The neurobiology of visual hallucinations

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Associate Professor in Cognitive Neuroscience
What is the problem?

- Misperception
  - Failure to successfully integrate stimuli that have been physically presented

- Hallucination
  - Perception in the absence of any stimulus

- A hallucination is a fact, not an error; what is erroneous is a judgment based upon it.

*Bertrand Russell*
Psychosis & Hallucinations in PD

• Common
  – 70% after 10 years

• Pattern
  – Initially: Visual
  – Advanced: Tactile and Auditory
Psychosis & Hallucinations in PD

- **Phenotype**
  - Akinetic-Rigid > Tremor dominant
  - Executive dysfunction (attentional control)
  - Dementia (memory)

- **Risk factors**
  - Disease duration
  - Dopaminergic therapy
  - Concomitant illness/new medication
  - REM Sleep Behaviour Disorder
Spectrum of psychosis

- Vivid dreams/Nightmares
- Daytime illusions/misperceptions
- Benign hallucinosis
- Florid psychosis
Management of psychosis in PD

• If ‘unexpected’
  – Metabolic/Septic screen
  – Recently introduced medication

• Acute management (danger/distress)
  – Diazepam (p.o./i.v. 2-5mg, i.m. 10mg doses)

• If ‘expected’
  – ‘Last in, first out’
  – Simplify medications withdrawing agents sequentially
  – MAO-I (e.g. Selegiline)
  – Dopamine agonist (e.g. Cabergoline, Pramipexole)
  – COMT-I (e.g. Entacapone/Stalevo)
Pervasive psychosis

- Anti-psychotics may worsen motor symptoms
- AVOID traditional anti-psychotics
  - Haloperidol/Chlorpromazine
- Atypical antipsychotics
- Cholinesterase inhibitors
- Pimavanserin
Clozapine

- Double blind RCT
  - 60 patients over 4 weeks
- Clozapine 6.25-50mg (Mean 24.7mg)
- Improved
  - Clinical Global Impression Scale
  - Brief Psychiatric Rating Scale
  - Scale for the Assessment of Positive Symptoms
- Tremor improved and other symptoms stable

Clozapine

• 4 RCTs showing benefit of Clozapine
  – 2 v Placebo & 2 v Quetiapine
• Open label extensions
  – Limited duration
• Common side effects
  – Dizziness/Drooling/Sedation
• Agranulocytosis
  – 0.38%
  – Special monitoring

Seppi et al Mov Disord 2011
Other Atypical Antipsychotics

- Olanzapine
  - 3 RCTs v Placebo
    - No benefit
- Quetiapine
  - 4 RCTs v Placebo, 2 v Clozapine
    - Small numbers
    - Mixed patient groups (dementia, ?DLB)
    - Mixed results

Seppi et al Mov Disord 2011
Rivastigmine

• Consider ‘off license’ treatment of hallucinations

• Rivastigmine
  – Reduced psychosis in PDD\(^1\) (secondary outcome)
  – Rivastigmine (initially 1.5mg bd, maintenance 1.5-6mg bd)

Pimavanserin

• Hallucinations associated with stimulation
  – Dopamine and 5-HT2A receptors
  – LSD stimulates 5-HT2A receptors

• Anti-psychotics block
  – Dopamine and 5-HT2A receptors

• Pimavanserin
  – Selective serotonin 5-HT2A inverse agonist
  – No significant affinity or activity at 5-HT\textsubscript{2B} or dopamine receptors
Inverse agonist

- Receptors have “basal activity” level
- Agonist
  - Increases activity by stimulating receptor
- Antagonist
  - Blocks agonist thus reducing activity
  - BUT basal activity continues
- Inverse agonist
  - Blocks agonist AND basal activity
Pimavanserin

- Double blind RCT
  - 4 week
  - Pimavanserin 40mg (n=90) v Placebo (n=95)
- Improved
  - Parkinson's disease-adapted scale for assessment of positive symptoms
- Well tolerated
  - No significant safety concerns
  - No worsening of motor function

Cummings et al Lancet 2014
Neuropathology

• Retinal
  – Loss of dopaminergic cells
• Brainstem
  – Subcoeruleus nucleus (regulator of REM sleep)
• Cortex
  – Medial temporal lobe (amygdala/parahippocampus)
  – Frontal/Parietal
• Neurotransmitters
Models of Hallucinations

Visual Hallucinations in Parkinson’s Disease: Theoretical Models

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• Dream Imagery Intrusion Model
• Reality Monitoring Deficit Model
• Activation, Input & Modulation (AIM)
• Perception & Attention Deficit Model (PAD)
• Bottom-up & Top-down Model
• Attentional Networks Control Model
Bottom-up & Top-down processing

- Event related fMRI in a single hallucinator
- Increased activation in anterior regions
- Relative deactivation in posterior regions
- Misalignment of occipital-frontal circuits

Goetz et al Mov Disord 2014
Bottom-up & Top-down processing

- Aberrant “top-down” processing
- Cingulate gyrus activation
  - Altered attentional and sensorimotor systems
- Limbic lobe activation
  - Altered self-perception and sensory integration
  - Self referential hallucinations
- Primary visual system deactivation
  - Feedback suppression directly or indirectly from frontally mediated circuits

Goetz et al Mov Disord 2014
Visual misperceptions and hallucinations in Parkinson’s disease: dysfunction of attentional control networks?

James M. Shine, MBBS, Sharon L. Naismith, BA Hons, MClinNpsych, DPsych, MAPS, CCN, Glenda M. Halliday, PhD and Simon J.G. Lewis, MBBCh, BSc, MRCP, FRACP, MD*
Ventral Attention Network: VAN

- Dorsal Anterior Cingulate Cortex
- Anterior Insula
- Rapid attention
  - Evaluate ‘stimulus’
  - Quick override for directing attentional resources
Default Mode Network: DMN

- Hippocampal formation
- Posterior Cingulate
- Intraparietal sulcus
- Mind wandering
  - Replays events laid down in long term memory
Dorsal Attention Network: DAN

- Frontal Eye Field
- Superior Parietal Lobule
- Decision making
  - Conflict resolution
Impaired Visual Processing → Ambiguous Percept → Basal Ganglia

DMN

Episodic Memory Recall
“I don’t remember leaving a hose here”

DAN

Correct perception

VAN

Saliency
“That could be a snake”
Impaired visual processing leads to an ambiguous percept. This percept is processed by the DMN, VAN, and DAN. The DMN is associated with episodic memory recall, as indicated by the statement "I don't remember leaving a hose here." The VAN is associated with salience, as indicated by the statement "That could be a snake." The basal ganglia play a role in mediating the communication between these networks.
EPISODIC MEMORY RECALL
“I don’t remember leaving a hose here”

SALIENCE
“That could be a snake”
• Endeavour to trick the brain
• Provoke misperceptions and hallucinations
• Assess visual perception
Bistable Percept Paradigm

- Monostable

- Fail to perceive
  - Bistable percept

- Misperceive
  - Monostable or Bistable percept

- Error score
Paradigm
Results

- 18 Controls
- 45 Patients
- Age and depression matched
- Error score (>1.5 sd Controls)
  - BPP Impaired 23 patients
  - BPP Unimpaired 22 patients
  - Matched age, stage, duration, medication, cognition
## Results

<table>
<thead>
<tr>
<th>Descriptives</th>
<th>BPP impaired</th>
<th>BPP normal</th>
<th>t Value</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Number</td>
<td>23</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>67.3 ± 8.3</td>
<td>60.1 ± 9.1</td>
<td>1.64</td>
<td>0.108</td>
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<tr>
<td>Disease duration, yr</td>
<td>9.0 ± 5.8</td>
<td>5.6 ± 7.8</td>
<td>1.63</td>
<td>0.111</td>
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<tr>
<td>H &amp; Y, stage</td>
<td>2.5 ± 0.9</td>
<td>2.0 ± 0.8</td>
<td>1.96</td>
<td>0.056</td>
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<tr>
<td>UPDRS-III</td>
<td>32.3 ± 16.8</td>
<td>27.1 ± 16.1</td>
<td>1.06</td>
<td>0.296</td>
</tr>
<tr>
<td>Dopa dose equivalent (mg/day)</td>
<td>644.3 ± 354.3</td>
<td>542.0 ± 430.1</td>
<td>0.87</td>
<td>0.391</td>
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<tr>
<td>MMSE</td>
<td>26.7 ± 3.2</td>
<td>27.8 ± 2.9</td>
<td>−1.23</td>
<td>0.225</td>
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<td>MoCA</td>
<td>22.9 ± 5.4</td>
<td>25.0 ± 3.9</td>
<td>−1.52</td>
<td>0.135</td>
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<td>BDI-II</td>
<td>9.6 ± 6.5</td>
<td>11.5 ± 9.7</td>
<td>−0.76</td>
<td>0.450</td>
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</table>

### Outcome measures

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>BPP impaired</th>
<th>BPP normal</th>
<th>t Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hidden (%)</td>
<td>64.5 ± 14.4</td>
<td>76.8 ± 11.7</td>
<td>−6.10</td>
<td>0.000***</td>
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<tr>
<td>Single (%)</td>
<td>68.7 ± 19.7</td>
<td>85.8 ± 12.8</td>
<td>−5.12</td>
<td>0.000***</td>
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<tr>
<td>Misperceptions (%)</td>
<td>23.6 ± 19.2</td>
<td>7.3 ± 6.2</td>
<td>4.87</td>
<td>0.000***</td>
</tr>
<tr>
<td>Missed images (%)</td>
<td>14.3 ± 7.6</td>
<td>10.6 ± 6.5</td>
<td>4.14</td>
<td>0.000***</td>
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</table>

### Predicted impairments

<table>
<thead>
<tr>
<th>Imppairments</th>
<th>BPP impaired</th>
<th>BPP normal</th>
<th>t Value</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>SCOPA-PC₁₋₄</td>
<td>1.8 ± 2.4</td>
<td>0.6 ± 1.2</td>
<td>2.23</td>
<td>0.033*</td>
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<tr>
<td>RBDQ</td>
<td>6.8 ± 3.8</td>
<td>3.6 ± 2.5</td>
<td>3.42</td>
<td>0.002**</td>
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<tr>
<td>TMTₐ₋ₐ</td>
<td>86.8 ± 38.3</td>
<td>36.7 ± 21.5</td>
<td>−3.64</td>
<td>0.002**</td>
</tr>
</tbody>
</table>

- SCOPA-PC₁₋₄
- RBDQ
- Attentional set shifting task (Trail Making Test)
Neuronal Integrity

- Posterior cingulate and temporal cortices
  - Dementia in PD

- Anterior Cingulate Cortex
  - Major hub across Attentional Networks
$^1$H-MRS

- 20 patients
  - 10 BPP Impaired (Hallucinators)
  - 10 BPP Unimpaired (Non-Hallucinators)
- 20 age matched controls
- ACC & PCC
- Behavioural testing
Group differences

• ACC NAA/Cr
  – Controls > PD (t=2.2, p<0.05)
  – Non-Hallucinators > Hallucinators (t=2.2, p<0.05)

• PCC NAA/Cr
  – Controls = PD (t = 0.3, ns)
  – Non-Hallucinators = Hallucinators (t = 0.5, ns)
Neuronal Integrity and VH

$R^2 = 37.2\%$
The role of dysfunctional attentional control networks in visual misperceptions in Parkinson’s disease

Shine, J. M.¹, Halliday, G. M.², Gilat, M.¹, Matar, E.¹, Bolitho, S. J.¹, Carlos, M.¹, Naismith, S. L.¹ and Lewis, S. J. G.¹*

In press

- Brain activity during BPP
  - fMRI
- Brain activity during rest
  - rsfMRI
- Volumetric cortical loss
  - VBM
Methodology

• Patients
  – 13 Unimpaired patients
  – 9 Impaired patients

• Imaging analysis
  – SPM8

• ROI network analysis
  – VAN: AI & dACC
  – DAN: SPL & FEF
  – DMN: Hippocampal Formation & aIPL
Hypoactivation in Hallucinators

\[ p < 0.001 \text{ and clusters } = 10 \]
Attentional Networks
rsfMRI

- Hallucinators vs Non-Hallucinators
- Reduced functional connectivity
  - DAN $\Leftrightarrow$ VAN
  - VAN $\Leftrightarrow$ DMN
Voxel-based morphometry

FDR p < 0.01
Network breakdowns
Evolution of misperception

Unpublished data
Network breakdowns

Unpublished data
Summary

• Hallucinations
  – Common and clinically challenging
• Disseminated pathology
  – Neuronal loss and Neurotransmitters
  – Common mechanisms across diseases?
• Pathophysiology
  – Neural network level
• Greater understanding
  – Improved therapies
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