Principles and Experimental Design of fMRI
功能性磁振造影：基本原理與實驗設計

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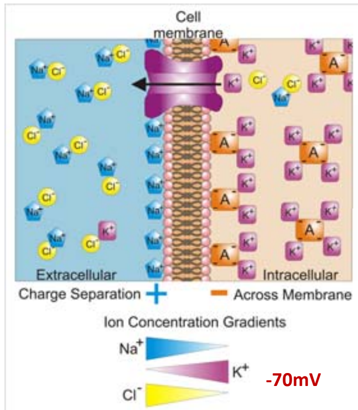
Principles of BOLD fMRI

fMRI BOLD signal

- fMRI does not measure neuronal activation directly, but the consequences of metabolic processes associated with activation.
- **Blood Oxygenation Level Dependent (BOLD)** contrast
  (Ogawa et al., PNAS, 1990; Turner et al., MRM, 1991)
- The MR signal in the vicinity of blood vessels and in perfused brain tissue decreased with a decrease in blood oxygenation.

Membrane Potential

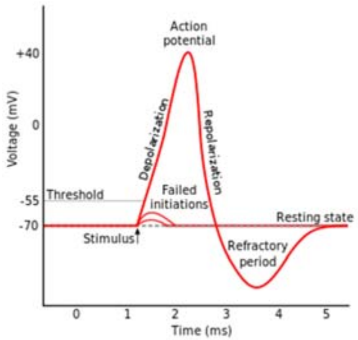
- Neuronal membranes prevent free diffusion of ions.
- A neuron at rest has…
  - a greater concentration of K^+ inside its membrane;
  - a greater concentration of Na^+, Ca^{2+}, and Cl^- outside.
- The difference in electric potential between the interior and the exterior of a biological cell is typically ranged from –40 mV to –80 mV.



https://en.wikipedia.org/wiki/Membrane_potential

Action Potential

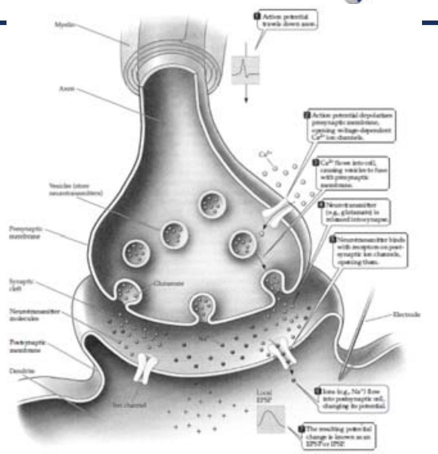
- **All-or-none** principle
  - Action potentials are said to be all-or-none signals, since either they occur fully or they do not occur at all.
- **Depolarization**
  - At the beginning of the action potential, the Na^+ channels open and Na^+ moves into the axon, causing depolarization.
- **Repolarization (Sodium-potassium pumps)**
  - Repolarization occurs when the K+ channels open and K^+ moves out of the axon. This creates a change in polarity between the outside of the cell and the inside.



The resting potential is around –70 millivolts (mV) and the threshold potential is around –55 mV.

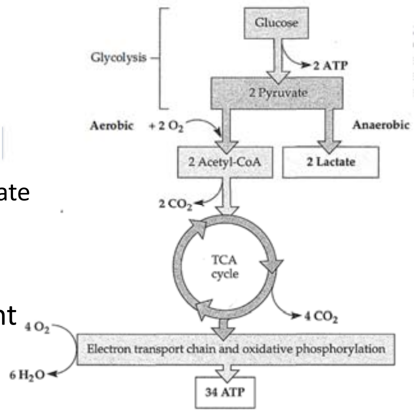
Synapses

- **Glutamate**: One of the most important excitatory neurotransmitters.
- **excitatory postsynaptic potential (EPSP)**: A depolarization of the postsynaptic cell membrane.
- **γ-aminobutyric acid (GABA)**: One of the most important inhibitory neurotransmitters.
- **inhibitory postsynaptic potential (IPSP)**: A hyperpolarization of the postsynaptic cell membrane.



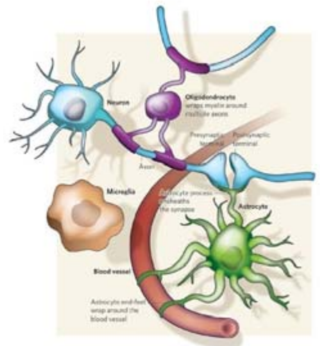
Neurovascular Coupling

- ATP is essential for neural activity
  - Restoration of ionic gradients
  - neurotransmitter recycling
- Glycolysis
  - a small amount of ATP (2 ATP) → produce lactate
- **Oxidative glucose metabolism (90% in brain)**
  - a large amount of ATP (34 ATP)
- Cerebral metabolism depends on a constant supply glucose and oxygen



Neurovascular Coupling

- Multiple mechanisms…
  - Astrocytes links neurotransmitter activity (glutamate cycling) to vascular responses.
  - Direct neuronal innervation of smooth muscle cells can also control blood flow.
- Requirement of metabolic nutrients
- Elimination of waste products
  - CO_2 and excessive heat



Neurovascular Coupling

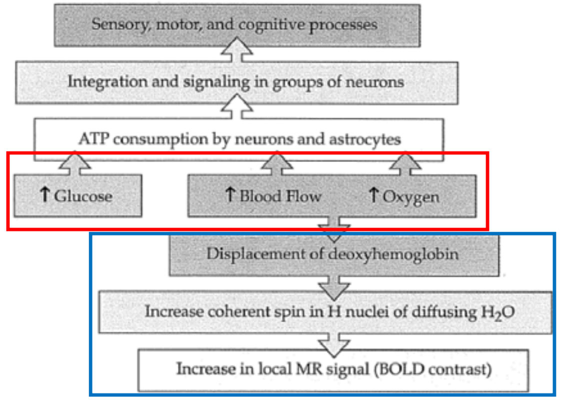
- A continuous supply of energy substrates is maintained by CBF
- Neural activity
  - Blood perfusion via capillaries ↑
  - regional cerebral blood flow (rCBF) ↑
  - regional cerebral blood oxygenation (rCBO) ↑
- Changes in rCBF or rCBO can be used to map brain activity
  - Functional neuroimaging

Brain vascular system: glucose and oxygen

Zlokovic & Apuzzo, 1998.

Biomarkers of brain activation

- Oxygen
  - **BOLD fMRI**
  - Functional near-infrared spectroscopy (fNIRS)
  - Positron emission tomography (PET)
- Blood Flow
  - Arterial spin labeling (ASL)
- Glucose (still impractical now)
  - PET
  - MR CEST techniques

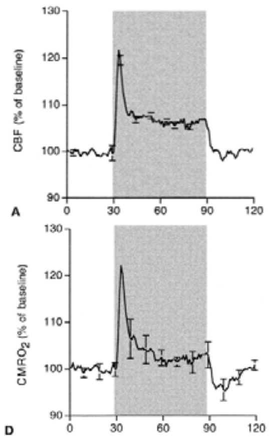


CBF and O_2 Consumption Mismatch

- During neural activity…
  - The fractional increases in CBF and glucose consumption are similar in magnitude.
  - Oxygen consumption increases much less than CBF.
- ➔ A net increase of oxygen in the blood and tissue.

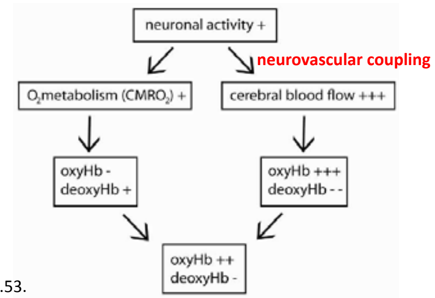
CMRO2: cerebral metabolic rate of oxygen

Ances et al., JCBFM 2001.



Metabolic and hemodynamic changes

- Mismatch between CBF and O_2 consumption
- Neural/Brain activation
  - Elevated oxy-Hb fraction
  - Decrease deoxy-Hb fraction

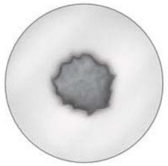


Neuroimaging – Methods, pp.53.

Hemoglobin

Oxygenated Hemoglobin

- Diamagnetic
- Doesn't distort surrounding magnetic field
- No signal loss in BOLD signal



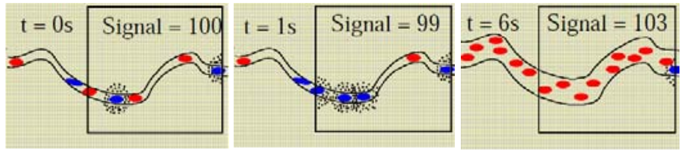
Deoxygenated Hemoglobin

- Paramagnetic
- **Distorts surrounding magnetic field**
- **Signal loss in BOLD signal !!!**

fMRI slides from http://culhamlab.ssc.uwo.ca/fmri4newbies/Tutorials.html

fMRI BOLD signal

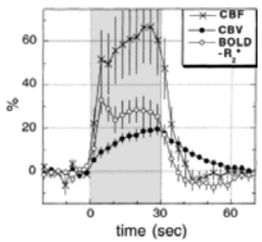
- t = 0s, a steady state in which there is an given amount of oxygenated and deoxygenated hemoglobin.
- t = 1s, an increased of deoxygenated hemoglobin due to the oxygen demands of neuronal activation.
- t = 6s, an increased of blood supply and oxygenated hemoglobin "flush away" the deoxygenated ones.



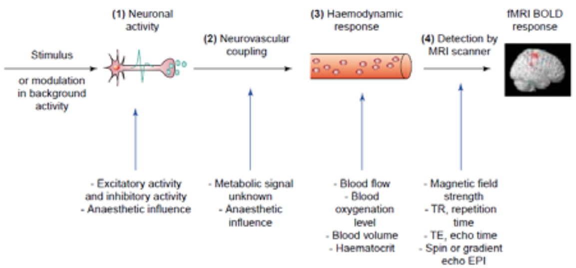
Matthijs Vink, Preprocessing and analysis of functional MRI data, 2007.

Neuronal activity and BOLD

- Blood-oxygenation level dependent (BOLD)
- BOLD fMRI detects the alterations in
  - The level of deoxygenated hemoglobin
  - Cerebral blood volume



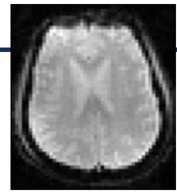
Mandeville et al.,MRM 1999.



Common fMRI protocol

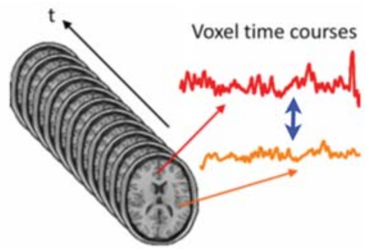
- Single-Shot 2D EPI (GRE-EPI), T2* weighting
- Repetition Time = 2000 ms
- Echo Time = 20 ms
- Flip Angle = 70~90°
- NEX = 1
- Slice thickness = 3.4 mm
- Field of View = 220 x 220 mm^2
- Matrix size = 64 x 64
- Volume number = 240 ~ 360

(depends on experiment design)

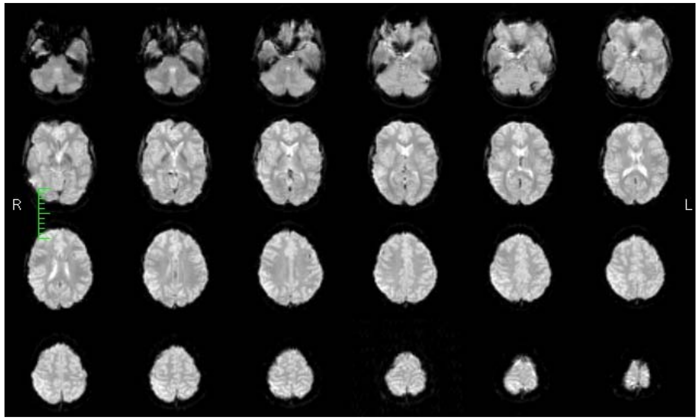


1 voxel ~10^6 neurons

3.44 x 3.44 x 3.40 mm^3



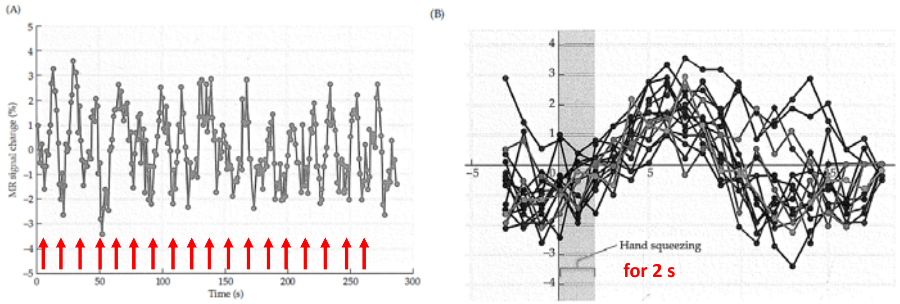
EPI BOLD raw images



http://practicalfmri.blogspot.tw/2012/05/rare-intermittent-epi-artifacts-spiking.html

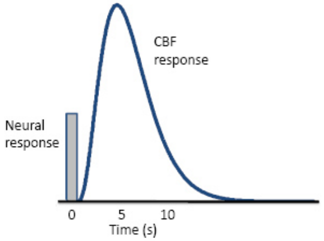
fMRI signal example

- A sample fMRI time course from a single voxel in the motor cortex during a task in which the subject squeezed her hand for 2 s every 16 to 18 s.



Neurovascular Coupling Properties

- Use of vascular responses to infer neural activity
  - **Time**: lack of temporal information in vascular response
  - **Space**: focal activation of neurons ⇔ local vascular response?
  - **Amplitude**: linear relationship?



Alteration Factors

- Disease
  - the chemical mediators
  - the dynamics of the vascular system
  - hypertension, diabetes, and AD alter Ionic channels on vascular smooth muscle
- Aging
  - change the vascular system
  - increasing tortuosity or reducing elasticity of the blood vessels
- Pharmacology
  - Diazoxide is used as a vasodilator →large vascular responses with little or no change in neural activity.
  - Hypercapnia (the concentration of CO_2 in the blood ↑) → vasodilation.

Experimental Design of fMRI

Goal of Experimental Design

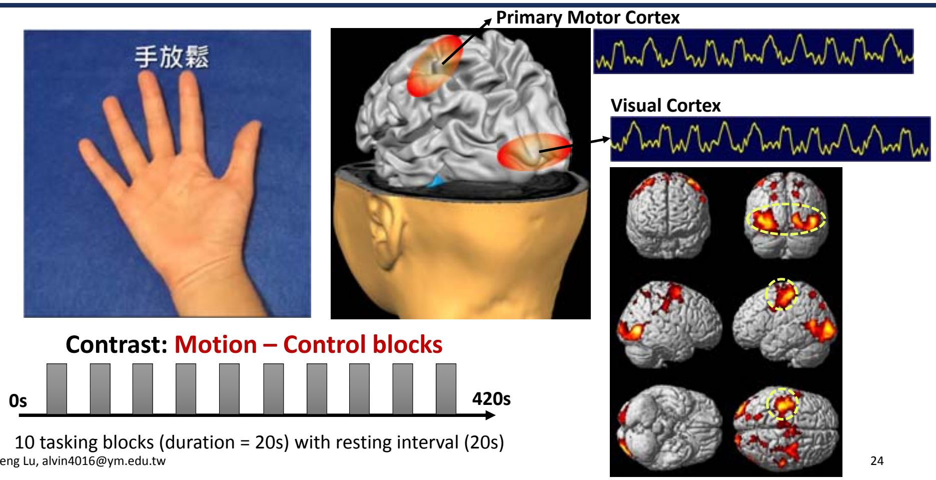
- To manipulate the participants experience and behavior in some way that is likely to produce a functionally specific neurovascular response.

- What can we manipulate?
  - **Stimulus properties** (what is presented?)
  - **Stimulus timing** (when is it presented?)
  - **Participant instructions** (what do subjects do with it?)

Types of Experimental Design

- **Simple Subtraction**
- **Categorical Design**
  - Cognitive subtraction: the assumption of pure insertion
- **Factorial Design**
  - Considering the interaction between multiple factors
- **Parametric Design**
  - Correlating behavior with brain activity

Simple Subtraction



Categorical Design (1/3)

Comparing the brain activity between stimulus types.

Example:

- **Stimulus:** visual presentation of 12 common nouns.
- **Tasks:** decide for each noun whether it refers to an **animate** or **inanimate** object.

TIGER	BOOK	BUCKET

Categorical Design (2/3)

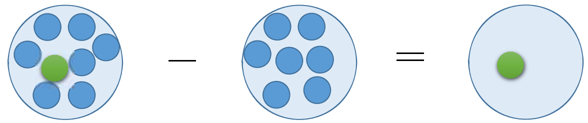
- **Cognitive subtraction**: the assumption of **pure insertion**

Aim

- Neural structures underlying a single process Y (e.g. face recognition)?

Procedure

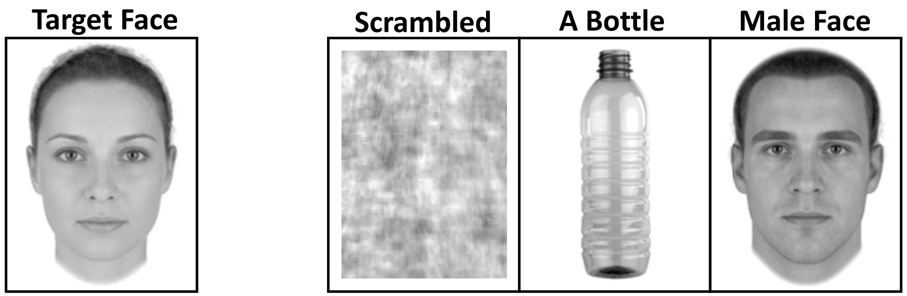
- Contrast: [Task with Y] – [control task without Y] = Y



Categorical Design (3/3)

To identify the face recognition area…

Which one is the proper Control stimulus?



Factorial Design (1/2)

- Combining two or more factors within a task and looking at the effect of one factor on the response to other factor.

- **Main effects**
  - Main effect of task: (A1+B1) – (A2+B2)
  - Main effect of stimuli: (A1+A2) – (B1+B2)

Task (1/2) / **Stimuli (A/B)**

	Viewing	Naming
Gray-level	A1	A2
Color	B1	B2

Factorial Design (2/2)

- Combining two or more factors within a task and looking at the effect of one factor on the response to other factor.

- **Interaction of task and stimuli**
  - (A1 – B1) – (A2 – B2)

Does not make the assumption of pure insertion.

Stimuli (A/B)	Task (1/2)	
	Viewing	Naming
Gray-level	A1	A2
Color	B1	B2

Parametric Design

Exploring systematic changes in brain responses according to some performance attributes of the task.

Parametric designs use **continuous rather than categorical design**.

For example, we could **correlate response times with brain activity.**

4 – 1 = 3

36 – 17 = 18

116 – 22 = 96

Stimulus Delivery

- **MRI compatible hardware**
  - In-room viewing monitor/projector
  - Goggles with integrated EyeTracking cameras
  - Audio system
  - Response pads/grips/buttons
  - Trigger/synchronization box (MR scanner ⇔ stimulus presentation software)
- **Stimulus presentation software**
  - E-prime (BIOPAC Systems)
  - Presentation (Neurobehavioral Systems)

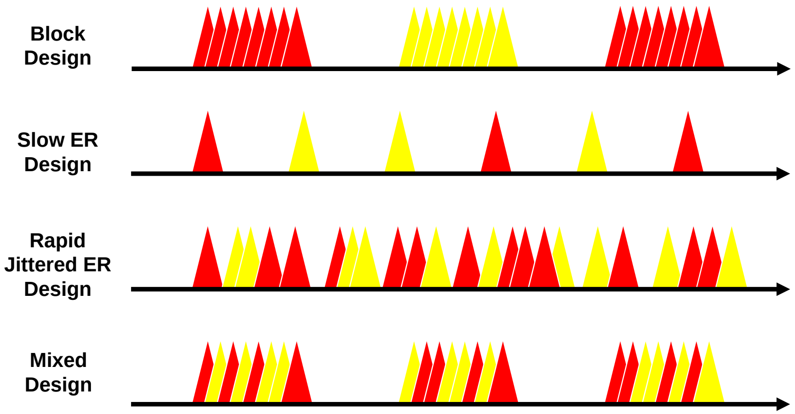
Stimulus Timing Design

- **Block design**
  - Combine BOLD response to a number of continuous trials (events)
- **Event-related (ER) design**
  - Obtain the BOLD response to a single event

- The more *efficient* a design, the less scan time is needed to achieve sufficient *power*.

Design Types

= trial of one type = trial of another



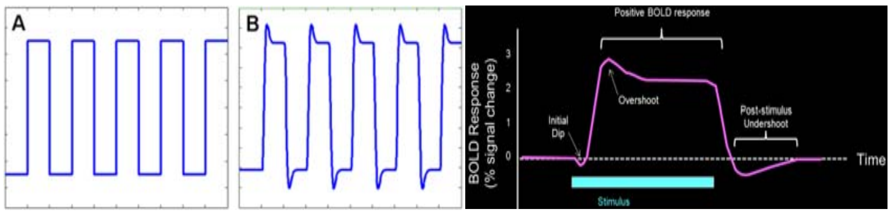
fMRI slides from http://culhamlab.ssc.uwo.ca/fmri4newbies/Tutorials.html

Block Design

- A design in which the task is presented in so-called blocks (15~30s), alternated with resting blocks.
- The number of scans should be equal in all conditions, so that the variance in all factors is the same.
- The longer the blocks are, the more chance there is for a correlation with low-frequency noise.
- The strength of the brain signal can decrease over time.

Block Design

- **Box-car function**
  - A 0 for no-task and a 1 for task period
- **Hemodynamic (BOLD) changes do not suddenly activate and stop activating in the way modeled by the box-car function.**
  - A better estimation by convolving the box-car input function with an **HRF**.

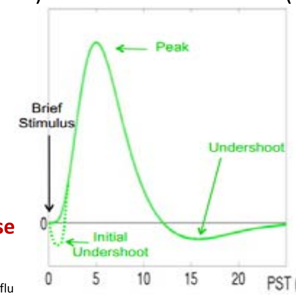


Matthijs Vink, Preprocessing and analysis of functional MRI data, 2007.

BOLD and HRF characteristics

- The relationship between neural activation and BOLD signal
  - Neuronal firing and postsynaptic potentials occur very soon (tens to hundreds of milliseconds)
  - BOLD: initial dip (~1s) → maximal value (4~6s) → return to baseline (~20s)
- **Hemodynamic response function (HRF)**

BOLD Impulse response



Friston et al, Neuroimage, 1995, 1998.

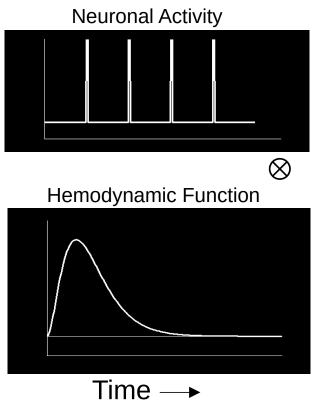
Pros of Block Designs

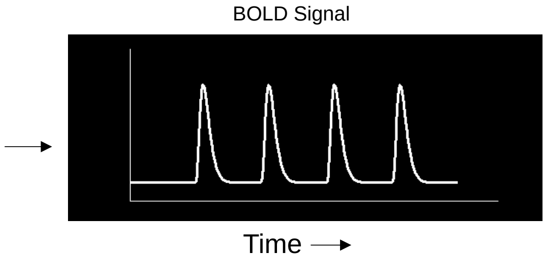
- high detection power of activated voxel/region
- has been the most widely used approach for fMRI studies
- accurate estimation of hemodynamic response function is not as critical as with event-related designs

Cons of Block Designs

- poor estimation power to differentiate the time courses in response to different conditions
- very predictable for subject
- Can't look at effects of single events
- becomes unmanageable with too many conditions (e.g., more than 4 conditions + baseline)

Slow Event-Related (ER) designs





Optimal constant **inter-trial interval (ITI)**

- For brief(<2s) stimuli = 12 s
- For longer stimuli = 8 + 2*stimulus duration

Pros of Slow ER Designs

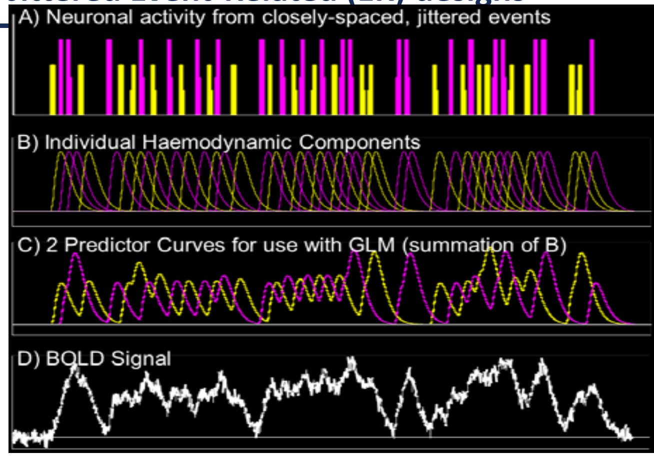
- excellent estimation of BOLD changes
- useful for studies with delay periods
- very useful for designs with motion artifacts because you can tease out artifacts

Cons of Slow ER Designs

- poor detection power because of very few trials per condition
- subjects can get VERY bored and sleepy with long ITI.

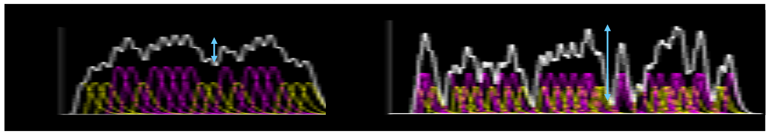
How about making it fast?

Rapid Jittered Event-Related (ER) designs



Why jitter?

- Yields larger **fluctuations** in signal



When pink is on, yellow is off
→ pink and yellow are anticorrelated

Includes cases when both pink and yellow are off
→ less anticorrelation

- Without jittering predictors from different trial types are strongly **anticorrelated.**
  - As we know, the GLM doesn't do so well when predictors are correlated (or anticorrelated)

Pros of Rapid-ER Designs

- High detection power compared to slow ER design
- Trials can be put in unpredictable order.
- Subjects don't get so bored.

Summary of Experiment Design

- **Rules of thumb**
  - **Blocked Designs:**
    - Powerful for detecting activation
    - Useful for examining state changes
  - **Event-Related Designs:**
    - Powerful for estimating time course of activity
    - Allows determination of baseline activity
    - Best for post hoc trial sorting
  - **Mixed Designs**
    - Best combination of detection and estimation
    - Much more complicated analyses

Quoted from Yingying's slide.

THE END

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fMRI Teaching Materials:
http://www.ym.edu.tw/~cflu/CFLu_course_fMRIana.html