Frontal lobe dysfunction may give rise to episodic memory deficits in mild cognitive impairment

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Background
- Cerebrovascular Disease (CVD) is prevalent in the aged population.
- Recent studies suggest that CVD may compromise dorsolateral prefrontal cortex (DLPFC) functions.
- We propose that CVD may indirectly affect episodic memory in MCI by compromising frontal lobe dependent working memory functions.

Experiments
1. To compare performance of individuals with MCI and CVD (MCI-CVD) with MCI and hippocampal atrophy (MCI-HA) on episodic memory and working memory tasks.
2. To use fMRI to examine the effect of CVD on DLPFC activity during a working memory task in normal elderly individuals.

Participants
MCI-CVD: severe white matter hyperintensities, low hippocampal atrophy
MCI-HA: severe hippocampal atrophy, low white matter hyperintensities
Normal elderly controls: range of H4 and CVD

Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>MCI-HA</th>
<th>MCI-CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Age</td>
<td>76.65</td>
<td>74.55</td>
<td>77.64</td>
</tr>
<tr>
<td>Education</td>
<td>13.6 (1)</td>
<td>13.8 (2)</td>
<td>13.5 (1)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>9/11</td>
<td>6/5</td>
<td>9/2</td>
</tr>
<tr>
<td>MRSE</td>
<td>21.63 (2)</td>
<td>27.46 (2)</td>
<td>27.27 (2)</td>
</tr>
<tr>
<td>Left HC Volume</td>
<td>.147 (4)</td>
<td>.132 (4)</td>
<td>.148 (4)</td>
</tr>
<tr>
<td>Right HC Volume</td>
<td>.152 (3)</td>
<td>.107 (3)</td>
<td>.147 (3)</td>
</tr>
<tr>
<td>CVD Severity</td>
<td>13.15 (15)</td>
<td>7.65 (8)</td>
<td>34.36 (12)</td>
</tr>
</tbody>
</table>

*differs from other groups, p < .05
 exposing each subject to hidden group analysis

Experimental Tasks
Episodic Memory
- color-object association task:
  Working Memory
  - verbal item recognition: 2, 4, 6 loads
  - spatial item recognition: 4 item load
  - n-back: 1 & 2-back

Behavioral Results

Summary of Results
Experiment 1
- MCI-HA and MCI-CVD are equally impaired on the episodic memory task.
- MCI-CVD are additionally impaired on working memory tasks.
- CVD severity is negatively correlated with 2-back performance in normal elderly individuals.

Experiment 2
- In cognitively normal elderly, DLPFC activity is negatively correlated with severity of CVD on the 4-item and 6-item working memory task.
- No correlation between severity of CVD and visual cortex activity.

Conclusions
1. CVD can lead to MCI by disrupting frontal dependent working memory processes critical to episodic memory performance.
2. CVD can impair working memory performance even in cognitively normal elderly.
3. The mechanism of CVD impairment on working memory performance may be compromised DLPFC activity.

Detailed methods

- Participants recruited from UC Davis Alzheimer's Disease Center. All subjects had neuropsychological testing, neurologic exam, and MCI clinically diagnosed based on presence of episodic memory impairment. Participants were excluded for presence of subdural or clinical depression.
- MRI used to further categorize MCI into MCI-CVD and MCI-HA. Hippocampal volumes quantified on T1-weighted images and white matter hyperintensities (MRSE) used as proxy density weighted images using a semi-automated procedure. 80% percentile used for hippocampal volumetry was used to classify average hip.
- CVD severity correlated with working memory performance.
- MCI-CVD and normal controls only:
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