Multi-echo EPI for resting state and activation based fMRI

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WHAT IS MULTI-ECHO (ME) FMRI

WHAT CAN YOU DO WITH ME TIMESERIES

• Compute static $S_o$ and $T_2^*$ Maps
• Compute voxel-wise time-series of $S_o$ (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
Why ME-fMRI?

**RAW DATA**

\[ S(x,t) \]

**SIGNAL CHANGE**

\[ \Delta S(x,t) = \frac{S(x,t) - \overline{S(x)}}{\overline{S(x)}} \]
Single-Echo fMRI (a.k.a. Your regular fMRI)

One Time series per voxel (x)

Time [s]

S(x,t)

Time [s]
Now you have $N_e$ (e.g., 3) Time series per voxel, one per echo time ($TE_n$):

- 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.
Multi-Echo fMRI (II)
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

$$S_o(x,t) = S_o(x) + \Delta S_o(x,t)$$

$$\Delta S_o(x,t) << S_o(x), \forall x$$

Captures local fluctuations in field inhomogeneity (including BOLD)

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

$$\Delta R_2^*(x,t) << R_2^*(x), \forall x$$
Agenda

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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:

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

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

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

$$y(x,TE) = a(x) \cdot TE + b(x)$$

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 $T_2^*$

Static $S_0$ Map (s0v.nii)

Static $T_2^*$ Map (t2sv.nii)
How to Compute Time series of $\Delta S_o$ and $\Delta R_2^*$ fluctuations

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

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

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

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

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

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

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

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

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

\[ \Delta \rho(x,t) = \frac{\Delta S_o(x,t)}{\overline{S_o(x)}} \]

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

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

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

- Raw Data
- $\Delta S_o$
- $\Delta R_2^*$

Motion Correction & Smoothing (6mm)
No Filtering | No Detrending
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**

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

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

$$w_v(TE_n) = \frac{TE_n e^{-\frac{TE_n}{T_{2,v}}}}{\sum_n TE_n \cdot e^{-\frac{TE_n}{T_{2,v}}}}$$

*Posse et al., MRM 1999*
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\[
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\]

\[
w_v(TE_n) = \frac{TE_n e^{-TE_n/T_{2,v}}}{\sum_n TE_n e^{-TE_n/T_{2,v}}}
\]

- 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*
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)
Echo Time (TE) Dependence Analysis

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

We could then use the difference between two curves to examine which is the optimal TE to maximize BOLD contrast.
Echo Time (TE) Dependence Analysis

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

Most importantly for our discussion, for T2* signal changes, there is a linear relationship between echo time and measured signal (in terms of signal percent change)
Echo Time (TE) Dependence Analysis

\[ S(x,t,TE) = S_0(x,t) e^{-R_2^*(x,t)TE} \]

Let’s now examine what happens when there is a change in \( S_0 \) (T1 effect)

Kundu et al., NeuroImage 2012
$S(x, t, TE) = S_0(x, t) e^{-R^*_2(x, t)TE}$

This time the difference between both curves looks very different.
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

\[
S(x,t,TE) = S_0(x,t)e^{-R_2^*(x,t)TE}
\]

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

Changes in R2* scale linearly with echo time.
Changes in So show a flat dependence with echo time.

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

[1] Voxel-wise Fit against all TEs

[2] Voxel-wise Goodness of Fit to R2* Model

[3] Voxel-wise Goodness of Fit to S0 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

Data is represented as a 2D matrix and decomposed into factor matrices (or modes)

FSL Documentation: [http://fsl.fmrib.ox.ac.uk/fslcourse/lectures/melodic.pdf](http://fsl.fmrib.ox.ac.uk/fslcourse/lectures/melodic.pdf)
ME-ICA Denoising: Introduction

(a) Functional Network Component

- TE-dependent signal change
- Component time course
- 360 sec.
- 0.5% - 0.5%
- 15 ms, 39 ms, 63 ms
- Kappa (κ) = 210
- Rho (ρ) = 10

Kundu et al., NeuroImage 2012
ΔR₂* scale linearly with TE

ΔS₀ has no TE dependence

ICA Representative Timeseries

Kappa (κ) = 32
Rho (ρ) = 81

Long distance correlation. With ME-ICA denoising, the insula shows greater correlation to premotor and sensory regions, and brainstem shows greater correlation to frontal and parietal regions.

Application to group level correlation maps

Group-level connectivity was evaluated using one-sample T-tests of the individual-level correlation maps from standard and ME-ICA de-noising. The group T-maps based on low κ-score, and ICA component number. All high κ components based on ME-ICA were more consistent across subjects than Z-transformed correlation coefficients based on standard de-noising. Comparing transformed correlation coefficients based on ME-ICA and standard de-noising. Unthresholded group T-maps for hippocampus and brainstem connectivity are shown in Figs. 7 and 8.

Maps show that ME-ICA denoising, without band pass filtering, reveals greater correlation to premotor and cingulate regions, hippocampus patterns proximal to the seed, but ME-ICA denoising exposes greater long distance correlation. With ME-ICA denoising, the insula shows greater correlation to premotor and sensory regions, and shows greater correlation to premotor and sensory regions, and hippocampus connectivity are shown in.

ΔR₂* maps of top κ 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

Low-$\lambda$ comps on flat tail spanning $\lambda \sim 10-20$
ME-ICA Denoising: Pipeline

**Pre-processing**
- Slice time correction
- Head motion correction
- Registration to ANAT

**Optimal Combination**
- ME\[N_v,N_t,N_e\]

**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)**

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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 κ and ρ 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

- Uses fast-ICA algorithm (spatial independence).
- Component Characterization includes:
  - Variance Explained
  - \( \kappa \) ("BOLD likeliness")
  - \( \rho \) ("Non-BOLD likeliness")
  - Nvoxels that significantly fit the \( S_o \) 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 \( FS_o \) 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

# ME-ICA Denoising: Primary Inputs / Outputs

<table>
<thead>
<tr>
<th><strong>Inputs</strong></th>
<th><strong>Outputs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Minimum: fMRI Datasets for all echoes, echo times</td>
<td>- List of accepted components</td>
</tr>
<tr>
<td>- Extras: Anatomical, Pre-processing options, kdaw, rdaw,</td>
<td>- List of rejected components</td>
</tr>
<tr>
<td></td>
<td>- List of Mid-k components</td>
</tr>
<tr>
<td></td>
<td>- List of ignored components</td>
</tr>
<tr>
<td></td>
<td>- Kappa and Rho values for all components</td>
</tr>
<tr>
<td></td>
<td>- Total Variance Explained by the ICA decomposition</td>
</tr>
</tbody>
</table>

- **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`


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
  - TSNR
- 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](https://github.com/BenGutierrez/Meica_Report)
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- ME-ICA Applications
Suitability for ultra-high field fMRI animal studies

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., Neurolmage 2015
Alternative Approach for Brainstem Imaging: Gated fMRI + ME-ICA

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

Gonzalez-Castillo et al. 2015 (OHBM)
Alternative Approach for Brainstem Imaging: Gated fMRI + ME-ICA

Gonzalez-Casillo et al. 2015 (OHBM)
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
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.

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