Multi-echo EPI for task-based and resting-state fMRI

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Section on Functional Imaging Methods, NIMH, NIH

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Agenda

- **WHAT IS MULTI-ECHO (ME) FMRI**

- **WHAT CAN YOU DO WITH ME TIMESERIES**
  - Compute static $S_0$ and $T_2^*$ Maps
  - Compute voxel-wise time-series of $S_0$ (Non-BOLD) and $T_2^*$ (BOLD)
  - Combine echoes to improve SNR/spatially equalize functional contrast
  - Echo Time Dependence Analysis

- **ME-ICA Denoising**
  - ME-ICA Pipeline
  - ME-ICA Outputs
  - ME-ICA Web Reporting Tool

- **ME-ICA Applications**
Multi-echo fMRI: A review of applications in fMRI denoising and analysis of BOLD signals

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\textsuperscript{b} Behavioral and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK
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\textsuperscript{e} Section on Functional Imaging Methods, National Institute of Mental Health, Bethesda, MD, USA
Single-Echo fMRI (a.k.a. Your regular fMRI)

\[ S(x_1, t) \]

One Time series per voxel (\(x\))
Now you have $N_e$ (e.g., 3) Time series per voxel, one per echo time ($T_{E_n}$):

- No SAR cost, as there are not additional excitation pulses.
- Slight lost in temporal resolution to fit the third echo.
- Slight lost in spatial resolution to make sure you have signal in last echo.
Signal Model

Signal in voxel \( x \), at time point \( t \), measured at echo time \( TE \)

\[
S(x, t, TE) = S_o(x, t) e^{-R_2^*(x, t) \cdot TE} + \text{Noise}
\]

Captures local fluctuations due to T1 changes (e.g., inflow) and HW instabilities

\[
S_o(x, t) = \bar{S}_o(x) + \Delta S_o(x, t)
\]

\[
\Delta S_o(x, t) \ll \bar{S}_o(x), \forall x
\]

Captures local fluctuations in field inhomogeneity (including BOLD)

\[
R_2^*(x, t) = \bar{R}_2^*(x) + \Delta R_2^*(x, t)
\]

\[
\Delta R_2^*(x, t) \ll \bar{R}_2^*(x), \forall x
\]
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- ME-ICA Applications
By definition, the average across time of $\Delta S_o(x,t)$ and $\Delta R_2^*(x,t)$ are zero, and then it follows that the average signal across time for a given voxel $(x)$ and echo time (TE) is:

$$
\overline{S(x,TE)} = S_o(x) \cdot e^{-R_2^*(x)TE}
$$

$$
\log(\overline{S(x,TE)}) = \log(S_o(x) \cdot e^{-R_2^*(x)TE})
$$

$$
\log(S(x,TE)) = -R_2^*(x) \cdot TE + \log(S_o(x))
$$

$$
y(x,TE) = a(x) * TE + b(x)
$$

Linear system of equations for 3 echoes

$$
\begin{align*}
\log(S(x,TE_1)) &= -R_2^*(x) \cdot TE_1 + \log(S_o(x)) \\
\log(S(x,TE_2)) &= -R_2^*(x) \cdot TE_2 + \log(S_o(x)) \\
\log(S(x,TE_3)) &= -R_2^*(x) \cdot TE_3 + \log(S_o(x))
\end{align*}
$$
How to Compute Spatial Maps of $S_0$ and $T_2^*$
**WHAT IS MULTI-ECHO (ME) FMRI**

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**ME-ICA Applications**
How to Compute Time series of $\Delta S_o$ and $\Delta R_2^*$ fluctuations

\[ S(x,t,TE) = S_o(x,t)e^{-R_2^*(x)TE} \]

\[ S_o(x,t) = S_o(x) + \Delta S_o(x,t) \]

\[ R_2^*(x,t) = R_2^*(x) + \Delta R_2^*(x,t) \]

\[ S(x,TE) = S(x) \cdot e^{-R_2^*(x)TE} \]

\[ S(x,t,TE) = \left[ S_o(x) + \Delta S_o(x,t) \right] \cdot e^{-R_2^*(x) + \Delta R_2^*(x,t)TE} \]  \hspace{1cm} (1)

\[ S(x,t,TE) = S(x,TE) \left[ 1 + \frac{\Delta S_o(x,t)}{S_o(x)} \right] \cdot e^{-\Delta R_2^*(x,t)TE} \]  \hspace{1cm} (2)

Using a first order Taylor expansion for the exponential term: $e^{-\Delta R_2^*(x,t)TE} \approx \left( 1 - \Delta R_2^*(x,t) \cdot TE \right)$

\[ S(x,t,TE) \approx S(x,TE) \left[ 1 - \Delta R_2^*(x,t) \cdot TE + \frac{\Delta S_o(x,t)}{S_o(x)} \right] - \frac{\Delta R_2^*(x,t) \cdot TE \cdot \Delta S_o(x,t)}{S_o(x)} \]  \hspace{1cm} (3)

\[ S(x,t,TE) \approx S(x,TE) \left[ 1 - \Delta R_2^*(x,t) \cdot TE + \frac{\Delta S_o(x,t)}{S_o(x)} \right] \]  \hspace{1cm} (4)

\[ \Delta \rho(x,t) = \frac{\Delta S_o(x,t)}{S_o(x)} \] \hspace{1cm} (5)

\[ \Delta \kappa(x,t) = \Delta R_2^*(x,t) \cdot \frac{TE}{TE} \]

\[ \rightarrow S(x,t,TE) \approx S(x,TE) \cdot \left[ 1 + \Delta \rho(x,t) - \frac{TE}{TE} \Delta \kappa(x,t) \right] \]  \hspace{1cm} (5)

\[ S(x,t,TE) - S(x,TE) \approx S(x,TE) \left[ \Delta \rho(x,t) - \frac{TE}{TE} \Delta \kappa(x,t) \right] \]  \hspace{1cm} (6)
How to Compute Time series of $\Delta S_o$ and $\Delta R_2^*$ fluctuations
How to Compute Time series of $\Delta S_o$ and $\Delta R_2^*$ fluctuations
WHAT IS MULTI-ECHO (ME) FMRI

WHAT CAN YOU DO WITH ME TIMESERIES

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ME-ICA Denoising

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• ME-ICA Web Reporting Tool

ME-ICA Applications
Combination of Multi-Echo Time series

We have $N_e$ pseudo-concurrent measurements → why not simply combine them to reduce uncorrelated white noise present in each individual measurement?

1. **Simple Summation**

\[
\hat{S}(x,t) = \sum_{n=1}^{N} S(x,t,TE_n)
\]

- Noisy data at longer echoes reduce the overall gain in sensitivity.

2. **Weighted Summation**

\[
\hat{S}(x,t) = \sum_{n=1}^{N} S(x,t,TE_n) \cdot w_v(TE_n)
\]

\[
w_v(TE_n) = \frac{TE_n e^{-\frac{TE_n}{T_2^*}}}{\sum_n TE_n \cdot e^{-\frac{TE_n}{T_2^*}}}
\]

- Helps to spatially maximize CNR and also to recover some signal level in regions affected by drop-out.

*Posse et al., MRM 1999*
Combination of Multi-Echo Time series

We have \( N_e \) pseudo-concurrent measurements, why not simply combine them to reduce uncorrelated white noise present in each individual measurement.

1. **Simple Summation**

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- Noisy data at longer echoes reduce the overall gain in sensitivity.

2. **Weighted Summation**

\[
\hat{S}(x,t) = \sum_{n=1}^{N} S(x,t,TE_n) \cdot w_v(TE_n)
\]

- Optimizes CNR compared to Single Echo.
- Helps to spatially maximize CNR, by helping recover some signal in regions with large drop-outs at regular single echo acquisitions.

Posse et al., MRM 1999
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❖ ME-ICA Applications
**Echo Time (TE) Dependence Analysis**

\[ S(x,t,TE) = S_o(x,t)e^{-R^*_2(x,t)TE} \]

Let’s assume that a given voxel (x) and time (t) …. So(x,t)=5000 and T2*(x,t)=30ms
Let’s assume now, that a local change in oxygenation happens ($T_2^*$ effect)
\[ S(x, t, TE) = S_0(x, t) e^{-R_2^*(x, t)TE} \]

We could then use the difference between two curves to examine which is the optimal TE to maximize BOLD contrast.
Most importantly for our discussion, for $T_2^*$ signal changes, there is a linear relationship between echo time and measured signal (in terms of signal percent change).
Echo Time (TE) Dependence Analysis

\[ S(x, t, TE) = S_o(x, t) e^{-R_2^*(x, t)TE} \]

Let’s now examine what happens when there is a change in \( S_o \) (T1 effect)

Kundu et al., NeuroImage 2012
Echo Time (TE) Dependence Analysis

\[ S(x, t, TE) = S_o(x, t) e^{-R^*_2(x, t) TE} \]

This time the difference between both curves looks very different

Kundu et al., NeuroImage 2012
In term of signal percent change, changes in $S_0$ have a flat dependence with echo time.

\[ S(x, t, TE) = S_o(x, t) e^{-R_2^*(x, t) TE} \]

Kundu et al., NeuroImage 2012
Echo Time (TE) Dependence Analysis

\[ S(x,t,TE) = S_o(x,t)e^{-R^*_2(x,t)TE} \]

In terms of signal percent change, changes in So have a flat dependence with echo time.

Kundu et al., NeuroImage 2012
**Echo Time (TE) Dependence Analysis**

**MULTI-ECHO DATASET**

<table>
<thead>
<tr>
<th>TE$_1$</th>
<th>TE$_2$</th>
<th>TE$_3$</th>
</tr>
</thead>
</table>

**TE-DEPENDENCE MODEL**

- $\Delta R_2^*$ scale linearly with TE
- $\Delta S_0$ has no TE dependence

**TIMESERIES OF INTEREST**

Task Paradigm

[1] Voxel-wise Fit against all TE's

[2] Voxel-wise Goodness of Fit to $R^*_2$ Model

[3] Voxel-wise Goodness of Fit to $S_0$ Model


\[ \kappa = \frac{\sum_{\text{All Voxels}} z_v^2 F_{v,R_2^*}}{\sum_{\text{All Voxels}} z_v^2} = 98.41 \]

\[ \rho = \frac{\sum_{\text{All Voxels}} z_v^2 F_{v,S_0}}{\sum_{\text{All Voxels}} z_v^2} = 26.02 \]

Kundu et al., NeuroImage 2012
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- **ME-ICA Applications**
ME-ICA Denoising: Introduction

**FSL Documentation:** [http://fsl.fmrib.ox.ac.uk/fslcourse/lectures/melodic.pdf](http://fsl.fmrib.ox.ac.uk/fslcourse/lectures/melodic.pdf)

**TE-DEPENDENCE MODEL**

- \( \Delta R_2^* \) scale linearly with TE
- \( \Delta S_0 \) has no TE dependence

**MULTI-ECHO DATASET**

- TE1
- TE2
- TE3

**TIMESERIES OF INTEREST**

ICA Representative Timeseries

---

Data is represented as a 2D matrix and decomposed into factor matrices (or modes)
ΔR₂* scale linearly with TE

ΔS₀ has no TE dependence

ICA Representative Timeseries

Kappa (κ) = 210
Rho (ρ) = 10

Kundu et al., NeuroImage 2012
ΔR$_2^*$ scale linearly with TE

ΔS$_o$ has no TE dependence

**MULTI-ECHO DATASET**

| TE$_1$ | TE$_2$ | TE$_3$ |

**TE-DEPENDENCE MODEL**

ICA Representative Timeseries

Kappa (κ) = 32

Rho (ρ) = 81
Axial views of R de-noising with standard noise regressors and band pass reveals greater functional connectivity to gray matter clusters than networks. Shows greater correlation to premotor and sensory regions, and greater correlation to premotor and cingulate regions, hippocampus long distance correlation. With ME-ICA de-noising, the insula shows patterns proximal to the seed, but ME-ICA de-noising exposes greater.

Application to group level correlation maps

Group-level connectivity was evaluated using one-sample T-tests for insula and hippocampus connectivity are shown in. For a representative subject, each component is clearly functional. For a representative subject. Each component is clearly functional. The $\Delta R^2$ maps of top $\kappa$ ranked components for a representative subject.

$\kappa$ vs. ICA rank

$\kappa$ spectrum

$\kappa$ spectra across subjects

$\Delta R^2$ maps of top $\kappa$ ranked components for a representative subject.
ME-ICA Denoising: Introduction

a \( \rho \) vs. ICA rank

b \( \rho \)-spectrum

c \( \rho \)-spectrum across subjects

d \( \Delta S_0 \) maps of top \( \rho \)-ranked components for a representative subject

Kundu et al., NeuroImage 2012
ME-ICA Denoising: Introduction

Kundu et al., NeuroImage 2017
ME-ICA Denoising: Pipeline

PRE-PROCESSING
- SLICE TIME CORRECTION
- HEAD MOTION CORRECTION
- REGISTRATION TO ANAT

OPTIMAL COMBINATION

ME-BASED PRINCIPAL COMPONENT ANALYSIS (ME-PCA)
- PCA DECOMPOSITION
- COMP. CHARACTERIZATION
- COMP. SELECTION
- GENERATE DIM. RED. OCTS

ME-BASED INDEPENDENT COMPONENT ANALYSIS (ME-ICA)
- ICA DECOMPOSITION
- COMP. CHARACTERIZATION
- COMP. SELECTION
- GENERATE DENOISED TS

REGULAR ANALYSIS (TASK OR REST)

Kundu et al., NeuroImage 2012
ME-ICA Denoising: Pipeline

- Uses PCA Decomposition (orthogonality).
- Yet, estimation of model order (Ncomp) is not based on variance, but on $\kappa$ and $\rho$ thresholds.
  - $\kappa_{\text{thr}} = f(\kappa_{\text{elbow}}, \kappa_{\text{daw}})$; Default $\kappa_{\text{daw}} = 10$
  - $\rho_{\text{thr}} = f(\rho_{\text{elbow}}, \rho_{\text{daw}})$; Default $\rho_{\text{daw}} = 1$
- SELECTION RULE: $\kappa > \kappa_{\text{thr}}$ are kept
- SELECTION RULE: $\rho > \rho_{\text{thr}}$ are kept

ME-ICA

- Uses fast-ICA algorithm (spatial independence).
- Component Characterization includes:
  - Variance Explained
  - $\kappa$ ("BOLD likeliness")
  - $\rho$ ("Non-BOLD likeliness")
  - Nvoxels that significantly fit the $S_0$ model
  - Nvoxels that significantly fit the $R_2^*$ model
  - Spatial overlap (D) between ICA map and $FR_2^*$ map
  - Spatial overlap (D) between ICA map and $FS_0$ map
  - Other...

If $\kappa_c < \rho_c \rightarrow$ Discard c

If $N_{so,c} < N_{R2,c} \rightarrow$ Discard c

If $D_{so,c} < D_{R2,c} \rightarrow$ Discard c

Denoised Time series

### ME-ICA Denoising: Primary Inputs / Outputs

#### Inputs
- Minimum: fMRI Datasets for all echoes, echo times
- Extras: Anatomical, Pre-processing options, kdaw, rdaw,

#### Outputs
- T2* Static Map: \( t2v.nii \)
- So Static Map: \( s0v.nii \)
- Optimally Combined time series: \( ts\_OC.nii \)
- Denoised time series: \( dn\_ts\_OC.nii \)
- Spatial Maps for all ICA components: \( betas\_OC.nii \)
- Spatial Maps for Accepted Components only: \( betas\_hik\_OC.nii \)
- Time series for all PCA Components: \( mepca\_mix.1D \)
- Time series for all ICA Components: \( meica\_mix.1D \)
- Summary of ICA Decomposition: \( comp\_table.txt \)
  - List of accepted components
  - List of rejected components
  - List of Mid-k components
  - List of ignored components
  - Kappa and Rho values for all components
  - Total Variance Explained by the ICA decomposition

Latest experimental versions (P. Kundu) available at: [https://bitbucket.org/prantikk/me-ica.git](https://bitbucket.org/prantikk/me-ica.git)
ME-ICA Denoising: Web Reporting Tool

Your ME-ICA Report!

The program meica.py was created to form an algorithmic method for performing independent component analysis on multi-echo data and then algorithmically deciding which components represent BOLD-like phenomena.

The following content is a report that has taken information provided by meica.py and summarizes a few of the results.

This report form was created by the Section on Functional Imaging Methods in the NIMH. The creators of this report form are Benjamin Gutierrez, Prantik Kundu, Daniel Handwerker, Javier Gonzalez-Castillo, Souheil Inati, and Peter Bandettini.

Contents:

- Intro
- Preliminary Diagnostics
  - TSMR
- Component Visualization
  - Graphs
  - Accepted Components with anatomical
  - Rejected Components
  - Middle Components
  - Ignore Components

Search

- Search Page

(Ben Gutierrez) available at: https://github.com/BenGutierrez/Meica_Report
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ME-ICA Applications
Suitability for ultra-high field fMRI animal studies

<table>
<thead>
<tr>
<th>SINGLE-ECHO ICA</th>
<th>MULTI-ECHO ICA</th>
</tr>
</thead>
<tbody>
<tr>
<td>M2</td>
<td>M1,M2</td>
</tr>
<tr>
<td>V1</td>
<td>V1</td>
</tr>
<tr>
<td>RSGc</td>
<td>S1</td>
</tr>
<tr>
<td>DCPu</td>
<td>DCPu</td>
</tr>
<tr>
<td>S1</td>
<td>VCPu</td>
</tr>
<tr>
<td>M2</td>
<td>S1</td>
</tr>
<tr>
<td>S1</td>
<td>S1</td>
</tr>
</tbody>
</table>

Scanner 11.7T | 0.5x0.5x0.5mm | TR = 3s |
TE=8.25/20.25/32.35 ms | 400 volumes | Rats

Kundu et al., NeuroImage 2014
Separate BOLD-like Slow Fluctuations from Scanner Drift

Evans et al., NeuroImage 2015
Separate BOLD-like Slow Fluctuations from Scanner Drift

Evans et al., NeuroImage 2015
Separate BOLD-like Slow Fluctuations from Scanner Drift

Evans et al., NeuroImage 2015
Separate BOLD-like Slow Fluctuations from Scanner Drift

Evans et al., NeuroImage 2015
Alternative Approach for Brainstem Imaging: Gated fMRI + ME-ICA

Brooks et al. 2014
Alternative Approach for Brainstem Imaging: Gated fMRI + ME-ICA

ME-ICA Analysis, $\kappa$ vs $\rho$

- Accepted
- Rejected
- Middle
- Ignore

Component TS

$\Delta$TR

Gonzalez-Castillo et al. NeuroImage 2016
Alternative Approach for Brainstem Imaging: Gated fMRI + ME-ICA

Gonzalez-Castillo et al. NeuroImage 2016
ME+ICA for Rapid Event Related fMRI

**ACTIVATION EXTENT**

- **Number of Active Voxels**
  - Motor
  - Houses
  - B.Motion
  - Music
  - Read

<table>
<thead>
<tr>
<th></th>
<th>Single Echo</th>
<th>Optimally Combined</th>
<th>ME-ICA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td></td>
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<tr>
<td>Houses</td>
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<td>B.Motion</td>
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<td>Music</td>
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<tr>
<td>Read</td>
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</tbody>
</table>

**T-STATISTIC**

- **Average T-stat**
  - Motor
  - Houses
  - B.Motion
  - Music
  - Read

Gonzalez-Castillo et al. NeuroImage 2016
Multi-Echo & Simultaneous Multi-Slice (MESMS)

Non-BOLD Component: Vascular Pulsation

Non-BOLD Component: MSS Artifact

Number of BOLD-like components significantly larger for MESMS

Olafsson et al., NeuroImage 2015
Conclusions

- Multi-echo fMRI allows to capture additional information with minimal costs in terms of temporal and spatial resolution.

- Such additional information can be used to:
  - Increase CNR in drop-out regions (e.g., Optimal Combination of Echoes).
  - Automatically separate BOLD-like from Non-BOLD-like components (ME-ICA).

- ME-ICA is a promising denoising methodology that combines ICA with TE-Dependence Analysis:
  - Will not clean every single artifact in the data.
  - Still under development.
  - Can substantially improve the SNR of the data → Quality of the results.

\[
\text{ME-fMRI} = \text{ACCEPTED} + \text{REJECTED}
\]

Kundu et al., NeuroImage 2012
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