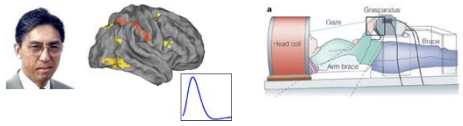


fMRI applications in cognitive neuroscience

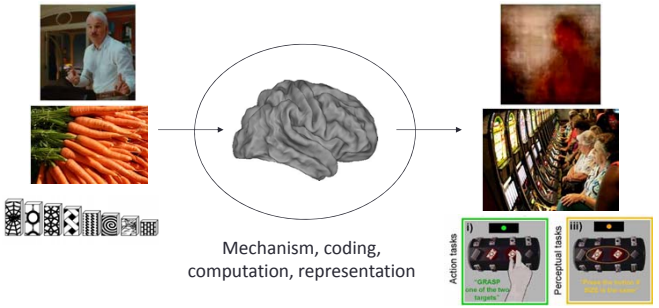
講師: 張智宏 副教授
中央大學認知神經科學研究所
行動與認知實驗室

acknowledgement

Dr. Shih-wei Wu
NYMU

The fundamental quest

- In neuroscience, it is about understanding and characterizing the relationship between brain and behavior



Mechanism, coding, computation, representation

Goal of today

- Is to provide a general overview of fMRI as a tool being applied to different fields in cognitive neuroscience

- Will briefly introduce signal transmission carried out by neurons and how neuronal activity relates to fMRI signal

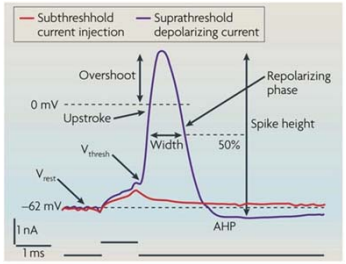
- Will discuss basic methodology on how to analyze fMRI signal and how to make statistical inference

- Will provide examples on fMRI applications to different fields/topics in cognitive neuroscience

How do neurons communicate?

Signal transmission

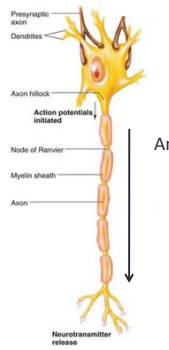
- Action potential is the basic signaling unit for neuronal communication



Nature Reviews | Neuroscience

Action potential

- It is generated at the axon hillock

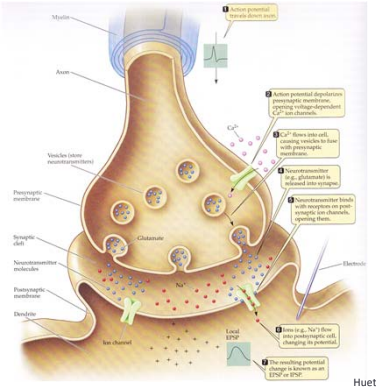


And propagates down the axon

http://humanphysiology2011.wikispaces.com/

Synaptic transmission

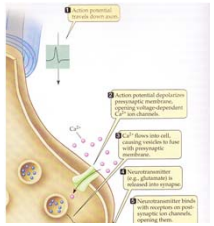
- An action potential triggers a cascade of events leading to changes in member potential of the postsynaptic neuron



Huettel et al (2008). Functional magnetic resonance imaging

Synaptic transmission

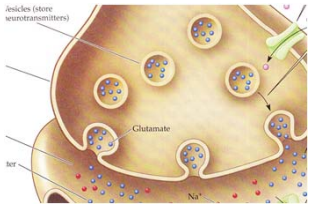
- 1. AP triggers opening of voltage-gated Ca^{2+} channels, letting Ca^{2+} in



Huettel et al (2008). Functional magnetic resonance imaging

Synaptic transmission

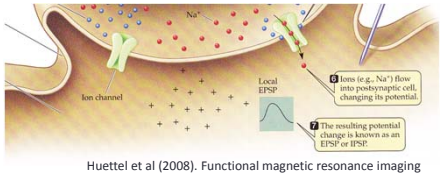
- 2. The influx of Ca^{2+} produces high concentration of Ca^{2+}, causing vesicles containing neurotransmitter to fuse with presynaptic membrane and subsequently release the neurotransmitter



Huettel et al (2008). Functional magnetic resonance imaging

Synaptic transmission

- 3. The neurotransmitter binds to specific receptors on the post-synaptic membrane. The receptors cause ion channels to open or close and thus changing the postsynaptic membrane potential



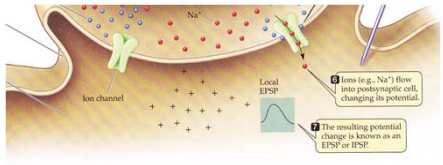
Huettel et al (2008). Functional magnetic resonance imaging

Synaptic transmission

- There are two types of postsynaptic membrane potential

  Excitatory postsynaptic potential (EPSP) slightly depolarizes the postsynaptic neuron

  Inhibitory postsynaptic potential (IPSP) slightly hyperpolarize the postsynaptic neuron



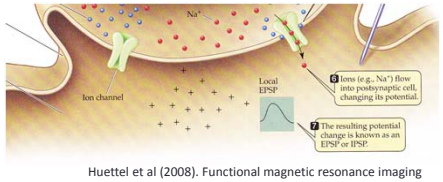
Huettel et al (2008). Functional magnetic resonance imaging

Synaptic transmission

- Neurotransmitters interact with receptors to produce EPSP or IPSP

  Glutamate opens Na+ channels, NMDA receptors opens Ca2+ channels. These actions causes the influx of Na+ and Ca2+ to the postsynaptic neuron (EPSP)

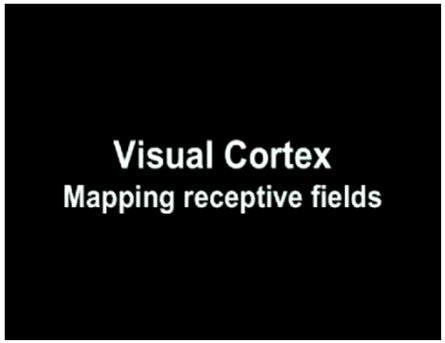
  GABA interacts with other receptors to open Cl- or K+ channels, causing influx of Cl- to the neuron or K+ efflux out of the neuron (IPSP)



Huettel et al (2008). Functional magnetic resonance imaging

Recordings of neuronal activity

Hubel and Wiesel



Cerebral metabolism: Neuronal energy consumption

- Adenosine triphosphate (ATP) is the principal *energy currency* for cells in the human body

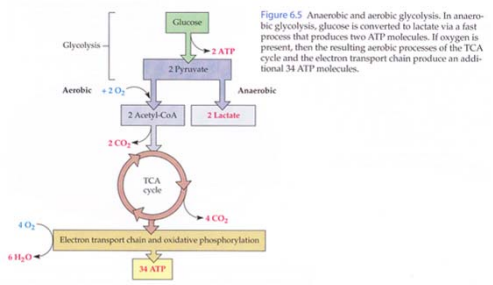
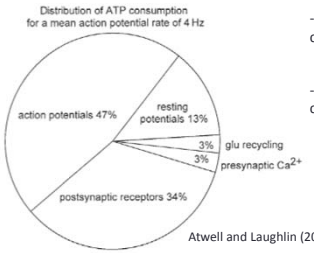


Figure 6.5 Anaerobic and aerobic glycolysis. In anaerobic glycolysis, glucose is converted to lactate via a fast process that produces two ATP molecules. If oxygen is present, then the resulting aerobic processes of the TCA cycle and the electron transport chain produce an additional 34 ATP molecules.

Huettel et al (2008). Functional magnetic resonance imaging

Cerebral metabolism: Neuronal energy consumption

- What is ATP being used for?



Atwell and Laughlin (2001)

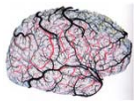
- Primarily (47%) used for restoring membrane concentration gradients following action potential

- 34% for restoring postsynaptic membrane concentration following EPSP or IPSP

To meet these energy demands, the vascular system must continuously supply glucose and oxygen!

Vascular system

- Neuronal activity evokes changes in blood flow



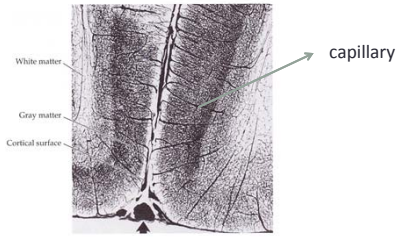
Blood flow $\propto$ radius^4

(A small change in vessel diameter would cause a big change in flow)

- Active neurons release substances to the nearby vessels that cause the vessels to dilate (this mechanism coordinates with control mechanisms that oppose to flow)

Blood flow

- The extraction of oxygen and glucose from the blood and the removal of waste carbon dioxide occur at the surface of the capillaries



- Capillary density indicates cellular metabolism. Gray matter has twice the capillary density of white matter

Oxygen extraction, deoxygenated hemoglobin

- Following oxygen extraction, the *deoxygenated hemoglobin* molecules are carried from the capillaries to small venules

- SUPER IMPORTANT: Deoxygenated hemoglobin is *paramagnetic* (having the property of being attracted to a magnetic field)

- The intensity of magnetization of a substance placed in a magnetic field is called the *magnetic susceptibility*

- Completely deoxygenated blood has 20% greater magnetic susceptibility than fully oxygenated blood

Blood flow and neuronal activity

- Increased neuronal activity leads to increased blood flow in the arterioles that supply those neurons

- Such increase in blood flow can occur in vessels up to several millimeters distant from the center of neuronal activity

- This emphasizes that the distribution of hemodynamic responses measured in functional neuroimaging techniques will be ultimately determined by the local architecture of the microvascular blood supply

Deoxygenated hemoglobin and T2*

- Paramagnetic substances distort surrounding magnetic field, causing nearby protons to experience different field strengths

- Protons experiencing different field strengths would precess at different frequencies, resulting in the more rapid decay of transverse magnetization, i.e. shorter T2*

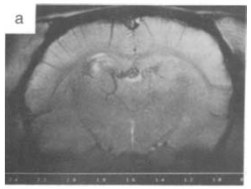
- MR pulse sequence sensitive to T2* should show more MR signal where blood is highly *oxygenated* and less signal when blood is highly *deoxygenated*

Blood-oxygen-level-dependent contrast

- Ogawa et al. (1990): The first to demonstrate BOLD contrast

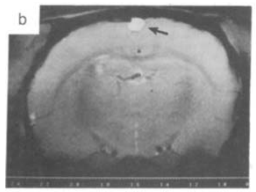
Manipulation: the amount of oxygen the animal breathed

100% O_2



Strong BOLD contrast

90% O_2/10% CO_2



Weak BOLD contrast

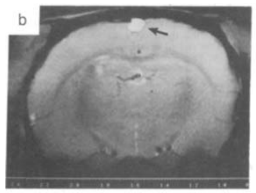
Blood-oxygen-level-dependent contrast

What just happened?

Blood-oxygen-level-dependent contrast

- Ogawa et al. (1990)

90% O_2/10% CO_2



Weak BOLD contrast

- Increased CO_2 in gas led to increase in blood CO_2

- Increased blood CO_2 caused increased blood flow

- Increased blood flow increased blood oxygenation level in the vessels, thereby increase signal strength in those areas

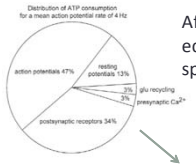
Blood-oxygen-level-dependent contrast

Ogawa et al. successfully showed that different levels of oxygenation (through manipulation) could produce different levels of signal intensity in the image

Blood-oxygen-level-dependent contrast

BUT … How would BOLD contrast reveal neuronal activity?

Recap



After neuronal firing, it needs energy to return to equilibrium state. The biggest proportion of energy is spent to restore of membrane potential caused by AP

This causes increase in blood flow

When oxygen is extracted from the blood, it causes the blood to become deoxygenated (increase in deoxygenated hemoglobin)

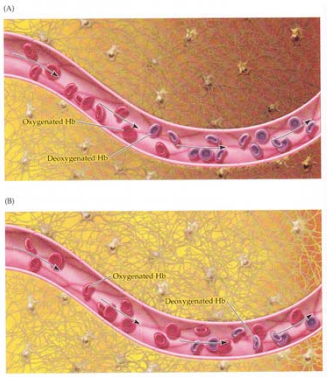
Recap

BUT …

didn't you just say MR signal would become weaker when it is more deoxygenated? Why would we observe stronger in BOLD signal when a group of neurons is active?

Recap

Turns out that …



- The increase in blood flow results in more oxygenated hemoglobin than is needed by the neurons

- This results a decrease in deoxygenated hemoglobin and thus an increase in BOLD signal

Huettel et al (2008). Functional magnetic resonance imaging

From neuronal activity to BOLD signal

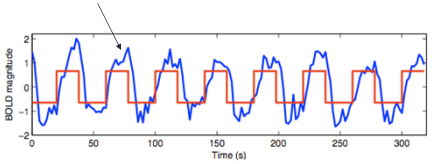
From neuronal activity to BOLD signal

Key

- Understanding and characterizing the relationship between BOLD signal and neural activity

From neuronal activity to BOLD signal

- Observed BOLD signal (example)



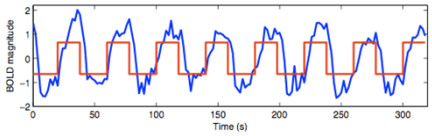
- BOLD signal did not look exactly like the predicted neural activity (in red)

From neuronal activity to BOLD signal

- BOLD signal as a transformation of neural activity

$x \xrightarrow{f(x)}$ BOLD

(neural activity)



From neuronal activity to BOLD signal

- BOLD signal as a transformation of neural activity

$x \xrightarrow{f(x)}$ BOLD

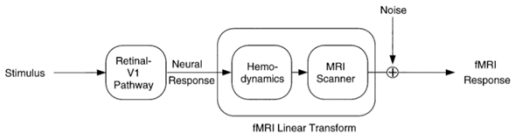
(neural activity)

- Identifying the properties of the transformation function is critical

- The first thing to check is if BOLD is a linear transform of neural activity

The linear transform model

- Boynton et al. (1996, J Neurosci.) tested the linear transform model in primary visual cortex (V1)

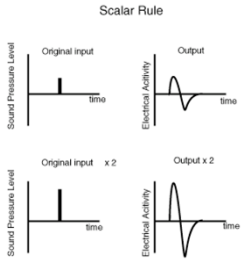


Important: It was only assumed that the transformation from neural response to fMRI response is linear.

The linear transform model

Properties of a Linear Time-Invariant (LTI) system

- Homogeneity

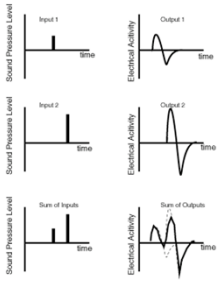


When the input magnitude is doubled, the output response is also doubled

The linear transform model

Properties of a Linear Time-Invariant (LTI) system

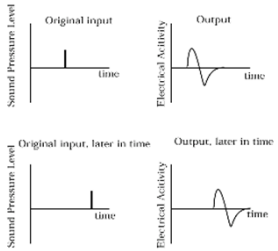
- Additivity



The linear transform model

Properties of a Linear Time-Invariant (LTI) system

- Shift invariance



Shift invariance with respect to time (time invariant)

The linear transform model

Why is LTI system important?

The linear transform model

If LTI holds,

Convolution

$$(h * f)(t) = \int_0^{\infty} h(\tau) f(t-\tau) d\tau.$$

The output of a LTI system is simply the convolution of the input and the impulse response function, *h(t)*

The linear transform model

If LTI holds,

Convolution

$$(h * f)(t) = \int_0^\infty h(\tau) f(t-\tau) d\tau.$$

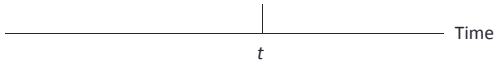
The output of a LTI system is simply the convolution of the input and the impulse response function, *h(t)*

Visualizing convolution

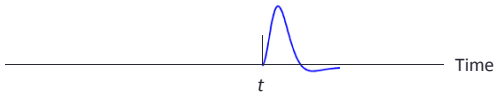
$$(h * f)(t) = \int_0^\infty h(\tau) f(t-\tau) d\tau.$$

- Suppose *h(t)* looks like

- There is an impulse (an input) at time *t*



- The impulse response to this input is obtained by convolving the impulse with the impulse response function *h(t)*

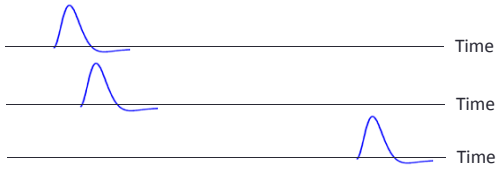


Visualizing convolution

$$(h * f)(t) = \int_0^\infty h(\tau) f(t-\tau) d\tau.$$

- Input time series

- Output (response) time series (the sum of the 3 time series)



The linear transform model

Why is LTI system important?

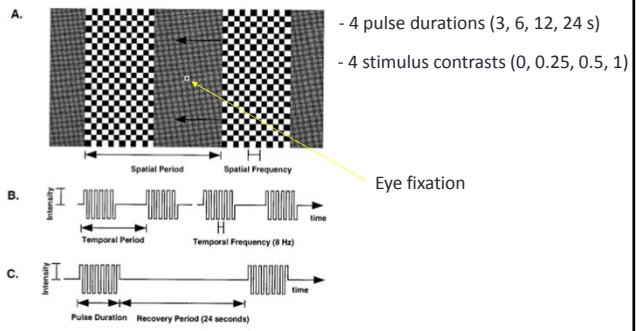
- The output of a LTI system is simply the convolution of the input and the impulse response function, *h(t)*

- All we need to know is *h(t)*

Testing the linear transform model

Boynton et al. (1996)

- flickering checkerboard task



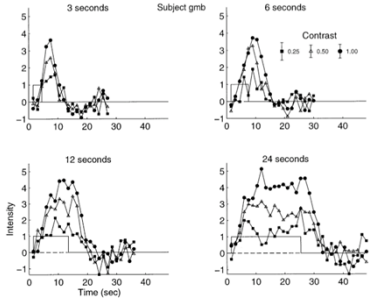
- 4 pulse durations (3, 6, 12, 24 s)
- 4 stimulus contrasts (0, 0.25, 0.5, 1)

Eye fixation

Testing the linear transform model

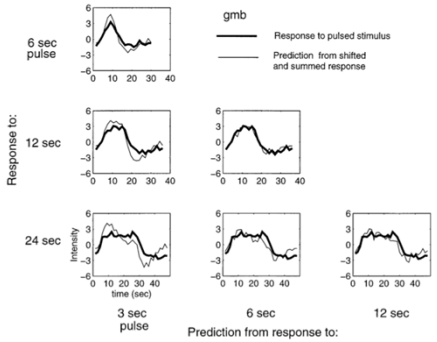
- Results

Look how response varies as a function of contrast and duration; Could you tell if LTI is hold?



Testing the linear transform model

- LTI assumption holds in most cases



The hemodynamic response function (HRF)

Modeling *h(t)*

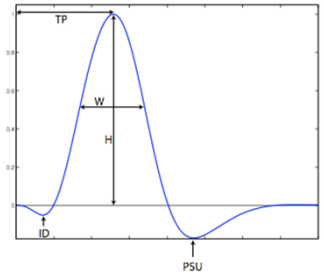
We need to have a good estimate of *h(t)*

The hemodynamic response function (HRF)

Modeling *h(t)*

We need to have a good estimate of *h(t)*

Friston et al. (1994), Lange & Zeger (1997)

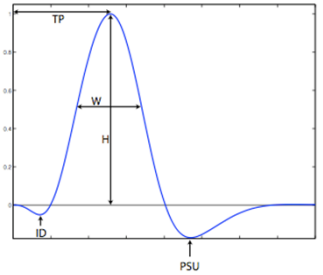


The hemodynamic response function (HRF)

Modeling *h(t)*

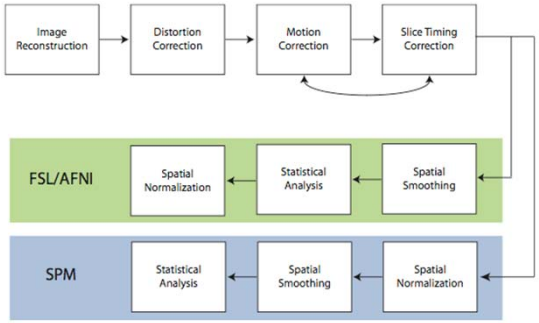
We need to have a good estimate of *h(t)*

Canonical HRF (double-gamma function)



Overview of data processing and analysis pipeline

The analysis steps are not the focus of today

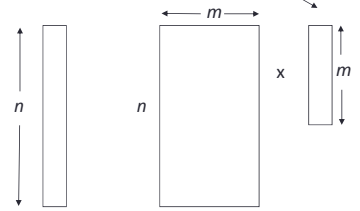


Poldrack et al. (2011)

Statistical modeling: General linear model (GLM)

- General linear model

$$Y = X\beta + \varepsilon, \varepsilon : N(0, \sigma^2)$$

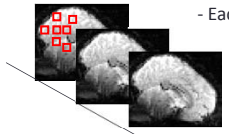


BOLD times series Design matrix Parameter vector

(BOLD: Blood Oxygenation Level Dependent)

Statistical modeling: General linear model (GLM)

Univariate appraoch



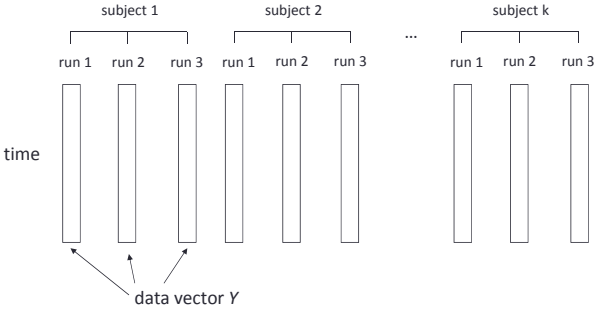
- Each voxel in the brain is analyzed *separately*
- Each voxel presents a time-series data

...

Time

GLM

In an fMRI experiment, below is a typical design



GLM

- Given the independent variables manipulated

An experimenter may wish to know what areas in the brain are sensitive to the manipulation(s)

Example:

As an experiment alternates between visual fixation (a baseline condition) and finger movements, what areas are more 'active' during finger movements?

A standard approach in fMRI to address questions like the above is the General Linear Modeling analysis

GLM

For each run's time-series data *Y,*

$$Y = X\beta + \varepsilon \quad \text{where } \varepsilon: N(0, \sigma^2 I)$$

$$X = \begin{pmatrix} 1 & 0 \\ 1 & 1 \\ 1 & 0 \\ M & M \\ 1 & 1 \end{pmatrix} \quad n_t \qquad \beta = \begin{pmatrix} \beta_0 & \beta_1 \end{pmatrix}$$

β_0 β_1 : finger movement

GLM and hypothesis testing

Hypothesis testing on linear combination (contrast) of β

$$H_0 : \beta_0 = 0$$

$$c = [1\ 0\ \ldots 0] \qquad \beta = \begin{bmatrix} \beta_0 \\ \beta_1 \\ \text{M} \\ \beta_m \end{bmatrix} \qquad \text{hence} \quad c\beta = \beta_0$$

It can be shown that the distribution of $c\beta$ is normal with mean $c\beta$ and variance $c\left(X^T X\right)^{-1} c^T \sigma^2$

GLM and hypothesis testing

Since we do not know the variance, we compute the *t* statistic

$$t = \frac{c\hat{\beta}}{\sqrt{c\left(X^T X\right)^{-1} c^T \hat{\sigma}^2}} \qquad \text{with } df = n_t - (n_m + 1)$$

For one-tailed test $H_1 : c\beta > 0$

$$P(T_{n_t-(n_m+1)} \geq t)$$

For two-tailed test $H_1 : c\beta \neq 0$

$$P(T_{n_t-(n_m+1)} \geq |t|)$$

Some example studies

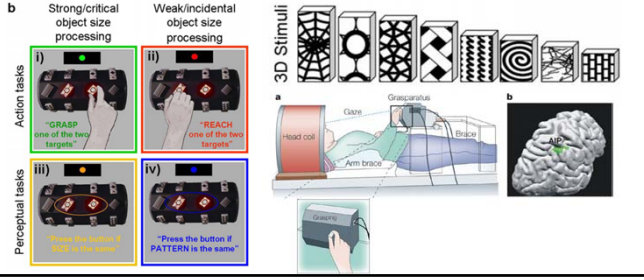
Study 1: perception vs. action

Cavina-Pretasi et al. (2007) PLoS One

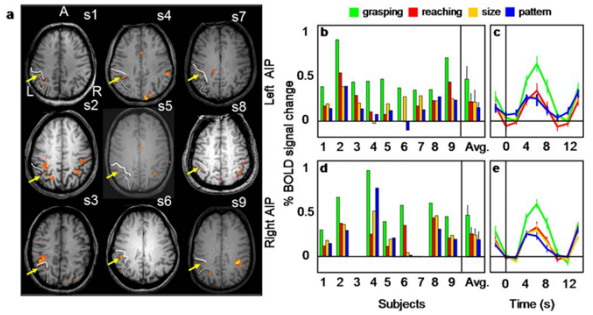
Cristiana Cavina-Pretasi

- Question: whether or not brain areas mediating size computation for grasping are distinct from those mediating size computation for perception

- Experimental design:



Study 1: decision making



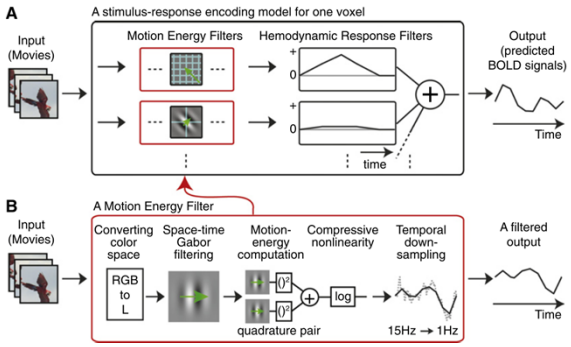
Study 2: Neurocinematics

Nishimoto, et al. (2011, Current Biology): Trained computer models to match human visual brain activities and dynamic visual scenes, and then reconstruct novel visual scenes based on brain activities.

Presented clip

Clip reconstructed from brain activity

Study 2: Neurocinematics



Self control

Question

- What are the neural mechanisms for self-control?

- example: Hare et al. (2009, Science)

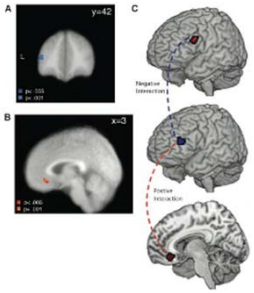
Tasty, bad for health

Or

Not tasty, good for health

Self control

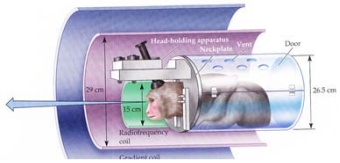
- How might the brain exercise self control?



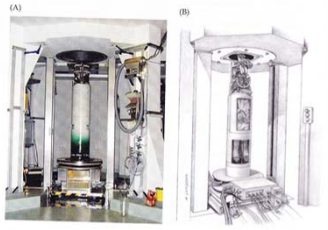
- Looking at the SC group:
  - Decreased functional connectivity during unhealthy trials between DLPFC and IFG (seed: DLPFC)
  - Increased functional connectivity during unhealthy trials between IFG and vmPFC (seed: IFG)
  - No PPI effect on NSC group

Neural mechanism: DLPFC exercise self-control to vmPFC through IFG

Study 4: human and monkey fMRI



- Monkey in typical human MRI scanner



- Logothetis and colleagues: custom-made MRI for monkey