Clinical Applications of fMRI

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Funding

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  • Atlanta VAMC RR&D Center of Excellence

• National Institute on Aging
  • Emory Alzheimer’s Disease Research Center
  • Michigan Alzheimer’s Disease Core Center

• National Institute on Mental Health (MH102539-02)
  • Michigan Alzheimer’s Disease Core Center (pilot)
Overview

1. Aging & Dementia
   • Understanding memory deficits
   • Evaluating & targeting treatment

2. 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 and other dementias
  • Predicted multi-fold increase in rate of AD

• Existing pharmacologic agents have limited effects
  • Slight cognitive effects for ~12 – 18 months
  • Do not alter disease process
  • Side effects may outweigh benefits

• Non-pharmacologic approaches hold promise
  • Can we re-engage (or maximize) critical explicit memory regions?
    • Yes – Cognitive Rehabilitation & transcranial direct current stimulation
Explicit (Declarative) Memory

• Explicit memory
  – Consciously aware
  – Episodic – personal experiences (e.g., what, when, where, who)
    • recall sipping warm cider on a chilly fall day
    • Impaired in AD, FTD, & other forms of dementia
  – Semantic – overlearned information about yourself and/or world
    • recall that people often drink cider in the fall
    • Better preserved than episodic but deficits often evident
Explicit Memory System
Memory Changes with Age

- 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)
Defining Mild Cognitive Impairment (MCI)

- Albert et al., 2011 (Petersen, 2004; Winblad et al., 2004)
  - Official diagnosis
  - Characterized by cognitive impairment, particularly with learning & memory
  - Preserved everyday functioning
  - Rapidly growing population

By identifying early symptoms (dysfunction):
- Identify/develop targeted & effective interventions
- Prolong functioning – improve quality of life
- Reduce healthcare costs
- Pair with disease modifying medications (once available)
Ecologically Relevant Memory Test

All are common complaints
Functional MRI: Task-based
Ecologically Relevant: Object-location paradigm

A. Postma et al./Neuroscience and Biobehavioral Reviews 32 (2008) 1339–1345

B.M. Hampstead et al. / Neuropsychologia 49 (2011) 2349–2361

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Support for Postma et al.'s Model

Object
Novel > Repeated

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What Happens in MCI Patients?

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

HEC > MCI

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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

Cognitive Rehabilitation of Memory

- Rehearsal-based Approaches
  - Repeated exposure
  - Spaced retrieval
  - Vanishing cues
- Computer training programs/games
- Procedural learning
- Modeling

Compensatory Approaches

- External Aids
  - Calendars
  - Notebooks
  - Lists
  - Smart phones
  - Guided Cueing

Internal Approaches (Mnemonic Strategies)

- Semantic Organization
- Semantic Elaboration
- Mental Imagery
- Method of Loci

Rachel

Feature: Smooth skin.
Reason: Smooth, clear skin, like she had a facial. You could call her "facial-Rachel."

Feature: Sinks
Reason: You place your ring between the sinks so it won’t fall down the drain as you wash your dirty hands.

Fig. 2. Examples of stimuli and the mnemonic cues used in the faces & names (left) and objects & locations (right) paradigms. Patients are instructed to close their eyes and develop a mental image after completing the feature and reason steps.

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• Includes same & novel stimuli

• Examine training-specific effects (List A: post > pre) and generalization (List B > List A pre)
Single-blind RCT Study Design

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

Note: 4 completed studies (3 single blind RCTs) – all with same general results

1. Can patients use on their own? – YES ~90%
2. Is MST more effective than SRT?
3. Do the techniques engage different cognitive processes/brain regions?

Hampstead et al., in progress

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Spaced Retrieval Training (SRT)

Tightly matched condition: trials, duration, experience

Remember the location of the object over progressively longer delays (0” – 128”)

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MST is Better in the Long-Term

Group x time: p = 0.046

Hampstead et al., in progress

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Patients Transferred MST but not SRT

Post vs. Baseline

More Accurate

Improved Accuracy (in cm)

Less Accurate

Free Recall

Cued Recall

MST

SRT

n.s. p = 0.0049

d = 0.37 d = 0.89

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Intervention Specific Changes in Activation

Novel Stimuli
Post training > Pre training

MST

SRT

Beta (% signal change)

Trained Novel

effects

Hampstead et al., in progress
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

Hampstead et al., in progress

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Findings Replicate Earlier Work

Hampstead et al. (2008) *JINS*

“untrained” (i.e., Novel) stimuli
Post>pre

Feature: Mouth
Reason: Large mouth that opens wide to yawn, so we could call him “Yawn–Shawn”
Comparable Findings in “Healthy” Older Adults

**Table 1. Demographic and neuropsychological test performance data.**

<table>
<thead>
<tr>
<th></th>
<th>MST (n=15)</th>
<th>SC (n=15)</th>
<th>t(28)=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>67.1 (7.94)</td>
<td>72.0 (7.62)</td>
<td>1.71, p=0.098</td>
</tr>
<tr>
<td>Education</td>
<td>16.8 (1.32)</td>
<td>16.0 (2.29)</td>
<td>1.17, p=0.252</td>
</tr>
<tr>
<td>WTAR (scaled score)</td>
<td>113.7 (10.71)</td>
<td>108.8 (11.70)</td>
<td>1.18, p=0.244</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.7 (0.49)</td>
<td>29.1 (1.30)</td>
<td>1.40, p=0.149</td>
</tr>
<tr>
<td>RBANS indices (standard score)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Memory</td>
<td>106.13 (9.94)</td>
<td>109.53 (10.99)</td>
<td>0.89, p=0.382</td>
</tr>
<tr>
<td>Visuospatial/constructional</td>
<td>102.07 (12.61)</td>
<td>101.40 (15.38)</td>
<td>0.13, p=0.898</td>
</tr>
<tr>
<td>Language</td>
<td>104.33 (10.20)</td>
<td>104.87 (12.24)</td>
<td>0.13, p=0.898</td>
</tr>
<tr>
<td>Attention</td>
<td>107.80 (13.73)</td>
<td>105.33 (17.00)</td>
<td>0.44, p=0.685</td>
</tr>
<tr>
<td>Delayed Memory</td>
<td>105.93 (7.99)</td>
<td>103.13 (15.07)</td>
<td>0.64, p=0.530</td>
</tr>
<tr>
<td>Total</td>
<td>107.13 (10.43)</td>
<td>106.73 (14.10)</td>
<td>0.09, p=0.930</td>
</tr>
</tbody>
</table>

**Trained stimuli (post>pre)**

**Novel stimuli (post>pre)**

- MST Group
- SCT Group

> "SCT primarily resulted in reduced activation in the prefrontal cortex and ventral visual stream areas (not shown), suggesting repetition suppression effects. Increased activation was restricted to the left angular gyrus, consonant with the role this region plays in memory (though the magnitude of change was greater in the MST group)."

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Hampstead et al., *in progress* 23
MST Facilitates Hippocampal Activation in MCI

No changes in the SRT group

No changes in the exposure group

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Overview

1. Aging & Dementia
   • Understanding memory deficits
   • Evaluating & targeting treatment

2. 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
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Types of Surgery for Epilepsy

- Removing brain tissue may cause cognitive impairment
- Wada test is “gold standard” for evaluating functioning
- Language & memory

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http://emedicine.medscape.com/article/1874484-overview
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 mapping
  - Memory functioning
fMRI uses in Epilepsy: Memory

Functional MRI predicts post-surgical memory following temporal lobectomy

Marcie L. Rabin,¹ Veena M. Narayan,¹ Daniel Y. Kimberg,¹,² Daniel J. Casasanto,¹ Guila Glosser,¹ Joseph I. Tracy,³ Jacqueline A. French,¹ Michael R. Sperling³ and John A. Detre¹,²

Fig. 5 fMRI results from HPF ROI versus change in discrimination score on scene recognition testing between pre-surgical and post-surgical testing. (A) fMRI AR versus discrimination score change. fMRI AR is calculated from fractional positive activation within the ROI using \( [(\text{contralateral} - \text{ipsilateral})/(\text{contralateral} + \text{ipsilateral})] \). (B) Absolute fMRI activation ipsilateral to the clinical seizure focus and resection versus change in discrimination score. (C) Absolute fMRI activation contralateral to the clinical seizure focus and resection versus change in discrimination score. Absolute activation is expressed as the fractional positive ROI. Plot symbols differentiate left- (triangles) and the right-sided (squares) TLE patients. Dashed lines show regression results \( r = 0.550, P = 0.007 \) for HPF AR, \( r = -0.560, P = 0.005 \) for absolute ipsilateral HPF activation, \( r = -0.146, P = 0.506 \) for absolute contralateral HPF activation. Vertical dotted lines indicate 2 SD of normative results.
fMRI uses in Epilepsy: Memory

Bringing Memory fMRI to the Clinic: Comparison of Seven Memory fMRI Protocols in Temporal Lobe Epilepsy

• Compared Hometown walking (mental imagery) (B), scene encoding (B&E), picture encoding (B&E), and word encoding (B&E)

• 16 patients with TLE (13 with complete data) – each task in each of 3 sessions

• Group level analyses = significant bilateral MTL activation for all protocols

• Effects differed by seizure laterality and paradigm
fMRI uses in Epilepsy: Memory

Comparing Memory fMRI to the Clinic: Comparison of Seven Memory fMRI Protocols in Temporal Lobe Epilepsy


Karren Towgood,1 Gareth J. Barker,2 Alejandro Caceres,2 William R Crum, Robert D.C. Elwes,1 Sergi G. Costafreda,5 Mitul A. Mehta,2 Robin G. Morris,6 Tim J. von Oertzen,7 and Mark P. Richardson1*

Comparable between-session performances – rules out a potential confound

Figure 1.

Mean recognition accuracy for participants across session and fMRI protocol. Recognition accuracy is calculated as hit rate minus false alarm rate. Error bars represent 1 SEM.

Hampstead fMRI Training Course 2016
fMRI uses in Epilepsy: Memory

• ~Fair reliability
• Data analysis techniques matter
• No “gold standard?”

<table>
<thead>
<tr>
<th>TABLE II. Reliability of medial temporal lobe ROI BOLD signal laterality index for each fMRI protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>fMRI protocol</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Hometown</td>
</tr>
<tr>
<td>Scenes-block</td>
</tr>
<tr>
<td>Scenes-event</td>
</tr>
<tr>
<td>Pictures-block</td>
</tr>
<tr>
<td>Pictures-event</td>
</tr>
<tr>
<td>Words-block</td>
</tr>
<tr>
<td>Words-event</td>
</tr>
</tbody>
</table>

Here, we take an ICC value of less than 0.40 to be poor, 0.40–0.59 as fair, 0.60–0.74 as good and values exceeding 0.75 as excellent. T1 is compared with T2, and T2 with T3 (n = 12). ICC = intraclass correlation coefficient, ICC(3,1) is defined in the Methods section. Significance threshold set according to false discovery rate.

Overlap values of activated voxels in medial temporal lobe ROI for each fMRI protocol (n = 13). Black bars show overlap values comparing T1 with T2; gray bars show overlap values comparing T2 with T3. The upper panel shows overlap of binary maps of voxels thresholded for significance at $P < 0.001$, within the MTL ROI, by task; the lower panel shows overlap values generated from raw t-images individually normalized to peak t values within the medial temporal lobe ROI.
**fMRI uses in Epilepsy: Memory**

**Bringing Memory fMRI to the Clinic: Comparison of Seven Memory fMRI Protocols in Temporal Lobe Epilepsy**

Asymmetry index $= \beta(\text{ipsilateral mTL ROI}) - \beta(\text{contralateral mTL ROI})$

**TABLE III. Classification of patients into right-onset and left-onset groups**

<table>
<thead>
<tr>
<th>fMRI protocol</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>AUC</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hometown</td>
<td>0.943</td>
<td>0.012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scenes-block</td>
<td>0.686</td>
<td>0.291</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scenes-event</td>
<td>0.686</td>
<td>0.291</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pictures-block</td>
<td>1.000</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pictures-event</td>
<td>0.886</td>
<td>0.028</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Words-block</td>
<td>1.000</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Words-event</td>
<td>1.000</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ROC was applied to the laterality index for each subject, for each fMRI protocol and session ($n = 12$). To examine whether repeating a protocol on more than one session contributes to accuracy of lateralisation, asymmetry values were averaged across T1 and T2 for each subject and protocol, and averaged across T1, T2, and T3 for each subject and protocol. AUC = area under curve.

*P < 0.001* for each fMRI protocol and session. Error bars show SEM. Upper left panel shows laterality index as right-minus-left ROI for all patients, which may provide an indication of material-specific lateralisation of the fMRI tasks; lower left panel shows laterality index as contralateral-minus-ipsilateral ROI for this is the same as right-minus-left ROI; lower right panel shows laterality index as contralateral-minus-ipsilateral ROI for right-onset patients (note this is the same as left-minus-right ROI). Black bars are for T1, white bars T2 and gray bars T3.

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fMRI uses in Epilepsy: Memory

- Pictures & words = 14 alternating blocks separated by 20s rest block
- Each stimulus shown 3,500ms + 2,000ms ISI; 10 stimuli/block
  - Pictures = color images
  - Words = concrete words (8 neutral and 2 (undefined) emotional words)

What are the challenges/limitations as it relates to this population?
Is a single run enough? (Power lectures)
How might cognitive processing preferences play in? Strategies?

Hampstead fMRI Training Course 2016
Use of preoperative functional MRI to predict verbal memory decline after temporal lobe epilepsy surgery

*Manoj Raghavan, and †Wade M. Mueller

Table 1. Patient data

<table>
<thead>
<tr>
<th></th>
<th>Left ATL Mean (SD)</th>
<th>Right ATL Mean (SD)</th>
<th>L vs. R p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>60</td>
<td>62</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age at surgery, y</td>
<td>37.4 (10.0)</td>
<td>40.3 (10.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>29/31</td>
<td>39/23</td>
<td>n.s.</td>
</tr>
<tr>
<td>Education, y</td>
<td>13.2 (2.3)</td>
<td>13.4 (2.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Handedness, R/L/A</td>
<td>48/11/1</td>
<td>49/9/4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age at epilepsy onset, y</td>
<td>15.1 (10.2)</td>
<td>14.9 (11.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Epilepsy duration, y</td>
<td>21.6 (13.0)</td>
<td>24.5 (13.9)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Full scale IQ</td>
<td>93.0 (12.4)</td>
<td>93.3 (12.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>91.9 (11.4)</td>
<td>93.3 (12.8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>95.8 (13.9)</td>
<td>94.6 (12.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Wada language asymmetry</td>
<td>0.548 (0.531)</td>
<td>0.825 (0.249)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Wada memory asymmetry</td>
<td>0.251 (0.446)</td>
<td>0.634 (0.310)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>fMRI lateral hemisphere</td>
<td>0.447 (0.431)</td>
<td>0.638 (0.381)</td>
<td>0.0125</td>
</tr>
</tbody>
</table>

F, female; M, male; R, right-handed; L, left-handed; A, ambidextrous; y, years.

aWada data are based on 56 left ATL and 62 right ATL patients.
bfMRI data are based on 60 left ATL and 57 right ATL patients.
fMRI uses in Epilepsy: Memory

- LTS = long term storage
- CLTR = consistent long term recall

Hampstead fMRI Training Course 2016
fMRI uses in Epilepsy: Memory

- LTS = long term storage
- CLTR = consistent long term recall

Stepwise regression

fMRI added before Wada due to non-invasive nature

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