Evaluating Cerebellar Contributions to Physical Performance and Cognition in Multiple Sclerosis

Nora Fritz, PhD, PT, DPT, NCS
CMSC Annual Meeting
5.29.15

Background

• Individuals with multiple sclerosis (MS):
  – 85% report gait (motor) dysfunction that interferes with daily functioning (Kelleher et al. 2010)
  – 40-65% report cognitive dysfunction (Amato et al. 2010)

• The cerebellum:
  – Plays an important role in both motor and cognitive processing (Kozel et al. 2014; Stoodley et al. 2012)
  – Is a common site for MS-related disability (Weier et al. 2015)
    • Cerebellar signs and symptoms are the predominant manifestation in 11-33% of individuals with MS (Weier et al. 2015)
• Rehabilitation for individuals with cerebellar dysfunction is limited
  – A better understanding of the relationship of clinical features to structural anatomy would be useful in this heterogeneous patient population.

• Ultimately:
  – Drive clinical practice forward
    • Utilize what we know about these relationships to predict future function
    • Develop more effective rehabilitation protocols that target mechanism of dysfunction/disability
Cerebellar Anatomy

Background

• Diffusion:
  – Primary outcome measures:
    • Fractional Anisotropy (FA): degree of anisotropy in a given voxel
    • Mean Diffusivity (MD): total diffusion within a voxel
Background

• **Diffusion**
  – SCP ↑ FA Linked with rate of learning a visuomotor task in healthy adults (Della-Maggiore et al. 2009)

![Diagram showing relationships between SCP, FA, MD, and T25FW in PPMS and RRMS]

• **Volumes**
  – Reduction in total cerebellar volume in MS compared to controls; more prominent in PPMS (Anderson et al. 2009; Calabrese et al. 2010)
  
  – Established Relationships Between:
    • Cerebellar lesion volume and cognition (Damasceno et al. 2014)
    • Cerebellar grey matter volume and fine motor skill (Anderson et al. 2009)
Objective

To examine the relationship of motor and cognitive performance to cerebellar volumes and diffusivity measures in individuals with MS.

Physical Function Measures

- Strength
- Sensation
Physical Function Measures

- Walking
  - Timed Up and Go (TUG)
  - Timed 25 Foot Walk (T25FW)
  - Two Minute Walk Test (2MWT)
  - Fast Walking Velocity
- Fall History

Cognitive Measures

- Symbol Digit Modality Test (SDMT)

(Parmenter et al. 2007; Deloire et al. 2006; Genova et al. 2009; Strauss et al. 2006; Drake et al. 2010; Rao 2004.)
Structural Measures

- Philips 3T Scanner
- DWI for FA & MD measurement
- Automatic segmentation method (Ye et al., 2015)

Structural Measures

- MPRAGE for volume measurement
- Automatic Segmentation with lobule parcellation (Yang et al. 2013; Bogovic et al. 2013)
- Lobules I-V, VIII: related to motor function
- Lobules VI-VII: related to cognitive function (Stoodley & Schmahmann, 2010)
### Inclusion Criteria & Demographics

- Diagnosis of Relapsing Remitting MS
- No active exacerbations
- No corticosteroid use in past 30 days
- No other orthopedic or neurologic disorders that would influence walking
- Able to follow study-related commands

### Age & Gender

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (SD)</th>
<th>Gender</th>
<th>Symptom Duration Mean (SD)</th>
<th>EDSS Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS n=29</td>
<td>50.0 ± 11.3 Years</td>
<td>18F; 11M</td>
<td>12.8 ± 9.9 years</td>
<td>4.0 [1-6.5]</td>
</tr>
<tr>
<td>Control n=23</td>
<td>51.9 ± 11.0 Years</td>
<td>15F; 8M</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*All values listed mean±SD with the exception of EDSS, which is listed median[range]*

### Comparisons between Individuals with MS and Controls

<table>
<thead>
<tr>
<th>Test</th>
<th>MS Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls (&gt;1 past month)</td>
<td>0.52 (0.51)</td>
<td>0 (0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Summed Strength (lbs)</td>
<td>235.4 (89.6)</td>
<td>305.1 (64.4)</td>
<td>0.0029</td>
</tr>
<tr>
<td>Vibration Sensation (vu)</td>
<td>6.7 (3.5)</td>
<td>3.1 (2.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Walk Velocity (m/s)</td>
<td>1.6 (0.49)</td>
<td>2.0 (0.35)</td>
<td>0.0077</td>
</tr>
<tr>
<td>TUG (s)</td>
<td>7.7 (2.3)</td>
<td>5.9 (1.1)</td>
<td>0.0021</td>
</tr>
<tr>
<td>T25FW (s)</td>
<td>5.6 (2.3)</td>
<td>4.2 (0.73)</td>
<td>0.0139</td>
</tr>
<tr>
<td>2MWT (m)</td>
<td>163.8 (45.4)</td>
<td>197.0 (32.4)</td>
<td>0.0057</td>
</tr>
<tr>
<td>SDMT</td>
<td>47.7 (12.4)</td>
<td>59.9 (6.2)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
Diffusion Results

- Diffusivity of the **SCP**, was significantly worse in individuals with RRMS compared to controls.
  - FA: $p=0.029$

- MD: $p=0.002$
Diffusion Results

• Decreased MD in the SCP was significantly associated with:
  – Reduced falls in the past month
    • r=-0.37; p=0.007
  – Better SDMT performance
    • r=-0.45; p=0.0009

– Better performance on walking tests
  • T25FW:
    r=0.29; p=0.044
  • TUG:
    r=0.33; p=0.025
  • 2MWT:
    r=-0.39; p=0.009
  • Walking speed:
    r=-0.28; p=0.041
Volume Results

• Higher volume of the motor lobules (I-V, VIII) was significantly associated with:
  – Higher strength
    • $r=-0.37$, $p=0.007$
  – Better performance on the T25FW
    • $r=-0.30$, $p=0.035$

• Higher volume of the motor lobules (I-V, VIII) was significantly associated with:
  – Faster walking speed
    • $r=0.30$, $p=0.032$
Volume Results

• Motor lobule volume was **not** related to sensory performance ($r=0.23; p=0.108$).

Volume Results

• Higher volume of the cognitive lobules (VI-VII) was associated with:
  
  – Better performance on the SDMT
    • $r=0.43; p=0.002$
Volume Results

• Larger MCP Volume is related to:
  – **Better SDMT performance**
    • $r=0.3703$; $p=0.0075$

![Graph showing correlation between MCP volume and SDMT performance](image)

Volume Results

• Fallers (n=15) vs. non-fallers (n=14)
• Fallers perform significantly worse on:
  – Walk velocity ($p=0.026$)
  – SDMT ($p=0.010$)
Volume Results

• Fallers have lower volumes in:
  – MCP (p=0.033)
  – Lobules I-V and VIII (p=0.038)
  – Lobules VI-VII (p=0.008)

Summary

• Cerebellar volumes and diffusivity are selectively associated with:
  – Physical performance
  – Cognition

• Unique Findings in RRMS:
  – Differences in diffusivity among RRMS & controls.
  – Differences among fallers and non-fallers.
  – Relationships among clinical impairment and diffusivity measures.
Conclusion

**Cerebellar MRI:**
- Improves our understanding of:
  - Structure-function relationships in individuals with MS
  - Individualized differences in this heterogeneous group
- May provide an avenue for:
  - Understanding motor skill learning in MS
  - Targeted, *individualized rehabilitation*

Acknowledgments

**National MS Society Research Grant**

- **Kennedy Krieger Motion Analysis Lab**
  - Kathleen Zackowski, PhD, OTR
  - Jennifer Keller, MS, PT
  - Chen Chun Chiang
  - Rhul Marasigan
  - Allen Jiang

- **Department of Biostatistics, Johns Hopkins School of Public Health**
  - Ani Eloyan, PhD
    - Kennedy Krieger Kirby Center for Functional Imaging
  - Kathie Kahl
  - Terri Brawner

- **Department of Neurology, Johns Hopkins School of Medicine**
  - Peter Calabresi, MD
  - Scott Newsome, DO
  - Pavan Bhargava, MD

- **Department of Electrical & Computer Engineering, Johns Hopkins University**
  - Jerry Prince, PhD
  - Chuyang Ye, PhD
  - Zhen Yang
References


References