Magnetization Transfer Imaging in Brain Corticospinal Tract is Associated with Clinical Walking Performance in Multiple Sclerosis

Fritz NE, Marasigan R, Keller J, Chiang CC, Calabresi PA, Zackowski KM.

Background

- Up to 85% of individuals with MS report gait disturbance as their main complaint. (Kelleher et al 2010)
- Walking is frequently tested in the clinic as a measure of physical function.
- EDSS
  - Walking evaluation based on distance and assistance level
  - No measure of:
    - Time to complete walking tasks
    - Quality of walking
    - Functional tasks during walking

Background

- Previous work in Diffusion Tensor Imaging (DTI) and Magnetization Transfer Ratio (MTR) has focused on impairment measures (strength) and has shown:
  - An association between strength and:
    - spinal cord MTR of the lateral column
    - spinal cord FA of whole spinal cord ROIs
  - Brainstem corticospinal tract (CST) MTR dissociates stronger vs. weaker muscle strength
- Walking represents a global disability measure and may be more practical for monitoring change over time and with intervention.
  - **There are no previous studies examining the relationship between walking performance and DTI or MT measures**

Objectives

- Explore the relationship of clinical measures of walking and CST-specific MRI measures.
- Determine the extent that quantitative measures of walking may add to basic clinical measures (age, gender, symptom duration and EDSS).

Hypotheses

- Tract-specific imaging measures of the CST will be related to walking.
- Quantitative measures of walking will add information about the MRI that is complimentary to basic clinical information.

Demographics

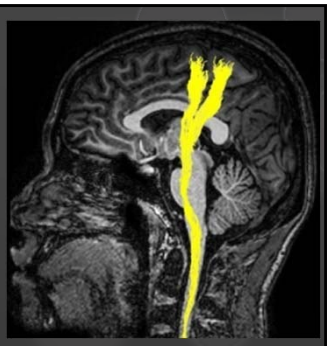
	Age Mean(SD)	Gender	Symptom Duration Mean(SD)	EDSS Median (range)
MS n=23	49.1 (11.5) Years	12F; 11M	14.1 (10.2) Years	4.0 (1-6.5)
Control n=20	52.2 (10.4) Years	13F; 7M	--	--

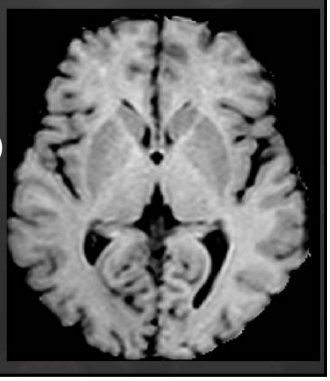
Clinical Measures

- Fall History
- Strength
- Sensation
- Walking
  - Timed Up and Go (TUG)
  - Timed 25 Foot Walk (T25W)
  - Two Minute Walk Test (2MWT)

MRI Measures

- **Phillips 3T Scanner**
- **Diffusion Tensor Imaging (DTI)**
  - 33 direction
  - FOV: 212 x 154 x 212
  - 70 slices
  - 2.2 SENSE
  - TR = 7173 ms
  - Scan Resolution 96x96
- **Magnetization Transfer Ratio (MTR)**
  - FOV: 212 x 154 x 212
  - 70 slices
  - Scan Resolution 144x140
  - TR: 64.411 ms





Results

Table 1. Comparisons Between Individuals with MS and Controls

	MS Mean(SD)	Control Mean(SD)	P-value
Falls (# past month)	0.43 (0.51)	0	p=0.0009 ǂ
Hip Flexion Strength (lbs)	34.1(14.8)	46.6(10.5)	p=0.0025
Vibration Sensation (vu)	7.5(3.5)	3.2(2.4)	P=0.0002 ǂ
TUG (s)	8.1(2.5)	5.9(1.0)	p=0.0006
T25W (s)	5.7(2.4)	4.2(0.65)	p=0.0102 ǂ
2MWT (m)	162.6(45.5)	199.4(32.4)	p=0.0067

ǂ Indicates Mann-Whitney Tests; all others T-tests

Results

Table 2. Correlations between Clinical Measures and MRI Measures

	MTR Mean(SD)	$\lambda_{\perp}$ Mean(SD)	$\lambda_{\parallel}$ Mean (SD)	Fractional Anisotropy Mean (SD)
TUG	**-0.4297 (0.0071)**	0.2948 (0.0613)	0.1772 (0.2873)	-0.2877 (0.0681)
T25W	**-0.3972 (0.0101)**	**0.3404 (0.0294)**	-0.0970 (0.5461)	**-0.4085 (0.0080)**
2MWT	0.2889 (0.0828)	-0.3059 (0.0656)	-0.1420 (0.4017)	0.2209 (0.1889)
EDSS	-0.1812 (0.2570)	**0.3829 (0.0135)**	**0.3639 (0.0193)**	-0.1530 (0.3395)
Hip Flexion Strength	0.2256 (0.1561)	-0.1301 (0.4175)	0.2476 (0.1186)	0.2319 (0.1445)

Spearman's R-value (p-value)

Results

- Can walking measures provide information that is not obtained from basic clinical data?
  - *age, gender, symptom duration, EDSS*
- We analyzed the data to determine the unique contribution of:
  1. Basic clinical information to MRI.
  2. Basic clinical information + walking measures to MRI.

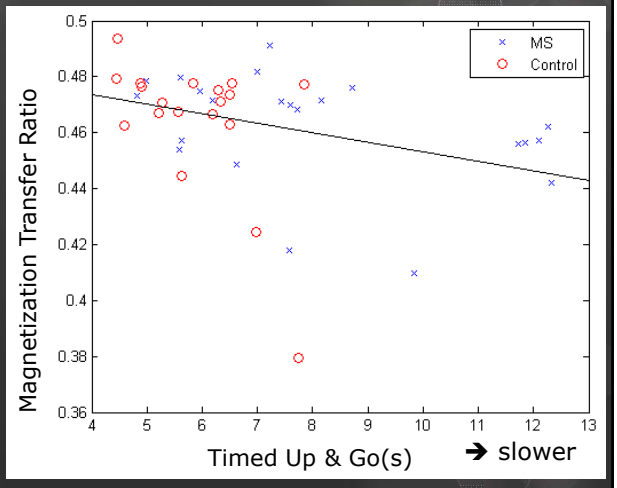
MTR and Walking Measures

Basic Clinical Measures alone:

- R^2 =-0.01489

Model with TUG, falls & age:

- R^2 =0.2657
  - TUG p=0.000811
  - Falls p=0.004645



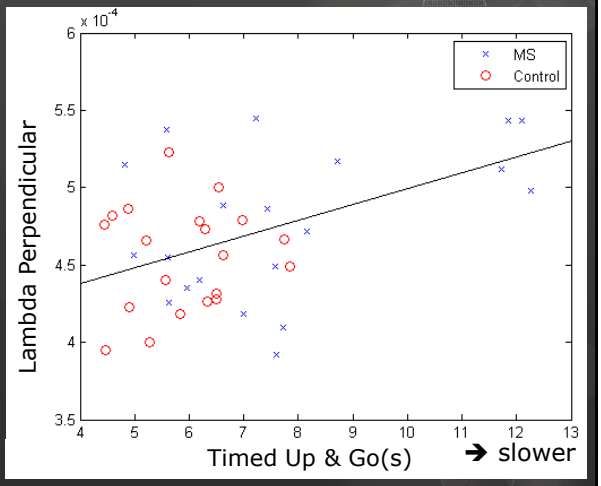
λ⊥ and Walking Measures

Basic Clinical Measures alone:

- R^2 = 0.2469

Model with TUG, symptom duration & EDSS

- R^2 =0.3268
  - TUG p=0.0257
  - Symptom duration p=0.0134
  - EDSS p=0.0299



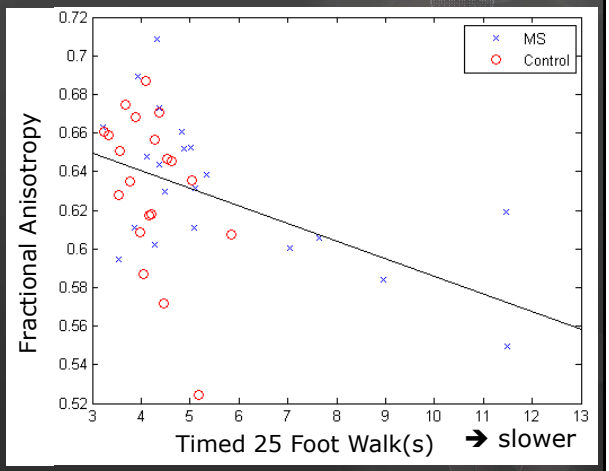
Fractional Anisotropy and Walking Measures

Basic Clinical Measures alone:

- R^2 = 0.055

Model with T25W and symptom duration:

- R^2 =0.2153
  - T25W p=0.000957



Summary

Quantitative measures of walking (T25W, TUG):

- Are related to MRI measures (MTR, $\lambda_{\perp}$, FA).
- Add additional information to the EDSS that is relevant to MRI measures.
- Are specific to the primary complaint (walking) of our patients.

Conclusions

- Our data links the CST to walking measures and highlights MTR as an important addition to structural MRI protocols.
- Evaluating structure-function relationships is important for the development of quantitative outcome measures that are specific to patient complaints.

Future Directions

- Establish Minimal Detectable Change (MDC) for these walking measures in MS
- Expand the analysis to include volumetric imaging
- Understand the relationship of MRI to falls data
- Determine the predictive value of MRI and clinical measures in evaluating intervention responsiveness

Acknowledgments

National MS Society
- NMSS Research Grant
- Kathy Costello

Department of Neurology, Johns Hopkins School of Medicine
- Peter Calabresi
- Scott Newsome
- Dorlan Kimbrough
- Bryan Smith
- Pavan Bhargava

Kennedy Krieger Motion Analysis Lab
- Nicole Cornet
- Allen Jiang
- Brian Diaz

Kennedy Krieger Kirby Center for Functional Imaging
- Craig Jones
- Kathie Kahl
- Terri Brawner

Department of Biostatistics, Johns Hopkins School of Public Health
- Ani Eloyan
- Ciprian Crainiceanu

References

Basser PJ, Mattiello J, LeBihan D.MR diffusion tensor spectroscopy and imaging. *Biophys J.* 1994;66:259-267.

Beaulieu C, Allen PS.Determinants of anisotropic water diffusion in nerves. *Magn Reson Med.* 1994;31:394-400.

Ge Y, Law M, Grossman RI. Applications of diffusion tensor MR imaging in Multiple Sclerosis. *Ann NY Acad Sci.* 2005; 1064: 202-219.

Ibrahim I, Tintera J, Skoch A, Jirů F, Hlustik P, Martinkova P, Zvara K, Rasova K. Fractional anisotropy and mean diffusivity in the corpus callosum of patients with multiple sclerosis: the effect of physiotherapy. *Neuroradiology*. 2011; 53: 917-926.

Kelleher KJ, Spence W, Solomonidis S, Apatsidis D. The characterization of gait patterns in people with multiple sclerosis. *Disabil Rehabil.* 2010; 32(15): 1242-1250.

Lin X, Tench CR, Morgan PS, Constantinescu CS. Use of combined conventional and quantitative MRI to quantify pathology related to cognitive impairment in multiple sclerosis. *J Neuro Neurosurg Ps.* 2008; 79: 437-441.

Madden DJ, Bennett IJ, Song AW. Cerebral white matter integrity and cognitive aging: contributions from diffusion tensor imaging. *Neuropsychol Rev.* 2009; 19: 415- 435.

Mori S and Zhang J. Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron*. 2006; 51(5): 527-539.

Newsome SD, Wang JI, Kang JY, Calabresi PA, Zackowski KM. Quantitative measures detect sensory and motor impairments in multiple sclerosis. *J Neurol Sci.* 2011; 305: 103-111.

Oh J, Zackowski K, Chen M, Newsome S, Saidha S, Smith SA, Diener-West M, Prince J, Jones CK, Van Zijl PC, Calabresi PA, Reich DS. Multiparametric MRI correlates of sensorimotor function in the spinal cord in multiple sclerosis. *Mult Scler.* 2013; 19(4): 427-435.

Reich DS, Zackowski KM, Gordon-Lipkin EM, Smith SA, Chadkowski BA, Cutter GR, Calabresi PA. Corticospinal tract abnormalities are associated with weakness in multiple sclerosis. *Am J Neuroradiol*. 2008; 29: 333-339.

Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage*. 2002; 17: 1429-1436.

Wilson M, Trench CR, Morgan PS, Blumhardt LD. Pyramidal tract mapping by diffusion tensor magnetic resonance imaging in multiple sclerosis: improving correlations with disability. *J Neuro Neurosurg Ps*. 2003; 74: 203-207.

Zackowski KM, Smith SA, Reich S, et al. Sensorimotor dysfunction in multiple sclerosis and column-specific magnetization transfer-imaging abnormalities in the spinal cord. *Brain.* 2009; 132: 1200-1209.