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

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Agenda

- **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

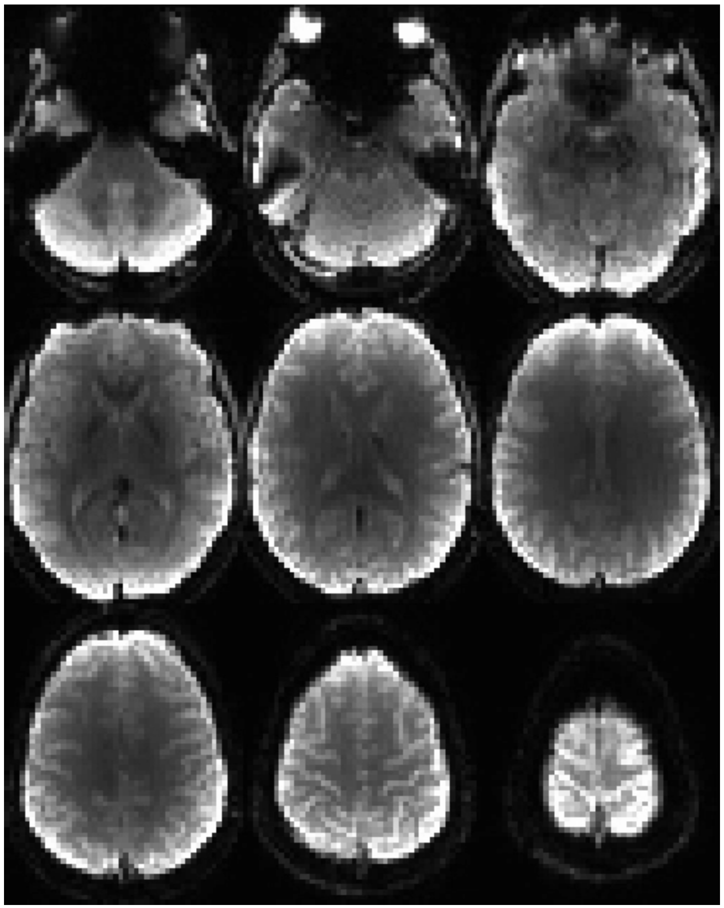
- **ME-ICA Denoising**

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

- **ME-ICA Applications**

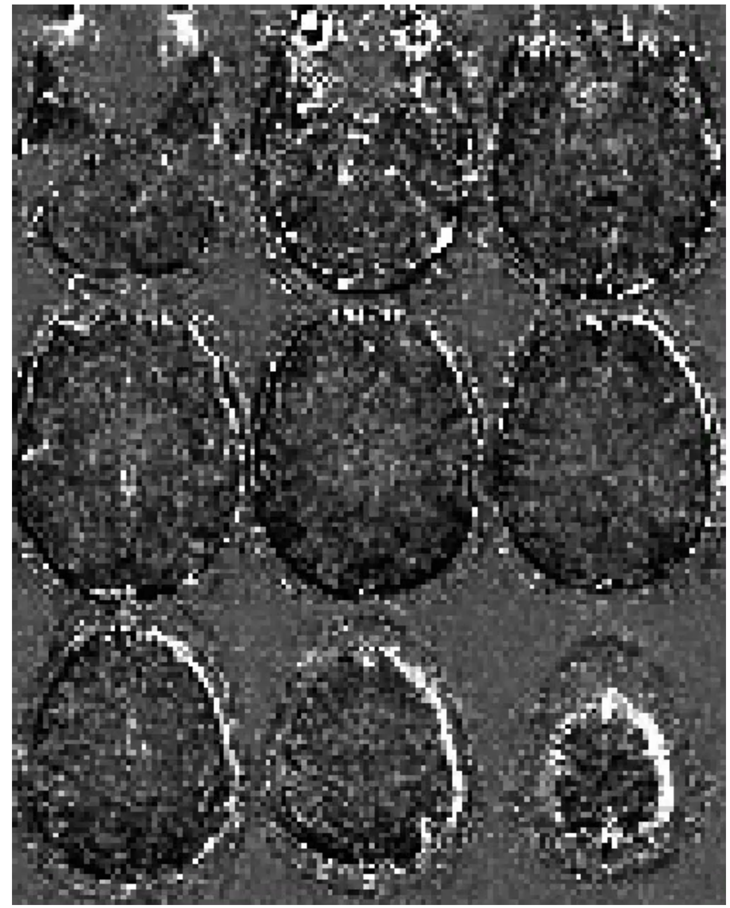
Why ME-fMRI?

RAW DATA



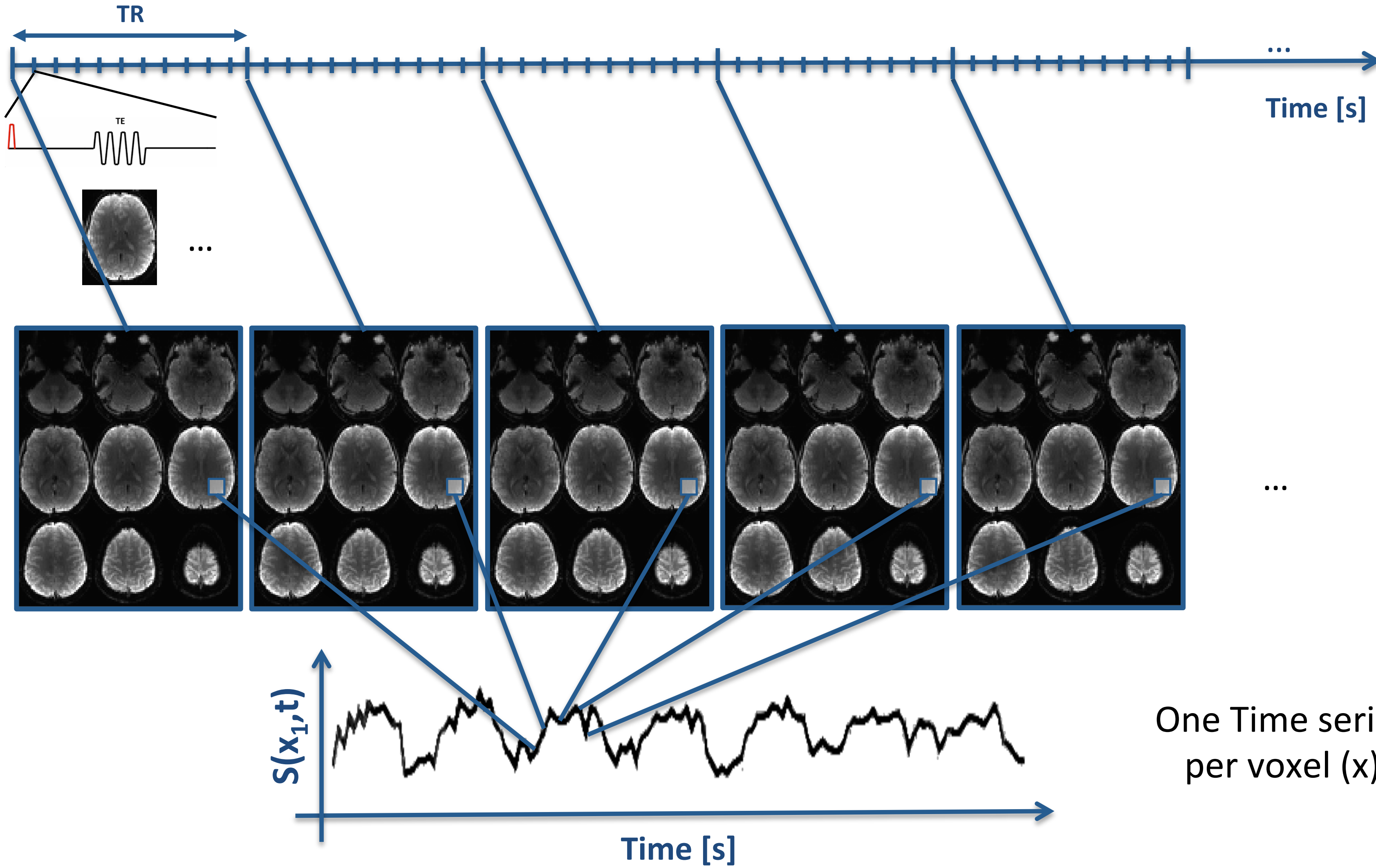
$S(x,t)$

SIGNAL CHANGE



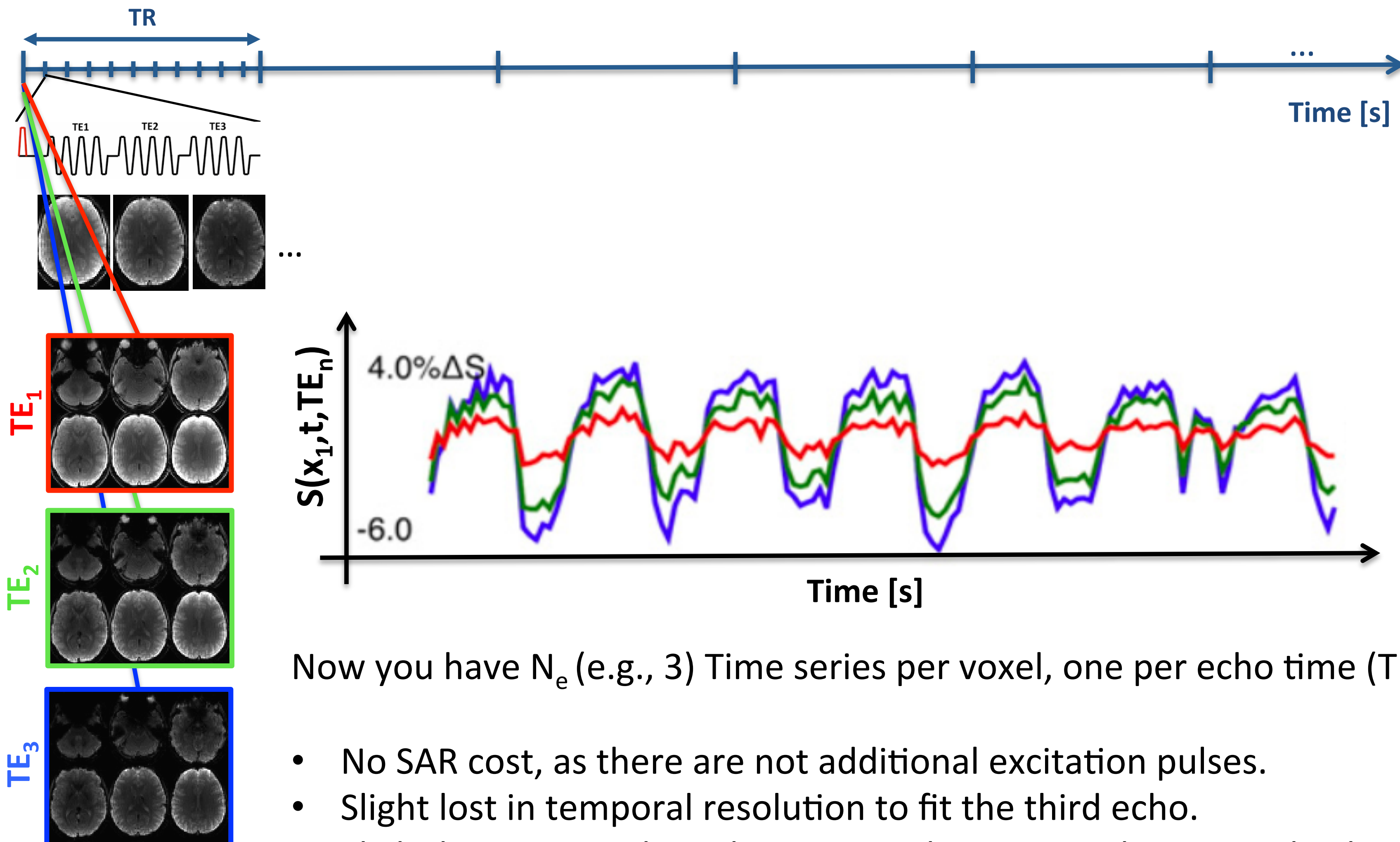
$$\Delta S(x,t) = \left[S(x,t) - \overline{S(x)}\right] \Big/ \overline{S(x)}$$

Single-Echo fMRI (a.k.a. Your regular fMRI)



One Time series
per voxel (x)

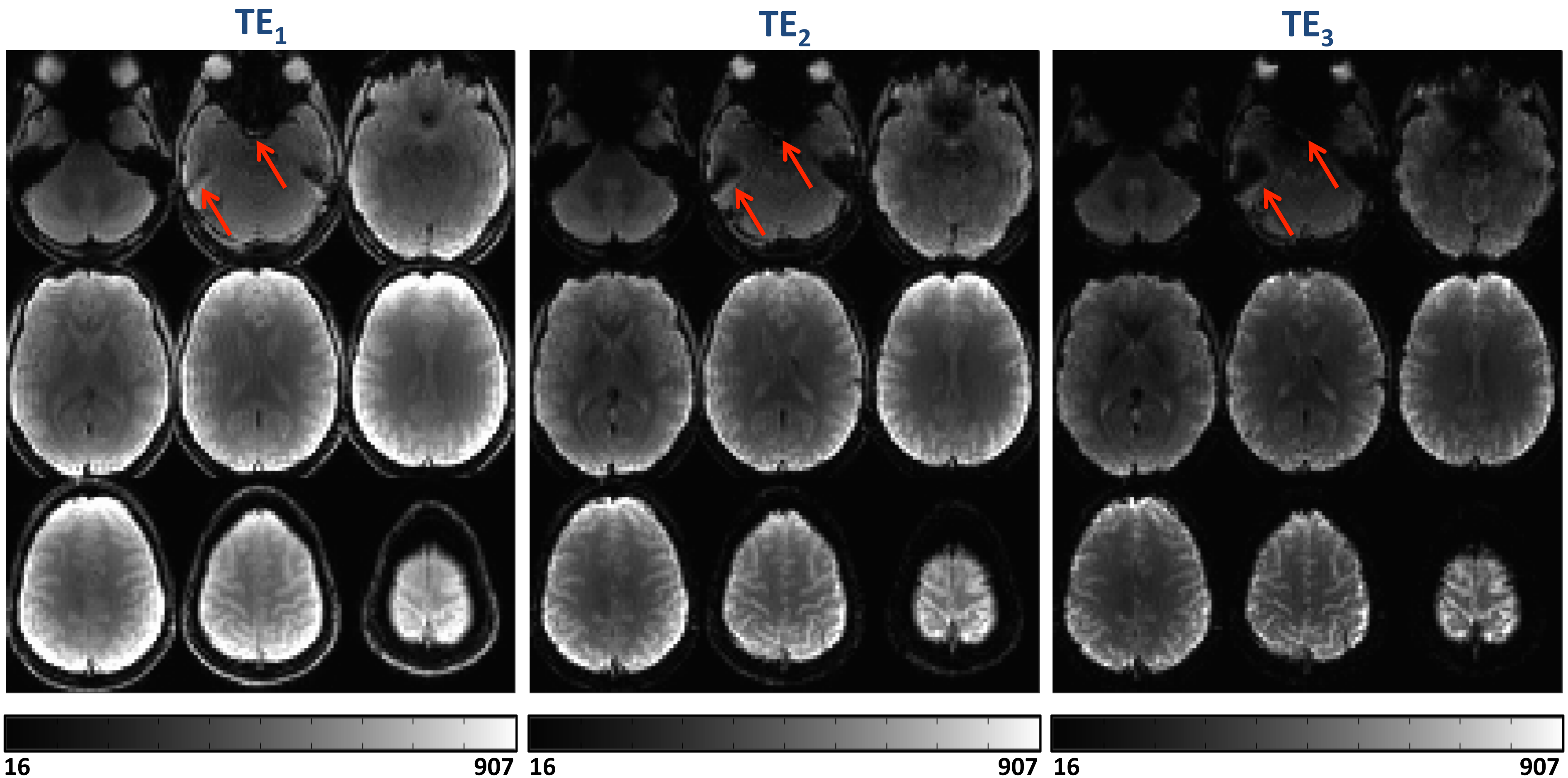
Multi-Echo fMRI



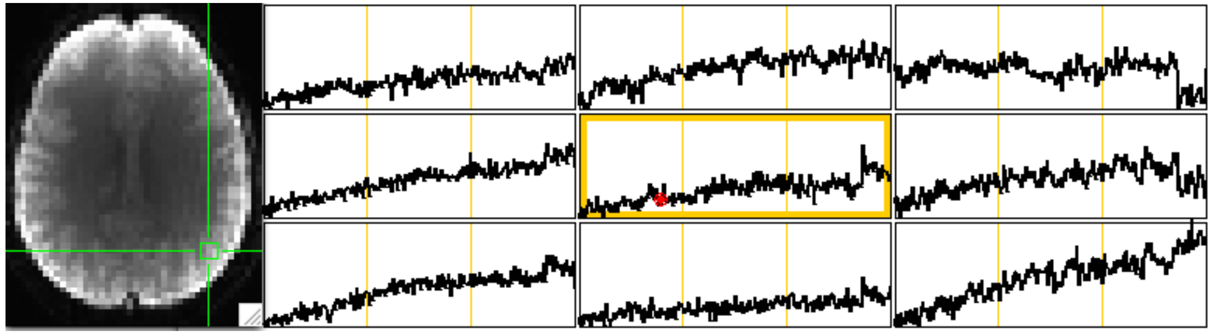
Now you have N_e (e.g., 3) Time series per voxel, one per echo time (TE_n):

- 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 Model



Signal in voxel *x*, at time point *t*, measured at echo time *TE*

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

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

Captures local fluctuations in field inhomogeneity (including BOLD)

$$S_o(x,t) = \boxed{\overline{S_o(x)}} + \boxed{\Delta S_o(x,t)}$$

$$\Delta S_o(x,t) << \overline{S_o(x)}, \forall x$$

$$R_2^*(x,t) = \boxed{\overline{R_2^*(x)}} + \boxed{\Delta R_2^*(x,t)}$$

$$\Delta R_2^*(x,t) << \overline{R_2^*(x)}, \forall x$$

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How to Compute Spatial Maps of $\overline{S_o}$ and $\overline{T_2^*}$

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

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:

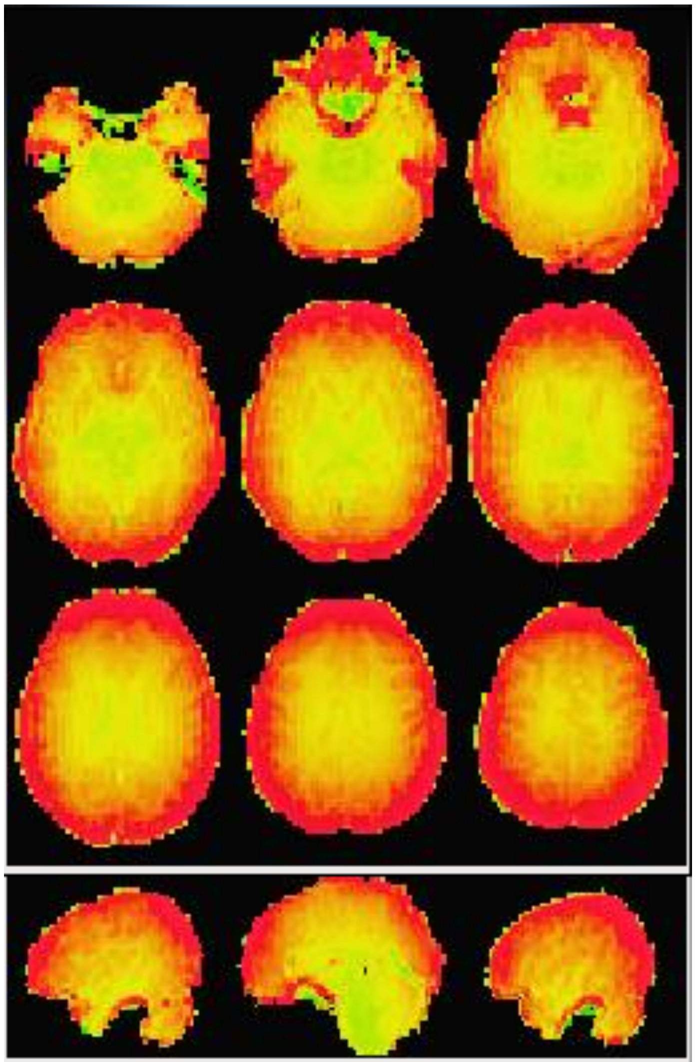
$$\overline{S(x,TE)} = \overline{S_o(x)} \cdot e^{-\overline{R_2^*(x)}\cdot TE}$$
$$\downarrow$$
$$\log\left(\overline{S(x,TE)}\right) = \log\left(\overline{S_o(x)} \cdot e^{-\overline{R_2^*(x)}\cdot TE}\right)$$
$$\downarrow$$
$$\log\left(\overline{S(x,TE)}\right) = -\overline{R_2^*(x)}\cdot TE + \log\left(\overline{S_o(x)}\right)$$

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

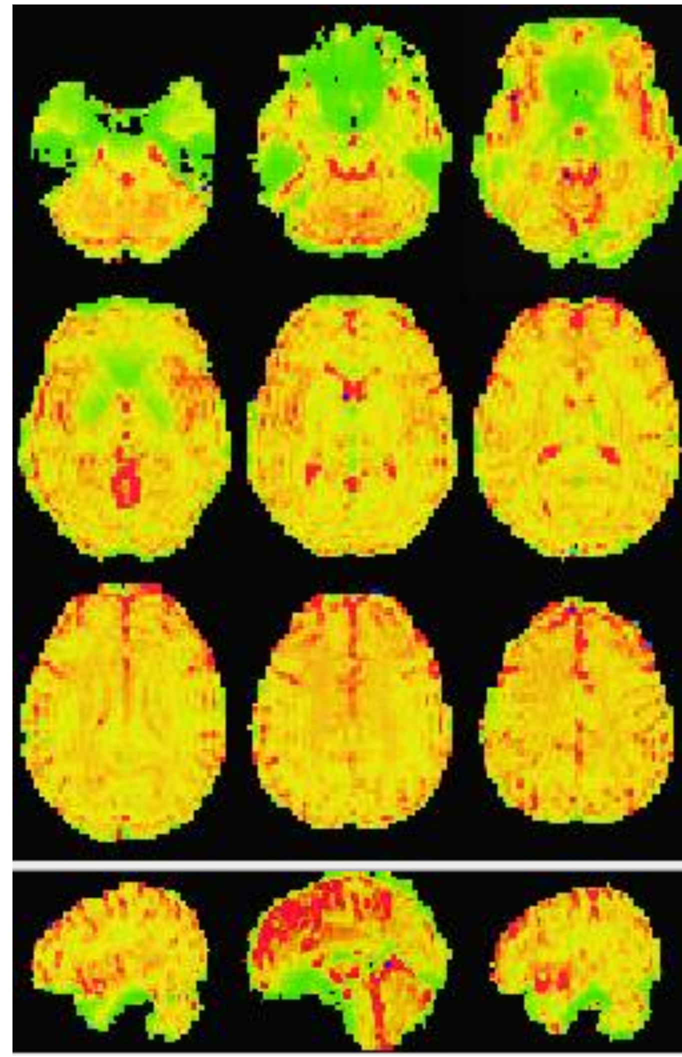
Linear system of equations for 3 echoes

$$\begin{cases} \log\left(\overline{S(x,TE_1)}\right) = -\overline{R_2^*(x)}\cdot TE_1 + \log\left(\overline{S_o(x)}\right) \\ \log\left(\overline{S(x,TE_2)}\right) = \boxed{-\overline{R_2^*(x)}}\cdot TE_2 + \boxed{\log\left(\overline{S_o(x)}\right)} \\ \log\left(\overline{S(x,TE_3)}\right) = -\overline{R_2^*(x)}\cdot TE_3 + \log\left(\overline{S_o(x)}\right) \end{cases}$$

How to Compute Spatial Maps of $\overline{S_o}$ and $\overline{T_2}^*$



Static So Map (s0v.nii)



Static T_2^* Map (t2sv.nii)

How to Compute Time series of ΔS_o and ΔR_2^* fluctuations

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

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

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

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

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

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

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

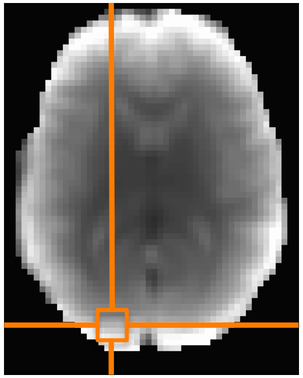
$$S(x,t,TE) \approx \overline{S(x,TE)}\left[1 - \Delta R_2^*(x,t)\cdot TE + \frac{\Delta S_o(x,t)}{\overline{S_o(x)}} - \frac{\Delta R_2^*(x,t)\cdot TE \cdot \Delta S_o(x,t)}{\overline{S_o(x)}}\right] \qquad \textbf{(3)}$$

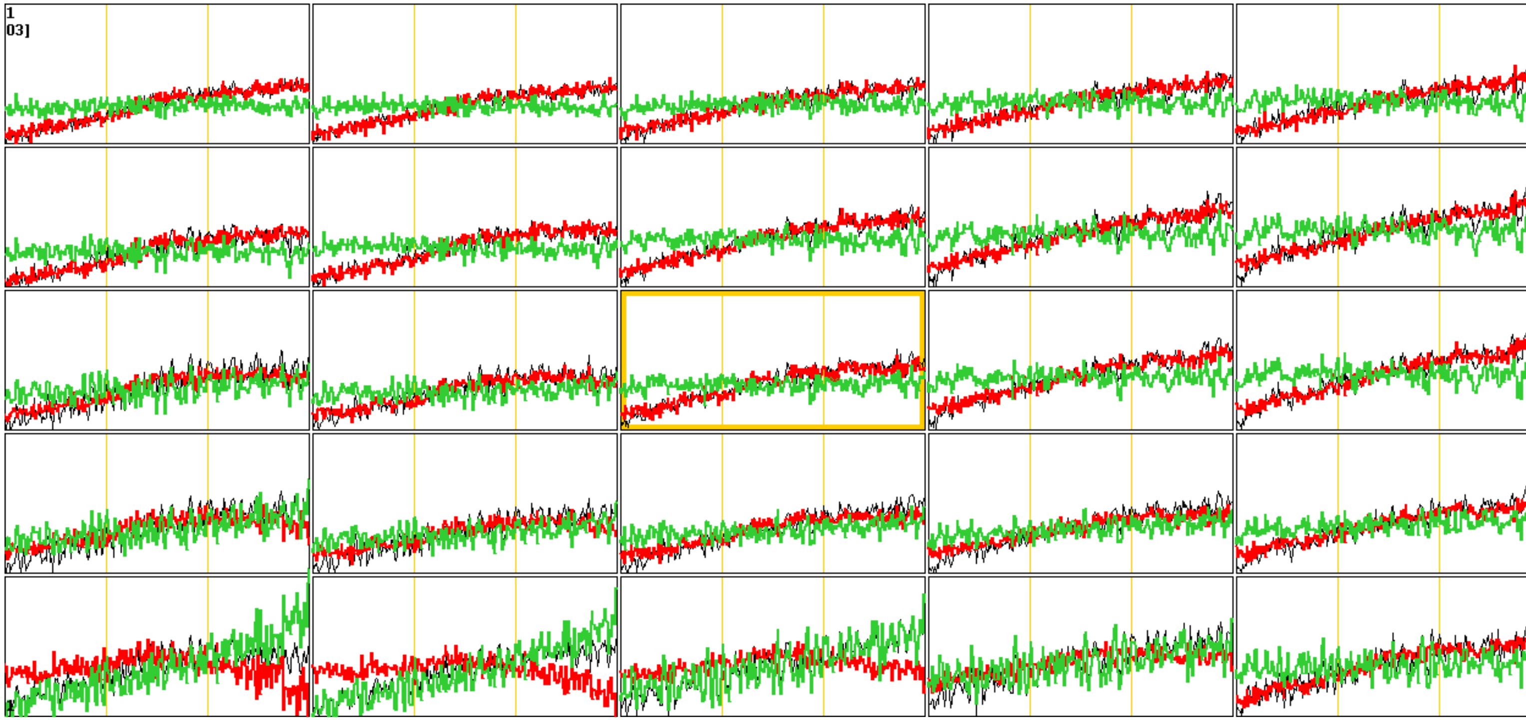
$$S(x,t,TE) \approx \overline{S(x,TE)}\left[1 - \Delta R_2^*(x,t)\cdot TE + \frac{\Delta S_o(x,t)}{\overline{S_o(x)}}\right] \qquad \textbf{(4)}$$

$$\left.\begin{array}{l} \Delta\rho(x,t) = \Delta S_o(x,t)/\overline{S_o(x)} \\ \Delta\kappa(x,t) = \Delta R_2^*(x,t)\cdot \overline{TE} \end{array}\right\} \rightarrow S(x,t,TE) \approx \overline{S(x,TE)} \cdot \left[1 + \Delta\rho(x,t) - \frac{TE}{\overline{TE}}\Delta\kappa(x,t)\right] \qquad \textbf{(5)}$$

$$S(x,t,TE) - \overline{S(x,TE)} \approx \overline{S(x,TE)}\left[\Delta\rho(x,t) - \frac{TE}{\overline{TE}}\Delta\kappa(x,t)\right] \qquad \textbf{(6)}$$

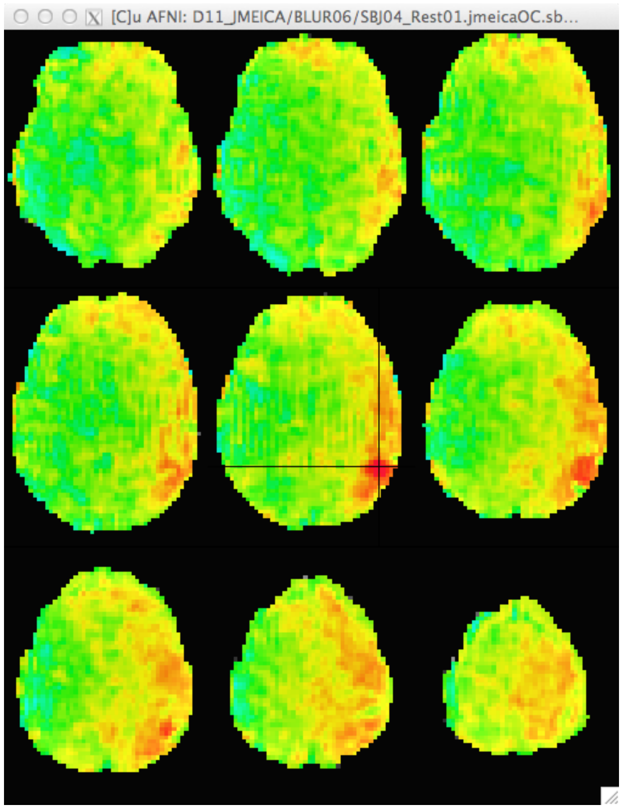
How to Compute Time series of ΔS_o and ΔR_2^* fluctuations



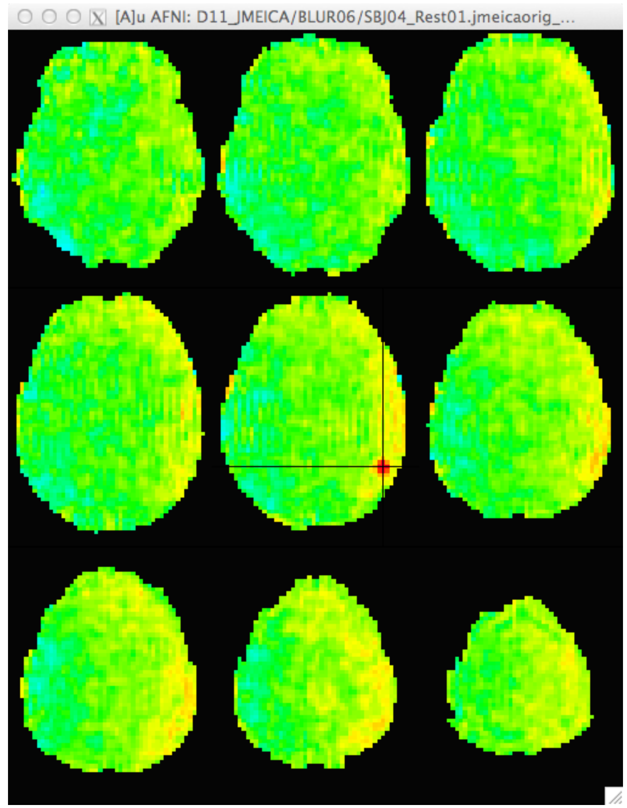


$S(x,t,TE_2)$ $\Delta S_o(x,t)$ $\Delta R_2^*(x,t)$

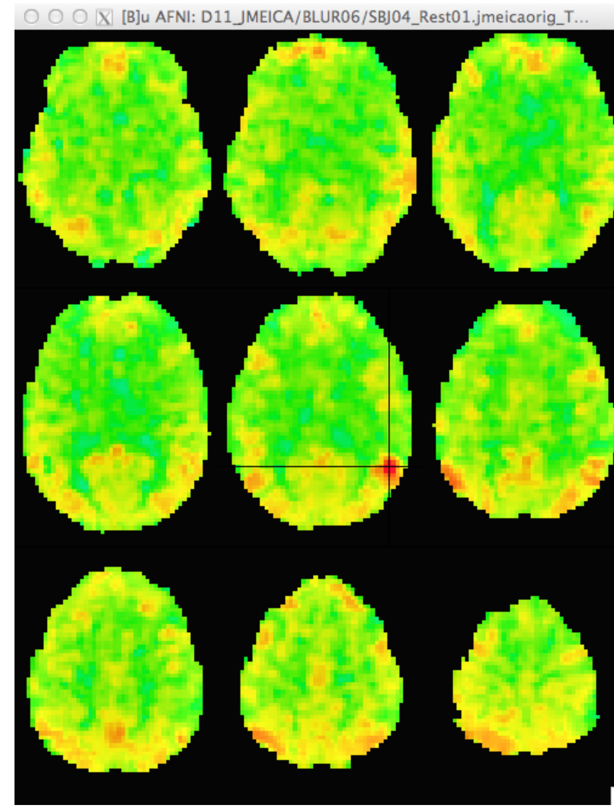
How to Compute Time series of ΔS_o and ΔR_2^* fluctuations



Raw Data



ΔSo



ΔR_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**

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

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

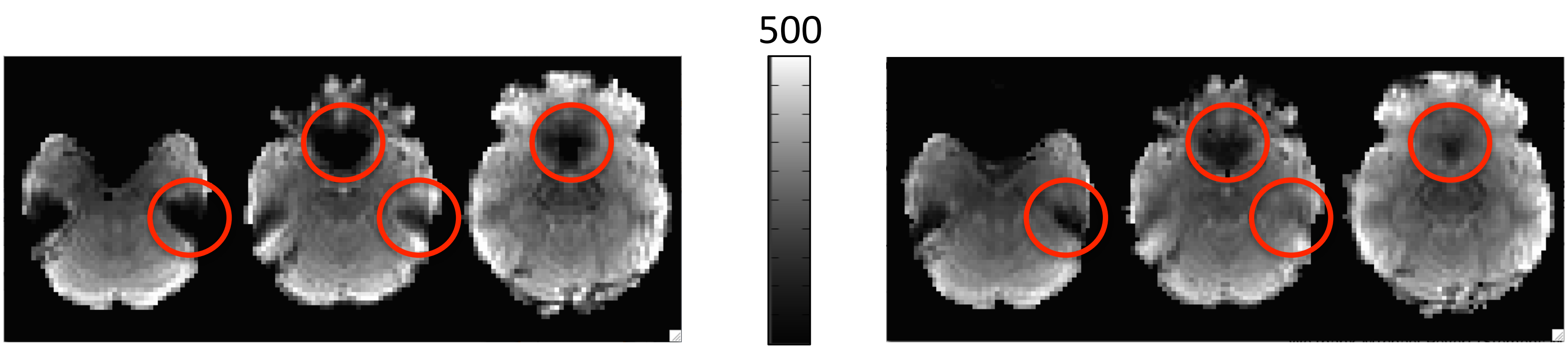
2. **Weighted Summation**

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

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

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

Posse et al., MRM 1999



SINGLE ECHO

OPTIMALLY COMBINED

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.

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

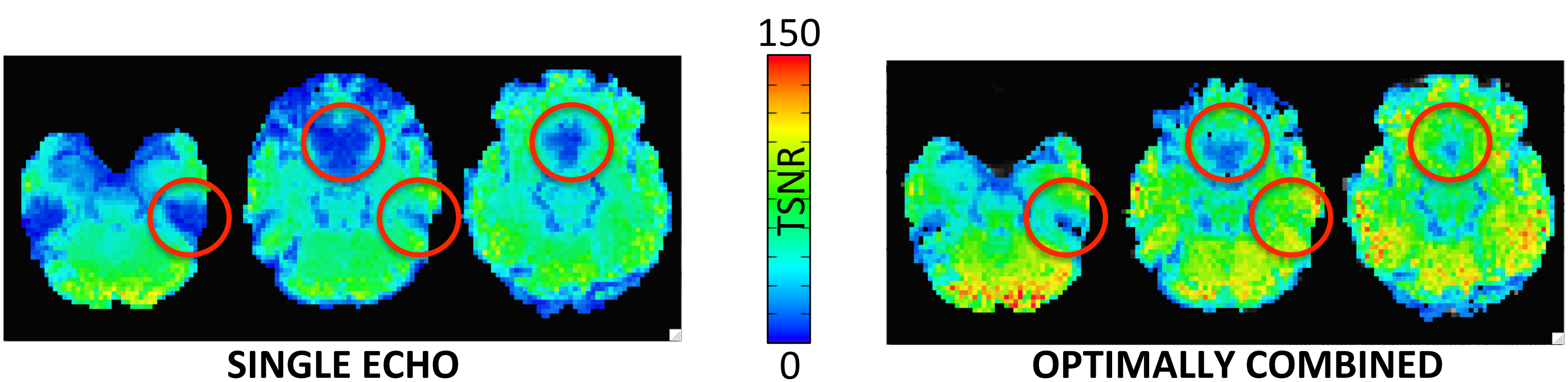
2. **Weighted Summation**

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

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

- 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.

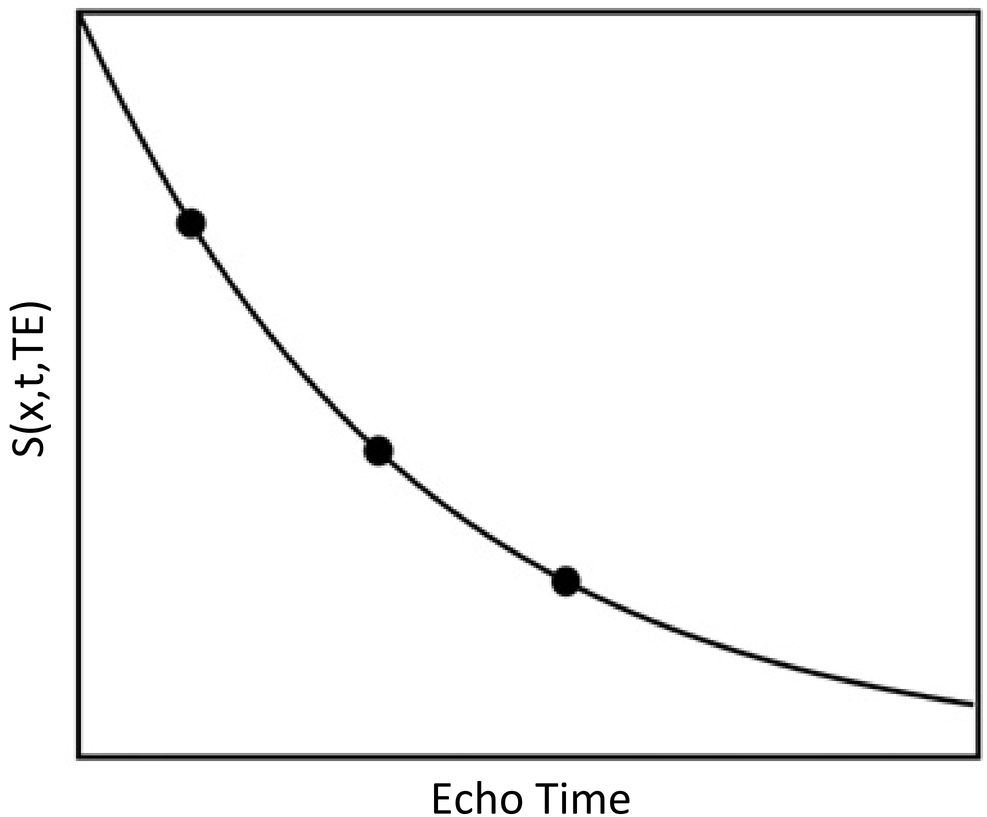
Posse et al., MRM 1999



Echo Time (TE) Dependence Analysis

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

Let's assume that a given voxel (x) and time (t) …. So(x,t)=5000 and T2*(x,t)=30ms

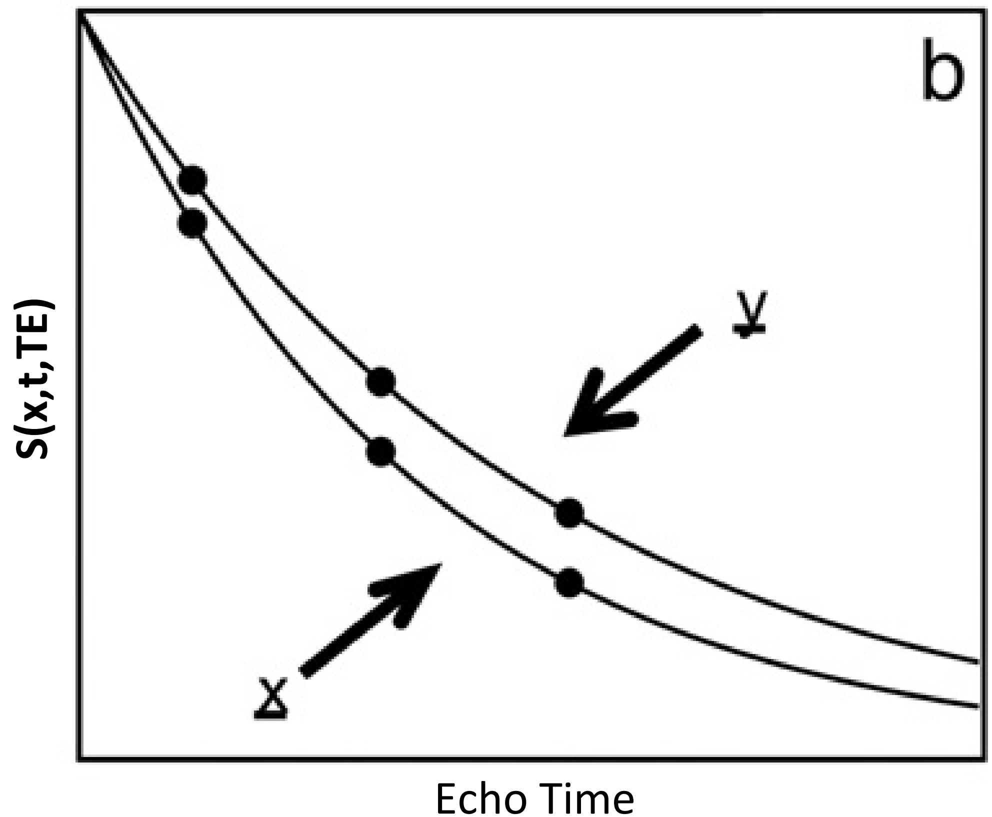


Kundu et al., NeuroImage 2012

Echo Time (TE) Dependence Analysis

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

Let's assume now, that a local change in oxygenation happens (T_2^* effect)

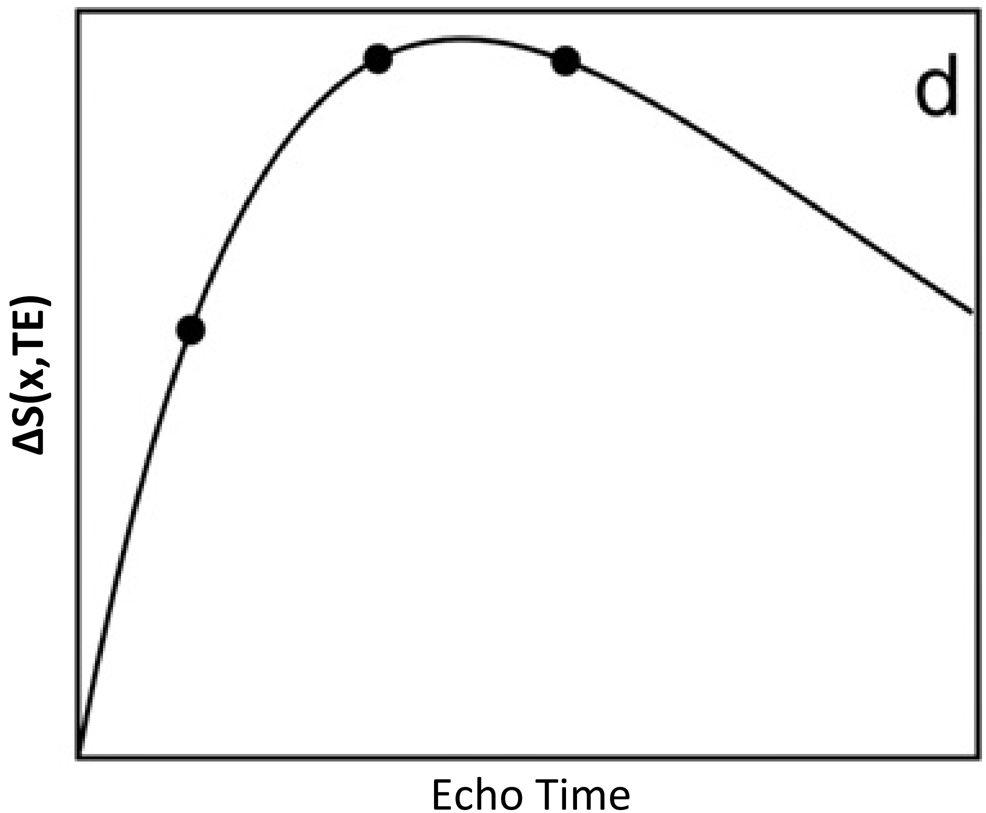


Kundu et al., NeuroImage 2012

Echo Time (TE) Dependence Analysis

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

We could then use the difference between two curves to examine which is the optimal TE to maximize BOLD contrast

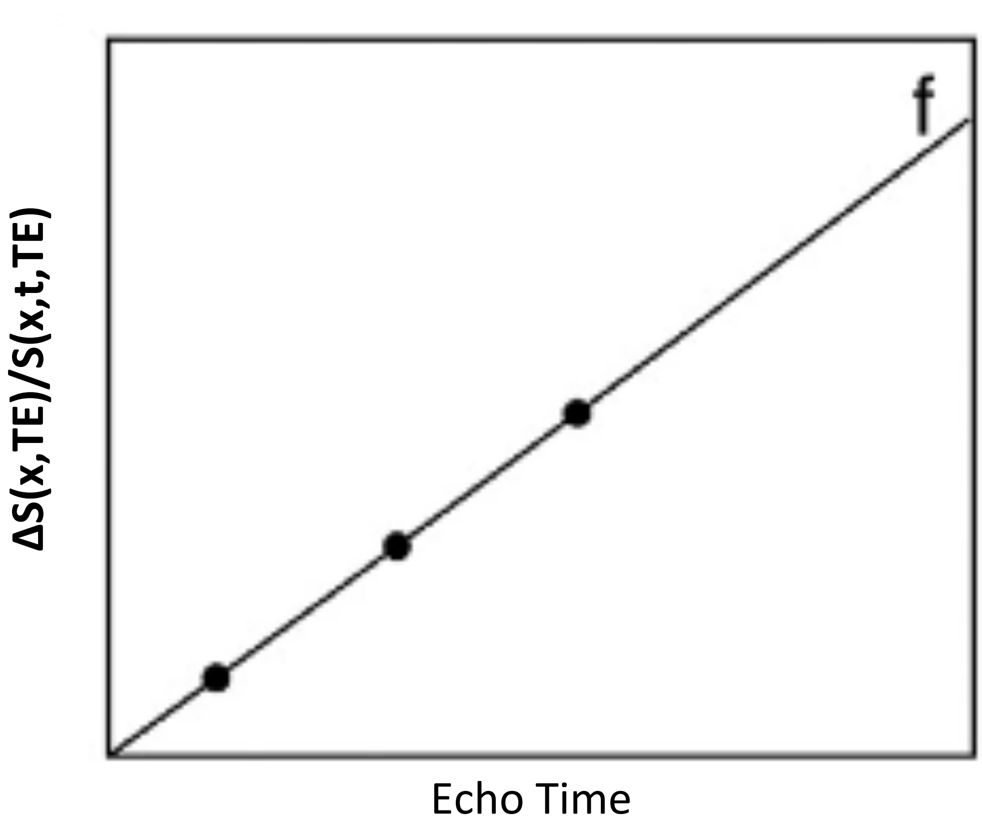


Kundu et al., NeuroImage 2012

Echo Time (TE) Dependence Analysis

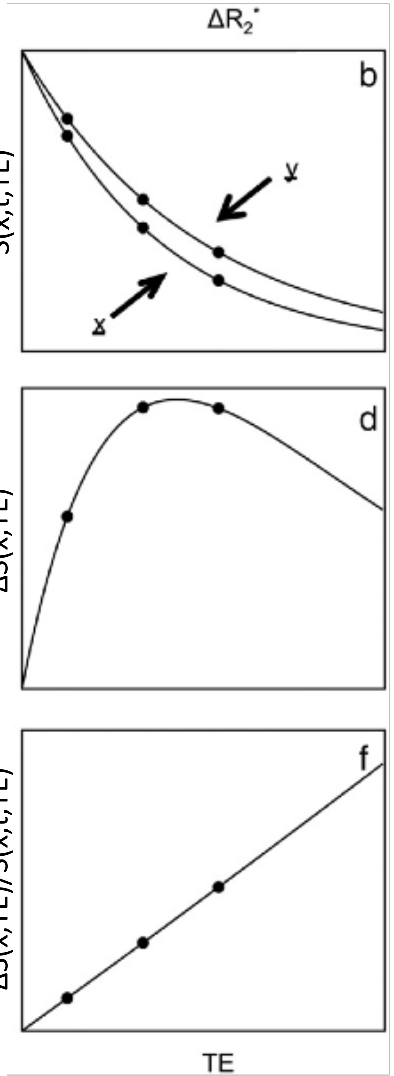
$$S(x,t,TE) = S_o(x,t)\,e^{-R_2^*(x,t)\cdot TE}$$

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)



Kundu et al., NeuroImage 2012

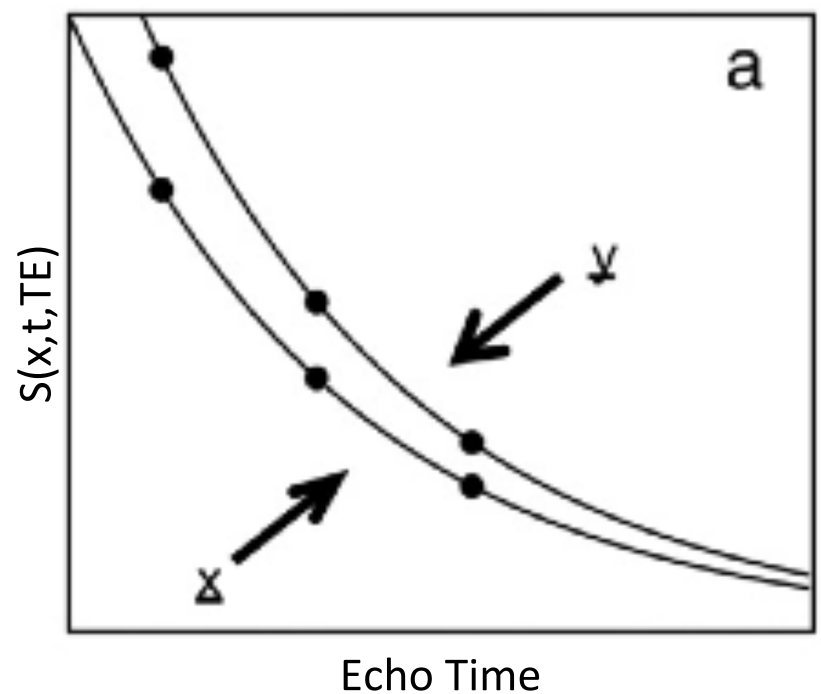
Echo Time (TE) Dependence Analysis



Changes in R2* scale linearly with echo time

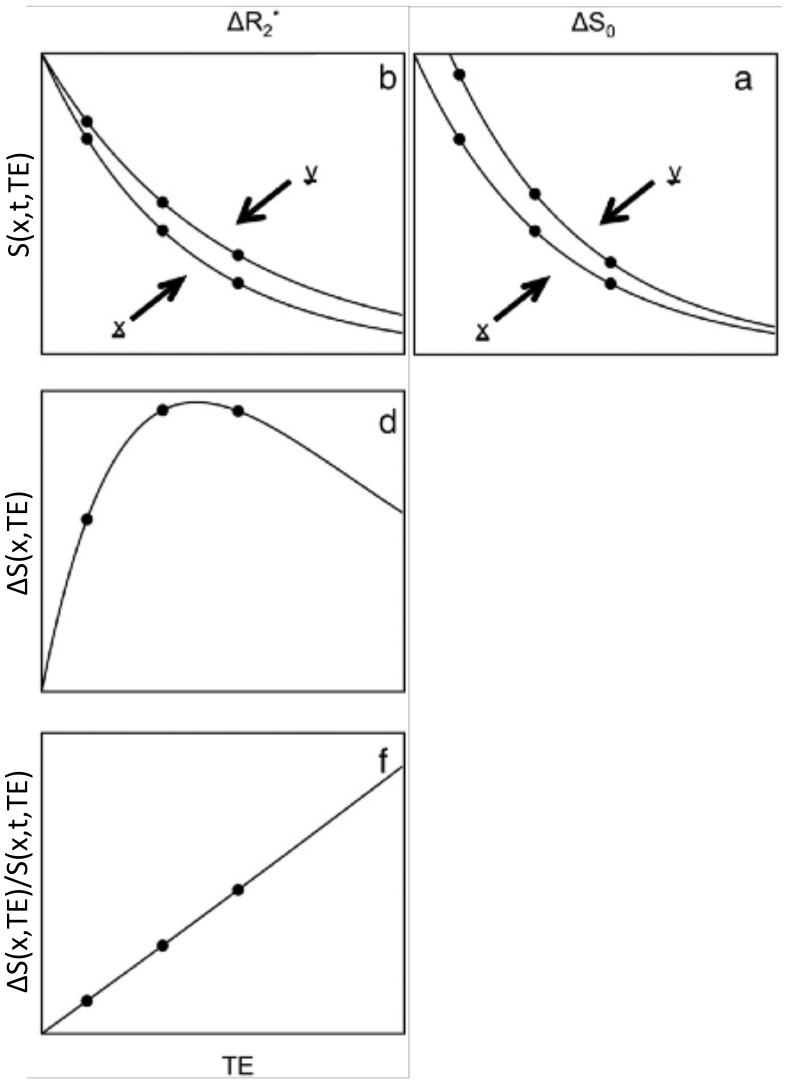
$$S(x,t,TE) = S_o(x,t)\,e^{-R_2^*(x,t)\cdot TE}$$

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



Kundu et al., NeuroImage 2012

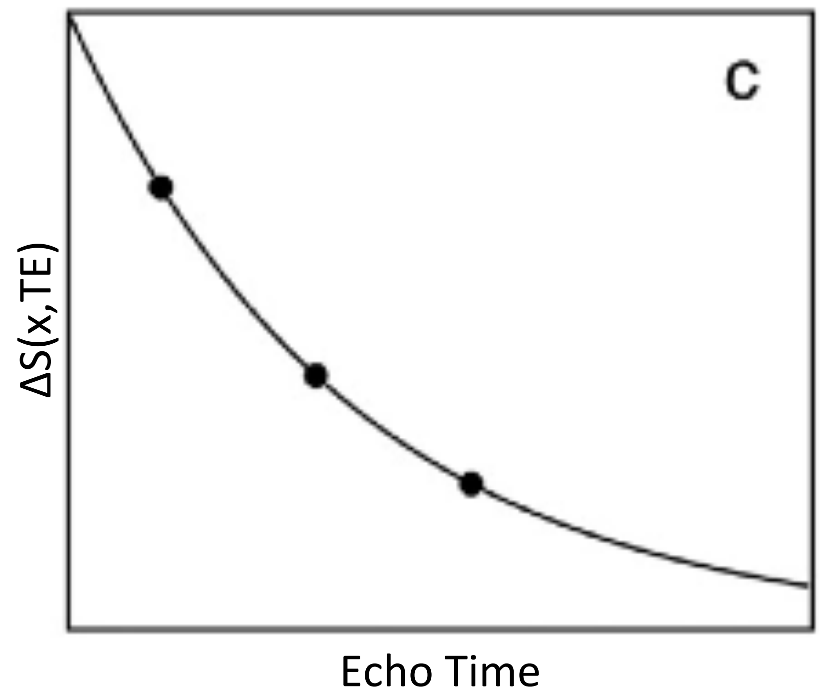
Echo Time (TE) Dependence Analysis



Changes in R2* scale linearly with echo time

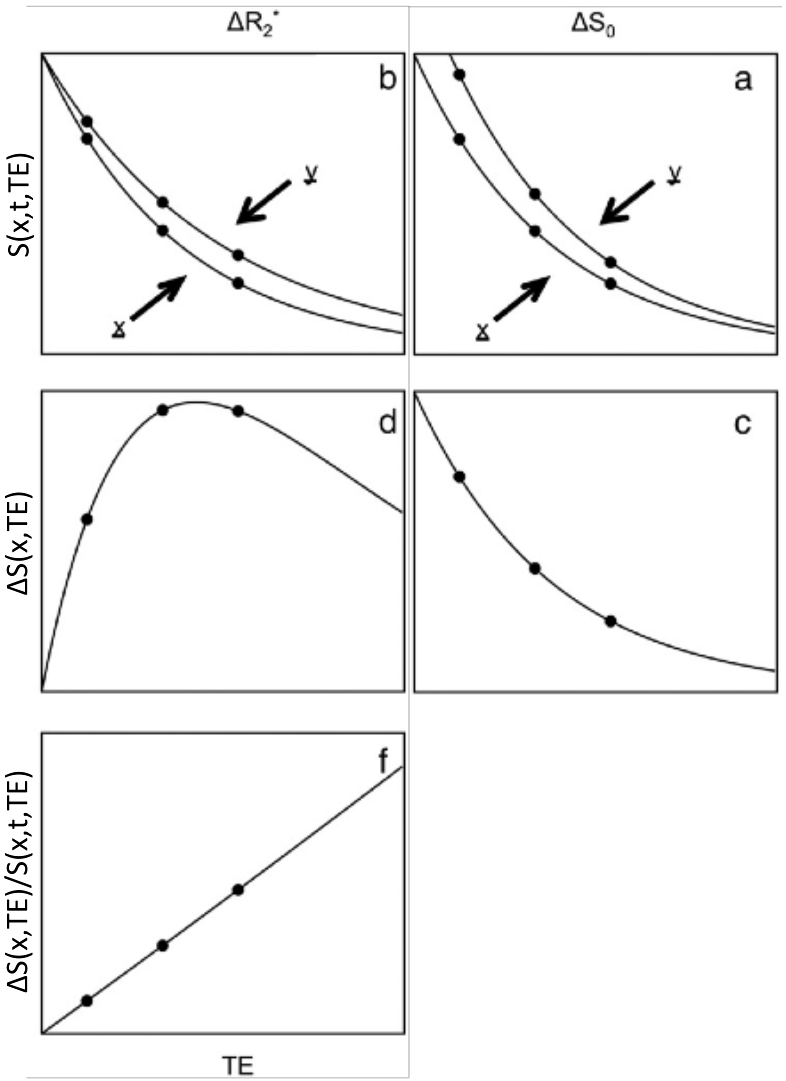
$$S(x,t,TE) = S_o(x,t)\,e^{-R_2^*(x,t)\cdot TE}$$

This time the difference between both curves looks very different



Kundu et al., NeuroImage 2012

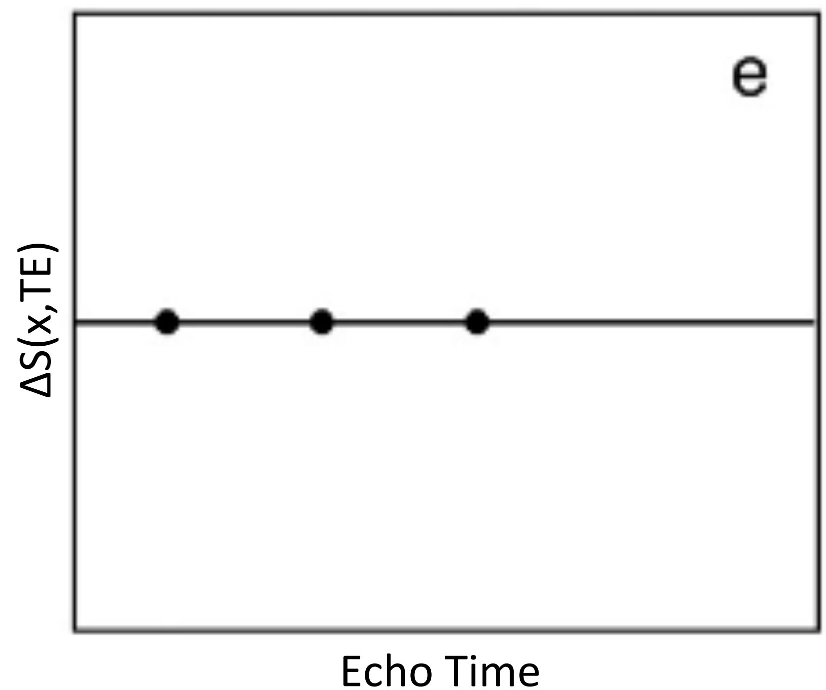
Echo Time (TE) Dependence Analysis



Changes in R2* scale linearly with echo time

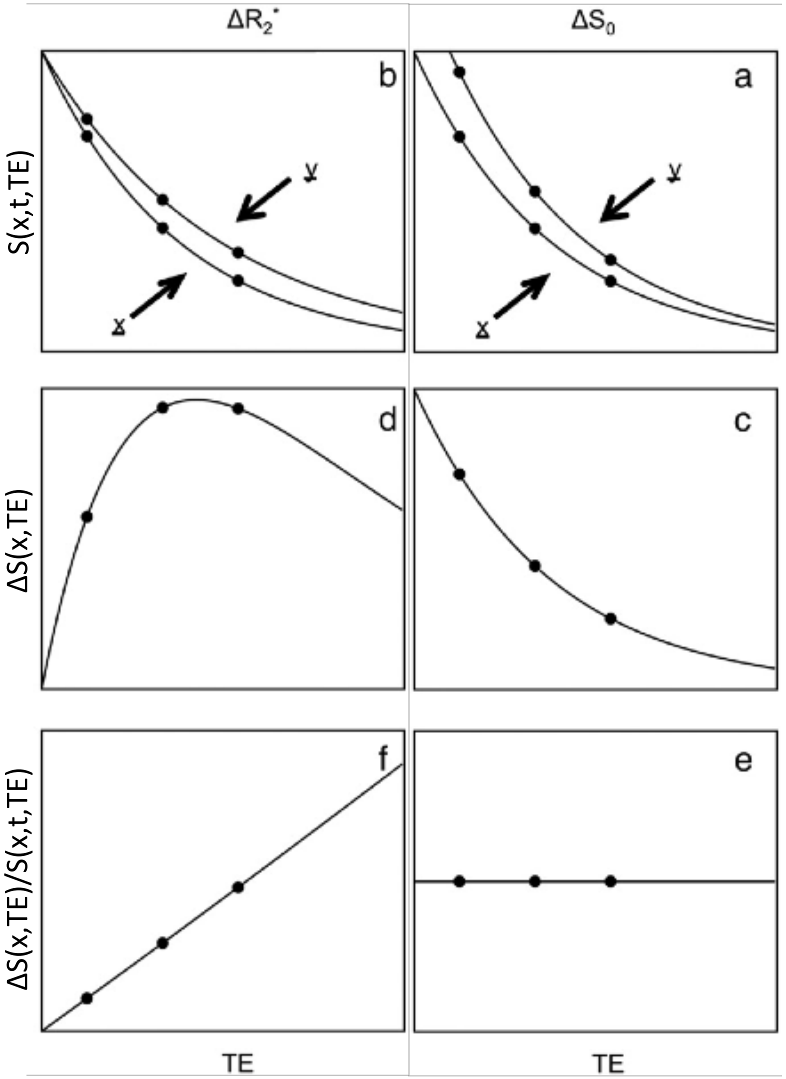
$$S(x,t,TE) = S_o(x,t)\,e^{-R_2^*(x,t)\cdot TE}$$

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



Kundu et al., NeuroImage 2012

Echo Time (TE) Dependence Analysis



Changes in R2* scale linearly with echo time

Changes in So show a flat dependence with echo time

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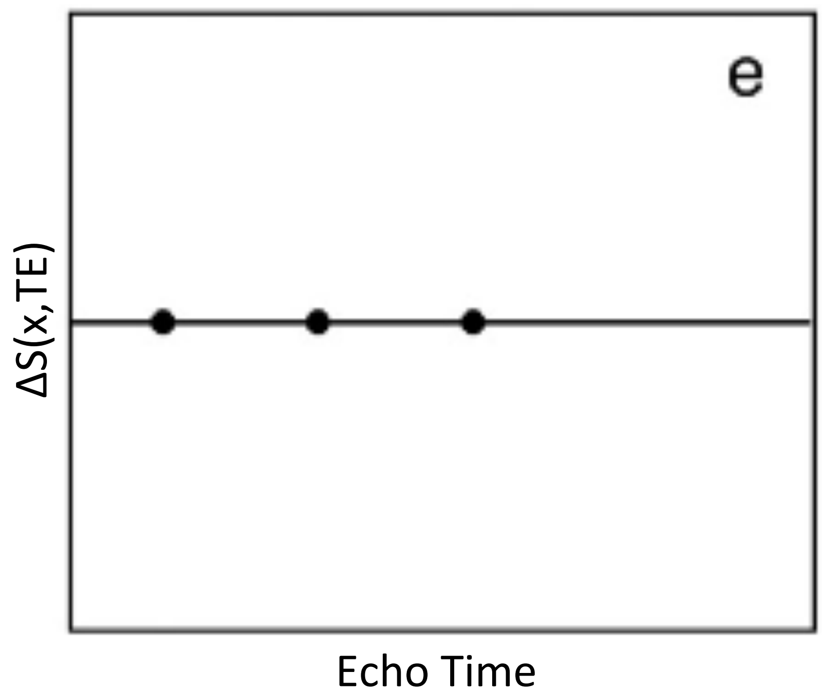
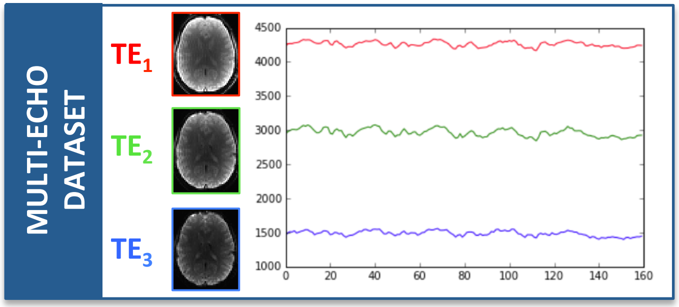
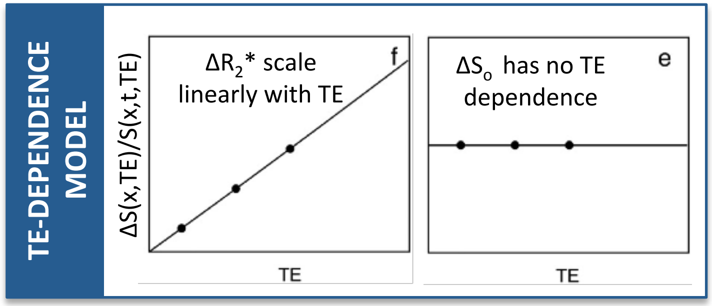
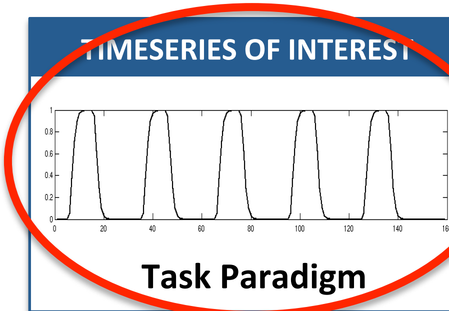


Kundu et al., NeuroImage 2012

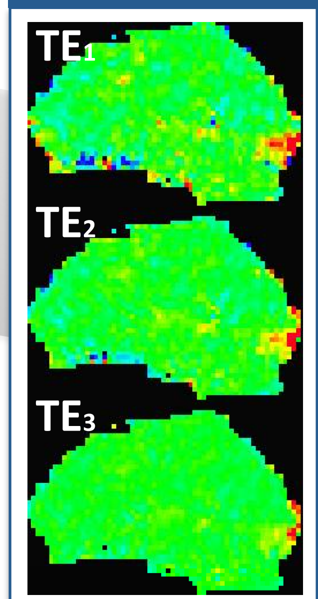
Echo Time (TE) Dependence Analysis



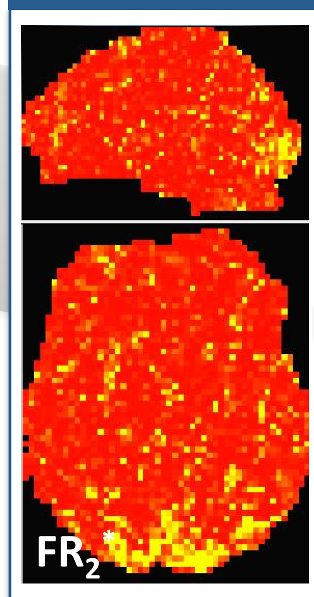




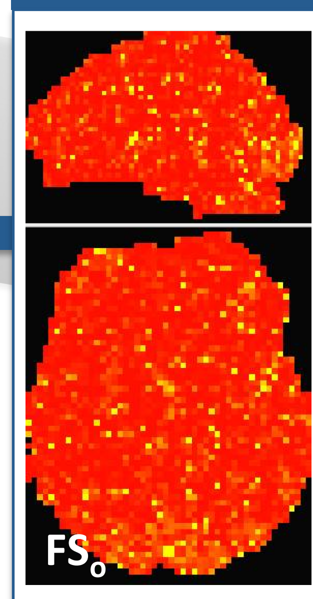
[1] Voxel-wise Fit against all TEs



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



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



[4] Compute Avg. Metric for each model

$$\kappa = \sum_{AllVoxels} z_v^2 F_{v,R_2^*} \Big/ \sum_{AllVoxels} z_v^2 = 98.41$$

$$\rho = \sum_{AllVoxels} z_v^2 F_{v,S_o} \Big/ \sum_{AllVoxels} z_v^2 = 26.02$$

Kundu et al., NeuroImage 2012

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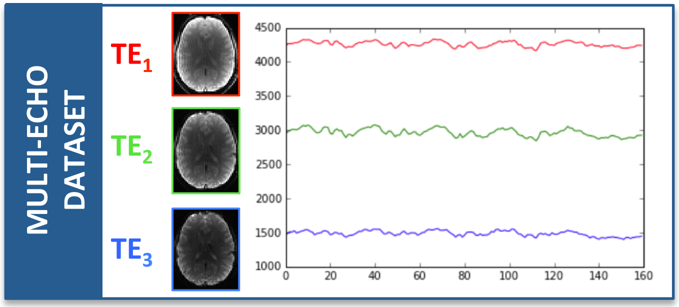
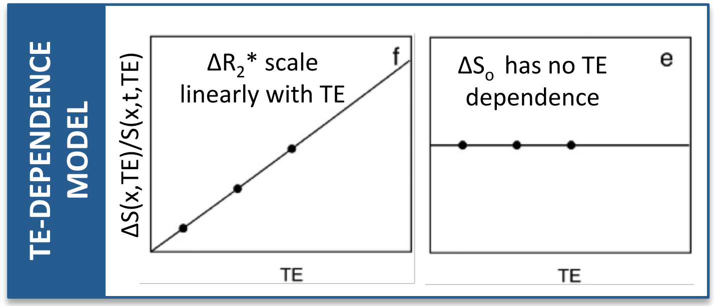
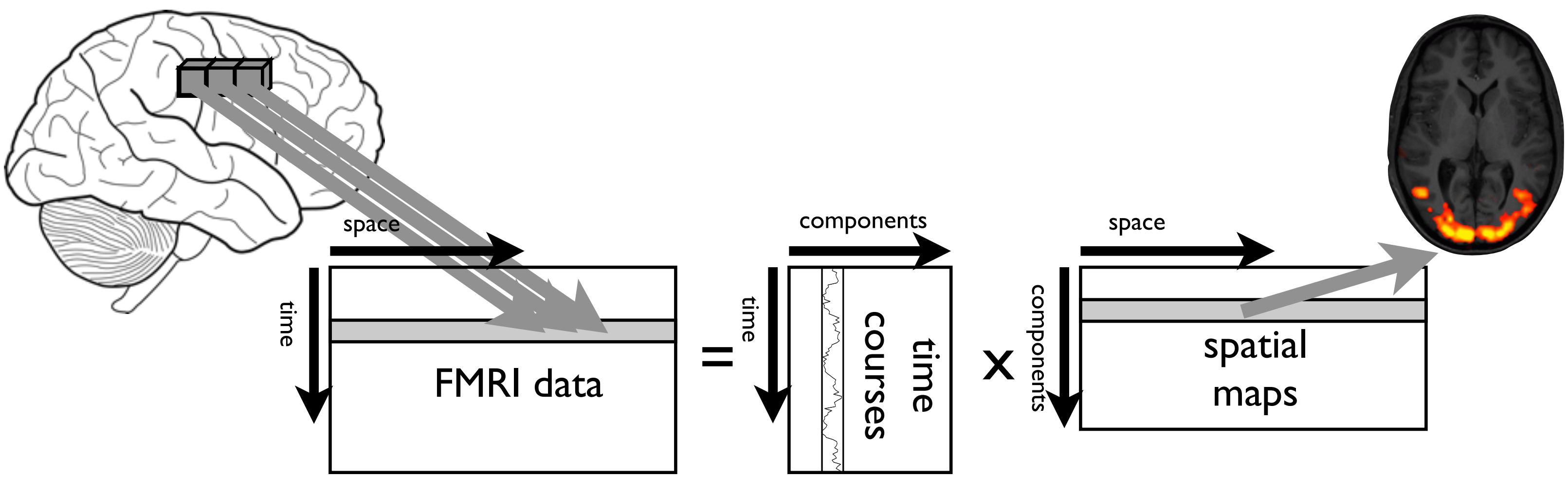
ME-ICA Denoising: Introduction





TIMESERIES OF INTEREST

ICA Representative Timeseries

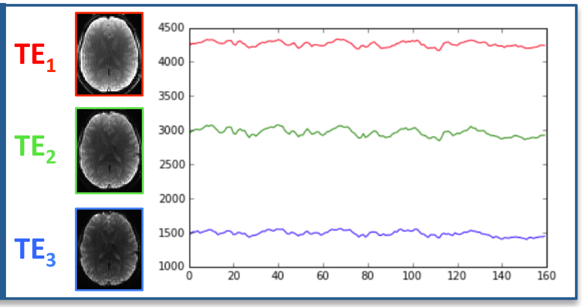


Data is represented as a 2D matrix and decomposed into factor matrices (or modes)

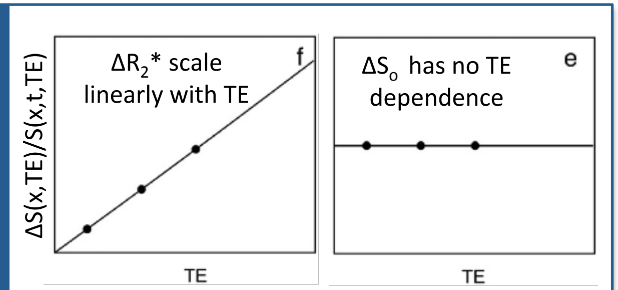
FSL Documentation: http://fsl.fmrib.ox.ac.uk/fslcourse/lectures/melodic.pdf

ME-ICA Denoising: Introduction

MULTI-ECHO DATASET

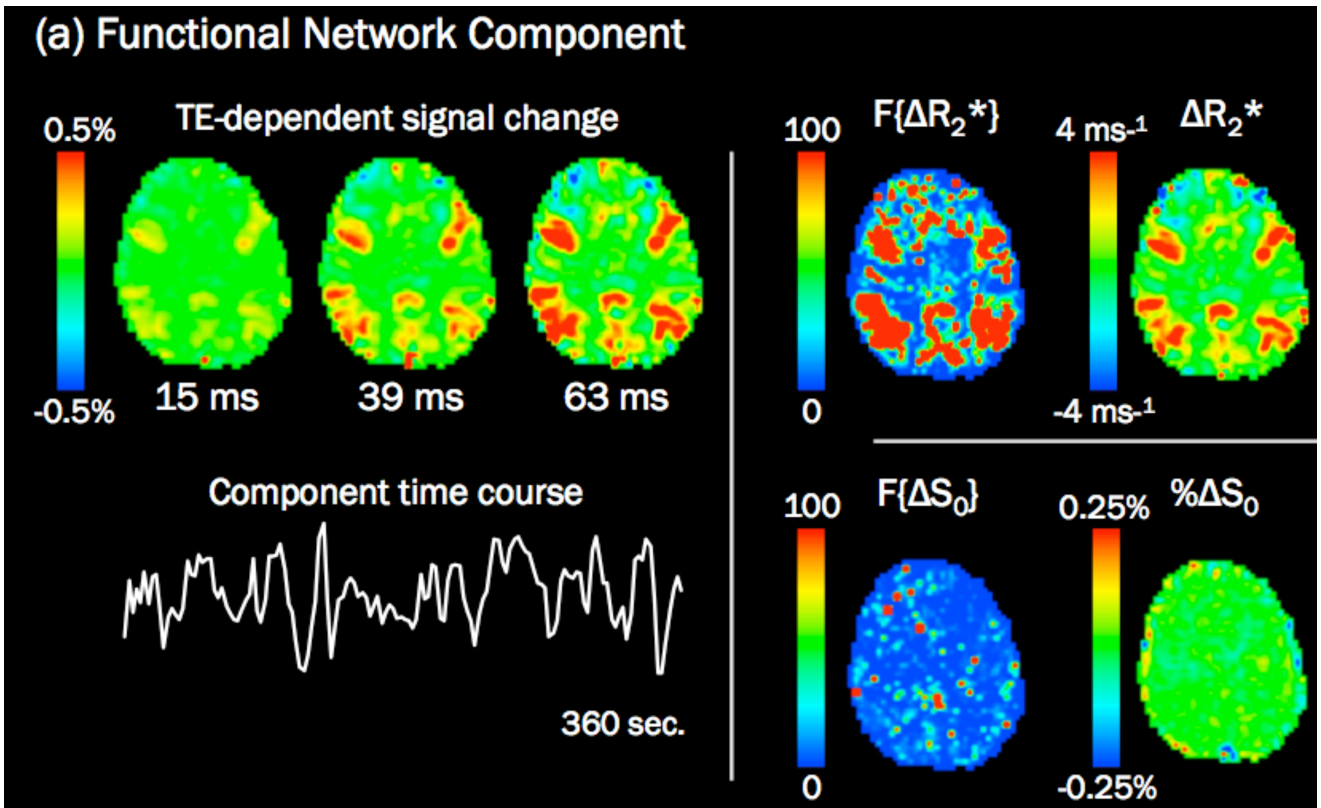


TE-DEPENDENCE MODEL



TIMESERIES OF INTEREST

ICA Representative Timeseries

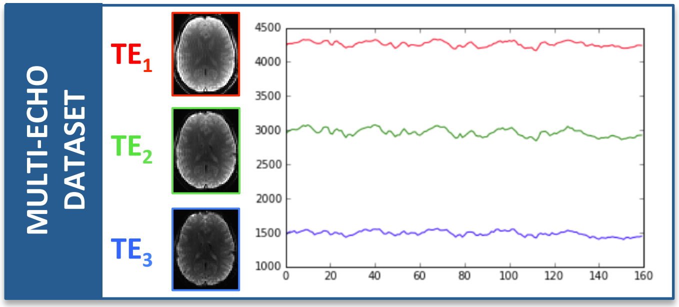


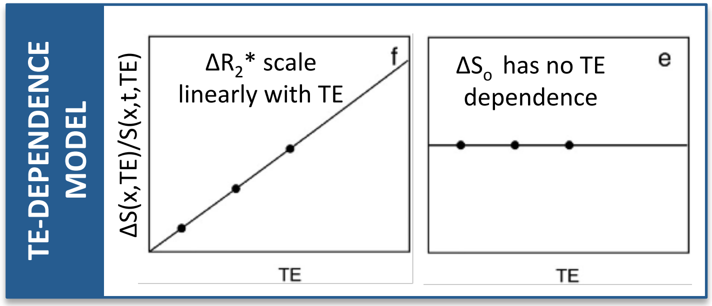
Kappa (κ) = 210

Rho (ρ) = 10

Kundu et al., NeuroImage 2012

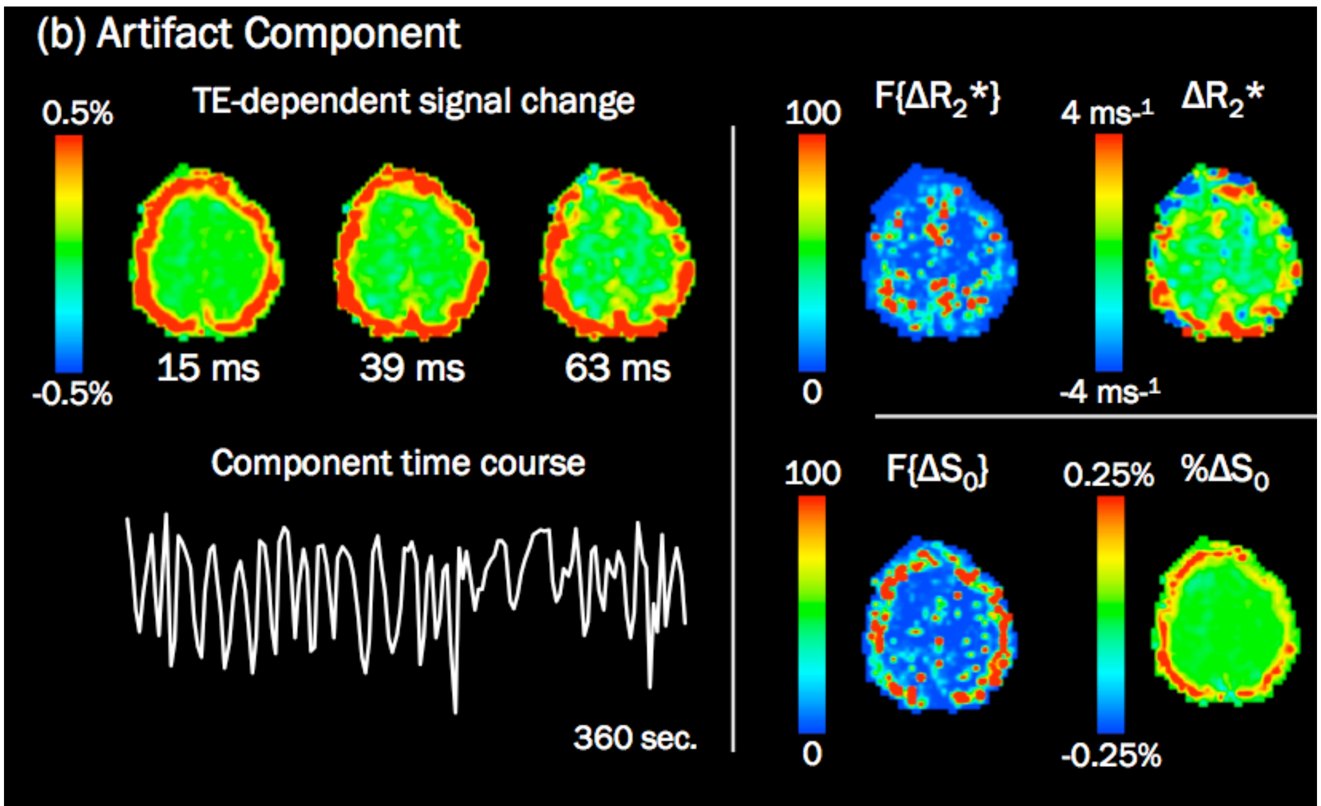
ME-ICA Denoising: Introduction





TIMESERIES OF INTEREST

ICA Representative Timeseries

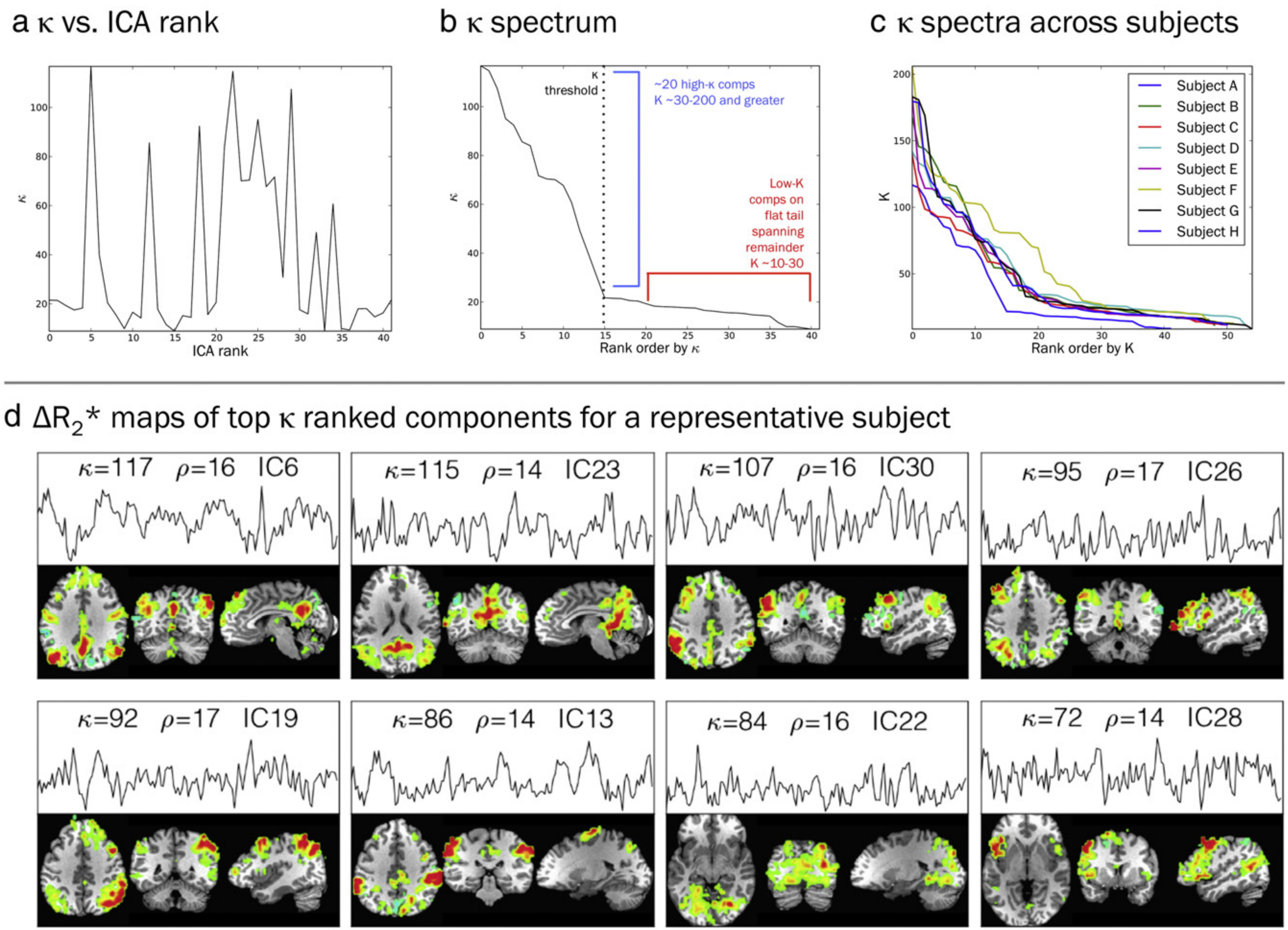


Kappa (κ) = 32

Rho (ρ) = 81

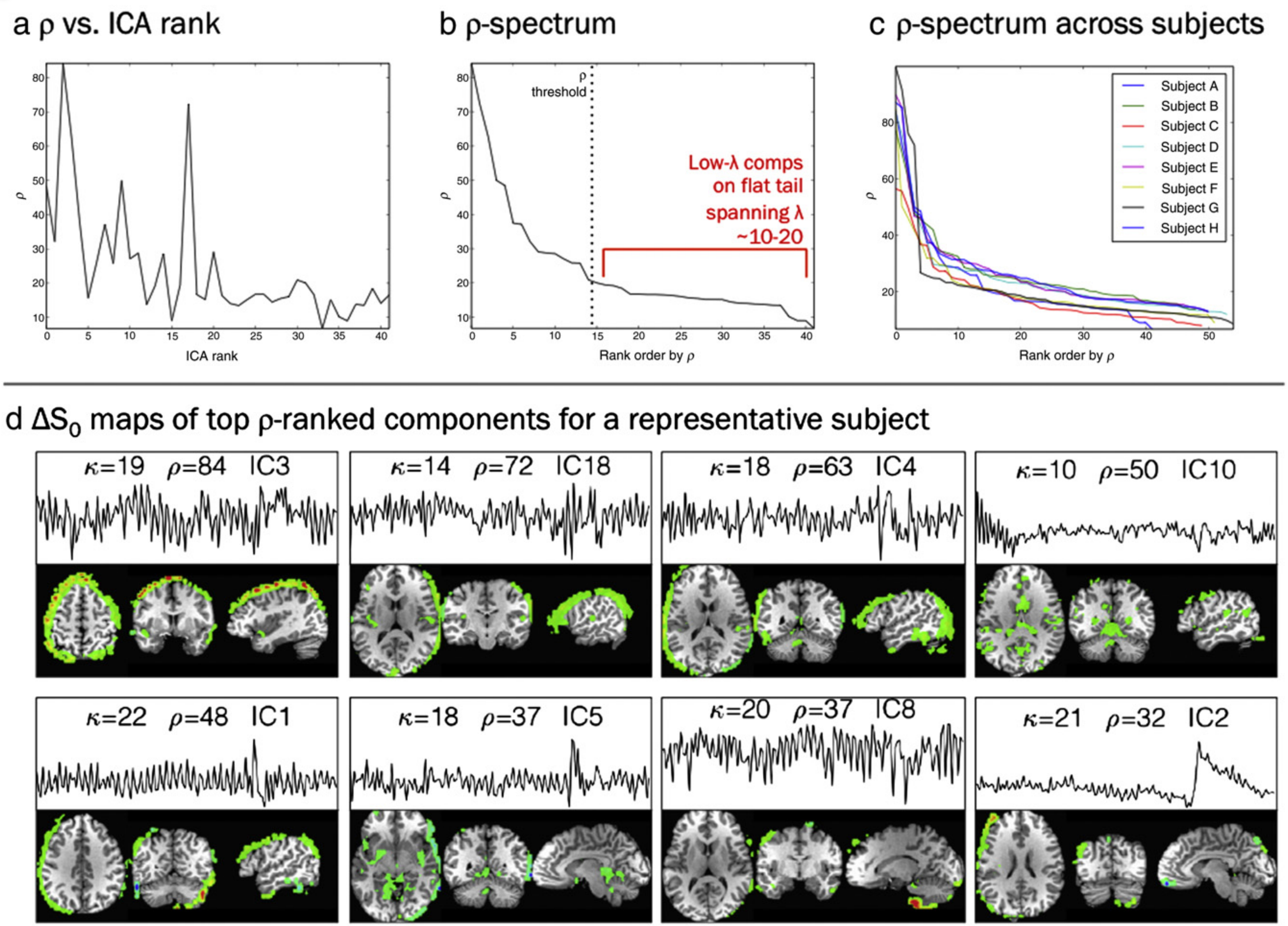
Kundu et al., NeuroImage 2012

ME-ICA Denoising: Introduction



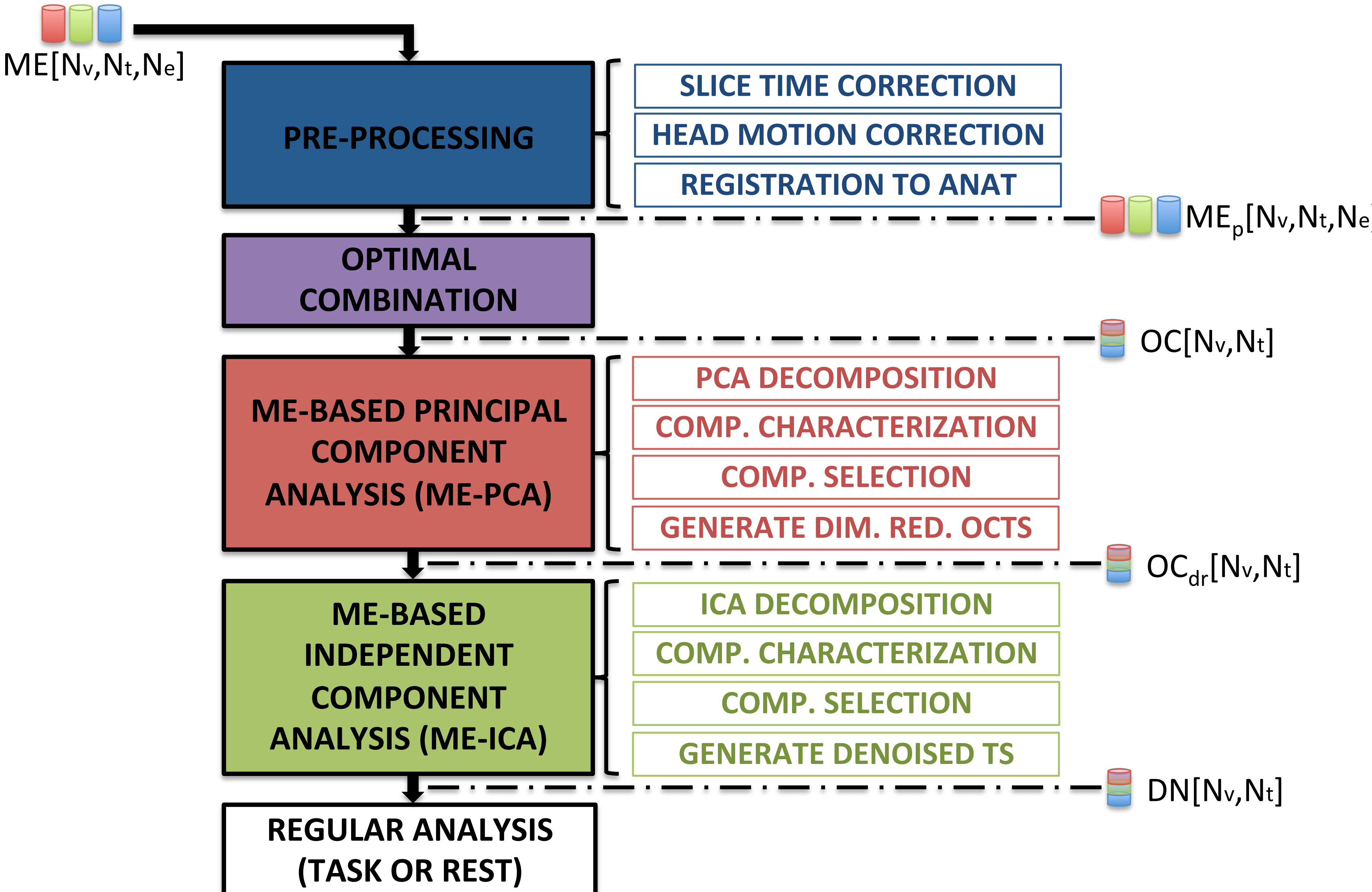
Kundu et al., NeuroImage 2012

ME-ICA Denoising: Introduction



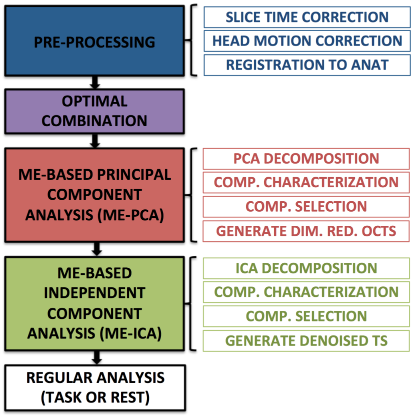
Kundu et al., NeuroImage 2012

ME-ICA Denoising: Pipeline



Kundu et al., NeuroImage 2012

ME-ICA Denoising: Pipeline



ME-PCA

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

ME-ICA

- Uses fast-ICA algorithm (spatial independence).
- Component Characterization includes:
  - Variance Explained
  - κ (*"BOLD likeliness"*)
  - ρ (*"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*

ACCEPTED | IGNORED | MID-κ | REJECTED

Denoised Time series

Kundu et al., NeuroImage 2012; Kundu et al. 2013 PNAS; Olafsson et al. NeuroImage 2015

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

ME-ICA Software available with AFNI: http://afni.nimh.nih.gov/afni

Latest experimental versions (P. Kundu) available at: https://bitbucket.org/prantikk/me-ica.git

ME-ICA Denoising: Web Reporting Tool

(Ben Gutierrez) available at: https://github.com/BenGutierrez/Meica_Report

Agenda

❖ **WHAT IS MULTI-ECHO (ME) FMRI**

❖ **WHAT CAN YOU DO WITH ME TIMESERIES**

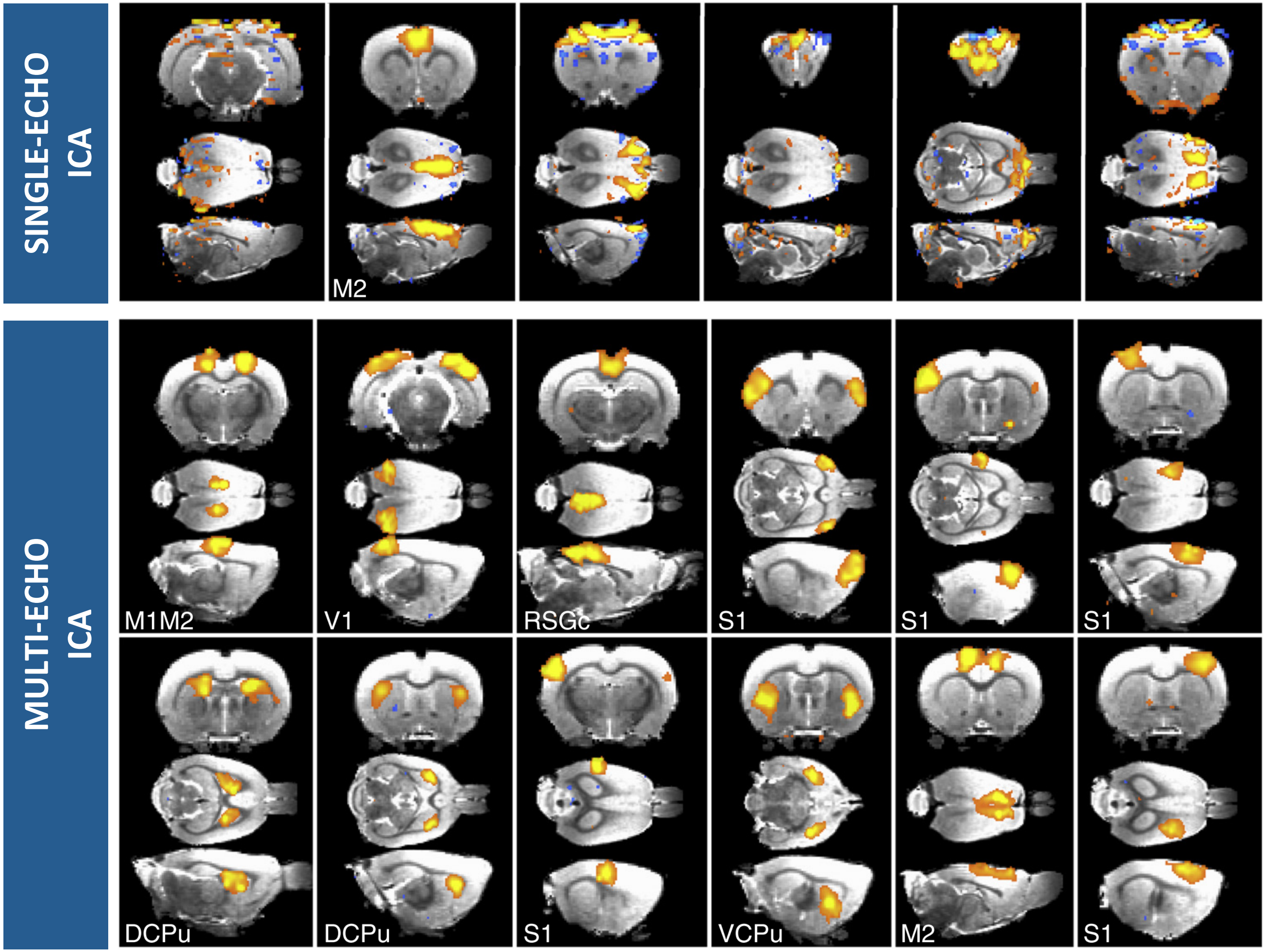
- Compute static S_o and T_2^* Maps
- Compute voxel-wise time-series of S_o (Non-BOLD) and T_2^* (BOLD)
- Combine echoes to improve SNR/spatially equalize functional contrast
- Echo Time Dependence Analysis

❖ **ME-ICA Denoising**

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

❖ **ME-ICA Applications**

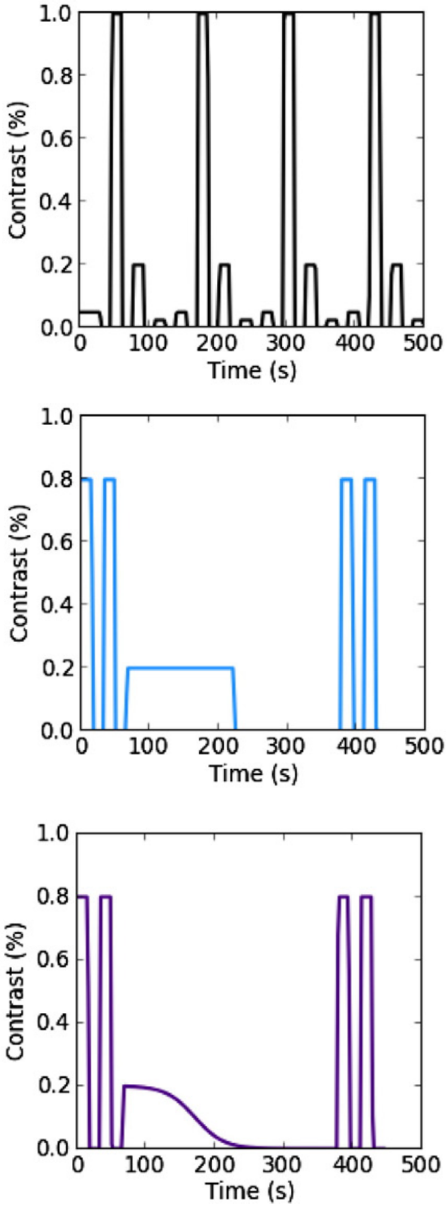
Suitability for ultra-high field fMRI animal studies

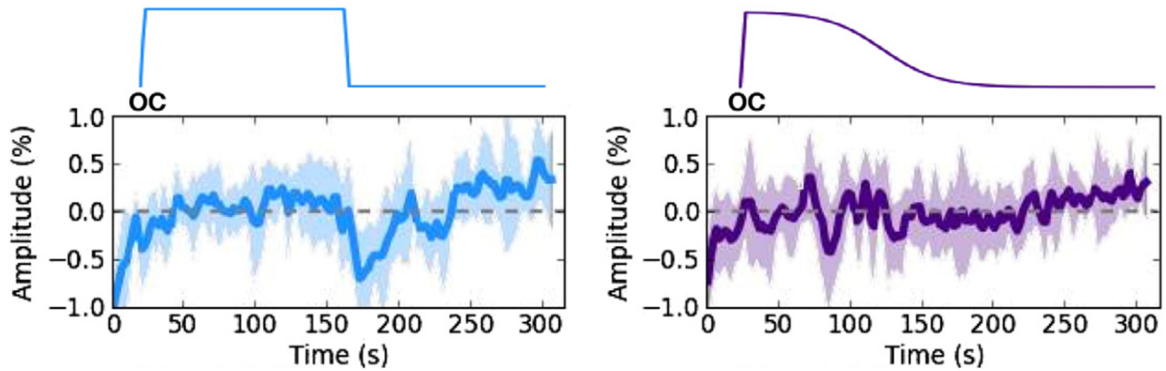


Scanner 11.7T | 0.5x0.5x0.5mm | TR = 3s |
TE=8.25/20.25/32.35 ms | 400 volumes | Rats

Kundu et al., NeuroImage 2014

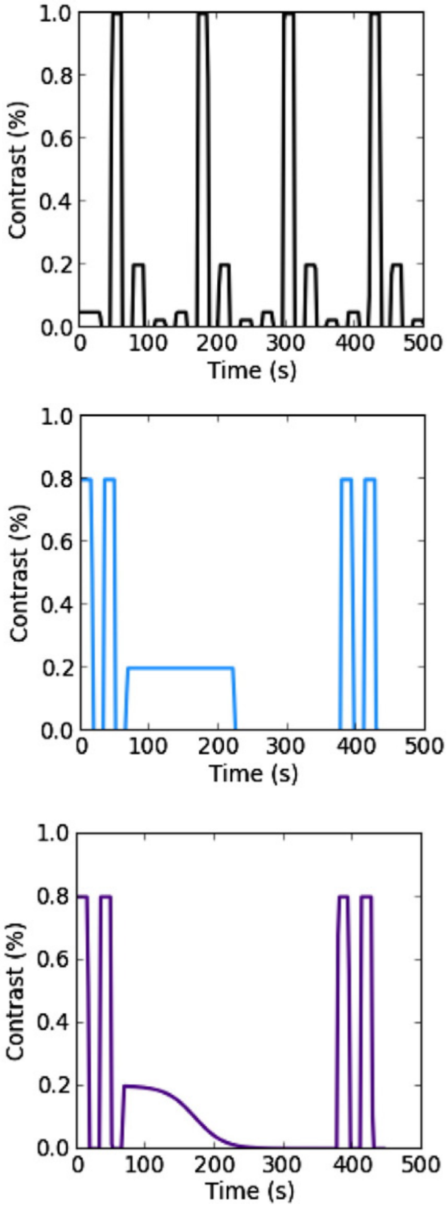
Separate BOLD-like Slow Fluctuations from Scanner Drift

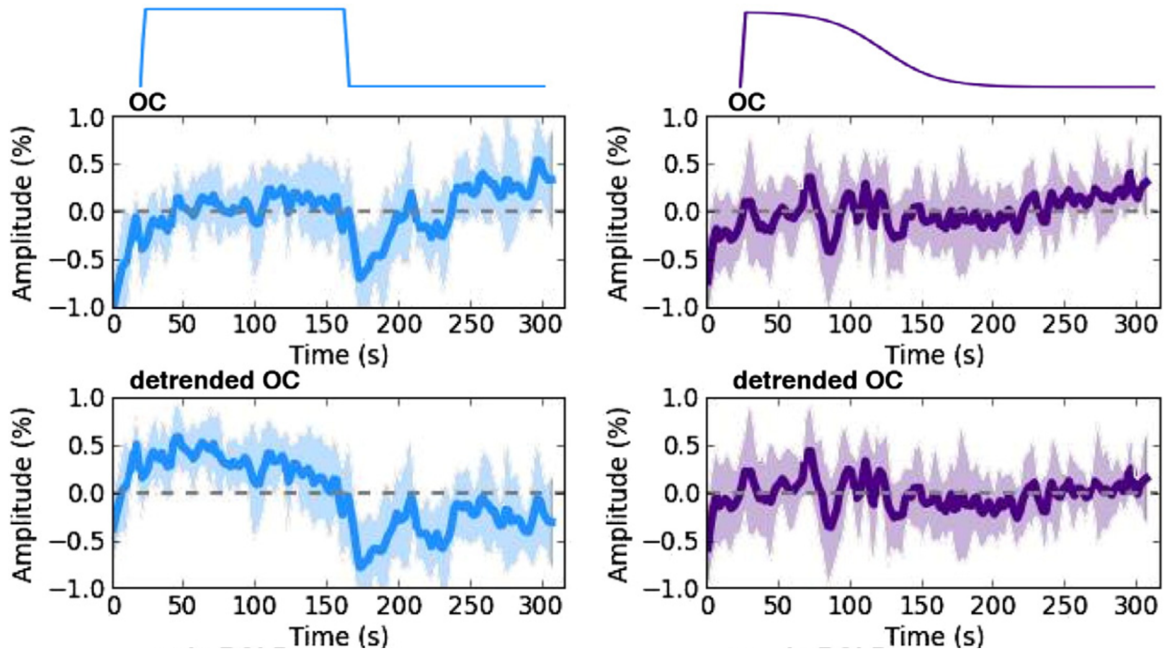




Evans et al., NeuroImage 2015

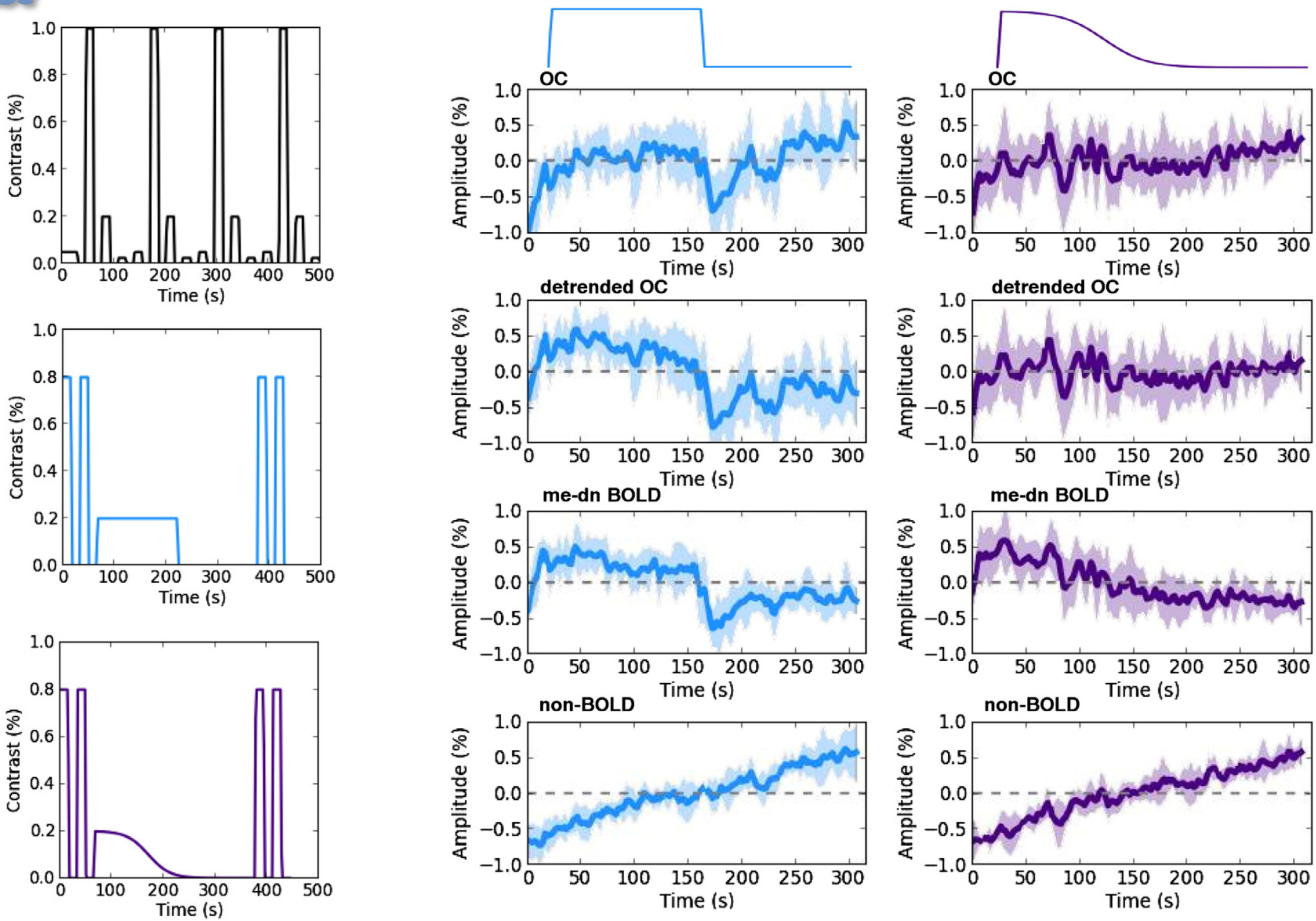
Separate BOLD-like Slow Fluctuations from Scanner Drift





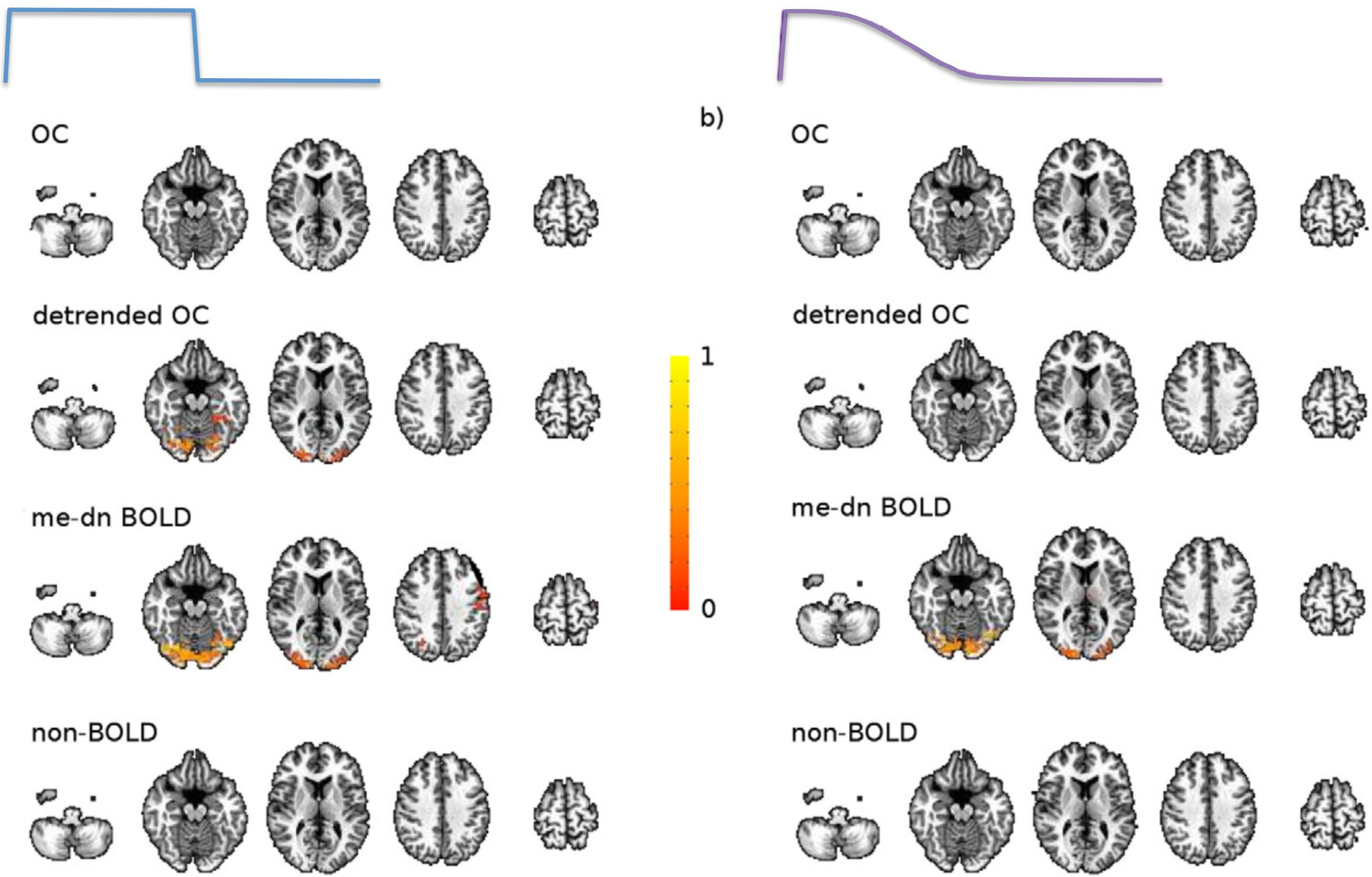
Evans et al., NeuroImage 2015

Separate BOLD-like Slow Fluctuations from Scanner Drift



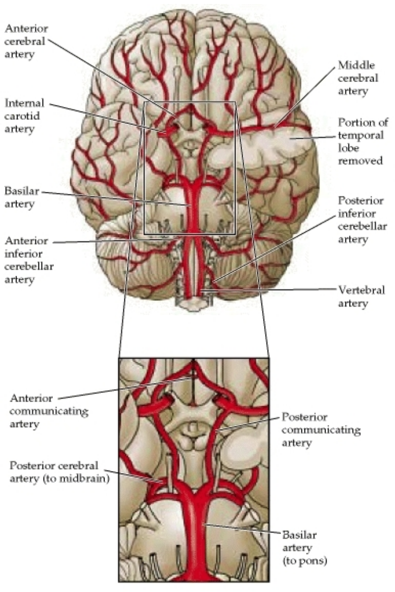
Evans et al., NeuroImage 2015

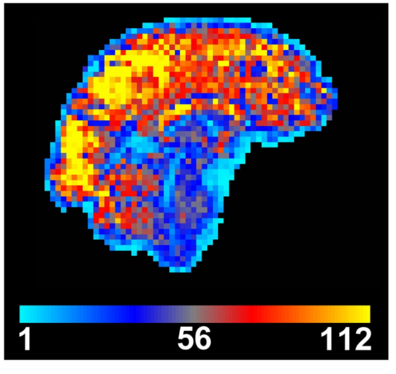
Separate BOLD-like Slow Fluctuations from Scanner Drift



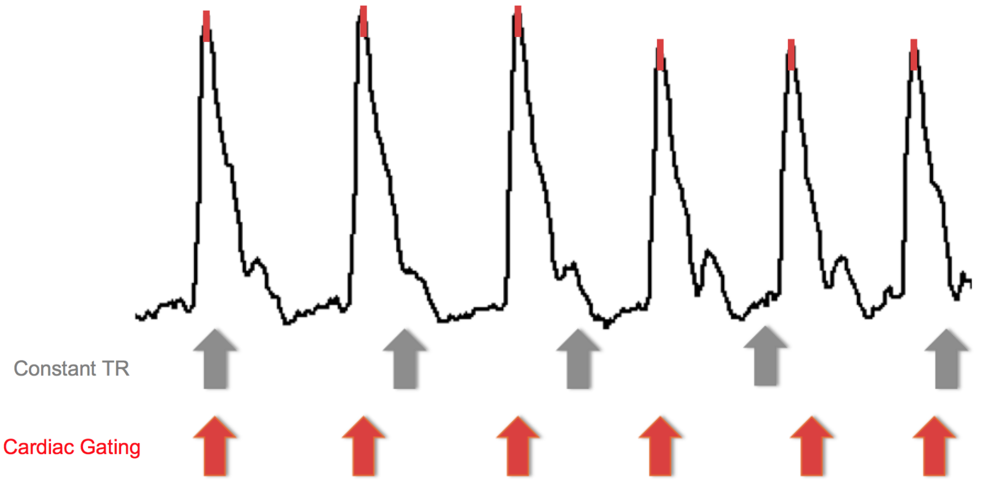
Evans et al., NeuroImage 2015

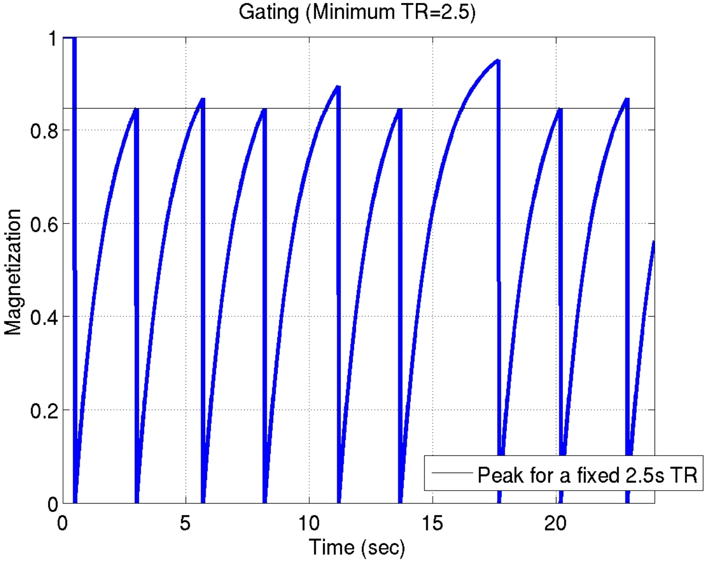
Alternative Approach for Brainstem Imaging: Gated fMRI + ME-ICA



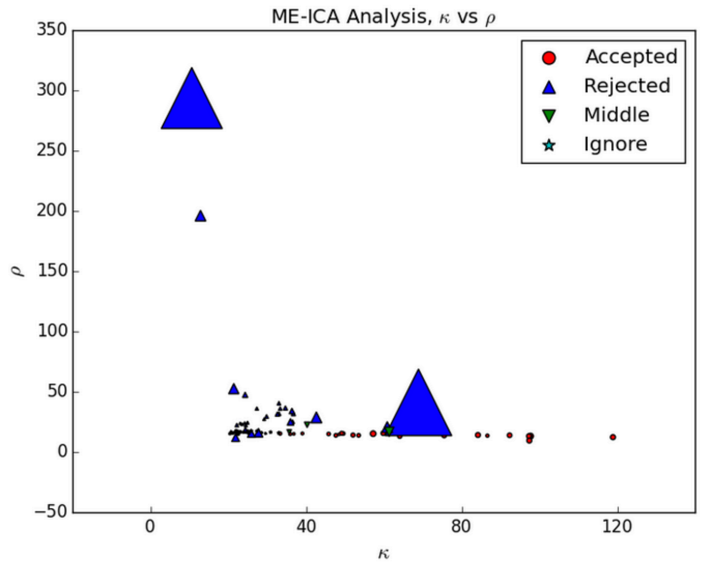


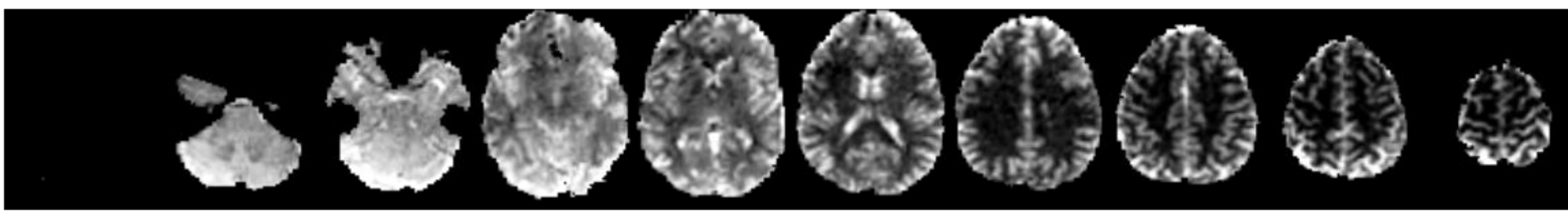
Brooks et al. 2014

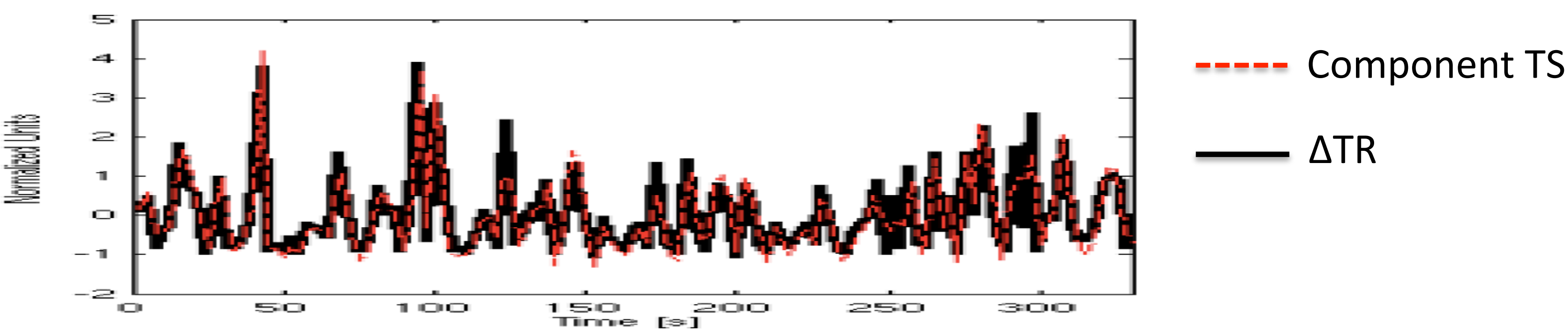




Alternative Approach for Brainstem Imaging: Gated fMRI + ME-ICA



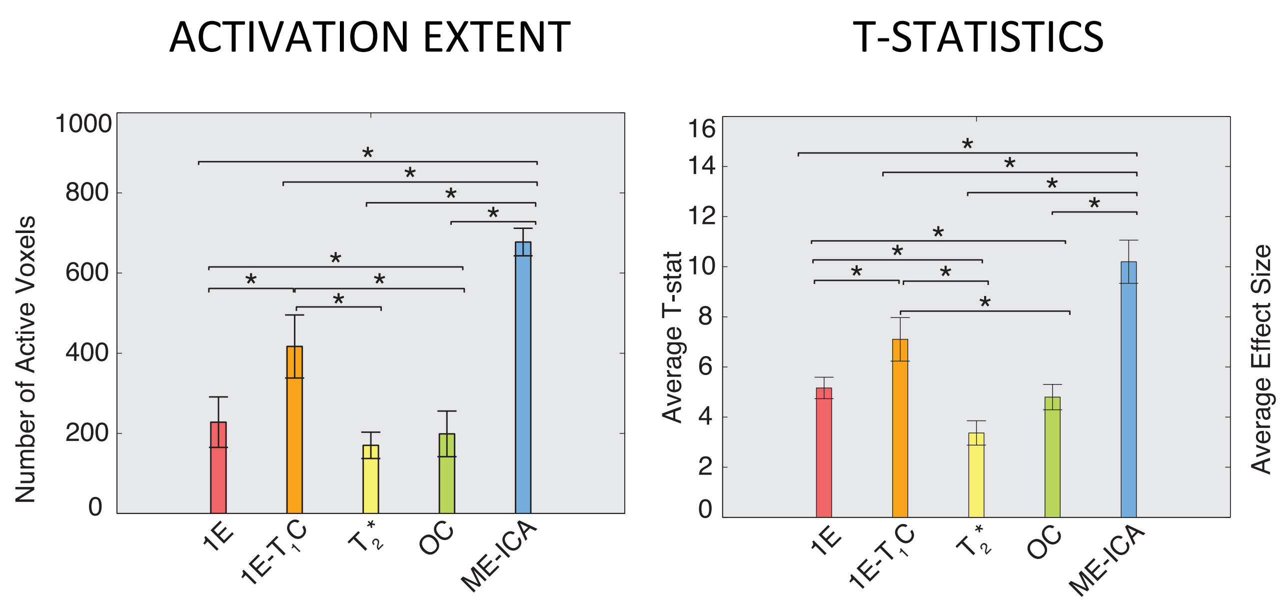


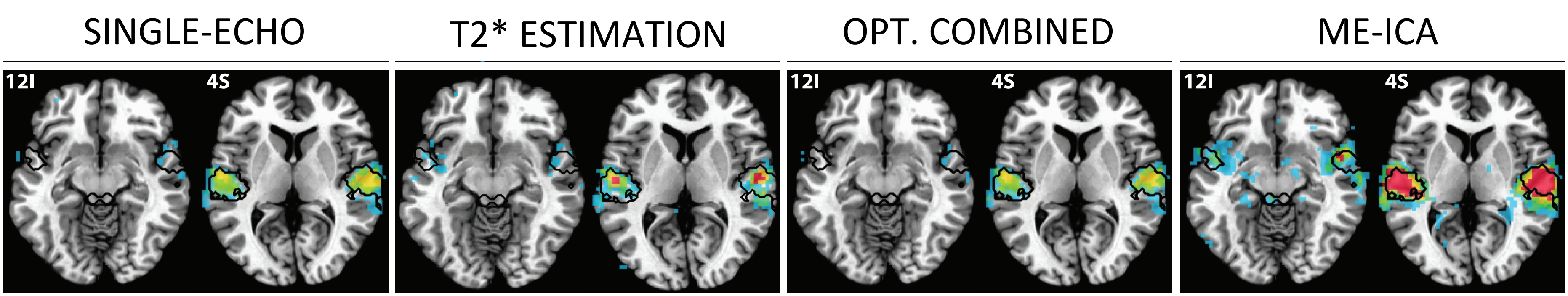


Gonzalez-Castillo et al. 2015 (Under Review)

Alternative Approach for Brainstem Imaging: Gated fMRI + ME-ICA

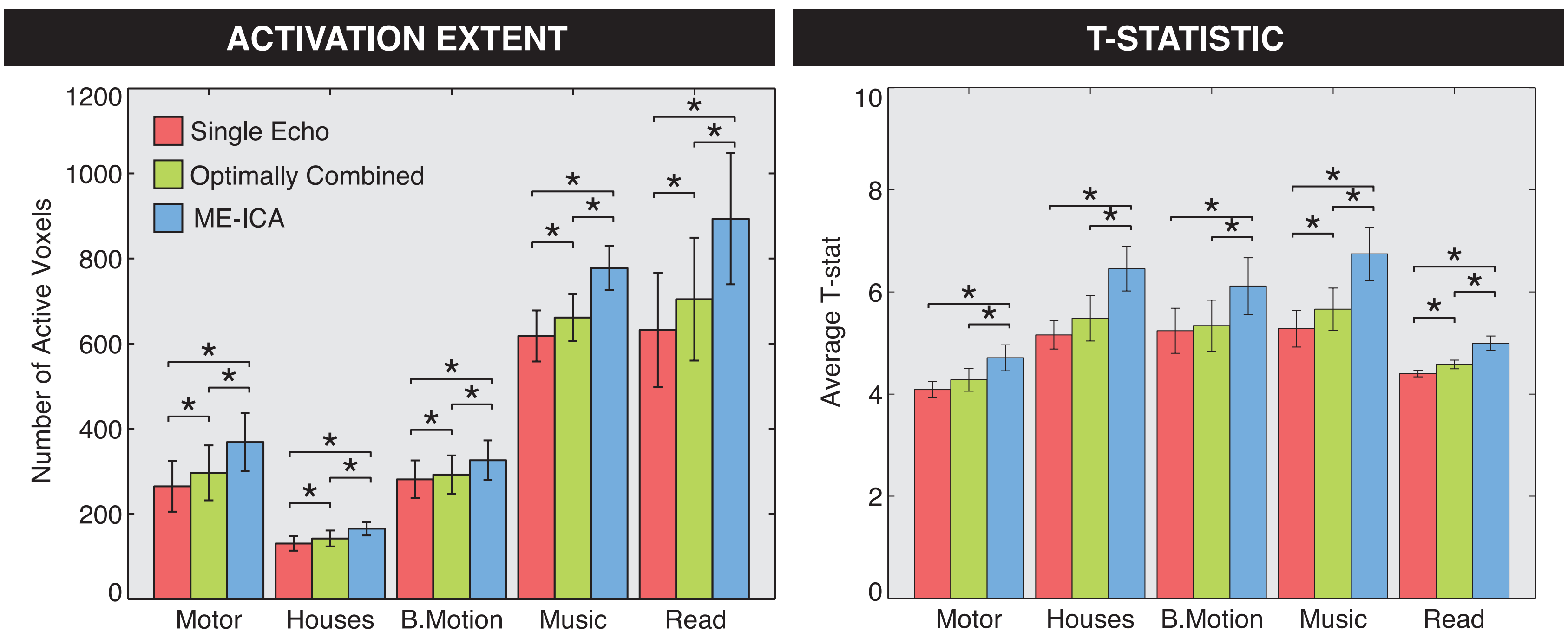
CARDIAC-GATED





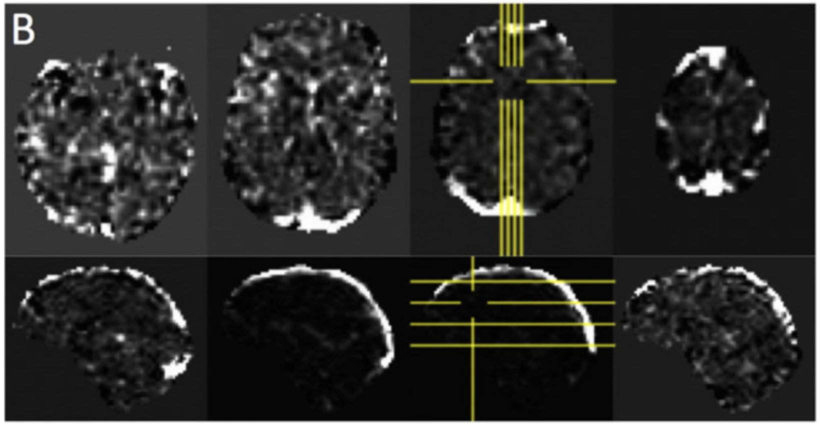
Gonzalez-Castillo et al. 2015 (Under Review)

ME+ICA for Rapid Event Related fMRI

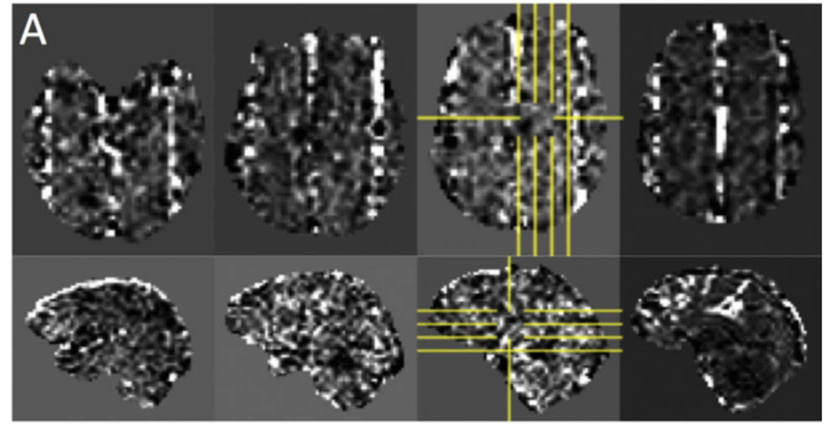


Gonzalez-Castillo et al. 2015 (Under Review)

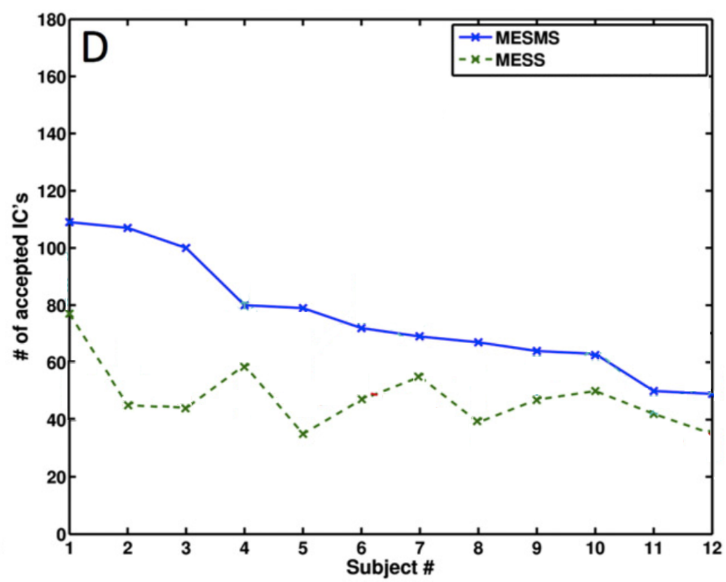
Multi-Echo & Simultaneous Multi-Slice (MESMS)

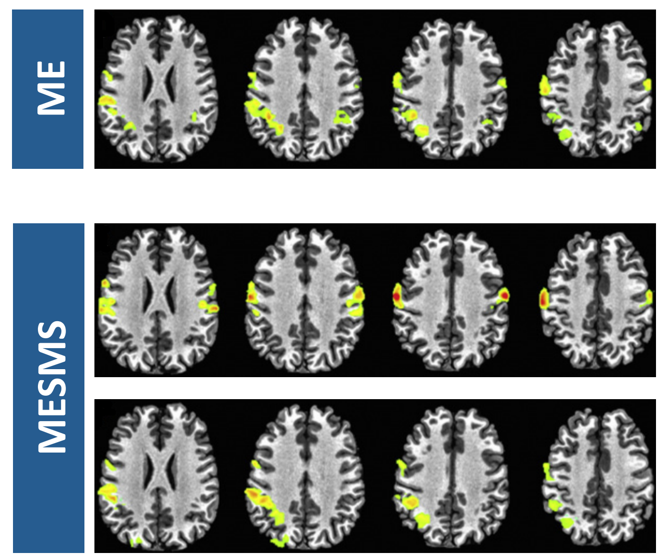


Non-BOLD Component: Vascular Pulsation



Non-BOLD Component: MSS Artifact





Number of BOLD-like components significantly larger for MESMS

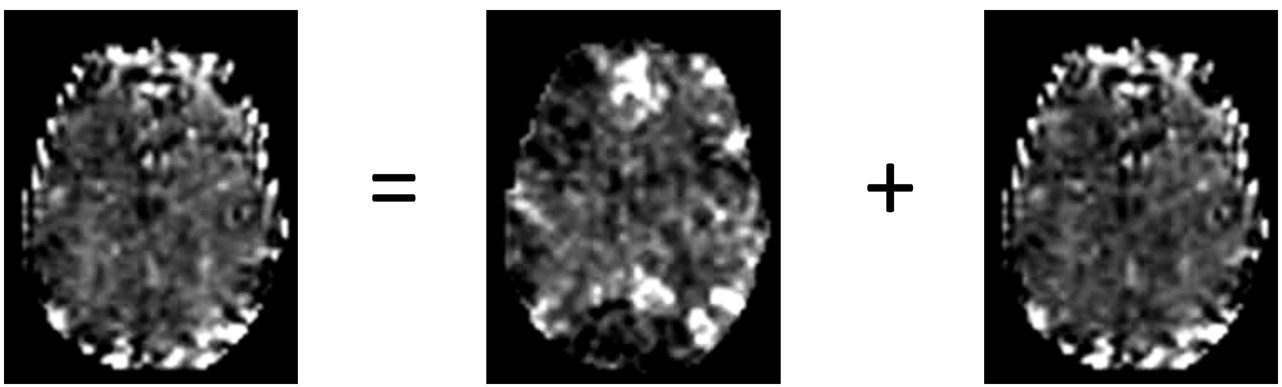
Olafsson et al., NeuroImage 2015

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.



ME-fMRI = ACCEPTED + REJECTED

Kundu et al., NeuroImage 2012

Acknowledgements

Section on Functional Imaging Methods

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