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Quantitative measures of walking and strength provide insight into brain corticospinal tract pathology in multiple sclerosis

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ABSTRACT

At least 85% of individuals with multiple sclerosis report walking dysfunction as their primary complaint. Walking and strength measures are common clinical measures to mark increasing disability or improvement with rehabilitation. Previous studies have shown an association between strength or walking ability and spinal cord MRI measures, and strength measures with brainstem corticospinal tract magnetization transfer ratio. However, the relationship between walking performance and brain corticospinal tract magnetization transfer imaging measures and the contribution of clinical measurements of walking and strength to the underlying integrity of the corticospinal tract has not been explored in multiple sclerosis. The objectives of this study were explore the relationship of quantitative measures of walking and strength to whole-brain corticospinal tract-specific MRI measures and to determine the contribution of quantitative measures of function in addition to basic clinical measures (age, gender, symptom duration and Expanded Disability Status Scale) to structural imaging measures of the corticospinal tract. We hypothesized that quantitative walking and strength measures would be related to brain corticospinal tract-specific measures, and would provide insight into the heterogeneity of brain pathology. Twenty-nine individuals with relapsing-remitting multiple sclerosis (mean(SD) age 48.7 (11.5) years; symptom duration 11.9(8.7); 17 females; median[range] Expanded Disability Status Scale 4.0 [1.0–6.5]) and 29 age and gender-matched healthy controls (age 50.8(11.6) years; 20 females) participated in clinical tests of strength and walking (Timed Up and Go, Timed 25 Foot Walk, Two Minute Walk Test) as well as 3 T imaging including diffusion tensor imaging and magnetization transfer imaging.

Individuals with multiple sclerosis were weaker ($p = 0.0024$) and walked slower ($p = 0.0013$) compared to controls. Quantitative measures of walking and strength were significantly related to corticospinal tract fractional anisotropy ($r > 0.26$; $p < 0.04$) and magnetization transfer ratio ($r > 0.29$; $p < 0.03$) measures. Although the Expanded Disability Status Scale was highly correlated with walking measures, it was not significantly related to either corticospinal tract fractional anisotropy or magnetization transfer ratio ($p > 0.05$). Walk velocity was a significant contributor to magnetization transfer ratio ($p = 0.006$) and fractional anisotropy ($p = 0.011$) in regression modeling that included both quantitative measures of function and basic clinical information.

Quantitative measures of strength and walking are associated with brain corticospinal tract pathology. The addition of these quantitative measures to basic clinical information explains more of the variance in corticospinal tract fractional anisotropy and magnetization transfer ratio than the basic clinical information alone. Outcome measurement for multiple sclerosis clinical trials has been notoriously challenging; the use of quantitative measures of strength and walking along with tract-specific imaging methods may improve our ability to monitor disease change over time, with intervention, and provide needed guidelines for developing more effective targeted rehabilitation strategies.

1. Introduction

At least 85% of individuals with multiple sclerosis (MS) report gait disturbance as their primary complaint (Kelleher et al., 2010). The most common measure of walking in MS clinical trials is the Expanded Disability Status Scale (EDSS). The EDSS is the gold standard of MS-

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related disability; however, ambulation score for the EDSS is based on distance and assistance level without regard for elements such as time to complete walking, quality of walking, or ability to adapt walking to meet functional demands. Issues with reliability (Amato et al., 1988; Koziol et al., 1996), responsiveness (Hobart et al., 2000), and other limitations (Avasarala, 2015; Meyer-Moock et al., 2015) of the EDSS have also been well-documented. Although valid, its use in clinical trials for tracking disease progression is based primarily on international acceptability (Meyer-Moock et al., 2015) and has been criticized for both high variability and because the non-linearity of the scale makes determination of change challenging (Amato and Ponziani, 1999; Hyland and Rudick, 2011). Quantitative measures of walking and strength impairment address the weaknesses of the EDSS (Zackowski et al., 2015) and may improve disease monitoring.

Tract-specific white-matter imaging, such as diffusion tensor imaging (DTI) and magnetization transfer (MT) imaging are not typically part of conventional magnetic resonance imaging (MRI) for monitoring disease progression. However, these techniques allow for quantification of individualized differences. DTI quantifies the directional diffusivity of water and provides information about the integrity of white matter tracts in the brain, while MT quantifies the degree of magnetization transfer among free water protons and protons bound to macromolecules, as occurs in lipids such as in myelin in the white matter. The primary outcome measure for DTI is fractional anisotropy (FA), a scalar value between 0 (isotropic diffusion) and 1 (anisotropic diffusion) (Jones, 2009); the primary outcome measure for MT is the magnetization transfer ratio (MTR), which is significantly correlated with myelin content in individuals with MS (Schmierer et al., 2004).

2MWT: Two Minute Walk Test	FA: fractional anisotropy	SCA: spinal cord area
AIC: Akaike Information Criterion	FSS: Functional Systems Score	T25FW: Timed 25 Foot Walk
CST: corticospinal tract	MS: multiple sclerosis	TUG: Timed Up and Go
DTI: diffusion tensor imaging	MT: magnetization transfer imaging	
EDSS: Expanded Disability Status Scale	MTR: magnetization transfer ratio	

In contrast to conventional MRI, these tract-specific techniques allow for quantification of the heterogeneity among individuals, and may ultimately lead to individualized treatments and rehabilitation.

Previous work using DTI and MT has focused on relationships among strength (Reich et al., 2008; Zackowski et al., 2009; Oh et al., 2013a) and walking (Zackowski et al., 2009; Naismith et al., 2013) with spinal cord imaging, particularly the lateral columns, which are assumed to be more closely related to the corticospinal tract (CST) in MS. Lower extremity strength is significantly related to MTR of the lateral columns (Zackowski et al., 2009) and FA of the whole cord (Oh et al., 2013a); while brainstem CST MTR dissociates stronger from weaker muscle strength (Reich et al., 2008). Walking performance has been associated with DTI (Naismith et al., 2013) and MTR (Zackowski et al., 2009) of the lateral columns in MS. T25FW performance (Tovar-Moll et al., 2015; Klineova et al., 2016; Hubbard et al., 2016) and walking velocity and endurance (Hubbard et al., 2016) were related to DTI measures, while both total EDSS and Functional Systems Score (FSS) pyramidal scores were related to FA of the brain CST measured from the pons to the cortex (Tovar-Moll et al., 2015), and total EDSS score was also correlated with cervical spinal cord area (Bernitsas et al., 2015). However, controls were not included in these studies, and relationships of quantitative measures of strength and walking to brain MTR have not been explored, and DTI of the whole-brain CST from medulla to cortex in relation to function is lacking in MS.

The use of more objective functional measures (i.e., strength and walking), as well as tract-specific imaging methods may improve our ability to monitor disease change over time, with intervention, and provide needed guidelines for developing more effective targeted rehabilitation strategies. Exploration of whole brain CST measures may be important for the development of sensitive outcome measures. Outcome measurement for MS clinical trials has been challenging (Hyland and Rudick, 2011). Though imaging outcomes are used to guide diagnosis and medical management in MS, the relationships among imaging variables and clinical measures remains unclear. We hypothesized that quantitative walking and strength measures would be related to brain CST-specific measures, and would provide insight into the heterogeneity of brain pathology. Therefore, the objectives of this study were to explore the relationship of clinical measures of walking and strength to whole brain CST-specific MRI measures and to determine the contribution of quantitative measures of function in addition to basic clinical measures (age, gender, symptom duration and Expanded Disability Status Scale) to structural imaging measures of the corticospinal tract.

2. Methods

Thirty participants with clinically definite MS using the 2005 McDonald criteria (Polman et al., 2005) and 29 healthy controls who had volunteered for a larger controlled intervention trial were recruited for this trial. All participants with MS were recruited from the Multiple Sclerosis Center at Johns Hopkins Medical Institutions between 2012 and 2014 from a parent study evaluating exercise responsiveness in MS. Participants with MS were included in the study if they had received a clinical diagnosis of relapsing-remitting MS and were ambulatory with or without an assistive device. Participants were excluded if they had experienced a MS relapse within three months of testing, reported corticosteroid use within 30 days prior to testing, or reported a history of peripheral neuropathy or any other orthopedic or neurologic condition that might interfere with strength, sensation and walking testing. All participants were able to follow study-related commands. Twenty-nine age and gender-matched healthy adults were recruited through flyers and word-of-mouth. Prior to participation, all participants gave written informed consent. The Institutional Review Boards at both Johns Hopkins Medical Institutes and Kennedy Krieger Institute approved the study procedures.

In a single session, demographic information, EDSS and quantitative measures of strength, sensation and walking were collected. Imaging measures were collected within 1 month of the functional measures.

2.1. Quantitative measures of impairment and function

2.1.1. Strength

Maximal voluntary contraction of bilateral hip flexion, hip extension and hip abduction was evaluated using a Microfet2 hand-held dynamometer (Hoggan Health Industries, West Jordan, UT). Quantitative strength testing has established reliability and validity in individuals with MS (Newsome et al., 2011). Hip flexion, extension and abduction were collected using the methods previously described by our laboratory (Keller et al., 2016). The average of two trials of each muscle was recorded and the sum of the right and left flexors, extensors and abductors were analyzed as the summed strength in pounds for each individual.

2.1.2. Ambulation measures

All walking measures were collected in random order across participants, and participants were permitted to rest between tests for as long as they preferred to minimize fatigue. Participants who utilized assistive devices were asked to perform each test with the least-restrictive device. Both laboratory (walk velocity) and clinical measures of walking were assessed to examine walking speed and walking function.

2.1.2.1. Walk velocity. All participants were instructed to ambulate at their fastest, safe speed across the Zeno Walkway (Protokinetics, Havertown, PA), a 20-ft walkway that records footfalls in real-time. Participants completed six passes across the mat, and the average walk

velocity for each person was calculated using a custom MATLAB program (The MathWorks, Inc., Natick, MA).

2.1.2.2. Timed Up and Go (TUG). Participants were instructed to rise from a chair, walk three meters, turn and return to a sitting position in the chair as quickly as possible without running. Participants performed two trials, with the first serving as a practice trial, and the time of second recorded as the final score. The TUG (Podsiadlo and Richardson, 1991) incorporates functional tasks of turning and transitioning from sitting to standing into walking. In individuals with MS, the TUG is both valid (Cattaneo et al., 2006) and clinically relevant (Nilsagård et al., 2007).

2.1.2.3. Timed 25 Foot Walk (T25FW). Participants were instructed to walk at their quickest, safe speed along a flat 25-ft walkway (Rudick et al., 1997). The average time of two trials was used as the final score. The T25FW has established reliability (Rosti-Otajarvi et al., 2008) and validity (Kieseier and Pozzilli, 2012) and is commonly used in MS clinical trials (Polman and Rudick, 2010).

2.1.2.4. Two-Minute Walk Test (2MWT). To examine walking endurance, participants were instructed to cover as much distance as possible while walking for 2 min. The 2MWT is strongly correlated with the first 2 min of the Six-Minute Walk Test (Gijbels et al., 2011), and is a feasible alternative to the Six-Minute Walk Test (Gijbels et al., 2011), which has established reproducibility and reliability (Goldman et al., 2008).

2.2. Magnetic resonance imaging

All MRI scans of the brain were collected on the same 3-Tesla Intera scanner (Philips Medical Systems, Best, The Netherlands). A full description of our scanning protocol can be found elsewhere (Reich et al., 2006; Reich et al., 2007; Reich et al., 2010). Briefly, we collected a 32-direction diffusion-weighted image as well as a MT-weighted image with a MT prepulse applied at 1.5 kHz off resonance to allow for calculation of MTR using the formula [(MToff-MTon)/MToff]. Cervical spinal cord imaging was collected following the methods of Oh et al., 2013a, 2013b for calculation of spinal cord area (SCA) at C3-4. Briefly, a region of interest of the axial cross-section of the spinal cord was delineated on each slice of the MToff image. Spinal cord area for each cervical level was then calculated with a custom Matlab program (The Mathworks; Natick, MA). The C3-4 level had minor image quality degradation due to motion artifact compared to other segments, and was therefore chosen for analyses.

2.3. Tract reconstruction

We used the Fiber Association by Continuous Tracking method (Mori et al., 1999) in DTIStudio (Jiang et al., 2006) to reconstruct the whole-brain CST bilaterally following the manual ROI selection methods of Reich et al., 2006. This method has excellent interrater reliability at $\kappa > 0.8$ (Wakana et al., 2007). After tract reconstruction, we normalized the data by interpolating to seven landmarks identifiable in every brain on axial sections from the DTI color maps following the methods of Reich et al., 2007. FA and MTR were calculated with a custom MATLAB program (The MathWorks; Natick MA). An average of the left and right tracts was used for both the FA and MTR values.

2.4. Statistical analyses

All statistical analyses were performed with Stata version 11.1 (StataCorp). The Skewness and Kurtosis test was used to assess normality of the data distribution. Outliers were determined for each condition using box-and-whisker plots. Mann-Whitney tests were used to compare individuals with MS to controls. These groups are known to be different; thus corrections for multiple comparisons were not performed following the methods of Spain et al., 2012, as these corrections would exaggerate the type II error. To understand the relationship of functional measures to structural MRI, the MS and control groups were combined and Spearman correlation coefficients were utilized to assess associations among quantitative measures of walking and strength and tract-specific imaging. These measures were corrected for multiple comparisons with an adjusted p-value of <0.007 indicating significance.

To understand what quantitative clinical and demographic measures best explain underlying microstructural integrity of the corticospinal tract, we used backward stepwise regression with Akaike Information Criterion (AIC) (Akaike, 1974). AIC accounts for the number of predictors used and allows for comparison of models with different numbers of variables to assess model goodness of fit. This novel analysis in which the MRI measures serve as the dependent variables was designed to target the utility of the tools already in clinical use.

3. Results

Thirty individuals with MS and 29 age- and gender-matched controls participated in this study. One participant with MS was a statistical outlier on all walking measures and was therefore excluded from the analysis. Thus, data from 29 individuals with relapsing-remitting MS (age: 48.7 ± 11.5 years; 17 females; symptom duration 11.9 ± 8.7 years and median EDSS 4.0 and 29 age- and gender-matched controls (age: 50.8 ± 11.6 years; 20 females) were analyzed. Three individuals with MS completed the 2MWT in a different location than the other individuals, so their data for this measure was also excluded. Control participants performed significantly better on all tests of impairment and function compared to individuals with MS (Table 1). Control participants demonstrated significantly greater SCA than individuals with MS, but controls and individuals with MS were not significantly different on MRI measures of the CST.

Quantitative measures of walking and strength were significantly related to CST FA and MTR measures. Both MTR and FA correlated strongly with walk velocity (Fig. 1 & 2A–B), TUG, T25FW, 2MWT, and summed strength. After corrections for multiple correlations, FA remained significantly related to walking velocity, T25FW, 2MWT and summed strength, while MTR remained significantly related to walk velocity and 2MWT (Fig. 2C–D). Although FA was related to total EDSS (trending, $p = 0.0523$) and FSS Pyramidal, ($p = 0.0202$), MTR was

Table 1
Participant demographics and clinical performance.

	Multiple sclerosis (n = 29)	Control (n = 29)	p-Value
Age (years)	48.69 (11.46)	50.76 (11.61)	0.497
Gender	17 F; 12 M	20 F; 8 M	0.417
Symptom duration (years)	11.94 (8.68)	–	–
EDSS	4.0 [1.0–6.5]	–	–
FSS Pyramidal	2 [0–3]	–	–
Summed strength (lbs)	240.05 (84.11)	301.90 (62.15)	**0.0024**
Walk velocity (m/s)	1.4 (0.47)	1.97 (0.32)	**0.0030**
TUG (s)	7.74 (2.33)	5.77 (1.06)	**0.0003**
T25FW (s)	5.42 (1.99)	4.06 (0.71)	**0.0013**
2MWT (m)	161.17 (46.37)	200.85 (32.28)	**0.0005**
CST FA	0.625 (0.039)	0.634 (0.036)	0.1256
CST MD	0.00081 (0.000052)	0.00078 (0.000026)	**0.0110**
CST AD	0.0015 (0.000088)	0.0014 (0.000069)	**0.0380**
CST RD	0.00048 (0.000062)	0.00045 (0.000031)	0.1104
CST MTR	0.460 (0.018)	0.464 (0.017)	0.5494
SCA (mm^2)	74.9 (12.6)	83.6 (10.1)	**0.0053**

All values are listed as mean (SD) with the exception of EDSS and FSS Pyramidal which are listed as median [range]. Bolded values indicate significance at $p < 0.05$. 2MWT: Two-Minute Walk Test; CST: corticospinal tract; EDSS: Expanded Disability Status Score; FA: fractional anisotropy; FSS: Functional Systems Score; MTR: magnetization transfer ratio; SCA: spinal cord area; T25FW: Timed 25-Foot Walk; TUG: Timed Up and Go.

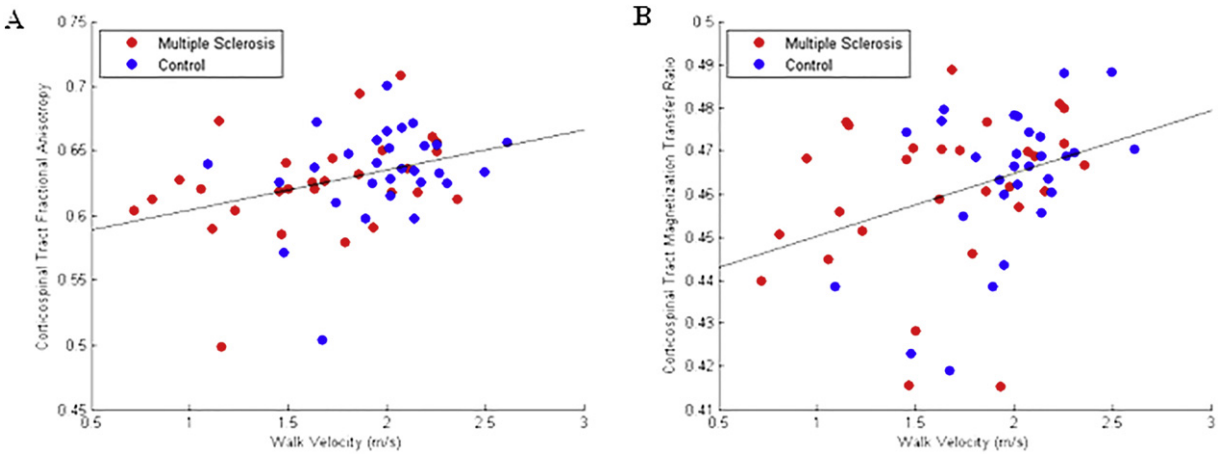

Fig. 1. Scatterplots showing the relationship of walk velocity to CST MRI measures. A) FA (whole group: $r = 0.36$; $p = 0.006$; MS alone: $r = 0.38$; Control alone ($r = 0.15$) and B) MTR (whole group: $r = 0.35$; $p = 0.006$; MS alone: $r = 0.34$; Control alone: $r = 0.35$) are significantly related to walking velocity. Controls are shown in blue, while individuals with MS are shown in red. The correlation line reflects the relationship of the two measures with all participants.

not related to either of these measures ($p > 0.21$). SCA was strongly related to T25FW as well as the EDSS and FSS Pyramidal (Table 2).

To understand what quantitative clinical and demographic measures best explain underlying microstructural integrity of the corticospinal tract, we investigated the MRI factors with the strongest correlations to walking (i.e., MTR, FA, SCA) with regression modeling (Figs. 3–5). We show the results of three models designed to determine the unique contribution of (1) basic clinical information (age, gender, symptom duration and EDSS), (2) strength and walking (walk velocity, TUG, T25FW, 2MWT and summed strength), and (3) the combination of basic clinical information, strength and walking to each of the three MRI measures (FA, MTR and SCA).

3.1. Contribution of basic clinical measures to brain CST and SCA MRI measures

Using **CST MTR** as the dependent variable, the final model includes age resulting in an adjusted R^2 of 0.0345. Age is not a significant contributor to MTR ($p = 0.087$). Using **CST FA** as the dependent variable, the final model includes gender and EDSS with an adjusted $R^2 = 0.0951$. Gender is a significant contributor to FA ($p = 0.016$), while EDSS does not significantly contribute to FA ($p = 0.078$). Using **SCA** as the dependent variable, the final model includes age and EDSS with an adjusted $R^2 = 0.3112$. Both age and EDSS are significant contributors ($p = 0.008$ and $p < 0.001$ respectively) to SCA.

3.2. Contribution of quantitative measures of walking and strength to brain CST and SCA MRI measures

Using **CST MTR** as the dependent variable, the final model includes 2MWT with an adjusted $R^2 = 0.1188$. 2MWT is a significant contributor to MTR ($p = 0.006$). Using **CST FA** as the dependent variable, the final model includes walk velocity, with an adjusted $R^2 = 0.1085$. Walk velocity is a significant contributor to FA ($p = 0.007$). Using **SCA** as the dependent variable, the final model includes T25FW, 2MWT and summed

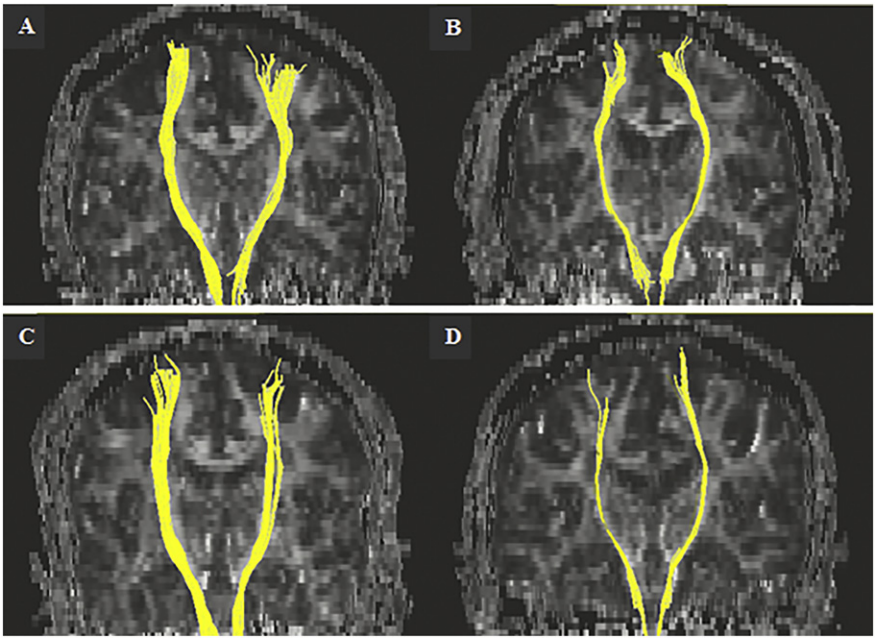

Fig. 2. Corticospinal tract integrity is related to both walking and strength. Bilateral CST reconstruction for representative individuals with relapsing-remitting MS demonstrates larger tracts associated with faster walking and greater hip strength. A) 46 year old female with 2.2 m/s fast walking velocity compared to B) 49 year old female with 0.8 m/s fast walking velocity. C) 48 year old male with summed strength of 395 lbs compared to D) 36 year old male with summed strength 164 lbs.

Table 2
Relationships among quantitative measures of strength and walking to corticospinal tract-specific MRI measures.

	MTR	FA	AD	RD	MD	SCA
Walk velocity	**0.3541**[†]	**0.3592**[†]	0.0537	−0.1597	−0.0120	**0.3069**
	(0.0064)	**(0.0056)**	(0.6997)	(0.2487)	(0.9306)	**(0.0191)**
TUG	**−0.2939**	**−0.2661**	0.0536	0.1056	0.0456	**−0.2949**
	(0.0251)	**(0.0434)**	(0.7002)	(0.4473)	(0.7412)	**(0.0246)**
T25FW	**−0.3322**	**−0.3923**[†]	−0.0665	0.1664	0.0367	**−0.3932**[†]
	(0.0108)	**(0.0023)**	(0.6329)	(0.2291)	(0.7905)	**(0.0023)**
2MWT	**0.3672**[†]	**0.3882**[†]	0.1188	−0.0994	0.0772	0.2368
	(0.0058)	**(0.0034)**	(0.3923)	(0.4745)	(0.5753)	(0.0818)
Summed strength	**0.3237**	**0.3794**[†]	0.1529	−0.0203	0.0898	**0.3339**
	(0.0132)	**(0.0033)**	(0.2697)	(0.8844)	(0.5146)	**(0.0104)**
EDSS	−0.1171	−0.2561	**0.3275**	0.2513	**0.3039**	**−0.4616**[†]
	(0.3814)	(0.0523)	**(0.0156)**	(0.0668)	**(0.0241)**	**(0.0003)**
FSS Pyramidal	−0.1672	**−0.3044**	0.2614	0.2212	**0.2906**	**−0.4400**[†]
	(0.2097)	**(0.0202)**	(0.0562)	(0.1079)	**(0.0314)**	**(0.0005)**

All values are listed as rho (p-value). Bolded values indicate significance at $p < 0.05$. 2MWT: Two-Minute Walk Test; EDSS: Expanded Disability Status Score; FA: fractional anisotropy; FSS: Functional Systems Score; MTR: magnetization transfer ratio; SCA: spinal cord area; T25FW: Timed 25-Foot Walk; TUG: Timed Up and Go.
[†] Indicates significance at $p < 0.007$ (corrected for multiple comparisons).

strength with an adjusted $R^2 = 0.0840$. No individual measures are significant contributors to SCA.

3.3. Contribution of clinical measures and quantitative measures to brain CST and SCA MRI measures

Using **CST MTR** as the dependent variable, the final model includes walk velocity with an adjusted R^2 value of 0.1129. Walk velocity is a significant contributor to MTR ($p = 0.006$). Using **CST FA** as the dependent variable, the final model includes gender and walk velocity with an adjusted $R^2 = 0.1490$. Walking velocity is a significant contributor ($p = 0.011$) to FA, while gender is not ($p = 0.061$). Using **SCA** as the dependent variable, the final model includes age, EDSS and 2MWT, with an adjusted $R^2 = 0.3127$. Age and EDSS are significant contributors to SCA ($p = 0.002$ and $p < 0.001$, respectively), while 2MWT is not ($p = 0.067$).

4. Discussion

A better understanding of how clinical factors, such as walking and strength, contribute to underlying neural integrity would be useful to advance targeted rehabilitation techniques. Our data shows that quantitative measures of strength and walking are associated with brain CST pathology while EDSS and FSS Pyramidal measures are associated with spinal cord pathology. Quantitative measures of walking and strength are more functionally and clinically relevant to brain imaging than the EDSS. Others have discussed the relationship of strength measurement to brainstem CST diffusivity (Reich et al., 2008) and of EDSS and T25FW performance to CST diffusivity (Klineova et al., 2016; Hubbard et al., 2016; Tovar-Moll et al., 2015). Our results add to the literature by examining whole brain CST, quantifying MTR as well as diffusivity and including quantitative walking and strength measurements. The addition of a measurement more specific to myelin (i.e., MTR) is novel and particularly relevant in the context of the demyelinating nature of MS. The results of our regression modeling show that adding quantitative measures to basic clinical information (Figs. 3C and 4C) explains more of the variance in CST FA and MTR than the basic clinical information alone. Interestingly, this result was not as robust in the spinal cord, with age and EDSS being the primary contributors to SCA. Given the heterogeneous nature of the disease differences among individuals with MS and healthy controls are not unexpected. Studies examining CST-specific measures have shown no difference in FA between controls and individuals with RRMS (Daams et al., 2015; Reich et al., 2007). One study demonstrated significant differences in CST MTR between individuals with MS and controls; however, the inclusion of progressive patients (i.e., greater disability) may have affected their results (Reich et al., 2007). By and large, controls have not been included in studies examining relationships between CST DTI measures and walking (Hubbard et al., 2016; Klineova et al., 2016; Naismith et al., 2013; Tovar-Moll et al., 2015). Overall, our CST FA and MTR values are in agreement with prior work (Reich et al., 2006; Reich et al., 2007; Reich et al., 2008), and we highlight here the results of our regression modeling showing that functional outcome measures explain some of the variance in the microstructural integrity of the CST.

The search for quantitative outcomes has led to the use of both spinal cord and brain MRI measures to provide information about overall disability. Our results confirm the finding that SCA is correlated with EDSS (Bernitsas et al., 2015; Daams et al., 2015), FSS Pyramidal (Daams et al., 2015), and T25FW (Daams et al., 2015), commonly used functional measures in MS clinical trials. We suggest that using quantitative measures of strength and walking, in place of rating scales may provide valuable clinical information about brain pathology in individuals with MS. Two recent studies have noted relationships among brain CST diffusivity measures and EDSS (Daams et al., 2015; Tovar-Moll et al., 2015) and FSS Pyramidal (Tovar-Moll et al., 2015). However, our results show that CST FA and MT are strongly related to quantitative measures of walking and strength, with a much weaker relationship to the EDSS or FSS Pyramidal. This builds upon recent work demonstrating a poor relationship between EDSS and CST FA (Hubbard et al., 2016). Furthermore, neither EDSS nor FSS Pyramidal were significant contributors explaining variance in CST FA or MTR. Indeed, our data from individuals with similarly long disease durations to those in the Daams et al. (2015) study, shows that quantitative motor measures explain more of the variance in CST FA than basic clinical measures such as age, gender, symptom duration and EDSS. These discrepancies may be due to several factors: both Daams et al. (2015) and Tovar-Moll et al. (2015) included individuals with progressive phenotypes of MS in their studies and excluded parts of the brainstem from the tracking of the CST starting their ROIs at the pons or the midbrain. Our work includes only individuals with relapsing-remitting MS, as well as full brain tracking from medulla to cortex and additional quantitative measures of function including summed strength, 2MWT, walk velocity and TUG. Hubbard et al. (2016) utilized similar imaging methods to our study and also demonstrated a significant relationship among T25FW, walking velocity and walking endurance and CST AD, RD and MD, although no relationship was seen between FA and walking measures. Taken together, our results suggest that although the EDSS may be an appropriate approximation of spinal cord integrity (i.e., SCA), quantitative measures of function better reflect the microstructural integrity of the brain CST (i.e., FA and MTR). Disability in MS is often linked with spinal cord integrity (Oh et al., 2013a); however, measurement of quantitative motor measures by healthcare professionals may provide a window into brain pathology in MS.

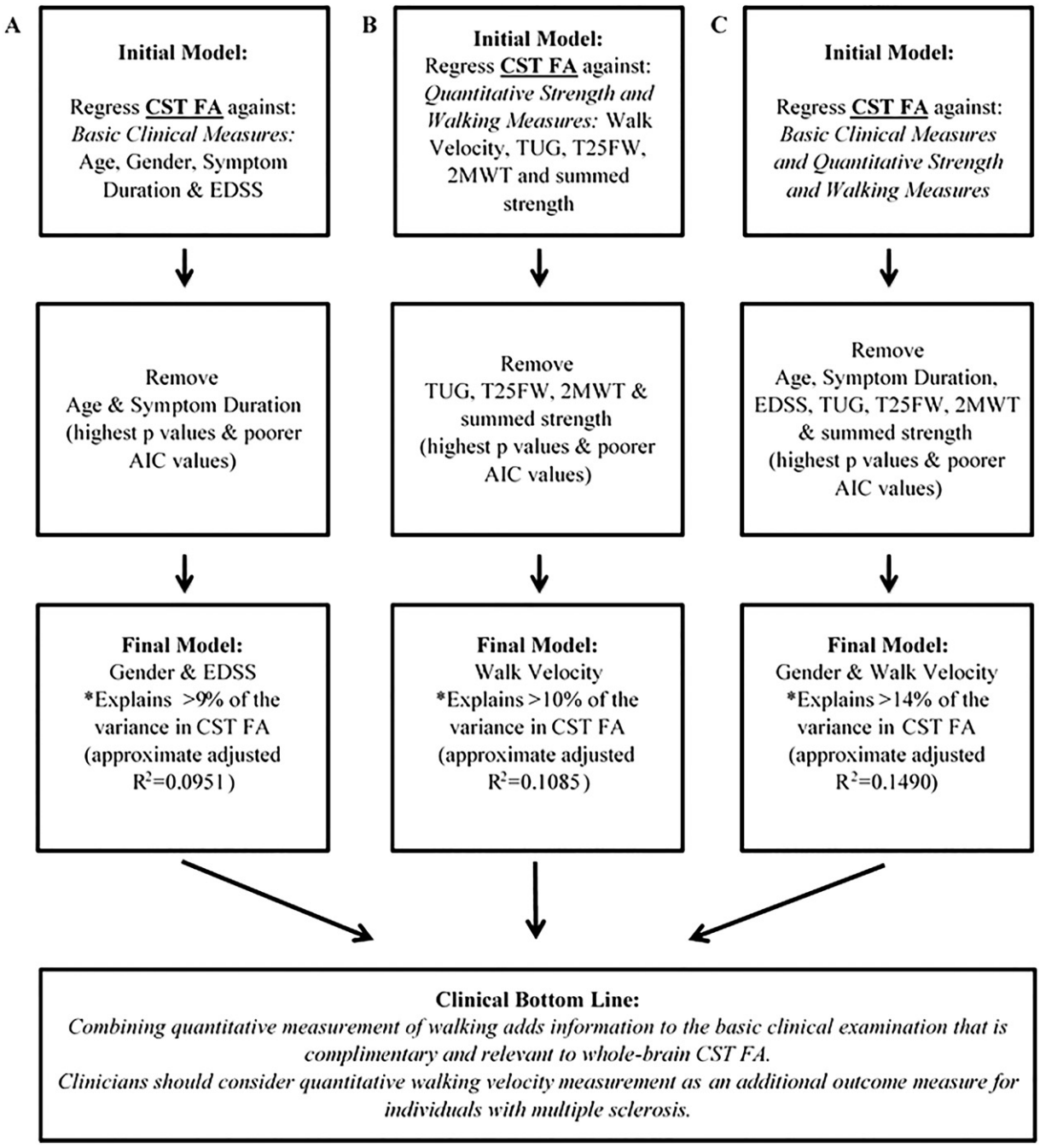

Fig. 3. Diagram of three regression models exploring the factors best explaining CST FA when A) basic clinical measures are considered in isolation; B) quantitative strength and walking measures are considered in isolation; and C) basic clinical measures and quantitative strength and walking measures are considered together.

Although MRI is sensitive to changes associated with MS pathology (Agosta et al., 2006; Sämann et al., 2012; Filippi et al., 2013; DeStefano et al., 2014), sequences are used in combination, as no single technique is specific enough to serve alone as a diagnostic tool. For example, MRI sequences such as T1 and MPRAGE of the brain and spinal cord are used to monitor medical progression of MS through structural changes, such as atrophy. While conventional MRI scans can detect the evolution of MS lesions, these techniques are not able to capture subtle changes in tract-related pathology and are poorly related to the clinical status of individual patients (Miller et al., 1998). This study shows that MTR is a relevant and unique method that shows strong relationships to quantitative measures of walking. MT imaging has been found to be highly reproducible (Vavasour et al., 2006; Tjoa et al., 2008), and data from our group has reported the utility of MT to detect differences between individuals with MS and healthy controls and between MS disease subtypes (Oh et al., 2013a; Oh et al., 2013b). This imaging technique may provide insight into motor function that is commonly missed with conventional imaging. MT imaging in combination with conventional imaging may improve our understanding of the role of MRI as a surrogate marker for MS progression.

Outcome measurement selection for clinical trials has been notoriously challenging (Bermel et al., 2014). Combining sensitive MRI measures with quantitative measures of function (i.e. strength and walking) that address weaknesses of the EDSS (i.e., reliability and non-linearity) could improve disease monitoring both conservatively and with intervention. The T25FW and EDSS are the most commonly utilized functional measures in MS clinical trials. However, the results of our regression models show that walk velocity and 2MWT explain

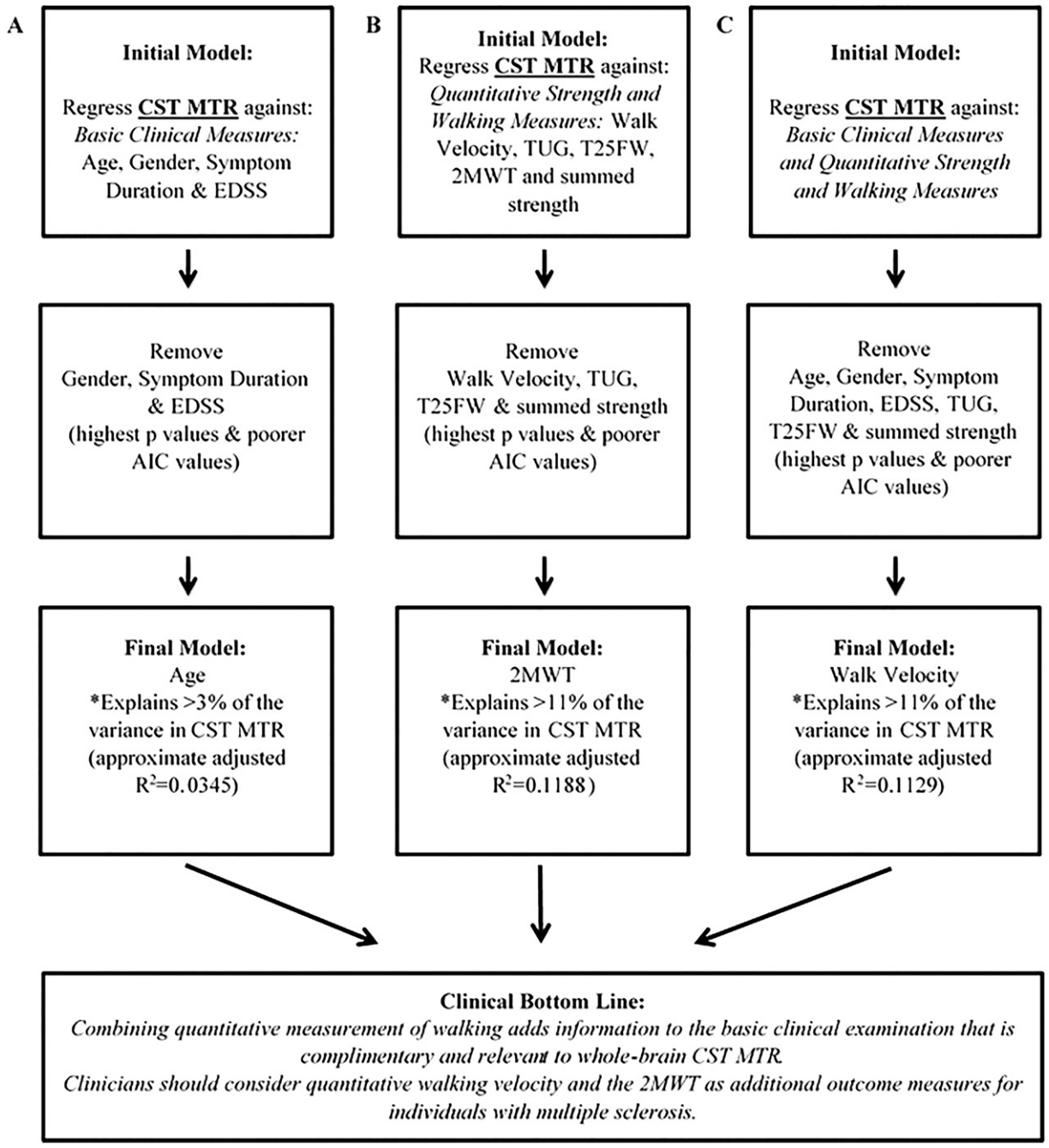

Fig. 4. Diagram of three regression models exploring the factors best explaining CST MTR when A) basic clinical measures are considered in isolation; B) quantitative strength and walking measures are considered in isolation; and C) basic clinical measures and quantitative strength and walking measures are considered together.

more of the variance in CST-specific MRI measures than T25FW and EDSS, which fall out of the models (Fig. 3B–C and Fig. 4B–C). In particular, 2MWT is important in explaining variance in CST MTR and may address an element of MS-related fatigue, as well as walking endurance. It is perhaps worthwhile to revisit the walking measures included in MS clinical trials. The addition of objective, precise measures of walking, such as walking velocity, may reduce human error inherent in timed walking tests and explain more of the variance in CST-specific measures. The reality may be that more than one walking test or the addition of strength measures are required to better understand brain pathology, since the disease itself is so heterogeneous. Furthermore, the use of tract-specific imaging may also improve disease monitoring and individualized care; indeed an annualized rate of change in CST MTR has been established (Harrison et al., 2011), suggesting that tract-specific MRI measures of the CST may add information about disease progression if quantitative measures of function were also assessed at these time points.

4.1. Limitations

There are several limitations in this study. The sample size was small, and there was no correction for lesions within the tracts. However, we did not experience any issues with tracking the CST in any of our participants, suggesting that tracking took into account any lesions present in the tract. Furthermore, chronic black hole lesion volume within the CST has been shown to be strongly correlated with not only FSS Pyramidal and T25FW, but also total EDSS and FSS Sensory (Tovar-Moll et al., 2015), suggesting that it is a non-specific marker of disability, rather

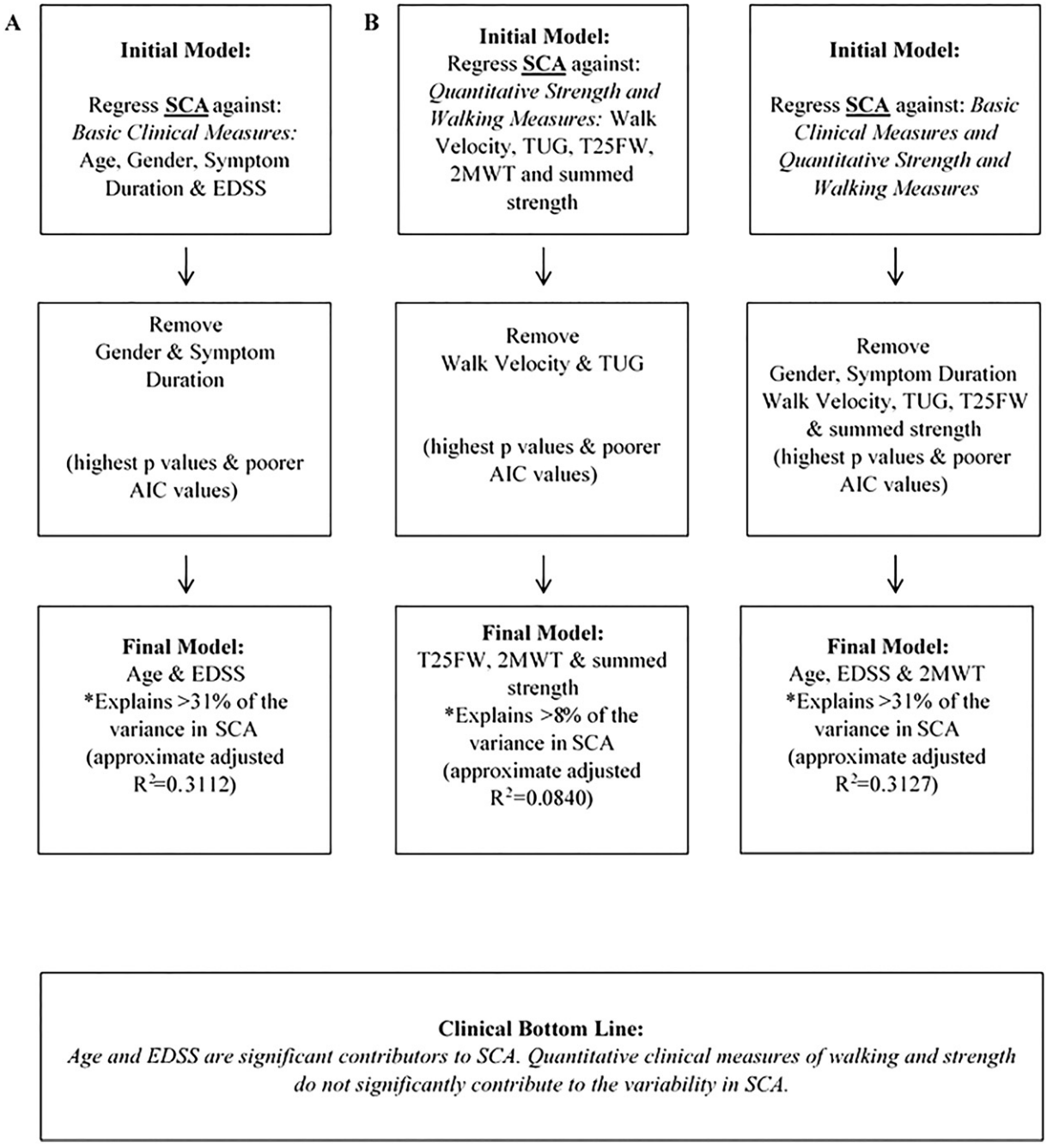

Fig. 5. Diagram of three regression models exploring the factors best explaining SCA when A) basic clinical measures are considered in isolation; B) quantitative strength and walking measures are considered in isolation; and C) basic clinical measures and quantitative strength and walking measures are considered together.

than specific to motor disability. Finally, accounting for lesions within the CST has yielded disparate results with some finding of relationships to EDSS (Tovar-Moll et al., 2015) while others do not (Daams et al., 2015), perhaps due to large intra- and inter- observer variability in manual lesion segmentation (Jain et al., 2015). For the spinal cord tracking we incorporated the entire axial area to calculate FA and MTR, as in Oh et al. (2013a, 2013b); this may have contributed to our findings. Hand-held dynamometry was used for strength assessment, which can be variable between testers. To limit this variability, all testers were trained by one experienced tester (KMZ) using a standardized technique. The reliability of hand-held dynamometry for hip strength measurement has been established by our group (Newsome et al., 2011). In addition to quantitative strength and walking measures, there are other factors that may contribute to CST pathology that were not evaluated in this study. Future work should examine the relationship of other variables on CST pathology. Finally, the utility of the quantitative strength and walking measures presented here in conjunction with the CST-specific MRI measures have not been evaluated longitudinally to understand its sensitivity to change. Future studies should investigate whether these quantitative strength and walking measures are useful outcome measures for MS clinical trials that could show changes over time more rapidly than the gold-standard EDSS.

4.2. Conclusions

Quantitative measures of walking and strength provide a window into the pathology of MS. These quantitative measures are not only related to brain CST-specific measures, but add additional information to

the EDSS and current clinical exam to help explain the underlying microstructural integrity of the CST. Whole-brain CST-specific measures, especially MT imaging, improve our understanding of structure-function relationships in individuals with MS and highlight differences in this heterogeneous cohort. Use of quantitative measures of function collected in the clinical exam in addition to structural imaging may provide an avenue for targeted, individualized rehabilitation.

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