Inefficient Memory Networks in Patients with Late Life Depression

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I HAVE NO FINANCIAL RELATIONSHIPS TO DISCLOSE
Epidemiology

- The prevalence of late life Major Depressive Disorder (LLD) in community samples of older adults ranges from 1-5% (Hasin et al., 2005), though clinically significant depressive symptoms are present in approximately 15% of older adults (Blazer, 2003).

- Rates of LLD are higher in medical outpatients (5-10%), medical inpatients (10-15%), hospice and palliative care patients (10-25%), and residents of long term care facilities (14-42%) (see Fiske et al., 2009 for review).
Disability in LLD

- Greater impairment in activities of daily living, including shopping, preparing meals, and getting to places that are at a distance (Kiosses et al., 2004)
- Increased risk of falling (Sheeran et al., 2004)
- Reduced performance on measures of memory and executive functioning (Elderkin-Thompson, et al, 2005)
General Background

• Memory loss and executive dysfunction are common among individuals with late life Major Depressive Disorder (LLD; Mesholam-Gately et al., 2012; Sexton et al., 2012).

• There is evidence of atrophy to prefrontal cortex and hippocampal structures (Lavretsky et al., 2004; Steffens et al., 2000).

• fMRI studies in small samples have demonstrated abnormal activation in cognitive control circuitry (Aizenstein et al., 2006, 2009), though less study has been dedicated to the functioning of fronto-limbic circuitry.
MEMORY AND FRONTO-LIMBIC CIRCUITRY
Memory in Depression and Aging

• Studies of LLD have demonstrated memory deficits in older adults (Elderkin-Thompson et al., 2007; Lamar et al., 2012; O’Brien et al., 2004)

• Memory deficits in LLD patients may reflect reduced hippocampal volume (O’Brien et al., 2004; Steffens et al., 2000) and/or functioning of fronto-limbic circuitry
Neuropsychological Data: Methods

• 53 older adults with LLD (31 female) and 67 never-depressed controls (NDC, 37 female), ages 55-88)
  • Age: LLD: M = 65.9±7.6 NDC: M = 69.6±9.4
  • Education: LLD: M = 16.1±3.1 NDC: M = 16.6±2.2
  • HAM-D: M: LLD = 17.0±6.2 NDC: M = 1.5±2.5
• Completed the California Verbal Learning Test-2
Neuropsychological Data: Results

Dx: F(1, 104) = 4.8, p = .03
^p < .05

California Verbal Learning Test-2

Number Correct

Trial

T1 T2 T3 T4 T5 SDFR SDCR LDFR LDCR Recog

LLD HC

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### fMRI Data: Methods

<table>
<thead>
<tr>
<th>Variables</th>
<th>LLD ($n = 24$)</th>
<th>NDC ($n = 23$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.8 (8.2)</td>
<td>67.9 (8.1)</td>
</tr>
<tr>
<td>Education</td>
<td>15.9 (2.7)</td>
<td>16.7 (2.1)</td>
</tr>
<tr>
<td>Sex (female $n$)</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale$^1$</td>
<td>15.71 (5.2)</td>
<td>.96 (1.0)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>024 (0.49)</td>
<td>0.1 (0.34)</td>
</tr>
<tr>
<td>Years of illness$^2$ (MDD only)</td>
<td>39.8 (16.8)</td>
<td>NA</td>
</tr>
<tr>
<td>On psychotropic medication$^3$ (%)</td>
<td>74</td>
<td>NA</td>
</tr>
<tr>
<td>Diabetes ($n$)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension ($n$)</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Sleep apnea ($n$)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Heart condition ($n$)</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Anemia</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*Note.* LLD = Late Life Depression. NDC = Non-Depressed Comparison.

1. $t(45) = -13.64, p < .001$
2. Years ill missing for one subject
3. Medication status missing for one LLD; one NDC subject was taking trazadone for sleep.
fMRI Data: Methods

- High-resolution T₁ SPGR anatomical images were obtained after SLLT administration and used in voxel-based morphometry analyses, to test for group differences in hippocampal volume using the VBM8 toolbox in SPM8 (Kurth et al., 2010) with a hippocampal ROI constructed using the WakeForest PickAtlas (Maldjian et al., 2003). Threshold was set at with small volume correction ($p < .05$, minimum threshold cluster of 80mm³).

- fMRI data preprocessing included slice timing correction, realignment, coregistration, warping, and smoothing (5 mm FWHM; see Weisenbach et al., 2012 for details). AlphaSim correction (1000 iterations) was used for all whole brain analyses, balancing height ($p < .003$) and extent (264 mm³) thresholds to achieve a whole brain correction of $p < .05$. For the hippocampal ROI analyses, a relaxed threshold of $p < .05$, 80mm³ was utilized to account for small volume correction.

- First and second level models processed in SPM8
Semantic List Learning Test

Semantic List Learning Task

List 1 (86.25 sec)

Three lists per run. Five runs in total. Lists order and word order within list randomized for each subject.

Duration
58250

Encoding

Distraction (CPT) “Go” task, targets x, y, z, serial letters 500 ms ISI

Duration
14000

Silent Recall
Parts of Buildings

...12 more words

Fixation, jitter 1000-4000 ms

Parts of Buildings

= 500

= 1000

= 1000

= 2500

Langenecker, Caveney, Persad, & Giordani, 2004, Semantic List Learning Test, Ann Arbor, MI
SLLT: Performance

Weisenbach et al. (Under Review). Inefficiencies of Prefrontal and Subcortical Circuitry During Encoding of Semantically Related Words in Patients with Late Life Depression
Encoding minus Silent Rehearsal

LLD exhibit less activation in structures known to be relevant for new learning and memory (PFC, fusiform-content processing, hippocampus-storage, and parietal regions-attention) despite similar performance and hippocampal volumes.

Largest areas of activation in LLD were in dorsal cingulate, MFG, thalamus, and cerebellum, suggesting inefficiencies in loops relevant to verbal memory and activation of networks supporting cognitive control.

Weisenbach et al. (Under Review). Inefficiencies of Prefrontal and Subcortical Circuitry During Encoding of Semantically Related Words in Patients with Late Life Depression
Encoding of Recalled versus Not Recalled Words

ILLUSTRATES MEDIAL FRONTAL REGIONS THAT ARE STATISTICALLY SIGNIFICANT IN THE LLD GROUP (BLUE), THE NDC GROUP (RED), AND NDC GREATER THAN LLD (GREEN)

LLD: dorsal ACC: error detection

NDC: ventral PFC: self-referential processing

Weisenbach et al. (Under Review). Inefficiencies of Prefrontal and Subcortical Circuitry During Encoding of Semantically Related Words in Patients with Late Life Depression
Greater IFG Activation in LLD During Encoding of Correctly Recognized versus Not Recognized Words

(A) Activation of IFG greater in LLD than NDC. (B) Mean extracted activation values from the IFG in each group during three contrasts.

The IFG is involved in cognitive control and controlled semantic/phonological retrieval and analysis. LLD may be utilizing this as a compensatory region during encoding, potentially part of a process that is crucial for consolidation, or the subsequent inhibitory process of correctly rejecting words during the recognition trial.

Weisenbach et al. (Under Review). Inefficiencies of Prefrontal and Subcortical Circuitry During Encoding of Semantically Related Words in Patients with Late Life Depression
Summary

• LLD demonstrate poorer encoding of verbal material relative to NDC

• During encoding of new verbal material, LLD patients demonstrate less activation in regions important for new learning and memory, and may go about encoding material differently, despite equivalent performance and hippocampal volume.
Conclusions

• Changes on neuroimaging can appear prior to behavioral changes, and may serve as markers to predict the course / prognosis of depression later in life.

• In addition to longitudinal studies, future research might utilize neuroimaging findings to better understand the heterogeneity of the disease, and how disruption to specific pathways might predict response to treatment of various kinds (e.g., problem solving therapy, behavioral activation, dopaminergic agents, etc.)
Depression and Dementia

**Prodrome**
- Depression can represent the first signs of dementia
- 1.16 to 3.50 relative risk (Jorm, 2000, *Gerontology*)

**Risk Factor**
- **YES**
  - Speck et al 1995, *Epidemiology*
  - Wetherell et al. 1999 *Alzheimer Dis Assoc Disord*
  - Kessing et al. 1999 *Act Psychiatr Scand*
  - Jorm et al. 2001 *Aust N Z J Psychiatry*
- **NO**
  - Ganguli et al. 2006 *Arch Gen Psychiatry*
  - Butinx et al. 1996 *Age & Aging*

Depression During Late Life: A Prognostic Conundrum

Symptom Presentation (Depression + Cognitive Problems)

- Response to treatment and improvement in symptoms
- Sustained depression and/or Alzheimer’s disease (or other dementia)
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