“Optimizations” (or at least improvements) in fMRI

Peter A. Bandettini, Ph.D.

Section on Functional Imaging Methods
Laboratory of Brain and Cognition
http://fim.nimh.nih.gov

&

Functional MRI Facility
http://fmrif.nimh.nih.gov

bandettini@nih.gov

In general

Technology
- Coil arrays
- High field strength
- High resolution
- Novel functional contrast

Methodology
- Functional Connectivity
- Multi-modal integration
- Pattern-effect imaging
- Real time feedback
- Task design

Interpretation
- Fluctuations
- Dynamics
- Spatial patterns

Applications
- Healthy Brain Organization
- Clinical Pathology

fMRI before any optimizations (fall of 1991)
TR = 2 sec
TE = 50 ms
One slice
In plane 3.75 x 3.75
Focus of this lecture

- Field Strength
- Echo Time
- Spin-echo vs Gradient Echo
- Velocity Nulling
- RF coil arrays
- High Spatial Resolution
- High Temporal Resolution
- Choice of Flip Angle
- Choice of Slice Thickness
- Paradigm Design
- Ultimate Sensitivity?
- Separating “good” and “bad” signal in Resting State fMRI.
- Understanding dynamic nonlinearities
- Understanding and Using fMRI Patterns
Focus of this lecture

Technology
- High field strength
- Coil arrays
- High resolution
- Novel functional contrast

Methodology
- Paradigm Designs
- Processing Methods

Interpretation

Applications

Characteristics of the BOLD signal: T2* effect.

Contrast depends on:
activation-induced changes in T2* and resting T2*

Contrast at 1.5T (dR2* = -0.8 1/s)

Contrast at 3T (dR2* = -1.6 1/s)

Functional Contrast at Optimal TE
Spin-Echo vs. Gradient-Echo

Transverse Relaxation

\[ T2 \]

\[ T2^* \]

90° 180° 180°

\[ \approx 30 \text{ms} \]

\[ \approx 100 \text{ms} \]

Exchange Regimes

D: Fast

R: Intermediate

\( R2 \times R2^* \times \gamma (\times \chi) \text{ Bo} \)

\[ \ll 1 \]

\[ \gg 1 \]

compartment radius

- \(< 3 \mu m\>
- \(3 \text{ to } 15 \mu m\>
- \(> 15 \mu m\>

Spin echo vs. Gradient echo
Bolus Injection of Gadolinium

Spin-Echo, TE = 105 ms
TR = \(\infty\)

Gradient-Echo, TE = 50 ms

Gradient-Echo functional, TE = 50 ms

Spin-Echo functional, TE = 105 ms

Field strength dependence of intravascular signal

Spin-echo, \(\%HbO_2 = 60\)

Gradient-echo, \(\%HbO_2 = 60\)

Source of most contrast in venograms.
Susceptibility Weighted Imaging (SWI)

E. Mark Haacke,1,4* Yingbiao Xu,1,2 Yu-Chung N. Cheng,1 and Jürgen R. Reichenbach5

**Pros and Cons of Spin-Echo**

- Increased specificity (esp at high fields where IV signal is low)
- Less sensitive to rapidly flowing blood
- Less signal dropout.
- Less slices per TR
- Lower fCNR by x 2 to 4.
- Acquisition window still T2*
- Very large IV signal still present at most field strengths.

I would only use at 7T if also imaging at high resolution and interested in something like columns or layers.
...so let’s remove the intravascular signal...

Velocity Nulled (or diffusion weighted) fMRI.

![Summary of Diffusion-Weighted fMRI Data](image)

**Hemodynamic Specificity**

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>Perfusion</th>
<th>BOLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Arterial inflow (BOLD TR < 500 ms)
- Venous inflow (Perf. No VN)

**High Field Tradeoffs**

- Increased SNR
- Increased functional contrast
- Ability to reduce voxel volume
- Reduced intravascular signal
- At standard resolution, enhanced sensitivity to fluctuations
- Increased SAR
- Decreased B0 and B1 homogeneity
- (still somewhat prohibitive)
- Increased costs and effort
- At standard resolution, enhanced sensitivity to fluctuations

**Coil Arrays**

![Graph showing progression of human MRI field strength over years](image)
Sensitivity vs. Time needed to scan

Temporal Signal to Noise Ratio (TSNR) vs. Signal to Noise Ratio (SNR)

K. Murphy, J. Bodurka, P. A. Bandettini, How long to scan?

Going to High Spatial Resolution

MRI vs. fMRI

MRI

fMRI

one image

many images
(e.g., every 2 sec for 5 mins)

T2* decay

EPI Readout Window
= 20 to 40 ms

Multi-shot Imaging

T2* decay

EPI Window 1

T2* decay

EPI Window 2

Single Shot Echo Planar Imaging (EPI)
**Multi Shot EPI**

<table>
<thead>
<tr>
<th>Excitations</th>
<th>Matrix Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64 x 64</td>
</tr>
<tr>
<td>2</td>
<td>128 x 128</td>
</tr>
<tr>
<td>4</td>
<td>256 x 128</td>
</tr>
<tr>
<td>8</td>
<td>256 x 256</td>
</tr>
</tbody>
</table>

30 ms

10 sec to 1 min

**Partial k-space imaging**

T2* decay

**Single - Shot EPI at 3T:**
Half NEX, 256 x 256, 16 cm FOV


SSENSE Imaging

≈ 5 to 30 ms

Pruessmann, et al. (and Sodickson et al)

3T single-shot SENSE EPI using 16 channels: 1.25x1.25x2mm

Orientation Columns in Human V1 as Revealed by fMRI at 7T

Yacoub et al. PNAS 2008

Scalebar = 0.5 mm

Going to High Temporal Resolution


Hemi-field with 500 msec asynchrony

Average of 6 runs  Standard Deviations Shown
Hemodynamic Response Modulation

Even if no hemodynamic variability exists...

1 run:
- 1% Noise
- 4% BOLD
- 256 time pts /run
- 1 second TR

Smallest latency Variation Detectable (ms) (p < 0.001)

Bellgowan, et al (2003), PNAS 100, 15820-15823
Choosing a Flip Angle

Physiological noise effects on the flip angle selection in BOLD fMRI

J. Gonzalez-Castillo 1, 2, V. Roopchansingh 3, P.A. Bandettini 3, 4, J. Bodurka 4

1 Section on Functional Imaging Methods, Laboratory of Brain and Cognition, National Institute of Mental Health, National Institutes of Health, 10 Center Dr, Bethesda, MD 20892, USA
2 Section on Functional Imaging Methods, National Institute of Mental Health, National Institutes of Health, 10 Center Dr, Bethesda, MD 20892, USA
3 Functional MRI Facility, National Institute of Mental Health, National Institutes of Health, 10 Center Dr, Bethesda, MD 20892, USA
4 Section on Functional Imaging Methods, National Institute of Mental Health, National Institutes of Health, 10 Center Dr, Bethesda, MD 20892, USA

Keywords: Blood Oxygenation Level Dependent, Blood Oxygenation Level Dependent (BOLD) phenomenon, functional magnetic resonance imaging (fMRI), Temporal signal-to-noise ratio (TSNR)

How do we typically select flip angle?

Ernst Angle...

$$\Theta = \cos^{-1} \left( e^{-\frac{TR}{T1}} \right)$$
Fig. 2. (A) TSNR vs. Flip angle for $T_1 = T_{1,GM} = 1.34$ s, $SNR_o = SNR_{o,GM} = 652$ and different values of $\lambda$ ranging from 0 to 0.05. For each curve, a square marks the angle below the Ernst angle for which TSNR has decreased to 50\% from its maximum value ($\theta_{50\%}$). (B) Evolution of $\theta_{50\%}$ with $\lambda$. The higher the amount of physiological noise present, the flatter the TSNR curve and consequently the lower the angle for which TSNR reaches 50\% of its maximum value.

Fig. 3. Simulations of the suggested fMRI flip angle ($\theta_S$). The black dotted line shows a linear behavior for the Silicone Oil Phantom. The red and blue continuous lines show behavior for grey and white matter respectively. Ernst angle for these two tissue compartments is marked with filled dots, while other exemplary angles are masked as transparent dots. The suggested flip angle for both tissue compartments are also marked in each curve as filled squares with black outline.

Discussion

Physiological noise is a major source of undesired variance in BOLD fMRI time courses in a vast majority of experimental situations (Kruger and Glover, 2001; Kruger et al., 2001; Triantafyllou et al., 2005; Bodurka et al., 2007). We have investigated, both theoretically and experimentally, the effect that MR-signal strength-dependent physiological noise exerts on BOLD fMRI temporal signal to noise ratio (TSNR) as a function of the flip angle in situations where physiological noise constitutes a dominant source of time course variance. We have scanned 8 subjects at a commonly used BOLD fMRI voxel volume of $3.75 \times 3.75 \times 4$ mm$^3$, where physiological noise is the dominant source of time course variance (Bodurka et al., 2007); and physiological noise introduces a non-linear dependence in TSNR, which translates into a flattening of the TSNR vs. flip angle curve. We have also demonstrated that this TSNR behavior can be exploited to perform BOLD-fMRI at flip angles other than the Ernst angle with no detrimental effects in our ability to detect statistically significant neuronal activations.

Fig. 7. Averaged hemodynamic response across all eight subjects for all flip angles in three different anatomically defined ROIs: right visual cortex, left visual cortex and left primary motor cortex. The top panel shows 3D renderings of the ROIs. The middle panel shows estimations of the hemodynamic response without intensity normalization (i.e., only constant, linear and quadratic trends were removed). The bottom panel shows estimations of hemodynamic response in terms of signal percent change. These were obtained by means of intensity normalization prior to the detrending step.
Effect of Slice Thickness on TSNR
Neuronal Activation Input Strategies

1. Block Design
2. Frequency Encoding
3. Phase Encoding
4. Event-Related
5. Orthogonal Block Design

Neuronal Activation Input Strategies

1. Block Design
2. Frequency Encoding
3. Phase Encoding
4. Event-Related
5. Orthogonal Block Design
Neuronal Activation Input Strategies

1. Block Design
2. Frequency Encoding
3. Phase Encoding
4. Event-Related
5. Orthogonal Block Design
Neuronal Activation Input Strategies

1. Block Design
2. Frequency Encoding
3. Phase Encoding
4. Event-Related
5. Orthogonal Block Design


Contrast to Noise Images

(1SD)

20, 20 12, 2 10, 2 8, 2 6, 2 4, 2 2, 2

S1

S2

Detectability vs. Average ISI

Estimation accuracy vs. average ISI

fMRI during tasks that involve brief motion


Overt Responses - Simulations

SD = stimulus duration

More Motion Artifacts

Better BOLD Detection

Neuronal Activation Input Strategies

1. Block Design
2. Frequency Encoding
3. Phase Encoding
4. Event-Related
5. Orthogonal Block Design

What is the Ultimate Sensitivity of fMRI?
Is the whole brain activated by even simple tasks?

- 9 hours of averaging
- Unconstrained response model
- Clustering (K-means or Hierarchical)

J. Gonzalez-Castillo, Z. Saad, D. A. Handwerker, P. A. Bandettini,
Whole-brain, time-locked activation with simple tasks revealed using
massive averaging and model-free analysis. Proceedings of the
**Predictive Response Model effect on fMRI Results (III)**

- **BLOCK DESIGN & HEMIFIELD VISUAL STIMULATION**
- **SUSTAINED RESPONSE MODEL**
- **ONSET/OFFSET RESPONSE MODEL**

**DIFFERENT RESPONSE SHAPES ARE PRESENT ACROSS DIFFERENT REGIONS OF THE BRAIN FOR A SINGLE STIMULUS TYPE**

---

**Experimental Methods (I)**

- 3 Healthy Volunteers: 1M/2F; Age = 27 ± 2.5
- 3T GE Signa HDx
- Anatomical Scan: MPRAGE | .9x9x1.2 mm³ | 192 Slices
- Functional Scans: GRE-EPI
  - TR/TE = 2s/30ms
  - FOV = 240mm
  - In-Plane Res = 64x64
  - Slice Thickness = 3.8 mm
  - #Slices = 32 Oblique
  - Flip Angle = 75°

---

**Experimental Methods (II)**

- **VISIT**
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7
  - 8
  - 9
  - 10

- **ANATOMICAL**
  - (1x)
  - (1x)
  - (1x)
  - (1x)
  - (1x)
  - (1x)
  - (1x)
  - (1x)
  - (1x)

- **FUNCTIONAL SCANS**
  - (10x)
  - (10x)
  - (10x)
  - (10x)
  - (10x)
  - (10x)
  - (10x)
  - (10x)
  - (10x)

- **EXPERIMENTAL METHODS (II)**
  - X 100 (QA Axial EPs)
  - 100 FUNCTIONAL RUNS/SUBJECT
  - 500 TRIALS/SUBJECT
  - 9 HOURS OF DATA/SUBJECT

---

**IS THE SPARSENESS OF FMRI ACTIVATIONS REAL?**

**OR**

**IS IT THE RESULT OF INSUFFICIENT TSNR + OVERLY STRICT RESPONSE MODELS?**

---

### Data Analysis

#### Data Pre-processing
- Remove Physiological Noise
- Slice Timing Correction
- Head Motion Correction
- Inter-run Co-registration
- Discard Initial 5 Volumes
- Remove Motion & 1st Der.
- Intensity Normalization

#### Data Averaging
- \[ N_{\text{avg}} = 1 \leftrightarrow N_{\text{avg}} = 100 \]
- 10 Random Permutations per \[ N_{\text{avg}} \] Level

Example \[ N_{\text{avg}} = 5 \]

#### Statistical Analysis
- Sustained Response Only (SUS)
- Onset + Sustained + Offset Response (SUS)
- Unconstrained Model (UNC)

#### Clustering Analysis

### Results: TSNR vs. # Averaged Scans

- TSNR_{WM, task} = 339
- TSNR_{WM, 100} = 2218

- TSNR_{WM, ttask} increased by approx. a factor of 6 from \[ N_{\text{avg}} = 1 \] to \[ N_{\text{avg}} = 100 \]

### Results: Time-series in Primary Visual Cortex

#### Individual Runs

#### Averaging

Gonzalez-Castillo J, Saad ZS, Handwerker DA, Inati SJ, Brenowitz N, Bandettini PA, PNAS (in press)
Results: Time-series in Anterior Insular Cortex

INDIVIDUAL RUNS

AVERAGING

Gonzalez-Castillo J, Saad ZS, Handwerker DA, Inati SJ, Brenowitz N, Bandettini PA, PNAS (in press)

Results: Time-series in Primary Auditory Cortex

INDIVIDUAL RUNS

AVERAGING

Gonzalez-Castillo J, Saad ZS, Handwerker DA, Inati SJ, Brenowitz N, Bandettini PA, PNAS (in press)

Results: Time-series in Parieto-Occipital Junction

INDIVIDUAL RUNS

AVERAGING

Gonzalez-Castillo J, Saad ZS, Handwerker DA, Inati SJ, Brenowitz N, Bandettini PA, PNAS (in press)

Results: BOLD responses are present all over the brain

Responses time-locked with the task were observed in over 90% of the voxels for all three subjects

Gonzalez-Castillo J, Saad ZS, Handwerker DA, Inati SJ, Brenowitz N, Bandettini PA, PNAS (in press)
Area of Activation vs. #Scans

Subject 1

P_{Bonf}<0.05

The sustained model: Sustained Model

ARE RESPONSE SHAPES RANDOMLY DISTRIBUTED ACROSS THE BRAIN?

OR

DO THEY CLUSTER IN A FUNCTIONALLY/ANTOMICALLY MEANINGFUL MANNER?

INPUT

- Time series of length 30 for each of N voxels (e.g., all GM voxels)
- Pearson Correlation Distance: $D = 1 - r$
  - $D = 0$ ($r = 1$) if time series from 2 voxels are perfectly correlated
  - $D = 2$ ($r = -1$) if time series from 2 voxels are perfectly anti-correlated
- $K =$ Set a priori by the experimenter

K=2

OUTPUT

The output consists of $K$ clusters, each defined by:

- Set of Voxels (not necessarily contiguous)
- Centroid Time Series = average of time series across all voxels in the cluster

NO SPATIAL INFORMATION ENTERS THE CLUSTERING ALGORITHM

Clustering Analysis: K-means applied to fMRI data

Gonzalez-Castillo J, Saad ZS, Handwerker DA, Inati SJ, Brenowitz N, Bandettini PA, PNAS (in press)
Clustering Analysis: Whole Brain GM Results

Subject 03 – K=20

- Not randomly distributed in space
- Symmetrical across hemispheres
- Functionally & anatomically meaningful
- Reproducible parcellations across subjects
Clustering Analysis: Whole Brain GM Results

- Not randomly distributed in space
- Symmetrical across hemispheres
- Functionally & anatomically meaningful
- Reproducible parcellations across subjects

Clusters as a function of $K$

Clusters as a function of clustering algorithm (I)
Clustering Analysis: Subcortical GM Results

FREESURFER ANATOMICAL SEGMENTATION

- Thalamus
- Putamen
- Caudate
- Pallidus
- N. Accumbens

K-MEANS CLUSTERING (K=5)

- Gonzalez-Castillo J, Saad ZS, Handwerker DA, Inati SJ, Brenowitz N, Bandettini PA, PNAS (in press)

Future Directions (I)

(1) Evaluate the Stability of the Clusters

- Gonzalez-Castillo J, Saad ZS, Handwerker DA, Inati SJ, Brenowitz N, Bandettini PA, PNAS (in press)

Future Directions (II)

(2) Evaluate how these clusters relate to Resting State Networks

- Gonzalez-Castillo J, Saad ZS, Handwerker DA, Inati SJ, Brenowitz N, Bandettini PA, PNAS (in press)
Separating “good” and “bad” signal in Resting State fMRI.

Resting state clustering in multiple and single subjects.
- Multi-echo denoising
- Hierarchical clustering


Resting State Correlations

Activation:
correlation with reference function

Rest:
seed voxel in motor cortex

Endogenous Oscillations
("resting state" OR fluctuations OR "spontaneous oscillations" OR "endogenous oscillations") AND fMRI

B. Biswal et al., MRM, 34:537 (1995)
Sources of time series fluctuations

- Blood, brain and CSF pulsation
- Vasomotion
- Breathing cycle ($B_0$ shifts with lung expansion)
- Bulk motion
- Scanner instabilities
- Changes in blood $CO_2$ (changes in breathing)

**Spontaneous neuronal activity**

Noise and Fluctuations

Fig. 4. Pie charts showing the fMRI data variance explained (VE, %, upper bold) by nonthermal noise sources 1-4, thermal noise and spontaneous activity. We also show fMRI signal change (SC, %, lower italic) attributed to the same noise sources. Average (S.E.) values across subjects are shown. The contribution of thermal noise at the ROI level was negligible.

Sources of time series fluctuations:

- Blood, brain and CSF pulsation
- Vasomotion
- Breathing cycle ($B_0$ shifts with lung expansion)
- Bulk motion
- Scanner instabilities
- Changes in blood $CO_2$ (changes in breathing)
- Spontaneous neuronal activity

Spontaneous changes in respiration and end-tidal $CO_2$

Respiration

Respiration Volume / Time (RVT)

$$RVT = \frac{\text{max} - \text{min}}{T}$$

RVT precedes end tidal $CO_2$ by 5 sec.

Respiration induced signal changes

Breath-holding

Rest

RVT Correlation Maps & Functional Connectivity Maps

Group (n=10)

Resting state correlation with signal from posterior cingulate

Resting state correlation with RVT signal

Effect of Respiration Rate Consistency on Resting Correlation Maps

Group (n=10)

Constant Respiration Rate

Spontaneously Varying Respiration Rate


Respiration Changes vs. BOLD

How are the BOLD changes related to respiration variations?

fMRI response to a single Deep Breath

RRF(t) = 0.6 t^{2.1} e^{1.6t} - 0.0023 t^{3.54} e^{4.25}

Respiration response function predicts BOLD signal associated with breathing changes better than activation response function.

Breath-holding

Rate Changes

Depth Changes


**BOLD magnitude calibration**

**Before Calibration**

**After Calibration**

**Respiration-induced BOLD**

- BOLD T$_2^*$ signal has echo-time (TE) dependence, such that the percent signal change of a BOLD signal time course scales linearly with TE

\[
\Delta \frac{S_i}{S_i} = -\Delta R_2^* T E_i
\]

**TE-Dependence model**

- Acquiring multi-echo (ME) fMRI enables analysis of TE-dependence for any signal, task-correlated or spontaneous

- TE-dependence can be quantified, per-voxel, as an F-statistic for the TE-dependence model

---


TE-Dependence

Image contrast changes with TE

ME timecourses and TE-dependent scaling

ME Signal Timecourses

1. ME activation during block-design task

Fits in Eq. 2

2. Precocious activity during resting state

\( F(\text{beta}) \)

Regress out all low components to de-noise
Effect of de-noising on functional connectivity measures

<table>
<thead>
<tr>
<th>T maps</th>
<th>R. Insula</th>
<th>L. Hippocampus</th>
<th>Brainstem</th>
</tr>
</thead>
<tbody>
<tr>
<td>RETROICCR + RVT + Motion + Bandpass</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td>Drifts + Low-k / High-λ MEICs</td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Denoising

Test-retest of **individual** clustering at 350 clusters

Rest 1

Rest 2 (color matched to Rest 1)

**Kundu, Guillod, Inati, Luh, Bandettini**

Detailed whole brain functional organization from resting state fluctuations?

A. Dendrogram of Hierarchical Parcellation

B. Parcellation at Increasing Cluster Levels

**Kundu, Guillod, Inati, Luh, Bandettini**
Two other issues with imaging resting state fluctuations:

1. Global signal correction or not?

2. Short range correlations may be scanner-related.

Test-retest of group clustering at 350 clusters

Rest 1

Rest 2
(color matched to Rest 1)

The issue of global signal regression

The issue of correlation across voxels due to scanner instabilities


Focus of this lecture

Technology
- High field strength
- Coil arrays
- High resolution
- Novel functional contrast

Methodology
- Paradigm Designs
- Processing Methods

Healthy Brain Organization

Interpretation

Applications

Interpretation

Neuronal Activation

Measured Signal

Hemodynamics

Noise

Understanding Dynamic Nonlinearities In fMRI
Nonlinearity of BOLD response

measured  ideal (linear)

visual stimulation

250 ms  500 ms  1000 ms  2000 ms

motor task

500 ms  1000 ms  2000 ms  4000 ms

Bandettini and Ungerleider, Nature Neuroscience, 4, 864-866

Understanding and Using Activation Patterns In fMRI

Ventral temporal category representations

Object categories are associated with distributed representations in ventral temporal cortex

Haxby et al. Nature 2001

Visual Stimuli

Dissimilarity Matrix Creation

compute dissimilarity (1-correlation across space)

response patterns

ROI in Brain


Human IT

(1000 visually most responsive voxels)

Human Early Visual Cortex

(1057 visually most responsive voxels)
Human
- fMRI in four subjects (repeated sessions, >12 runs per subject)
- "quick" event-related design (stimulus duration: 300ms, stimulus onset asynchrony: 4s)
- fixation task (with discrimination of fixation-point color changes)
- occipitotemporal measurement slab (5-cm thick)
- small voxels (1.95x1.95x2mm³)
- 3T magnet, 16-channel coil (SENSE, acc. fac. 2)

Monkey (Kiani et al. 2007)
- single-cell recordings in two monkeys
- rapid serial presentation (stimulus duration: 105ms)
- fixation task
- electrodes in anterior IT (left in monkey 1, right in monkey 2)
- 674 cells total
- windowed spike count (140-ms window starting 71ms after stimulus onset)

Kamitani & Tong (2005)
Lower spatial frequency clumping
Focus of this lecture

- **Technology**
  - High field strength
  - Coil arrays
  - High resolution
  - Novel functional contrast

- **Methodology**
  - Paradigm Designs
  - Processing Methods

- **Interpretation**
  - Fluctuations / Correlations
  - Dynamics

- **Applications**
  - Healthy Brain Organization

- **Technology**
  - Field Strength
  - Echo Time
  - Spin-echo vs Gradient Echo
  - Velocity Nulling
  - RF coil arrays
  - High Spatial Resolution
  - High Temporal Resolution
  - Choice of Flip Angle
  - Choice of Slice Thickness
  - Paradigm Design
  - Ultimate Sensitivity?
  - Separating “good” and “bad” signal in Resting State fMRI.
  - Understanding dynamic nonlinearities
  - Understanding and Using fMRI Patterns