Some Announcements

• For those taking lab: Meet in this lecture hall today at 2:00 for lab preview
• Each lab will have a lab preview; this week, those will occur just prior to the lab after lunch; meet in the lecture hall; next week, those will occur at the end of lecture prior to the lunch break
• Need to split lab group in three for lab Wed (at first break today)
• Lectures available each afternoon on the course website:
  – https://fmri-training-course.psych.lsa.umich.edu
1. You can re-watch the lecture videos from this training course

2. The free online course site called Coursera has some great classes that you can take as a formal class or just watch the videos at your own pace such as "Statistical Analysis of fMRI Data": https://www.coursera.org/course/fmri

3. There is also a new course being offered that seems like it may be good: "Exploring Neural Data": https://www.coursera.org/course/neuraldata

4. This is a useful course to learn about Matlab: https://www.coursera.org/learn/matlab
Michigan Neuroimaging Initiative

Interaction & Shared Knowledge
Talks/workshops
Tuesdays @ 4pm
4464 East Hall

Methodological and Statistical Training
Join us!
michigan-nii@umich.edu

Computing Resources, Training, and Support
<table>
<thead>
<tr>
<th>Day/Date</th>
<th>Time</th>
<th>Topic</th>
<th>Instructor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mon. 8/6/2018</td>
<td>8:00 AM – 1:00 PM</td>
<td>Introduction to Neuroanatomy &amp; Experimental Design</td>
<td>John Jonides University of Michigan</td>
</tr>
<tr>
<td>Tues. 8/7/2018</td>
<td>8:30 AM – 12:30 PM</td>
<td>MRI Physics</td>
<td>Doug Noll University of Michigan</td>
</tr>
<tr>
<td>Wed. 8/8/2018</td>
<td>8:30 AM – 12:30 PM</td>
<td>MRI &amp; BOLD Physics</td>
<td>Doug Noll University of Michigan</td>
</tr>
<tr>
<td>Thurs. 8/9/2018</td>
<td>8:30 AM – 12:30 PM</td>
<td>Artifacts &amp; Preprocessing</td>
<td>Luis Hernandez-Garcia University of Michigan</td>
</tr>
<tr>
<td></td>
<td>6:00 PM – 7:00 PM</td>
<td>Clinical applications of fMRI</td>
<td>Benjamin Hampstead University of Michigan</td>
</tr>
<tr>
<td>Fri. 8/10/2018</td>
<td>8:30 AM – 12:30 PM</td>
<td>DTI, Non-BOLD, &amp; Arterial Spin Labeling</td>
<td>Robert Welsh University of Utah Luis Hernandez-Garcia University of Michigan</td>
</tr>
<tr>
<td>Date</td>
<td>Time</td>
<td>Lecture Topic</td>
<td>Instructor(s)</td>
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<tr>
<td><strong>SUNDAY,  8/12/2018</strong></td>
<td>6:00 – 7:00 PM</td>
<td>Intro Stats Lecture (Optional)</td>
<td>Jeanette Mumford University of Wisconsin-Madison</td>
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<tr>
<td><strong>Mon.  8/13/2018</strong></td>
<td>8:30 AM – 12:30 PM</td>
<td>Overview, First Level Analysis, &amp; Experimental Design</td>
<td>Jeanette Mumford University of Wisconsin-Madison</td>
</tr>
<tr>
<td><strong>Tues.  8/14/2018</strong></td>
<td>8:30 AM – 12:30 PM</td>
<td>Experimental Design (cont.), Contrasts, &amp; Group Analysis</td>
<td>Jeanette Mumford University of Wisconsin-Madison</td>
</tr>
<tr>
<td></td>
<td>6:00 – 7:00</td>
<td>Pattern Recognition &amp; Real-Time Lecture</td>
<td>Stephen LaConte Virginia Tech</td>
</tr>
<tr>
<td><strong>Wed.  8/15/2018</strong></td>
<td>8:30 AM – 12:30 PM</td>
<td>Group Analysis (cont.) &amp; Theoretical Considerations</td>
<td>Jeanette Mumford University of Wisconsin-Madison</td>
</tr>
</tbody>
</table>
| **Thurs.  8/16/2018**  | 8:30 AM – 12:30 PM | Network Analysis & Tools—PPI, Connectivity, Resting State Connectivity, DCM, & Granger causality | Jeanette Mumford University of Wisconsin-Madison  
<p>|                        |                  |                                                   | Scott Peltier University of Michigan              |
|                        |                  |                                                   | Luis Hernandez-Garcia University of Michigan      |
| <strong>Fri.  8/17/2018</strong>    | 8:30 AM – 12:30 PM | Structured Q &amp; A                                  | All instructors                                   |</p>
<table>
<thead>
<tr>
<th>Day/Date</th>
<th>Time</th>
<th>Topic</th>
<th>Instructor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mon. 8/6/2018</td>
<td>2:00 – 5:00 PM</td>
<td>Matlab (Basic) B250/B254</td>
<td>Luis Hernandez-Garcia, Robert Welsh, Scott Peltier, Andy Jahn</td>
</tr>
<tr>
<td></td>
<td>6:00 – 8:00 PM</td>
<td>E-Prime (Optional) B250</td>
<td>Lilian Cabrera, Tessa Abagis, &amp; Colleen Frank</td>
</tr>
<tr>
<td>Tues. 8/7/2018</td>
<td>1:30 – 5:00 PM</td>
<td>Matlab (Image Analysis) B250/B254</td>
<td>Luis Hernandez-Garcia, Robert Welsh, Scott Peltier, Andy Jahn</td>
</tr>
<tr>
<td></td>
<td>6:00 – 8:00 PM</td>
<td>E-Prime (Optional) B250</td>
<td>Lilian Cabrera, Tessa Abagis, &amp; Colleen Frank</td>
</tr>
<tr>
<td>Wed. 8/8/2018</td>
<td>1:00 – 2:30</td>
<td>fMRI Lab Tour Group A: 1:00 – 2:30 PM Group B: 2:30– 4:00 PM Group C: 4:00-5:30</td>
<td>fMRI LAB TOUR: John Jonides, Doug Noll &amp; Scott Peltier</td>
</tr>
<tr>
<td></td>
<td>2:30 - 4:00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4:00 - 5:30</td>
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<td></td>
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<tr>
<td>Thurs. 8/9/2018</td>
<td>2:00 PM – 5:00 PM</td>
<td>Matlab GLM (Single Voxel)</td>
<td>Luis Hernandez-Garcia, Robert Welsh, Scott Peltier, Vincent Koppelmans, Andy Jahn</td>
</tr>
<tr>
<td>Fri. 8/10/2018</td>
<td>1:30 PM – 5:00 PM</td>
<td>Pre-processing &amp; SPM 1</td>
<td>Luis Hernandez-Garcia, Scott Peltier, Robert Welsh, Vincent Koppelmans, Andy Jahn</td>
</tr>
</tbody>
</table>
## Week 2 Lab Schedule

<table>
<thead>
<tr>
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<th>Date</th>
<th>Time</th>
<th>Session</th>
<th>Instructor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mon.</td>
<td>8/13/2018</td>
<td>1:30 PM – 5:00 PM</td>
<td>SPM I Single Subject Analysis</td>
<td>Luis Hernandez-Garcia, Robert Welsh, Scott Peltier, Vincent Koppelmans, Jeanette Mumford, Andy Jahn</td>
</tr>
<tr>
<td>Tues.</td>
<td>8/14/2018</td>
<td>1:30 PM – 5:00 PM</td>
<td>SPM II Experimental Design</td>
<td>Luis Hernandez-Garcia, Robert Welsh, Scott Peltier, Vincent Koppelmans, Jeanette Mumford, Andy Jahn</td>
</tr>
<tr>
<td>Wed.</td>
<td>8/15/2018</td>
<td>1:30 PM – 5:00 PM</td>
<td>SPM III Group Analysis Region of Interest Analysis</td>
<td>Luis Hernandez-Garcia, Robert Welsh, Scott Peltier, Vincent Koppelmans, Jeanette Mumford, Andy Jahn</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6:00-8:00 PM</td>
<td>Multi-Voxel Pattern Analysis Real-Time MEET AT SCANNER AT fMRI CENTER Functional MRI Laboratory 1072 BIRB 2360 Bonisteel Blvd. MAPS will be available</td>
<td>Steve LaConte, Luis Hernandez-Garcia, Scott Peltier, Robert Welsh, John Jonides</td>
</tr>
<tr>
<td>Thurs.</td>
<td>8/16/2018</td>
<td>1:30 PM – 5:00 PM</td>
<td>Special Topics (i.e., Connectivity, PPI, Causality, Resting State, MVPA)</td>
<td>Luis Hernandez-Garcia, Robert Welsh, Scott Peltier, Steve LaConte, Vincent Koppelmans, Jeanette Mumford, Andy Jahn</td>
</tr>
<tr>
<td>Fri.</td>
<td>8/17/2018</td>
<td>NO LAB</td>
<td>NO LAB</td>
<td>NO LAB</td>
</tr>
</tbody>
</table>
1. What You Can Do With Neuroimaging Data

2. Very Basic Gross Human Neuroanatomy

3. Elements of Experimental Design for fMRI
Agenda

• What neuroimaging data can tell us
  – Brain Mapping: Localization
  – Associations among psychological processes
    • Relationship to other association strategies
  – Dissociations among psychological processes
    • Relationship to other dissociation strategies
  – Individual differences
  – Testing psychological models
Brain Mapping: Localization

- Correlate structure with function
- Provide data to predict loss of function with brain injury
- Guide neurosurgical planning
- Map networks of regions that participate in complex tasks
  - Structural connectivity determined by DTI
  - Functional connectivity determined by techniques such as seed-based connectivity or multi-voxel pattern analysis
Caveats

• Neuroimaging data do not establish necessity
  – Must accompany them with lesion data

• Are you localizing the process you want?
  – Control over subject’s processing path
    • Alternative strategies
Localization of Object Recognition

- Downing et al. (2001)
  - Ss view pictures of human bodies or body parts
  - Compared to viewing of other objects (e.g., cars, birds, fish, trees, clothes, chairs, tools)
  - Right lateral occipitotemporal cortex selectively activated by body parts
Localization is Distributed

- Haxby et al. (2001)
  - Ss viewed faces, cats, houses, chairs, scissors, shoes, nonsense objects
  - Find lots of inferior temporal activation
  - Within-category correlations higher than between-category
  - Taking out highest activation, remaining pattern still predicts the object class
    - Indicates need for pattern classification, not just univariate analysis
Localization is Distributed

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Using Neuroimaging to Associate Psychological Processes

General Logic

Assume:
- System A underlies performance in Task 1
- System A underlies performance in Task 2

Implementation

Task 1 → Recruitment of System A → Activation of Area a but not Area b

Task 2 → Recruitment of System A → Activation of Area a but not Area b
Associations

• Caution: reliance on null results
• Stronger inference with planned comparisons based on prior data
• Stronger inference when examining a network of regions
• Danger of reverse inference
  – Just because the same region is activated, one can’t conclude that the same process is engaged
  – Regions may have multiple functions
Associating Perception and Imagination

Ganis et al., 2000

4.5 sec after instruction, given question about object

Auditory instruction to image or perceive

Compare activations to baseline
Perception and Imagery

Comparison of Imagery and Perception Conditions in Anterior and Posterior Cortex: 92% Overlap
What Can Neuroimaging Tell Us?

Dissociating psychological processes

**General Logic**

Assume:
- System A underlies performance in Task 1
- System B underlies performance in Task 2

**Implementation**

- Task 1: Recruitment of System A → Activation of Area a but not Area b
- Task 2: Recruitment of System B → Activation of Area b but not Area a
Spatial and Verbal Working Memory

Similar tasks with different materials

Spatial Memory Condition

Spatial Control Condition

Letter Memory Condition

Letter Control Condition
Results from PET Measurements

Different regions of activation depending on type of material
Dissociations
Applied to data from patients

General Logic
Assume:
System A underlies performance in Task 1
System B underlies performance in Task 2

Implementation
Task 1 → Pt with damage to System A → Deficit on Task 1 but not Task 2
Task 2 → Pt with damage to System B → Deficit on Task 2 but not Task 1
Dissociations

- Applied to verbal vs. spatial working memory
  - Behavioral studies of patients
    - e.g., Basso et al. (1982) -- PV: left posterior lesion and deficit in verbal working memory
    - e.g., Hanley et al. (1991) -- ELD: right diffuse anterior and posterior lesion and deficit in spatial working memory
Studying Individual Differences

- Canli et al. (2002)
  - Ss classify emotional or neutral faces by gender
  - Fearful faces activated amygdala across subjects regardless of extraversion
  - Happy faces activated amygdala only to the extent that Ss scored high on a measure of extraversion
Studying Individual Differences

• Canli et al. (2002)
  – Ss classify emotional or neutral faces by gender
  – Fearful faces activated amygdala across subjects regardless of extraversion
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Modeling the Aging Brain

Dedifferentiation

• Increased intercorrelations among perceptual and cognitive processes
• Thought to reflect a decline in integrity of the aging brain: reduced distinctiveness of neural representations
• Frequently seen in more bilateral activation in older adults
  • Could reflect compensation
  • Could reflect impaired neural processing
Carp et al. (2011) on Dedifferentiation

- Had older and younger adults view faces, houses, chairs, pseudowords, control images
- Used MVPA to test for distinctiveness in neural response
- Neural response to each category vs control images
- Compare within and between category correlations across all pairs of categories
- Neural distinctiveness = difference of between-within correlations
- Searchlight analysis:
  - For each voxel, assess how distinctive neural patterns for different categories are for a sphere surrounding that voxel
Older adults show less neural distinctiveness than young adults; activation patterns discriminate among categories less well in older adults.

Older adults show lower within-category correlations and higher between-category correlations than younger adults.
Searchlight Analysis

Higher neural distinctiveness regions for younger than older adults
No higher neural distinctiveness for older than younger adults
The Place of Neuroimaging Data: No Time for Imperialism

- They provide information about brain-behavior correlations
- They provide a source of associations and dissociations to converge with other sources
- They permit an assessment of individual differences to complement other assessments
- They permit one to test models of processes
- In some cases (e.g., imagery, responding with interference), they are more probative
- In some cases (e.g., storage in memory), they may be redundant with other data
- In some cases (e.g., inductive reasoning), they have been less probative because of task complexity
1. What You Can Do With Neuroimaging Data

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Directions in the Nervous System

• For Human Brain:
  – Anterior/rostral: front
  – Posterior/caudal: back
  – Superior/dorsal: top
  – Inferior/ventral: bottom
  – Medial: toward middle
  – Lateral: toward outside
Planes of Section

• Sagittal
  – Mid-sagittal
  – Para-sagittal

• Horizontal/axial/transaxial

• Coronal/frontal
Coronal
Sagittal
Early Brain Development

• Starts out as flat plate in ectodermal tissue that folds over to create a tube
• Parts of tube differentiate into different parts of nervous system
What Happens to the Lumen (hole) in the Tube

- Spinal cord channel
- Ventricles
  - Lateral
  - Third
  - Fourth
Layout of the Ventricle

- Lined with choroid plexus especially in lateral ventricles
  - Makes cerebrospinal fluid (CSF)
Basal Ganglia

caudate nucleus

putamen

Medial view

Anterior view
Coronal Section

- Lateral ventricle (anterior horn)
- Caudate nucleus
- Internal capsule (anterior limb)
- Putamen
- Longitudinal (interhemispheric) cerebral fissure
- Cingulate gyrus
- Corpus callosum
- Septum pellucidum
- External capsule
- Extrem capsule
Blood Supply to Brain

- Internal carotid artery feeds to anterior and middle cerebral arteries
- Vertebral arteries join to form basilar artery that feeds to posterior cerebral artery
Internal carotid artery

Circle of Willis

Middle cerebral artery

Basilar artery

Bottom view of brain
Distribution of Main Arteries
Coarse Structure of the Brain
Lateral View

- Cortical and subcortical structures
- Cortex divided into 4 lobes
  - Lobes have folded structure
    - Bumps are gyri (singular: gyrus)
    - Indentations are sulci (singular: sulcus)
Coarse Structure of the Brain

Medial View

• Note connecting fibers between hemispheres
Coarse Structure of the Brain
Ventral View
Brodmann’s Map
Words of Wisdom

- If you want to do fMRI, you must take neuroanatomy

- You need to always have a good atlas handy, such as:


- You should not describe areas of activation only in terms of Brodmann’s designations. Pay attention to gyri and sulci also
Lateral Sulci

- Superior frontal sulcus
- Middle frontal sulcus
- Inferior frontal sulcus
- Precentral sulcus
- Central sulcus
- Postcentral sulcus
- Intraparietal sulcus
- Sylvian Fissure
- Transverse occipital sulcus
- Lateral occipital sulcus
- Inferior occipital sulcus
- Superior temporal sulcus
- Inferior temporal sulcus
Medial Sulci

- Cingulate sulcus
- Central sulcus
- Precentral sulcus
- Transverse parietal sulcus
- Subparietal sulcus
- Parieto-occipital sulcus
- Calcarine sulcus
- Lingual sulcus
- Collateral sulcus
- Temporo-occipital sulcus
- Corpus callosum
- Fornix
A Canonical Brain
Dealing with different heads: spatial normalization

subject A  standard space  subject B

Caveats:
- inter-subject variability in anatomy (gyral and sulcal variation)
- variability in structure/function relationships
T1 and T2 Images

- Note gray-white matter distinction in T1
- Note reversed contrast of CSF in T1 and T2
- Note finer anatomical detail in T1
Which is More Caudal?

Third ventricle
thalamus
hippocampus
pons
Back (splenium) of Corpus callosum
Fourth ventricle
cerebellum
Which is more Dorsal?
Which is more Dorsal?

- amygdala
- hippocampus
- cerebellum
- midbrain
- Front (genu) of Corpus callosum
- Lateral ventricle
- caudate
- putamen
- Globus pallidus
- Back (splenium) of Corpus callosum
- Lateral ventricle
Identifying Structures

- Caudate
- Ventricle
- Central sulcus
- Parietal lobe
- Occipital lobe
- Interhemispheric fissure
- Corpus callosum
- Insula
Low Axial Slice

- Eye
- Thalamus
- Lateral ventricle
- Sylvian fissure
- Temporal lobe
- Third ventricle
- Corpus callosum
Lower Still

- Optic chiasm
- Amygdala
- Lateral ventricle
- Superior colliculus
Lowest of All

Hippocampus

Inferior colliculus

Inferior Temporal lobe
1. What You Can Do With Neuroimaging Data

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3. Elements of Experimental Design for fMRI
A Bit of Background

- What do you *want* to measure versus what *is* measured?
  - Interested in neural activity of single neurons or ensembles of neurons
  - No direct way of measuring neural activity in normal humans or most cases of pathology
  - Instead, need indirect measures that are correlated with neural activity
  - The **BOLD** (Blood Oxygenation Level Dependent) effect measures blood oxygenation in bulk neurons
    - (Actually, the name is a misnomer; it should be Blood Deoxygenation Level Dependent)
    - in a typical 3x3x3 mm voxel, there are 10 million neurons)
Hemodynamics: Basal State

<table>
<thead>
<tr>
<th></th>
<th>O2 &amp; Glu Metabolism</th>
<th>Blood Flow</th>
<th>Blood Volume</th>
<th>Blood O2</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
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</tbody>
</table>
Hemodynamics: Active State

<table>
<thead>
<tr>
<th></th>
<th>O2 &amp; Glu Metabolism</th>
<th>Blood Flow</th>
<th>Blood Volume</th>
<th>Blood O2</th>
</tr>
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<tbody>
<tr>
<td>Active</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↑</td>
<td>↑↑</td>
</tr>
</tbody>
</table>
So, What Actually Causes the Signal?

- Increased flow of blood to an active region
- Increased delivery of oxygen that is magnetically inert
- Increased production of deoxygenated hemoglobin; this is magnetically susceptible
- But the increased production of deoxygenated hemoglobin is outstripped by the increased flow which removes the deoxy-hemoglobin
- Therefore, decreased perturbation of magnetic field in the active region
- So, signal due to reduction in level of deoxy-hemoglobin in draining veins
Digging Down

• BOLD signal coupled vascularly to neural activity
  – Neural activity causes increased flow of sodium, calcium, and potassium ions
  – Changes in extracellular potassium activates capillary endothelial cells
    • This causes upstream arteriolar dilation leading to increased blood flow
The BOLD Effect

### MR Properties
- Physical Effects
- Physiological Effects
- Metabolic Rates
- Brain Function

### T2*-weighted Image Intensity
- Physical Effects
- Magnetic Field Uniformity (microscopic)
- Cerebral Blood Volume (CBV)
- Blood Oxygenation
- Cerebral Blood Flow (CBF)
- Glucose and Oxygen Metabolism
- Neuronal Activity

### Other Factors
- Vessel Diameter
- Vessel Orientation
- Hematocrit
- Blood Volume Fraction
The BOLD fMRI signal has no direct, absolute interpretation. Must be compared between states studied close together in time.
A Solution: Cognitive Subtraction

• Identify the task that interests you
• Analyze the task into component processes
• Create another task that has all the same processes save the one of interest
  – Assumption of pure insertion
• Compare the two tasks
A Simple Case of Cognitive Subtraction

Hand Clenching

Rest

Statistical Parameter Map

Overlay of Activation onto Anatomical Image

Supplementary Motor Area

Primary Motor Area
Caveats

• You don’t have direct access to the processes
  – Changing from one task to another may cause subjects to change strategies and component processes

• Adding a process may change the ones already in place
Separating Components of Memory

- **stimulus encoding**
- **working memory**
- **response preparation**
- **response execution**

**Delay:**
- Stimulus: 100 ms
- Delay: 7400 ms
- Response: 500 ms

**No-Delay:**
- Stimulus: 100 ms
- Response: 500 ms
- Delay: 7400 ms
Separating Components of Memory

Note:
For this analysis to work, the assumption of linearity of the BOLD signal must hold true.

Suppose that in the no-delay condition, the signal saturates so that activation to the stimulus and the delay is not the sum of each separately.

This will result in underestimation of no-delay activity and a conclusion that the difference between delay and no-delay is due to memory when it is, in fact, due to underestimation of the control.
Can you add a cognitive process to a pre-existing set without interaction between processes?

Pure Insertion
An Alternative to Cognitive Subtraction

• Cognitive Conjunction Design
  – Create two situations each of which involves the same putative subtraction
  – See if the activations that result are the same
  – e.g., two different kinds of verbal working memory

• A Strong Case
  – Parametric design: Increase the level of a variable parametrically
  – Examine whether (Level 2-Level 1) yields activation similar to (Level 3-Level 2)
  – e.g., variations of working memory load
This design manipulates the amount of the cognitive process present in each condition.

Test for systematic (linear or otherwise) relationships between the level of the cognitive process and neural activity.

Renders pure insertion more plausible

### Parametric Design

<table>
<thead>
<tr>
<th>Load 1</th>
<th>Load 2</th>
<th>Load 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulus</td>
<td>Delay</td>
<td>Response</td>
</tr>
<tr>
<td>100 ms</td>
<td>7400 ms</td>
<td>500 ms</td>
</tr>
</tbody>
</table>

**fMRI signal**

- memory load

**Renders pure insertion more plausible**
Another Alternative: Factorial Designs

• Examine more than one process to see whether there are interactions
• e.g., Do working memory load and response selection difficulty affect different brain systems?
  – e.g., if variation of memory load influences response selection regions, the two are not independent
Validating the Why/How contrast for functional MRI studies of Theory of Mind

Robert P. Spunt *, Ralph Adolphs

California Institute of Technology, USA
Paradigm for Studying Theory of Mind

- Theory of Mind
  - Imputing mental states to others
  - e.g., What was Jill thinking after Jack made a comment?
  - e.g., What was the motive behind Jill slapping Jack?
Paradigm for Studying Theory of Mind

A. Is the person...

Why Action
- helping someone?
- pressing a button?
- expressing gratitude?
- gazing down?

B. Fixation Baseline
- variable duration

Question Cue
- 2500 ms
- 1750 ms (max)

Target 1 of 7
- 350 ms
- 1750 ms (max)

Reminder

Target 2 of 7

Is the person smiling?

smiling?
The questions used in the Yes/No Why/How Task to manipulate and measure attention to “why” versus “how” for actions and expressions. All questions began with the string “Is the person”. The questions used in Study 3 are marked with an asterisk.

<table>
<thead>
<tr>
<th>Why</th>
<th>How</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intentional actions</td>
<td>Emotional expressions</td>
</tr>
<tr>
<td>Competing against others?*</td>
<td>Admiring someone?*</td>
</tr>
<tr>
<td>Concerned with their health?*</td>
<td>Being affectionate?</td>
</tr>
<tr>
<td>Having fun?</td>
<td>Expressing gratitude?</td>
</tr>
<tr>
<td>Helping someone?*</td>
<td>Expressing self-doubt?*</td>
</tr>
<tr>
<td>Protecting themselves?*</td>
<td>In an argument?*</td>
</tr>
<tr>
<td>Sharing knowledge?</td>
<td>Proud of themselves?*</td>
</tr>
<tr>
<td>Intentional actions</td>
<td>Emotional expressions</td>
</tr>
<tr>
<td>Holding a ball?</td>
<td>Gazing down?</td>
</tr>
<tr>
<td>Lifting something?*</td>
<td>Looking at the camera?*</td>
</tr>
<tr>
<td>Pressing a button?*</td>
<td>Looking to their side?*</td>
</tr>
<tr>
<td>Reaching for something?*</td>
<td>Opening their mouth?*</td>
</tr>
<tr>
<td>Using a writing utensil?</td>
<td>Showing their teeth?</td>
</tr>
<tr>
<td>Using both hands?*</td>
<td>Smiling?*</td>
</tr>
</tbody>
</table>
Summary of ANOVA Design

<table>
<thead>
<tr>
<th>STIMULUS</th>
<th>QUESTION</th>
<th>Why</th>
<th>How</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>Is the person</td>
<td>Is the person expressing self-doubt?</td>
<td>Is the person looking to their side?</td>
</tr>
<tr>
<td></td>
<td>looking to their</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>side?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>Is the person</td>
<td>Is the person helping someone?</td>
<td>Is the person using both hands?</td>
</tr>
<tr>
<td></td>
<td>helping someone?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A Problem

So: What are the properties of the hemodynamic response?
subject makes a bilateral button press in response to visual cue every 16 seconds

assumed pattern neural activity

voxels with significant signal within motor regions of interest

Defining the Hemodynamic Response Function

trial-averaged BOLD signal, an estimate of the HRF

avg BOLD signal from active voxels
Systems Analysis of the Signal

- Systems theory characterizes input/output relationships
- When examining the BOLD response we often look at a system composed of several subsystems

![Diagram of systems analysis]
A Piece of Good News: The HRF is Roughly Linear

A linear system satisfies the following:

- **Scaling**
  - Increasing stimulation by some ratio will increase the output by the same ratio

- **Superposition (additivity)**
  - Combining (adding) any two stimuli will lead to an output that is the sum of the two responses

- **Time-invariance**
  - A response is the same irrespective of when it comes or what precedes or follows it
The BOLD fMRI System in Time

- original
- increase intensity
- increase duration
- delay onset
Why Is Linearity Good?

• Use theory of linear systems to predict responses

• Start with definition of an impulse response function
  – Hemodynamic response to a brief stimulus
  – Commonly known as the hemodynamic response function (HRF)

• Predicted responses are easily determined by mathematical operations performed on hemodynamic response functions
  – Can also allow “deconvolution” of response to get estimates of the system input
Predicted Responses

- Impulse response or HRF
- Individual responses to each stimulus
- Superposition of responses
- Time-invariance
- Scaling

stimulus → HRF → time

Individual responses to each stimulus

Superposition of responses
Keep This in Mind

Detectable
• a bulk change in neural activity

Undetectable
• a change in population code

The BOLD fMRI signal integrates neural activity over seconds and millimeters.
Harnessing the Linear System

• Blocked Experimental Designs
  – Like tasks are clustered together in blocks of length 15-120 seconds
    • What’s the optimal block length? More in a moment
  – Tasks are close together to allow the appearance of continuous activation during the block
  – Superior statistical power because you can construct a block to recognize low frequency noise and avoid it (more in a moment)
Task Design and Predicted Responses

A blocked design and predicted fMRI response based on linear system analysis
A Prototypical Experiment

Measure magnitude of neural response within primary visual cortex to a standardized patch of light in a group of subjects

- relative signal
- indirect measure
- bulk activity change

- subtraction design
- blocked order
The HRF favors designs with low temporal frequencies. You could not, for example, have blocks of 1 sec each.
Arranging Timing

The HRF favors designs with power at low temporal freqs.

Hemodynamic response
There is increasing power at low frequencies in the noise also (due to drift of the MRI signal) with power roughly equal to $1/f$. 

**The Problem**

intrinsic noise
The Problem

The $1/f$ noise favors designs with power at high temporal frequencies, but the nature of the HRF does not allow this.
The Rock and the Hard Place

hemodynamic response

intrinsic noise
The Rock and the Hard Place

Note the difference right here, though
• Considering the two effects of noise and hemodynamic response, there is a sweet spot where the best blocked fMRI can be carried out
  – Full cycle every 30 to 60 seconds
  – Epochs of duration 15 to 30 seconds
Comparing Differences

**Goal:** determine if the difference in BOLD fMRI signal between dark and stimulation is greater in controls compared to patients with optic neuritis.

![Graph showing fMRI signal changes over time with controls and patients data points.]
Two-Condition Blocked Designs

- Cognitive subtraction assumption
- Design issues:
  - Two conditions differ by process of interest
  - Conditions should be as homogeneous as possible to minimize variation within block
  - Conditions should be densely populated by tasks to maximize actual performance time: high duty cycle
  - Trials within condition should be roughly equally spaced with SOA’s of less than 3-5 second
Two-Condition Blocked Designs

• Challenges:
  – Might need instruction blocks
  – Task start-up time (e.g. N-back task requires N trials to fully load memory)
  – Habituation and anticipation effects due to similar sequential trials
  – In some tasks, blocks of similar trials aren’t psychologically appropriate
    • e.g., blocks of old and new items in recognition
  – Violations of pure insertion (e.g. difficult blocks may lead to changes in attention)
  – Rigid format – not suitable for all studies

• Advantages:
  – Simple analysis
  – Excellent statistical power
  – Very good for localizing regions to be tested in other designs
    • e.g., localizing face region for another task
Multiple-Condition Blocked Designs

• Typical:
  – Use a fixed order within a run (e.g., ABCABC…)
  – Counter-balance across runs (e.g., ABCABC vs. BCABCA vs. CABCAB)
  – Randomized blocks are also OK but be careful if only a small number of blocks are used
    • Randomized order may allow very low or high frequencies to creep into the design, neither of which is within the range that is optimal
      – e.g., AABCCB
  – Block should be long enough to reach signal plateau
Parametric Blocked Designs

- Uses blocks with a parametric task manipulation
  - e.g. graded visual stimuli, graded memory conditions (such as varying memory load)
  - Often easier to interpret and justify than the cognitive subtraction hypothesis – look for those areas that vary exactly as the parametric manipulation (by principle of scaling)
  - Analysis might use an ANOVA to find main effect of manipulation and then do a post-hoc analysis looking for increases that match manipulation
  - Pure insertion still assumed, but with the same process repeatedly (more plausible)
Event-Related fMRI

• Responses to brief events are almost always weaker than responses to blocks of events

• Event-related fMRI studies must consider the long duration of the BOLD hemodynamic response (delay = 2-3 sec; overall duration 8-16 sec)
  – How does one observe the course of a hemodynamic response to a neural event in this case?
Event Related Designs

• Several different variants
  – Simple task, non-overlapping epochs, stretched out with fixed timing
  – Randomized ITI with faster presentation
  – Fixed ITI, randomized conditions with faster presentation
  – Mixed block/event-related designs
Event-Related fMRI - Extended Trials

- Behavioral trials have long gaps between them (long ITI)
  - Typically 10-20 sec ITI is used
- Example:

![Diagram showing individual events in an Event-Related Task and corresponding fMRI Response](image)
Event-Related fMRI - Extended Trials with Fixed Timing

• Behavioral trials are extended in duration to allow responses to the individual events to be seen
  – Often 10-15 sec is added at the end to get back to baseline state
  – Subtasks have unique temporal signature

• Working memory example:

![Graph showing timeline with extended trials and fixed timing for working memory example.][1]

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[1]: http://example.com/graph.png
Event-Related fMRI with Randomized ITI, One Condition

- Behavior trials are presented rapidly, but with random timing
  - Overlapping responses are superimposed to yield a unique time-course (by principle of superposition)
  - Randomization causes the variation in the time-course
Event-Related fMRI with Randomized Trials, Two Conditions

- Behavioral trials are presented rapidly, but with random ordering
  - Overlapping responses are superimposed to yield a unique time-course (by principle of superposition)
  - E.g. AABBBAAABBBABB...
  - Trial types A and B will have a unique temporal signature if the timing between them is right
  - In effect, you are detecting the low frequency envelopes caused by haphazard ordering
Arranging Timing in Event-Related Designs

**Goals:**
1) maximize statistical power
2) avoid the predictability of events

If the signal is linear (i.e., there is no saturation), events can be spaced as closely as 1-2 sec
Event-Related Design

- Advantages
  - Avoids habituation/behavioral issues
  - Very flexible
  - Allows self-paced tasks
  - Can model sub-epochs when they occur (e.g. a behavioral response, encoding, or memory storage)
  - Can separately analyze correct/incorrect responses
  - Can still do parametric manipulations
Event-Related Designs

• Disadvantages
  – Sensitive to accuracy of shape of the BOLD response
  – Reduced sensitivity relative to blocked designs
    • The most sensitive ER designs have trials clustered into mini-blocks – that is, long runs of particular trial types (so they become blocked designs)
  – Difficult to include instruction blocks
Mixed ER/Blocked Designs

• Looks like a blocked design, but individual trials are analyzed within blocks
  – Often done so that behavioral errors can be analyzed
  – But they compromise on packing of trials within a block
Control/Baseline Conditions

• Raichle hypothesis *(Nature Reviews: Neuroscience 2:685-692, 2001)*:
  – There are a set of “mental activities” associated with resting with eyes open (e.g. passive viewing of a blank screen)
  – During goal-directed behavior these resting-state activities are suppressed
  – May often see deactivations related to suppression of resting state activity

• Therefore, selection of control conditions must be carefully considered
Acquire Functional Structurals (T1) → Slice Timing Correct → Realign → Smooth → Predictors

Acquire Functional s → (De-noise) → Slice Timing Correct → Realign → Smooth → Predictors

Determine Scanning Parameters → Slice Timing Correct → (De-noise) → Slice Timing Correct

Co-Register

Template

Apply Warp → Normalize

β · Normalize (All subjects) → 2nd level (Group) GLM

β · Normalize (All subjects) → 2nd level (Group) GLM

β_{face} - β_{house} · Threshold

y = Xβ + ε

β · Threshold

β_{face} - β_{house} · Threshold