Increased functional connectivity of the thalamus in patients with Parkinson’s disease

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Parkinson’s disease

• ~200 years since James Parkinson wrote essay on ‘the shaking palsy'
• 2nd most common neurodegenerative disorder
  – ~3% people > 65 (~110,000 in Australia)
• Now recognized as more than a motor disorder
  – Neuropsychiatric: executive, memory, mood, autonomic, sleep-wake and sensory dysfunction.
  – Motor: akinesia, tremor, posture and gait disturbances
Parkinson’s disease

• Pathology:
  – Misfolding $\alpha$-synuclein, causing aggregation, becoming neurotoxic – ‘Lewy body pathology’
  – Begins in brainstem neurons and olfactory system
  – Progresses along neuraxis (dark to light)
  – Crucial in PD: SNPC cell death
  – At diagnosis ~ 60% SNPC cells lost
  – 80% dopaminergic depletion striatum
Thalamus: function and connectivity

• Traditionally – just a relay station, now know it plays more complex modulatory role

• Thalamus implicated in PD:
  – 1. Pathological accumulation of $\alpha$-synuclein and neuronal loss in thalamus in PD [Halliday 2009]
  – 2. Circuit dysfunction cortico-basal ganglia-thalamo-cortical circuits (thalamo-cortical circuits)
Word on thalamo-cortical circuits

- 5 circuits – named according to function or site of origin in cortex [Alexander et al. 1986]
- Dysfunction associated with variety neuropsychiatric symptoms
- Our research looks for neuroimaging biomarkers of PD within these circuits
Neuroimaging Biomarkers: General approach

• Why do we want neuroimaging biomarkers
  – Scientist:
    • Help understand pathophysiology
    • Serve as proxy measure of treatment outcomes in clinical trials
  – Clinician:
    • Understand possible risk factors
    • Establish and communicate prognosis
Investigating neuroimaging biomarkers: Graph theoretic models

- Nodes/hub (nuclei)
  Investigate morphology with T1 structural MRI

- Edge (white matter)
  Investigate functional connectivity with functional MRI
Methods: Neuroimaging analysis

• Nodes (structural MRI):
  – Quantify size and shape of thalamus

• Edges (functional MRI):
  – Resting-state fMRI scan
  – Look at activity of the brain at ‘rest’
  – Measure signal changes over time
  – Infer functional connectivity (FC) of thalamic subdivisions with rest of brain
  – Seed-based rs-fMRI method
Note on rs-fMRI functional connectivity

– Does not directly study connections in brain
  • However there is a strong correspondence between functional connectivity and structural connectivity [Smith et al. 2009]

– FC is a statistical approach to investigate correlation between activity between brain regions

– Covariance of signals indicate regions that may be anatomically and functionally related
Methods: rs-fMRI functional connectivity

• Our contribution: a number of groups have studied the thalamus as one large structure

• Thalamus made up of number of smaller nuclei involved with different functional properties
  – We therefore subdivided the thalamus to look at FC of nuclei connected to motor and cognitive brain regions
  1. Motor thalamus: ventral lateral anterior/posterior and ventral anterior thalamic nuclei – connect with motor cortices
  2. Prefrontal thalamus: mediodorsal & anterior thalamic nuclei – connect with prefrontal cortex
Functional connectivity in PD: motor thalamus

Increased FC with: Supplementary motor area (SMA); paracingulate gyrus (PCG)
Functional connectivity in PD: prefrontal thalamus

Increased FC with: Dorsolateral prefrontal (DLPFC); caudate nuclei (CN); putamen (Put); globus pallidus (GP); anterior prefrontal cortex (APFC); anterior and paracingulate cortices (ACC & PCG)
Results: Thalamus volumes not significantly different in PD

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 20)</th>
<th>PD (n = 32)</th>
<th>Mean difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right thalamus volumes</strong></td>
<td>5774.13</td>
<td>5927.45</td>
<td>-153.32</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Left thalamus volumes</strong></td>
<td>5594.47</td>
<td>5749.24</td>
<td>-154.78</td>
<td>0.18</td>
</tr>
</tbody>
</table>
Results: Thalamus shape changes - PD vs Controls

- Small increases in surface area in PD compared to controls
- Results did not survive strict false-discovery rate correction
Discussion

• General results: PD associated with
  – Prefrontal thalamus: increased FC with DLPFC, anterior prefrontal cortex, anterior/paracingulate gyri and striatum
  – Motor thalamus: increased FC with SMA
  – No changes to morphology of structure

• Increased FC of thalamic nuclei support data from recent meta-analysis [Ji et al. 2018]
  – We demonstrate novel findings about important subdivisions of the thalamus
Motor circuit

• Increased FC between motor thalamus and SMA
  – Motor Circuit: motor cortices > putamen > GP/SNr > ventrolateral/ventral anterior nuclei thalamus > motor cortices
  – Possible mechanism: tremor related hyper-connectivity of circuit due to increased coupling between VL/VA and motor cortices

• Suggested as explanation for increased FC between subthalamic nucleus and motor cortices in PD [Beaudrexel et al. 2011]
Dorsolateral prefrontal circuit

- Increased FC between prefrontal thalamus and DLPF cortex
- DLPFC Circuit: DLPF cortex $\rightarrow$ dorsal caudate $\rightarrow$ GP/SNr $\rightarrow$ ventral anterior and mediodorsal thalamus $\rightarrow$ DLPF cortex
  - Possible mechanism: functional compensation to restore exec func capabilities
- PD subjects recruit larger brain areas when performing exec func tasks [Caspers et al. 2017]
  - Results suggests thalamus may also increase its role in PD, resulting in increased FC
Anterior cingulate circuit

- Increased FC between prefrontal thalamus and anterior cingulate
- ACC circuit: AC ctx > ventral striatum > ventral anterior thalamic nuclei > AC ctx
- ACC links with DLPFC to mediate exec func processes [Fornito et al. 2004]
  - Further support for increased FC representing compensatory mechanisms to alleviate cognitive dysfunction
Discussion

• **Compensatory functional rewiring:**
  - Recruitment of new neuroanatomical areas to alleviate cognitive dysfunction
  - Due to breakdown in thalamo-cortical circuits in PD, thalamus increases activity (and thus FC) to compensate
  - Probably requires dopaminergic medication
    • Patients in study were on medication
  - Reductions of FC to posterior putamen (loss of dopamine) coincide with increase of FC in anterior putamen – compensation [Helmich 2012]
Discussion

• Thalamic morphology:
  – No differences in volume or shape (trend towards increased volumes and surface inflation in PD)

• Result conflicts with our hypothesis
  – We predicted size and shape of thalamus would be reduced in PD
    • Thalamus demonstrates Lewy pathology and cell death
    • Other subcortical nuclei (caudate + putamen) atrophy in PD [Owens-Walton 2018]
  – Thalamus may thus be not vulnerable to structural damage in PD
Discussion: Implications

Why does this matter?

• Learn more about activity of thalamus in PD
  – DBS surgery restores functioning to thalamo-cortical circuits

• Learn more about role of certain nuclei of thalamus
  – Selective vulnerability of some nuclei to pathophysiology of PD
  – Uncover unique contribution of nuclei to PD symptoms
Limitations and future directions

• Key limitation: Reproducibility of neuroimaging work in PD difficult
  – Heterogeneity of clinical cohort (akinetic/rigid vs tremor dominant cohorts)

• Future research:
  – Cohorts with untreated PD patients – investigate functional connectivity between PD on medication and off
  – FC indirect measure: Combine with other imaging modalities (DTI) to better understand thalamo-cortical circuitry
Conclusion

• **Morphology**
  – PD pathology does not have significant impacts on the morphology of thalamic structure

• **Functional connectivity**
  – Motor circuit – tremor related increase in FC
  – DLPFC and ACC circuits functional compensation in response to disease
Collaborators

- David Jakabek - UWoll
- Brian Power - UNDA
- Mark Walterfang - UniMelb
- Dennis Velakoulis - UniMelb
- Danielle van Westen - Lund
- Marnie Shaw - ANU
- Oskar Hansson - Lund
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References