fMRI : MR Imaging of Brain Function

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Our First Lecture …

• MR not just a morphology tool
  – Function + metabolism
• Diagnosis & therapy monitoring
• What functions can MRI show?
Functional Info in MRI

- Flow velocity (PC-MRI)
- Fiber tracking (DTI)
- Hemodynamics (perfusion)
- Metabolism (spectroscopy) ...
What Else Can MR Show?

- Brain neuron activation?
  - What are you thinking now?
  - Lie detector??
  - Politian sex scandal???
  - Endocrinology???
CNS Reaction upon Acupuncture

Wu MT et al., Radiology 1999
Brain Decides Behavior

- Behavior = pattern of brain neuron activation physiologically
- I can know what you are thinking as long as I see what part of your brain is activating
Neuron upon Stimulation

- Action potential firing ...
- Energy required (from ATP) ...
- Blood supplies nutrients ...
MRI Can Detect …

• Action potential firing …
• Energy required (from ATP) …
• Blood supplies nutrients …
  – Blood, oxygen
First on Blood Flow

• Neural activation needs blood supply for nutrients
• Stimulation $\rightarrow$ blood flow increases
  – Known long time ago
• Can perfusion MRI see it?
Experiment One

- Gd-DTPA injection
- Perfusion MRI for rCBV
- Compare rCBV before & after visual stimulation
  - Twice Gd injection
Note

- Not a particularly new research
- Just show functional MRI feasible
- Similar to routine nuclear medicine
- MRI superior in no radiation
rCBV Changes upon Visual Stimulation

Increased CBV (Science 1991)
Then on Oxygen

- Neural activation needs oxygen
- Energy supplied by ATP
- 1 glucose + O_2 = 36 ATP
- Oxidative phosphorylation
Then on Oxygen

• Oxygen level should change upon neural stimulation
• Hemoglobin in blood releases oxygen into tissue
• Can MRI see this change?
Hemoglobin Property

- Oxy: diamagnetic ($\Delta \chi = -10^{-6} \sim 10^{-5}$)
- Deoxy: paramagnetic ($\Delta \chi = +10^{-3} \sim 10^{-2}$)
- Tissue: mostly diamagnetic
- Deoxy-Hb disturbs Bo homogeneity
Hemoglobin Property

- Deoxy-Hb presence $\rightarrow$ Bo disturbed $\rightarrow$ T2* shortened $\rightarrow$ low signal in gradient-echo
- GrE signal $\sim$ blood oxygenation
Bo Distortion from Susceptibility

Diamagnetic

Paramagnetic

Distorted Bo $\rightarrow$ shortened T2*
Bo Distortion from RBC Susceptibility

Signal decay from inhomogeneous Bo
Experimental Evidence?

- Altered blood oxygenation
  - Inhale pure oxygen
  - Inhale pure nitrogen
- Signal changes in brain MRI
Blood Susceptibility vs. Oxygenation

Less oxygen, stronger paramagnetism
Rat Brain T2* Images

Normal air  Pure oxygen
Signal Changes in Cat Brain

T2* shortened after inhaling pure nitrogen
MRI Can Detect ...

- Action potential firing ...
- Energy required (from ATP) ...
- Blood supplies nutrients ...
  - Blood, oxygen
No Longer Mysterious

- rCBV detectable
- Blood oxygenation detectable
- Brain functional MRI feasible
  - Functional MRI (fMRI)
Experiment 2

- Give a simple “behavior”
  - Visual stimulation
- MRI, T2*-weighted (EPI)
- Compare signal before & after
Signals upon Visual Stimulation

Signal stronger with stimulation
Spatial Distribution of Signal Behavior

Kwong et al., PNAS 1992
Why Signal Increases?

- Increase in oxygen required upon stimulation
- Blood supply over-compensates with even more oxygen (homeostasis)
- Deoxy-Hb reduced (venous side)
Let’s Name It

- Blood Oxygenation Level Dependent contrast (BOLD)
- Signal change upon stimulation is “related” to blood oxygenation
Lie Detector Then!

- Don’t panic ...
  - Look at fMRI data again
  - Note vertical signal scale!
- BOLD signal sensitivity
BOLD Signal for Visual Stimulation

Signal increase about 4% only
BOLD Sensitivity (1.5T)

- Visual cortex: strongest BOLD
- Signal change: 1~6% (2% typical)
  - Cf: 40 gray levels naked eye
- SNR < 50: noise > BOLD signal
Increase Sensitivity

- More experiments!
- Data averaged to reduce noise
- Expense: experiment time & memory size
Common Stimulation Paradigm

Box Car Paradigm

ON
OFF
ON
OFF
ON
OFF
continuous scanning
Simplest fMRI

- Continual image acquisition
  - Stimulus on $\sim 10 \times 4$
  - Stimulus off $\sim 15 \times 5$
- ON averaged – OFF averaged
Scanning Technique

- Sufficient T2* weighting
  - Gradient-echo (TE~60 @ 1.5T)
- Fast scan for continuous scan
  - EPI, short TR GrE, spiral
fMRI Signal Behavior

- ON: higher, OFF: lower
  - At least roughly
- Signal pattern generally follows stimulus paradigm
Signal Follows Stimulus Paradigm
Improved Analysis

• Compare similarity of signal pattern to stimulus paradigm
• Correlation analysis
  – High correlation: strong response
  – Low correlation: weak response
Correlation Analysis

High correlation → functional activation
Student’s t Test

Compare statistical difference of OFF vs. ON
Simple to Complex

• Since Student’s t test works, why not advanced statistics?
• Analysis of variance, principal component analysis …
• Whatever shows “activation”
The SPM Concept in fMRI

- Statistical Parametric Maps
- Calculate statistical parameters for every pixels
- Show the parameter as a map
- Finally got it …
But Then, the Functional Map ...

What ????
Can’t See Anything?

- Activation is surely not global
  - Different functions localized in different brain regions
- Simple function $\rightarrow$ less areas seen
Overlapped on T1WI

• T1 image: gray scale
  – High resolution, good contrast
• Functional activation: color
  – Now you see activation areas
BOLD Signal Overlapped on T1WI

T1WI: gray, functional signal: color
fMRI of Left Auditory Stimulation
Then Do 3D Localization

- Three-plane visualization
- Volume/surface rendering
- Cortical surface & inflation
- All digital image processing!
- Becomes somewhat tedious …
fMRI of Left Auditory Stimulation

gray : anatomy  
color : activation
fMRI of Left Auditory Stimulation

Gray: anatomy, color: activation
Cortical Surface and Inflation

Cortical surface  Cortical inflation
Of Course Then …

• T1WI ideally has coronal, axial, & sagittal orientations
• Or just high-resolution 3D T1WI
  – 3D gradient-echo, large flip angle
• Scan time, SNR …
More Problems Arise

• EPI shows geometric distortions, but T1WI does not
  – Corrections needed
• Image registration
Geometric Distortions in EPI

EPI T2

FSE T2
Even Registered ...

- Results from single subject not necessarily representative
- Sensitivity inadequate (cognitive)
- Multiple subject data combined
  - Inter-subject averaging
- What about head size difference?
Inter-Subject Averaging

- Talairach coordinate common
- Register with cerebral landmarks
- Anterior/posterior commissure
  - Or called the AC-PC line
Talairach Coordinate System

Most common intersubject average method

- Corpus Callosum
- Thalamus

Anterior Commissure
Posterior Commissure
Talairach Coordinate System

3-plane for spatial coordinate
... to Finally Get fMRI Like This

professional

amateur

corrected p-value 0.05

corrected p-value 0.05
Summary: fMRI Principle

- Blood & oxygenation changes with neural stimulation
- Blood + oxygen ~ BOLD contrast
  - Susceptibility of oxy- & deoxy-Hb
  - T2* decay from Bo inhomogeneity
Summary: fMRI Steps

- T2*WI continual acquisition
  - 1.5T often uses EPI
- Off-on-off-on boxcar paradigm
- Compare ON/OFF signals
Summary: fMRI Steps

- Signal & paradigm correlation
- Statistical significance ($p$ or $t$ scores) overlapped on anatomical T1WI
- Talairach coordinate system for inter-subject averaging
Resource Requirements

- Continual acquisition
  - ON $\sim 10 \times 4$
  - OFF $\sim 15 \times 5$
- 8 slices $\rightarrow$ nearly 1000 images!
Resource Requirements

- MRI-compatible stimulation (visual, auditory ...) equipments
- Large console hard disk space
- Off-line calculation hard/software
- Cross-disciplinary human resource
Human Resource (1)

- Clinical diagnosis: radiologist
- Scan operation: technologist
- Analysis: statistician
- Stimulus paradigm: psychologist
Human Resource (2)

- Brain pathology: neurologist
- Registration software: engineer
- MRI sequences: physicist
- Subject: patient + student (??)
Brain Functional MRI

• Looks quite tedious indeed
  – I feel tired …
• But these troubles are not important at all
fMRI Technical Issues

- Low sensitivity (1~6% at 1.5T)
- Low confidence in experiment result
- Difficult interpretation in possible physiological mechanisms
- High clinical false positive/negative
BOLD Signal for Visual Stimulation

Signal increase about 4% only (typical 2%)
Low Sensitivity Problems

• Noise relatively large
  – ON – OFF = mostly noise
  – Functional map unreliable
• Fundamental solution: high SNR
How to Increase SNR?

• Larger voxel size
  – Lower spatial resolution
• Signal averages, long TR ...
  – Lower temporal resolution
Spatial Resolution

- Voxel ideally isotropic
  - 3.0x3.0x3.0 mm$^3$
- Ideal for “geometry & SNR” only
- Not in terms of activation areas!
Can You Sacrifice Spatial Resolution?

If you need detailed localization, no!
Temporal Resolution

- Roughly fine for boxcar paradigm (repetitive experiments anyway)
- What if you want immediate response following stimulation?
  - Hemodynamics? Single trial?
Can You Sacrifice Time Resolution?

If you want immediate response, no!
Functional Signal Time Course (FID)

Time scale of signal change: within 1 sec
How to Increase SNR?

- Shorten TE
  - T2*-weighting lowered (BOLD)
- Surface coil for receiving
  - No global functional info
Not Just SNR ...

- fMRI for brain functional mapping
- Is the geometry accurate?
  - EPI has lots of artifacts!
  - Localization with distorted image?
- Unless use non-EPI (FLASH ...)

Geometric Distortions in EPI

EPI T2

FSE T2
EPI Geometric Distortion

- Off resonance displacement
  - Along EPI phase direction
- Shimming before scanning
- Correction using Bo field map
Field Map to Correct EPI Distortions

Spin-echo

Before correction

But field map sequence not widely available

After correction

Bo map
MRI System Stability

• EPI so sensitive to Bo
  – What if Bo unstable?
• Scan phantom for signal change?
• Scan phantom for phase change?
Motion Effects (1)

• Imprecise localization
  – Resembles cortical activation after subtraction

• Some region not excited previously
  – Like flow-related enhancement
Motion Resembles Cortical Activation

Motion only

With stimulus
Unsaturated Spins “Enhanced”

Unsaturated signal similar to false activation

actual slice with motion

slice for continual scan

problematic

Unsaturated signal similar to false activation
Motion Effects (2)

• Ghosts in non-EPI scans
  – Cardiac pulsation, CSF flow ...
• Susceptibility $\rightarrow$ Bo changes
  – Different EPI geometry in every images
Ghosts from Involuntary Motion

Desired image

Motion ghosts
Motion Leads to Bo Distortion Change

$5^0$ rotation can lead to 50Hz change (2~4 pixels)
Even Worse ...

- Involuntary motion often correlated with stimulus paradigm
  - Moving fingers vs. not moving
  - Visual stimulation vs. lights off
- Motion easily induced by stimuli
Motion May Resemble Stimuli

Stimulus paradigm

Horizontal & vertical head movements

Rotation angle
Some More Problems!

- Choice of statistical analysis
- Subtraction gives noise
- Then use statistical analysis
- Various methods give different analysis results?
Comparison of Statistical Analysis

Which one do you believe then?

- Analysis of variance (ANOVA)
- Student’s t-test
- Subtraction
Which fMRI Is Correct?

Correlation      SPM ’99
I Found Something …

• … that never got reported before!
• New discovery? Artifacts?
• Where is the boundary?
• How to interpret the results?
Inter-Subject Averaging

• For increased sensitivity
• Can you average different brains?
• Individual emphasized in psychology
• Even if yes, is Talairach accurate?
• Cultural difference in head shape
Individual Difference Always Exists

Talairach shows sulci displaced by ~cm
Cultural Difference in Head Shape

Sweden

Japanese
Never Mentioned Before?

• Clinical MRI: visible difference
  – Problems relatively minor
• fMRI relies on 1~6% changes
  – All influences “magnified”
In Fact ...

• Almost all fMRI difficulties arise from sensitivity (1~6% at 1.5T)
  – 1~6%: primary visual cortex
  – Cognitive: Much smaller!
I Found Something New!

- New discovery? Artifacts?
  - Hard to distinguish
- Removing artifacts risks removing new discovery
- Reporting new findings risks reporting garbage
For Research People

- Treat as artifacts!
  - Research without new finding?
- Treat as new findings!
  - How to convince other people?
Great! Cerebrospinal Fluid Thinks!
For Clinicians

• As long as fMRI helps diagnosis, I don’t care about new finding …
• Patient fMRI is another story
Performing a Task

- If patient has difficulty executing the task, interpretation has to be very, very careful
Patient fMRI Difficulty (1)

- Has difficulty in moving fingers
- BOLD signal smaller than normal?
  - Brain function deficits?
  - Less moving $\rightarrow$ less signal?
Patient fMRI Difficulty (1)

- Has difficulty in moving fingers
- BOLD signal larger than normal?
  - Patient tries his best moving?
  - Inhibitory neuron activated?
  - More area recruited for the task?
Performing a Task

- If patient has difficulty executing the task, interpretation has to be very, very careful
- Scanning patients with tasks they can perform!
Patient fMRI Difficulty (2)

- Patient condition surely different
  - Lesion size, location, property ...
- Inter-subject averaging meaningless
- Low-sensitivity experiments (e.g., higher-order cognition) impossible
fMRI Conclusion

- Either nothing particular
- Or you see too many activations
- High uncertainty, unless all technical details well controlled
fMRI So Unsure, But …

- Only noninvasive tool for brain
  - EEG: low spatial resolution
  - PET: radioactive isotope
  - ECoG: open surgery
  - MEG: 2 in Taiwan only …
Information from MRI

- MR not just a morphology tool
  - Function + metabolism
- Diagnosis & therapy monitoring
- fMRI: direct functional mapping
fMRI Reliability

- Scientists worldwide know that it is believable
- Most people know that it is not easy
- Noting the details aggressively is better than ignoring the problems
- To let results reflect the truth
A Lot More Difficulties!

- Aerobic or anaerobic metabolism?
- Post-stimulus undershoot
- Initial dip
- Neural & psychological fatigue...
Problems Everywhere!

- People hating fMRI are completely understandable
- What about you guys who are unlucky to be assigned fMRI topics?
  - Single trial, event-related, …
My Only Suggestion

- Repeat **simplest** fMRI many times
- Assure your result is meaningful
- No wild speculation, don’t neglect artifact details
- They all take time!
fMRI (Left Auditory Stimulation)

2001 Calium (2 years spent on fMRI)
Brain fMRI (Right Finger Tapping)

Gray: anatomy, color: activation
Brain fMRI (Checkerboard Visual)

Gray: anatomy, color: activation
2003 Connie, Cox (2 More Years)

professional

amateur

corrected p-value 0.05
corrected p-value 0.05
2004 William (n = 32) (1 More Year)

amateur female

professional female

amateur male
2006 Jerome, Peixin (2 More Years)
2006 Jerome, Peixin (2 More Years)
Comparison: 2001 Visual fMRI

Gray: anatomy, color: activation
Sensitivity Level (2006 Visual fMRI)
In Taiwan ...

- High-field MRI is a hope ...
- High-field: fundamental increase of SNR & BOLD contrast
- BOLD is not the only possibility
High-Field Pros

- Larger susceptibility effects
- Better fMRI sensitivity
  - 1.5 Tesla: 1% ~ 6%
  - 3.0 Tesla: 4% ~ 15%
  - 7.0 Tesla: ??
High-Field fMRI Signal

1.5T & 4.0T comparison
High-Field Cons

- Larger susceptibility effects
- Strong distortion & signal loss from air cavities
- Shimming gets harder
- EPI hardware requirement increases
Pros and Cons?

- Use the advantages
- Solve the disadvantages
  - Not directly doable by just “saying” or “claiming”
High-Field Is a Hope ...

- 3T/7T Bruker vs. 1.5T/3T
  Siemens/GE is yet another story
- You need to spend efforts!
  much more
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BOLD Effect 與無氧代謝

• 神經活動需要氧氣供應
• 血流過度代償，去氧血紅素變稀？
• 有氧呼吸過程極慢
• 神經活動所需 ATP 由無氧呼吸合成
有沒有辦法驗證呢？

• 無氧代謝的產物： 乳酸

• Lactate 可由 MRS 測得 ...  
  – MRS 的困難度我們下次會學  
  – 瞬間的 Lac 變化 ??????
無氧代謝的證據

Lactate doublet 的出現 (Frahm 1996)
信號的 Undershoot

• 見於刺激剛結束後的休息狀態下
fMRI 信号的 Undershoot

Stimulus ON

意义至今仍有争论
Undershoot 的困擾

- Timing
- 干擾分析
- 來源如何解釋？
  - 與生理是否有關？
fMRI 信號的 Initial Dip

爭論甚多 而且推論還十分嚴謹
Initial Dip

- 每次刺激，信號都先降後升
- 來源如何解釋？
  - Frahm (1998) : artifacts
  - Ugurbil (1999) : BOLD T2*
神經與心理的疲勞...

- 刺激太久了，反應開始降低
  - 心理作用？
  - 生理改變所引發？
  - 實驗設計不良？