Diffusion-Tensor Imaging: Frontal Executive Function in Vascular Cognitive Impairment

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Goal

To develop diffusion-tensor imaging as an imaging biomarker of white matter integrity in aging and dementia
Research Focus

Frontal Systems Disruption
↓
Changes in Executive Cognition and Behavior
↓
Functional Disability/Conversion to Dementia
Frontal Systems: Subcortical-thalamic connections

- The prefrontal cortex is connected to the striatum and thalamus in parallel but separate circuits that help regulate behavior.
- Topographic mapping of caudate and thalamus.
- Subcortical white matter connections:
  - Long tracts
  - Cortical U-fibers
- Injury anywhere in a circuit can produce a major deficit and small subcortical lesions can mimic large cortical lesions.
Frontal Systems Function

- Processing speed
- Mental flexibility
- Planning
- Sequencing
- Decision-making
- Working memory
- Behavioral regulation, self-monitoring
- Motivation, drive, interest
White Matter Changes in Aging

- Volume loss
  - Greater than grey matter loss
  - Greater in frontal lobes
- Loss of myelin
- Wallerian degeneration
- Subcortical ischemic vascular changes
- Selective vulnerability of frontal regions
- Increased interstitial fluid

Subcortical Hyperintensities

Vascular Cognitive Impairment

- Cognitive impairment due to cerebrovascular disease
- **Subcortical Ischemic Vascular Disease (SIVD)**
  - Most common form
  - Increases with age & cardiovascular risk factors
- **Features of SIVD:**
  - Impaired executive function/mental flexibility
  - Cognitive slowing
  - Apathy & depression
Diffusion-Tensor Imaging

- MRI technique that provides *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.
  - Detects changes in normal-appearing white matter (NAWM) that correlate w/cognition
DTI Basics

DTI Basics

- Measures water diffusion in at least 6 directions – we use 12 for better resolution
- 1.5T magnet or greater capable of diffusion encoding
- Echo-planar imaging (fast acquisition)
- Collecting small voxels, scanning takes about 14 minutes
- Off-line post-processing (Laidlaw lab)
- Image analysis: Butler Hospital Quantitative Imaging Lab
DTI – Tractography

Bammer, 2003
DTI Scalar Parameters

- **Trace**: Magnitude of diffusion in a voxel.
  - Increases in damaged white matter

- **Fractional Anisotropy (FA)**: Measure of directionally-restricted diffusion.
  - Decreases in damaged white matter

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)
  - Those DTI changes more strongly correlated w/executive function than DTI in SH. (O’Sullivan 2004)
AIMS

- To determine the integrity of anterior vs. posterior normal appearing white matter (NAWM) in VCI vs. controls using DTI.
  - H: VCI will show poorer anterior & posterior NAWM integrity than controls on DTI
- To determine the association between anterior DTI parameters in NAWM and executive function and processing speed.
  - H: DTI parameters in anterior NAWM will correlate with executive functioning and processing speed
Subjects

- 6 VCI (scanned 9)
  - SIVD (sporadic or genetic forms [CADASIL])
  - Impaired executive function &/or memory
  - MMSE > 24
  - No cortical strokes
  - No dementia
- 6 Normal elderly controls (NEC) (scanned 10)
Method

- **Structural MRI, DTI**
  - Primary imaging outcomes:
    - DTI: FA & Trace
    - Structural: parenchymal & SH volumes

- **Cognitive battery**
  - Executive function
    - DRS I/P, TMT-B, COWA
  - Processing Speed
    - TMT-A, Symbol-digit

- **Analysis:** ANOVA, chi-square, correlation
## Results

<table>
<thead>
<tr>
<th></th>
<th>NEC (n=6)</th>
<th>VCI (n=6)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>64.83 ± 7.89</td>
<td>62.13 ± 11.40</td>
<td>ns</td>
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<tr>
<td>Education (yrs)</td>
<td>15.17 ± 4.12</td>
<td>14.00 ± 4.00</td>
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<tr>
<td># Female</td>
<td>2</td>
<td>4</td>
<td>ns</td>
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<tr>
<td>MMSE</td>
<td>28.83 ± 1.62</td>
<td>28.17 ± 1.33</td>
<td>ns</td>
</tr>
</tbody>
</table>

Correia S (2005) *33rd INS meeting*; St. Louis, MO
Laidlaw, L (2004) *12th ISMRM meeting*; Kyoto, Japan
DTI Analysis – ROI Placement
Imaging Results

- VCI group had higher estimated SH volume ($p = .040$)

- Estimated parenchymal volume not different across groups ($p = .378$)

- DTI: No significant differences in FA or Trace in SH
Anterior-Posterior Trace in NAWM

Trace units: $x \times 10^{-3}$ mm$^2$/s

$p = .033$  $p = .033$
DTI – FA

Anterior-Posterior FA in NAWM

\[ p = \text{ns} \quad \text{and} \quad p < 0.001 \]
Processing Speed

Sym-Dig

$p = \text{ns}$

TMT-A

$p = .052$
Executive Measures

**COWA**

\[ p = \text{ns} \]

**DRS I/P**

\[ p = \text{ns} \]
Executive Measures

$p = .003$
Correlations

- **DTI in NAWM:**
  - TMT A & B:
    - Inversely correlated with anterior & posterior FA
    - Positively correlated with anterior & posterior Trace
    - all $p < .05$

- **DTI in SH:**
  - TMT A & B not correlated with FA or Trace ($p > 0.5$)

- **SH Volume:**
  - TMT A & B correlate inversely with SH volume ($r = -0.70, p < .05$)
Conclusions

- Patients with VCI perform more poorly than NEC on tests of processing speed and executive functioning.
- VCI alters anterior and posterior NAWM.
- Processing speed and executive functioning correlate with DTI parameters in NAWM but not in SH.
- DTI in NAWM may predict executive/processing speed better than SH volume.
Future Directions

- Successful R03 to study further
- Continue data collection and analysis
- Compare with amnestic MCI & AD
- Progression of white matter changes as imaging biomarker in clinical trials
- DTI in cerebrovascular risk factors (HTN, DM)
- Tractography
Fiber Clustering

Courtesy of Song Zhang
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Threshold to Dementia

Cognitive Continuum

Normal

Mild Cognitive Impairment

Dementia

Functional Continuum

Adapted from Petersen
MCI not a unitary construct

MILD COGNITIVE IMPAIRMENT

MCI → DEMENTIA

- Alzheimer’s disease
- Vascular dementia
- Frontotemporal dementia
- Lewy body dementia
- Primary progressive aphasia
- Depression

Petersen, 2003
Why study frontal systems in VCI?

- Independent probes of frontal systems:
  - Tests of executive function & processing speed
  - DTI

- The combination may help identify patients at greatest risk for dementia
Image Analysis

Skull stripping and parenchymal volume estimation
Image Analysis

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

- **Exploratory regression**
  - IV: SH volume, anterior & posterior FA, Trace
  - DV: TMT A & B

- **Results**
  - Posterior FA significantly predicted TMT A & B; SH volume, anterior FA did not.
  - Trace: overall model significant only.
DTI Results

Anterior-Posterior Trace in NAWM

- Between subjects effect: $p = .032$
- Within subjects effect: $p = .025$
- Interaction effect: $p = .057$

Trace units: $10^{-3} \text{ mm}^2/\text{s}$
DTI Results

Between subjects effect: $p = .012$
Within subjects effect: $p = .058$
Interaction effect: $p < .001$
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 mm²/s) or (0, 1000 mm²/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.