FUNCTIONAL MRI AND NEUROPSYCHOLOGY

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NO DISCLOSURES.

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LEARNING OBJECTIVES

- State why clinical fMRI is a cognitive assessment.
- State two questions clinical fMRI can answer.
- State a first step you could take to begin learning clinical fMRI.
1. **FMRI AND COGNITIVE ASSESSMENT.**
2. **WHAT FMRI CAN AND CANNOT DO.**
3. **THE LANGUAGE SYSTEM THROUGH FMRI.**
4. **HOW TO GET INTO FMRI.**

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**KEY MILESTONES IN THE DEVELOPMENT OF FUNCTIONAL SRI**

- Late 1980s: MRI applied in humans.
- fMRI similar to the Wada at lateralization (1995).
- fMRI v Wada in predicting language decline (2003).
- CPT codes allow billing (2007) by MDs and psychologists.

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**WHY WOULD NEUROPSYCHOLOGISTS BE INVOLVED IN FMRI**

- In fMRI:
  - An individual completes a cognitive task in an MRI machine.
  - Images of blood flow are acquired simultaneously.
  - A map of brain regions active during that task is constructed.
WHY WOULD NEUROPSYCHOLOGISTS BE INVOLVED IN FMRI

- In fMRI:
  - An individual completes a cognitive task in an MRI machine.
  - Images of blood flow are acquired simultaneously.
  - A map of brain regions active during that task is constructed.
  - That is, a cognitively-defined metric is acquired.

- A "cognitive biomarker:" An objective, reliable, and valid metric “measured as an indicator of normal... processes, pathogenic processes, or... responses to an exposure or intervention, including therapeutic interventions.”

FMRI IS A FORM OF COGNITIVE ASSESSMENT

- As are:
  - Wada testing
  - Electrical stimulation mapping

FMRI IS A FORM OF COGNITIVE ASSESSMENT

- Neuropsychologists are trained in key clinical fMRI skills.
- Knowledge required:* 
  - Structural & functional neuroanatomy;
  - Statistics;
  - Use and development of cognitive assessment;
  - Basic MR physics;
  - Image analysis.

This is not widely appreciated.

Example: Manuscript feedback.

- Discussing controlling cognitive strategy to ensure valid results.
- Reviewer - ‘Two points about the discussion of potential differences in [cognitive] strategy. One would be to explicitly call this a “confound,” which it is.’
- Cognition is central. The biomarker is just an index.

When the centrality of cognition is not appreciated, it goes unstandardized.
When the centrality of cognition is not appreciated, it goes unstandardized.

Consequences

American Society of Functional Neuroradiology–Recommended fMRI Paradigm Algorithms for Presurgical Language Assessment

Table 1

<table>
<thead>
<tr>
<th>Feature</th>
<th>Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fixation</td>
<td>Scramble (40%)</td>
</tr>
<tr>
<td>2. Eyes closed, rest</td>
<td>Scramble (30%)</td>
</tr>
<tr>
<td>3. Eyes closed, rest</td>
<td>Button (44%)</td>
</tr>
<tr>
<td>4. Eyes closed, rest</td>
<td>Button (50%)</td>
</tr>
<tr>
<td>5. Eyes closed, rest</td>
<td>Button (58%)</td>
</tr>
<tr>
<td>6. Eyes closed, rest</td>
<td>None (44%)</td>
</tr>
<tr>
<td>7. Eyes closed, rest</td>
<td>Button (100%)</td>
</tr>
<tr>
<td>8. Eyes closed, rest</td>
<td>Postrun query (100%)</td>
</tr>
<tr>
<td>9. Eyes closed, rest</td>
<td>Evaluation of task compliance</td>
</tr>
</tbody>
</table>

1. FMRI and Cognitive Assessment.
2. What FMRI can and cannot do.
3. The Language System through FMRI.
4. How to get into FMRI.

White Paper: American Society of Functional Neuroradiology; BOLD for Presurgical Language Assessment

Appendix B

Supporting Information

1. FMRI and cognitive assessment.
2. What FMRI can and cannot do.
3. The language system through FMRI.
4. How to get into FMRI.
POSSIBLE GOALS OF FMRI

▸ Language lateralization.
▸ Prediction of post-surgical language change.
▸ Language localization.

LANGUAGE LATERALIZATION

▸ Wada v fMRI
▸ Broader literature:
  ◆ Discordance 0-20%.
  ◆ Average weighted discordance: 15%.

▸ Wada v fMRI (1993-2009, n=229)
  ◆ 86% concordance.
  ◆ 92-94% when one measure is left.
  ◆ Discordance: typically “bilateral” (38/42).
  ◆ Four truly discordant cases: all right handed, right foci.
  ◆ Only predictor of discordance: strength of right-shift in fMRI LI.

Szaflarski et al. (2017) Neurology 88:1

Swanson et al., 2009 Janecek et al. 2013, Epilepsia 54(2):314

Figure 2. Reported rates of discordance in language dominance classification by Wada and fMRI testing. The studies are arranged from top to bottom in order of increasing sample size.

Janecek et al. 2013, Epilepsia 54(2):314

appcn_fmri_epilepsy.key - 2022-04-29
PREDICTING LANGUAGE CHANGE

- Less often evaluated.
  - 56 temporal lobe cases (24L).
  - Prediction of decline >10 points on the BNT (n=60).
  - Temporal ROI: 100% sensitivity, 57% specificity.
  - Wada: 100%/43%.

Sabsevitz et al. 2003, Neurology 60:1788
Note: 42% of L ATL cases declined >10pts.

- 44 temporal lobe cases (24L).
- Prediction of decline >3pts, UK Naming Task (n=30).
- Frontal (MFG) ROI: 100% sensitivity, 33% specificity.
- Language measures alone: 100%/17%.

DECIDING WHETHER FMRI IS APPROPRIATE

- Language fMRI
  - Predicts language decline.
  - Not risk of amnesia.
- Wada testing
  - Predicts language decline.
  - Predicts risk of amnesia.

“CRUCIAL[LY]… RESULTS HOLD ONLY FOR THE PARTICULAR METHODS USED IN THE STUDY AND MAY NOT GENERALIZE … FMRI LANGUAGE MAPS SHOULD NOT YET BE ROUTINELY USED FOR PLANNING RESECTION BOUNDARIES”

Jeff Binder, 2011


**SO... HOW IS LANGUAGE EVALUATED, & FMRI USED?**

- Survey of Presurgical Language mapping - fMRI (n=81).
  - Lateralization: 100%.
  - Localization: 44% (guide margins).


**WHY IS LANGUAGE LOCALIZATION A TRICKY ENTERPRISE?**

- Theoretically: is language localized?
WHY IS LANGUAGE LOCALIZATION A TRICKY ENTERPRISE?

» Theoretically: is language localized?
» The fMRI signal (‘BOLD’) is indirect.

» fMRI relies on a series of assumptions and does not simply state “language is here”.
  » Unlikely to affect lateralization.
  » Likely to affect localization.

<table>
<thead>
<tr>
<th>Acquisition</th>
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<tr>
<td>Analysis</td>
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<tr>
<td>Presentation and interpretation</td>
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</table>
If this RESTING INSTRUCTIONS used in the specific instruction phase of this study are implicated in self-referential processing, with regard to SBN. MEDIAL PREFRONTAL AREAS have specifically been shown to increase activation in dmPFC. INCREASED ACTIVATION IN DMFC when participants are instructed to ATTEND to SBN than with no instruction at all, which may explain the increased awareness of external stimuli. WHETHER THE EFFORT was to IGNORE or ATTEND to SBN, the participant's awareness of SBN should be greater with external stimuli: SBN. Whether the effort was to ignore or attend to SBN when instructed to relax and stay still; this might cause increased dmPFC activation in the patient group only. Interestingly, DMN HYPERACTIVITY (including dmPFC) was used in the current study. The other four studies used functional connectivity analyses also revealed differences in the connectivity of previously reported components of the DMN, and therefore a careful consideration of results in patient populations which may show a systematic bias are important.

THE TASK USED

- Instructions on how to rest alter the activation pattern.
- Using rest as baseline also a key issue in language mapping.

It is worth noting that of the five papers used to derive clinical question, clarity, patients' awareness of SBN, is impacted by specific resting instructions on how to attend to SBN lead to alterations within prefrontal cortex (PFC). Differences between patients and healthy controls are therefore not limited to the dmPFC rather than the DMN as a whole. However, it is possible that DMN differences between patients and controls may be partially influenced by different approaches to resting strategies than healthy adults. For instance, patients may rest systematically treat rest differently; for instance, in patients with auditory hallucinations. Unfortunately, it is more likely that they will systematically treat rest differently; for instance, in patients with auditory hallucinations. Unfortunately, it is possible that patients with auditory hallucinations may systematically treat rest differently; for instance, in patients with auditory hallucinations.
Postoperative language decline who developed seizures at an earlier age generally have a lower risk for.

Previous studies have identified that reliably identifying patients at risk for postoperative naming decline is predictive of language outcome, though the actual evidence on this issue is limited to a few case reports. Wada language testing is predictive of language outcome, though the right hemisphere typically shows greater involvement in cases where naming is delayed postoperatively.

Better preoperative naming performance is associated with better postoperative naming performance. In assessing concordance, patients are typically scored on each test, and the proportion of concordant cases depends strongly on how these arbitrary categories are defined.

Surgeries were performed blind to the fMRI data, but were tailored using separate LI calculations for the whole hemisphere, frontal lobe, temporal lobe, and angular gyrus. All patients also underwent Wada language lateralization testing and preoperative assessment of confrontation naming using the 60-item Boston Naming Test (BNT). The BNT was administered to patients at the time of their first outpatient visit, again 6 months after surgery, and a change score was calculated as the difference between postoperative and preoperative scores. Surgeries were performed again 6 months after surgery, and a change score was calculated as the difference between postoperative and preoperative scores.

Fig. 1. Functional MRI data from 26 healthy volunteers performing two language mapping paradigms. The activation maps are displayed as serial sagittal sections, and the three steps in each color continuum represent voxelwise comparisons. The top panel shows the mean LI for each task contrast, and the error bars represent SE. Adapted, with permission, from J.R. Binder / Epilepsy & Behavior 20 (2011) 214.

Sabsevitz et al. studied 24 consecutively encountered patients, and their results showed that lateralization toward the left (surgical) temporal lobe was the strongest predictor of outcome relative to the control group. The temporal lobe fMRI LI was the strongest predictor of outcome.
who developed seizures at an earlier age generally have a lower risk for postoperative language decline. Previous studies have identified that Wada language testing is predictive of language outcome, though associated with a higher risk for decline. It has long been assumed that left temporal lobe lateralization on the Wada test is the strongest predictor of outcome, relative to the control group. The temporal lobe fMRI LI was the relative to poorer naming outcome, whereas lateralization toward the left (surgical) temporal lobe was associated with a higher probability of language shift to the right hemisphere, presumably because earlier age at onset is associated with a higher probability of language shift to the right hemisphere.

2.2. Predicting outcome

The fMRI paradigm used a contrast between an auditory semantic decision task and a nonlinguistic tone decision task (see Fig. 1). Blue arrows in the middle image indicate left hemisphere language areas that are active during the resting state. The graph at the bottom left shows the mean volume of activation in the left and right hemispheres for each task contrast. The graph at the bottom right shows the mean LI for each task contrast. Error bars represent SE. Adapted, with permission, from J.R. Binder / Epilepsy & Behavior 20 (2011) 214.

Data presentation

<table>
<thead>
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<td>Patient</td>
<td>Practice, intelligence, fatigue</td>
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<tr>
<td>Task</td>
<td>Broca's, Wernicke's, Control used</td>
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<tr>
<td>Sequences</td>
<td>TE, Multiband</td>
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<tr>
<td>Analysis components</td>
<td>Realignment, smoothing</td>
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<td>Parameters</td>
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<td>Operator knowledge</td>
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<td>Report</td>
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For the Sabsevitz et al. study, intraoperative electrical stimulation mapping. With so many studies focusing on fMRI, it is easy to understand why many clinicians believe that fMRI would be a valuable clinical tool, especially if the fMRI results added information over and above that provided by other available tests.
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Smoothing:
0mm

Smoothing:
8mm

Identical data, analysis

Considerations

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THE ABOVE VARIABLES DIFFER BETWEEN SITES

- Task used? Baseline of rest 59%, active control, 37%.
- Smoothing? Mode of 8mm ($\mu$=6, range 2-10).
- Interpretation of maps?
  - Surgical margin: average of 10mm (range 3-50).

Benjamin et al. (2018a), HBM 39:4032.
Benjamin et al. (2018b), HBM 39:2777.

DOES THIS MATTER?

- It depends: interpretation and evidence.
- Surveyed sites report:
  - Unexpected decline when no fMRI-positive language cortex is resected: 17% report $\geq$1 instance.
  - Unexpected preservation when fMRI-positive language cortex is resected: 54% report $\geq$1 instance.

Benjamin et al. (2018a), HBM 39:4032.

WELL, WHAT ABOUT ELECTRICAL STIMULATION MAPPING . . .

- Gold standard spatial information, essential presurgically, can predict post-surgical deficits.
- Weaknesses:
  - Mapping epileptogenic areas.
  - Invasive, complications (up to 9.9% of cases).
  - Again: key parameters vary dramatically.
  - 40% of sites report $\geq$1 patients suffer enduring deficits.

Wong et al. (2009), Acta Neurochir. 151:1-27
Nehberger et al. (2016), Epilepsia 57:333
1. FMRI AND COGNITIVE ASSESSMENT
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TEAM FOCUS ON BROCA'S & WERNICKE'S AREAS

- You may not identify areas if you are not looking for them.
- Sites using fMRI to localize language (orange bars) rarely look beyond Broca’s and Wernicke’s areas.

![Proportion of sites seeking to identify various language areas](image)

A COMPREHENSIVE MODEL OF LANGUAGE

- 1. Broca’s area
- 2. Exner’s area
- 3. Supplementary motor area
- 4. Angular Gyrus
- 5. Wernicke’s: Superior and inferior
- 6. Basal temporal language area
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Key role of anterior insula.

1. BROCA’S AREA

A syndrome ranging from anarthria to dyspraxia, to agrammatism.

Key role of anterior insula.

A COMPREHENSIVE MODEL OF LANGUAGE

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GRAPHEMIC MOTOR FRONTAL AREA

- Transforming phonological into written language.
- Focal posterior MFG resection: severe focal reading and writing deficits (A).
- Stimulation disrupts handwriting (n=6/12). Resection causes agraphia (n=2/12) (B).

(A) Anderson 1990, Brain 113:749
(B, C) Roux 2009, Ann Neurol 66:537

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SUPPLEMENTARY MOTOR AREA

- Initiation and sequencing for speech.
  - Language: transient, to mutism
  - Motor: transient changes.
  - IMRI: SMA activation is bilateral.
  - Deficit ∝ resected activation extent.
  - Motor deficits-more posterior resection.

Krainik et al. (2003), Neurology 60:587

Discussion.
The current results confirm that speech deficit that followed medial frontal lobe surgery was similar across patients. It consisted in a global speech reduction, ranging from complete mutism to a less severe speech reduction. This deficit recovered in all patients within 3 to 8 months. Based on an fMRI verbal fluency task, it was shown that speech disorders occurred after resection of at least 16% of the area activated in the SMA of the dominant hemisphere. Increased activation in the SMA contralateral to the tumor was observed, suggesting that a reorganization of SMA function occurred in the presence of brain tumor.
SUPPLEMENTARY MOTOR AREA

- Zentner: "unilateral SMA removal can be accomplished without resulting in significant permanent deficits."
- Recovery
  - Appears to reflect recruitment of contralateral SMA.
  - If contralateral SMA or corpus callosum impaired, ability to recover decreases (e.g., Endo, 2014).

ANGULAR GYRUS

- 1. Broca’s area
- 2. Exner’s area
- 3. Supplementary motor area
- 4. Angular Gyrus
- 5. Wernicke’s: Superior and inferior
- 6. Basal temporal language area

Reading, transitioning written - spoken language.

- Stimulation can interrupt writing, or cause irregular or unintelligible writing (also, e.g., repetition).
  - Agraphia (and acalculia) in 6/6 patients.
  - Reading and object naming disturbance in 5/6.
A COMPREHENSIVE MODEL OF LANGUAGE

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WERNICKE’S AREA

▸ Speech comprehension:
  (1) Analysis of speech sound for phonemes. Supported bilaterally. Bilateral STG and STS.
  (2) Retrieval of meaning (semantic information).

A COMPREHENSIVE MODEL OF LANGUAGE

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**BASAL TEMPORAL LANGUAGE AREA (BTLA)**

- A region of, mainly, fusiform cortex critically involved in associating names with concepts.
- Large variation in outcome after temporal lobe surgery.
- Extent of damage to the BTLA explains ~50% of decline in naming after temporal resection.

Binder et al. (2020). Epilepsia 61:1939

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**A COMPREHENSIVE MODEL OF LANGUAGE**

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Benjamin et al. (2017) HBM 38:4239

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**WHO IS A GOOD FIT**

In addition to skills required for neuropsychology you will benefit from -

- A particular interest in neuroanatomy.
- Enjoy working with computers.*
- Obsessive (analysis) and ultimately, practical (reporting).
- Good presentation skills (reporting).

**GETTING INTO FMRI**

- Ideally begin through research.
  - Analyze at least one large (n >20) fMRI dataset.
  - Ideally with a mentor, aim to publish the results.

**GETTING INTO FMRI**

- Can also begin through an academic clinical setting.
  - Approach radiology.
  - Sit in on some of their scans, analysis, reporting.
  - With permission, analyze a copy of the data.
WHERE TO GO TO LEARN MORE

- Sample initial lectures, or take a course.
  - MIT Martinos Center.  [https://education.martinos.org/home/fmri-visiting-fellowship/](https://education.martinos.org/home/fmri-visiting-fellowship/)
  - FSL fMRI Course.  [https://open.win.ox.ac.uk/pages/fslcourse/website/](https://open.win.ox.ac.uk/pages/fslcourse/website/)

GETTING INTO FMRI

- The main software is freely available, and includes data sets and step-by-step instructions.
  - Statistical Parametric Mapping (SPM) - analysis.  [https://www.fil.ion.ucl.ac.uk/spm/](https://www.fil.ion.ucl.ac.uk/spm/)

- FSL - analysis.  [https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/](https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/)

- Open multilingual fMRI battery - stimulus presentation software.  [www.cogneuro.net](http://www.cogneuro.net)