Imaging Methodologies

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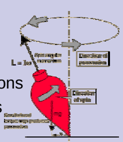
How do we know stuff about the brain in humans?

- Structural Imaging
  - Structural MRI
  - DTI
- Functional Imaging
  - Lesions*
  - fMRI
  - PET
  - EEG/ERP
  - MEG
  - TMS
  - NIRS
  - Single cell recording*
- Applications to Development and Autism

Structural Imaging: MRI

- Magnetic resonance imaging (MRI)
  - Protons align to magnetic field of magnet
  - Apply Radio Frequency (RF) pulse
  - Causes protons to tip and spin out of alignment
  - Records recovery time to baseline for spinning protons
  - Different tissue types have different 'recovery' times

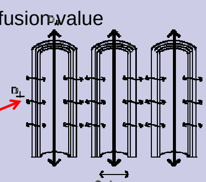


MRI Questions

- Volume
  - Whole brain volume, gray matter, white matter
- Cortical Thickness
- Shape
  - Sulcal mapping

Structural Imaging: DTI

- Diffusion Tensor Imaging (DTI)
  - Can determine the organization of white matter tracts
  - Measures diffusion of water molecules through axons
    - Direction of axon has largest diffusion value
  - Performed in MRI scanner

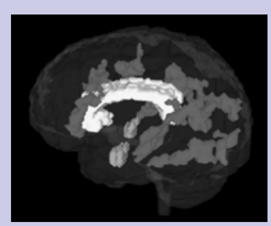


Axons (white matter)

DTI Questions

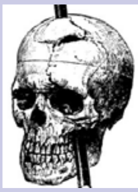
- White matter organization
- Index of brain connectivity

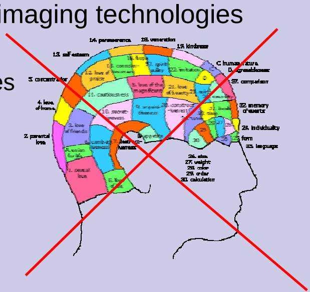
Areas of abnormal white matter structure in autism as compared to controls (dark grey)



What about brain function?

- Before fancy imaging technologies
  - Phrenology
  - Lesion studies



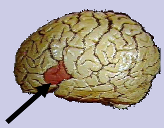


Lesion Studies

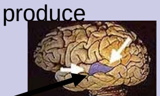
Key Features of the Lesion Approach

- Patient shows deficit in behavior, identify where brain is damaged (before MRI used post-mortem)
- Lesions may be acquired or developmental
- Learn about normal function through dysfunction
- Emphasis on deficit measurement
  - Determine which regions are necessary for task

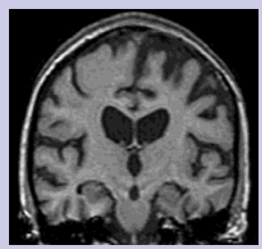
Classic Lesion Studies



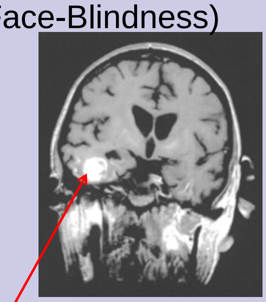
- Broca's Aphasics
  - Damage to Broca's Area (Left Inferior Frontal Gyrus)
  - Patients can comprehend but not produce language
- Wernicke's Aphasics
  - Damage to Wernicke's area (Left posterior Superior Temporal Gyrus)
  - Can produce but not comprehend speech



Prosopagnosia (Face-Blindness)



Normal
(coronal section)



Fusiform
Gyrus

Prosopagnosics
(coronal section)
Marotta et al 2001

Disadvantages of lesions for cognitive neuroscience

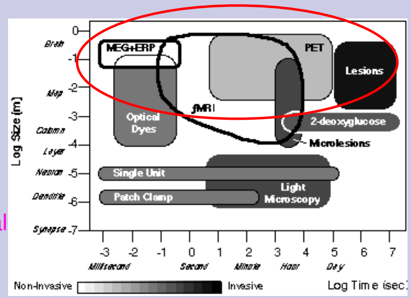
- Can't experimentally manipulate in humans
- Can't control size of lesion (often multiple brain areas)
- Age of lesion can affect recovery
- Brain-damaged brain is not normal

Functional Imaging Technologies

- Accelerated field of cognitive neuroscience
- Measure brain activity during task performance in healthy individuals
  - Language, attention, social interactions, emotional states, perception

Methods address different questions

- Temporal
  - ms to days
- Spatial
  - mm to whole brain
- Invasiveness
- Developmental Applicability



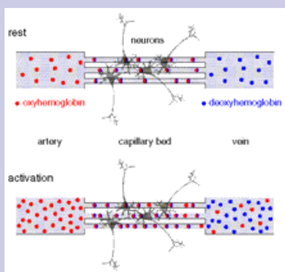
Churchland & Sejnowski, 1988

Techniques to address "Where" something happens in the brain

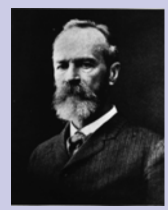
- Techniques with pretty good spatial resolution
  - Functional magnetic resonance imaging (fMRI)
    - Best spatial resolution of all three
  - Positron Emission Tomography (PET)
  - Magnetoencephalography (MEG)

FMRI

- Similar principles to MRI
- Measures changes in blood flow
  - Indirect measure of neural activity
- MRI can detect changes in ratio of oxygenated to deoxygenated hemoglobin
- Blood Oxygenated Level Dependent (BOLD) Signal



"The subject to be observed lay on a delicately balanced table which could tip downwards either at the head or at the foot if the weight of either end were increased. The moment emotional or intellectual activity began in the subject, down went the balance at the head-end, in consequence of the redistribution of blood in his system …



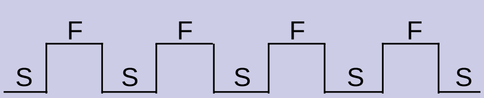
We must suppose a very delicate adjustment whereby the circulation follows the needs of the cerebral activity. Blood very likely may rush to each region of the cortex according as it is most active, but of this we know nothing."

William James (1890)

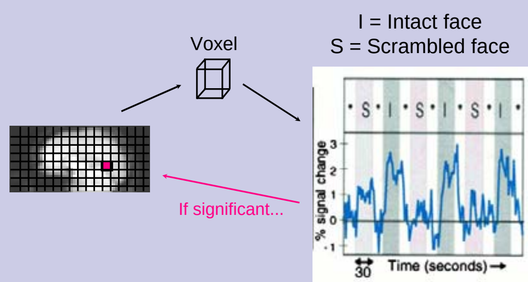
FMRI: A typical experiment

Faces

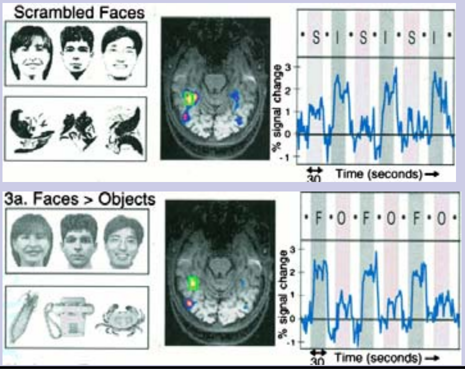
Scrambled Faces



fMRI Analysis



fMRI relies on subtraction method



FMRI

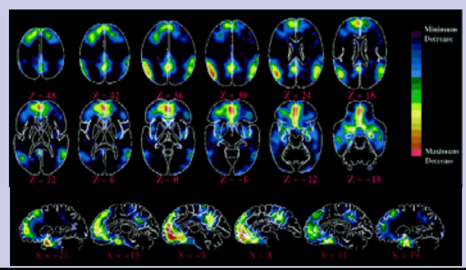
- Advantages
  - Very good spatial resolution
  - Non-invasive
  - Common at most universities
- Disadvantages
  - Poor temporal resolution (seconds)
  - Noisy, unnatural
  - Very sensitive to motion
  - Expensive

PET

- Examines glucose metabolism
  - Indirect measure of neural activity
- Inject radioactive tracer (e.g. fluorodeoxyglucose (FDG) tagged with flourine radioactive atom)
  - FDG acts like a sugar
- Increased metabolism in area leads to decay of radioactive tracer which produces a positron
- When positron hits electron, gamma ray emitted
- PET scanner detects gamma rays → map of metabolic activity

When to use PET

- 'Where' questions during task
- Baseline metabolism



Raichle et al., PNAS 2001

PET

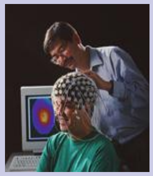
- Advantages
  - Ok Spatial resolution (4-16 mm)
  - Can record task-related and resting activity
  - Quiet (good for auditory studies)
- Disadvantages
  - Poor temporal (minutes)
  - Invasive
  - Spatial worse than fMRI

Methods to address 'when' question

- Techniques with good temporal resolution
  - EEG (ERP)
  - MEG

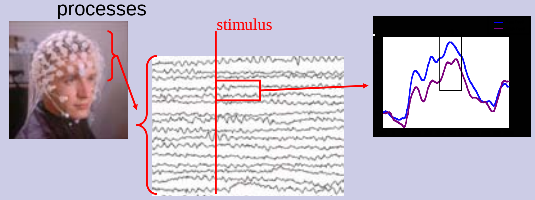
EEG

- Electroencephalography (EEG)
  - Patterns of ongoing electrical activity
  - Only sensitive to large groups of neurons, firing in synchrony
  - Some uses
    - Identify seizures
    - Sleep-stage identification
    - Coherent patterns of activity (EEG coherence)
  - Not a measure of when unless time lock to a stimulus (ERP)



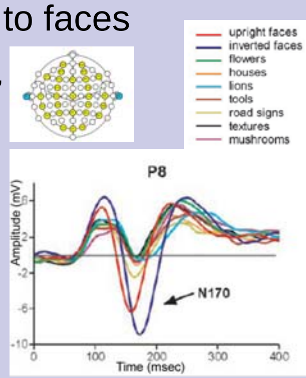
ERP

- Event-Related Potentials (ERPs)
  - Time-locked response to a specific stimulus
  - Reveal changes in extent and timing of brain response to stimulus
  - Provide excellent temporal resolution of neural processes



ERP to faces

- Identify 'components' that reflect neural processing
  - i.e. N170 specific to faces
- Present different visual stimuli and examine ERP over various electrodes



EEG/ERP

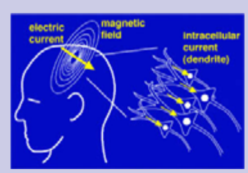
- Advantages
  - Non-invasive
  - Excellent temporal resolution
  - Can be used with babies without behavioral response needed
- Disadvantages
  - Poor spatial resolution
  - Not clear where signal coming from
  - Can't measure subcortical activity

Magnetoencephalography (MEG)

- Records magnetic activity from sensors around head
- Similar principles to EEG/ERP

MEG

- When neurons fire, electrical current created
- Produces orthogonally oriented magnetic field
- MEG sensitive to these magnetic fields



MEG

- Like EEG: good temporal resolution, identify components
- Spatial resolution is better than EEG because not affected by brain and scalp Can use MRI image to determine where magnetic signal comes from

MEG

- Advantages
  - Good temporal and ok spatial resolution
  - Quiet
- Disadvantages
  - Can not image below cortex
  - Expensive and not very common

Summary

-	EEG	MEG	PET	fMRI
Strengths	excellent temporal	temporal & spatial	ok spatial	excellent spatial
Weaknesses	poor spatial	limited regions	poor temporal	ok temporal
Measuring?	electrical currents	magnetic currents from scalp	radioactive markers	bloodflow

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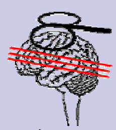
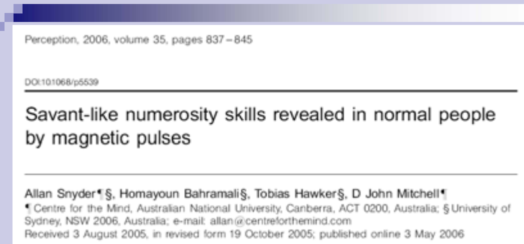
Transcranial Magnetic Stimuluation (TMS)

- Can non-invasively (?) stimulate regions of the brain with magnetic current
- TMS – single pulse can briefly activate area (i.e. motor cortex)
- rTMS – repetitive TMS
  - Stimulate at 1-60 Hz
  - Fast rTMS excites
  - Slow rTMS inhibits
  - can cause temporary lesion

TMS Questions



- Single TMS
  - Typically used to study response of motor system
  - Stimulate over M1 hand area and measure time to move contralateral finger
- Repetitive TMS
  - What is certain brain area necessary for (‘temporary lesion’)
  - i.e. stimulate over Broca’s area and patient can’t talk


Perception, 2006, volume 35, pages 837 – 845

DOI:10.1068/p5539

Savant-like numerosity skills revealed in normal people by magnetic pulses

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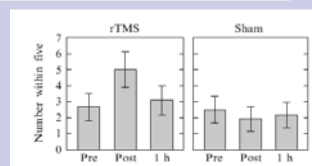
Received 3 August 2005, in revised form 19 October 2005; published online 3 May 2006



TMS

- Advantages
  - Relatively non-invasive method to stimulate brain areas
  - Can say whether area necessary, not just involved
  - May be useful for treatment of depression, schizophrenia, autism … (maybe)
- Disadvantages
  - New and unclear if there are long-term effects
  - Can only examine single area at a time

Techniques to use to study brain functional development

- EEG (ERP)
  - Pros: Non-invasive, quiet, not as susceptible to motion artifacts
  - Excellent index of behavior without bias
- MEG
  - Pros: Non-invasive, quiet
  - Cons: somewhat susceptible to motion, requires MRI scan
- fMRI
  - Pros: Non-invasive
  - Cons: Requires child to remain very still, noisy

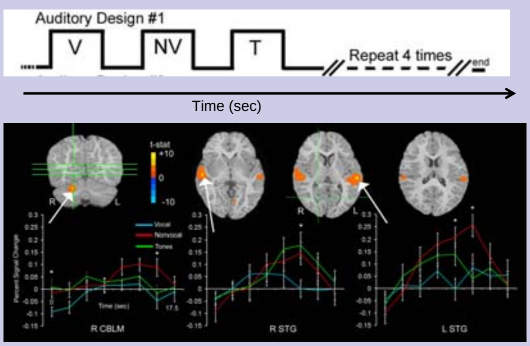
Methods to image very young children with fMRI

- Image awake children >4 years
- Image during anesthesia
  - Invasive, only patient populations
- Image during sleep
  - Current research: 2-3 months and 1-3 years

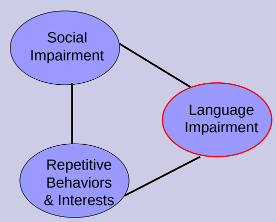
How do we study kids during sleep?

- Children don't nap during the day
- Arrive at scanner at 9 PM
- Fall asleep and place in scanner
- Lots of sound protection
- Member of research team remains in scanner room

Can we study brain function during sleep?

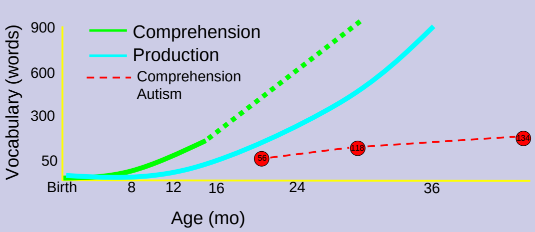


Can use fMRI to study Autism when first diagnosed



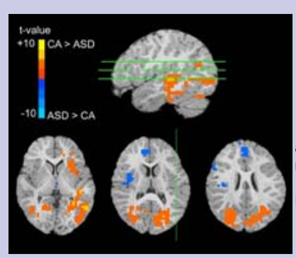
- Emerges during first years of life
- Diagnosed around age 3
- One early sign of autism is language delay in second year of life

Language Delay in Words Comprehended in Autistic Toddlers



Charman et al., 2003

Response to Speech in 2-3 year old children with autism



Control > ASD
ASD > Control
Speech vs. Rest

- Control Group shows greater activity in LH temporal and parietal regions than ASD
- ASD group shows greater activity in RH and medial frontal regions

Questions?

- Anyone know a 14-month-old who wants an image of his brain (whose parents want an image of his brain)?
  - Email me at eredcay@ucsd.edu