sHIC was extracted from each cortical region structurally connected to the posterior CC and correlated with each diffusion metric in the posterior CC, controlling for age and gender. sHIC extracted from individual cortical regions, as parcellated by the Desikan–Killiany atlas, correlated most strongly with FA, MD, and restricted volume fraction in the posterior CC. Correlations between sHIC and axon diameter/axon density in the posterior CC were generally weak or did not survive correction for age and gender. Average sHIC extracted over all cortical regions connected to the posterior CC (posterior sHIC) correlated with FA \( (r = 0.389, p = 0.025) \) and restricted volume fraction \( (r = 0.361, p = 0.036) \) in the posterior CC, adjusting for age and gender. Global sHIC also significantly correlated with FA \( (r = 0.426, p = 0.013) \), MD \( (r = -0.348, p = 0.047) \), and restricted volume fraction \( (r = 0.399, p = 0.020) \) in the posterior CC, adjusting for age and gender (Fig. 3).

Measures of cortical sHIC did not correlate well with diffusion measures in the anterior, mid-anterior, central, and mid-posterior segments of the CC. The only significant partial correlation found was between mean sHIC in
caudal middle frontal cortex and MD in the central CC, controlling for age and gender \((r = -0.389, p = 0.025)\).

Otherwise, there were no significant associations between sHIC and diffusion measures in these four CC segments. In addition, there were no correlations between global sHIC and any diffusion measures extracted from the whole CC.

### sHIC and clinical outcomes

Clinical test scores were correlated with sHIC extracted from each cortical region, regardless of connectivity to the CC. Cortical regions with significant correlations between mean sHIC and clinical test scores, controlling for age and gender, are reported in Table 5. For several cortical regions, reduced sHIC correlated with poor performance on tests of visual learning and memory (BVMT-TR), information processing speed (SDMT and PASAT), slower 9-hole peg test times, and higher overall disability as measured by EDSS. There were no correlations between global sHIC and any of the clinical measures. We also investigated EDSS using a vertex-wise general linear model in the MS group, controlling for age and gender, applying vertex and cluster-wise significance thresholds of \(p < 0.05\) (Fig. 4). Significant clusters associating decreased sHIC with elevated EDSS were found in several regions, notably motor and somatosensory cortex. We also observed that years of education correlated with global sHIC \((r = 0.402, p = 0.018)\) and posterior sHIC \((r = 0.396, p = 0.020)\) in MS, controlling for age and gender.

### sHIC interaction effects

Multiple linear regression was used to assess the interaction between posterior sHIC and posterior CC damage in predicting clinical disability, while controlling for age, gender, and years of education. All \(\beta\) coefficients reported are standardized. For the regression model predicting EDSS, we observed a significant effect of age \((\beta = 0.524, p = 0.002)\), posterior sHIC \((\beta = -2.756, p = 0.019)\), posterior restricted

### Table 3  Cortical regions with areas of decreased sHIC in participants with MS

| Cortical region          | Cluster sizes (mm²) | Cluster-wise \(p\) values |
|-------------------------|---------------------|--------------------------|
| Cuneus                  | 288**               | 0.0001                   |
| Fusiform                | 64                  | 0.011                    |
| Inferior temporal       | 58                  | 0.020                    |
| Lateral occipital       | 123*                | 0.001                    |
| Lingual                 | 81*                 | 0.002                    |
| Middle temporal         | 127**, 137**, 66*   | 0.0001, 0.0001, 0.009    |
| Paracentral             | 349**               | 0.0001                   |
| Pars opercularis        | 55                  | 0.029                    |
| Pericalcarine           | 124**               | 0.0001                   |
| Postcentral             | 290**, 71*, 54      | 0.0001, 0.004, 0.036     |
| Precuneus               | 94**, 124**         | 0.0001, 0.0001           |
| Superior frontal        | 51, 55              | 0.048, 0.031             |
| Superior parietal       | 170**               | 0.0001                   |
| Superior temporal       | 841**, 64           | 0.0001, 0.011            |
| Supramarginal           | 96**                | 0.0006                   |

The clusters described below correspond to the MS vs HC vertex-wise group analysis depicted in Fig. 2

\(\ast p < 0.01\), \(\ast\ast p < 0.001\)

### Table 4  Pearson partial correlations between sHIC (assessed within regions connected to the posterior corpus callosum) and diffusion measures in the posterior corpus callosum, adjusting for age and gender (\(p\) values are shown in parenthesis)

| Mean sHIC extracted from cortical regions | Restricted volume fraction | FA  | MD  | Axon diameter | Axon density |
|-----------------------------------------|----------------------------|-----|-----|---------------|--------------|
| Caudal anterior cingulate               | -0.077 (0.666)\(^S\)        | 0.184 (0.305)\(^S\)  | -0.364 (0.037)\(^S\) | -0.177 (0.317)\(^S\) | 0.032 (0.855)\(^S\) |
| Inferior parietal                       | 0.358 (0.038)\(^S\)         | 0.356 (0.042)         | -0.385 (0.027)         | -0.212 (0.228) | 0.288 (0.098) |
| Inferior temporal                       | 0.306 (0.078)\(^S\)         | 0.406 (0.019)         | -0.293 (0.098)         | -0.035 (0.844) | 0.237 (0.177) |
| Isthmus cingulate                       | 0.216 (0.228)\(^S\)         | 0.216 (0.028)         | -0.231 (0.523)         | -0.364 (0.034) | 0.268 (0.126) |
| Lateral occipital                       | 0.403 (0.018)\(^S\)         | 0.354 (0.044)         | -0.218 (0.424)         | 0.286 (0.101) |
| Lingual                                 | 0.216 (0.221)\(^S\)         | 0.272 (0.126)         | -0.220 (0.218)         | -0.280 (0.109) | 0.341 (0.049) |
| Posterior cingulate                     | 0.355 (0.351)\(^S\)         | 0.272 (0.221)         | -0.364 (0.037)         | -0.177 (0.317) | 0.032 (0.855) |
| Superior parietal                       | 0.462 (0.006)\(^S\)         | 0.515 (0.002)         | -0.465 (0.006)         | -0.186 (0.292) | 0.326 (0.060) |
| Supramarginal                           | 0.156 (0.079)\(^S\)         | 0.287 (0.105)         | -0.389 (0.025)         | -0.099 (0.579) | 0.105 (0.553) |
| Whole cortex (global)                   | 0.359 (0.020)\(^S\)         | 0.426 (0.013)         | -0.348 (0.047)         | -0.088 (0.623) | 0.262 (0.134) |
| All regions connected to Posterior CC   | 0.361 (0.036)\(^S\)         | 0.389 (0.025)         | -0.322 (0.068)         | -0.256 (0.143) | 0.304 (0.080) |

Spearman partial correlation was assessed for non-parametric data. Significant correlations (\(p < 0.05\)) are bolded. Regions with no significant correlations are not reported

\(^S\)Spearman partial correlation
volume fraction ($\beta = -1.798, p = 0.007$), and the posterior restricted volume fraction/sHIC interaction term ($\beta = 3.390, p = 0.022$) (Fig. 5a). In an additional model for EDSS, significant effects were found for age ($\beta = -0.537, p = 0.001$), posterior sHIC ($\beta = 3.276, p = 0.005$), posterior restricted volume fraction ($\beta = 1.758, p = 0.007$), and the posterior restricted volume fraction/sHIC interaction term ($\beta = -3.825, p = 0.009$) (Fig. 5c). In an additional model for BVMT, significant effects were found for age ($\beta = -0.438, p = 0.005$), posterior sHIC ($\beta = 4.748, p = 0.005$), posterior FA ($\beta = 1.344, p = 0.011$), and the posterior FA/sHIC interaction term

Table 5 Pearson partial correlations between sHIC (assessed for all cortical regions) and clinical disability, adjusting for age and gender ($p$ values are shown in parenthesis)

| Mean sHIC extracted from cortical regions | BVMT | PASAT | SDMT | 25-foot walk | 9-HPT | EDSS |
|-------------------------------------------|------|-------|------|--------------|-------|------|
| Caudal anterior cingulate | $-0.026 (0.883)^S$ | **0.362 (0.035)^S** | $0.301 (0.083)^S$ | $-0.210 (0.234)^S$ | $0.051 (0.793)^S$ | $-0.133 (0.453)^S$ |
| Cuneus | **0.401 (0.019)^S** | $0.260 (0.138)^S$ | **0.442 (0.009)^S** | $0.017 (0.926)^S$ | $0.252 (0.188)^S$ | $-0.142 (0.423)^S$ |
| Inferior parietal | $0.177 (0.316)^S$ | **0.381 (0.026)^S** | $0.245 (0.163)^S$ | $-0.156 (0.379)^S$ | $0.243 (0.204)^S$ | $-0.030 (0.867)^S$ |
| Lateral occipital | **0.416 (0.014)^S** | $0.311 (0.074)^S$ | **0.340 (0.049)^S** | $-0.064 (0.718)^S$ | **0.401 (0.031)^S** | $-0.012 (0.95)^S$ |
| Lingual | **0.448 (0.008)^S** | $0.168 (0.343)^S$ | $0.172 (0.331)^S$ | $-0.068 (0.702)^S$ | $0.258 (0.176)^S$ | $-0.234 (0.182)^S$ |
| Paracentral | $0.209 (0.236)^S$ | **0.384 (0.025)^S** | **0.351 (0.042)^S** | $-0.197 (0.264)^S$ | $0.190 (0.324)^S$ | $-0.253 (0.148)^S$ |
| Pars triangularis | $0.200 (0.257)^S$ | $0.334 (0.053)^S$ | $0.303 (0.087)^S$ | $-0.191 (0.279)^S$ | $0.236 (0.217)^S$ | $0.033 (0.852)^S$ |
| Pericalcarine | **0.440 (0.009)^S** | $0.251 (0.153)^S$ | $0.317 (0.068)^S$ | $0.110 (0.535)^S$ | **0.390 (0.037)^S** | $-0.342 (0.048)^S$ |
| Postcentral | $0.308 (0.076)^S$ | $0.336 (0.052)^S$ | **0.378 (0.027)^S** | $-0.199 (0.260)^S$ | $0.138 (0.475)^S$ | $-0.326 (0.060)^S$ |
| Posterior cingulate | $0.106 (0.552)^S$ | **0.448 (0.008)^S** | **0.385 (0.025)^S** | $-0.204 (0.246)^S$ | $0.099 (0.610)^S$ | $-0.102 (0.565)^S$ |
| Precentral | $0.300 (0.085)^S$ | $0.245 (0.163)^S$ | **0.385 (0.025)^S** | $-0.239 (0.173)^S$ | $0.047 (0.808)^S$ | $-0.302 (0.082)^S$ |
| Rostral anterior cingulate | $-0.058 (0.744)^S$ | **0.449 (0.008)^S** | $0.282 (0.106)^S$ | $-0.039 (0.827)^S$ | $0.216 (0.260)^S$ | $-0.064 (0.719)^S$ |
| Superior parietal | $0.166 (0.348)^S$ | $0.333 (0.054)^S$ | **0.474 (0.005)^S** | $-0.087 (0.624)^S$ | $0.229 (0.233)^S$ | $-0.217 (0.214)^S$ |
| Superior temporal | $0.284 (0.103)^S$ | **0.435 (0.010)^S** | $0.293 (0.093)^S$ | $-0.104 (0.557)^S$ | $0.167 (0.388)^S$ | $-0.201 (0.255)^S$ |
| Supramarginal | $0.194 (0.272)^S$ | $0.164 (0.354)^S$ | $0.214 (0.224)^S$ | **-0.394 (0.021)^S** | $-0.097 (0.617)^S$ | $-0.059 (0.739)^S$ |
| Transverse temporal | $0.235 (0.181)^S$ | **0.477 (0.004)^S** | **0.516 (0.002)^S** | $0.094 (0.597)^S$ | $0.117 (0.544)^S$ | **-0.412 (0.016)^S** |
| All regions connected to mid-posterior CC | $0.194 (0.272)^S$ | **0.352 (0.041)^S** | **0.346 (0.045)^S** | $-0.224 (0.203)^S$ | $0.144 (0.457)^S$ | $-0.226 (0.198)^S$ |
| All regions connected to posterior CC | $0.288 (0.098)^S$ | $0.312 (0.072)^S$ | **0.397 (0.020)^S** | $-0.178 (0.313)^S$ | $0.191 (0.320)^S$ | $-0.211 (0.230)^S$ |

Spearman partial correlation was assessed for non-parametric data. Significant correlations ($p < 0.05$) are bolded. Regions with no significant correlations are not reported.

$^S$Spearman partial correlation
Interaction terms were not significant for the models predicting PASAT, SDMT, 25-Foot Walk, or 9-hole-peg test. Overall, these findings suggest that in participants with MS, the relationship between posterior CC damage and clinical disability, as measured by EDSS and BVMT, is partly dependent on the level of posterior sHIC.

Discussion

In this study, we investigated how functional inter-hemispheric connectivity relates to structural CC damage and clinical disability in MS. We found that decreased sHIC, generally in posterior cortical areas, correlates with structural abnormalities in the posterior CC, cognitive dysfunction, and physical disability. We also showed that MS participants with higher sHIC may have some preserved clinical function as measured by BVMT and EDSS, despite CC damage. These results support our hypothesis that callosal damage is associated with alterations in sHIC that contribute to disability.

Our results demonstrated that sHIC is significantly different in MS compared to HC participants. The patterns of sHIC observed in the MS and HC group average correlation maps indicate that inter-hemispheric connectivity was strongest in somatomotor and visual cortices, replicating previous work done by our lab and others (Stark et al. 2008; Tobyne et al. 2016; Zhou et al. 2013). We found that these regions were especially vulnerable to alterations in sHIC in participants with MS. sHIC was globally lower in the MS group, with the largest local reductions occurring in primary motor, somatosensory, visual, cuneus, and temporal cortical areas. While previous studies have also found reduced homologous connectivity in these regions (Lowe et al. 2008; Zhou et al. 2013), they did not demonstrate group differences in precentral, paracentral, superior frontal, and superior parietal cortical areas. Our more robust detection of group differences may be partly due to the superior accuracy of surface-based registration in comparison to volume-based registration methods (Fischl et al. 2008). It is notable that there were no cortical areas with significantly increased sHIC in the MS group. This is in contrast to other studies that have observed complex patterns of both increased and decreased functional connectivity when evaluating inter-hemispheric or network differences in MS and HC groups (Pasqua et al. 2020; Tona et al. 2014; Zhou et al. 2013). Our findings are consistent with the interpretation that callosal damage reduces transmission and synchrony between homologous regions.

In an unbiased general linear model, we found a significant relationship between increased EDSS scores and reduced sHIC in various clusters located in somatomotor cortex. These clusters also roughly overlapped with those observed in primary somatosensory cortex from the MS versus HC group difference analysis. Since inter-hemispheric connectivity tends to be highest in primary sensory regions, sHIC may be a sensitive tool to better understand sensory processing in MS.
dysfunction in MS. While we did not observe any significant associations between global homologous connectivity and clinical disability, lower posterior sHIC did correlate with cognitive impairment, as measured by SDMT. Similarly, reduced mid-posterior sHIC correlated with lower PASAT and SDMT scores. We also found that impaired performances on BVMT, PASAT, SDMT, and 9-hole peg test were associated with lower sHIC in many cortical regions, particularly in the parietal and occipital lobes. There were no cortical regions for which higher sHIC correlated with cognitive disability. Overall, our results support the hypothesis that reduced inter-hemispheric connectivity is predictive of poor clinical outcomes.

We found that the structure–function relationship between CC axonal integrity and sHIC was most evident in the posterior CC. This may be due to the anterior to posterior gradient previously observed by Tobyne et al. (2016) in a large healthy control dataset, in which posterior nodes of multiple functional networks generally had higher sHIC than the anterior regions. This phenomenon may help explain the lack of significant correlations between diffusion measures in the other four segments of the CC and the sHIC extracted from their more anterior cortical connections. While the CC is a major white matter bundle connecting the two hemispheres, our tissue microstructure measures did not account for potential changes in hemispheric white matter lateral to the CC. We found that FA and restricted volume fraction in the posterior CC correlated with global sHIC, posterior sHIC, and local sHIC extracted from individual regions in parietal, temporal, and occipital cortex. These results support findings from Zhou et al. (2013), who reported no significant correlations between VHMC and FA for CC segments 1–4, but did find a positive correlation between occipital VHMC and mean FA in the posterior CC (segment 5) in participants with MS. Our results build upon our previous findings that CC atrophy correlates with global sHIC (Tobyne et al. 2016) by adding more specific outcomes for axonal...
pathology derived from multi-compartmental modeling of the diffusion MRI signal.

Although sHIC correlated with restricted volume fraction, it was not strongly associated with axon density and apparent axon diameter in the CC. The only significant correlations occurred between axon density in the posterior CC and sHIC in lingual cortex and between axon diameter in the posterior CC and sHIC in the isthmus cingulate cortex. It is notable that while the other correlations between sHIC and these axonal imaging measures failed to reach statistical significance after controlling for age and gender, they trended in a meaningful direction. High apparent axon diameter (a marker of damage due to the vulnerability of small diameter axons) and low axon density in the CC have been observed in previous high-gradient diffusion MRI studies of MS (Huang et al. 2016, 2019) and trended with reduced sHIC in many cortical regions. Our results suggest that it may be useful to evaluate these metrics longitudinally and in a larger group of people with MS. Of the diffusion metrics we investigated in the CC, the metrics FA, MD, and restricted volume fraction were most highly correlated with inter-hemispheric connectivity. This is consistent with previous studies that looked at FA in the CC. Zhou et al. (2013) found that global VMHC correlated with average FA of the entire CC and Lowe et al. (2008) found that decreased inter-hemispheric functional connectivity was associated with decreased FA in transcallosal white matter, but both these results were only significant in combined MS and HC groups. Using sHIC, we demonstrated this relationship between homologous connectivity and CC damage in the MS group alone.

It is well established that CC damage contributes to clinical disability in MS; however, it has been unclear what role inter-hemispheric functional connectivity plays in this relationship. We found that higher levels of sHIC may attenuate the effects of structural CC damage on disability. This was demonstrated through a post hoc investigation in the posterior CC, looking at restricted volume fraction, FA, and posterior sHIC due to their prior significance. We found that in MS participants with higher average sHIC, alterations in CC microstructure were less associated with clinical impairments in MS participants with higher average sHIC, alterations in posterior sHIC due to their prior significance. We found that global sHIC for MS participants positively correlated with years of education, which has generally been thought to contribute to “brain reserve” in neurodegenerative disorders (Nithianantharajah and Hannan 2009). This suggests that environmental factors like education may help preserve inter-hemispheric functional connectivity and prevent progression of disability.

Limitations

This study was conducted on a group of participants with relapsing–remitting and progressive MS. The sample size of the progressive MS subgroup was too small to perform a meaningful sub-analysis. While combining these groups provided more statistical power, it limits the conclusions for specific MS phenotypes. Additionally, the cross-sectional nature of this study helps reveal associations between sHIC, CC damage, and disability, but a longitudinal study would be necessary to determine if sHIC plays a causal role in preserving clinical function as structural damage accumulates in the brain.

Although sHIC improves spatial accuracy, the technique has generally been thought to contribute to “brain reserve” in neurodegenerative disorders (Nithianantharajah and Hannan 2009). This suggests that environmental factors like education may help preserve inter-hemispheric functional connectivity. Another limitation is the relatively short fMRI acquisition time (6.26 min). Concatenating runs or acquiring a longer fMRI time series could potentially produce a more stable and repeatable pattern of resting-state based homologous connectivity. However, it should be noted that simultaneous multi-slice resting-state fMRI provides higher temporal resolution compared to conventional EPI (Feinberg and Setsompop 2013; Jahanian et al. 2019).

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Author contributions Conceptualization: ECK and AWR; data acquisition, analysis, and manuscript preparation: AWR, KES, SMT, CN, KB, AN, SYH, and ECK.

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Data availability The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request. Healthy control data from the Human Connectome Project and the MGH-Harvard-USC Lifespan Dataset are publicly available through the Laboratory of Neuro Imaging Image Data Archive (https://ida.loni.usc.edu) and the WU-Minn Connectome Database (https://db.humanconnectome.org).

Code availability Code is available upon request.

Declarations

Competing interests ECK has received consulting fees from Alexion, Banner Life Sciences, Biogen, EMD Serono, Genentech, and MedDay and research funding from Abbvie, Biogen, EMD Serono, Genentech/Roche, and Genzyme. All the other authors have no relevant financial or non-financial interests to disclose.

Ethics approval The study was approved by the Mass General Brigham institutional review board and is in accordance with the 1964 Helsinki Declaration.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publish All subjects provided written informed consent for publication of data.

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