Diffusion Tensor Imaging in Dementia

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Overview

• Examples of DTI findings in Alzheimer’s disease
  – And other dementias
• Explore potential unique utility of DTI in assessment of dementia
  – Examples
    • MCI
    • Cerebrovascular disease
    • Frontotemporal dementia
Dementia causes cortical damage, and functional decline in a specific network of cortical regions dedicated to memory.

Network effects in Alzheimer’s disease

Traditional approaches to characterizing network problems in AD:

- FDG-PET
- SPECT Perfusion
- Whole brain volumetrics
  - Brain volume
  - Ventricular volume
- Regional volumetrics
  - Hippocampus
  - Entorhinal cortex
  - Parietal cortex
  - Cingulate cortex
  - Frontal cortex

from: Buckner et al, J Nsci, 2007
Dementia causes cortical damage, and functional decline in a specific network of cortical regions dedicated to memory. This network is interconnected by specific white matter tracts.

from: Buckner et al, J Nsci, 2007

modified from: Papez, Arch Neurol Psychiatry 1937c
DTI in cingulum is abnormal in Alzheimer’s and MCI
Predictive of diagnosis beyond gray matter alone

<table>
<thead>
<tr>
<th>Classification</th>
<th>Factors</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>p Value*</th>
<th>AUC</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI vs CN</td>
<td>Total HV</td>
<td>55 ± 8</td>
<td>70 ± 5</td>
<td>63 ± 3</td>
<td>0.1</td>
<td>0.67 ± 0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>TotalHV+LeftPC-FA</td>
<td>69 ± 3</td>
<td>78 ± 2</td>
<td>74 ± 2</td>
<td>0.02</td>
<td>0.78 ± 0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AD vs CN</td>
<td>Total HV</td>
<td>75 ± 3</td>
<td>81 ± 3</td>
<td>78 ± 1</td>
<td>0.007</td>
<td>0.85 ± 0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>TotalHV+LeftPC-FA</td>
<td>88 ± 1</td>
<td>94 ± 2</td>
<td>91 ± 1</td>
<td>&lt;0.001</td>
<td>0.98 ± 0.002</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Zhang et al, Neurology, 2007
Cingulum MD is correlated with severity of cognitive impairment

Nakata et al, Mag Res Imaging, 2009
Diffusivity measures may be more sensitive than FA in dementia

Acosta-Cabronero et al, Brain, 2010
DTI has been used in a variety of diseases that cause dementia

- Alzheimer’s disease/MCI
- Lewy body disease
- Vascular dementia
- Parkinson’s disease
- Frontotemporal dementia
- Huntington’s disease
- Creutzfeldt-Jakob disease
- HIV
- Normal pressure hydrocephalus
MD in striatum is increased in Huntington’s disease gene carriers and associated with likelihood of impending symptoms

Magnotta et al, Brain Imag Beh, 2011
**FA is reduced in Parkinson’s dementia/DLB**

FA is correlated with MMSE:

Hattori et al, Human Brain Mapp, 2011
So, from a general review of DTI in dementia, what would one conclude?

• White matter abnormalities detectable
  – Often in a pattern consistent with proposed network of degeneration
  – Often persists after accounting for gray matter changes
  – Sometimes correlated with gray matter changes
  – Often correlate with measures of clinical severity
  – Diffusivity may be more sensitive than FA

• DTI may also detect changes in predominantly gray matter structures

• What is the utility of these findings?
  – We’re just beginning, but some clues to potential uses are emerging
Prognosis: Regional DTI predicts conversion from MCI to AD (2 yr follow-up study)
Increased sensitivity to pathology: White matter lesions associated with abnormalities in DTI (FA, D) in adjacent and distant regions
# Frontotemporal dementia (FTD): A behavioral syndrome

<table>
<thead>
<tr>
<th>Frontotemporal dementia</th>
<th>Alzheimer’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioral problems</strong></td>
<td></td>
</tr>
<tr>
<td>Disinhibition</td>
<td>Apathy</td>
</tr>
<tr>
<td>Apathy</td>
<td>Irritability/agitation</td>
</tr>
<tr>
<td>Emotional blunting</td>
<td>Depression</td>
</tr>
<tr>
<td>‘Euphoria’</td>
<td></td>
</tr>
<tr>
<td>Obsessions and compulsions</td>
<td></td>
</tr>
<tr>
<td>Mental rigidity</td>
<td>Memory loss</td>
</tr>
<tr>
<td>Depression</td>
<td>Visual-spatial impairment</td>
</tr>
<tr>
<td><strong>Cognitive deficits</strong></td>
<td>Poor planning</td>
</tr>
<tr>
<td>Poor planning</td>
<td></td>
</tr>
</tbody>
</table>
Regions of gray matter atrophy in FTD and AD

FTD vs. Controls

AD vs. Controls

p<0.05, corrected for multiple comparisons
Functional imaging/nuclear medicine techniques

SPECT Perfusion, Varrone, 2002

FDG-PET, Foster, 2003

Structural MRI

VBM FTD

rsFMRI, Zhou, 2010
DTI abnormalities are significant in FTD, are predominantly frontal and are *worse* than in AD

Zhang et al, Brain, 2009
Variants of FTD

Frontal variant: typical behavioral syndrome

Temporal variant: Semantic dementia

Left frontal opercular variant: Progressive nonfluent aphasia
DTI abnormalities in FTD variants associate with regional GM abnormalities

Zhang et al, in preparation
WM abnormalities are at least as good as gray matter loss in differentiating FTLD from controls.

Strong effects for diffusivity.
Dependent Variable: TASIT - EET

<table>
<thead>
<tr>
<th>Model Predictors</th>
<th>Beta</th>
<th>t</th>
<th>Sig.</th>
<th>Adj R Squ</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>0.64</td>
<td>1.35</td>
<td>0.19</td>
<td>0.35</td>
<td>0.000</td>
</tr>
<tr>
<td>R UNC-OF GM</td>
<td>-0.51</td>
<td>-1.08</td>
<td>0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R ANT TEMP GM</td>
<td>0.50</td>
<td>2.62</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Unc FA</td>
<td></td>
<td></td>
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</tbody>
</table>

Emotion processing in FTD is correlated with FA in the Uncinate Fasciculus

Independent of OFC and Anterior temporal gray matter volumes

Tartaglia et al, Submitted
FA in Uncinate fasciculus is reduced in asymptomatic carriers of FTLD mutation

No significant gray matter changes

FIG. 1. Pedigree of the studied family. Solid symbol indicated examined affected subjects, and likely affected patients on the basis of interview with the relatives. To protect confidentiality, gender of individuals is disguised. Proband marked with an arrow. *Directly examined individuals (n = 18); Progranulin (PGRN) mutation carriers but healthy (n = 7); ϕ - likely PGRN mutation carrier (III:1); ⊗ affected by hearsay (IV:17). Open diamond: still alive subjects; diamond with a line through: dead subjects.

Borroni et al, Rejuvenation research, 2008
Possible unique role for DTI

• Increased sensitivity to pathology (e.g. vascular changes)
  – Possible sensitivity to dual pathology (effects of vascular beyond neurodegeneration)

• Better characterization of some non-AD dementias, like FTD, where DTI is particularly abnormal

• Prognosis
  – In MCI
  – In mutation carriers (FTLD, HD, also AD)

• Longitudinal assessment
  – AD, non-AD
Major efforts are ongoing to incorporate DTI into the study of degenerative disease

- Alzheimer’s Disease Neuroimaging Initiative (ADNI)
- Frontotemporal Lobar Degeneration Neuroimaging Initiative (FTLDNI)
- Both longitudinal studies
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DTI may increase sensitivity to effects of dual pathology