Clinical applications of brain imaging

UCSD Clinical and Translational Research Institute (CTRI)
Translational Research Technology Division
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Overview

- Part 1: Nuts and bolts of neuroimaging
- Part 2: Clinical applications of brain imaging
- Part 3: CTRI Neuroimaging Technology Resource
Part 1: Nuts and bolts of neuroimaging

- Functional brain imaging
  - Functional magnetic resonance imaging (fMRI)
  - Arterial spin labeling (ASL)
  - Positron emission tomoraphy (PET)
  - Single photon emission computed tomoraphy (SPECT)

- Structural brain imaging
  - Structural magnetic resonance imaging (sMRI)
  - Voxel based morphometry (VBM)
  - Diffusion tensor imaging (DTI)
Functional brain imaging
fMRI

- Blood oxygen level dependent (BOLD) effect
  - Oxyhemoglobin and deoxyhemoglobin have different magnetic properties
  - Active cortical regions receive increased blood flow
  - $O_2$ delivery exceeds $O_2$ consumption
  - More signal from active cortical regions

- BOLD-fMRI may be combined with ASL, which provides a quantitative measure of cerebral blood flow

(Ogawa et al., 1990)
Tasks

- Contrast activation between two conditions

- Ecologically valid construct
  - Food stimuli in eating disorders
  - Traumatic images in PTSD
  - Emotion processing in MDD
Data processing and analysis

- Functional scans while performing tasks
  - ~8-12 minutes long
  - One brain volume approximately every 2s

- Processing
  - Movement
  - Physiological noise
  - Anatomical normalization

- Analysis
  - ROI
  - Whole brain
  - Functional connectivity

(Friston et al., 2001; Fox et al., 2005)
SPECT and PET

- Directly measure brain metabolic activity
  - Requires the administration of an exogenous contrast agent (i.e., radioligand),
  - Radioligand accumulates in a targeted area of the brain or body
  - Small amount of energy is emitted
  - Location and intensity of activation are reconstructed

- Metal and other MRI exclusions not an exclusion
Structural brain imaging

- sMRI provides a high resolution static brain image

- DTI measures water diffusion to infer white matter structure. Can use validated statistical methods to examine the integrity of connections between specific brain regions

- VBM allows for quantification of gray and white matter volumes
Part 2: Clinical applications of brain imaging

- Study 1: fMRI study investigating the brain basis of major depressive disorder (MDD)

- Study 2: Multimodal neuroimaging study in veterans with MDD and other combat-related stress disorders

- Study 3: Neurobehavioral mechanism of suicidal ideation
Study 1: fMRI study investigating the brain basis of MDD

(Mayberg et al., 1997)
What are the neural correlates of MDD?

Hypothesis: MDD individuals relative to matched non-depressed comparison subjects will show:

- more activation of brain structures involved in negative emotion processing
- less activation of brain structures involved in controlling behavior and emotion processing
Methods

□ MDD and non-MDD comparison subjects completed 2 study sessions:

■ Session 1: Clinical assessment

■ Session 2: fMRI
### Subjects

<table>
<thead>
<tr>
<th></th>
<th>MDD</th>
<th>Non-MDD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Men</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>24.5 (5.5) yrs</td>
<td>24.3 (5.0) yrs</td>
</tr>
<tr>
<td><strong>BDI</strong></td>
<td>18.6 (3.1)</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
fMRI tasks

- Emotional face matching task (emotion processing)
- Thermal heat pain task (aversive anticipation)
- Stop task (self control)
Emotional face matching task

(Hariri et al., 2002)
Amygdala hyperactivity and altered amygdala-cingulate connectivity during emotion processing in MDD

(Matthews et al., 2008)
Thermal heat pain task

(Strigo et al., 2008)
Altered activation during stimulation and anticipation of thermal heat pain in MDD

(Strigo et al. 2008)
Stop task

- “X” and “O” stimuli
- Instructions: “press unless you hear a tone”
- Behavioral session to construct individualized easy and hard trials
- Whole brain analyses of error and inhibitory processing

(Logan et al., 1984; Band et al., 2003; Matthews et al., 2005)
Maladaptive error and inhibitory processing in MDD

Errors

Inhibition

(Matthews et al., 2009)
Conclusions

- MDD is associated with:
  - Increased activity of emotion processing circuitry (amygdala, anterior insula, subgenual cingulate)
  - Decreased activity of brain structures that modulate emotion processing (supragnostic cingulate, DLPFC, inferior frontal gyrus)
Study 2: Multimodal neuroimaging study in veterans with MDD and other combat-related stress disorders
Blast injury

- Blast-related traumatic brain injury (TBI) is common among combat-exposed individuals
- The vast majority is mild TBI (i.e. concussion)
- MDD is common after head injury

(Seal et al., 2007; Hoge et al., 2008)
What are the neural correlates of MDD after blast-related concussion?

- Hypothesis: main and interactive effects of blast-related concussion and MDD on brain structure and function
Methods

- Subjects: 4 groups of OEF-OIF veterans
  - +mTBI +MDD
  - +mTBI -MDD
  - -mTBI +MDD
  - -mTBI –MDD

- Cross-sectional design
  - Emotional face matching and stop tasks during fMRI
  - DTI
fMRI results

Increased Bilateral Amygdala Activation to Fear in mTBI+MDD versus mTBI-MDD

Left Amygdala: -25/-5/-17, 1088μL; t=4.8
Right Amygdala: -18/-7/-12, 128μL; t=2.7

% Signal ± SEM

Left (p<0.01) and Right (p<0.01)

(Matthews et al., 2010)
DTI results

Decreased Left Superior Longitudinal Fasciculus FA in the mTBI+MDD versus mTBI-MDD

(Matthews et al., 2010)
Conclusions

- Cannot infer causation

- Findings suggest a structural and functional brain alterations may underlie MDD after blast-related concussion
Suicide is a major public health problem

The presence of suicidal ideation (SI) increases risk of future suicide attempts and completed suicide

Prior work has described altered functional brain activity in individuals with mood disorders who have attempted suicide relative to individuals with mood disorders who have never attempted suicide

However, the brain basis of SI is unknown
What are the neural correlates of suicidal ideation in combat exposed veterans?

- Hypothesis: Compensatory hyperactivation of brain systems involved in self monitoring and self control

- Structural differences?
Methods

- Cross sectional multimodal neuroimaging study

- Two groups of “highly distressed” combat veterans, defined by the presence of 2 of the following:
  - History of concussion
  - Current PTSD
  - Current MDD

- SI subjects had a history of clinically significant SI, whereas non-SI subjects did not
# Clinical results

<table>
<thead>
<tr>
<th></th>
<th>SI mean (SD)/%</th>
<th>non-SI mean (SD)/%</th>
<th>F/$\chi^2$</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age</td>
<td>29.54(4.68)</td>
<td>27.08(3.62)</td>
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<td>Ethnicity</td>
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<td></td>
<td></td>
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<tr>
<td>Non-Caucasian</td>
<td>7</td>
<td>7</td>
<td></td>
<td></td>
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<tr>
<td>Education (years)</td>
<td>13.85(1.21)</td>
<td>13.23(0.83)</td>
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<td>Current Meds</td>
<td>8</td>
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<td>1</td>
<td>0.6</td>
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<tr>
<td>History of Concussion</td>
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<td>2.17</td>
<td>0.34</td>
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<td>AOC</td>
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<tr>
<td>LOC</td>
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<td></td>
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<tr>
<td>Concussion type</td>
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<td>0.26</td>
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<tr>
<td>Blast</td>
<td>9</td>
<td>9</td>
<td></td>
<td></td>
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<tr>
<td>Mixed/Blunt</td>
<td>2</td>
<td>4</td>
<td></td>
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<tr>
<td>Number Concussions</td>
<td>1.82(0.98)</td>
<td>6.62(6.85)</td>
<td>5.27</td>
<td>0.03</td>
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<tr>
<td>MDD</td>
<td>10</td>
<td>8</td>
<td>0.72</td>
<td>0.68</td>
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<td>PTSD</td>
<td>13</td>
<td>11</td>
<td>2.16</td>
<td>0.24</td>
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<tr>
<td>CES total score</td>
<td>23.50(10.57)</td>
<td>25.45(6.38)</td>
<td>0.25</td>
<td>0.62</td>
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## fMRI results

<table>
<thead>
<tr>
<th>Volume (µl)</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Brain Regions</th>
<th>Brodmann Areas</th>
<th>t-value</th>
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<tbody>
<tr>
<td>SI&gt;non-SI</td>
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<td></td>
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<tr>
<td>9,984</td>
<td>54</td>
<td>-50</td>
<td>25</td>
<td>Right Supramarginal Gyrus</td>
<td>40</td>
<td>2.720</td>
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<tr>
<td>8,256</td>
<td>-6</td>
<td>4</td>
<td>39</td>
<td>Left Anterior Cingulate Cortex</td>
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<td>7,488</td>
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<td>52</td>
<td>-6</td>
<td>Left Middle Frontal Gyrus</td>
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<td>6,976</td>
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<td>-3</td>
<td>25</td>
<td>Right Precentral Gyrus</td>
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<tr>
<td>6,912</td>
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<td>-49</td>
<td>25</td>
<td>Left Supramarginal Gyrus</td>
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<td>5,632</td>
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<td>45</td>
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<td>Right Middle Frontal Gyrus</td>
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<td>2.550</td>
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<td>3,776</td>
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<td>Right Medial Frontal Gyrus</td>
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<td>3,264</td>
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<td>-31</td>
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<td>Right Superior Temporal Gyrus</td>
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<td>2,624</td>
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<td>Right Middle Frontal Gyrus</td>
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<td>2.454</td>
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<td>-40</td>
<td>55</td>
<td>Right Supramarginal Gyrus</td>
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<td>2.613</td>
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<tr>
<td>SI&lt;non-SI</td>
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<td></td>
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<td></td>
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<tr>
<td>3,712</td>
<td>-2</td>
<td>-78</td>
<td>-27</td>
<td>Left Pyramis of Vermis</td>
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<td>-2.440</td>
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<tr>
<td>3,072</td>
<td>-2</td>
<td>-60</td>
<td>56</td>
<td>Sagittal Sinus</td>
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<td>-2.709</td>
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</table>
Summary and conclusions

- Data indicate that SI individuals show inefficient utilization of a network of structures that includes the anterior cingulate and prefrontal cortex during self monitoring, suggesting a brain-based biomarker of SI.

- If replicated in larger samples, these findings may identify “targets” for psychopharmacological and psychotherapeutic treatments in individuals at increased risk for suicide before they engage in suicidal behavior.
Part 3: CTRI Neuroimaging Technology Resource

☐ Services:
  ■ Consultation regarding study design and data acquisition procedures
  ■ Analysis of structural and functional neuroimaging data

☐ Further information:
  ■ [http://ctri.ucsd.edu/laboratory/Pages/imaging-tech.aspx](http://ctri.ucsd.edu/laboratory/Pages/imaging-tech.aspx)

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