Neuropathological Changes In Late-life Depression
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Outline

1. Neuropathology of WMH
2. Morphometric studies in late-life depression
   I. Prefrontal
   II. Caudate
3. Conclusion
Neuropathology of WMH in Major Depression
What Causes MRI Hyperintensities?

- PVH
- BGH
- DWMH
Normal Perivascular Spaces

Dilated Perivascular Spaces
Normal Perivascular Spaces

Dilated Perivascular Spaces with ischemia
Normal white matter

Small focus of demyelination
Normal white matter

Small Ischemic Lesion
Frequency of Ischemic and Non-Ischemic DWMH

<table>
<thead>
<tr>
<th></th>
<th>Depressed</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic DWMH</td>
<td>16</td>
<td>8</td>
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<tr>
<td>Non-Ischemic DWMH</td>
<td>0</td>
<td>20</td>
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</table>

Fisher Test: P<0.001

(Thomas et al, Archives of General Psychiatry 2002)
# Frequency of Ischemic and Non-Ischemic PVH

<table>
<thead>
<tr>
<th></th>
<th>Depressed</th>
<th>Control</th>
</tr>
</thead>
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<tr>
<td>Ischemic PVH</td>
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<td>1</td>
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<tr>
<td>Non-Ischemic PVH</td>
<td>4</td>
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</tbody>
</table>

Fisher Test: 0.545  
(Thomas et al, Journal of Affective Disorders 2003)
Frontal-Subcortical Circuitry
Orbitofrontal Cortex
Reduction in pyramidal neuronal density in OFC in late-life depression (Rajkowska et al 2005)

- 15 elderly (mean 75) MDD and 11 age & sex matched controls (mean 72)
- 8 EOD (before 60) and 7 LOD
- Retrospective informant assessments on subjects from Coroner’s office
- Left rostral orbitofrontal cortex (BA 47)
Glia and All Neurones

- 14% (P=0.01) reduction in neuronal density
- But correlated with pH and not significant (0.089) after co-varying
- No alterations in glial density (in any layer)
Non-pyramidal Neurones

- No change in NPNs in any layer

![Graph showing non-pyramidal neurones comparison between control and MDD groups across different layers.](image)
Pyramidal Neurones

- Pyramidal neurones reduced by 30%
- Significant after Bonferroni correction in PNs in layers III and V
Morphometric Analysis of Neurones and Glia in OFC in Late-life Depression (Khundakar, Thomas 2011)

- Caudal OFC
- 11 Control and 13 MDD from NBTR
  - All subjects >60 years (mean 77.0 vs. 76.1 years)
  - All right hemisphere
Mean density of pyramidal neurons in the layers of the orbitofrontal cortex
Mean density of non-pyramidal neurons in the orbitofrontal cortex
Dorsolateral Prefrontal Cortex
Morphometric Analysis of the DLPFC in Late-life Depression
(Khundakar, Thomas 2009 BJPsych)

• DLPFC (BA9 and 46)
• 10 control and 17 MDD from Newcastle Brain Tissue Resource
  – All subjects >60 years (mean 77.0 vs. 76.1 years)
  – All right hemisphere
No significant change in glia, pyramidal or non-pyramidal density in the DLPFC
Non-Pyramidal Neuronal Volume

Layer 3  Layer 5

- No change in Non-pyramidal neuronal volume
Depressed
Control

Pyramidal Neuronal Volume (per um^3)

Layer 3    Layer 5

- Reduced pyramidal neuronal volume by 8% (P=0.02)
- Layer 5 (P=0.01) and trend in layer 3 (P=0.06)
Reductions in Neuronal Density in Elderly Depressed are Region Specific (Van Otterloo et al, 2009)

• 10 elderly (mean 75) MDD vs 10 controls
• All >60 and mean age 75 both groups
• Retrospective informant diagnosis via Coroner’s office
• Left DLPFC (BA 9 only)
No differences in pyramidal or non-pyramidal neuronal or glial density in any cortical layer or overall.
Anterior Cingulate Cortex
Cellular pathology within the Anterior Cingulate Cortex of Patients with Late-Life Depression: a Morphometric Study
(Khundakar, Thomas et al 2011)

- 9 Late-life MDD vs 11 controls
- All >60
- Clinical diagnoses by psychiatrists
- Right supragenual ACC

BA24a
Cell Densities in ACC

Glial Cell

Non-Pyramidal Neuron

Pyramidal Neuron

Cells x1000 per mm³

Control

Depressed
Pyramidal & Non-Pyramidal Neuronal Volume in ACC

Non-pyramidal Neuron

Pyramidal Neuron

Overall

Cells x1000 per mm³

Overall

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Basal Ganglia
(Caudate Nucleus)
Dorsolateral/Ventromedial Caudate Nucleus Circuitry

DLPFC → Dorsolateral Caudate Nucleus → Ventromedial Caudate Nucleus → OFC

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Morphometric Analysis of Neurones and Glia in the Caudate Nucleus in Late-life Depression (Khundakar, Thomas et al 2011)

- Dorsolateral and ventromedial parts of the caudate nucleus
- 9 control and 13 MDD
  - Mean age 75.1 vs. 73.5 years
  - Mean age of MDD onset 62.1 years
  - All right hemisphere
Mean Density of Glial Cells and Neurones in the Caudate Nucleus

### Dorsolateral

- **Glial Cells**: 
  - Control: 60 (±SD) 
  - MDD: 65 (±SD) 

- **Neurones**: 
  - Control: 30 (±SD) 
  - MDD: 25 (±SD)

### Ventromedial

- **Glial Cells**: 
  - Control: 70 (±SD) 
  - MDD: 65 (±SD)

- **Neurones**: 
  - Control: 40 (±SD) 
  - MDD: 35 (±SD)

*p = 0.039*

*p = 0.024*
Mean Neuronal Volume in the Caudate Nucleus

Mean Neuronal Volume (µm$^3$ +SD)

Dorsolateral  |  Ventromedial

Control     |  MDD

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Summary of Findings

**DLPFC:**
\[\downarrow \text{pyram. neuron volume} \leftrightarrow \text{glial cells}\]
(Khundakar 2009)
\[\leftrightarrow \text{non-pyramidal, pyramidal neurons} \leftrightarrow \text{glial cells}\]
(Van Otterloo 2009)

**OFC:**
\[\downarrow \text{pyr neuron density} \leftrightarrow \text{glial cells}\]
(Rajkowska 2005)
\[\leftrightarrow \text{non-pyramidal, pyramidal neurons} \leftrightarrow \text{glial cells}\]
(Khundakar 2011)

**ACC:**
\[\leftrightarrow \text{non-pyramidal, pyramidal neurons} \leftrightarrow \text{glial cells}\]
(Khundakar 2011)

**Caudate nucleus (dorsolateral and ventromedial regions):**
\[\downarrow \text{neuron density} \leftrightarrow \text{glial cells}\]
(Khundakar 2011)
<table>
<thead>
<tr>
<th>Study</th>
<th>MDD/CON</th>
<th>Age</th>
<th>Brain Area</th>
<th>Glial Density</th>
<th>Neuronal Density</th>
<th>Neuronal Size</th>
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<tbody>
<tr>
<td>Ongur 1998</td>
<td>4/5</td>
<td>Mix</td>
<td>ACC</td>
<td>Reduced (age diff)</td>
<td>No difference</td>
<td>No difference</td>
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<tr>
<td>Ongur 1998</td>
<td>9/10</td>
<td>Mid</td>
<td>ACC</td>
<td>20% red All layers</td>
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Causes of Changes?
Degenerative Disease?

• Absence of degenerative pathology in neocortex in MDD (no dementia) (O’Brien, Thomas et al 2001)
• Absence of ATP in brainstem in MDD, cognitively intact (Hendricksen, Thomas et al 2004, Syed et al 2005)
• MRC/CFAS (N=153): No difference in degenerative pathology in dementia-free subjets (Tsopelas, Thomas et al 2011)
Pyramidal Neurone Damage and the ‘Vascular Depression’ Hypothesis

- Ischaemia/hypoxia damage
- White matter hyperintensities
- Periventricular lesions

DLPFC

OFC

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Conclusion

- Neuronal (pyramidal) abnormalities are not clearly present in younger subjects but seem present in late-life depression

- May be present in caudate nucleus and affect both FSC relaying through it

- Changes may reflect vascular disease/WMH
And thanks to...

IAH Research Staff
• Ahmad Khundakar
• Chris Morris
• John O’Brien
• Arthur Oakley

NBTR Staff
• Debbie Lett
• Nicky Barnett
• Carein Todd
• Susan Richardson
• Lauren Walker

Patients and families for donating tissue