

Multi-echo fMRI

Daniel Handwerker

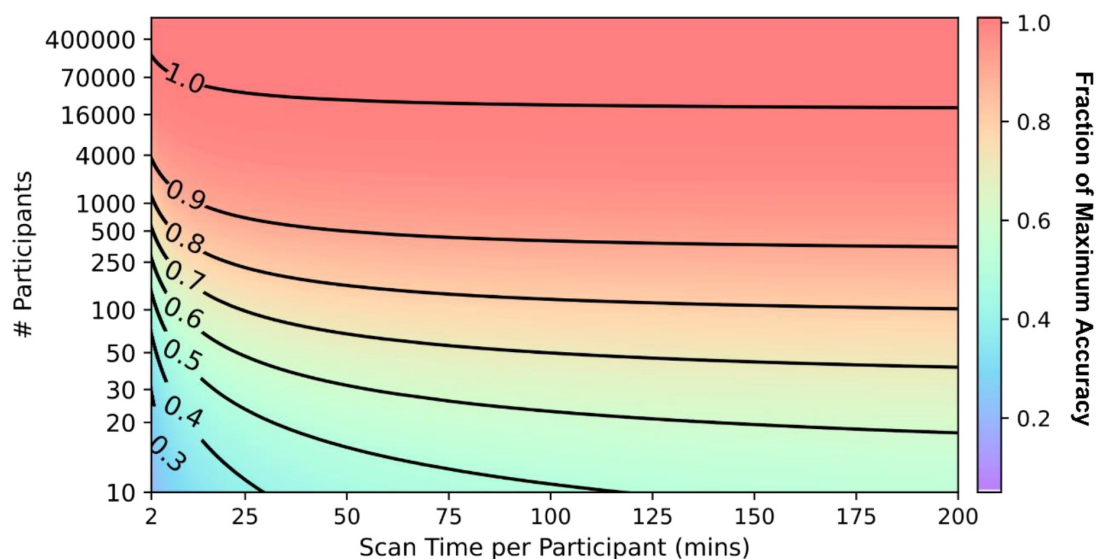
Section on Functional Imaging Methods
National Institute of Mental Health

July 16, 2024



National Institute
of Mental Health

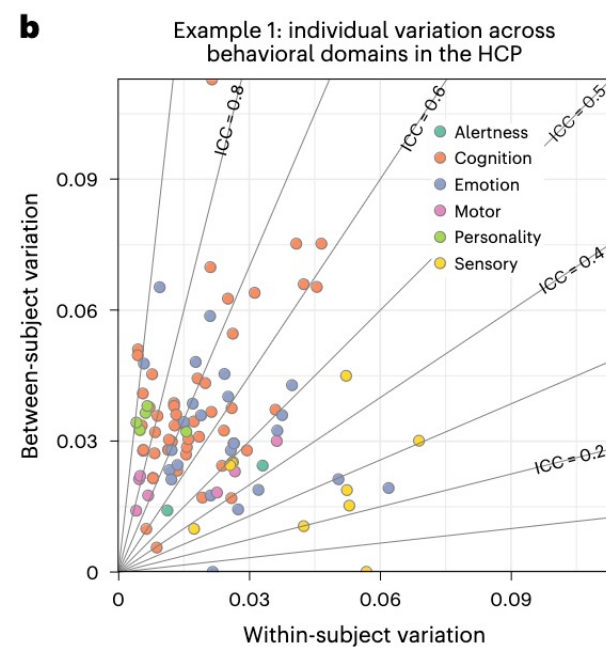
Many paths to better fMRI



Ooi et al “MRI economics: Balancing sample size & scan duration in BWAS”
<https://www.biorxiv.org/content/10.1101/2024.02.16.580448v1>

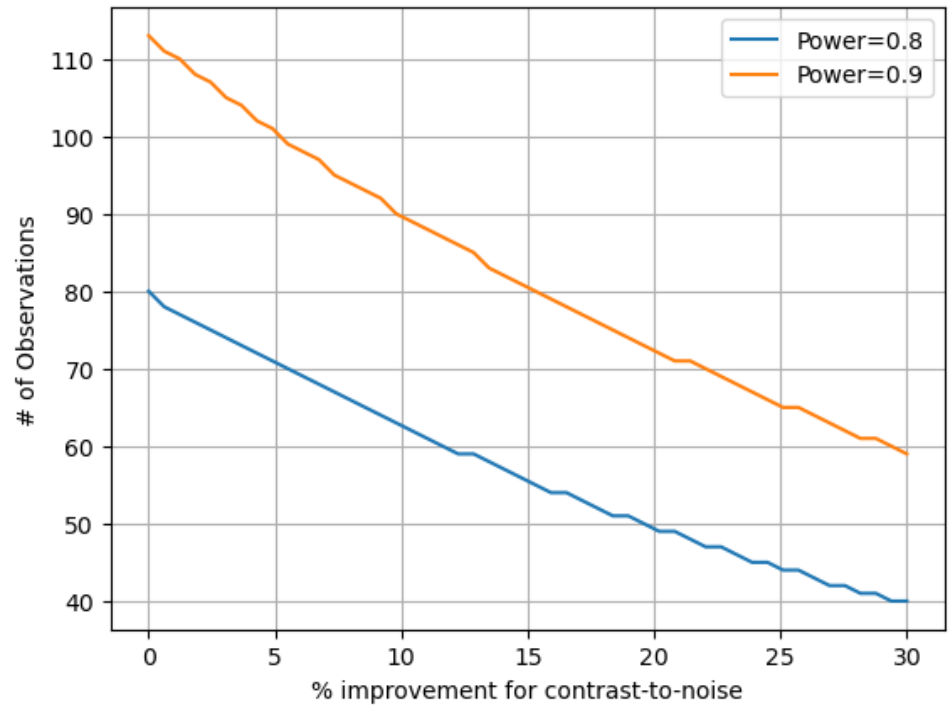
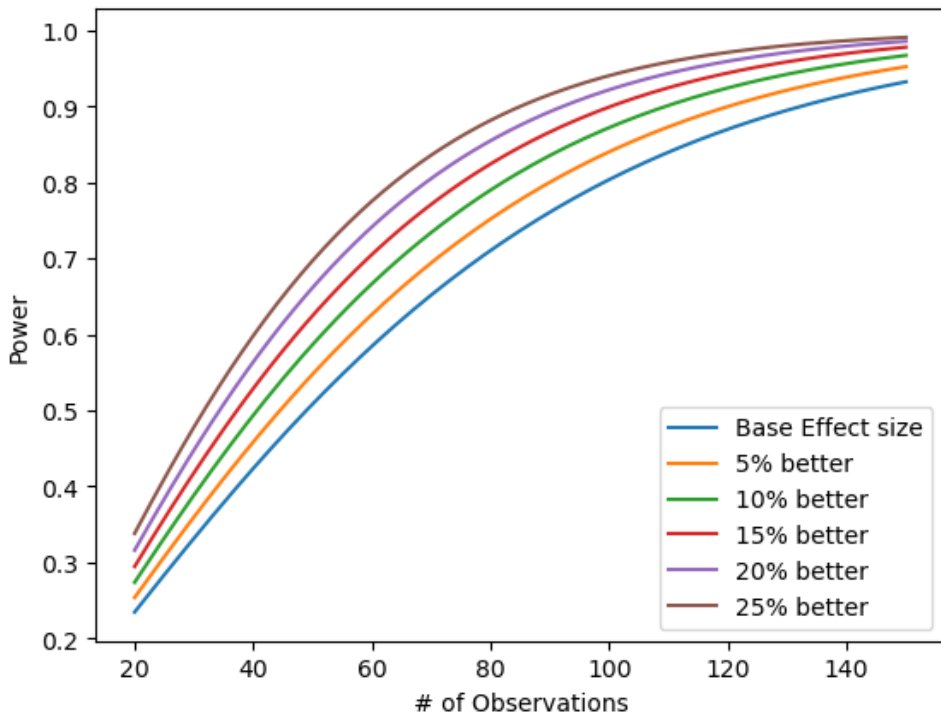
Following earlier work by Marek et al 2022, Nature

- Many discussions of improving fMRI focus on scan duration and sample size
- Even when within & between subject variation is discussed, it’s often presented as something we have limited control over



Xu et al. Nature Methods 2023

Data quality also matters!



A 10% improvement in contrast-to-noise could mean a statistical power of 0.8 is possible with 63 vs 80 subjects

Why I'm interested in multi-echo fMRI

- I want fMRI to directly help people
- Clinically useful scans require better data
- For population studies, better data → lower sample size
- Multi-echo is not the only path to better data
 - but it already helps and has the potential to address key road blocks towards better data

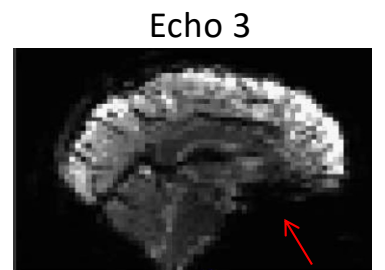
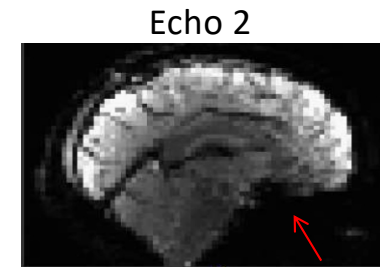
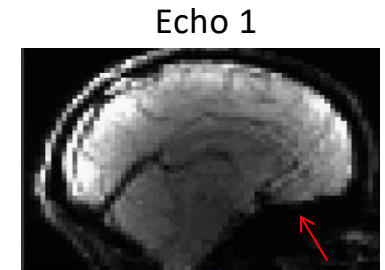
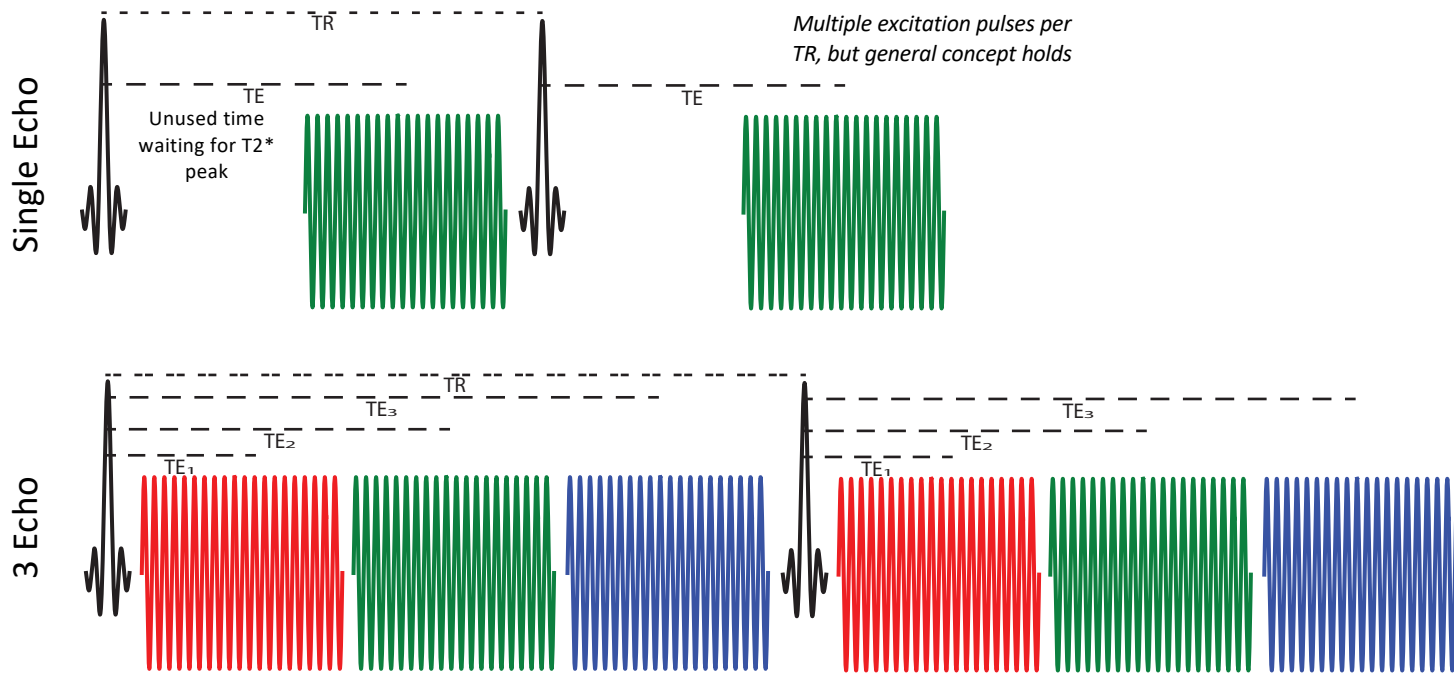
Overview

- Intro to multi-echo fMRI
- Multi-echo fMRI for noise removal
- A few examples of how multi-echo can help
- Considerations for acquisition
- tedana multi-echo software & community
 - “TE-dependent analysis of multi-echo fMRI with tedana”
JOSS 2021
 - How to contribute

Talks with pdfs and links to recordings: <https://fmrif.nimh.nih.gov/index.php/SummerCourse>

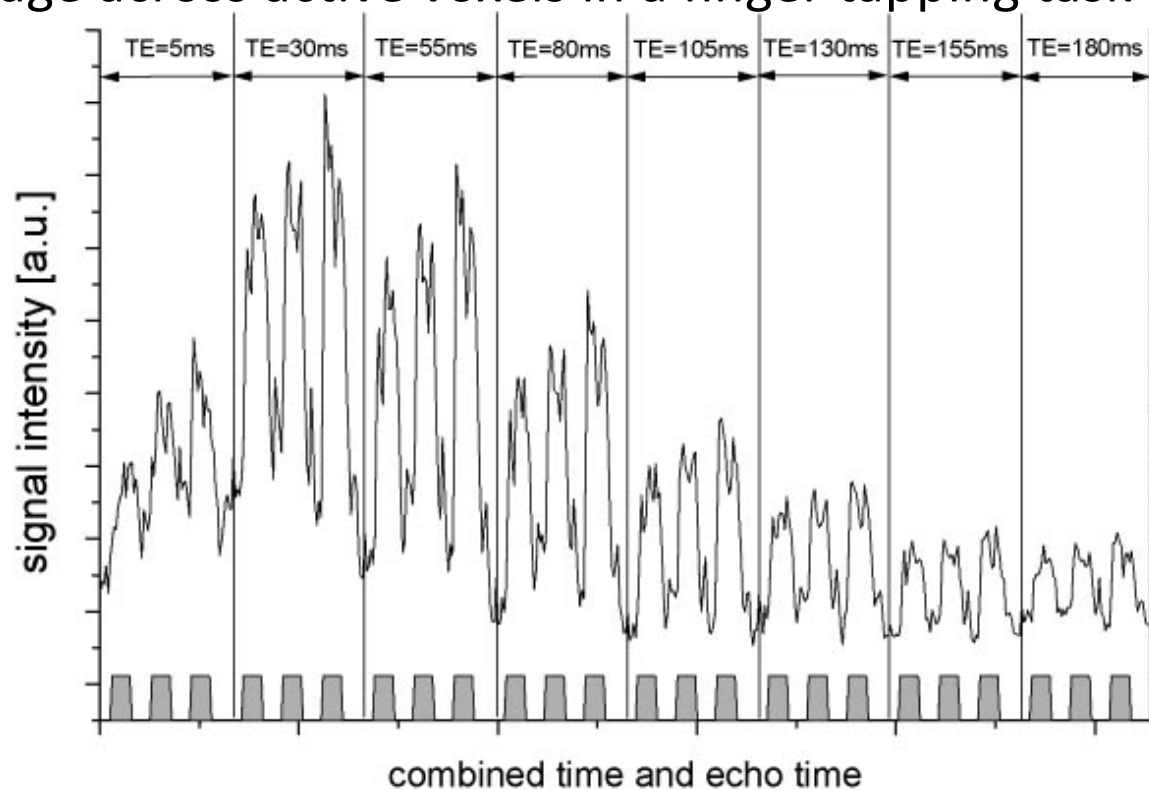
Recordings: <https://www.youtube.com/@nimhcmn>

What is multi-echo fMRI?



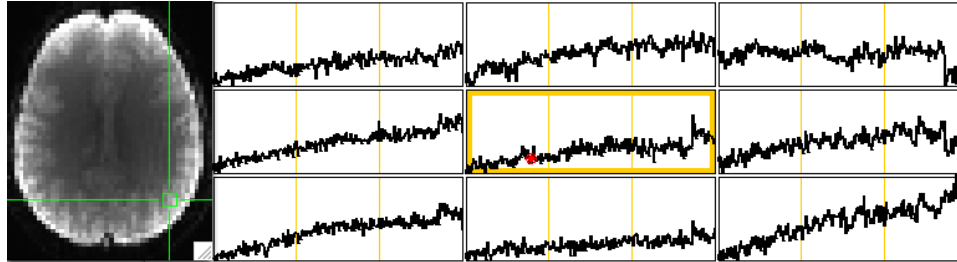
fMRI response magnitudes by echo time

Average across active voxels in a finger tapping task at 3T



Barth et al NMR Biomed 2001, p484

A bit of physics & math



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

Echo time dependence

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

$$R_2^* = \frac{1}{T_2^*}$$

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

Captures local fluctuations in field inhomogeneity (including BOLD)

- More math: Javier Gonzalez-Castillo's multi-echo fMRI talk from this series in 2018: <https://www.youtube.com/watch?v=83bavs4rIUg> (Thank you Javier for some slides)
- Appendix A of Olafsson, Kundu et al NeuroImage 2015
- https://me-ica.github.io/multi-echo-data-analysis/content/TE_Dependence.html
- Implementation in tedana: <https://github.com/ME-ICA/tedana/blob/main/tedana/metrics/dependence.py>

“Optimal” weighted combination of the echoes

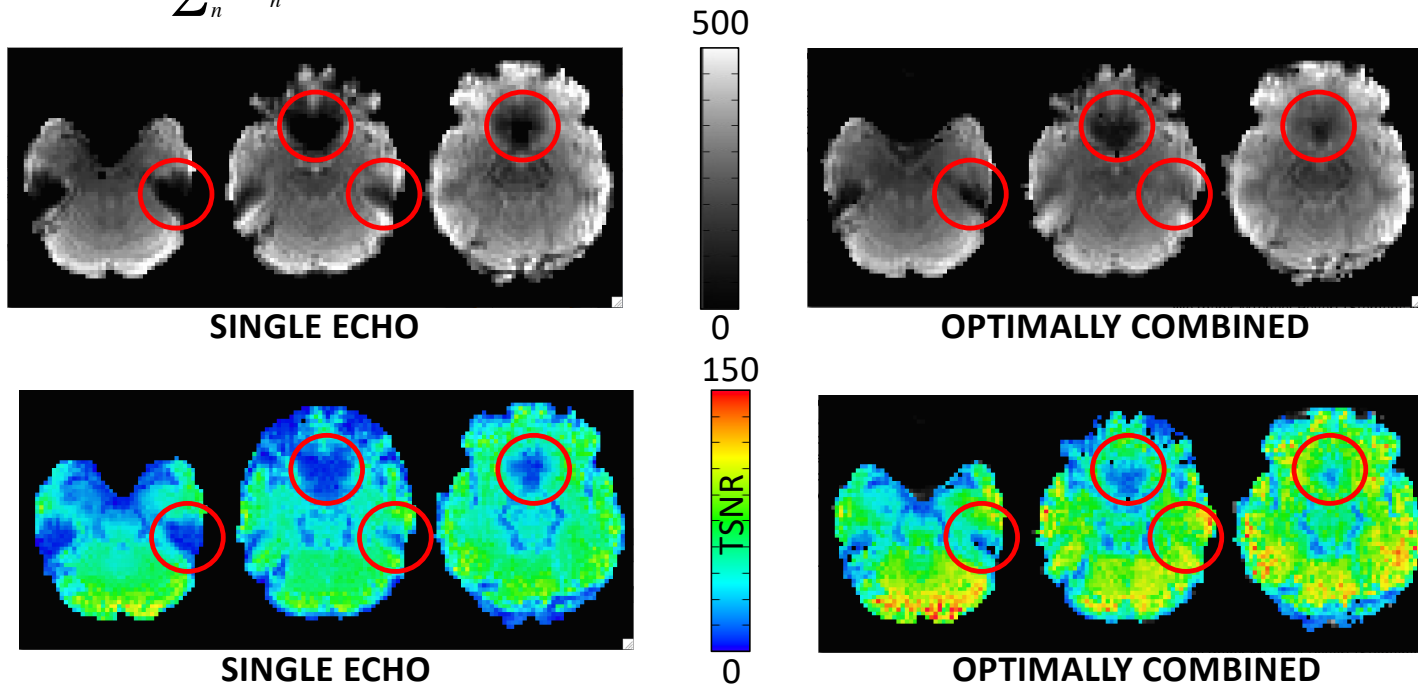
We have N_e pseudo-concurrent measurements

Combine them to reduce uncorrelated white noise present in each individual measurement

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

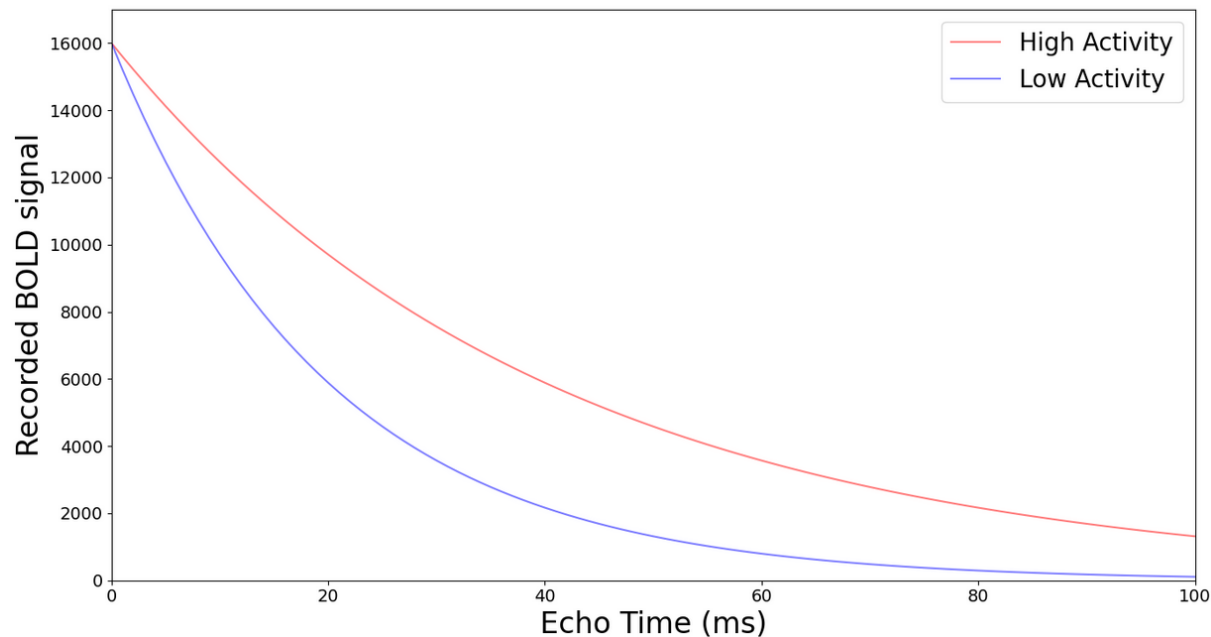
$$w_v(TE_n) = \frac{TE_n e^{-TE_n/T_{2,v}^*}}{\sum_n TE_n \cdot e^{-TE_n/T_{2,v}^*}}$$

- Weighted average of echoes skewed towards T_2^*
- Reduces thermal (measurement) noise and weights towards T_2^* signal
- Recovers signal in some dropout regions
- Straightforward math & reliable improvements
- Automatically calculated in AFNI, fMRIPrep, and tedana



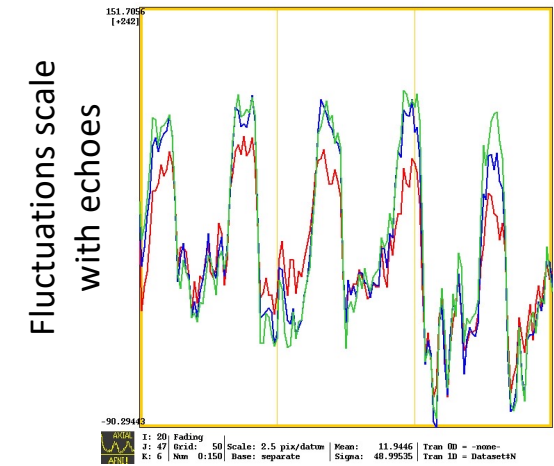
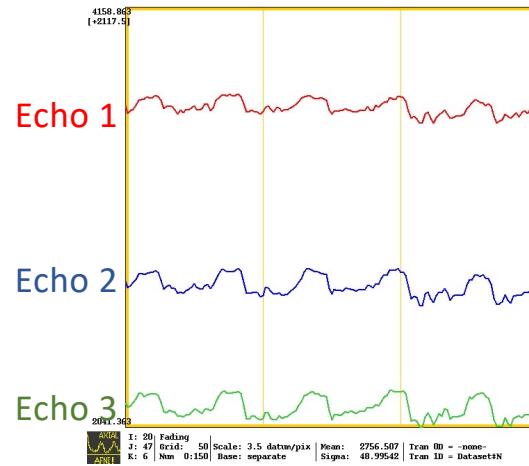
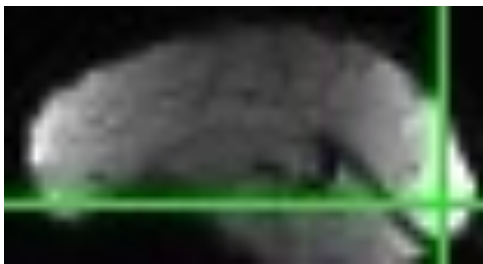
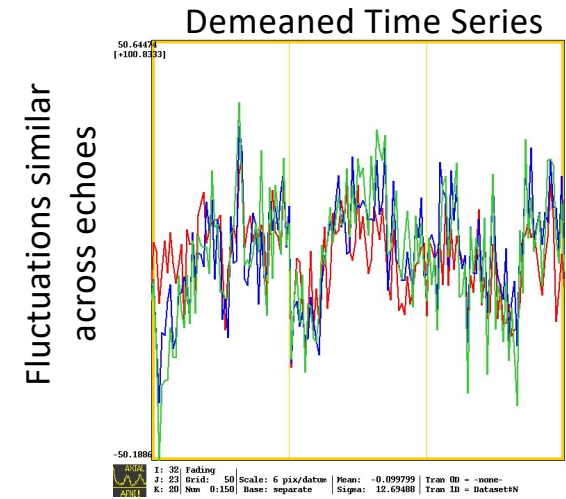
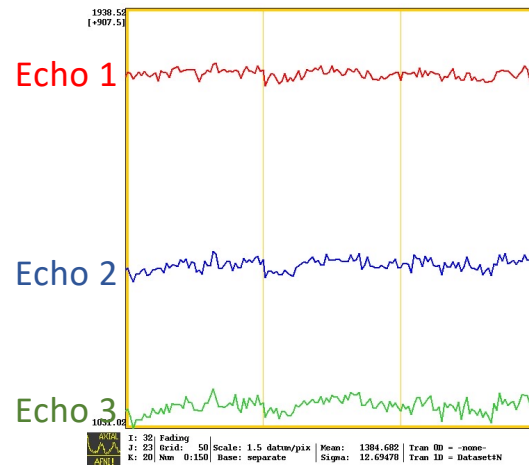
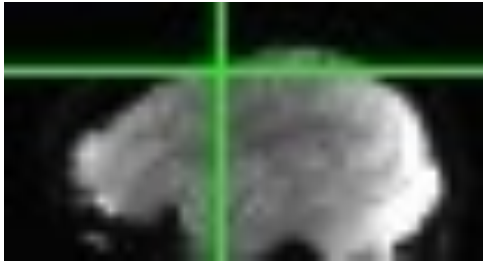
T_2^* is the curve of the decay across echoes

The BOLD signal is a T_2^* change
 S_0 is a change in the TE=0 intercept.



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

Separating S_0 from T_2^* signal



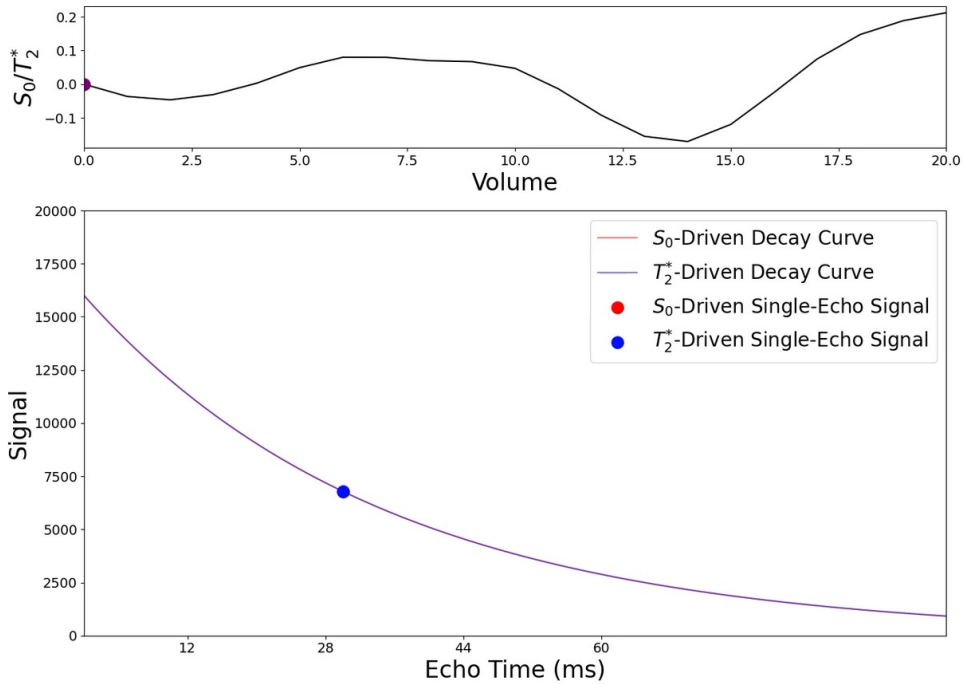
S_0 vs T_2^*

- S_0 changes over time
 - Head motion (Power, PNAS, 2018)
 - Slow signal drift (Evans, *NeuroImage* 2015)
 - Overt speech (Gilmore, *Front in Neuro*, 2022)
 - Phase shifts from respiration (looks like head motion)
 - Most scanner artifacts
- T_2^* changes over time
 - Deoxyhemoglobin concentration (BOLD)
 - Neurovascular coupling
 - Respiratory and Cardiac blood volume and blood oxygenation changes
 - Ghosting & signal leakage of MRI artifacts that contain T_2^* changes

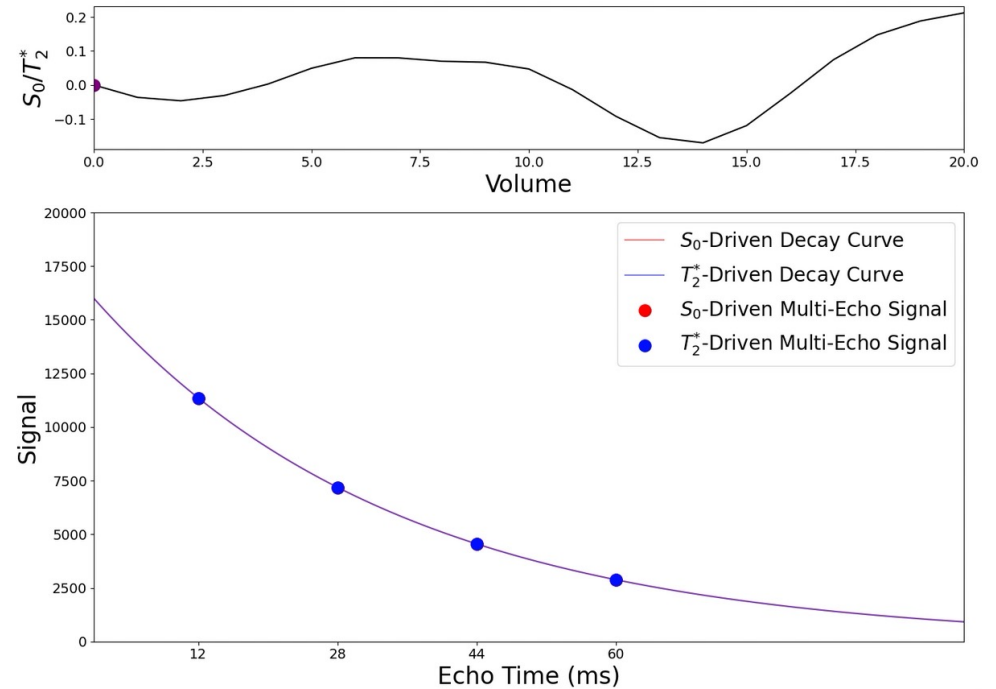
It would be VERY useful if we could remove the S_0 fluctuations and just look at T_2^*

Multi-echo gives us info to distinguish T_2^* and S_0


What we measure with single-echo fMRI



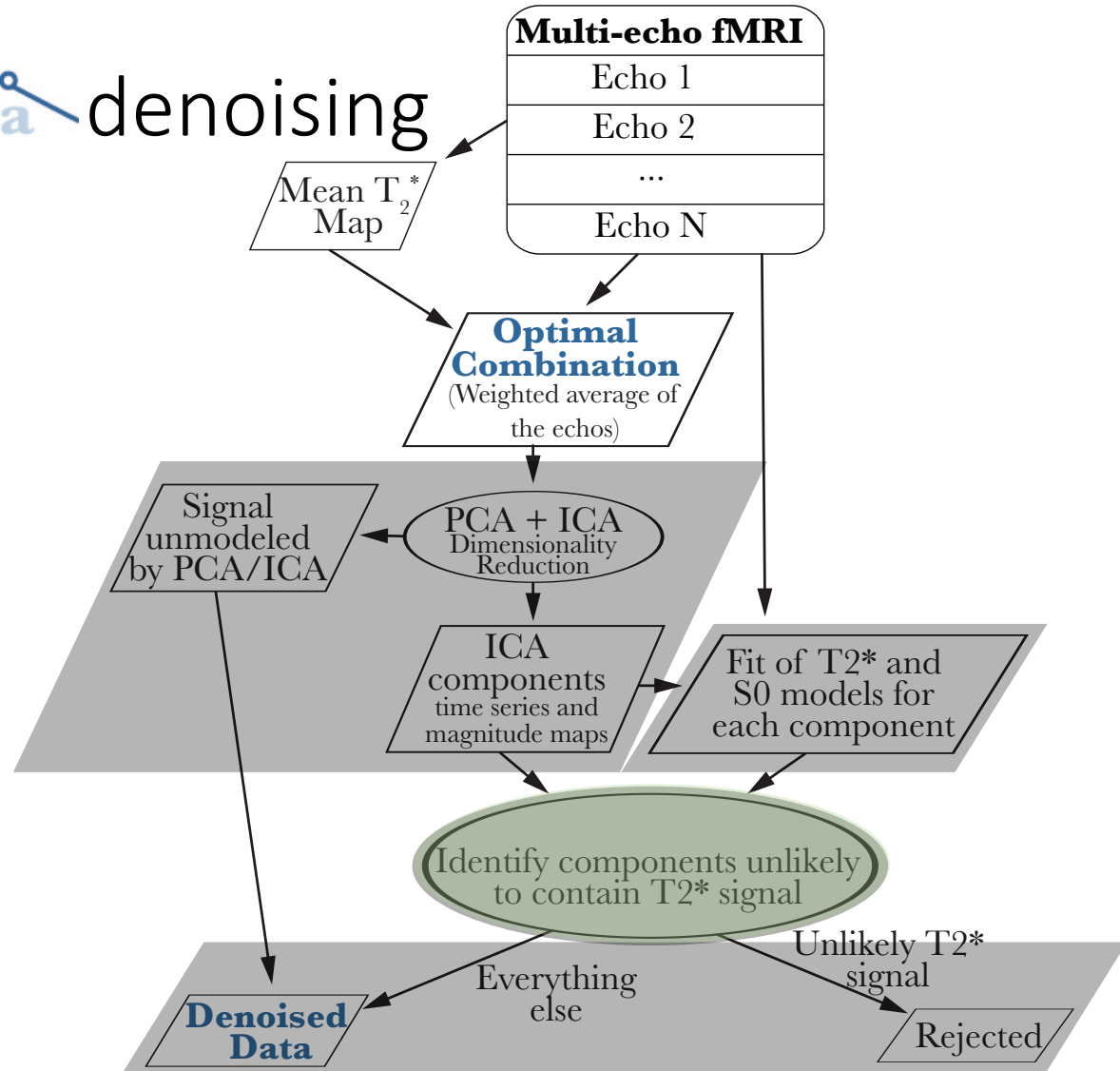
What we measure with multi-echo fMRI



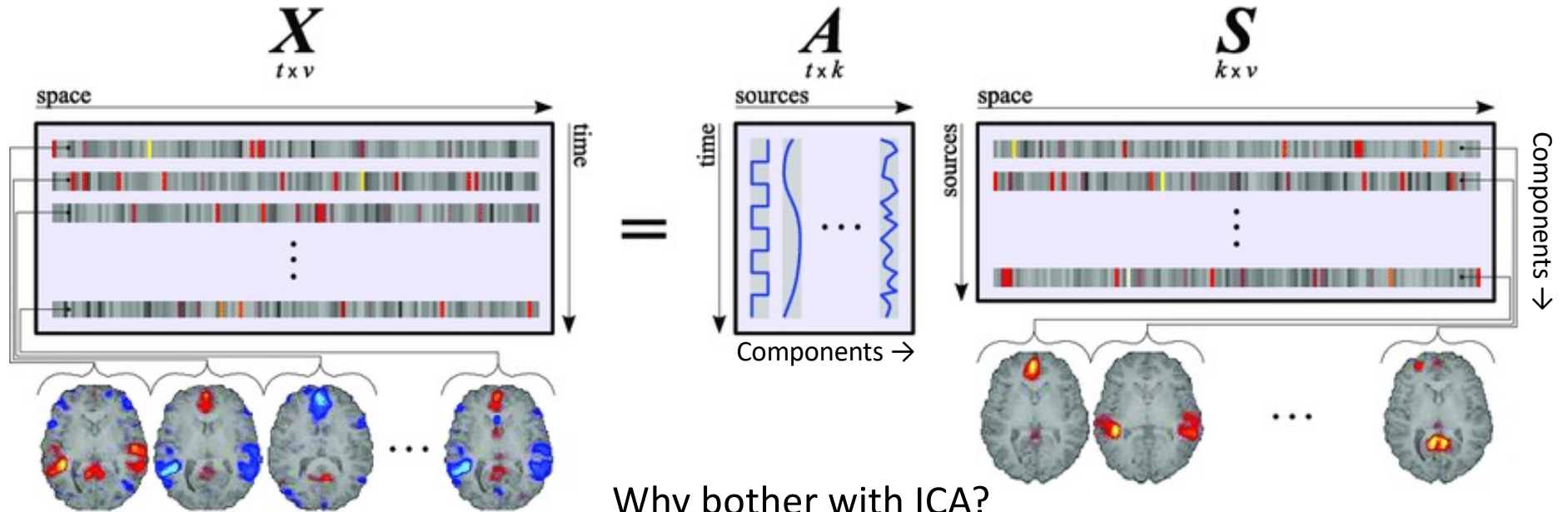
Denoising methods to reduce S_0 fluctuations

- ICA based: MEICA (Kundu 2012 & 2013) →
 (DuPre, Salo, et al, *JOSS*, 2011)
- Paradigm Free Mapping (Caballero-Gaudes, *NeuroImage*, 2019)
- Other methods: tedana.readthedocs.io/en/stable/multi-echo.html#other-software-that-uses-multi-echo-fmri

MEICA or denoising



Hand waving explanation of ICA



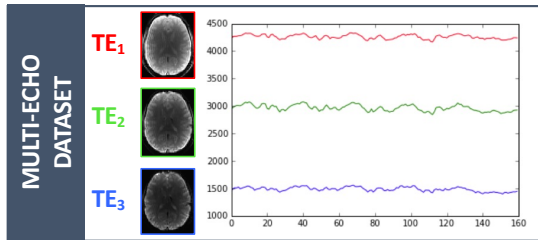
Why bother with ICA?

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

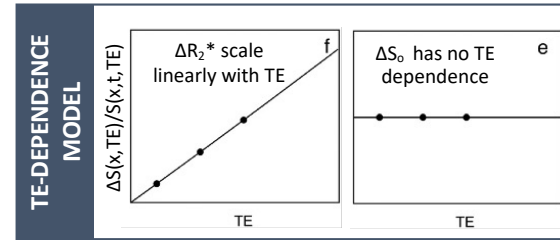
Solving for 2 variables
 ≥ 3 measurements

ICA is targeted
 signal averaging

Identifying components unlikely to contain T_2^*

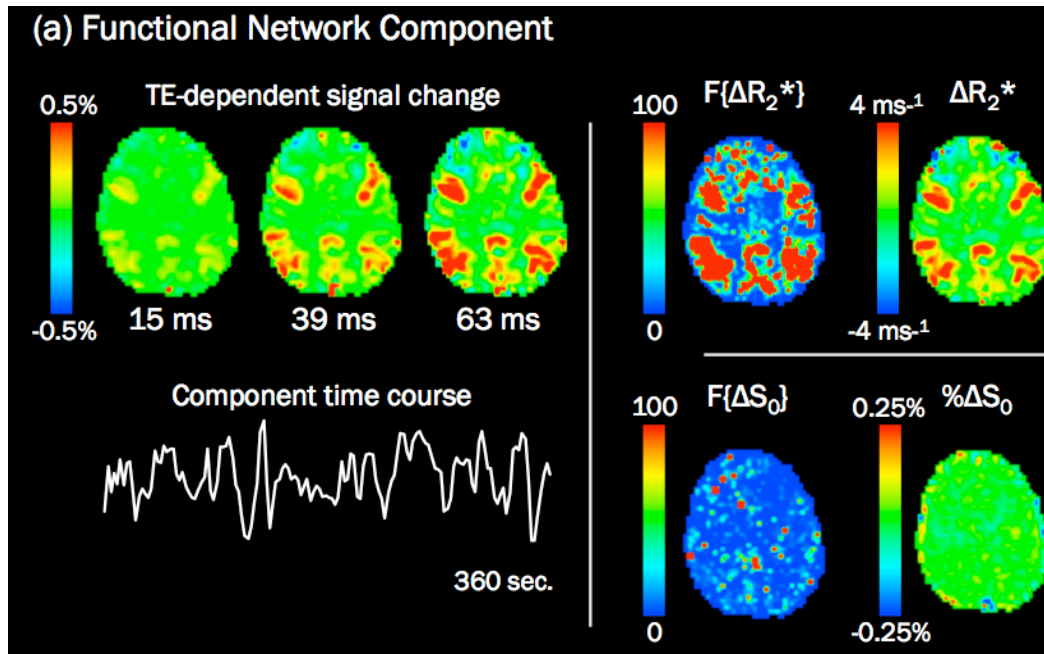


Linear fit of ICA component time series to each voxel and echo



Fit across echoes to

$$R_2^* \left(\frac{1}{T_2^*} \right) \text{ or } S_0 \text{ models}$$

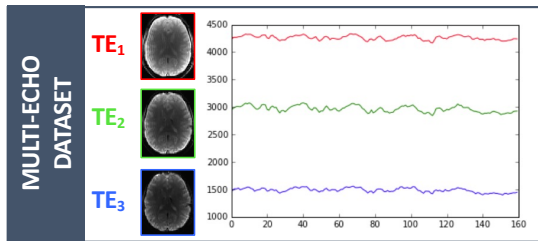


Calculate the weighted sum of the ICA component weight map and the model fit to T_2^* (Kappa) and S_0 (Rho)

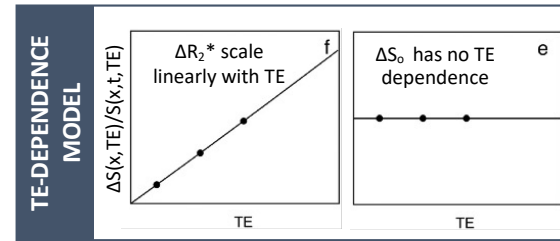
Kappa (κ) = 210

Rho (ρ) = 10

Identifying components unlikely to contain T_2^*

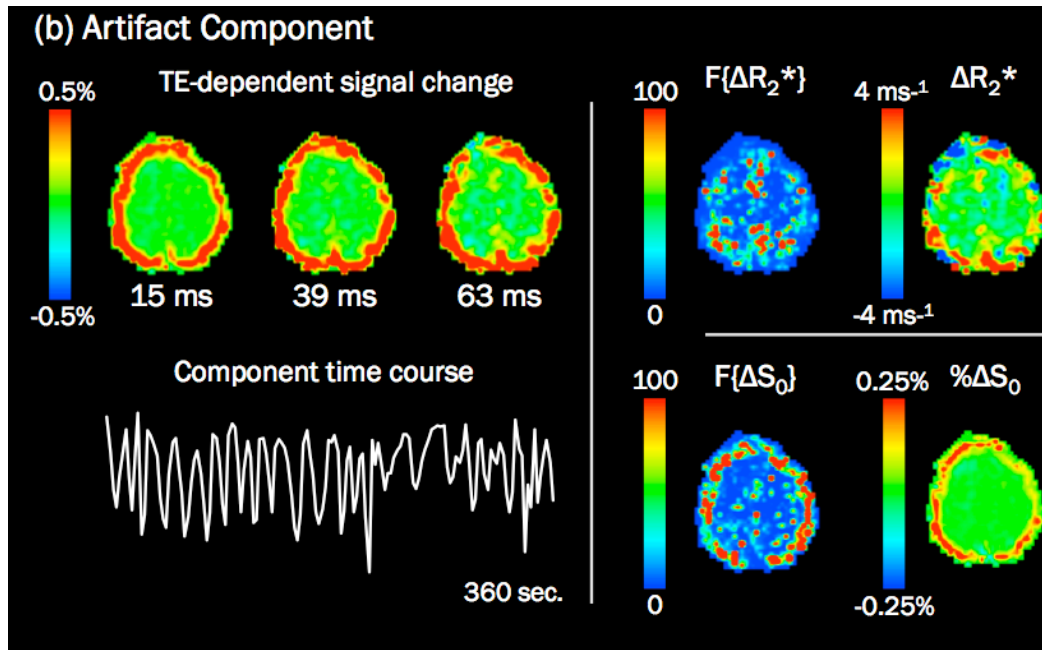


Linear fit of ICA component time series to each voxel and echo



Fit across echoes to

$$R_2^* \left(\frac{1}{T_2^*} \right) \text{ or } S_0 \text{ models}$$



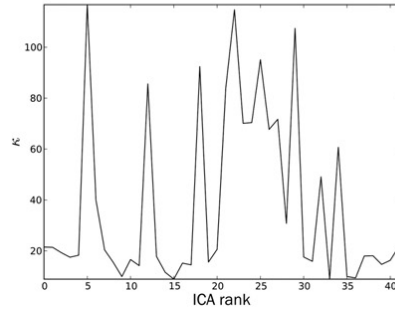
Calculate the weighted sum of the ICA component weight map and the model fit to T_2^* (κ) and S_0 (ρ)

$\kappa = 32$

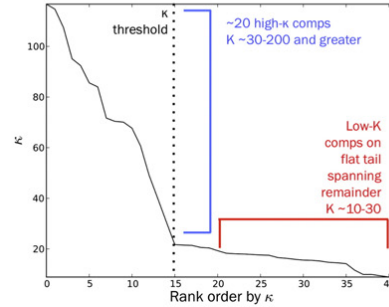
$\rho = 81$

Example retained components

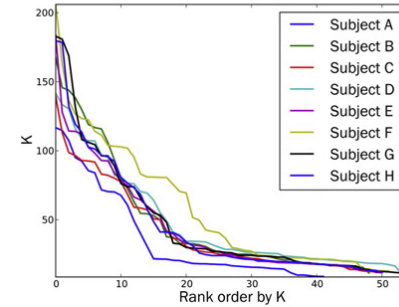
a κ vs. ICA rank



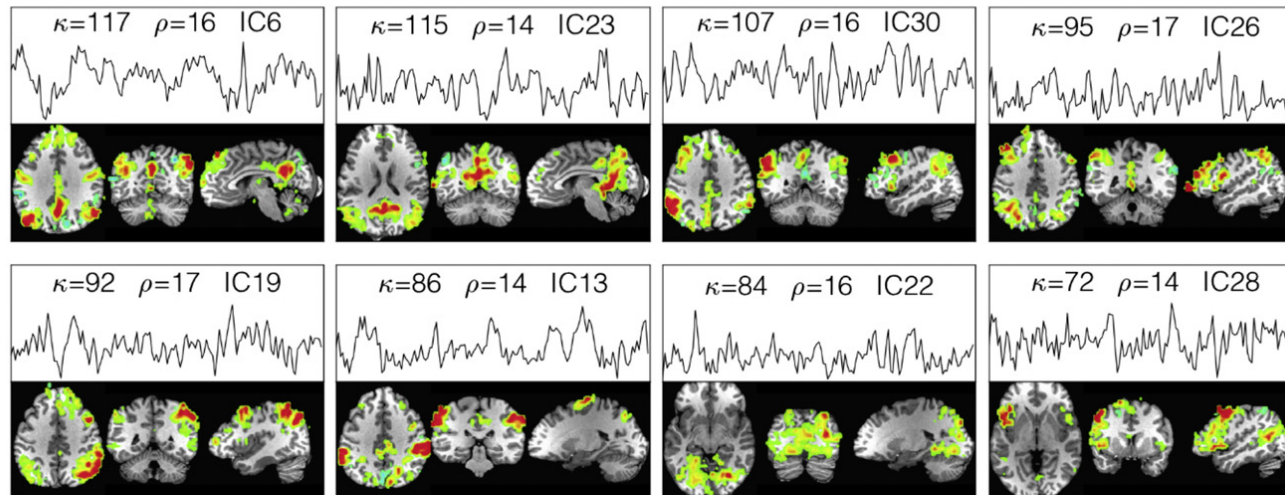
b κ spectrum



c κ spectra across subjects

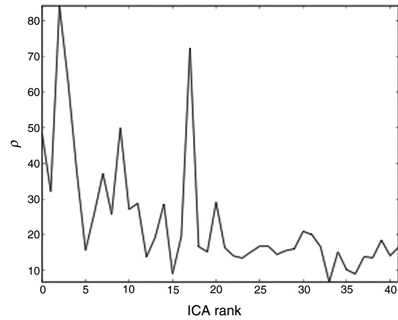


d ΔR_2^* maps of top κ ranked components for a representative subject

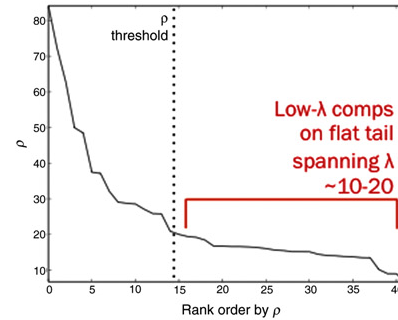


Example rejected components

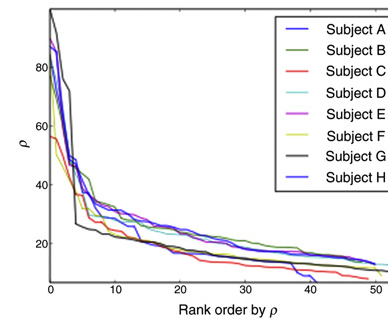
a ρ vs. ICA rank



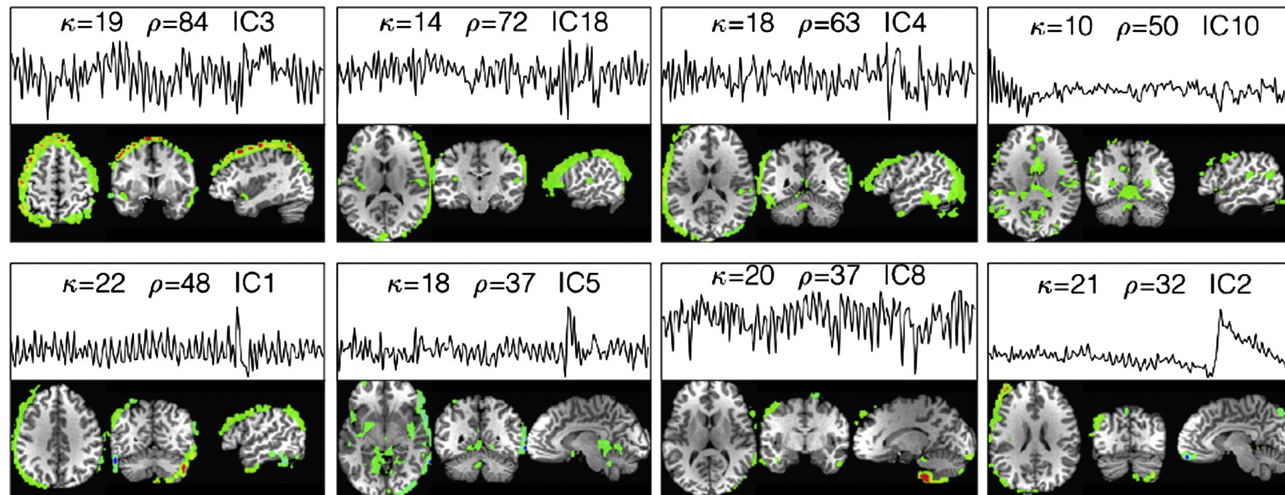
b ρ -spectrum



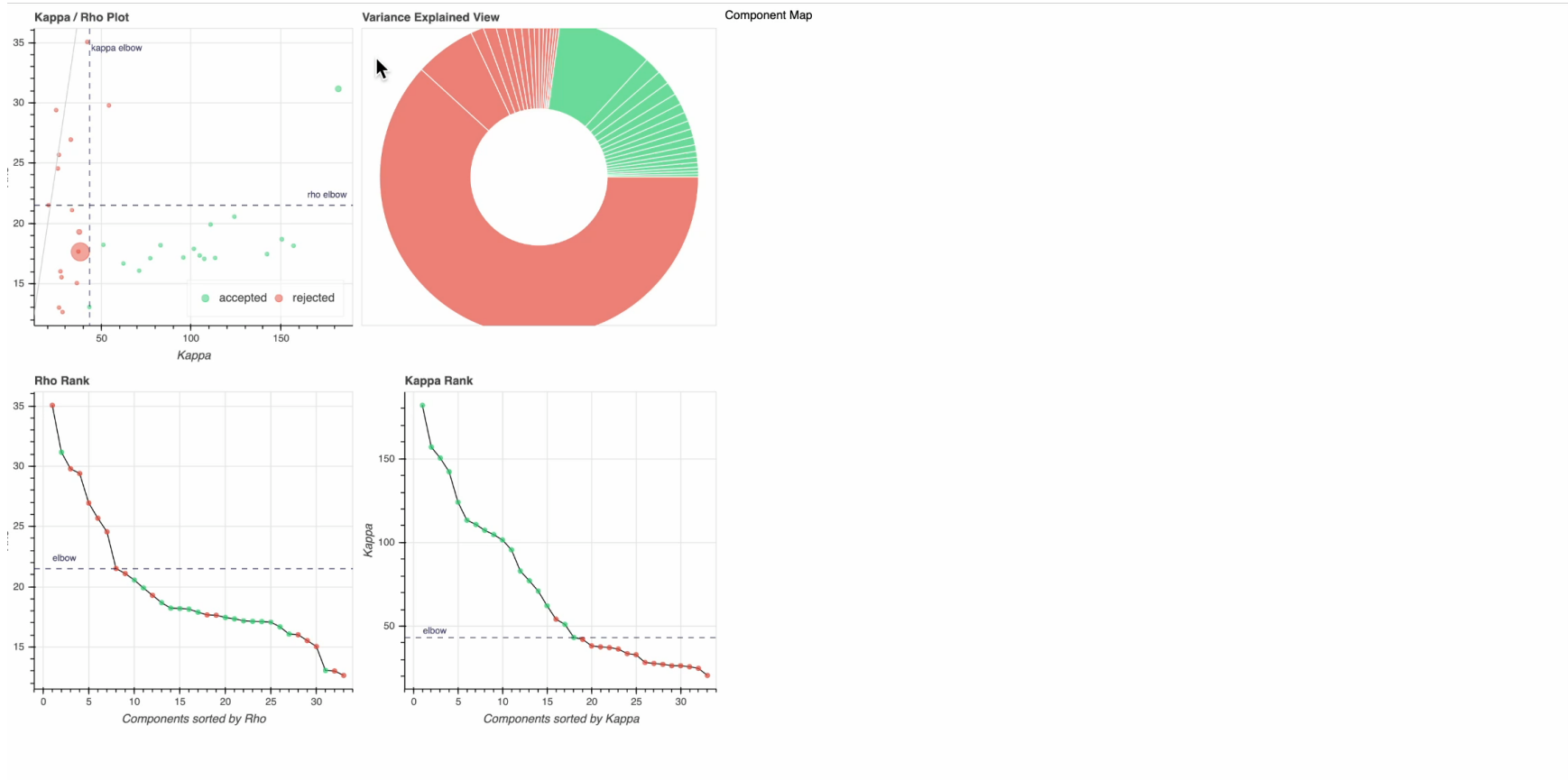
c ρ -spectrum across subjects



d ΔS_0 maps of top ρ -ranked components for a representative subject

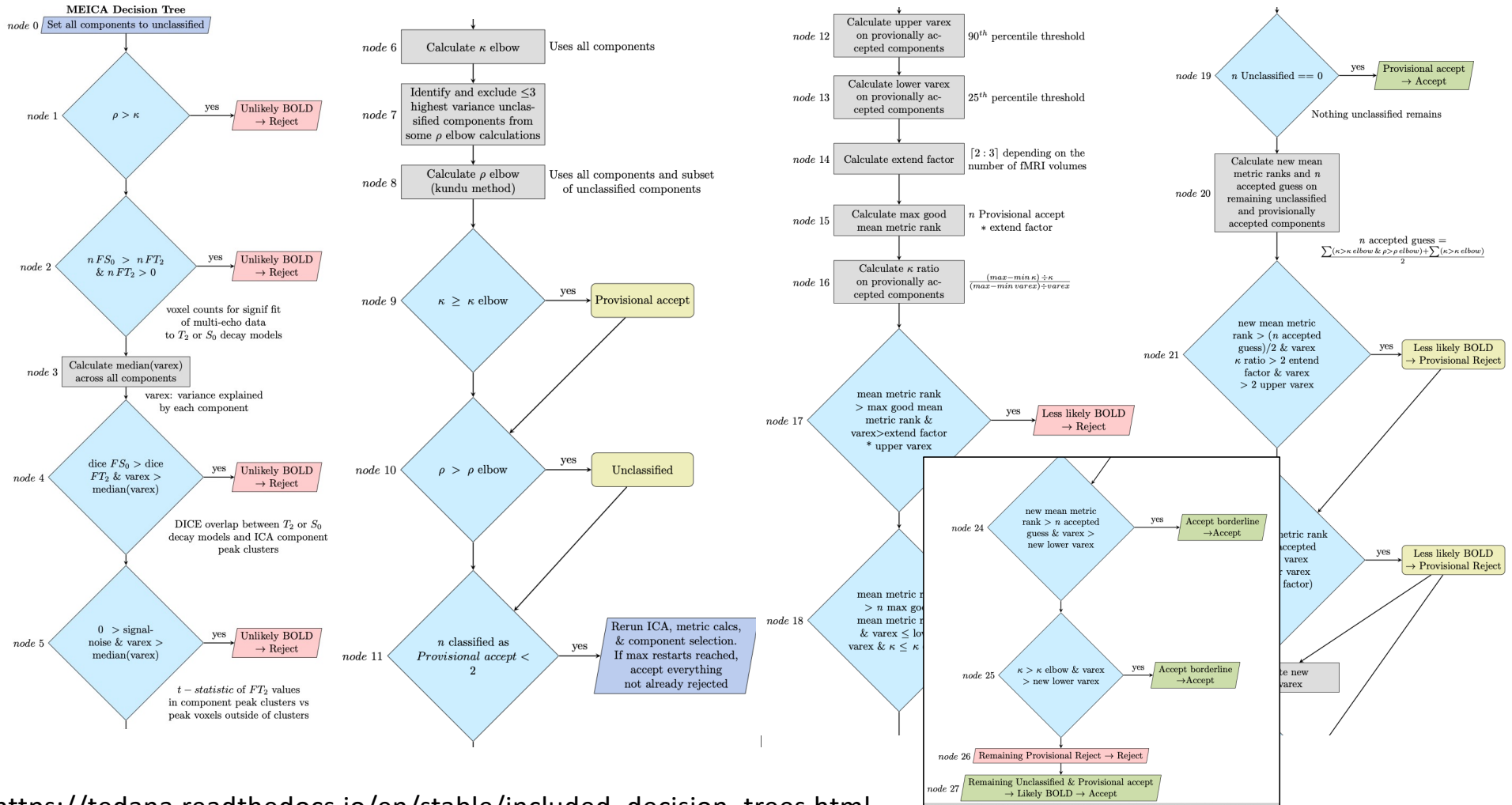


ICA component report in tedana



https://me-ica.github.io/ohbm-2023-multiecho/tedana/tedana_results_minimal_five-echo/tedana_report.html

The default decision process is a bit more... quirky



https://tedana.readthedocs.io/en/stable/included_decision_trees.html

Deciding what/how to reject is not a solved problem

- Benefits of this method don't show every improvement that's possible with multi-echo data
- Room for people to innovate
- Tedana software now includes multiple "decision trees" and tools for anyone to design their own.

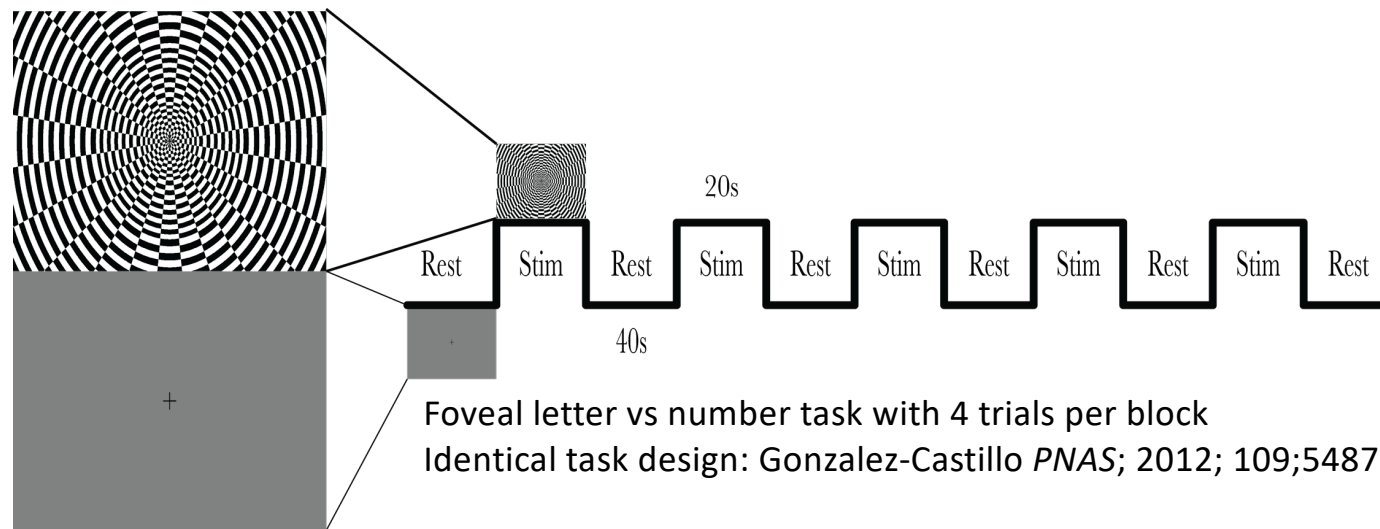
https://tedana.readthedocs.io/en/stable/building_decision_trees.html

Empirical evaluations of multi-echo fMRI methods

Evaluating Contrast-to-noise changes from multi-echo fMRI

Experimental Design

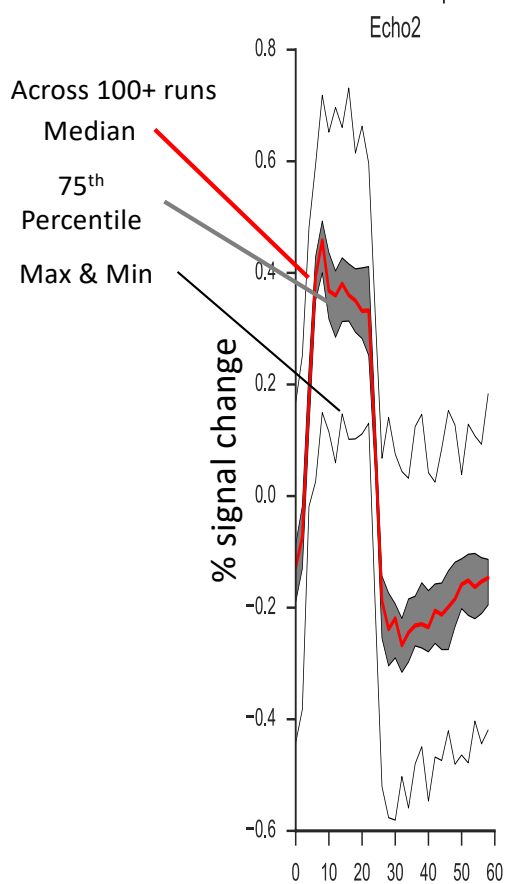
- 2 Volunteers, 9 sessions, 103 runs each, **9 hours of data per person**
- GE MR750, 3T, 32 channel coil
- EPI: 3.5mm³, **3 echoes, TE=15.4, 29.7, & 44.0ms** FA=75°, TR = 2s, 33 slices
- 5.5 minutes, 161 volumes (150 volumes used in each run)



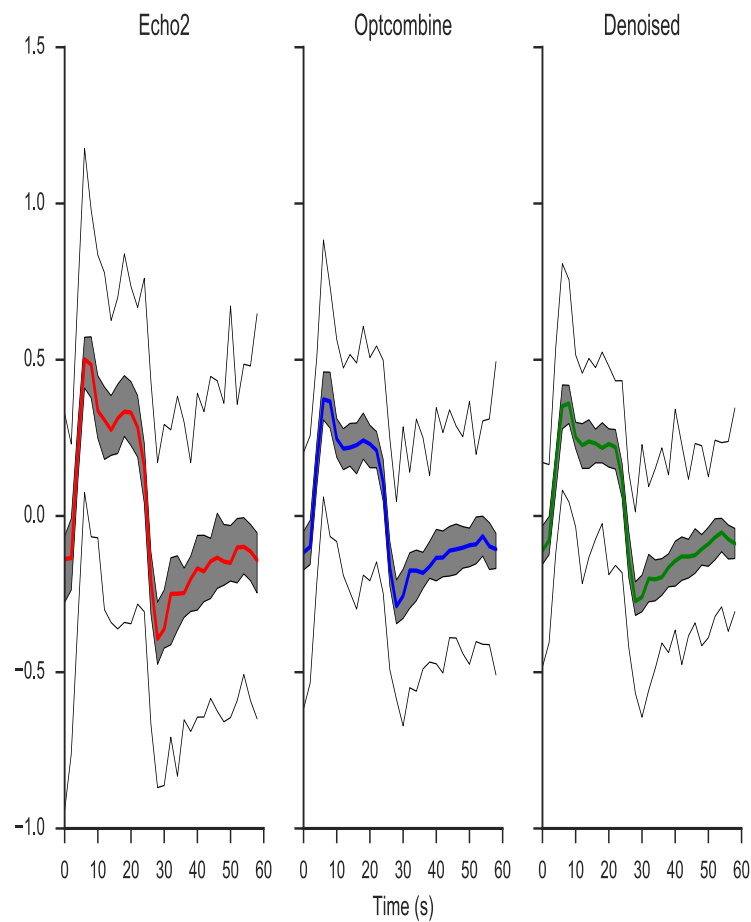
Optimal Combination & Denoising processed with: bitbucket.org/BenGutierrez/me-ica

Lateral Geniculate Nucleus (LGN) Responses

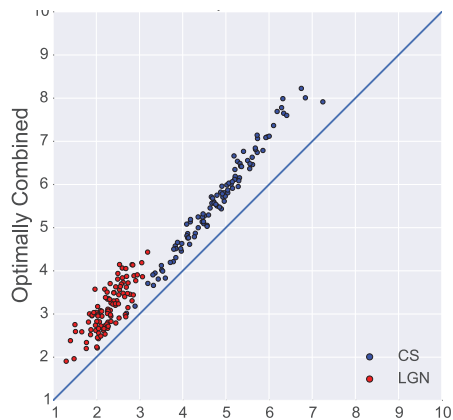
Volunteer 1



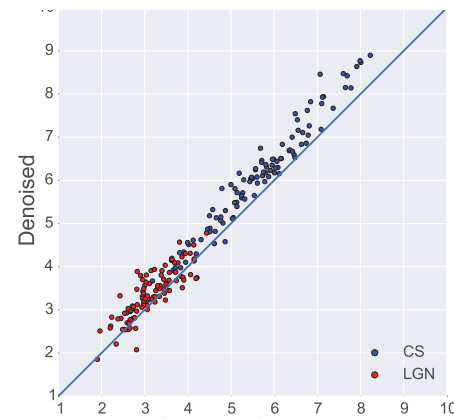
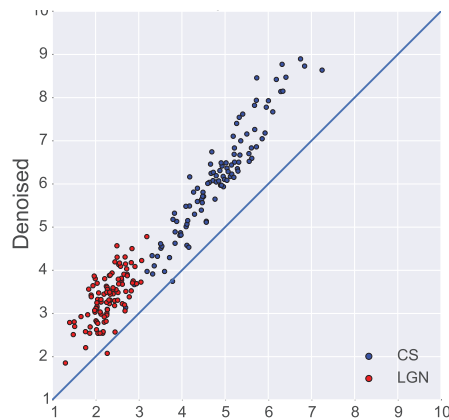
Volunteer 2



Contrast-to-Noise By Run



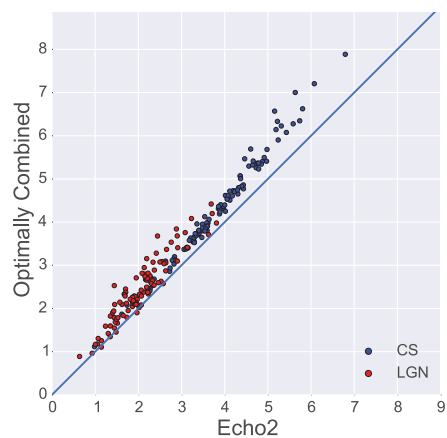
CNR Comparison for Volunteer 1



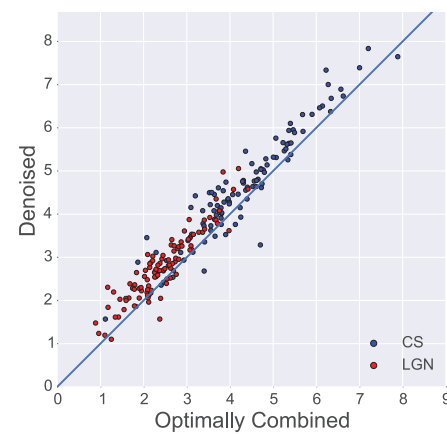
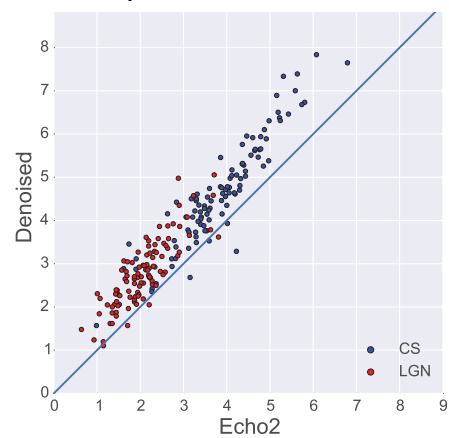
Regions of Interest

CS
Calcarine Sulcus

LGN
Lateral Geniculate Nucleus

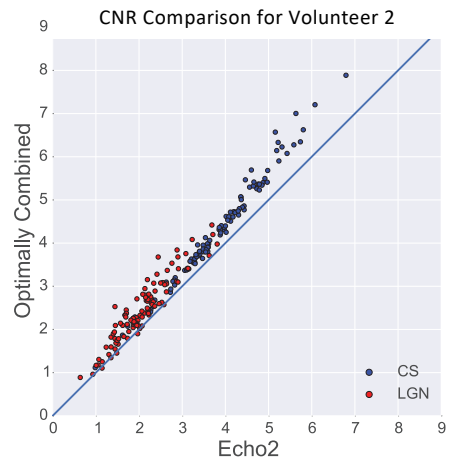
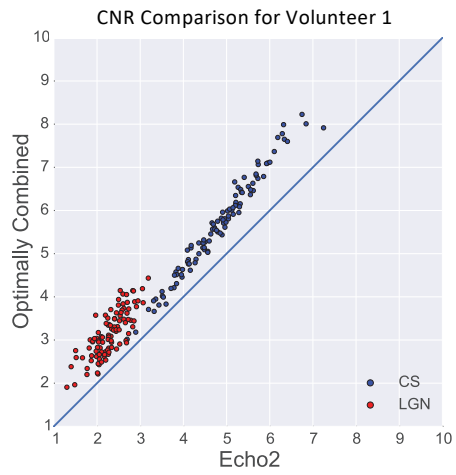


CNR Comparison for Volunteer 2

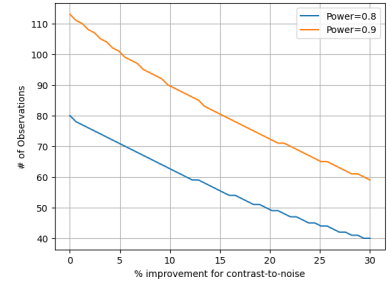
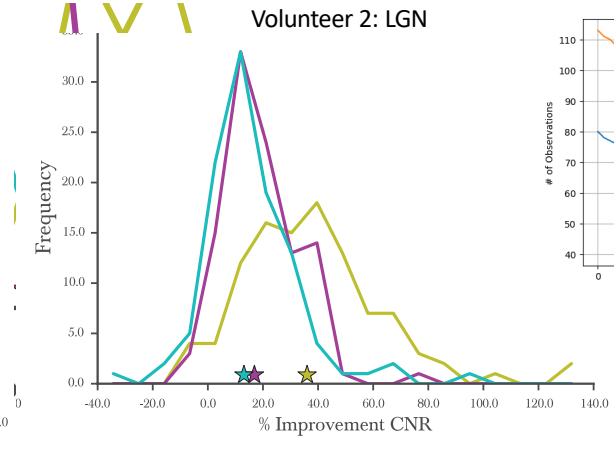
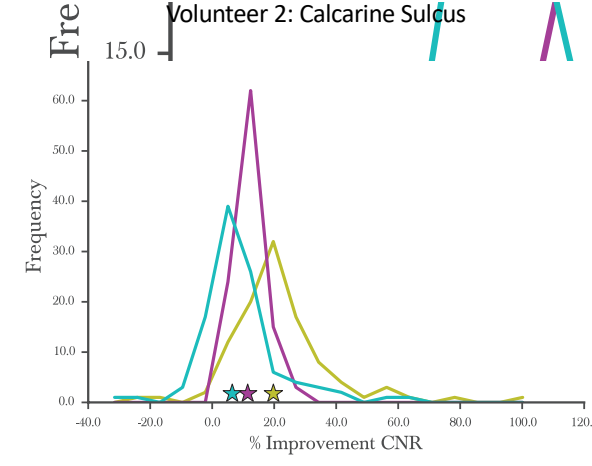
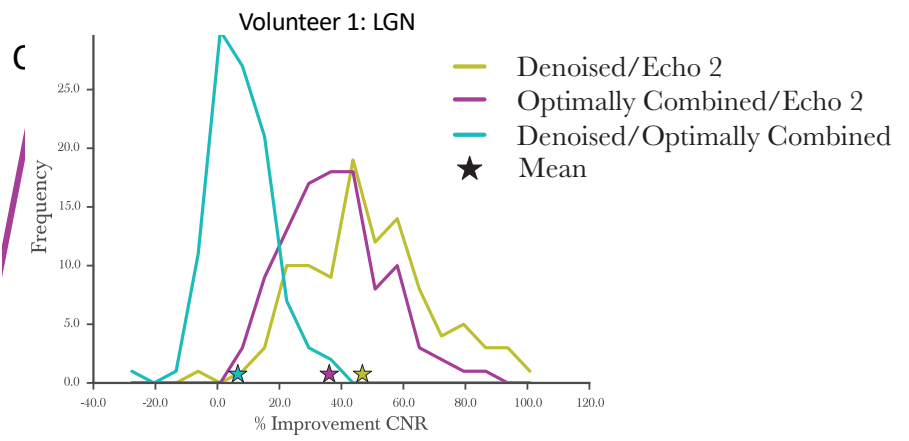
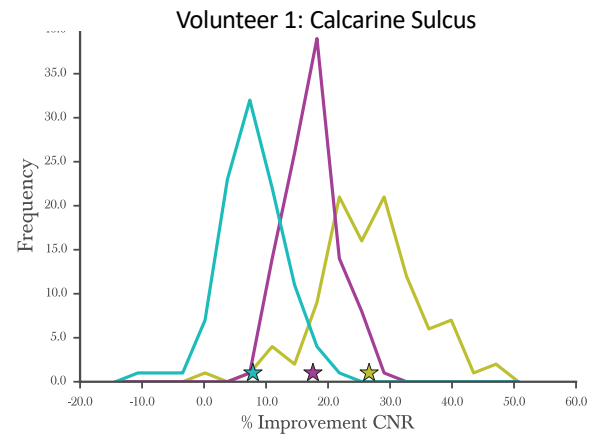


Each dot is the CNR values from 1 run

Contrast-to-Noise By Run



CNR % Improvement Between Preprocessing Methods

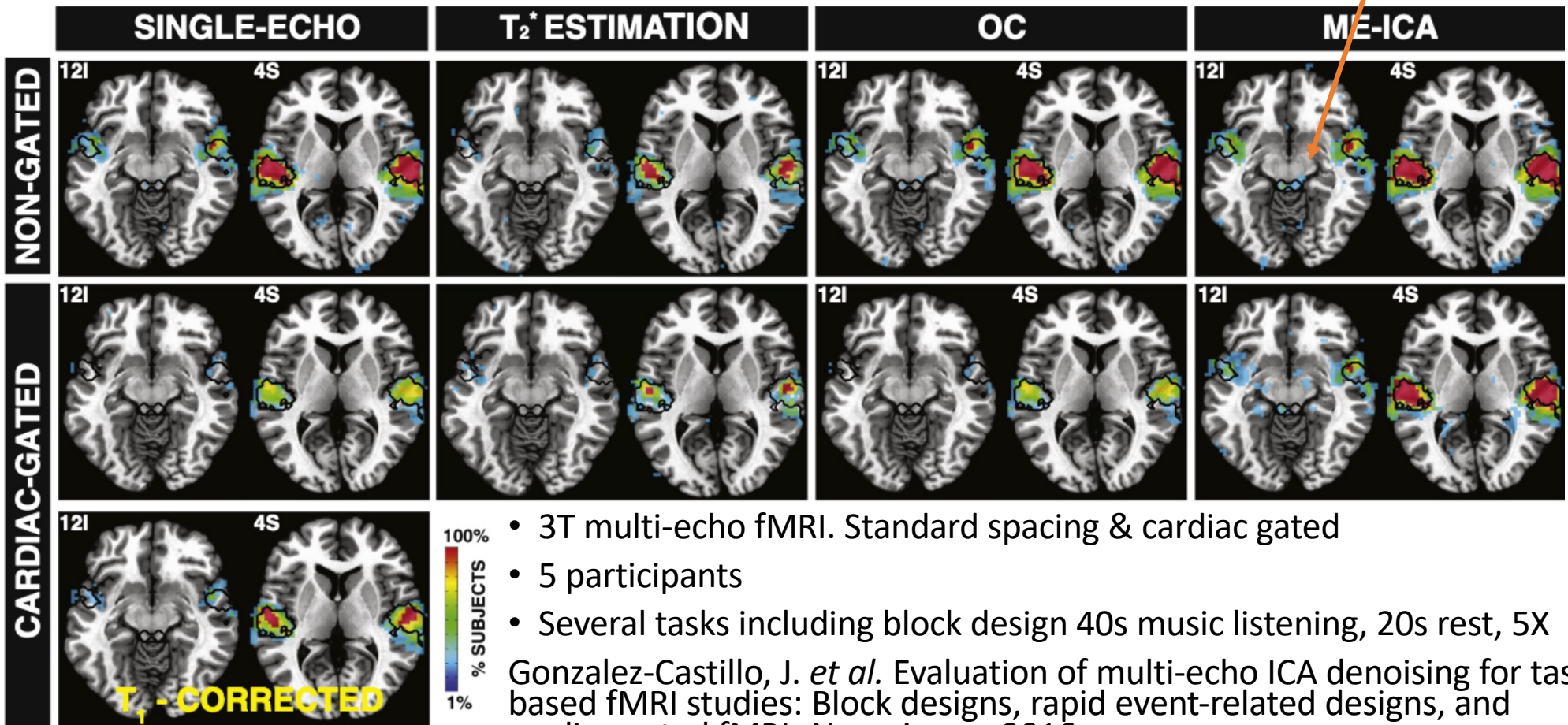


Take home message from this study

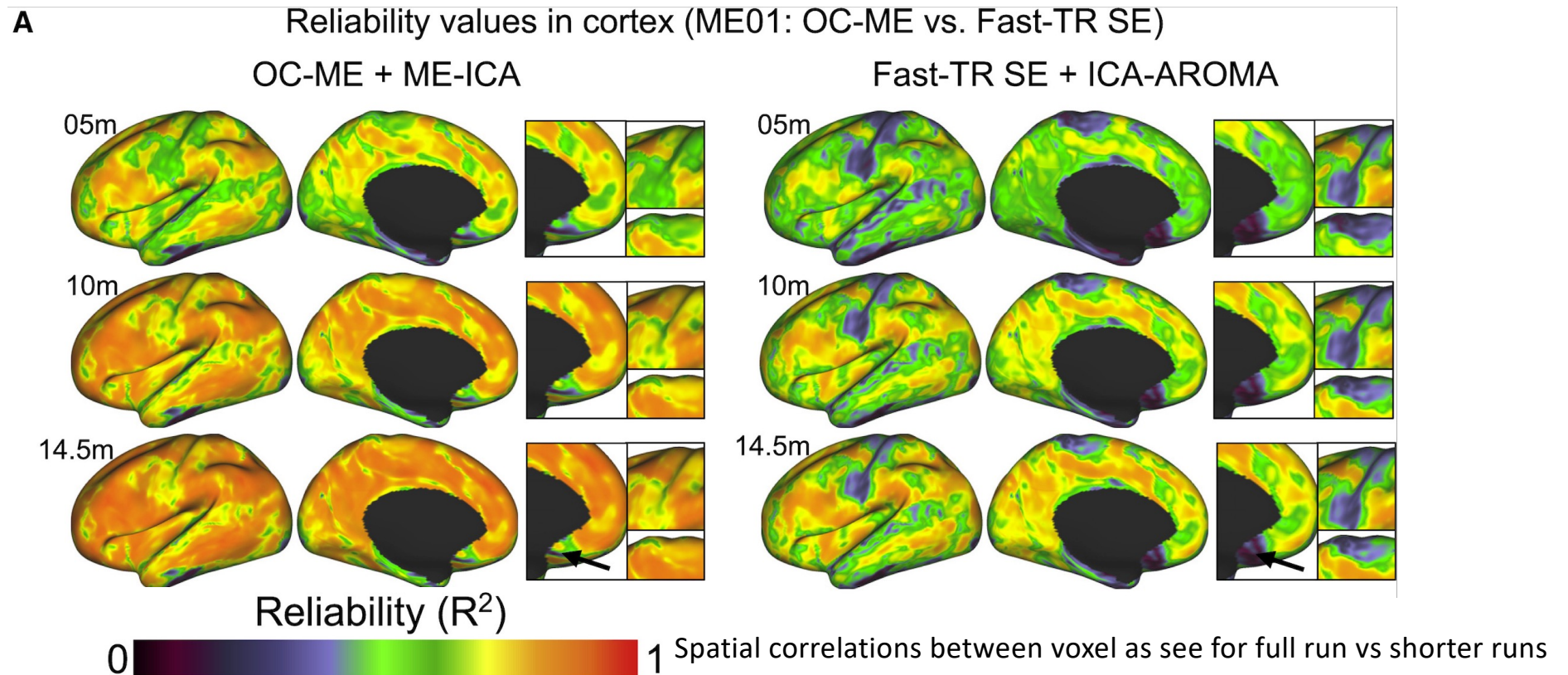
- Optimal Combination reliably improves CNR over single echo
- Denoising can be similar, much better, or worse than the optimal combination
 - More to understand & improve on denoising methods
 - Use denoising, but don't assume everything worked perfectly
- Limits of presented data
 - Awesome volunteers: <1.5mm max head motion in all but 2/206 runs
 - Single, stable scanner with a regular Quality Assurance testing
 - Benefits of denoising may be greater with more noise to potentially remove

Music listening task

Inferior Colliculus



Reliably for functional connectivity



“In four densely sampled individual humans, just 10 min of multi-echo data yielded better test-retest reliability than 30 min of single-echo data in independent datasets.”

Lynch et al Cell Reports 2020 “Rapid Precision Functional Mapping of Individuals using multi-echo fMRI”

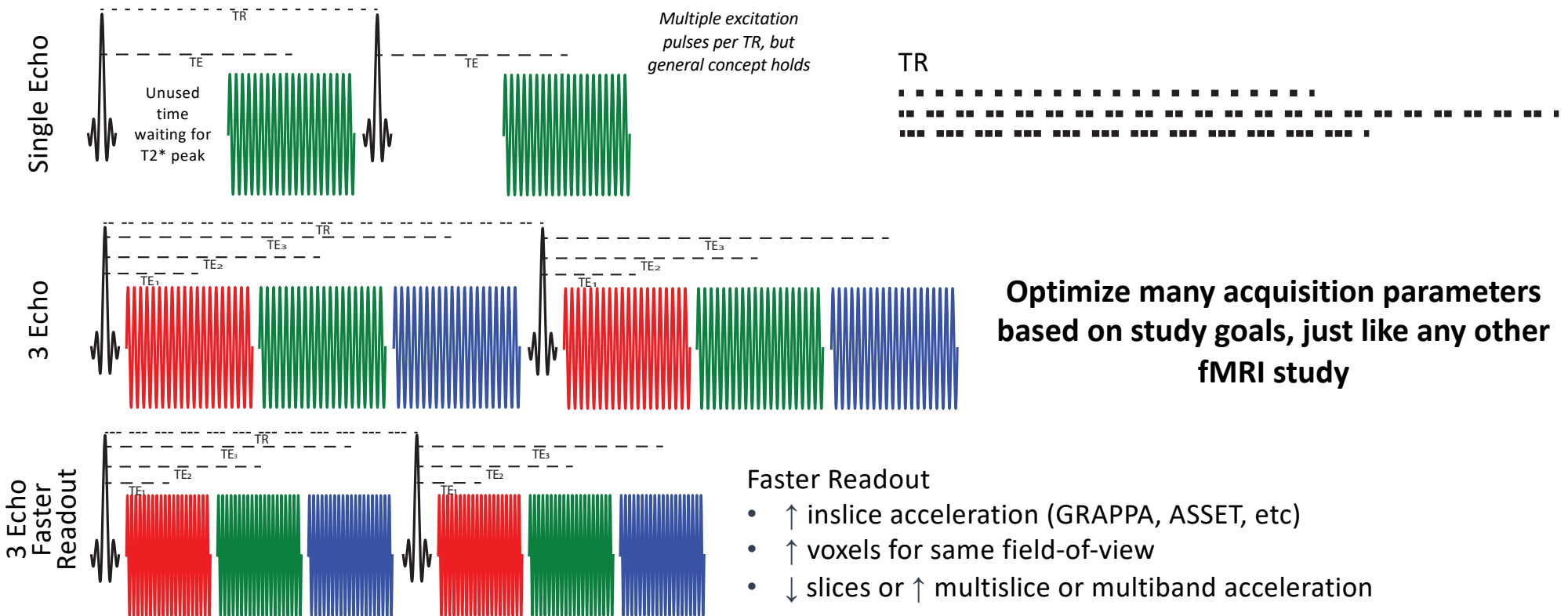
Growth of multi-echo fMRI usage

- Neurocognitive aging data release with behavioral, structural, and multi-echo functional MRI measures
 - N=181 younger, 120 older
- Cambridge Centre for Ageing Neuroscience (Cam-CAN)
 - N=649
- Heart rate variability biofeedback training and emotion regulation
 - N=193
- Le Petit Prince
 - N=112
- Multi-echo Cambridge
 - N=89
- Evidence supporting a time-limited hippocampal role in retrieving autobiographical memories
 - N=40

<https://tedana.readthedocs.io/en/stable/multi-echo.html#datasets>

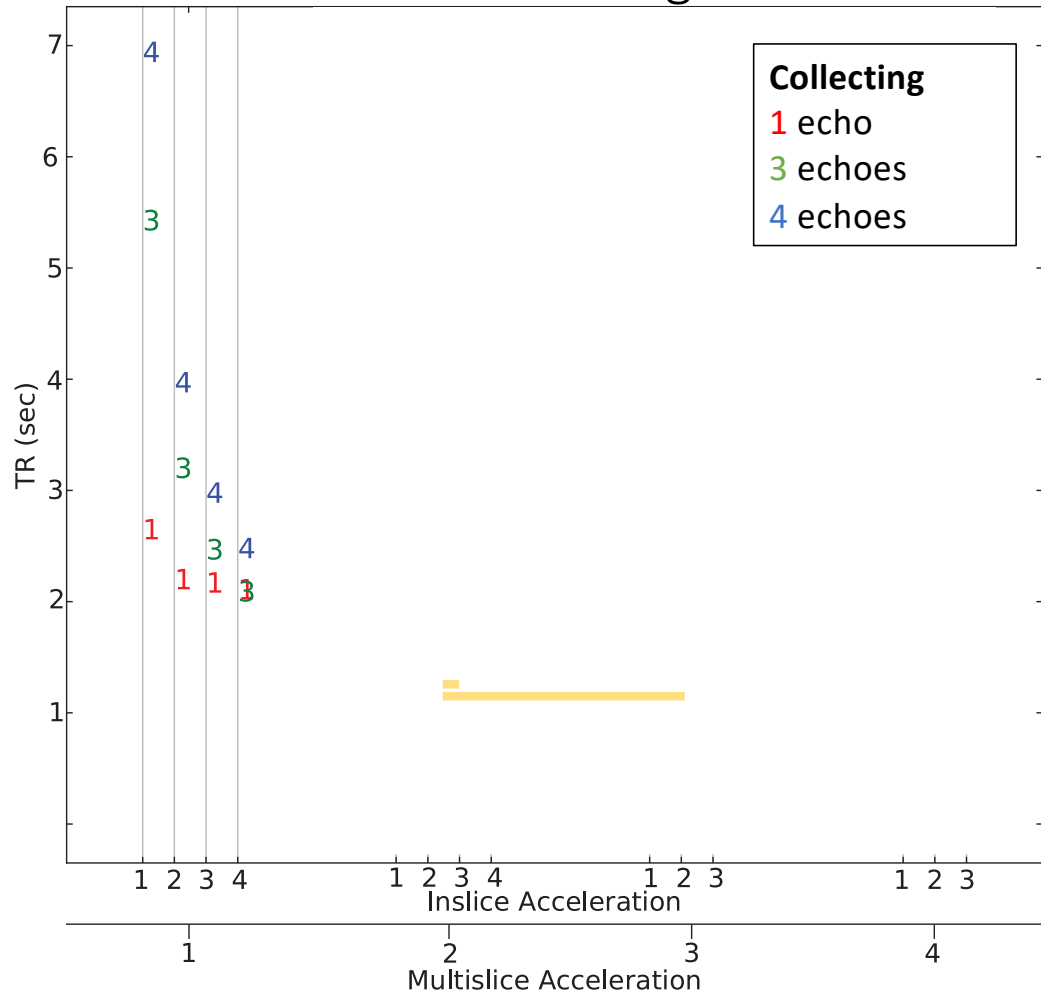
Acquisition Considerations

- Common question: Multi-echo fMRI or a short TR?
- Better question: How many echoes for how short a TR?



Acquisition Considerations

TR variation for multi-echo vs single-echo



Collected on a Siemens Prisma 3T MRI
Siemens OS VD11

CMRR Multiband pulse sequence
64 channel head coil
3mm³ voxels 42-44 slices
cortex & cerebellum coverage

3 vs 1 echo for:

Inslice Acceleration = 2: 40-50% TR cost

Inslice Acceleration = 3: ~14% TR cost

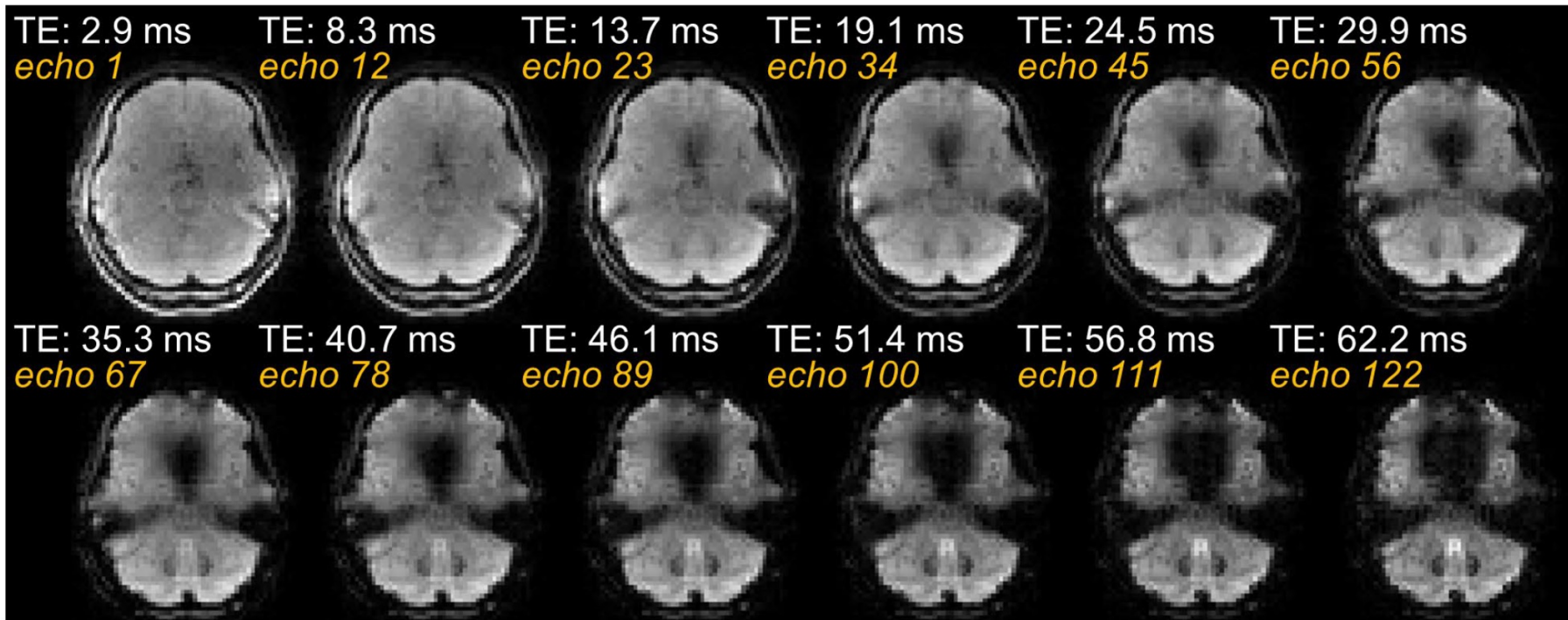
Inslice Acceleration = 4: ~-1% TR cost

Acquisition Considerations

Thinking through an acquisition plan

- Cost of acquiring multi-echo can be balanced with a combination of:
acceleration \uparrow , voxel size \uparrow , slices \downarrow , & TR \uparrow
- More CNR from “optimal combination” of echoes **should** balance lower SNR from acceleration \uparrow
- <https://tedana.readthedocs.io/en/stable/multi-echo.html#acquiring-multi-echo-data>
- **Recommendations**
 - If a scientific Q requires pushing the limits of small voxels or short TRs, multi-echo might not be practical
 - Planning a single-use data set: Consider multi-echo
 - You should see modest benefits with optimal combination
 - Denoising should help, but might require more effort
 - Planning a longer-term project with goals of data re-use: Strongly consider multi-echo
 - Immediate benefits, and larger longer-term benefits are likely
 - Development of additional ways to use multi-echo fMRI is likely

Echo Planar Time-resolved Imaging (EPITI)



- EPITI sequences are designed to evenly span different fractions of k-space over time
- Allows for a running average of images centered at close echo times
- NOTE: Identical data contributes to multiple echoes



Software & Community

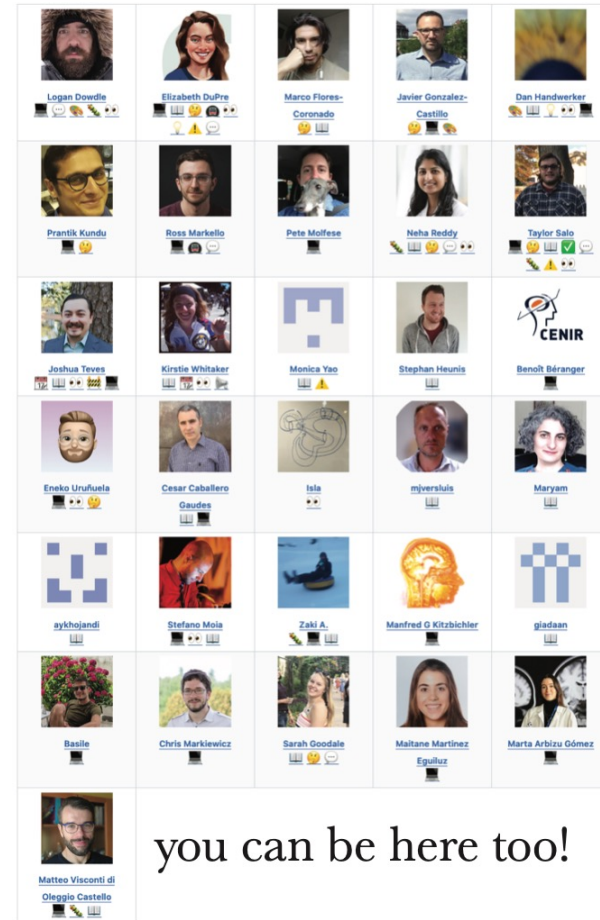
- Tedana started in May 2018 by Elizabeth DuPre to advance MEICA by Prantik Kundu
- Processing code
- Multi-echo education
- Approx 31 contributors and counting
- Monthly developer calls, a periodic newsletter, active issue board & code updates

Code:

<https://github.com/me-ica/tedana>

Documentation:

<https://tedana.readthedocs.io>



Command line program

The screenshot shows a web browser window with the URL `https://tedana.readthedocs.io/en/stable/usage.html`. The page has a blue header with the tedana logo and 'stable' version indicator. A search bar is present. The left sidebar contains a 'CONTENTS' section with links to 'Installation', 'About multi-echo fMRI', 'Using tedana from the command line', 'Running the tedana workflow', 'Running the t2smap workflow', 'tedana's denoising approach', 'Outputs of tedana', 'FAQ', 'Support and communication', 'Contributing to tedana', 'The tedana roadmap', and 'API'. The main content area is titled 'Running the tedana workflow' and contains a paragraph explaining the workflow, followed by a code block showing the command-line usage, and a section for 'Required Arguments'.

Running the tedana workflow

This is the full tedana workflow, which runs multi-echo ICA and outputs multi-echo denoised data along with many other derivatives. To see which files are generated by this workflow, check out the outputs page: <https://tedana.readthedocs.io/en/latest/outputs.html>

```
usage: tedana [-h] -d FILE [FILE ...] -e TE [TE ...] [--out-dir PATH]
             [--mask FILE] [--prefix PREFIX] [--convention {orig,bids}]
             [--fittype {loglin,curvefit}] [--combmode {t2s}]
             [--tedpca TEDPCA] [--seed INT] [--maxit INT] [--maxrestart INT]
             [--tedort] [--gscontrol {mir,gsr} [{mir,gsr} ...]]
             [--no-reports] [--png-cmap PNG_CMAP] [--verbose] [--lowmem]
             [--n-threads N_THREADS] [--debug] [-v] [--t2smap FILE]
             [--mix FILE] [--ctab FILE] [--manacc INT [INT ...]]
```

Required Arguments

-d

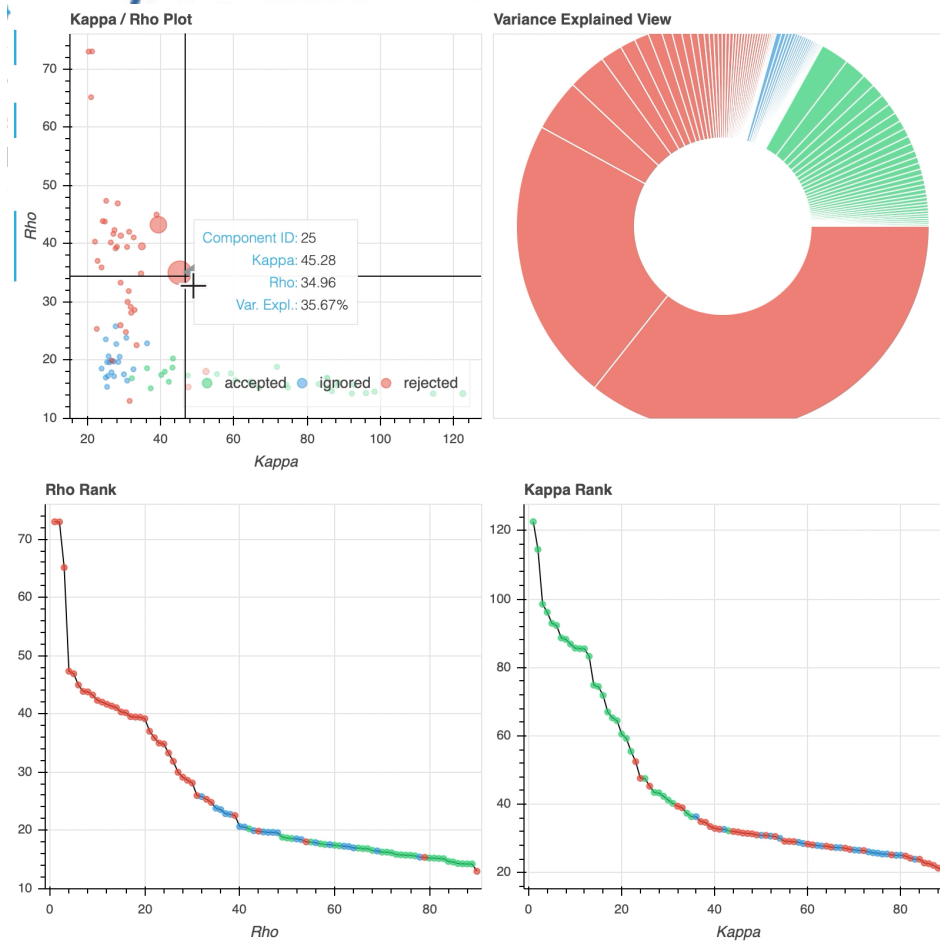
Multi-echo dataset for analysis. May be a single file with spatially concatenated data or a set of echo-specific files, in the same order as the TEs are listed in the -e argument.

-e

Echo times (in ms). E.g., 15.0 39.0 63.0



Results Viewer



Multi-echo Jupyter Book!

Work-in-progress by
Taylor Salo, software
engineering, U Penn

Jupyter Books have both the
code to generate figures and the
text in one place

https://me-ica.github.io/multi-echo-data-analysis/content/Signal_Decay.html

Download Data
Install Software
Recommended Reading

THEORETICAL BACKGROUND

MR Physics
Multi-Echo fMRI Sequences
Signal Decay
BOLD, non-BOLD, and TE-dependence with *tedana*
Generate *tedana* walkthrough figures

PRACTICAL RESOURCES

Open Multi-Echo Datasets
Acquiring Multi-Echo Data
Processing Multi-Echo Data


ANALYSIS TUTORIALS

Optimal combination with *t2smap*
Volume-wise T2*/S0 estimation with *t2smap*
Multi-Echo Denoising with *tedana*
Dual-Echo Denoising with *nilearn*
3dMEPFM
Cerebrovascular Reactivity Mapping
Manual Classification with *rica*
Denoising Data with ICA

FINAL THOUGHTS

Plot S_0 and T_2^* fluctuations and resulting multi-echo data

This shows how S_0 and T_2^* fluctuations produce different patterns in multi-echo data.

Click to show 

The top plot shows S_0/T_2^* fluctuations over 20 volumes. The y-axis ranges from -0.1 to 0.2, and the x-axis ranges from 0.0 to 20.0. A purple dot is marked at Volume 10.0, $S_0/T_2^* \approx 0.05$.

The bottom plot shows Signal vs Echo Time (ms). The y-axis ranges from 0 to 20000, and the x-axis ranges from 0 to 60. Two decay curves are shown: a red line for S_0 -Driven Decay Curve and a blue line for T_2^* -Driven Decay Curve. Two multi-echo signals are marked: a red dot for S_0 -Driven Multi-Echo Signal and a blue dot for T_2^* -Driven Multi-Echo Signal. The red signal is consistently higher than the blue signal.

Legend:

- S_0 -Driven Decay Curve
- T_2^* -Driven Decay Curve
- S_0 -Driven Multi-Echo Signal
- T_2^* -Driven Multi-Echo Signal

Echo Time (ms)

Once Loop Reflect

Discussions are open

https://github.com/ME-ICA/tedana/pulls?q=is%3Apr+is%3Aopen+sort%3Aupdated-desc

110%



🔗 12 Open ✓ 536 Closed

Author ▾

Label ▾

Projects ▾

Milestones ▾

Reviews ▾

Assignee ▾

Sort ▾

🔗 **Generate metrics from external regressors using F stats** ✓

#1064 opened on Mar 20 by handwerkerd • Review required ⌚ updated last week

🕒 1

💬 70

🔗 **Draft pre-tedana echo-wise denoising workflow** ✗ **enhancement**

#1097 opened on May 19 by tsalo • Draft ⌚ updated on May 19

🔗 **Update figure-generating notebook** ✓ **documentation**

#1074 opened on Apr 14 by tsalo • Review required ⌚ updated on Apr 30

💬 4

🔗 **Refactor gscontrol module** ✓ **refactoring**

#1086 opened on Apr 21 by tsalo • Review required ⌚ updated on Apr 29

🕒 1

💬 5

🔗 **Detrend optimally combined data before running PCA** ✗

#1090 opened on Apr 27 by tsalo • Draft ⌚ updated on Apr 28

💬 3

🔗 **Refactor metrics.dependence module** ✓ **refactoring**

#1088 opened on Apr 22 by tsalo • Review required ⌚ updated on Apr 26

💬 5

Support for new contributors

https://github.com/ME-ICA/tedana/blob/main/CONTRIBUTING.md

80%



lines (288 sloc) | 18.9 KB



Raw

Blame

Welcome to the `tedana` repository! We're excited you're here and want to contribute.

These guidelines are designed to make it as easy as possible to get involved. If you have any questions that aren't discussed below, please let us know by opening an [issue](#)!

Before you start you'll need to set up a free [GitHub](#) account and sign in. Here are some [instructions](#).

Already know what you're looking for in this guide? Jump to the following sections:

- [Joining the conversation](#)
- [Contributing small documentation changes](#)
- [Contributing through Github](#)
- [Understanding issues, milestones, and project boards](#)
- [Installing in editable mode](#)
- [Making a change](#)
- [Testing your change](#)
- [Viewing Documentation Locally](#)
- [Structuring contributions](#)
- [Recognizing contributors](#)
- [Monthly calls and testing guidelines](#)

Don't know where to get started? Read [Joining the conversation](#) and pop into Mattermost to introduce yourself! Let us know what your interests are and we will help you find an issue to contribute to. Thanks so much!

Joining the conversation

`tedana` is a young project maintained by a growing group of enthusiastic developers—and we're excited to have you join! Most of our discussions will take place on open [issues](#). We also maintain a [Mattermost chat room](#) for more informal conversations and general project updates.

There is significant cross-talk between these two spaces, and we look forward to hearing from you in either venue! As a reminder, we expect all contributions to `tedana` to adhere to our [code of conduct](#).

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board for
users

https://neurostars.org/tag/tedana

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Tags > tedana

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Topic	Replies
Recommended post-processing from tedana with fmriprep fmriprep, tedana	5
Ghosting in multi-echo EPI scans fmri, tedana	3
antsRegistration create transforms fmriprep, tedana	0
Converting between scanner- and T1w space using supplied affine transforms fmriprep, tedana	1
<input checked="" type="checkbox"/> Question About RICA (Tedana Manual ICA Classification) tedana, me-ica, rica	13
<input checked="" type="checkbox"/> Preprocessing multi-echo fMRI data by fmriprep amd Tedana fmriprep, tedana	5
<input checked="" type="checkbox"/> Tedana mask and components 2 fmriprep, tedana	31

More contributors are welcome!

- Code contributions
- New ideas for data processing and visualization
- Documentation & education
- Questions that can help us identify gaps in the code or documentation
- Shared datasets to help with validation
- Processing your datasets to us test code

Acknowledgements



- Slides: Javier Gozalez-Castillo
- 100-runs multi-echo study:
 - The volunteers!
 - Peter Bandettini
 - Javier Gonzalez-Castillo
 - Ben Gutierrez
 - Vinai Roopchansingh
 - Laura Buchanan
 - Colin Hoy
 - NIH Biowulf computing cluster: hpc.nih.gov

Many! Including:

- Taylor Salo
- Eneko Uruñuela
- Logan Dowdle
- Neha Reddy
- Stefano Moia
- Elizabeth DuPre