NEUROIMAGING TRAINING PROGRAM

EXPERIMENTAL DESIGN I

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NITP

THE ROYAL SOCIETY

If neuroimaging is the answer, what is the question?

S. M. Kosslyn

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"Attending a poster session at a recent meeting, I was reminded of the old adage 'To the man who has only a hammer, the whole world looks like a nail.' In this case, however, instead of a hammer we had a magnetic resonance imaging (MRI) machine and instead of nails we had a study. Many of the studies summarized in the posters did not seem to be designed to answer questions about the functioning of the brain; neither did they seem to bear on specific questions about the roles of particular brain regions. Rather, they could best be described as 'exploratory'. People were asked to engage in some task while the activity in their brains was monitored, and this activity was then interpreted post hoc."

-- Stephen M. Kosslyn (1999). If neuroimaging is the answer, what is the question? *Phil Trans R Soc Lond B*, 354, 1283-1294.

Some reasonable questions

- **Charting the territory**: what does a particular brain region do? How does it compute/represent the information presented? How specific is this region for certain types of information or certain processes?
- **Understanding the process/representations**: Can we learn more about a cognitive processes/representations by imaging the brain in action (than by doing a reaction time or performance test instead)?
- **Relating to external variables**: how do patterns of brain activation relate to differences in subject attributes like genetics, skills (not tested in the experiment)
- **Network questions/Information processing** (save for connectivity talks)

Some not great questions or conclusions

- **What brain areas light up when people do X?**
  - "Since these areas light up during task X, they must be essential for it."
- **How do 2 groups differ on this task** (where that task defines the group difference)
  - E.g. reading

We want to design experiments that need brain imaging to answer our questions; otherwise, this is a very expensive neuropsychological test

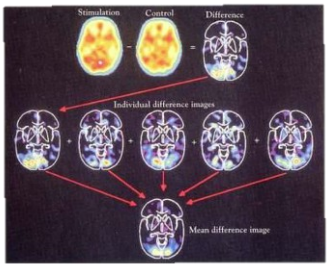
Conceptual and methodological aspects of experimental design

- There are two aspects of fMRI design that are important to distinguish

1. **Conceptual design**: what is the process of interest/biological question?
   - The issues here are very similar to those in cognitive psychology or other fields of biology
2. **Methodological design**: How can we turn the question/task into an fMRI experiment and processes onto blood flow?
   - The issues here are specific to the method employed (i.e., fMRI)

THE SUBTRACTION METHOD

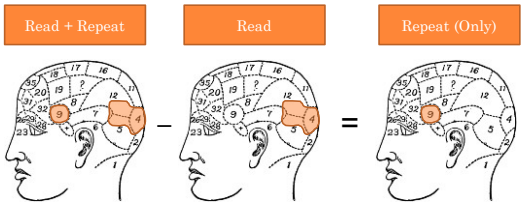
- Acquire data under two conditions
  - These conditions putatively differ only in the cognitive process of interest
- Compare brain images acquired during those conditions
- Regions of difference reflect activation due to the "subtracted" process of interest



Petersen et al., 1988

THE SUBTRACTION METHOD

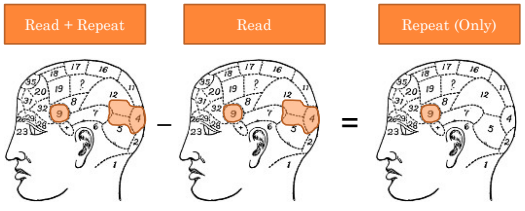
Interest: Neurocognitive processes of word repetition
Task: Repeat words presented on screen



THE SUBTRACTION METHOD: ISSUES

Could the "baseline" task be problematic?

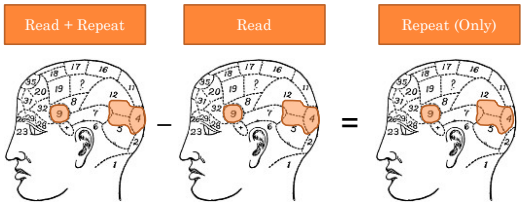
i. What if articulatory processes are automatic?



THE SUBTRACTION METHOD: ISSUES

Could the "baseline" task be problematic?

ii. What if reading alone is too boring?



IT DOES HAPPEN: TASK(LOGIC INFERENCE) V CONTROL(REST)

Table 3. Activation Clusters in a Contrast between the Images Acquired during All Four Sorts of Inference and Those Acquired during the Rest Intervals

Location	z Score	Size (Voxels)	Talairach Coordinates x	y	z
All inferences versus rest interval					
Parietal					
Left precuneus (BA 7)	6.00	25**	−18	−58	55
Right precuneus (BA 7)	4.72	16*	15	−65	45
Right superior parietal gyrus (BA 7)	6.59	41***	27	−56	55
Temporal					
Left middle temporal gyrus (BA 21)	7.40	46***	−59	−32	2
Right middle temporal gyrus (BA 21)	5.16	25**	65	−15	−2
Left superior temporal gyrus (BA 38)	4.57	15*	−54	14	−21
Frontal					
Left middle frontal gyrus (BA 46)	5.59	19*	−51	25	24
Left inferior frontal gyrus (BA 47)	5.16	27**	−48	43	−15
Right middle frontal gyrus (BA 6)	4.69	15*	30	−1	47

Specificity of the activations?

COMMON CONFOUNDS WITH CONTROL TASKS

- Attention required, or task difficulty, is greater in activation compared to control task
  - Pretesting task with RT, performance can help
- Assuming you know the processes involved in task and control
- Over-controlling in the control task
  - You can subtract out processes of interest if they are engaged automatically
  - Eg: nonsense speech is not a great control for real speech. Why? We try to interpret speech sounds. Nonsense speech is complex and novel. We may increase attention to speech areas in this task
  - Eg: memory: what is a good memory control (since we encode information all the time)

More confounds

- Novelty: item or task repetition usually results in decreased activation the second time around; always control for task/stimulus order
  - Event related designs: randomize and optimize
  - Blocked or mixed designs, counterbalance
- Calculate the number of variables and conditions to get number of different orders you require
- Complete counterbalance: when responses to one condition may affect what follows- order interactions (eg, mood induction)

-In 3 conditions, 3! orders: 123, 132, 213, 231, 312, 321

- Latin Square assumes no order interactions

-In 3 conditions, 3, 123 231 312

The pure insertion assumption

Is repeating after reading truly = Reading + Repeating?

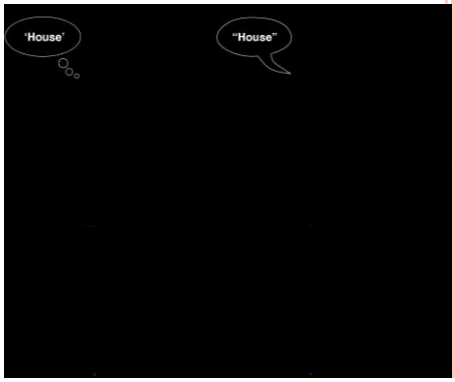
PI: Insertion of a single cognitive process does not affect

Read + Repeat | Read | Repeat (Only)

Does it hold up? Sometimes yes, sometimes no. Adding a process may completely change brain activity

Read "**HOUSE**"

Name



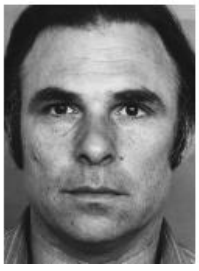
Common Experimental Designs

- Common Baseline
- Parallel Comparisons
- Tailored Baselines
- Hierarchical
- Parametric
- Selective Attention

Common Baseline

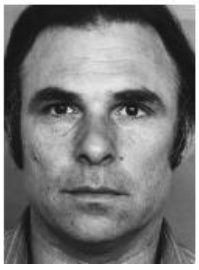
- Comparison of two experimental conditions to same control
  - Cond A > Ctrl
  - Cond B > Ctrl
- Cond A: Viewing pictures of faces
- Cond B: Viewing pictures of houses
- Ctrl: Scrambled images
- Allows you to say how each condition compares to the control task

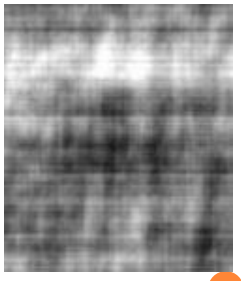
E.g. face processing



Face – scrambled face = face area

E.G. FACE PROCESSING





Face – scrambled face = face area
Controlled for visual stimulation; luminance, contrast, average spatial frequency etc

THE TASK ANALYSIS ASSUMPTION

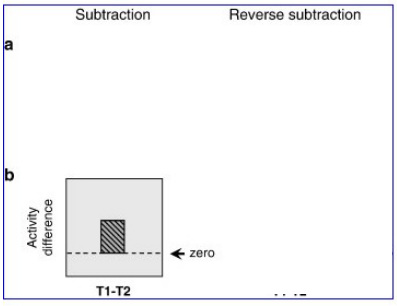
- Assumes that you controlled for everything except the process of interest
- In this example, we controlled for all visual aspects; are we left with only face processing?
- What else might differ between task and control?
  - Familiarity/novelty
  - Salience of stimuli
  - Attention to stimulation
  - Interest in stimulus
  - Emotional reactions
  - Language- naming the kind of stimulus
  - Memory- he looks like my uncle John
  - Cognitive: he looks like an ax murderer

Do the best you can, but question your assumptions

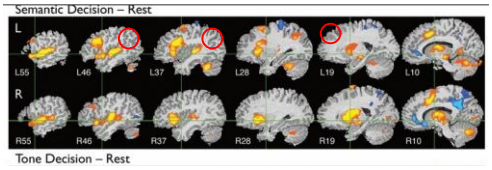
COMMON BASELINE

- Comparison of two experimental conditions to same control
  - Cond A > Ctrl
  - Cond B > Ctrl
- Assumes both experimental conditions have similar psychometric properties (i.e., task difficulty, equivalent degree of activation across subjects)

Common Baseline: What is Activation?



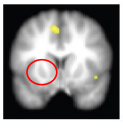
From Morcom and Fletcher, NeuroImage, 2006



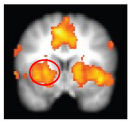
Semantic Decision – Tone Decision

Common Baseline: What is Significant?

Exp A > Ctrl

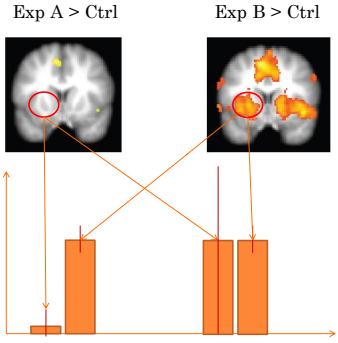


Exp B > Ctrl



- "The Imager's fallacy" (Henson, 2005)
  - "Striatum was more active in condition 2 than condition 1"
- Difference in significance does not imply a significant difference!

Common Baseline: What is significant?



Parallel Comparisons

- Compare both experimental tasks to each other (pics of faces vs pics of houses)
  - Ex A > Ex B
  - Ex B > Ex A
- Complements common baseline design
- Assumes similar psychometric properties in both A and B

Tailored Baseline

- Use different control tasks unique to each experimental condition
  - Ex A > Ctrl A
  - Ex B > Ctrl B

Linguistic Inference v Algebraic Inference

Exp A Linguistic Inference	*Exp B: Algebraic Inference*
Z was paid X by Y. It was X that Y paid Z. ✓	X minus Y is greater than Z. Z plus Y is smaller than X. ✓
It was to X that Z told Y. What Z told Y was X. ✗	Z equals X divided by Y. Y equals Z times X. ✗

- **Exp A/B:** Is the argument valid?
- **Ctrl A/B:** Are both sentences grammatical?

Linguistic Inference v Algebraic Inference

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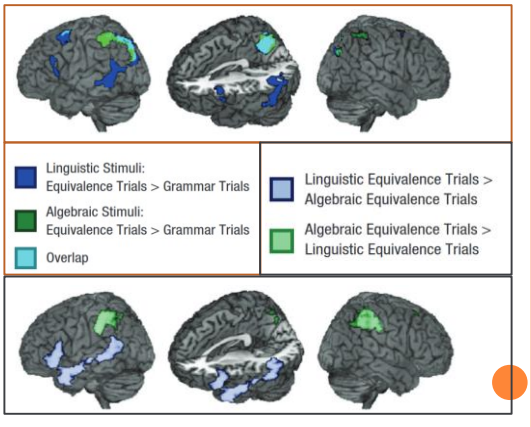
It was to X that Z told Y. What Z told Y was X. ✗	Z equals X divided by Y. Y equals Z times X. ✗
It was Z that X made for Y. To X was made by Z for Y.	Y equals Z times greater than X. X equals Z divided by Y.



Tailored Baseline

- Use different control tasks unique to each experimental condition
  - Ex A > Ctrl A
  - Ex B > Ctrl B
- Assumes each control task equally removes modality specifics
- Assumes similar psychometric properties for all conditions - unlikely in most cases
- Good idea to include a common baseline
- Good idea to compare the two baselines

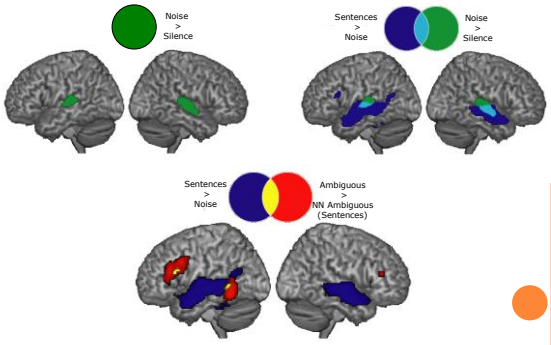
Common Experimental Designs

- Common Baseline
- Parallel Comparisons
- Tailored Baselines
- Hierarchical
- Parametric
- Selective Attention

Hierarchical Design

- Use a set of tasks, each sitting at a different level within a hierarchy of cognitive processes:
  - Task A > Rest
  - Task B > Task A
  - Task C > Task B
- Rodd et al., 2005:
  - Task A: listen to "noise" stimuli
  - Task B: listen to sentences
  - Task C: Listen to ambiguous sentences
  - Level 1: Noise > Rest
  - Level 2: Sentences > Noise
  - Level 3: Ambiguous sentences > Sentences

Rodd et al., 2005 Neural mechanisms of speech comprehension



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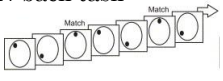
  - Level 1: Noise > Rest
  - Level 2: Sentences > Noise
  - Level 3: Ambiguous sentences > Sentences
  - **PI must hold at both neural and cognitive levels!**

Parametric Design

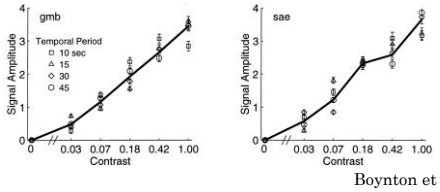
- Increasing level of difficulty or intensity of task
- Variation along a single dimension
  - A
- Example: working memory load
- N-back task



0-back

Parametric Design: Assumptions

- Assumes Pure Modulation
  - Each level of the task differs quantitatively in the level of engagement of the process of interest, rather than qualitatively
  - Assumes you can define the magnitude differences across levels



Boynton et al., 1996

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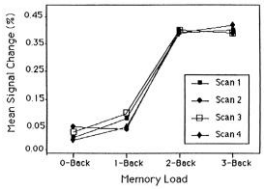
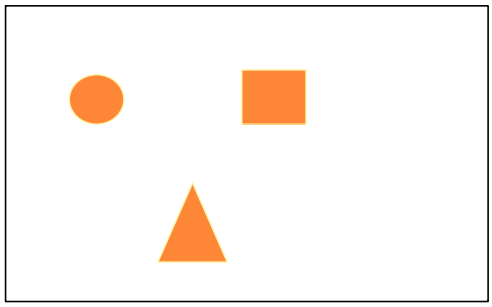


Cohen et al., 1996

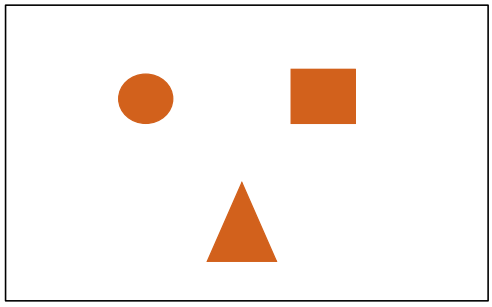
Selective Attention

- Present same stimuli in all conditions but instruct subject to attend to different features
  - **A** B C
  - A **B** C
  - A B **C**
- Corbetta, et al. presented squares, circles, and triangles that changed in color and moved
- On each trial all three parameters were varied
- By instructing subjects to attend to different features able to identify areas that respond uniquely to shape, color, and motion

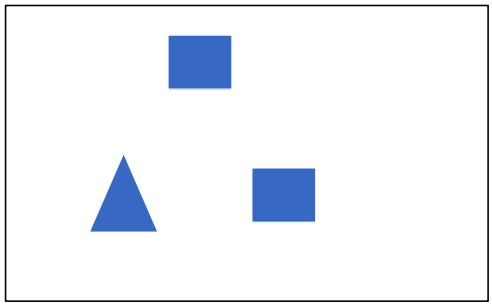
Trial 1



Trial 2



Trial 3



Selective Attention

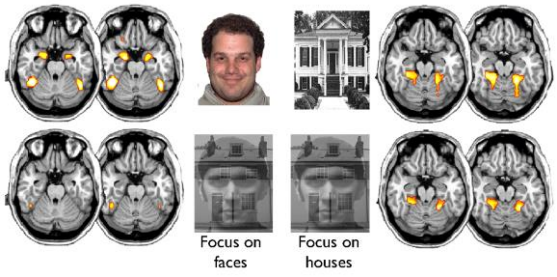
- Present same stimuli in all conditions but instruct subject to attend to different features
  - **A** B C
  - A **B** C
  - A B **C**
- Assumes cognitive process is modified by what is attended to
- Assumes variables of interest are modulated by selective attention
- Assumes passive processing of unattended features does not include cognitive processes of attended feature

Selective Attention

Focus on Face

Focus on House

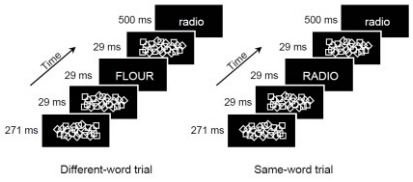
Selective Attention



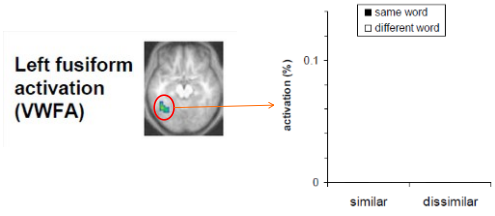
Priming/Adaptation Designs

- Presentation of an item multiple times leads to changes in activity
  - Usually decreased activity upon repetition
- Inference:
  - Regions showing decreased activity are sensitive to (i.e. represent) whatever stimulus features were repeated
- Requires version of pure modulation assumption
  - Assumes that processing of specific features is reduced but that the task is otherwise qualitatively the same

Priming/Adaptation Designs



1. SW-SF
2. DW-SF
3. SW-DF
4. DW-DF



Summary

- No design is perfect; all make assumptions that are not fully verifiable; know them!
- Use that which is most consistent with your specific research question; freely admit weaknesses
- Multiple "baseline" conditions help interpretation
- Beware of your assumptions