Clinical Applications of fMRI

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No Disclosures or Conflicts
Caveats

• Cannot cover all populations or methods in 1 hour

• This lecture is meant to be an overview of how fMRI can be applied in clinical populations

• Requires understanding / experience with clinical presentation and underlying disease mechanisms (i.e., neuroanatomically informed approach)
Overview

1. Aging & Dementia
   • Network level changes due to disease
   • Understanding memory deficits
   • Evaluating & targeting treatment

2. Depression

3. Stroke

4. Epilepsy
   • Presurgical evaluation
The Population is Aging

• Aging population in the USA
  • 234 million in USA; 1/3 age 55+ (77 million)
  • Age is the greatest risk factor for Alzheimer’s disease (AD) and other dementias
  • Predicted multi-fold increase in rate of AD

• Memory becomes less efficient
  – Potential reduction in specific hippocampal subregions (dentate gyrus; Brickman et al., 2011; Small et al., 2011)
  – Reduced strategy use

• Changes in activation
  – Multiple approaches have demonstrated a posterior to anterior shift with aging (Davis, Dennis, Daselaar, Fleck, Cabeza, 2008)
  – Increased functional connectivity between PFC & hippocampus (Dennis et al., 2008)
  – Appears to be compensatory in nature (e.g., scaffolding theory of aging and cognition - Park & Reuter-Lorenz, 2009)

• Disease-related effects are superimposed on “normal” age-related changes
FIGURE 18. Activity within the default network is disrupted in Alzheimer’s disease. Task increases (red) and decreases (blue) from a simple word classification task referenced to a passive baseline task are plotted for young adults (left panel), normal older adults (middle panel), and demented older adults with AD (right panel). The young adults show the classic pattern of task-induced deactivation within PCC/Rsp and MPFC. The effect attenuates significantly in AD. Adapted from Lustig et al. (2003, see also Greicius et al. 2004).
Two Primary Types of Pathology in Alzheimer’s Disease

Frequency of Stages of Alzheimer-Related Lesions in Different Age Categories

FIG. 2. Development of amyloid deposits in 2,661 nonselected autopsy cases. The first line displays the frequency of cases devoid of changes in relation to the total number of cases in the various age categories. The second, third, and fourth lines are similarly designed, and show the evolution of the AD-related changes. The dark areas of the columns refer to subgroups showing the presence of neurofibrillary changes.

FIG. 3. Development of neurofibrillary changes in 2,661 nonselected autopsy cases. The first line displays the frequency of cases devoid of changes in relation to the total number of cases in the various age categories. The second, third, and fourth lines are similarly designed, and show the evolution of the AD-related changes. The dark areas of the columns represent the subgroups displaying amyloid deposits.
Disease Begins Decades Before Symptoms

ANN NEUROL 2012;71:765–775

The graph illustrates the preclinical stage of disease progression, showing the biomarker magnitude over time. The stages are labeled as follows:

1. Cognitively Normal
2. MCI (Mild Cognitive Impairment)
3. Dementia

The graph also depicts the cut-points for identifying abnormal biomarkers, which are critical for early detection of disease stages.
Disease Begins Decades Before Symptoms

2018 National Institute on Aging—Alzheimer’s Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer’s disease


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Fig. 1. Alzheimer’s disease with dementia. A 75-year-old woman with amnestic multidomain dementia. Participant in the Mayo Alzheimer’s Disease Research Center. Abnormal amyloid PET with Pittsburgh compound B (top left), tau PET with flortaucipir (top right and bottom left), and atrophy on MRI (bottom right). Biomarker profile A+T+(N)+.

Fig. 2. Preclinical Alzheimer’s pathologic change. A cognitively unimpaired 67-year-old man. Participant in the Mayo Clinic Study of Aging. Abnormal amyloid PET (Pittsburgh compound B, top row), no uptake on tau PET (with flortaucipir, middle row), no atrophy on MRI (bottom row). Biomarker profile A+T−(N)−.
Relationships between Beta-Amyloid and Functional Connectivity in Different Components of the Default Mode Network in Aging

Elizabeth C. Mormino\textsuperscript{1}, Andre Smiljic\textsuperscript{1}, Amynta O. Hayenga\textsuperscript{1}, Susan H. Onami\textsuperscript{1}, Michael D. Greicius\textsuperscript{2}, Gil D. Rabinovici\textsuperscript{1,3,4,5}, Mustafa Janabi\textsuperscript{3}, Suzanne L. Baker\textsuperscript{3}, Irene V. Yen\textsuperscript{3}, Cindee M. Madison\textsuperscript{1}, Bruce L. Miller\textsuperscript{4,5} and William J. Jagust\textsuperscript{1,3,4,5}

\textbf{Figure 1.} DMN FC and global PIB uptake overlap. One sample \textit{t}-test of DMN best-fit components (yellow), 2-sample \textit{t}-test between high and low PIB subjects (blue), and overlap (red) are displayed. These maps highlight congruence and incongruence between the DMN and the brain regions showing high levels of A\textsubscript{\beta} deposition. The greatest amount of overlap is in precuneus/posterior cingulate, medial prefrontal, and angular gyri. Although PIB uptake is more diffuse than DMN, there is minimal overlap in retrosplenial and medial temporal portions of the DMN.

\textbf{Figure 2.} \textit{t}-Maps from voxelwise analysis correlating global PIB with DMN FC.
Our understanding of “normal” aging may be inaccurate
fMRI & Interventions: Memory Deficits
Ecologically Relevant Memory Test

All are common complaints
Functional MRI: Task-based

Ecologically Relevant: Object-location paradigm
What Happens in MCI Patients?

Healthy Controls Show Greater Activation During Encoding
Novel (correct) > Repeated

HEC > MCI

Hampstead fMRI Training Course 2018
MCI Patients Process Information Shallowly

HOC – left hemisphere – frontoparietal control network critical for encoding (IFJ, aIPS, PCC)

MCI – right FEF – basic attentional saccades
Mnemonic Strategy Training

<table>
<thead>
<tr>
<th>Mnemonic Strategy Training (MST)</th>
<th>Spaced Retrieval Training (SRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI 29 (21 fMRI)</td>
<td>29 (18 fMRI)</td>
</tr>
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</table>

### A)

<table>
<thead>
<tr>
<th>Session 1: Pre-training Encoding</th>
<th>Session 2 Training</th>
<th>Session 3 Training</th>
<th>Session 4 Training</th>
<th>Session 5: Post-training Encoding</th>
<th>1 month follow-up Memory test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hr delay Retrieval</td>
<td></td>
<td></td>
<td></td>
<td>1 hr delay Retrieval</td>
<td></td>
</tr>
</tbody>
</table>

### Graph

- X-axis: Delay (in seconds)
- Y-axis: Response time (in seconds)
- Data points: 1, 2, 3, 4, 5, 6, 7, 8, 9

Hampstead fMRI Training Course 2018

Hampstead et al., *in progress; DO NOT REPLICATE*
MST is Better in the Long-Term

Group x time: $p = 0.046$

Hampstead fMRI Training Course 2018

Hampstead et al., *in progress*; DO NOT REPLICATE
Intervention Specific Changes in Activation

Novel Stimuli

Post training > Pre training

Mnemonic strategies
1. Engage “top-down” cognitive control mechanisms
   -- Rostral and lateral prefrontal regions

2. Enhance self-referential processing
   -- Medial frontoparietal / posterior cortices
Findings Replicate Earlier Work

Hampstead et al. (2008) *JINS*

“untrained” (i.e., Novel) stimuli

Post>pre
MST Facilitates Hippocampal Activation in MCI

No changes in the exposure group

Overview

1. Aging & Dementia
   • Network level changes due to disease
   • Understanding memory deficits
   • Evaluating & targeting treatment

2. Depression
Major Depressive Disorder

DSM -5

- 5+ (including at least 1 of depressed mood & loss of interest in past 2 weeks) – that represent change & are present nearly every day
  - Depressed mood
  - Loss of interest/pleasure
  - Change in weight/appetite
  - Insomnia or hypersomnia
  - Psychomotor agitation or retardation
  - Loss of energy or fatigue
  - Worthlessness or guilt
  - Impaired concentration/indecisiveness
  - Recurrent thoughts of death or suicidal ideation/attempt
- Symptoms cause significant distress or impairment
- (various rule-outs)
Some DMN areas decrease

Some FPN/salience increase

How to interpret?
MDD. This suggests that areas involved in attention and cognitive control (Component 25) may play an important role in depression severity (Mittersichffthaler et al., 2008; Berman et al., 2011; Dillon et al., 2015) as well as treatment response and executive function (Component 24;
"Training" sessions

- Use mental imagery
- Suggested approach but no efforts to ensure use
- Similar sized ROIs used to monitor BOLD change
- Unclear if ruled out changes in other group’s ROI
"Training" sessions
- Some overlap in recruited regions
- Insula, MTL

More activation change in scene group
No differences in outcome but...

Both groups improved
- ~37% remission
- Results persisted at follow up
Overview

1. Aging & Dementia
   • Network level changes due to disease
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2. Depression

3. Stroke
Cerebrovascular Accident (Stroke)

Damage to the brain tissue that results from disruption of blood flow
- Hemorrhagic
- Ischemic
- Motor and/or cognitive deficits (e.g., aphasia, neglect)
- Typically expect some degree of spontaneous recovery
- Most rapid improvements over first 9-12 months
Used graph theory measures to examine change over first year after stroke in 107 patients vs. controls

Graph theory:
- Modularity – Global network measure that compares density of connections within vs. between networks (or “communities”)

Table 1 – Sample sizes and imaging quality metrics for controls, patients, and case study P108.

<table>
<thead>
<tr>
<th>Table 1A</th>
<th>Timepoint 1</th>
<th>Timepoint 2</th>
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<td>Controls</td>
<td>N</td>
<td>30</td>
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<td>N (incl.)</td>
<td>26</td>
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<td></td>
<td>Frames</td>
<td>571.4(210.0)</td>
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<td></td>
<td>FD</td>
<td>.234(.062)</td>
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<tr>
<td></td>
<td>Lag</td>
<td>.191(.046)</td>
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</table>

<table>
<thead>
<tr>
<th>Table 1B</th>
<th>2 weeks</th>
<th>3 months</th>
<th>1 year</th>
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<tbody>
<tr>
<td>Patients</td>
<td>N</td>
<td>132</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>N (incl.)</td>
<td>107</td>
<td>85</td>
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<tr>
<td></td>
<td>Frames</td>
<td>596.0(209.6)</td>
<td>649.4(177.8)</td>
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<td>.231(.063)</td>
<td>.224(.057)</td>
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<td>Lag</td>
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<tr>
<td>P 108</td>
<td>Frames</td>
<td>737/896</td>
<td>644/896</td>
</tr>
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<td></td>
<td>FD</td>
<td>.2392</td>
<td>.2495</td>
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<td></td>
<td>Lag</td>
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<td>.1448</td>
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</table>
Re-emergence of modular brain networks in stroke recovery

Joshua S. Siegel, Benjamin A. Seitzman, Lenny E. Ramsey, Mario Ortega, Evan M. Gordon, Nico U.F. Dosenbach, Steven E. Petersen, Gordon L. Shulman and Maurizio Corbetta
Fig. 2 — Group FC Similarity to controls. Pearson correlation between all members of a given group and control at timepoint 1. The X-axis is a simple measure of FC similarity. This measure is computed by turning the 324-by-324 FC matrix into a 52,326 vector for each subject. For a given group (i.e. patients at 2 weeks), a spatial correlation was computed between the FC vector of every subject and the FC vector of every subject in the control group. Each curve is a histogram of similarity values for one group. Similarity to controls increases between 2 weeks and 1 year post-stroke (paired t-test: \( t = 3.9, p < .0001 \).
Re-emergence of modular brain networks in stroke recovery
Joshua S. Siegel a,*, Benjamin A. Seitzman a, Lenny E. Ramsey a, Mario Ortega b, Evan M. Gordon c, Nico U.F. Dosenbach a, Steven E. Petersen a,b,c,d, Gordon L. Shulman a and Maurizio Corbetta a,b,c,d

Fig. 3 – Behavior recovery following stroke is predicted by recovery of brain network modularity. A: Modularity measures the density of links inside communities compared to links between communities. Modularity is decreased in acute stroke patients (B), but returns to near control levels at 3 month and 1 year timepoints (C). D: Modularity, normalized to controls and averaged across densities (2–20%) is shown for the whole brain, ipsi-lesional, and contra-lesional hemisphere (compared to single hemisphere modularity in controls). ** indicates $p < .005$ (uncorrected) for an unpaired t-test between patients and controls in B and for a paired t-test between 2 weeks and 1 year for patients in C/D.
Re-emergence of modular brain networks in stroke recovery

Joshua S. Siegel a, b, Benjamin A. Seitzman a, Lenny E. Ramsey a, Mario Ortega a, Evan M. Gordon f, Nico U.F. Dosenbach a, Steven E. Petersen a, b, c, d, Gordon L. Shulman a, and Maurizio Corbetta a, b, c, d

2 weeks
language z-score: -11.7
modularity: .66 (control avg = 1)

3 months
language z-score: -2.3
modularity: 1.0

1 year
language z-score: -1.2
modularity: 1.0

Control Average

Spring-embedded graph (4%)


[Brain images and network diagrams]
Re-emergence of modular brain networks in stroke recovery


<table>
<thead>
<tr>
<th></th>
<th>ΔModularity mean±SE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attention</strong></td>
<td>No Recovery (&lt;1SD)</td>
</tr>
<tr>
<td></td>
<td>Good Recovery (&gt;2SD)</td>
</tr>
<tr>
<td><strong>Spatial Memory</strong></td>
<td>n=11, 7</td>
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<tr>
<td><strong>Verbal Memory</strong></td>
<td>15, 8</td>
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<tr>
<td><strong>Language</strong></td>
<td>22, 8</td>
</tr>
<tr>
<td><strong>Motor contra-ipsi</strong></td>
<td>22, 5</td>
</tr>
<tr>
<td><strong>Visual contra-ipsi</strong></td>
<td>15, 23</td>
</tr>
</tbody>
</table>

* * P_FDR < 0.05
† † P_FDR < 0.1
Overview

1. Aging & Dementia
   • Network level changes due to disease
   • Understanding memory deficits
   • Evaluating & targeting treatment

2. Depression

3. Stroke

4. Epilepsy
   • Presurgical evaluation
Epilepsy

• Chronic disorder – characterized by recurrent and unprovoked seizures
• Seizure = sudden surge of electrical activity
• ~50% of those who have 1 seizure have 2
• ~80% of those who have 2 have more
• Severely disabling
• Surgical resection is common
  • Typically fail 2+ single medications & combination of 2+ medications

Source: http://www.epilepsy.com
Types of Surgery for Epilepsy

- Removing brain tissue may cause cognitive impairment
- Wada test is “gold standard” for evaluating functioning
- Language & memory
Language Regions (NeuroSynth)
Wada Test in Epilepsy

- Intracarotid amobarbital testing (IAT)
- http://pcs.hmc.washington.edu/Epilepsy/wadas.htm

Step 8

The test is almost completed. The patient's right brain has woken up and she now can follow instructions, name objects correctly, read cards accurately, and recall objects.
Wada Test in Epilepsy

Risks include:

- **Sensitivity to contrast dye.** Reactions may include nausea, hives, and itching. Patients rarely experience difficulty breathing.
- **Bleeding.** Insertion of the catheter requires the puncture of a blood vessel. If blood should leak around the catheter into the tissue, a hematoma (a swollen area filled with blood) may result. It will become black and blue but will get better in time as the blood is absorbed by the body.
- **Sensitivity to sodium amytal,** which is a strong sedative. Rarely it can cause difficulty breathing or low blood pressure.
- **A blood clot** in the leg or brain, which may cause a stroke. This only happens in about one in a thousand cases.

Direct source: http://www.dartmouth-hitchcock.org/epilepsy/wada_test.html#risks

- Dissection?
- Costs (financial, personnel, emotional)
fMRI uses in Epilepsy

- Relatively low cost
- Non-invasive
- Widely available
- Uses include:
  - Language lateralization
  - Memory functioning
- Acquisition and analyses are not (traditionally) standardized
fMRI uses in Epilepsy

Practice guideline summary: Use of fMRI in the presurgical evaluation of patients with epilepsy

- 11 Member Panel reviewed 172 published manuscripts; 37 selected for review based on quality/nature of the study
- Assigned levels of evidence around several key questions:

1. Is fMRI comparable with the current standard (IAP) for measuring language lateralization?
2. Can fMRI predict postsurgical language outcomes in patients with epilepsy undergoing brain surgery?
3. Is fMRI comparable with the current standard (IAP) for measuring memory lateralization?
4. Can fMRI predict postsurgical verbal memory outcomes in patients with epilepsy undergoing temporal lobectomy?
5. Can fMRI predict postsurgical nonverbal (visuospatial) memory outcomes in patients with epilepsy undergoing temporal lobectomy?
6. Is there sufficient evidence in terms of diagnostic accuracy and outcome prediction for fMRI to replace the IAP (Wada test) in presurgical evaluation for epilepsy surgery?
1. Does fMRI = Wada for language lateralization?

- Meta-analysis found
  - 87% (201/232) concordance for medial temporal lobe epilepsy (MTLE)
  - 100% (7/7) for MT lesions
  - 81% (48/59) for extratemporal foci

- Recommendations: “fMRI may be considered as an option in lateralizing language functions in place of IAP in patients with MTLE, temporal epilepsy, or extratemporal epilepsy...”

- Unclear evidence for temporal neocortical epilepsy or temporal tumors
2. Can fMRI predict postsurgical language outcome?

- Strong left frontal activation predicted postresection decline (100% sensitivity; 33% specificity)
- Strong left-lateralized temporal activation during semantic decision task predicted naming decline (100% sens; 73% spec).
- Wada lower prediction than fMRI
- Recommendation: “fMRI may be considered for predicting postsurgical language outcomes after anterior temporal lobe (ATL) resection for the control of TLE”
3. Is fMRI comparable for memory lateralization?

- Visuospatial task (scenes vs. noise) laterality index (LI) significantly related to IAP ($r=.31$, $p=.007$)
- No relationship in a second study (amytal dose?)
- Novel vs. repeated pictures & number of activated voxels were related to IAP LI in other studies

- Recommendation: “fMRI may be considered as an option to lateralize memory functions in place of IAP in patients with MTLE”

Hampstead fMRI Training Course 2018
4. Can fMRI predict verbal memory outcome?

- fMRI leftward LI during verbal encoding “probably predicts” verbal memory decline
- Presurgical Neuropsych testing accounted for 50% of variance; fMRI explained 10%

- Recommendation: “Presurgical fMRI of verbal memory or of language encoding should be considered as an option to predict verbal memory outcome in patients...undergoing evaluation for left MTL surgery”
5. Can fMRI predict visuospatial memory outcome?

- fMRI rightward LI during scene or facial encoding appears predictive of decline

- Recommendation: “Presurgical fMRI using nonverbal memory encoding may be considered as a means to predict visuospatial memory outcomes...”
Conclusions. Based on data from 1 Class II study and 1 Class III study, fMRI is possibly an effective method of lateralizing language functions in patients undergoing presurgical evaluation and may be a suitable replacement for the IAP for this purpose. Data on the ability of fMRI to predict language outcomes are limited.

Recommendation. Presurgical fMRI may be used instead of the IAP for language lateralization in patients with epilepsy who are undergoing evaluation for brain surgery (Level C). However, when fMRI is used for this purpose, task design, data analysis methods, and epilepsy type (temporal vs extratemporal, lesional vs nonlesional) need to be considered. Of particular importance for patients with lesional epilepsy is the fact that only small numbers of participants with variable lesion size/location were included in previous studies.

Conclusion. The correlations between fMRI and IAP memory asymmetry measures are modest, and the ability of the memory IAP to predict material-specific verbal memory change is relatively weak. Based on 9 Class II studies, including one study that showed that fMRI of language LI is possibly more accurate in predicting material-specific verbal memory change than was the memory IAP in patients undergoing left ATL resection, fMRI may be an alternative to IAP memory testing. The ability of fMRI to predict global amnesia has not been assessed.

Recommendation. fMRI of language and verbal memory lateralization may be an alternative to IAP memory testing for prediction of verbal memory outcome in MTLE (Level C). fMRI is not yet established as an alternative to the IAP for prediction of global amnesia in patients who have undergone ATL surgery.
Questions / Discussion