Diffusion-Tensor Imaging:

Executive Function in Subcortical Ischemic Vascular Disease and Mild Cognitive Impairment

Stephen Correia, Ph.D.
Dementia Research Fellow, Neuropsychology

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Diffusion-Tensor Imaging

- MRI technique for *in-vivo* characterization of 3D white matter microstructure.
  - Measures magnitude and direction of water diffusion in biological tissue in 3D.
- More sensitive to white matter changes than conventional MRI sequences.
DTI Basics – Water Diffusion

Adapted from: Beaulieu (2002). *NMR in Biomed*; 15:435-455
DTI Scalar Parameters

- **Trace**: The magnitude of diffusion in a voxel.

- **Fractional Anisotropy (FA)**: The extent to which diffusion is directionally restricted.
DTI Scalar Maps

T2-weighted  FA map  Trace map

T2* & FA: Moseley et al. (2002) *Brain & Cognition*; 50;396-413.
Trace: Molko et al. (2001) *Stroke*: 32(9) 2049-54
DTI Basics – White Matter Integrity

- Lesioned white matter:
  - Increased diffusion (increased Trace)
  - Decreased anisotropy (decreased FA)

- Etiology of DTI changes unclear
  - Axon loss & membrane breakdown
  - Demyelination
  - Gliosis/inflammation
Why study frontal systems in SIVD & MCI?

- Frontal-subcortical circuit disruption in SIVD
  - Executive and behavioral impairment
  - Functional decline and dementia.
- Executive impairment in MCI (CDR=0.5) may hasten conversion to dementia.
- Use DTI and cognitive testing as independent probes of frontal systems integrity and function to identify a subset of SIVD and MCI patients at greater risk for conversion to dementia.

Albert et al. (2001), *JINS* 7(5) 631-5.
Patient Groups

- SIVD: Subcortical ischemic vascular disease
  - Subcortical hyperintensities (SH) on T2-weighted MRI; lacunar infarction on T1
  - Gliosis and demyelination due to underlying small vessel disease.

Images of brain MRI scans for:
- 70-year-old normal
- 52-year-old CADASIL
- 65-year-old CADASIL
Patient Groups

- **CADASIL**: Cerebral autosomal dominant arteriopathy with subcortical infarction and leukoencephalopathy.
  - Inherited form of SIVD.
    - Effect on brain parenchyma same as in SIVD.
    - Relatively pure form of SIVD, excellent model.

- **MCI**
  - Petersen criteria for amnestic MCI

- **Normal controls**
Prior Studies of DTI

- **DTI in Aging:**
  - Anterior – posterior gradient of DTI changes. (e.g., Pfefferbaum, 2000)
  - Correlations w/executive function. (e.g.; O’Sullivan, 2001, Madden 2004)

- **DTI in SIVD:**
  - DTI abnormalities in normal appearing white matter (NAWM)
  - DTI in NAWM more strongly correlated w/executive function than DTI in SH. (O’Sullivan 2004)

- **DTI in MCI:**
  - Little progression of anterior-posterior gradient found in normal aging (Head, 2004)
  - DTI changes in regions expected for AD (left CSO, temporal lobes, left HC) (Fellgeibel, 2004)
  - Association of DTI w/cognitive function not well studied.
Objectives

1. To assess white matter integrity in patients with SIVD vs. MCI vs. normal controls using DTI.

2. To determine the association between DTI parameters in white matter and attention/executive function and processing speed.
Hypotheses

1. Increased FA and decreased Trace in SIVD & MCI vs. NC.

2. FA and Trace in NAWM will correlate significantly with performance on tests of attention/executive function and psychomotor processing speed.
Method

- Subjects recruited from Butler Hospital Memory & Aging Program @ Brown
- NC recruited from family members of patients
- MRI done generally within 2 months of cognitive testing.
Key inclusion criteria – SIVD

- n = 9 (4 CADASIL)
- Identified mainly on radiological grounds for protocol different than that of the MCI subjects.
- Greater than expected SH for age on a visual rating scale (Vataja et al., 2003 *Eur J Neurol* 10, 625-31)
- Cognitive complaint
- Consensus diagnosis of SIVD or genetically confirmed CADASIL
- MMSE ≥ 24
- Global CDR ≥ 0.5
- ADL normal or only slightly impaired
- Excluded: diagnosis of probable or possible AD
Key inclusion criteria – MCI

- n = 9
- Documented memory complaint
- MMSE ≥ 24
- Global CDR = 0.5
- ADL normal or only slightly impaired
- 1.5 SD below age-corrected mean on HVLT-R delayed recall or % retained
- Excluded: diagnosis of probable or possible AD
Key inclusion criteria – NC

- Absence of significant memory complaint
- MMSE within normal limits
- CDR = 0
- ADL normal
- Normal memory function for age
DTI Acquisition

- Siemens Symphony 1.5T
- 3 acquisitions with offset in slice direction by 0.0mm, 1.7 mm and 3.4 mm, 5mm thick slices
- 0.1mm inter-slice spacing, 30 slices per acquisition
- matrix = 128 mm x 128 mm; FOV = 21.7cm x 21.7cm, in-plane sample spacing was 0.85 mm
- TR=7200, TE=156
- b values: (0, 500, 1000 mm$^2$/s) or (0, 1000 mm$^2$/s)
- 12 non-collinear directions,
- The first three datasets were interleaved and zero-filled in the slice direction to form a fourth dataset with resulting inter-slice distance of 0.85 mm.
- FA and Trace maps derived.
Additional MRI Acquisitions

- 3D T1 volume (MPRAGE) for volumetric analysis
- 3 interleaved FLAIR acquisitions concatenated into a *pseudo* 3D volume for assessment of SH volume
- Voxel dimensions on MPRAGE & *pseudo* FLAIR match DTI.
Describing DTI parameters in NAWM, SH, and in anterior and posterior white matter.

Analyze AVW 5.0, 6.0 (Mayo Clinic)

ROI: 5 x 5 square voxels

Periventricular white matter

Centrum semiovale

ROIs were placed on T2-weighted images (b=0) images and transferred to FA and Trace maps for measurement

Recorded location as NAWM vs. SH; anterior vs. posterior
DTI in SIVD – ROI Placement
Image Analysis

- **Parenchymal volume estimation:**
  - Performed on MPRAGE sequences
  - Voxel estimation tool in Analyze following skull stripping.

- **SH volume:**
  - Performed on pseudo-3D FLAIR images
  - SH thresholding following skull stripping with operator correction
  - Sum of all voxels with intensity levels within SH threshold range
Cognitive Tests

- DRS I/P
- SDMT
- TMT A & B
- COWAT (FAS)
## Results – Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>NC (n=8)</th>
<th>SIVD (n=9)</th>
<th>MCI (n=9)</th>
<th>Overall p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age @ scan (yrs)</td>
<td>68.0±14.8</td>
<td>58.6±10.7a</td>
<td>76.7±8.4a</td>
<td>.011</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>12.6±3.4</td>
<td>14.0±3.3</td>
<td>13.7±2.9</td>
<td>ns</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.0±1.6</td>
<td>28.6±1.2</td>
<td>27.3±1.5</td>
<td>ns</td>
</tr>
<tr>
<td>% Female</td>
<td>50.0%</td>
<td>66.7%</td>
<td>55.6%</td>
<td>ns</td>
</tr>
</tbody>
</table>

- SIVD group younger than MCI
- All subsequent group analyses covaried for age @ scan
## Results – Parenchymal & SH volumes

<table>
<thead>
<tr>
<th>Variable</th>
<th>NC (n=8)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Parenchymal (cm³)</td>
<td>1099.9±96.28</td>
<td>1184.2±191.1</td>
<td>1103.7±153.8</td>
<td>ns</td>
</tr>
<tr>
<td>SH/parench</td>
<td>.002±.002ᵃ</td>
<td>.033±.025ᵃᵇ</td>
<td>.009±.009ᵇ</td>
<td>.003</td>
</tr>
</tbody>
</table>

- No significant differences across groups on estimated parenchymal volume.
- SIVD had higher ratio of SH to parenchymal volume than NC or MCI.
No group differences in SH or Trace in regions of SH
Results: NAWM FA & Trace

- SIVD had lower FA vs. NC and higher trace vs. MCI

NAWM FA & Trace
(periventricular & centrum semiovale)

NAWM FA & Trace
(mm²/s x 10⁻³)
Results – NAWM Anterior/Posterior

Estimated Marginal Means of A

Estimated Marginal Means of MEASURE_1
Results – DTI & Cognition

- SH:
  - SDMT with SH/parenchymal ratio ($r = .45, p = .02$)
  - SDMT with FA in SH ($r = -.61, p = .01$)

- NAWM
  - SDMT with NAWM FA ($r = -.42, p < .04$)
  - SDMT with anterior NAWM FA ($r = -.46, p < .02$)
  - SDMT with NAWM Trace ($r = .40, p < .05$)

- No other significant correlations between tests/dTI variables
Conclusions

- Consistent with previous results showing DTI changes in NAWM in SIVD.
- NC and MCI were similar on DTI.
- SIVD may alter the age-related gradient of anterior to posterior DTI changes.
- Processing speed associated with DTI parameters in both NAWM and SH.
- DTI may provide a method for describing differential effect of disorders on white matter and detect associations between NAWM and cognitive function.
Limitations

- Small n
- SIVD group younger than MCI
- SIVD group radiographically characterized.
- Limited range of cognitive deficits
- Correlation analyses exploratory
- ROI analysis not capture DTI differences in other regions
Future Directions

- Additional data collection underway
- Assess differential impact of CADASIL vs. SIVD
- Differential contribution of SH volume vs. DTI in these groups.
- Assess DTI correlation with experimental working memory measures.
Tractography

Superior view color fiber maps

Lateral view color fiber maps

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THANK YOU
Results – DTI & Cognition

- NC
  - SDMT with FA in NAWM FA ($r = -0.760, p < 0.03$)
  - SDMT with FA in ant. NAWM FA ($r = -0.750, p < 0.03$)
Research Focus

Frontal Systems Disruption

↓

Changes in Executive Cognition and Behavior

↓

Functional Disability/Conversion to Dementia
Results: FA & Trace in Genu & Splenium

- No group differences in SH or Trace in regions of SH
Results: FA & Trace in Temporal Lobe White Matter

- **FA**: Lower in SIVD and MCI groups vs. NC bilaterally.
- **Trace**: Higher in SIVD vs. NC on right; and higher in SIVD than both NC and MCI on left.
Image Analysis
Temporal lobe white matter: rectangular ROI (6 x 3) in left & right temporal stem
- 10 consecutive coronal slices starting at the mamillary bodies and proceeding posteriorly.

Corpus callosum: square (3 x 3) ROI in left & right genu and splenium on 5 consecutive slices.

Placed directly on FA or Trace maps

No classification of SH vs. NAWM
Image Analysis

- Analyze AVW 5.0, 6.0 (Mayo Clinic)
- **Periventricular white matter**: 3 ROIs (5 x 5) around each horn, 2 axial slices.
- **Centrum semiovale**: Up to 5 ROIs (5 x 5) in each hemisphere in NAWM and SH, 2 axial slices
- ROIs were placed on b=0 images and transferred to FA and Trace maps for measurement
- FLAIR and MPRAGE used for guidance.
- Recorded location as NAWM vs. SH; anterior vs. posterior
Results – Corpus Callosum

<table>
<thead>
<tr>
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<th>MCI (n=9)</th>
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<tbody>
<tr>
<td><strong>FA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genu</td>
<td>.813±.041</td>
<td>.720±.170</td>
<td>.769±.067</td>
<td>ns</td>
</tr>
<tr>
<td>Splenium</td>
<td>.811±.085</td>
<td>.807±.097</td>
<td>.815±.082</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Trace (mm²/s x 10⁻³)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genu</td>
<td>.730±.043</td>
<td>.893±.259</td>
<td>.935±.517</td>
<td>ns</td>
</tr>
<tr>
<td>Splenium</td>
<td>.675±.046</td>
<td>.747±.053</td>
<td>.692±.076</td>
<td>ns</td>
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</tbody>
</table>

- No group differences in FA or Trace in genu or splenium.
### Results – Temporal Lobe White Matter

<table>
<thead>
<tr>
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<th>MCI (n=9)</th>
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<tbody>
<tr>
<td><strong>FA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLWM – R</td>
<td>.574±.052&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>.502±.053&lt;sup&gt;a&lt;/sup&gt;</td>
<td>.527±.039&lt;sup&gt;b&lt;/sup&gt;</td>
<td>.027</td>
</tr>
<tr>
<td>TLWM – L</td>
<td>.551±.056&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>.445±.051&lt;sup&gt;c&lt;/sup&gt;</td>
<td>.487±.039&lt;sup&gt;d&lt;/sup&gt;</td>
<td>.001</td>
</tr>
<tr>
<td><strong>Trace</strong> (mm²/s x 10⁻³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLWM – R</td>
<td>.768±.061&lt;sup&gt;e&lt;/sup&gt;</td>
<td>.855±.062&lt;sup&gt;e&lt;/sup&gt;</td>
<td>.796±.050</td>
<td>.034</td>
</tr>
<tr>
<td>TLWM – L</td>
<td>.785±.070&lt;sup&gt;f&lt;/sup&gt;</td>
<td>.920±.076&lt;sup&gt;f,g&lt;/sup&gt;</td>
<td>.823±.070&lt;sup&gt;g&lt;/sup&gt;</td>
<td>.001</td>
</tr>
</tbody>
</table>

- **FA:** Lower in SIVD and MCI groups vs. NC bilaterally.
- **Trace:** Higher in SIVD vs. NC on right; and higher in SIVD than both NC and MCI on left.
Results: Attention/Executive

- SIVD intermediate on all measures except DRS I/P
- TMT-A: NC better than SIVD and MCI; MCI and SIVD not different.
- TMT-B: NC better than MCI; no other pair-wise differences
Results: Memory

- SIVD intermediate on all measures
- MCI significantly worse than NC on all measures
- MCI significantly worse than SIVD on all measures except HVLT-R Total Learning
### Results – Memory

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n=8)</th>
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<th>MCI (n=9)</th>
<th>Overall p</th>
</tr>
</thead>
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<tr>
<td><strong>HVLTR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24.88±4.64(^a)</td>
<td>24.63±3.25</td>
<td>14.44±4.50(^a)</td>
<td>.003</td>
</tr>
<tr>
<td>Delay</td>
<td>9.50±2.07(^b)</td>
<td>7.50±3.12(^b)</td>
<td>2.33±2.18(^b)</td>
<td>.031</td>
</tr>
<tr>
<td>% retn</td>
<td>97.38±17.82</td>
<td>74.13±24.36</td>
<td>34.44±30.54</td>
<td>ns</td>
</tr>
<tr>
<td>Discrn</td>
<td>10.38±1.69</td>
<td>9.88±2.64</td>
<td>6.22±2.19</td>
<td>ns</td>
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<tr>
<td>DRS-Mem</td>
<td>24.00±1.31</td>
<td>23.50±1.31</td>
<td>21.89±2.80</td>
<td>ns</td>
</tr>
</tbody>
</table>

- **HVLTR Total Learning**: MCI lower than NC or SIVD
- **HVLTR Delayed Recall**: Significant differences between all pairs
Results: Overall FA & Trace

Overall FA & Trace (all ROIs)

Overall FA  Overall Trace

NC  SIVD  MCI

*  *  *

(mm2/s x 10^-3)