Multimodal MRI markers of nigrostriatal pathology in Parkinson's disease

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Parkinson’s disease

First described in 1817 by James Parkinson as “Shaking Palsy.”

Cardinal Signs

- Resting tremor
- Bradykinesia-slowness
- Rigidity-stiffness
- Postural/Gait disorder
New definition of Parkinson’s disease and concepts of its progression (Lang 2007)

- Normal aging related cell loss
- DA cell loss at SNpc
- Non-DA cell loss
- Threshold for symptom
- Plateau of DA loss at SNpc
- Diagnosis

Time (years)

Remaining Neurons (%)

Modified from Lang 2007, The progression of Parkinson disease: a hypothesis
Basic Pathology of PD

*Nigrostriatal changes

Modified from Dauer & Przedborski, Neuron, 2003
Histopathological changes in Substantia nigra of PD brain

- Dopaminergic neuronal cell loss
- Presence of Lewy bodies or Lewy neurites
- Greater fibrillary astrocytosis.
- Inflammatory cell infiltration.
- Extraneuronal neuromelanin.

- Iron overload
  - First described in the 1988 (Reiderer et al.)
  - In most severe, but not milder, cases
Beauty of MRI in biomarker research:

- We can dissect brain in living person without using a scalpel
- We can capture spatial changes in nigrostriatal system in PD!
- We can detect cellular, chemical infrastructure changes in PD!
- We can delineate the temporal changes associated with PD progression!
Diffuse Tensor Imaging (DTI)

- Measure the diffusivity of water molecules.
- More limited in the direction of diffusion
  - high Fractional Anisotropy (FA) value
- Traditionally used to study white matter
  - Basser 1996;
- Recently also used to study gray matter
  - Mori and Zhang 2006
In a MTPT-treated murine model, DTI measures were significantly correlated with the number of SN DA neurons lost.

- Bosca 2007

In humans, decreased FA measures in the SN of PD patients have been reported.

## Pilot study

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>PD total</th>
<th>PDES &lt; 1 yr</th>
<th>PDMS 1-5 yrs</th>
<th>PDLS &gt; 5yr</th>
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</thead>
<tbody>
<tr>
<td><strong>Sex-M/F</strong></td>
<td></td>
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</tr>
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<td>13/15</td>
<td>23/17</td>
<td>7/8</td>
<td>8/6</td>
<td>8/3</td>
<td></td>
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<tr>
<td><strong>Age-yr</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>60 (7)</td>
<td>61 (8)</td>
<td>60 (10)</td>
<td>59 (6)</td>
<td>63 (8)</td>
<td></td>
</tr>
<tr>
<td><strong>HY-I/II/III</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NA</td>
<td>13/22/4</td>
<td>8/5/1</td>
<td>4/9/1</td>
<td>1/8/2</td>
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<tr>
<td><strong>Duration-yr</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NA</td>
<td>4.2 (4.7)</td>
<td>0.5 (0.5)</td>
<td>3.3 (1.1)</td>
<td>10.4 (4.3)</td>
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</tr>
<tr>
<td><strong>LEDD-mg/d</strong></td>
<td></td>
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</tr>
<tr>
<td>NA</td>
<td>528(400)</td>
<td>277(224)</td>
<td>456(199)</td>
<td>960(444)</td>
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<tr>
<td><strong>UPDRS III</strong></td>
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<tr>
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<td>23(15)</td>
<td>17(9)</td>
<td>22(11)</td>
<td>35(20)</td>
<td></td>
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</table>

Du et al, 2012
FA changes in SN follow the spatial and temporal pattern of cell loss in the SN

Du et al. 2012
Lack of clinical correlation of FA data

Du et al, 2012
What might be responsible for the DTI changes in SN of PD brain?

- Dopaminergic neuronal cell loss
- Presence of Lewy body, or Lewy Neurites
- Greater fibrillary astrocytosis.
- Inflammatory cell infiltration.
- Extraneuronal neuromelanin.
- Iron accumulation

- All possible except iron
  - but need pathological correlation of MRI data
The transverse relaxation rate ($R_2^*$) to measure SN changes in PD

- $R_2^*$ was correlated with Fe content \textit{in vivo}.
  - Graham et al., 2000; Martin, 2008; Langkammer 2010

- $R_2^*$ measures have been shown to be increased in the SN of PD patients

- Some reports that SN $R_2^*$ correlated selectively with certain aspects of clinical measurements
  - Martin 2008, Peran 2010
R2* may provide a valid Fe marker in the SN for PD progression

Du et al, 2012
Clinical correlations

Du et al, 2012
Aim 1: Establish the differential roles of FA and R2* in PD detection and progression

Hypothesis: FA and R2* measures reflect different aspects of nigrostriatal pathology that can be used as biomarkers for diagnosing PD and following its progression
- FA (DTI) may mark the PD-related pathological changes in the SN
- R2* may provide a valid Fe marker in the SN for PD progression

Approach
- 87 PD
  - 27 PD subjects < 1 yr,
  - 20 PD subjects with 1-5 yrs,
  - 20 PD subjects with 5-10 yrs,
  - 20 PD subjects > 10 yrs
- 58 Controls
- Brain MRI at baseline, 18 m, and 36 m
- Clinical measurement at every 6 m
Can combine FA and $R_2^*$ differentiate PD from PDism?

<table>
<thead>
<tr>
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<th>Controls</th>
<th>PD</th>
<th>PSP</th>
<th>MSA</th>
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<td>16</td>
<td>16</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Age</td>
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<td>59 (9)</td>
<td>78 (13)</td>
<td>75 (7)</td>
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<tr>
<td>Sex (F/M)</td>
<td>7/9</td>
<td>8/8</td>
<td>0/7</td>
<td>2/6</td>
</tr>
</tbody>
</table>

Huang’s group unpublished data
There is different pattern of FA and R2* in nigrostriatal structures in PDism

Huang’s group unpublished data
Combined FA and R2* enhance discrimination

Huang’s group unpublished data
Aim 2: Demonstrate that nigrostriatal DTI & R2* differentiate PD from PDism

- **Hypothesis:** Combined DTI and R2* measurement may capture these differential patterns of nigrostriatal injury and provide discrimination between PD and PDism.

- **Approach**
  - 20 PSP
  - 20 MSA
  - Brain MRI, clinical assessment will be obtained at baseline
  - Sensitivity and specificity of individual and combined MRI measures in diagnosing PD will be estimated.
Aim 3. Interrogate Fe-related proteins in body fluids as biomarkers of PD

► **Hypothesis**: Fe-related proteins will have a unique profile in PD that can be used as a biomarker to inform about disease onset and its progression.

► **Approach**
  - Obtain body fluid from all willing subjects
    - Blood
    - Urine
    - CSF
  - Obtain Fe-related proteins such as hepcidin, ferritin and transferrin in the above body fluid
  - Interrogate their relationships to clinical and MRI measures (in Aims 1 and 2).
Aim 4. Obtain MRI and postmortem pathological correlation data

► Obtain postmortem brain

► Perform postmortem diagnoses
  • α-synuclein, amyloid (Aβ), tau, ubiquitin

► Obtain following tests in nigrostriatal structures and correlate these levels with MRI measures.
  • Tyrosine hydroxylase positive neurons-(DA neuronal markers)
  • Myelin and glial derived growth factors (glial cell markers)
  • Fe staining, ferritin, hepcidin (iron markers)
Acknowledgements

- My patients and their families
- Many volunteers and their families
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  - NIA (K23, 2003-2008); NINDS (R01, 2009-2014), NIEHS (R01, 2011-2015)
- Pennsylvania Tobacco Settlement Fund
- Personal gifts from many donors to our program.
- .. and of course
Higher cholesterol associated with lower iron (R2* values) in SN

R=-0.429, p=0.011

R=-0.305, p=0.080

Du et al. PlosOne 2012