Watching the brain remember

**Neuroimaging techniques for
studying learning and memory**

David A. Ziegler

Image removed due to copyright reasons.
Cartoon.

Wednesday, Sept 12, 2007

Outline

- **Imaging brain anatomy**
    - Structural magnetic resonance imaging (MRI)
- **Imaging brain function**
    - Positron emission tomography (PET)
    - Functional MRI (fMRI)
    - Magnetoencephalography (MEG)
    - Strengths and limitations of each method

Please interrupt me if you have questions!

Functional neuroimaging techniques:
spatial and temporal resolutions
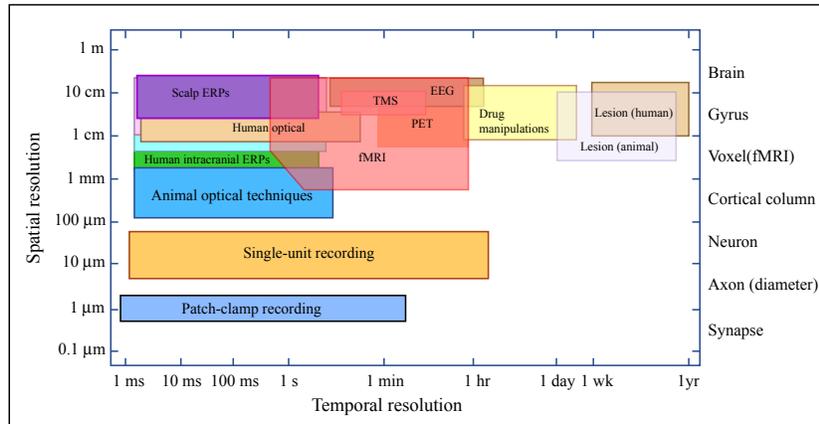
Figure by MIT OpenCourseWare.

Spatial resolution

Images removed due to copyright restrictions.
Three brain scan images of increasing resolution quality.

MRI then and now

Images removed due to copyright restrictions.
Photographs of original and modern MRI machines.

First MRI of a human chest

Images removed due to copyright restrictions.
First MRI, of a human chest; photograph of man in first MRI machine;
handwritten notes describing these results.

Basic modern MRI setup

Illustration of human insertion into MRI machine. Figure removed due to copyright restrictions.

- **A superconducting magnet creates static magnetic field (B_0)**
- **B_0 is aligned along head-toe axis**
- **How do we generate images of the brain?**

Images removed due to copyright restrictions.
Please see http://easymeasure.co.uk/principlesmri.aspx.

Low energy

High energy

B_0

excitation pulse

T1 relaxation time

Based on Huettel et al. (2004)
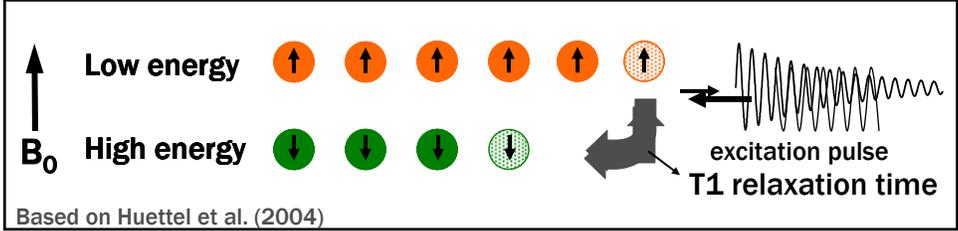
Radiofrequency excitation & relaxation time

Energy state

Low

High

Low

B_0

High

excitation pulse

Low

High
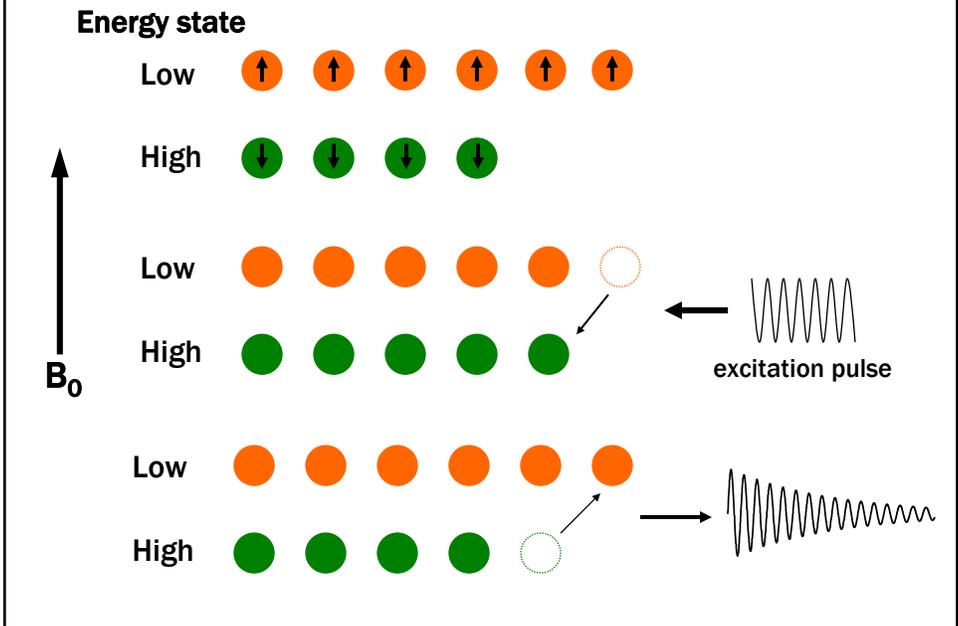
Longitudinal T1 relaxation time:

Following excitation, the amount of dephasing differs depending on the tissue type, leading to different T1 relaxation times

Images removed due to copyright restrictions.
MRI image with illustrative diagrams of white matter and CSF molecular dephasing activities. Figure from: Nitz, W.R., and P. Reimer. "Contrast Mechanisms in MR Imaging." *Eur Radiol* 9 (1999): 1032–1046.

Typical T1 relaxation times at 1.5 Tesla:
White matter = 787 ms
Gray matter = 921 ms
CSF = 2650 ms

Nitz & Reimer (1999)

Anatomical contrast

Images removed due to copyright restrictions.
MRI images of different brain slices, with contrast between the types of tissues highlighted.

Huettel et al. (2004)

MRI of medial temporal lobe (MTL) structures

Images removed due to copyright restrictions.

de Toledo-Morrell et al (2003)

Augustinack et al (2005)

Structure versus function

Image removed due to copyright restrictions. Mock MRI image of Homer Simpson's head, showing a very small brain surrounded by empty space inside the skull.

Image removed due to copyright restrictions. Cartoon of Homer Simpson's head, with different "brain regions" outlined and labeled; for example, a large region is labeled "Sleep."

Positron emission tomography (PET)

**Positron imaging invented
at MIT/MGH in 1950s**
by Gordon Brownell

Images removed due to copyright restrictions.
Photographs of people undergoing PET scans.

How PET works

- Radioactive tracer coupled to biologically active molecule
  - e.g., fluorine-18 + glucose (^{18}FDG)
- Tracers accumulate in active cells
- Radioisotopes decay, emitting positrons

Images removed due to copyright restrictions.
Illustration of radioactive fluorine decay and PET scan setup.

An early PET study of memory encoding

Images removed due to copyright restrictions. Rough diagram of areas of activation in the brain during shallow and deep encoding.

- Participants were scanned while they studied lists of words

- Compared oxygen-15 uptake during *shallow* versus *deep* encoding

- Deeper encoding led to significantly greater subsequent recognition
  - Consistent with the "*level of processing effect*" (Craik & Lockhart, 1972)

- Deep encoding resulted in increased blood flow to left prefrontal cortex
  - One of the first studies to show activity of PFC during memory encoding
  - Compare these results to Figure 3.4 in your text (i.e., an fMRI study by Lila Davachi)

Kapur et al (1994)

Strengths and limits of PET

High degree of specificity
- Glucose metabolism
- Blood flow
- Neurotransmitters

Image removed due to copyright restrictions. PET scans of a brain.

Limitations
- Radiation exposure is risky
  (FDA regulation: only one scan per 6 mo period)
- Relatively low spatial ($\geq$ 5mm) & temporal ($\geq$ 5sec) resolution
- Long acquisition times
- Costly and inconvenient

The rise of fMRI

Why has fMRI largely replaced PET in cognitive neuroscience?

- Cheaper
    - No radioactive tracers → no need for an on-site cyclotron
- Safer
    - No need to inject radioactive tracers
    - Can be repeated without side-effects
- Better temporal (~2sec) & spatial (2-5 mm) resolution
- Faster acquisitions
- Readily available to researchers
- Simultaneous whole brain coverage
    - Good for identifying of large-scale, distributed neural networks

So, how do we measure brain activity with MRI?

Sending blood to neurons

Artery

Vein

Oxyhemoglobin is diamagnetic Dc = 0 ppm

Deoxyhemoglobin is paramagnetic Dc = 0.08 ppm
↓
Magnetic susceptibility
↓
Spin dephasing & signal loss
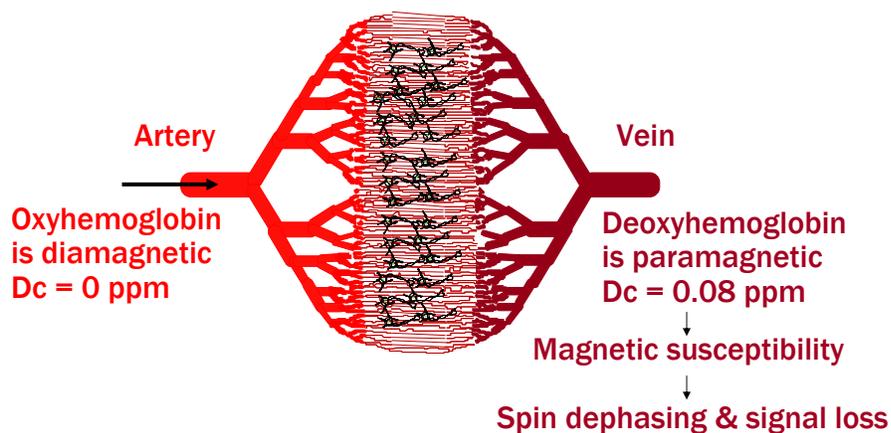
Courtesy of Ravi S. Menon. Used with permission.

Animation courtesy of Ravi S. Menon
Robarts Research Institute, University of Western Ontario

Sending blood to neurons

Artery   Vein
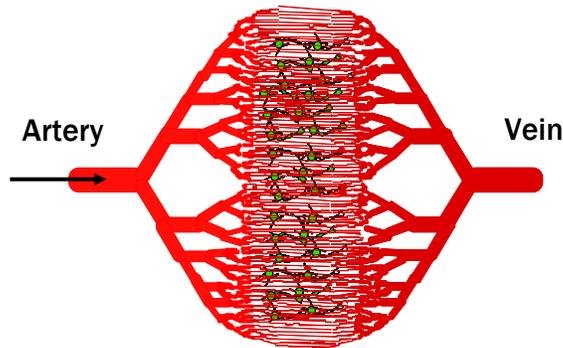
Courtesy of Ravi S. Menon. Used with permission.

The rise of oxygenated blood in veins leads to increased signal on MRI:
Blood Oxygenation Level Dependent (BOLD) signal

Animation courtesy of Ravi S. Menon
Robarts Research Institute, University of Western Ontario

Recap: what does fMRI really measure?

- **When neurons in the brain are firing, blood flow to that area increases** (Roy & Sherrington, 1890)
- **The increased blood flow brings more oxyhemoglobin to that area**
- **The inflow of oxyhemoglobin increases more than the increase in oxygen consumption → increased ratio of oxy-to-deoxyhemoglobin in veins**
- **The relative decrease in venous deoxyhemoglobin makes the magnetic field more homogeneous**
  - Because deoxyhemoglobin is paramagnetic and causes magnetic susceptibility, spin dephasing, & signal loss (T2*)
- **When the magnetic field becomes more homogeneous, the MR signal increases in intensity**
- **This is Blood-Oxygen-Level-Dependent (BOLD) contrast**

First BOLD experiment in humans (at MGH!)

Images removed due to copyright restrictions.

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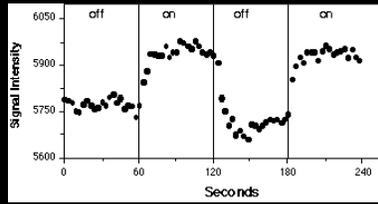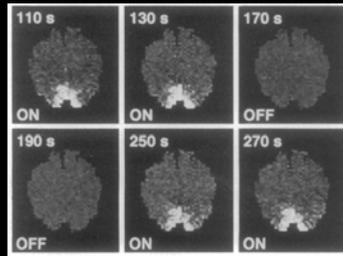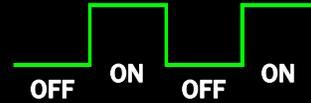
Kwong et al., 1992

Courtesy of National Academy of Sciences, U. S. A. Used with permission.
Source: Kwong, K. K., et al. "Dynamic Magnetic Resonance Imaging of Human
Brain Activity During Primary Sensory Stimulation." *PNAS* 89 (1992): 5675-5679.
Copyright 1992 National Academy of Sciences, U.S.A.

Experimental designs

Block design

Event-related design

Image removed due to copyright restrictions.
Please see Fig. 3 in Matthews, P. M. and P. Jezzard. "Functional Magnetic Resonance
Imaging." *Journal of Neurology Neurosurgery and Psychiatry* 75 (2004): 6-12.

Rapid event-related design

Image removed due to copyright restrictions.

Based on Huettel et al (2004)

Subsequent memory paradigm

Subsequently remembered

Subsequently forgotten

fRMI signal intensity

Study:

W1   W2   W3   W4

Test: Remembered: W1 & W3   Forgotten: W2 & W4
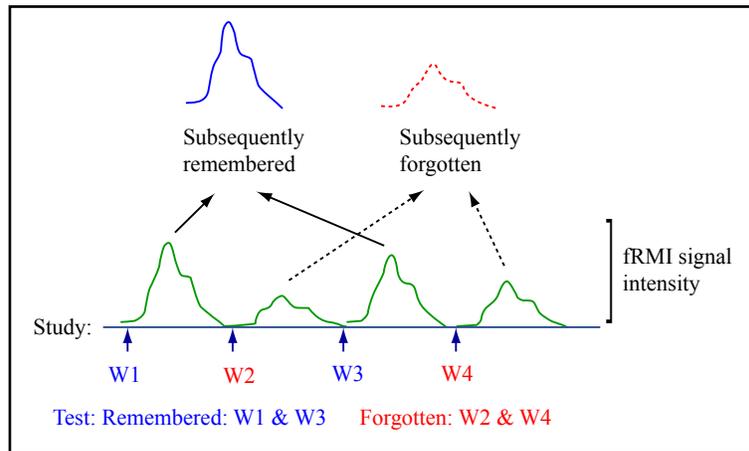
Figure by MIT OpenCourseWare.

- Encoding trials are sorted post hoc based on which items are actually remembered in a recognition test
- Powerful approach to examine encoding processes
  (e.g., Wagner et al., 1998 – student presentation)

Common criticisms of fMRI

- Limited temporal resolution
- Limited spatial resolution
  - Higher field strengths, better surface coils, & innovative statistics are improving both temporal and spatial resolution
- Only provides an indirect measure of neuronal activity
  - but the BOLD response IS correlated with neuronal activity
- Does increased activation = localization of function?
  - Complex cognitive tasks activate multiple cortical areas
  - fMRI is unable to establish the *necessity* of a given region
  - Other methods are still needed to infer causality
    (e.g., lesion, drug, or genetic studies)
  - Together, these complementary data are likely to yield far more interesting and meaningful conclusions

Getting closer to neural activity

All electrical currents generate a surrounding magnetic field

Image removed due to copyright restrictions. Model hand displaying the "right-hand rule."

This includes neurons!

Magnetoencephalography (MEG) basics

If enough brain cells are active at the same time, the generated magnetic field can be measured with special sensors

Images removed due to copyright restrictions.
Diagram of electrodes picking up magnetic brain waves and MEG setup; figures from Hämäläinen, Matti, et al. "Magnetoencephalography-theory, Instrumentation, and Applications to Noninvasive Studies of the Working Human Brain." *Reviews of Modern Physics* 65 (1993): 413-497.

Hamalainen et al 1993

Magnetic isofield & timecourse map

Right Anterior
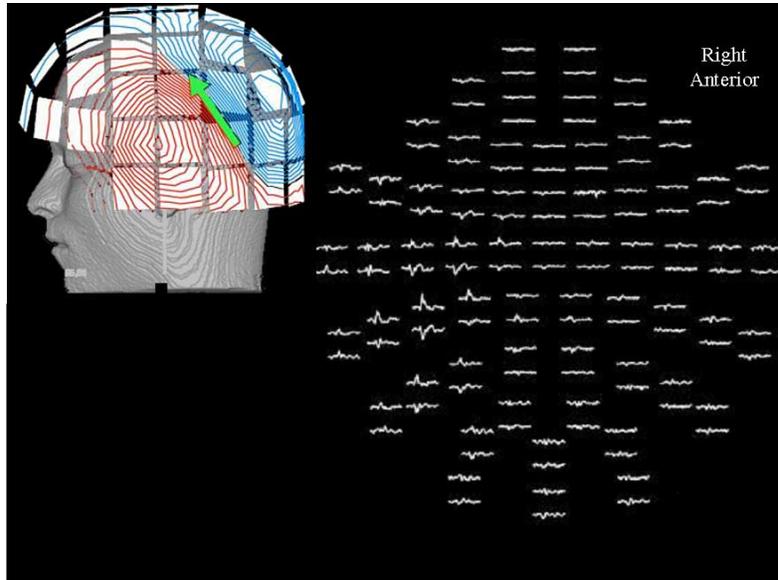
Courtesy of Michael Weisend. Used with permission. http://uuhsc.utah.edu/uumsi

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MEG study of encoding/retrieval

- **Encoding:** participants studied 240 real-life photographs
  - ½ buildings, ½ landscapes
  - Instructed to make building/landscape judgment
- **Retrieval: 240 original stimuli intermixed with 240 new stimuli**
  - Instructed to make "old"/"new" judgments
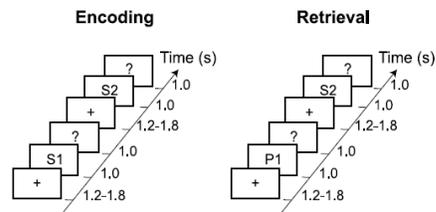
- **Brain activity recorded using whole-head MEG**
- **Looked for differences in oscillatory, or rhythmic, neural activity during encoding (i.e., subsequent memory paradigm) and during retrieval (old/new effect)**
- **Common neural rhythms:**

  Theta (4-12 Hz), Alpha (5-15 Hz), Beta (20-30 Hz), and **Gamma (35+ Hz)**

  Osipova et al (2006)

Subsequent memory effect: gamma activity

During encoding, gamma activity was greater in visual cortex for items later remembered compared to forgotten items

Source of gamma localized to occipital lobe (BA 18/19)

Osipova et al (2006)
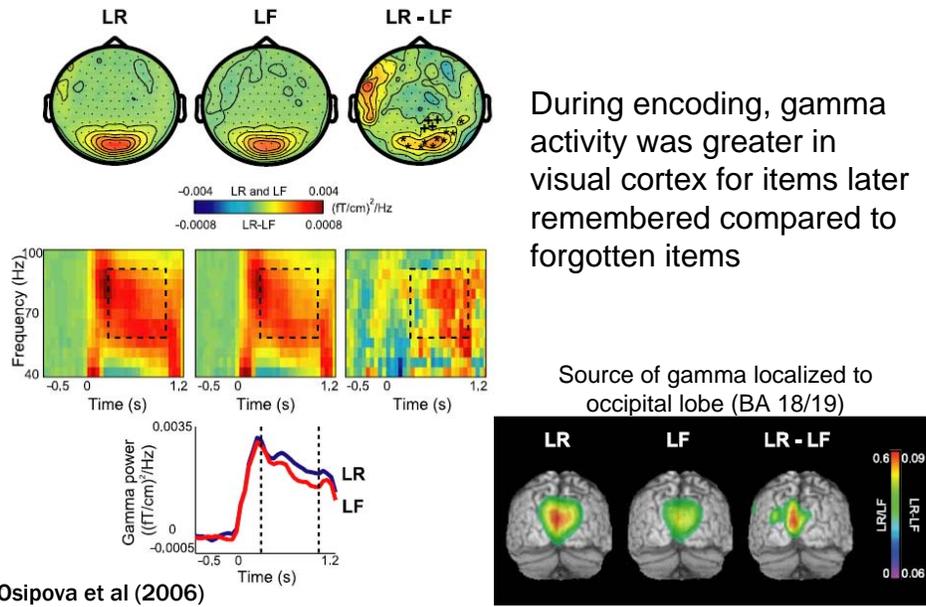
Courtesy of the Society for Neuroscience. Used with permission. Source: Figures 1, 2, & 4 from Osipova, Daria, et al. "Theta and Gamma Oscillations Predict Encoding and Retrieval of Declarative Memory." *The Journal of Neuroscience* 26 (2006): 7523-7531.

Gamma activity during retrieval

Gamma power was greater in visual cortex for remembered items compared to correctly rejected new items

Source of gamma localized to occipital lobe (BA 18/19)

Osipova et al (2006)
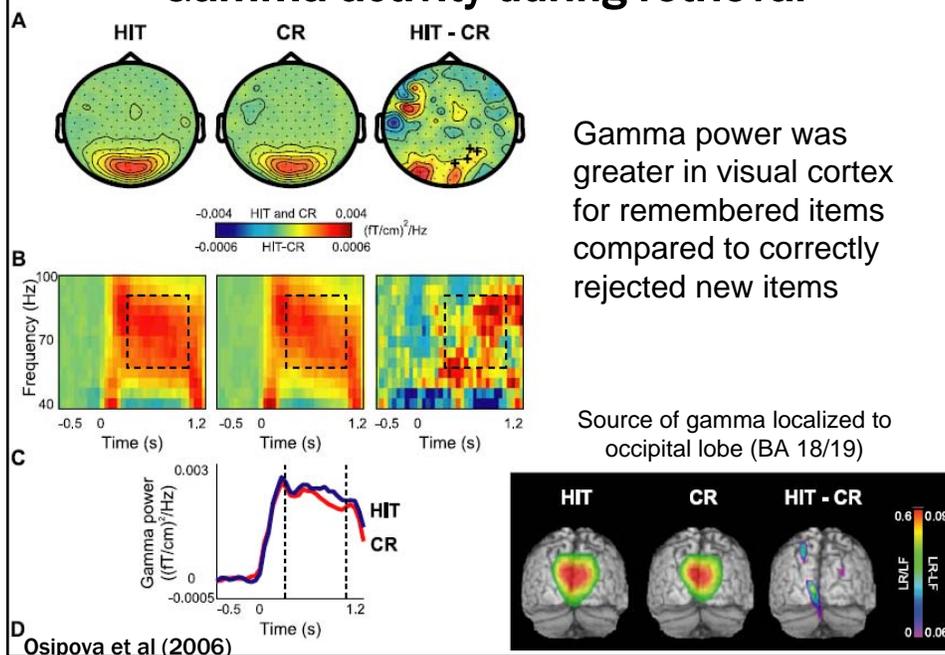
Putative role of gamma in LTM

- Gamma oscillations in visual areas during *encoding* may result in increased synaptic drive in downstream association areas
  - May facilitate plasticity
  - In rats, LTP can be induced by phase locking stimulus presentation with hippocampal theta rhythms
- Gamma activity during *retrieval* may reflect reactivation of visual representations
  - Likely via top-down, cognitive control mechanisms

Tradeoffs in functional neuroimaging

PET	• High specificity (e.g., glucose, neurotransmitters) – May be useful for clinical purposes • Specificity comes at a safety cost (radioactivity) • Spatial and temporal resolution are relatively poor

fMRI	• Only an indirect measure of neural activity
	   – BOLD contrast is actually caused by an increase in oxyhemoglobin
	• Relatively good spatial and temporal resolution
	• Allows for simultaneous whole-brain coverage
	   – Well suited for studying networks
	• No known health risks (good for longitudinal studies)

MEG	• Very high temporal resolution • Relatively direct measure of neural activity (magnetic fields) • Not good for measuring subcortical activity • Can be difficult to model sources of neural activity – Relies on complex model that may turn out to be incorrect