Neuroimaging Methods

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<th>Method</th>
<th>Contrast Mechanism</th>
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<td>Functional MR Spectroscopy (fMRS)</td>
<td>Lactate production and clearance during glycolysis</td>
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- 156 university undergraduates
- 4 articles summarizing faulty reasoning in results of a fictitious imaging study
- Data shown as brain image or (Exp. 1) text, bar graph (Exp. 2) spatial map
- Participants rated articles on 4-point scale
Some Common Misconceptions

- FMRI image is not a picture – a composite of many images
- Technically, FMRI does not measure neural activation
- The brain does not ‘light up’ when doing any task
- The colors displayed usually represent outcomes of statistical tests
- FMRI only describes, it does not ‘prove’ anything

Educational Objectives

- Identify areas of the brain used when reading, deficits in dyslexia, and effects of treatment
- Explain what FMRI really measures, how it relates to neural function, and what the images show
- Understand methodological issues involved in FMRI research
- Describe the differences between FMRI, FCMRI, DTI, MSI, and PET

Syllabus

I. What is the Neurobiology of Reading?
   A. Gross Anatomy
   B. The Reading Brain

II. Where do those images come from?
   A. MR Image Acquisition
   B. Functional MRI (FMRI)

III. How is FMRI data collected?
   A. Developing an Experiment
   B. Example FMRI Protocol

IV. Other Methods of Neuroimaging

Part IA: Brain Basics

1. Orientation
2. Structures
3. Brain Mapping
Brodmann Areas

Source: spot.colorado.edu/~dubin/talks/brodmann/brodmann.html

Broca's Area
BA 45

Wernicke's Area
BA 22

Language Processing Regions

Arcuate Fasciculus

Talairach Coordinates

Source: Brett et al., 2002. Box 1.
Brain Location

<table>
<thead>
<tr>
<th>Brain Location</th>
<th>Brodmann</th>
<th>Talairach</th>
<th>MNI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broca’s Area</td>
<td>45</td>
<td>-50, 12, 7</td>
<td>-51, 12, 8</td>
</tr>
<tr>
<td>Wernicke’s Area</td>
<td>22</td>
<td>-60, -35, 6</td>
<td>-61, -36, 5</td>
</tr>
</tbody>
</table>

Part IB: The Reading Brain

1. Cognitive Model of Reading
2. Skilled Reading Network
3. Reading Network in Dyslexia
4. Effects of Remediation

Cognitive Model of Reading

- Visual Word
  - Orthographic Processing
    - Lexical-Semantic Processing
    - Phonological Processing
  - Oral Pronunciation
Reading Network in Dyslexia

Source: Adapted from Shaywitz, S.E. 2003. Fig. 20.

Typical Dyslexic

NI DYS NI > DYS Nonword Reading


Remedial Treatment Effects

Processing Differences Baseline to One-Year Followup

Source: Shaywitz et al., 2004. Fig. 2
### Effects of Treatment

<table>
<thead>
<tr>
<th>Source</th>
<th>Method</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richards et al., 2000</td>
<td>FMRI</td>
<td>30 hours</td>
</tr>
<tr>
<td>Richards et al., 2000</td>
<td>FMRI</td>
<td>28 hours</td>
</tr>
<tr>
<td>Simos et al., 2002</td>
<td>MEG</td>
<td>80 hours</td>
</tr>
<tr>
<td>Aylward et al., 2003</td>
<td>FMRI</td>
<td>28 hours</td>
</tr>
<tr>
<td>Temple et al., 2003</td>
<td>FMRI</td>
<td>45 hours</td>
</tr>
<tr>
<td>Shaywitz et al., 2004</td>
<td>FMRI</td>
<td>105 hours</td>
</tr>
<tr>
<td>Eden et al., 2004</td>
<td>FMRI</td>
<td>112 hours</td>
</tr>
<tr>
<td>Simos et al., 2007</td>
<td>MEG</td>
<td>120 hours</td>
</tr>
</tbody>
</table>

### Part I Summary

1. Cortical lobes have some broadly specified functions
2. Brodmann, Talairach and MNI coordinates identify brain structure location
3. Cognitive model suggests two ways to read words
4. Neurological model shows 3 LH reading areas
   a. Dorsal (phonological analysis, semantics)
   b. Ventral (memory-based word identification)
   c. Frontal (phonological recoding)
5. LH posterior reading areas less active in dyslexia
6. Treatment for dyslexia impacts both behavior and brain function

### Part IIA: Magnetic Resonance Imaging

1. MRI Hardware
2. MR Signal
3. MR Image Acquisition
MRI Hardware: Scanner

MRI Hardware: Radio Frequency Coil

Longitudinal (T1) Recovery

Source: www.magnet.fsu.edu/education/tutorials/magnetacademy/mri/

Source: www.psychologicalscience.org/observer/getArticle.cfm?id=1547
T1-Weighted Image

Image Acquisition

MR Signal Time Series

Source: Huettel, Song, & McCarthy 2004 Fig. 8.3
Part IIIB: Functional MRI

1. Neural Activity and Metabolism
2. Blood Oxygenation Level Dependent Contrast (BOLD)
3. Hemodynamic Response Function

Source: www.drugabuse.gov/JSP/MOD3/page3.html

Neural Activity

Source: Huettel, Song, & McCarthy 2004 Fig. 6.3
**Metabolic Activity**

Glucose $\rightarrow$ Citric Acid Cycle $\rightarrow$ Electron Transport Chain

- 2 ATP
- 34 ATP
- O$_2$

Source: Huettel, Song, & McCarthy, 2004

**Neural-Vascular Coupling**

Source: www.web-books.com/eLibrary/Medicine/Physiology/Cardiovascular/capillary.jpg

**Blood Oxygenation Level Dependence (BOLD)**

- **Oxygenated Hemoglobin (Hb)**
  - Diamagnetic i.e. less magnetic
  - Stronger MR signal

- **De-oxygenated Hemoglobin (dHb)**
  - Paramagnetic i.e. more magnetic
  - Weaker MR signal
**Hemodynamic Response Function**

![Graph showing Hemodynamic Response Function](image)

**Hemodynamic Response Function Lag**

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>HRF Lag</th>
<th>Time Shift</th>
</tr>
</thead>
</table>

**Temporal and Spatial Resolution**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Neuronal Response</th>
<th>Vascular Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Frame</td>
<td>milliseconds</td>
<td>16 - 18 sec</td>
</tr>
<tr>
<td>Spatial Size</td>
<td>microns</td>
<td>3mm x 3mm x 3mm</td>
</tr>
</tbody>
</table>
Part II Summary

- Voxel is the primary unit of analysis
- FMRI measures BOLD, not neural activation per se
- Neurovascular coupling refers to correspondence of neural activity (metabolism) and blood flow
- Strength of BOLD signal depends on amount of oxygen-rich blood
- HRF peak lags 5-6 seconds after neural activity
- Significant differences in resolution of vascular and neural responses

Part IIIA: FMRI Research

1. Functional Tasks in Scanner
2. Stimulus Presentation
3. Participants

Functional Task Considerations

- Construct validity
- Psychologically specified
- Appropriate for sample
- Task equivalence between groups
- Appropriate baseline and comparisons
- Appropriate for environment
**Imaging Environment**

"Imaging Environment" text overlay.

**Subtraction Logic**

Diagram showing subtraction logic:
- Experimental Task (above baseline)
- Control Task (above baseline)
- Unique Activation

**Example of Hierarchical Tasks**

<table>
<thead>
<tr>
<th>Source: Shaywitz et al., 1998; 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual Spatial Orientation</strong></td>
</tr>
<tr>
<td><strong>Letter Case Judgment</strong></td>
</tr>
<tr>
<td><strong>Single Letter Rhyme</strong></td>
</tr>
<tr>
<td><strong>Nonword Rhyme</strong></td>
</tr>
<tr>
<td><strong>Semantic Category Judgment</strong></td>
</tr>
</tbody>
</table>
Experimental Design

Participants

I. Sampling
  - Demographics (e.g., Age, Gender)
  - Hemispheric Laterality
  - Phenotypic Heterogeneity
  - Co-morbid Conditions (e.g., ADHD)

II. Training
  - Task Performance
  - Mock Scanner
  - MR Safety

Participant Preparation
Differentiating the neural response to intervention in children with developmental dyslexia

- Functional abnormalities of dyslexia amenable to treatment\(^1\)
- Approximately 2-6% continue to struggle\(^2\)
- Participants were treatment responders and non-responders
- Study focus on brain function when doing a phonics task

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\(^1\) e.g., Simos et al., 2002; Shaywitz et al., 2004
\(^2\) Torgesen, 2000
Treatment Protocol

- Hospital Learning Disabilities Clinic
- Orton-Gillingham Based Curriculum
  - Articulatory Phonetics (10%)
  - Phonics (25%)
  - Fluency (18%)
  - Vocabulary/Comprehension Strategies (35%)
  - Spelling (17%)
- Instructed by Academic Language Therapists
- Small group instruction for 1.5 hours per day
- Four days / week for two academic years

* Avrit et al., 2006.

Scanner Apparatus

Adapted from Shaywitz, S.E. 2003. Fig 17.

Phoneme Task Response

/p/

p b
Tone Task Response

/beep/

Functional MR Imaging Series

Volume 1
TR = 2 Seconds

Image source: www.amri.ninds.nih.gov/sample_data.htm

Participant Debriefing
Motion Correction

Axial Image with Motion Artifacts

Axial Image without Motion

Preprocessing Steps

Original Space

Talairach Space

Spatial Smoothing

Data Analysis

Subjects' 147 Volumes

Subjects' Statistical maps

Combined statistical map

Source: Huettel, Song, & McCarthy, 2004 Fig. 12.2
Data Analysis

Tone Task activation above Rest State
Phoneme Task activation above Rest State

Results

TYPICAL
DYLEXIC

Source: Adapted from Shaywitz, S.E., 2003. Fig. 20.

Source: Odegard et al., 2008.
Results

Limitations
- Functional data collected only post-treatment
- Small samples limit generalizability
- Primary functional task focused on phoneme mapping to orthography – not reading
- Non-responders’ word recognition ability was significantly lower at baseline

Part III: Summary
1. Scanner tasks must be valid, specific and appropriate for sample
2. Inference from subtraction depends on appropriate baseline and contrast tasks
3. Safe data collection requires extensive participant training
4. Research reports should provide, at minimum
   a. Well-specified psychological construct(s)
   b. Detailed task descriptions
   c. Behavioral descriptions of participants
   d. Results described in context of research literature
   e. Acknowledgement of limitations

Source: Odegard et al., 2008.
1. Functional Connectivity (fcMRI)
2. Diffusion Tensor Imaging (DTI)
3. Magnetoencephalography (MEG)
   Magnetic Source Imaging (MSI)
4. Positron Emission Tomography (PET)

Part IV: Other Neuroimaging Methods

Functional Connectivity

Correlation of event timing in separate brain areas

Source: Villalobos et al., 2005.

Correlations of Angular Gyrus with Select Language and Visual Regions

<table>
<thead>
<tr>
<th></th>
<th>Left Hemisphere</th>
<th>Right Hemisphere</th>
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<tbody>
<tr>
<td></td>
<td>Dyslexic  NI</td>
<td>Dyslexic  NI</td>
</tr>
<tr>
<td>Wernickes’ (BA 22)</td>
<td>.13  .49*</td>
<td>.57*  .66*</td>
</tr>
<tr>
<td>Medial Striate (BA 18/19)</td>
<td>.34  .75*</td>
<td>.63*  .59*</td>
</tr>
<tr>
<td>Lateral Striate (BA 18/19)</td>
<td>.21  .32*</td>
<td>.32   .42*</td>
</tr>
<tr>
<td>Primary Visual (BA 17)</td>
<td>.26  .65*</td>
<td>.68*  .35*</td>
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Source: Adapted from Hughes et al. 2000. Eq. 1.
Diffusion Tensor Imaging (DTI)

isotropic

anisotropic

Source: Huettel, Song, & McCarthy 2004 Fig. 5.18

Diffusion Tensor Imaging (DTI)

Source: www.cmr.mcgill.ca/~shape/projects/tractography/tractography.html

Diffusion Tensor Imaging

Corona Radiata

Source: Ben-Shachar et al., 2007, Fig. 4c.
Magnetic Source Imaging (MSI)

Source: Simos et al., 2007 Figs. 4-5.

Typical Dyslexic
Average onset to visually presented pseudowords

Positron Emission Tomography (PET)

Source: health.howstuffworks.com/nuclear-medicine1.htm
**Positron Emission Tomography (PET)**

Areas of increased activation in control relative to dyslexic.

Source: McCrory et al., 2005 Fig. 2

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**Summary and Conclusions**

- FMRI is descriptive, not predictive\(^1\)
- FMRI is an indirect measure of neural activity
- FMRI interpretations based on chain of assumptions and decisions
- “Activation” reflects less about neural activity in individuals and more about statistical decisions about groups
- FMRI’s proper place is as one of several converging methods

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\(^1\) C.F., Hoeft et al., 2007.
Summary and Conclusions

• Cognitive abilities are distributed as functional networks
• Three regions consistently used for reading, but not necessarily unique to reading
• Dyslexia profile includes under-engagement of posterior left temporo-parietal and occipito-temporal regions
• Treatment effects include ‘normalization’ and compensation

Thank You