Multi-echo fMRI

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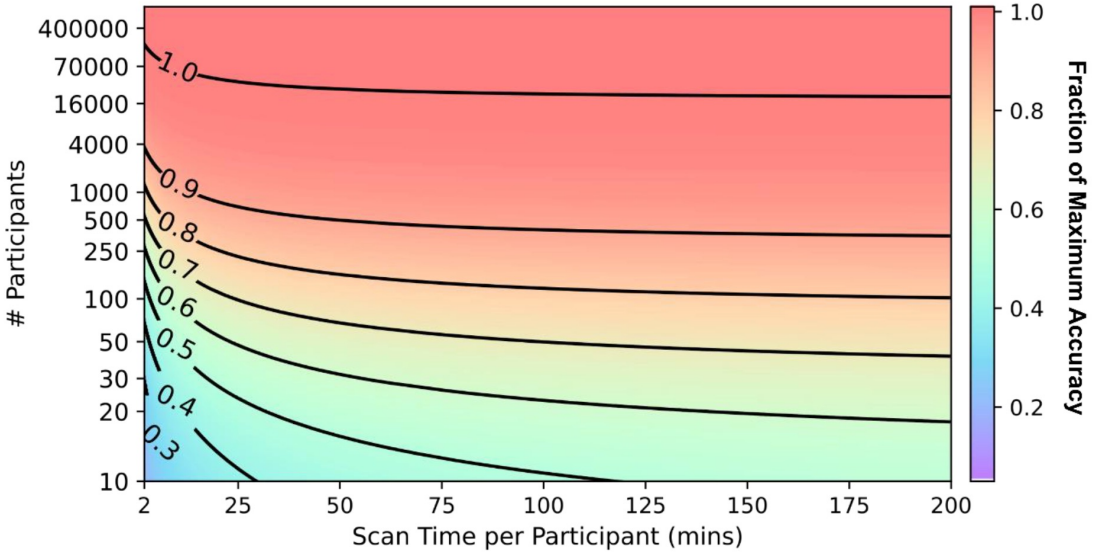
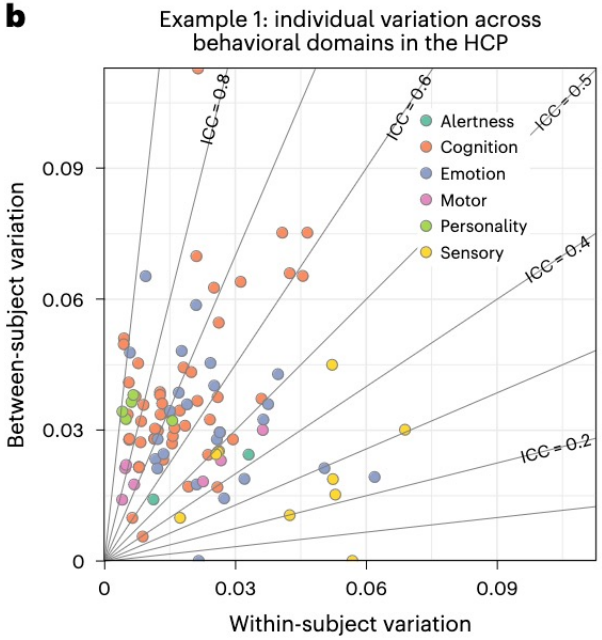
July 16, 2024

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

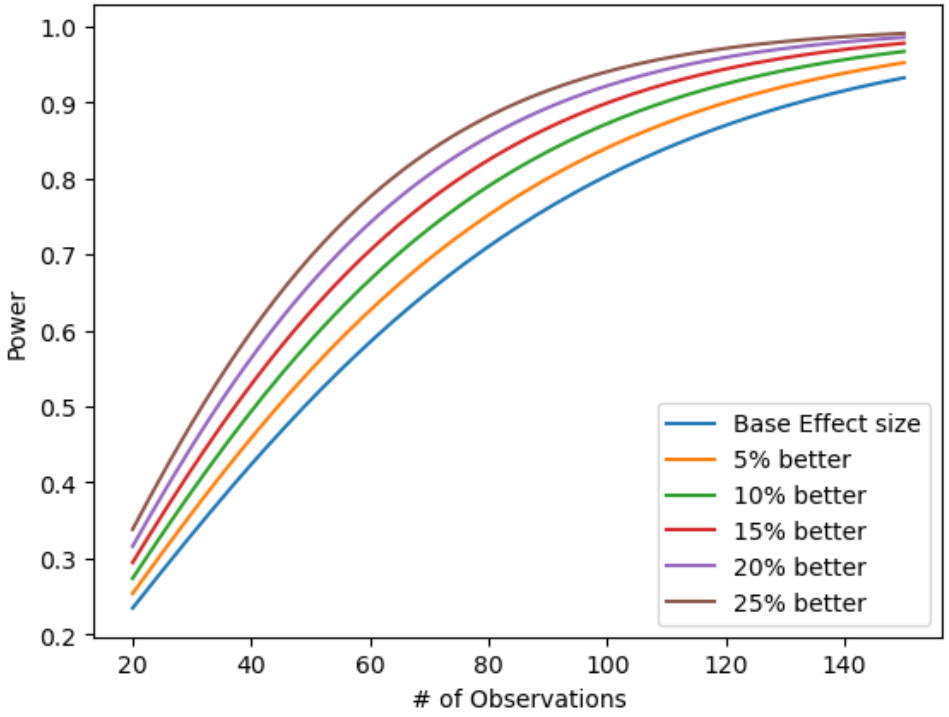


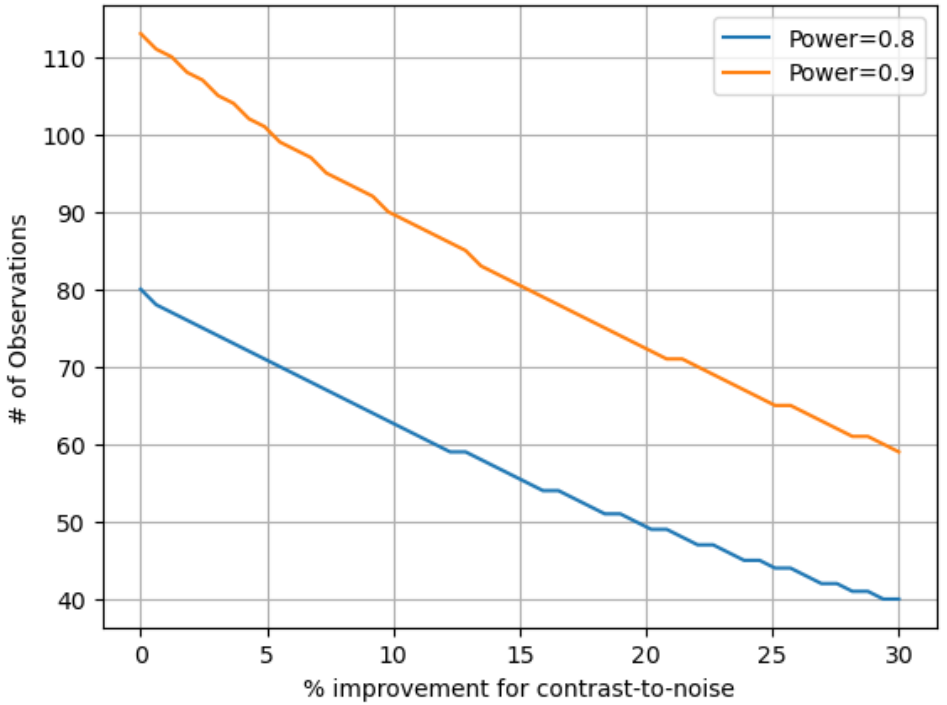
Xu et al. Nature Methods 2023

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

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

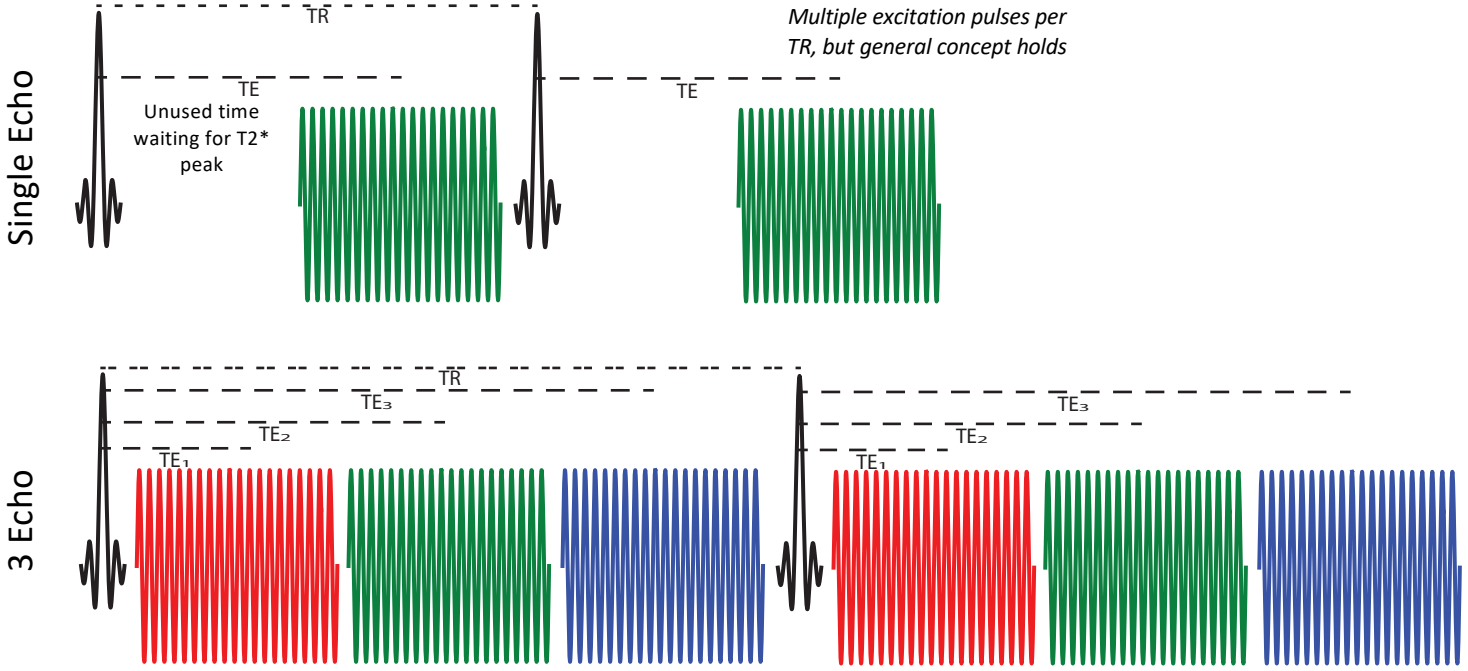
  but it already helps and has the potential to address key road bocks towards better data

Overview

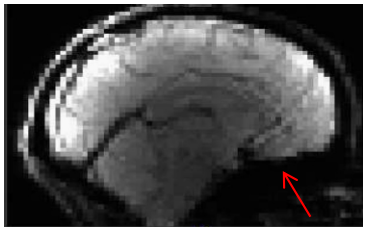
- Intro to multi-echo fMRI
- Multi-echo fMRI for noise removal
- A few examples of how multi-echo can help
- Considerations for acquisition
- tedana multi-echo software & community
  - “TE-dependent analysis of multi-echo fMRI with tedana” JOSS 2021
  - How to contribute

Talks with pdfs and links to recordings: https://fmrif.nimh.nih.gov/index.php/SummerCourse
Recordings: https://www.youtube.com/@nimhcmn

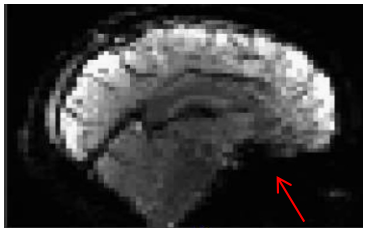
What is multi-echo fMRI?



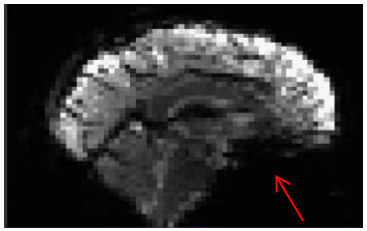
Echo 1



Echo 2

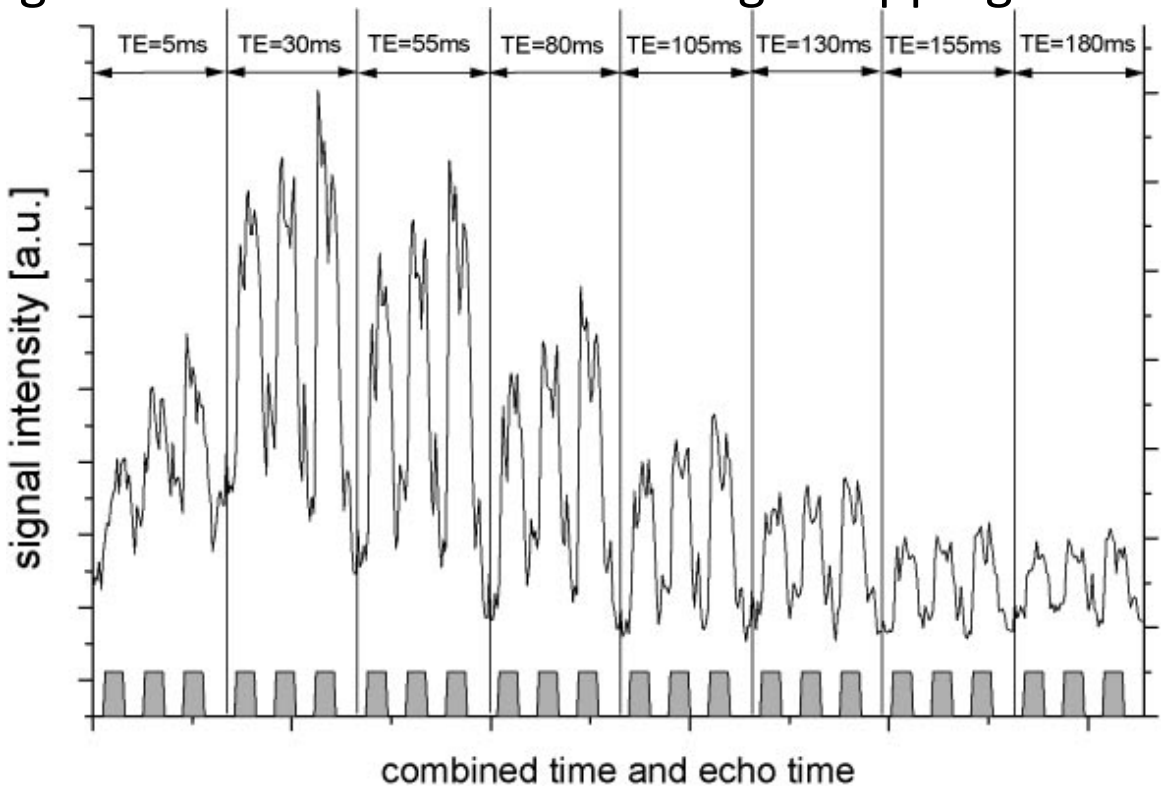


Echo 3



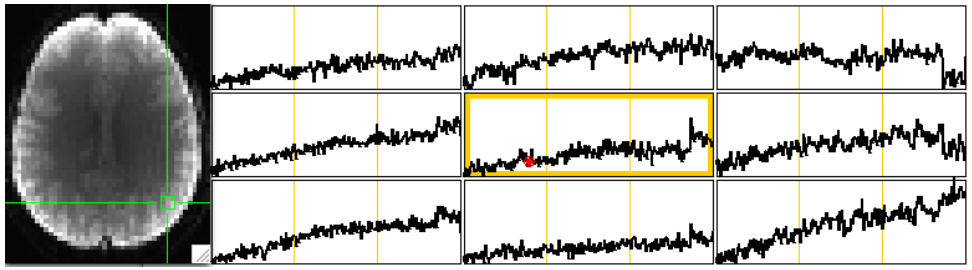
fMRI response magnitudes by echo time

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*

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

Echo time dependence

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

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=83bavs4rlUg (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

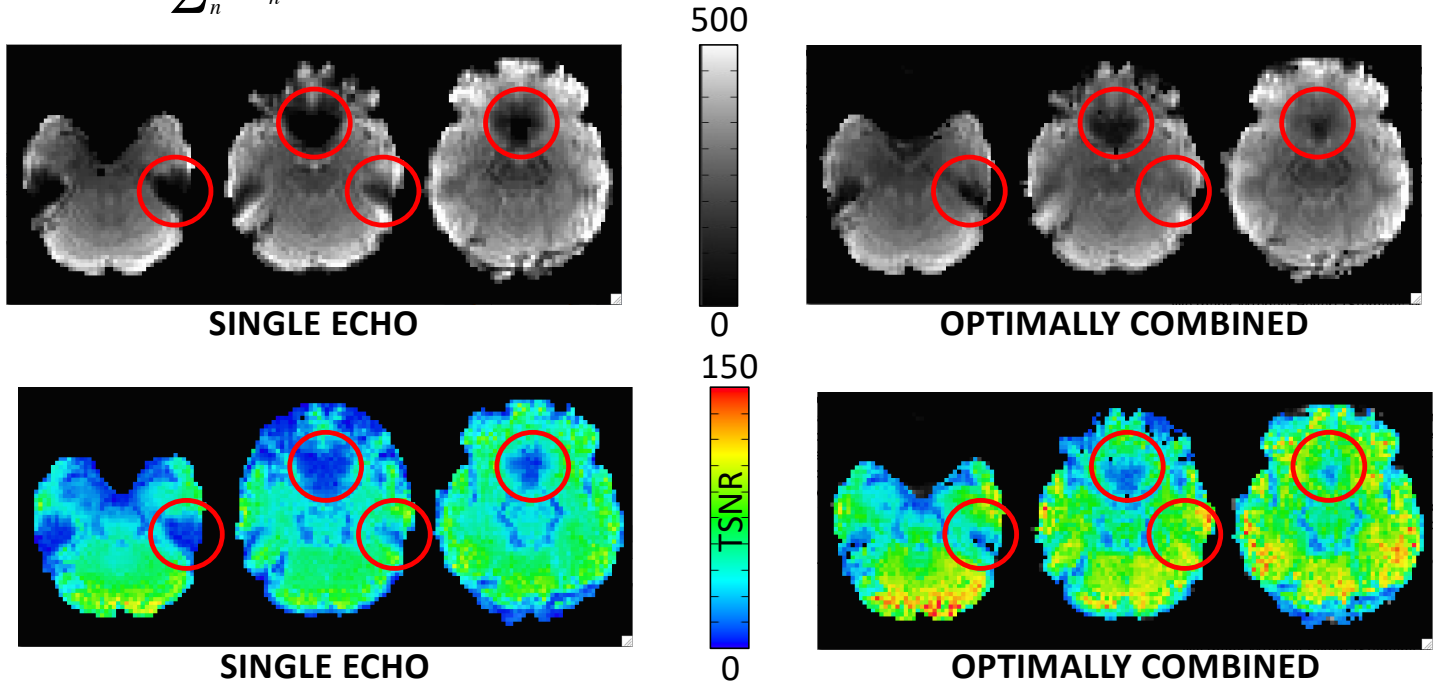
We have N_e pseudo-concurrent measurements

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

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

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

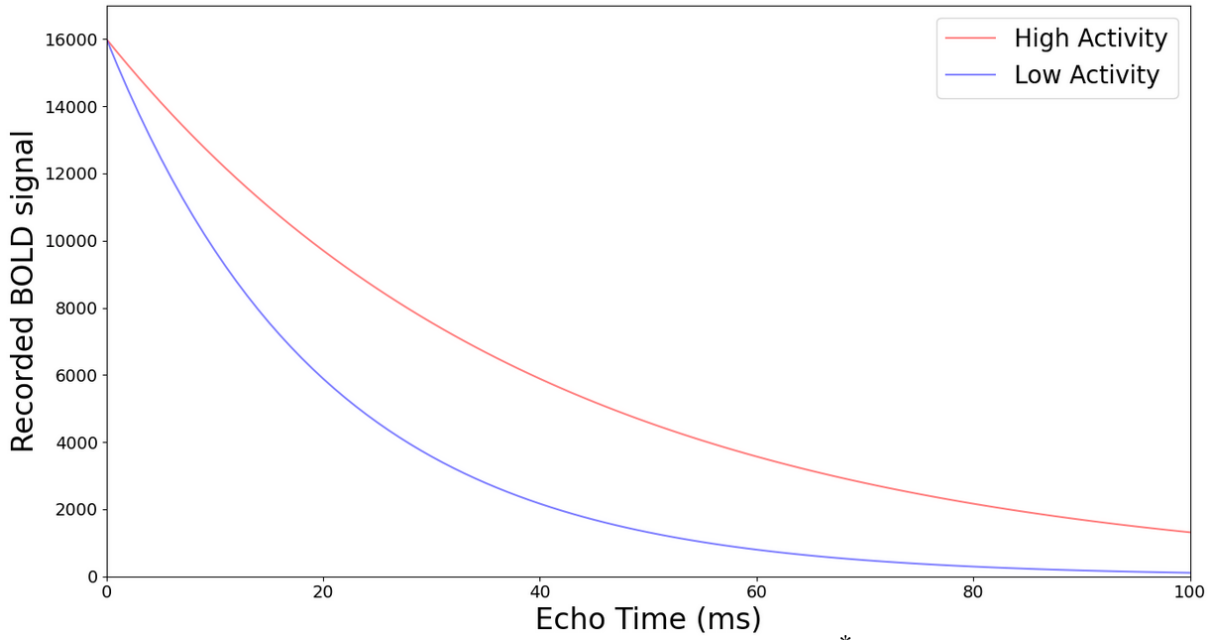
- Weighted average of echoes skewed towards T_2^*
- Reduces thermal (measurement) noise and weights towards T_2^* signal
- Recovers signal in some dropout regions
- Straightforward math & reliable improvements
- Automatically calculated in AFNI, fMRIPrep, and tedana



T_2^* is the curve of the decay across echoes

The BOLD signal is a T_2^* change

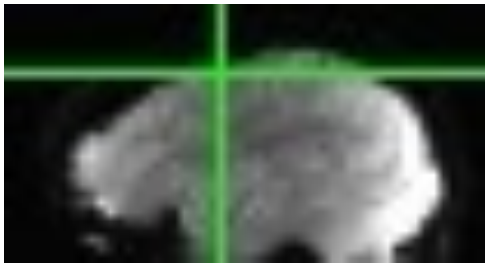
S_0 is a change in the TE=0 intercept.

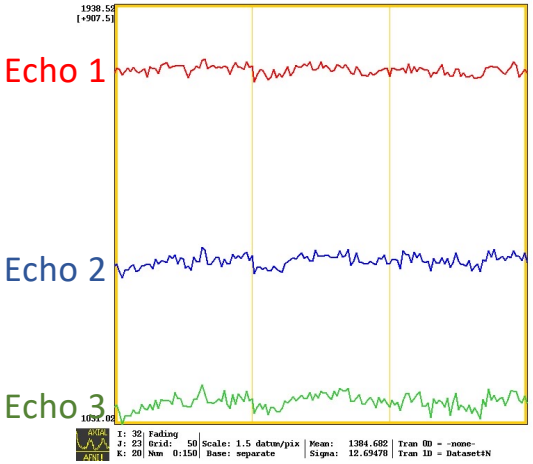


$$S(x,t,TE) = S_o(x,t)e^{-R_2^*(x,t)\cdot TE}$$

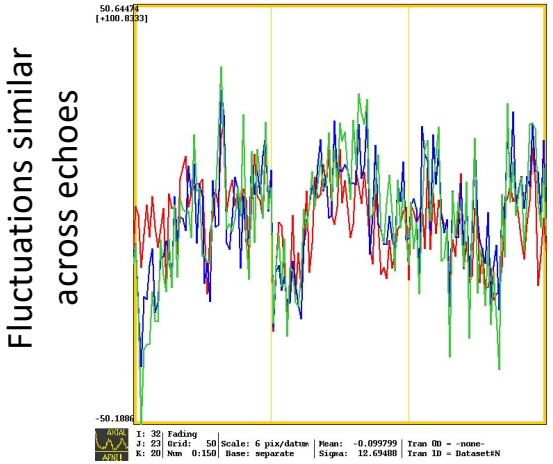
Taylor Salo: https://me-ica.github.io/multi-echo-data-analysis/content/Signal_Decay.html

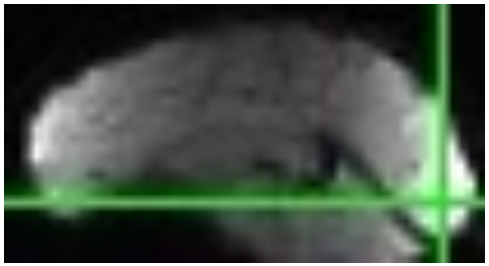
Separating S_0 from T_2^* signal

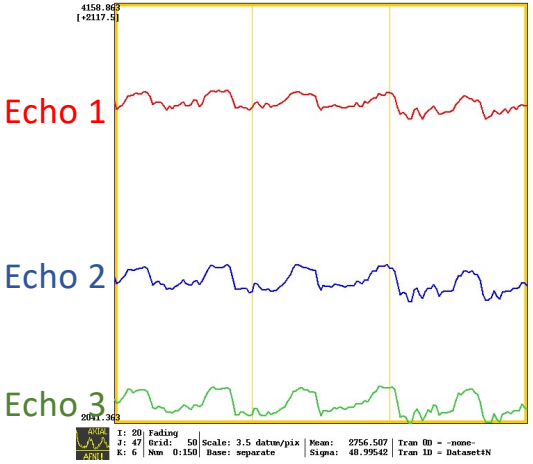


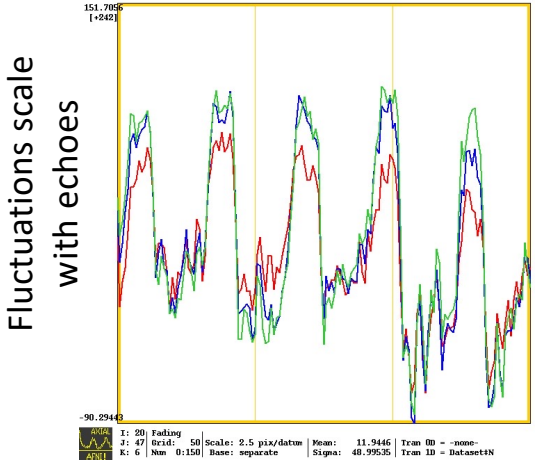


Demeaned Time Series









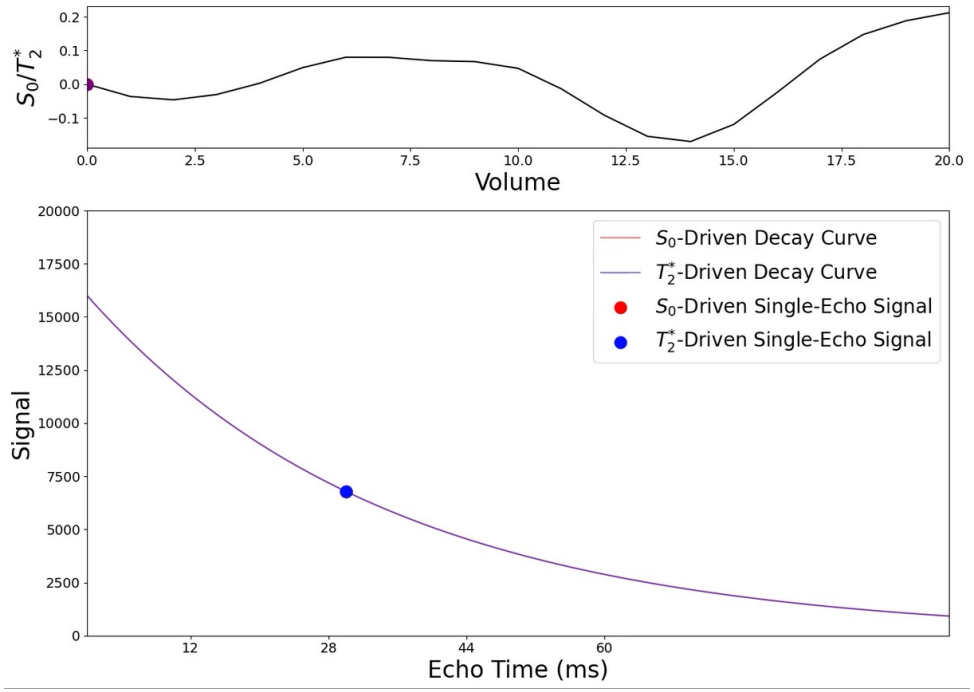
S_0 vs T_2^*

- 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

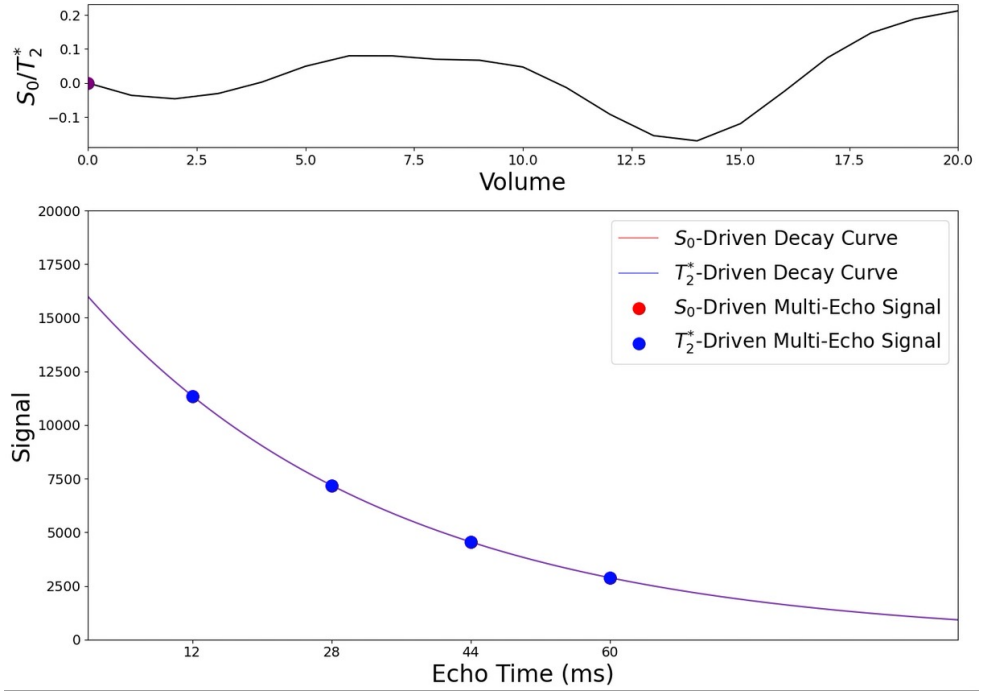
It would be VERY useful if we could remove the S_0 fluctuations and just look at T_2^*

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



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

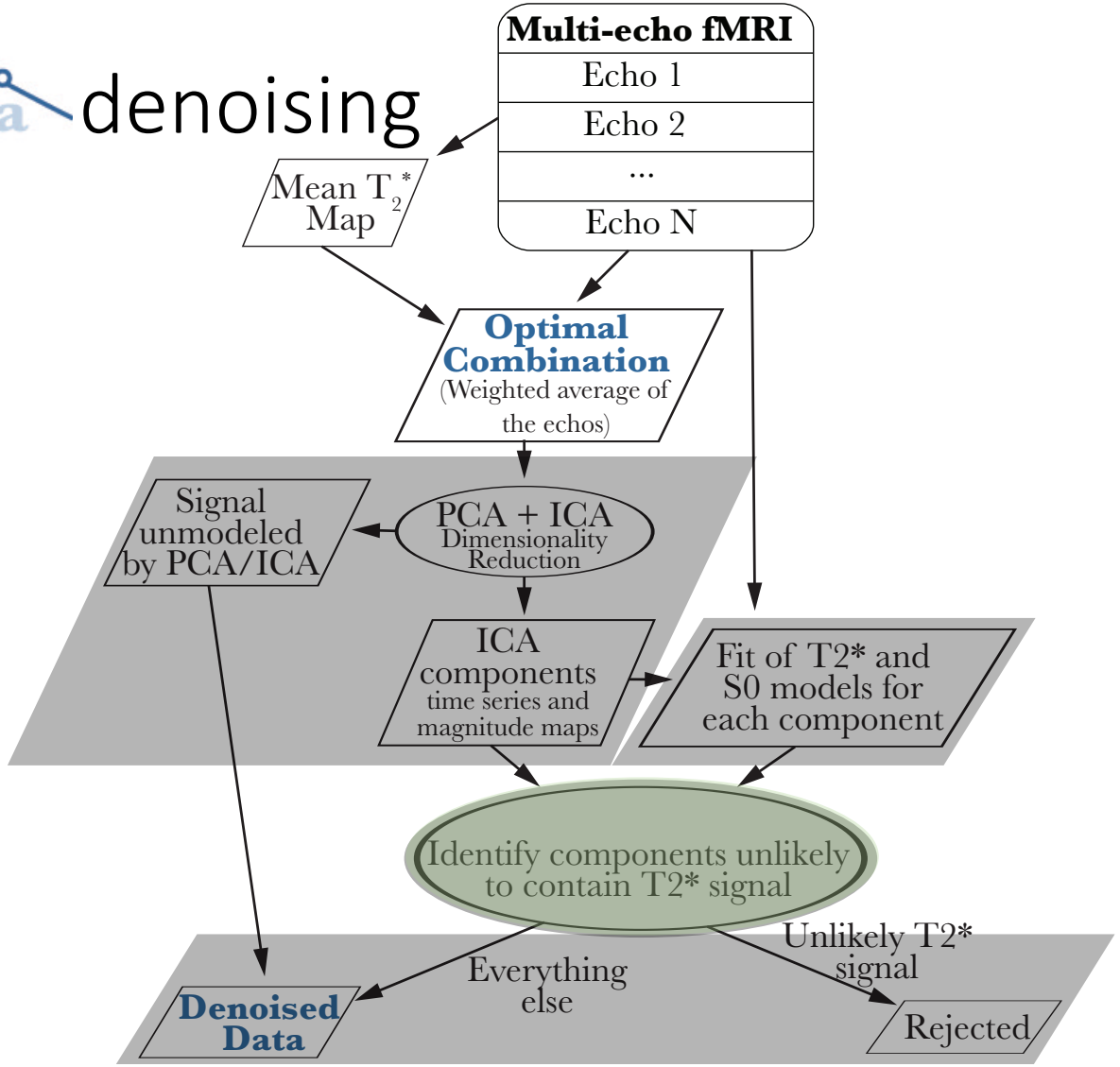
Denoising methods to reduce S_0 fluctuations

- ICA based: MEICA (Kundu 2012 & 2013) →

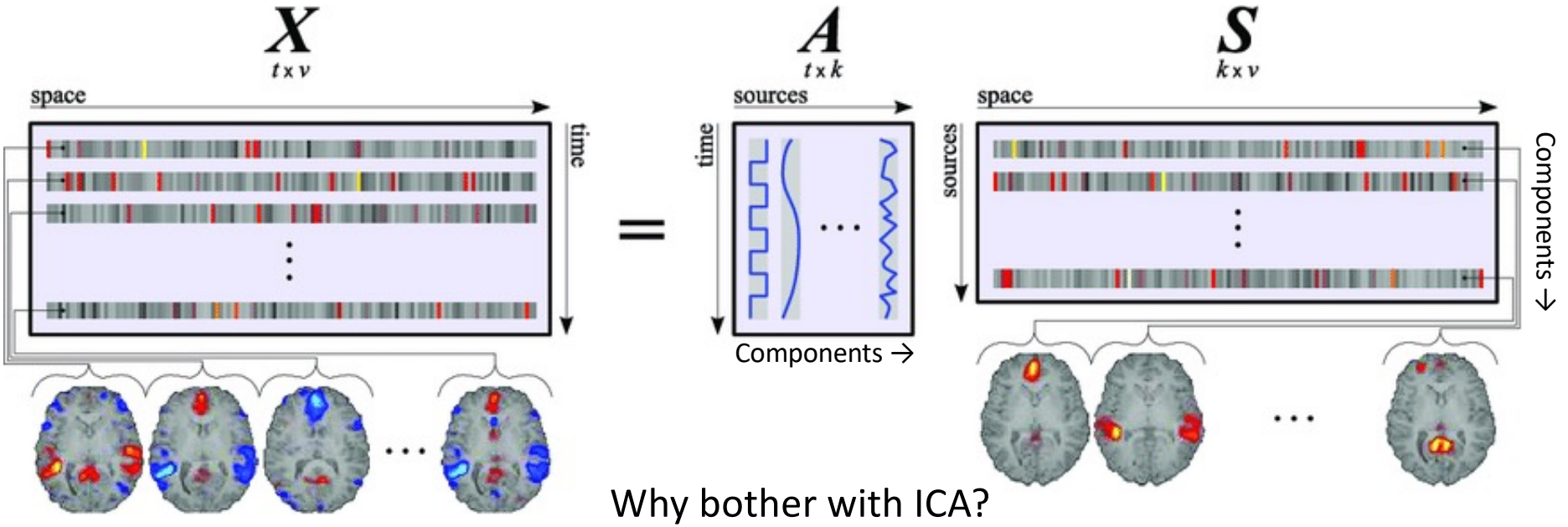
(DuPre, Salo, et al, *JOSS*, 2011)

- 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 tedana denoising



Hand waving explanation of ICA



Why bother with ICA?

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

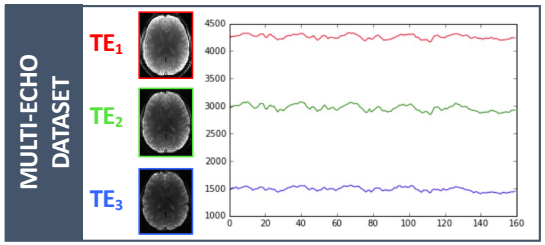
Solving for 2 variables

≥3 measurements

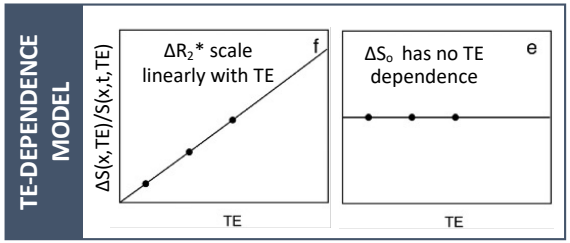
ICA is targeted signal averaging

Ylipaavalniemi, *Variability of Independent Components in functional Magnetic Resonance Imaging*. Available from: https://www.researchgate.net/figure/Spatial-ICA-of-fMRI-data-The-rows-of-the-data-matrix-X-and-sources-matrix-S-are_fig3_267419506

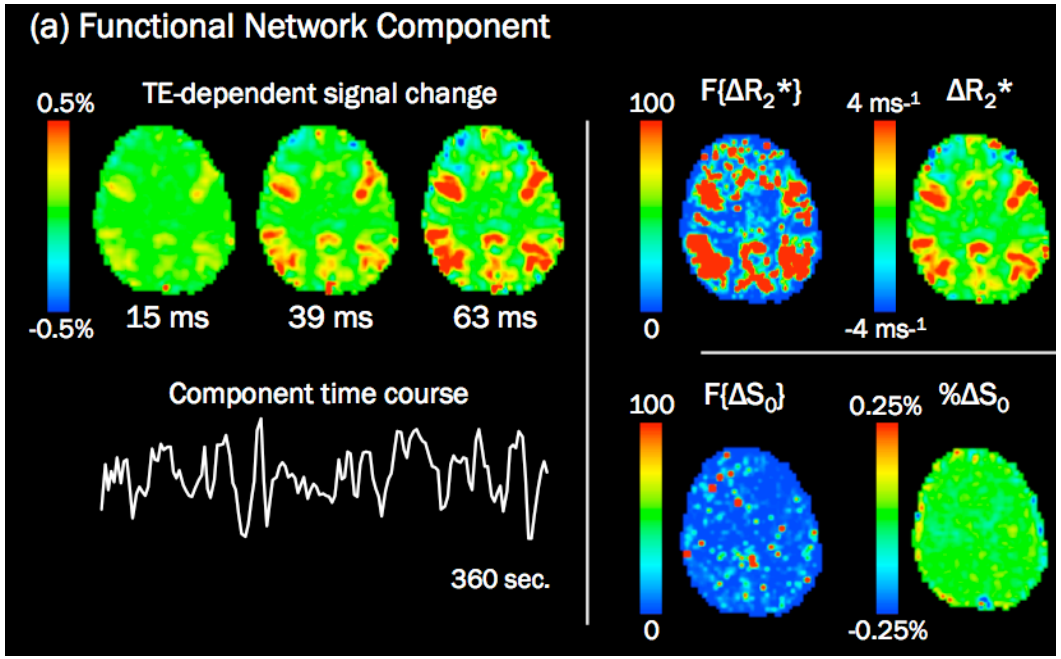
Identifying components unlikely to contain T_2^*



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



Fit across echoes to
R_2^* ($\frac{1}{T_2^*}$)
or S_0 models



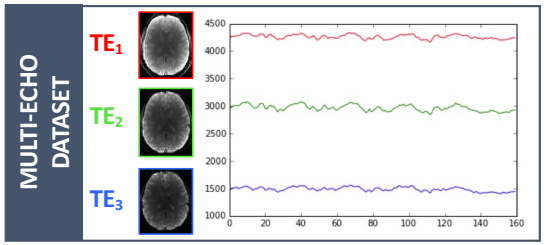
Calculate the weighted sum of the ICA component weight map and the model fit to T2* (Kappa) and S0 (Rho)

Kappa (κ) = 210

Rho (ρ) = 10

Kundu et al., NeuroImage 2012

Identifying components unlikely to contain T_2^*



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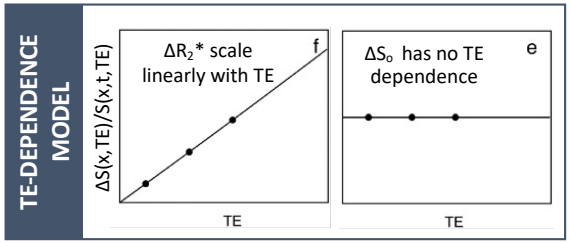

Fit across echoes to
R_2^* ($\frac{1}{T_2^*}$)
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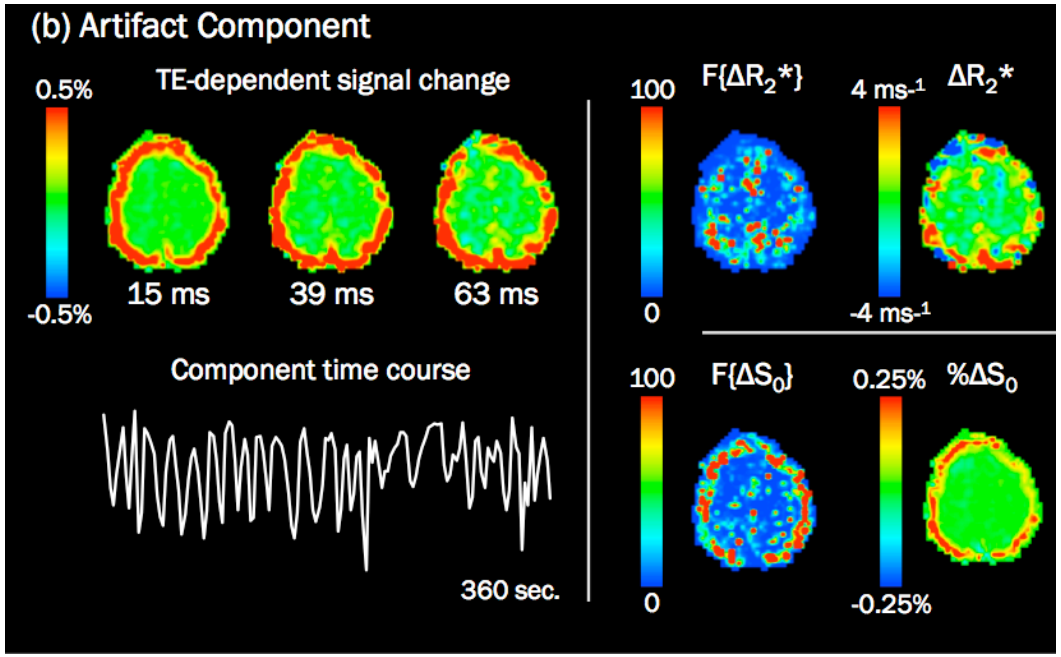


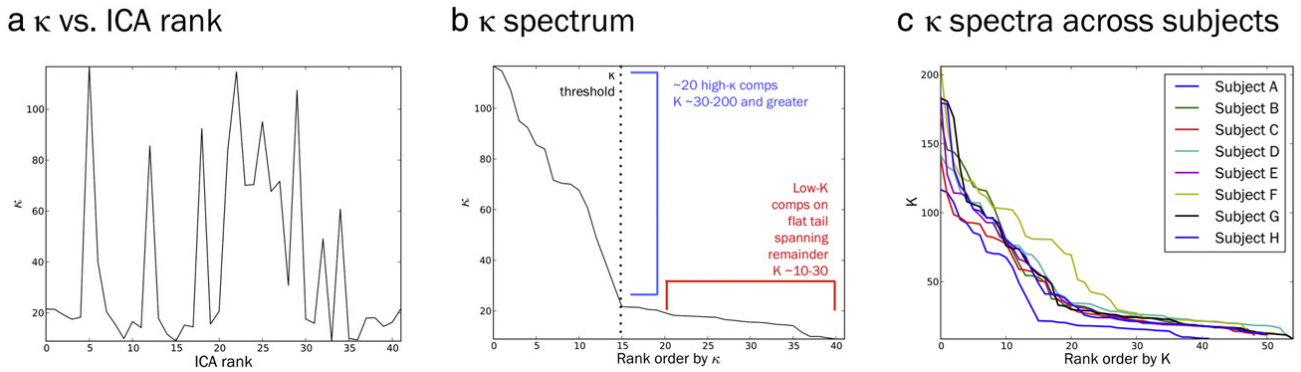
Calculate the weighted sum of the ICA component weight map and the model fit to T2* (Kappa) and S0 (Rho)

Kappa (κ) = 32

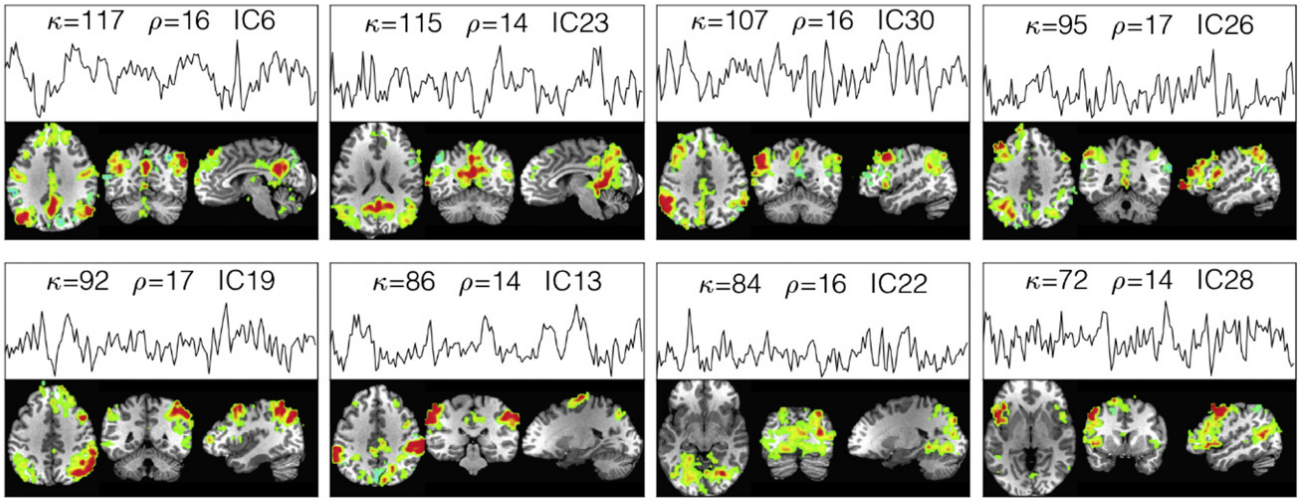
Rho (ρ) = 81

Kundu et al., NeuroImage 2012

Example retained components

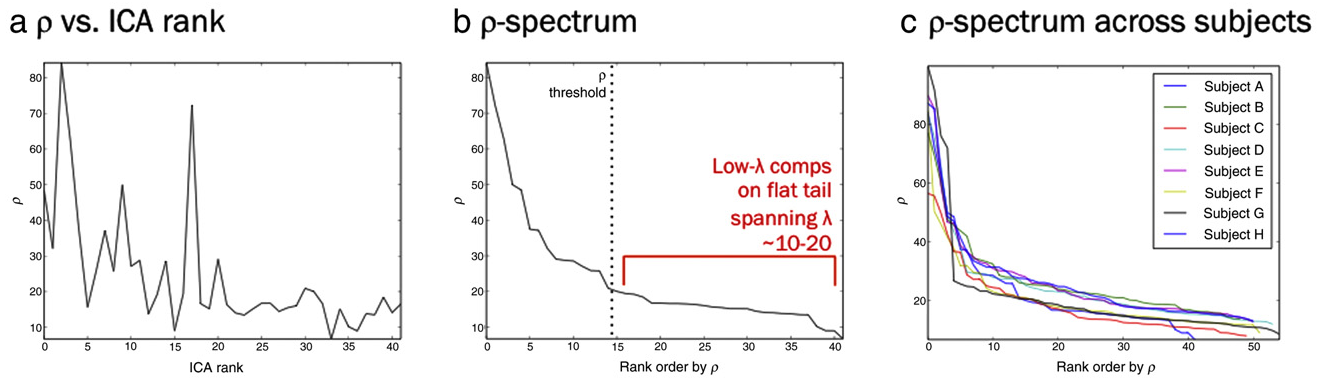


d ΔR_2* maps of top κ ranked components for a representative subject

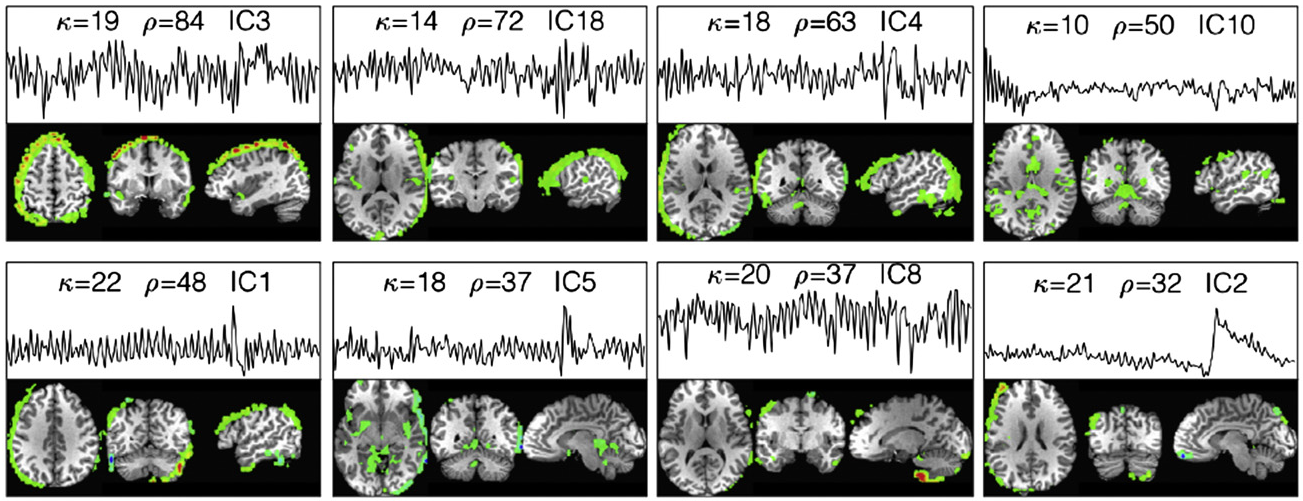


Kundu et al., NeuroImage 2012

Example rejected components

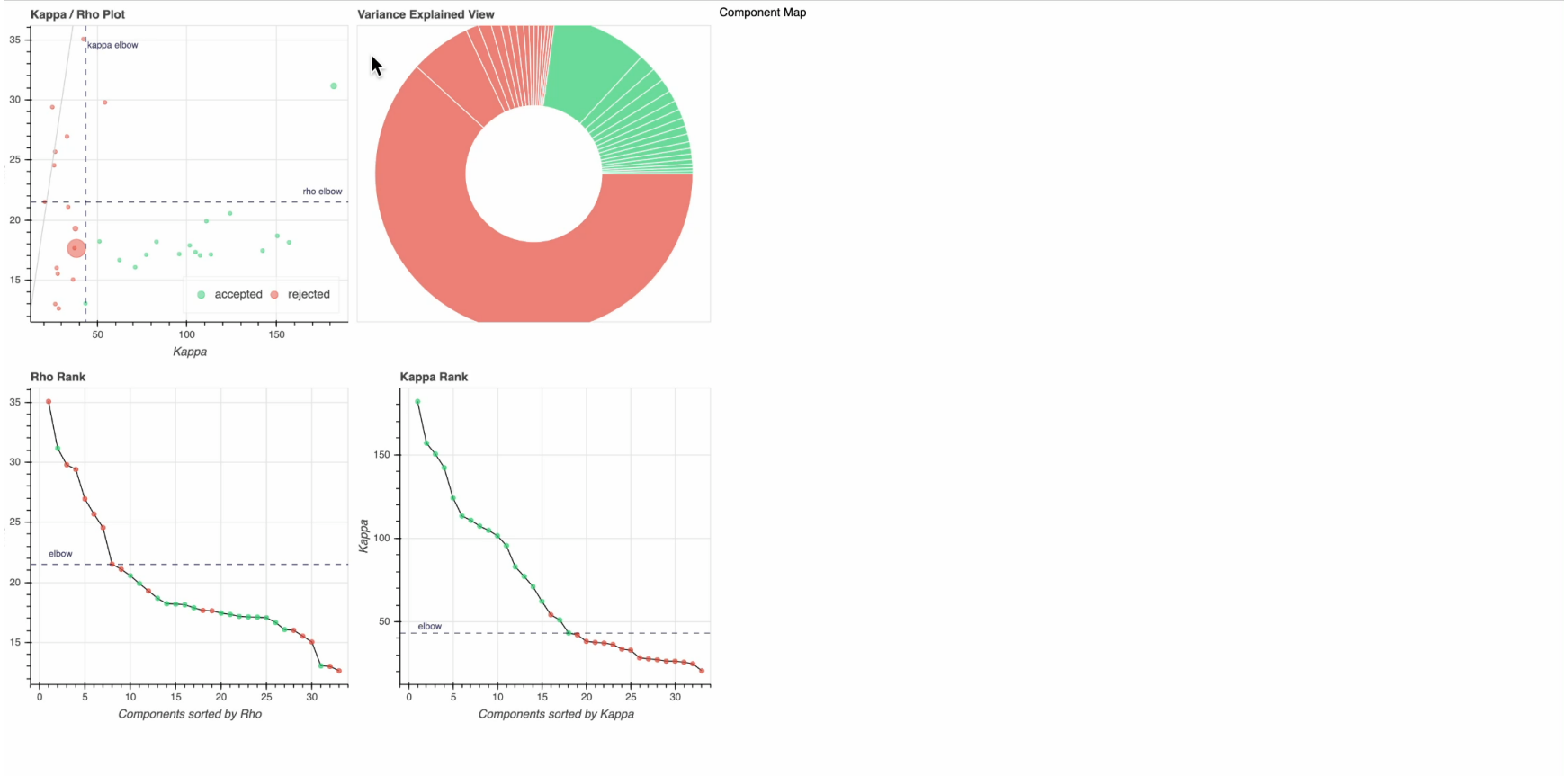


d ΔS_0 maps of top ρ-ranked components for a representative subject



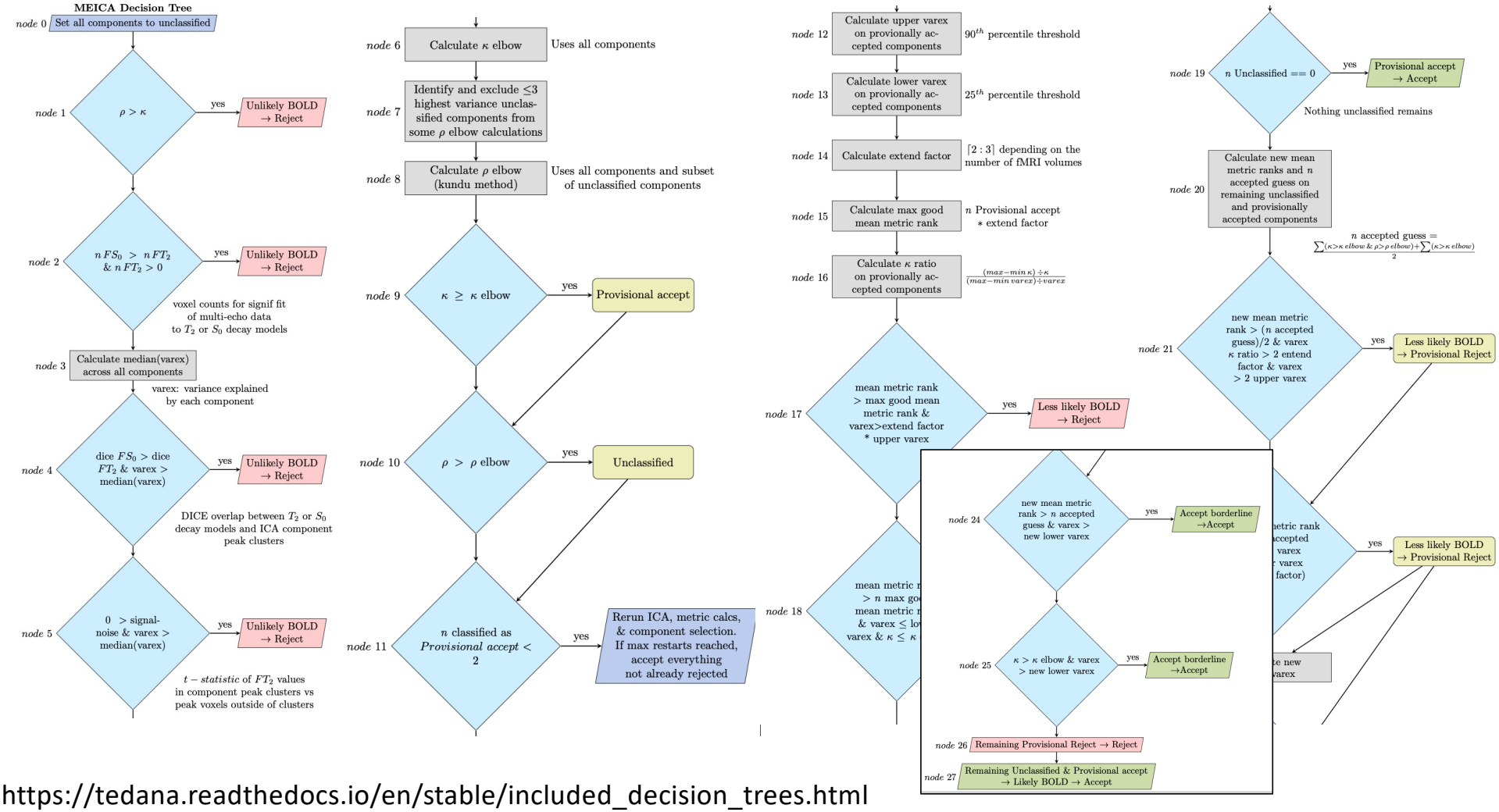
Kundu et al., NeuroImage 2012

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.

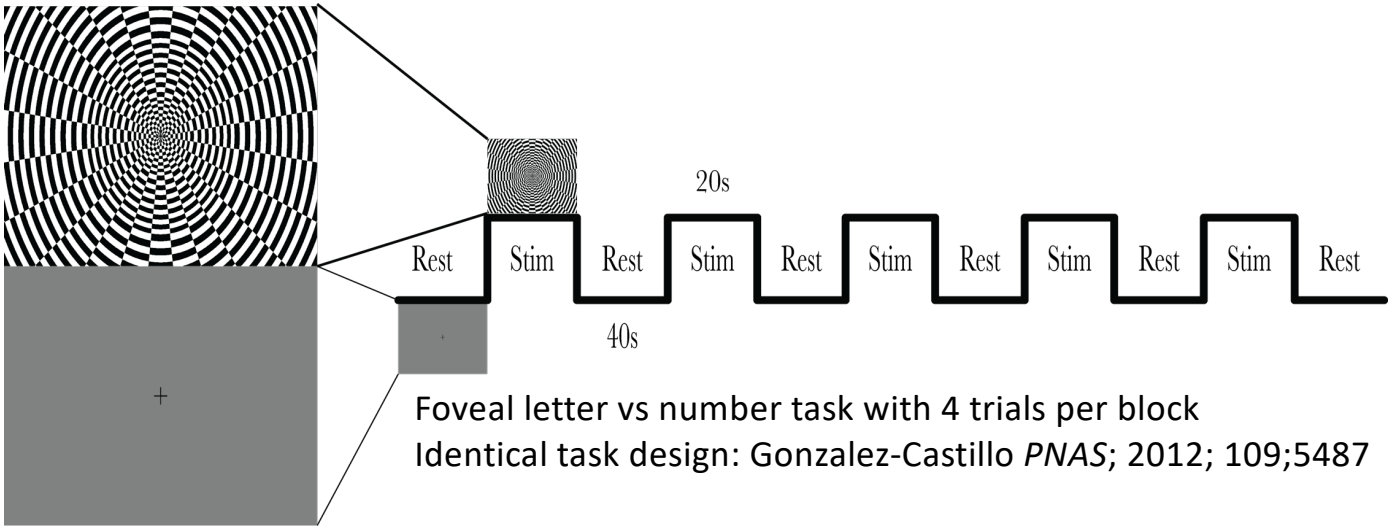
  https://tedana.readthedocs.io/en/stable/building_decision_trees.html

Empirical evaluations of multi-echo fMRI methods

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

Experimental Design

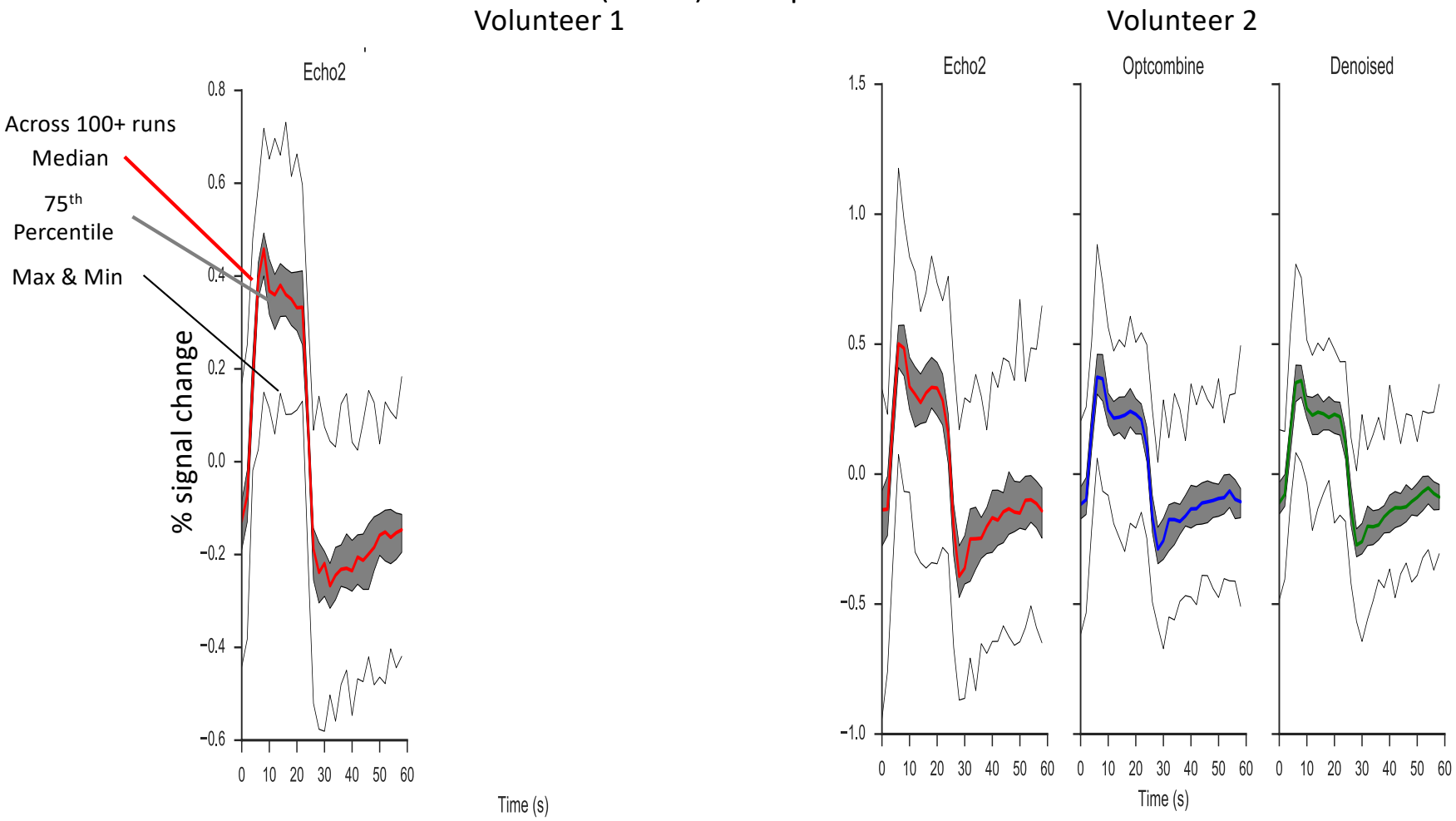
- 2 Volunteers, 9 sessions, 103 runs each, **9 hours of data per person**
- GE MR750, 3T, 32 channel coil
- EPI: 3.5mm^3, **3 echoes, TE=15.4, 29.7, & 44.0ms** FA=75°, TR = 2s, 33 slices
- 5.5 minutes, 161 volumes (150 volumes used in each run)



Foveal letter vs number task with 4 trials per block
Identical task design: Gonzalez-Castillo *PNAS*; 2012; 109;5487

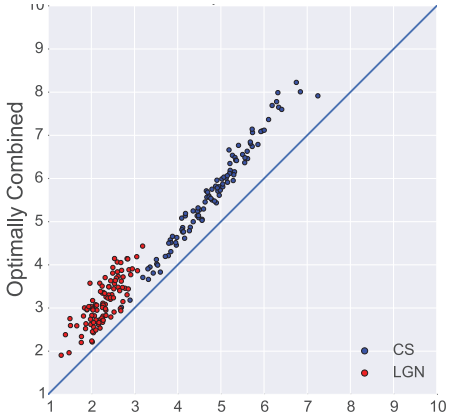
Optimal Combination & Denoising processed with: bitbucket.org/BenGutierrez/me-ica

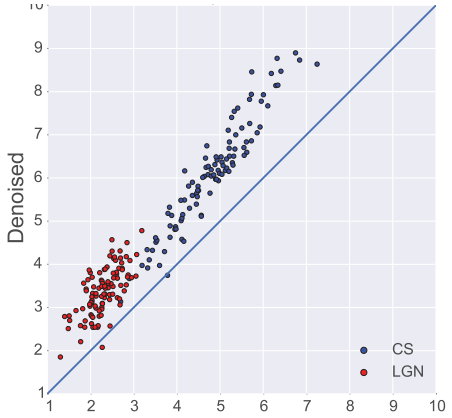
Lateral Geniculate Nucleus (LGN) Responses

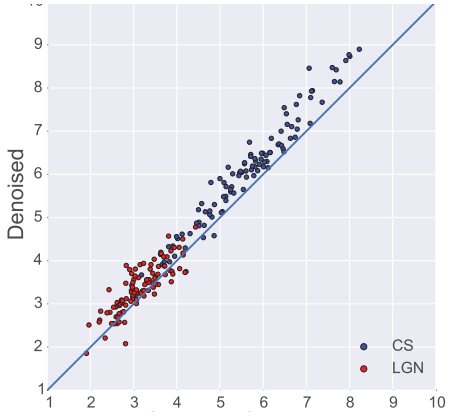


Contrast-to-Noise By Run

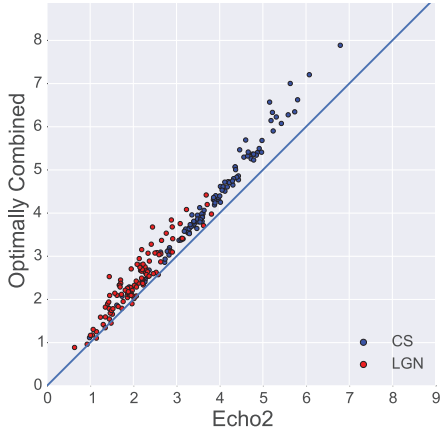
CNR Comparison for Volunteer 1

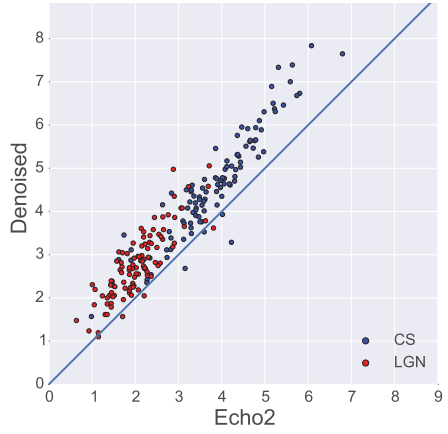


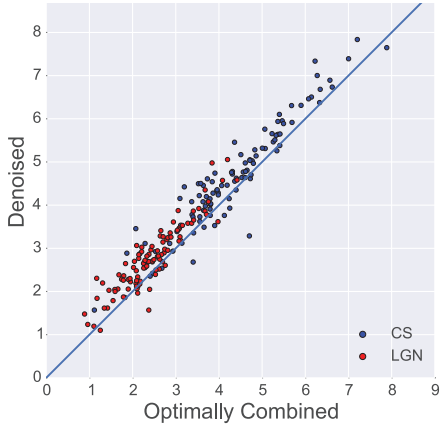




CNR Comparison for Volunteer 2







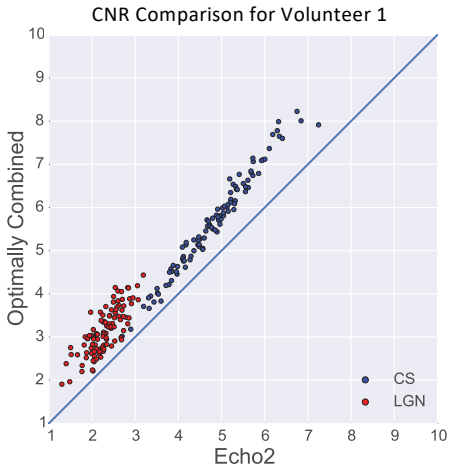
Regions of Interest

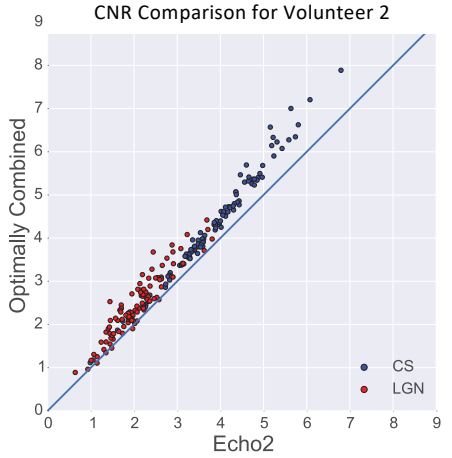
CS
Calcarine Sulcus

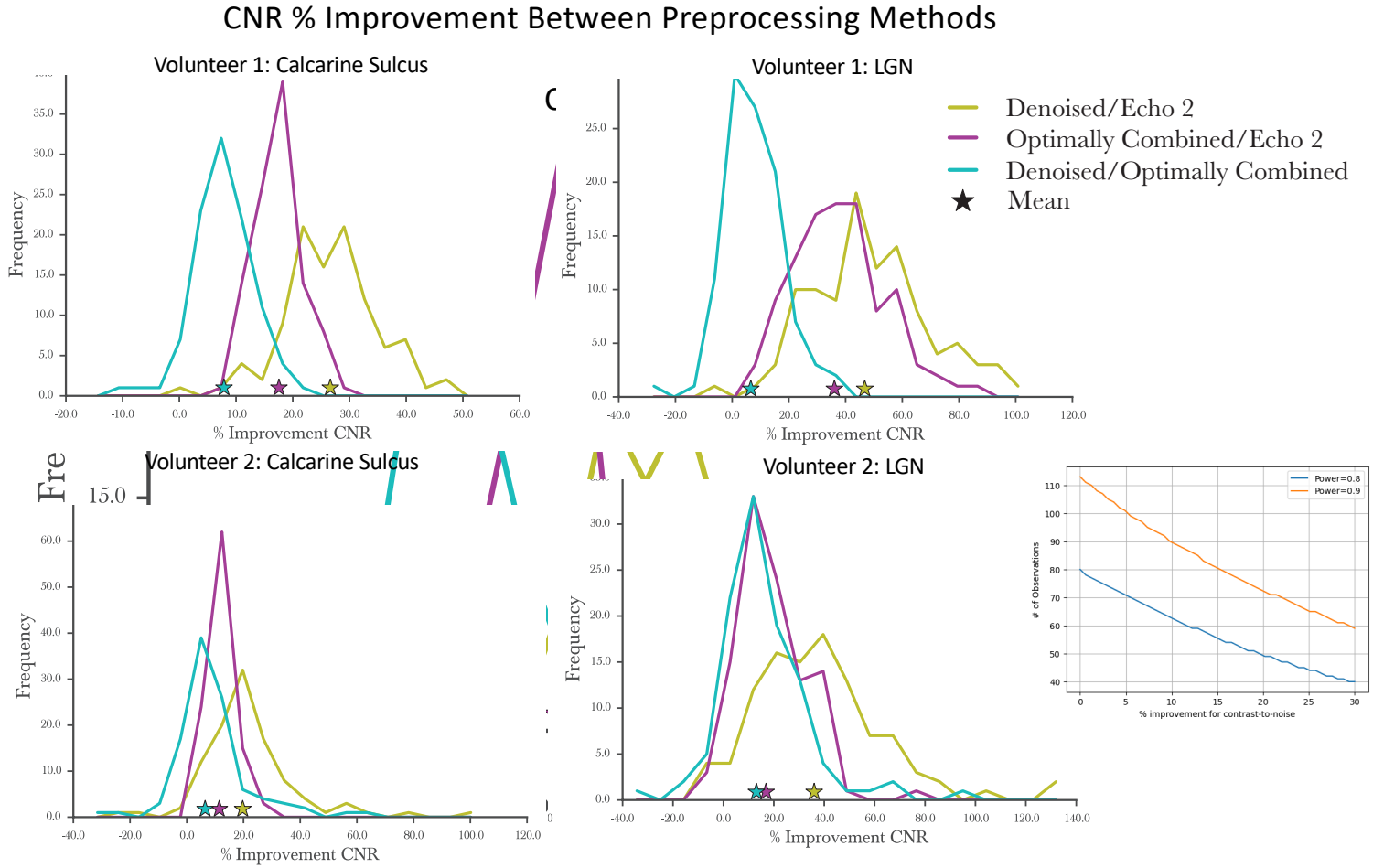
LGN
Lateral Geniculate Nucleus

Each dot is the CNR values from 1 run

Contrast-to-Noise By Run



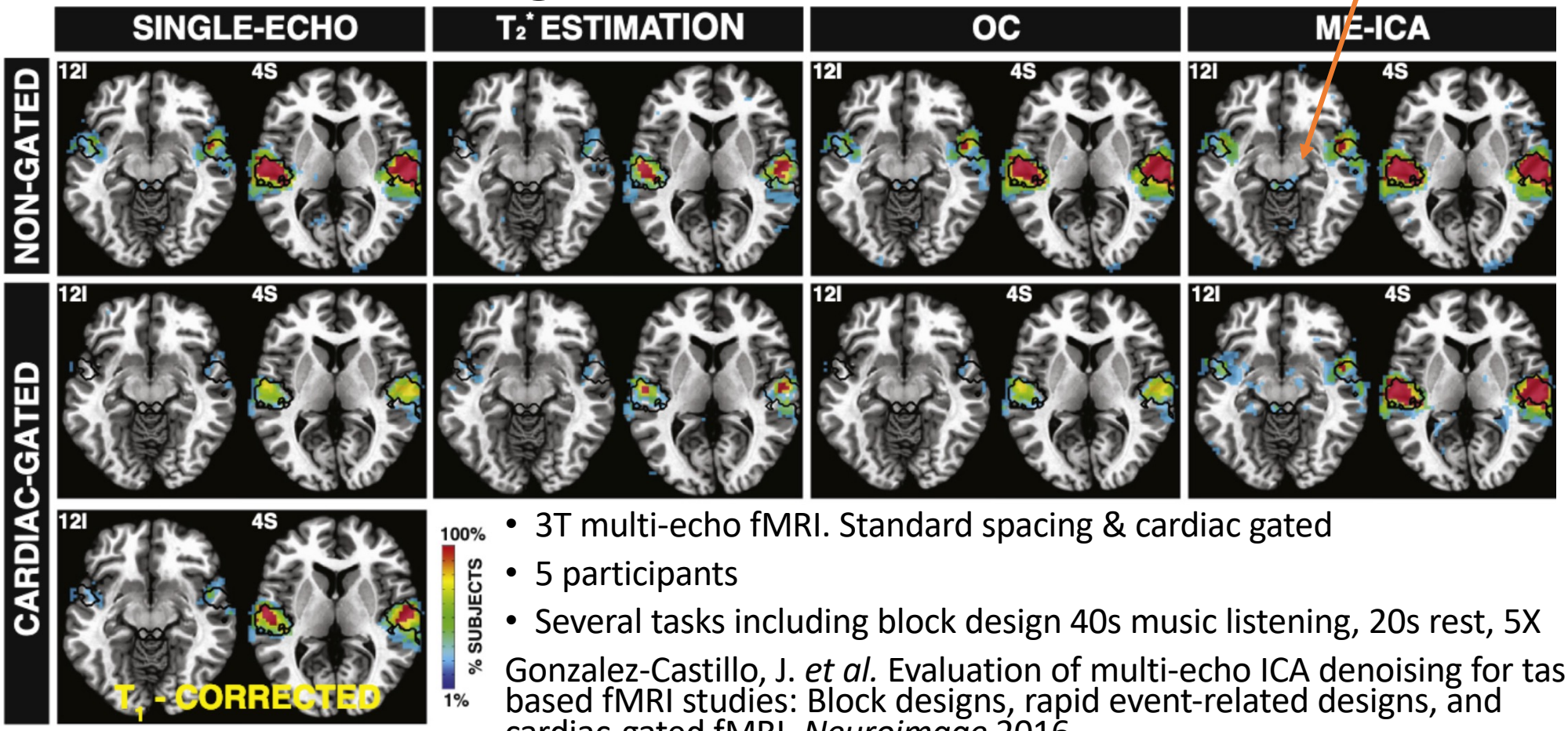




Take home message from this study

- 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

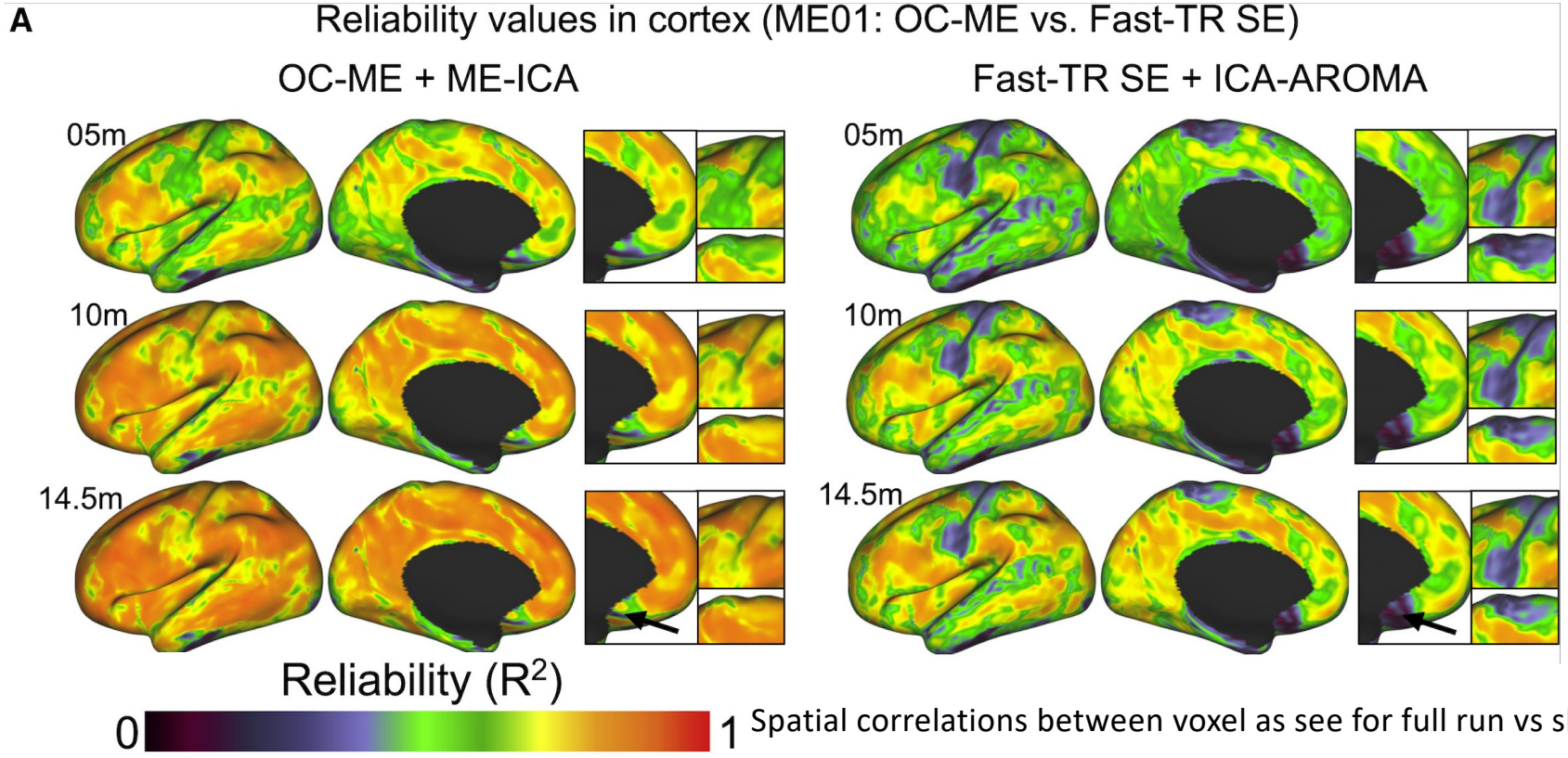
Music listening task



- 3T multi-echo fMRI. Standard spacing & cardiac gated
- 5 participants
- Several tasks including block design 40s music listening, 20s rest, 5X

Gonzalez-Castillo, J. *et al.* Evaluation of multi-echo ICA denoising for task based fMRI studies: Block designs, rapid event-related designs, and cardiac-gated fMRI. *Neuroimage* 2016

Reliably for functional connectivity



Spatial correlations between voxel as see for full run vs shorter runs

"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"

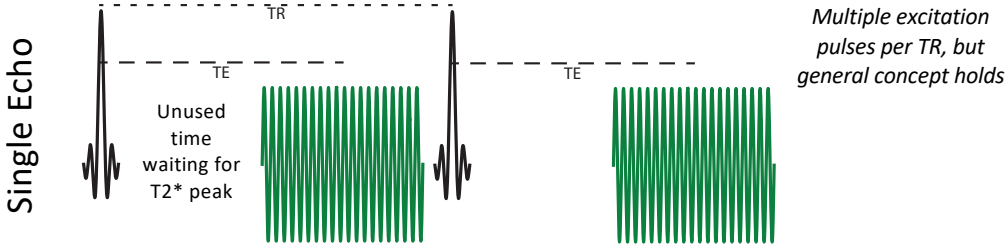
Growth of multi-echo fMRI usage

- 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

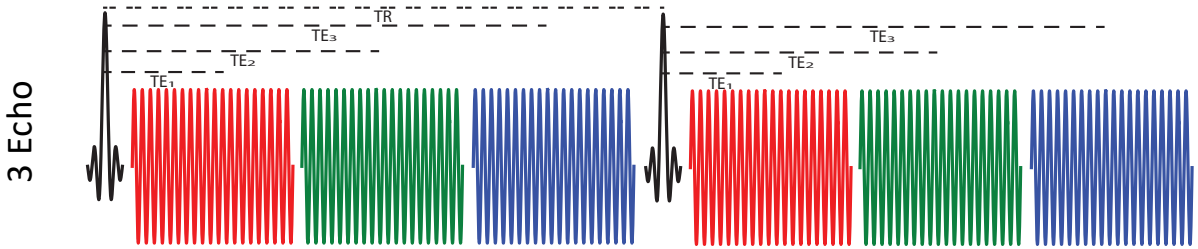
https://tedana.readthedocs.io/en/stable/multi-echo.html#datasets

Acquisition Considerations

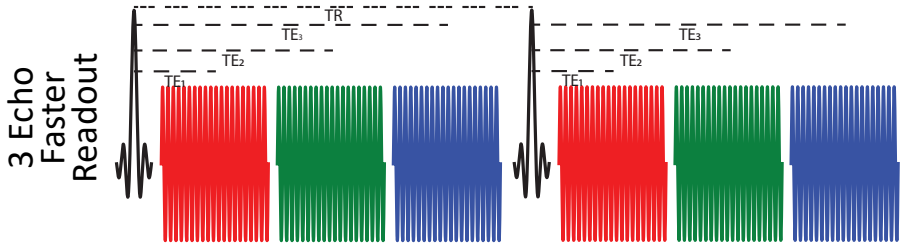
- Common question: Multi-echo fMRI or a short TR?
- Better question: How many echoes for how short a TR?



Multiple excitation pulses per TR, but general concept holds



Optimize many acquisition parameters based on study goals, just like any other fMRI study

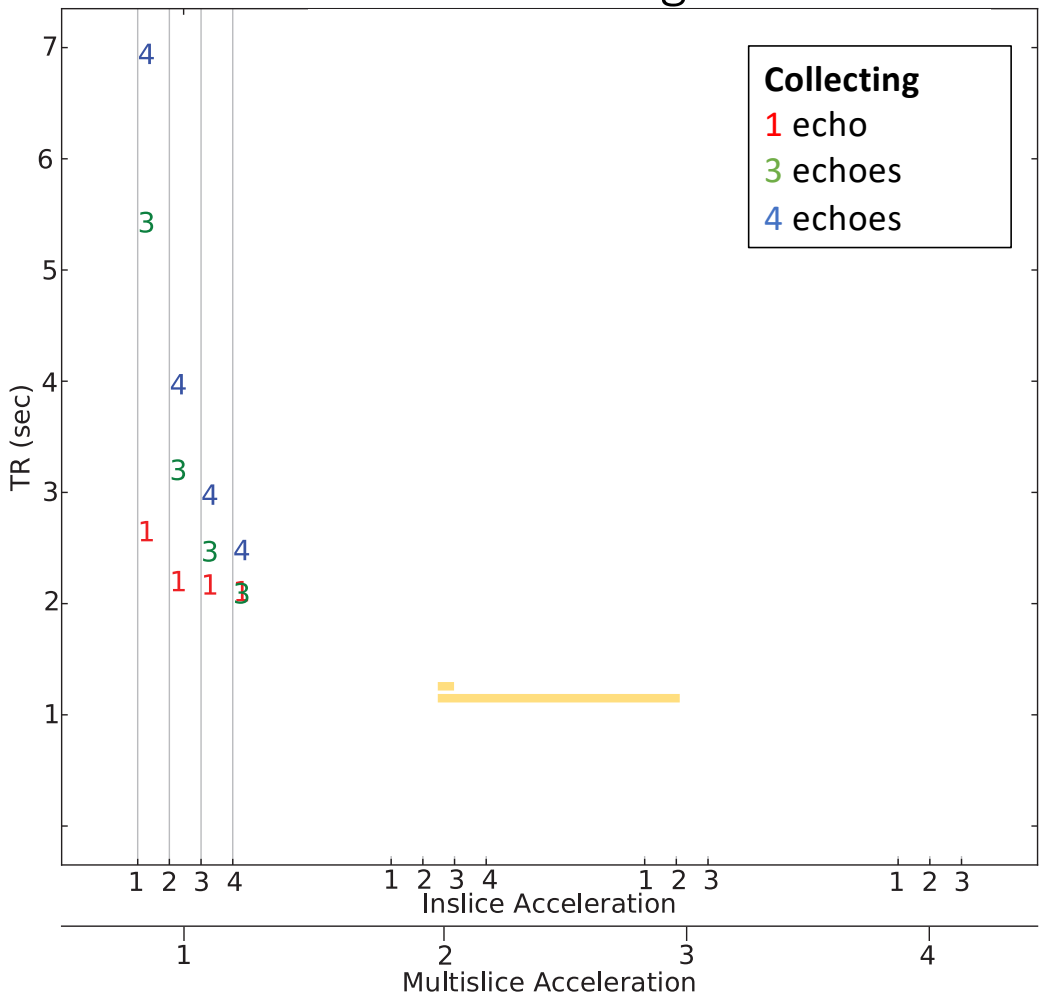


Faster Readout

- ↑ inslice acceleration (GRAPPA, ASSET, etc)
- ↑ voxels for same field-of-view
- ↓ slices or ↑ multislice or multiband acceleration

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

3mm^3 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

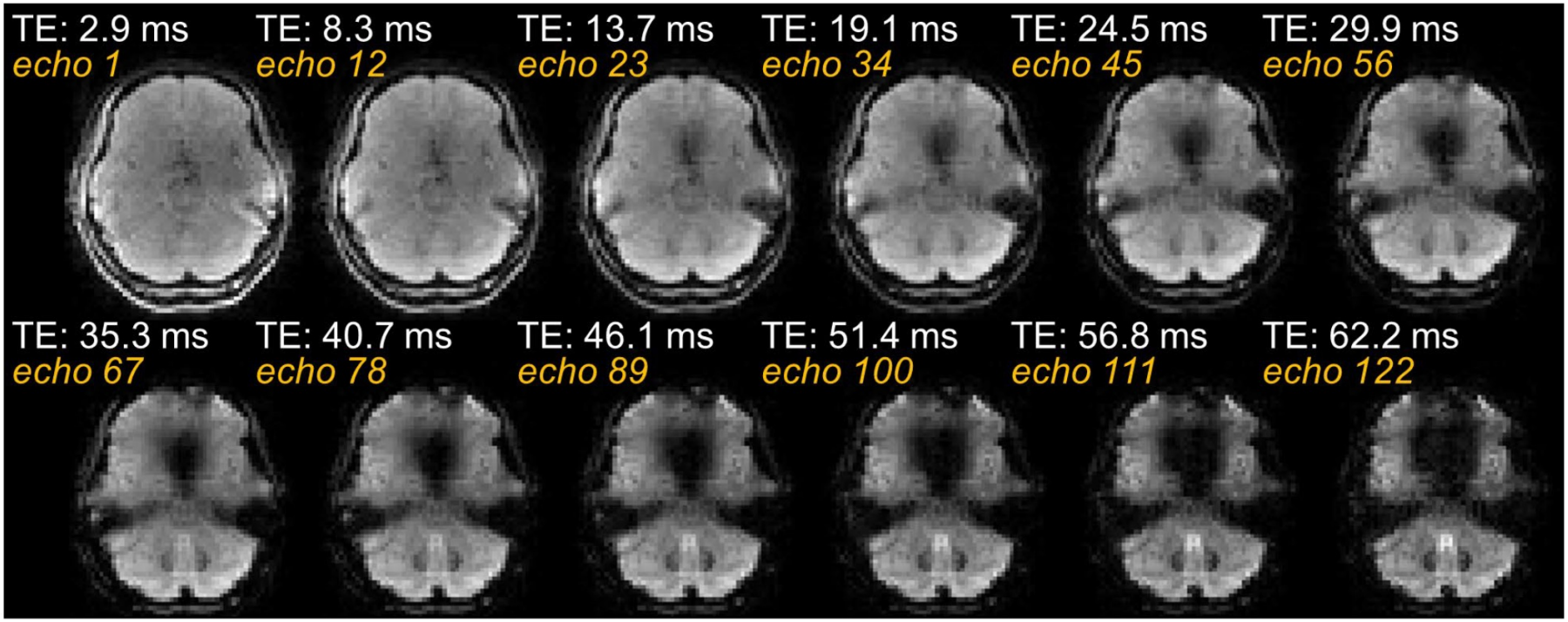
Inslice Acceleration = 4: ~-1% TR cost

Acquisition Considerations

Thinking through an acquisition plan

- Cost of acquiring multi-echo can be balanced with a combination of:
  acceleration↑, voxel size ↑, slices↓, & TR ↑
- More CNR from "optimal combination" of echoes **should** balance lower SNR from acceleration↑
- 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

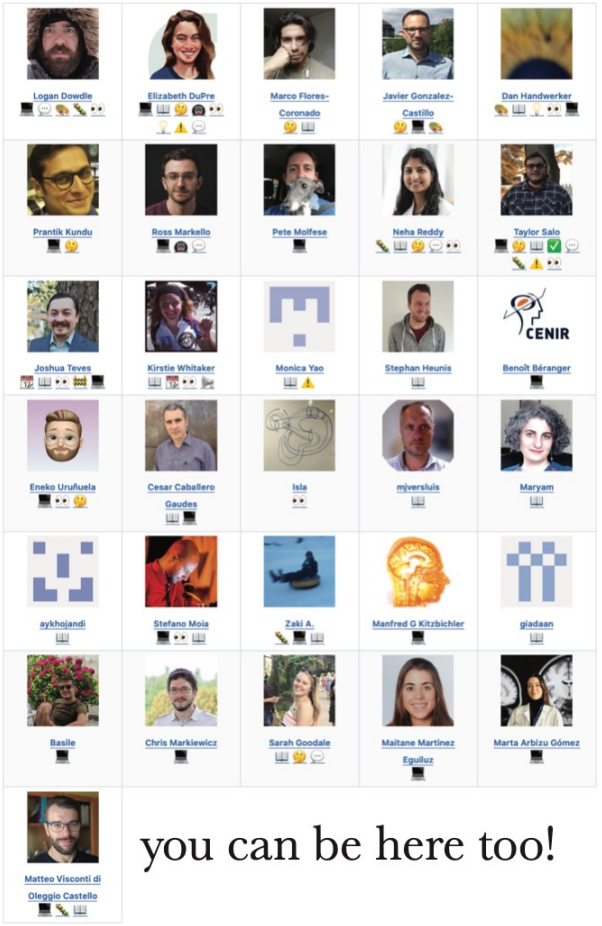
Dong et al https://www.biorxiv.org/content/10.1101/2024.01.24.577002v1

Software & Community

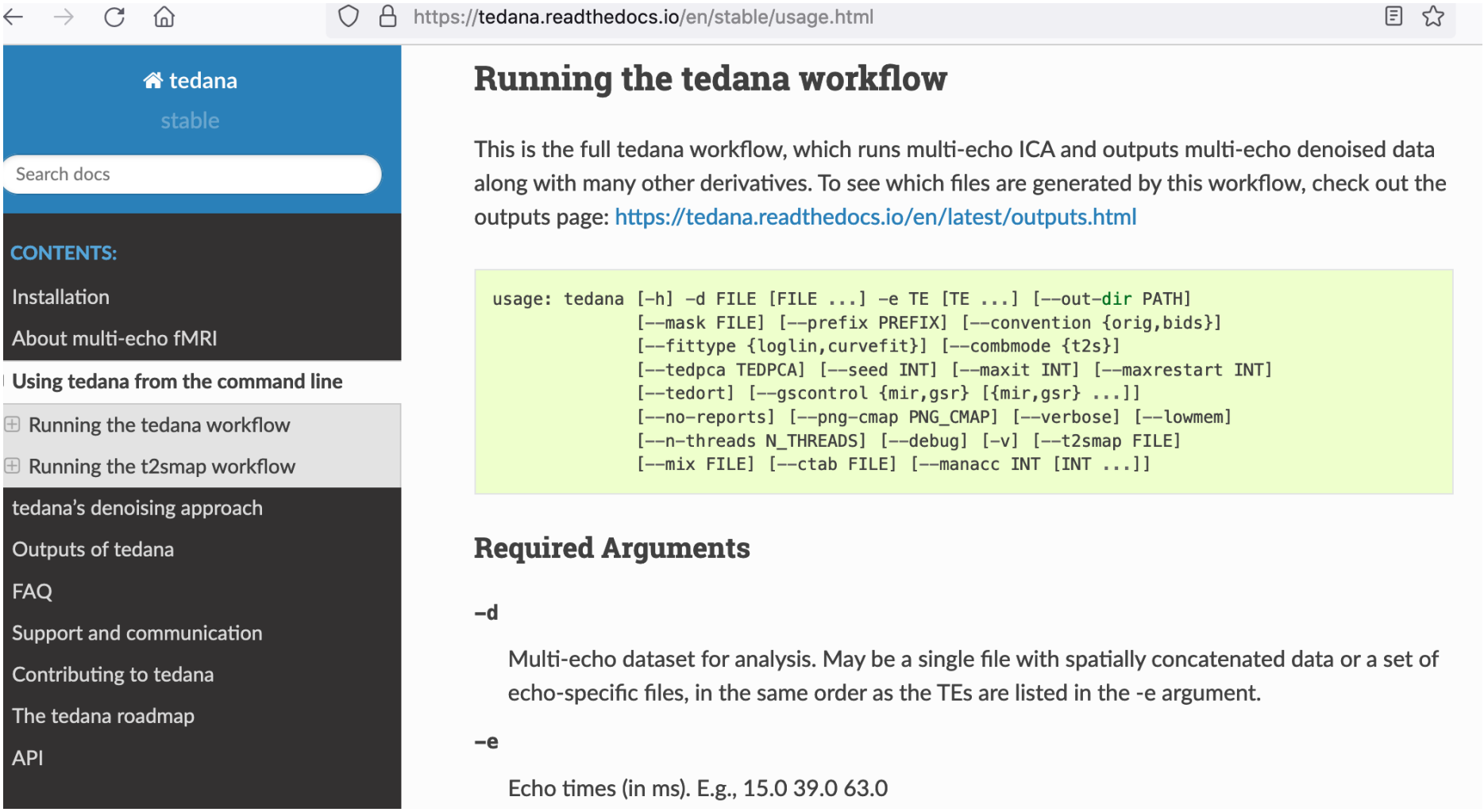
- Tedana started in May 2018 by Elizabeth DuPre to advance MEICA by Prantik Kundu
- Processing code
- Multi-echo education
- Approx 31 contributors and counting
- Monthly developer calls, a periodic newsletter, active issue board & code updates

Code:
https://github.com/me-ica/tedana

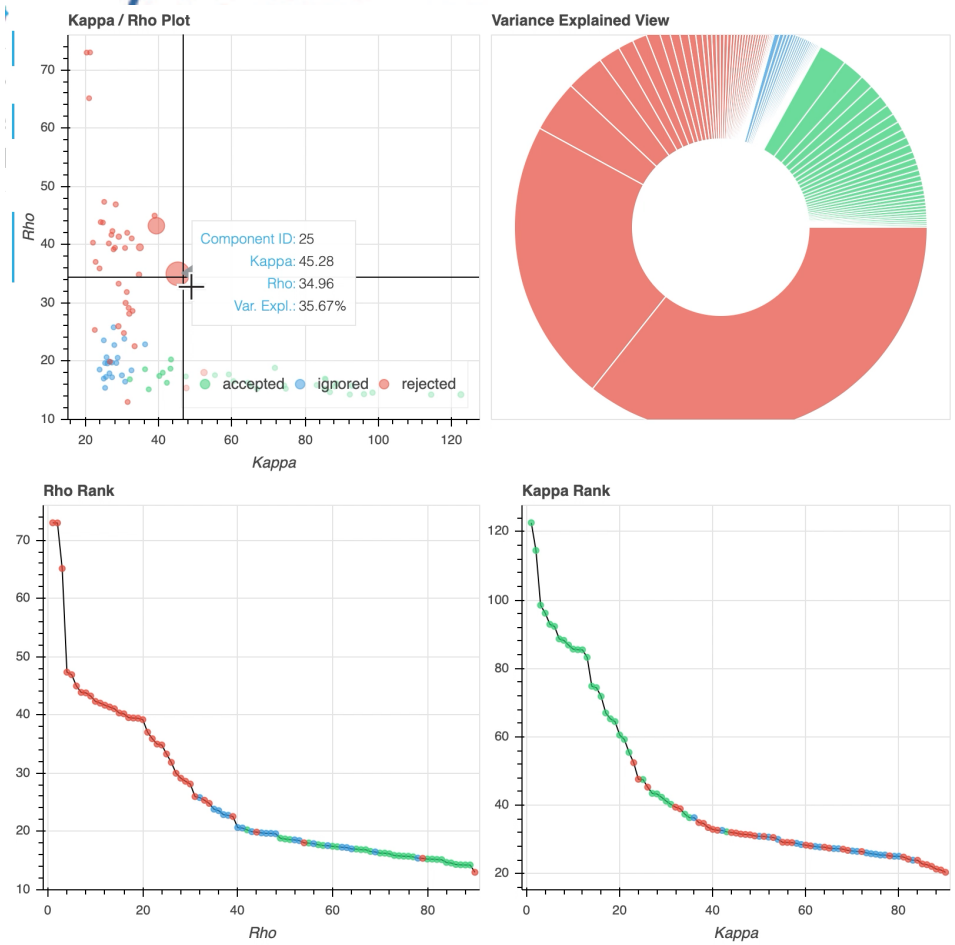
Documentation:
https://tedana.readthedocs.io



Command line program



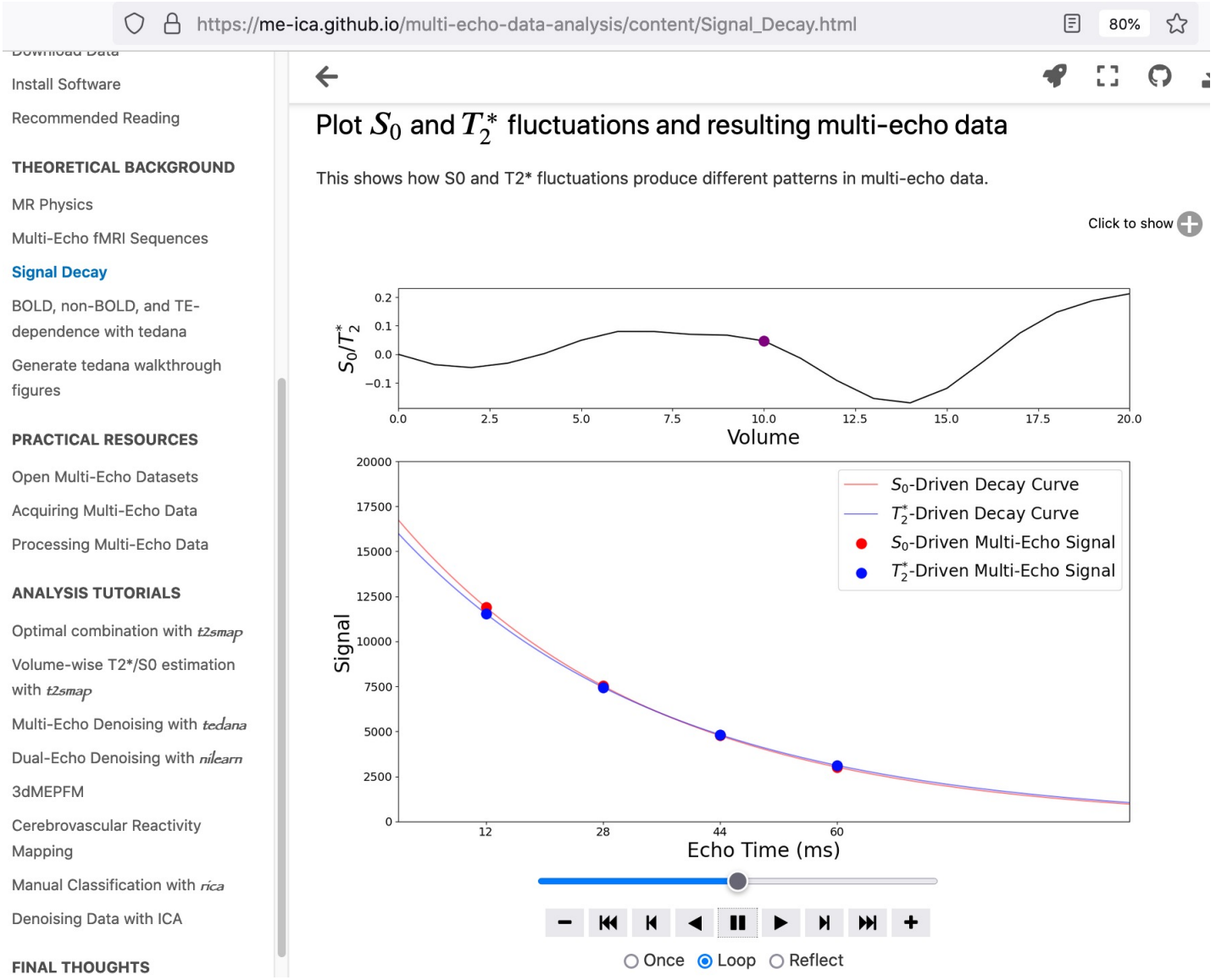
Results Viewer



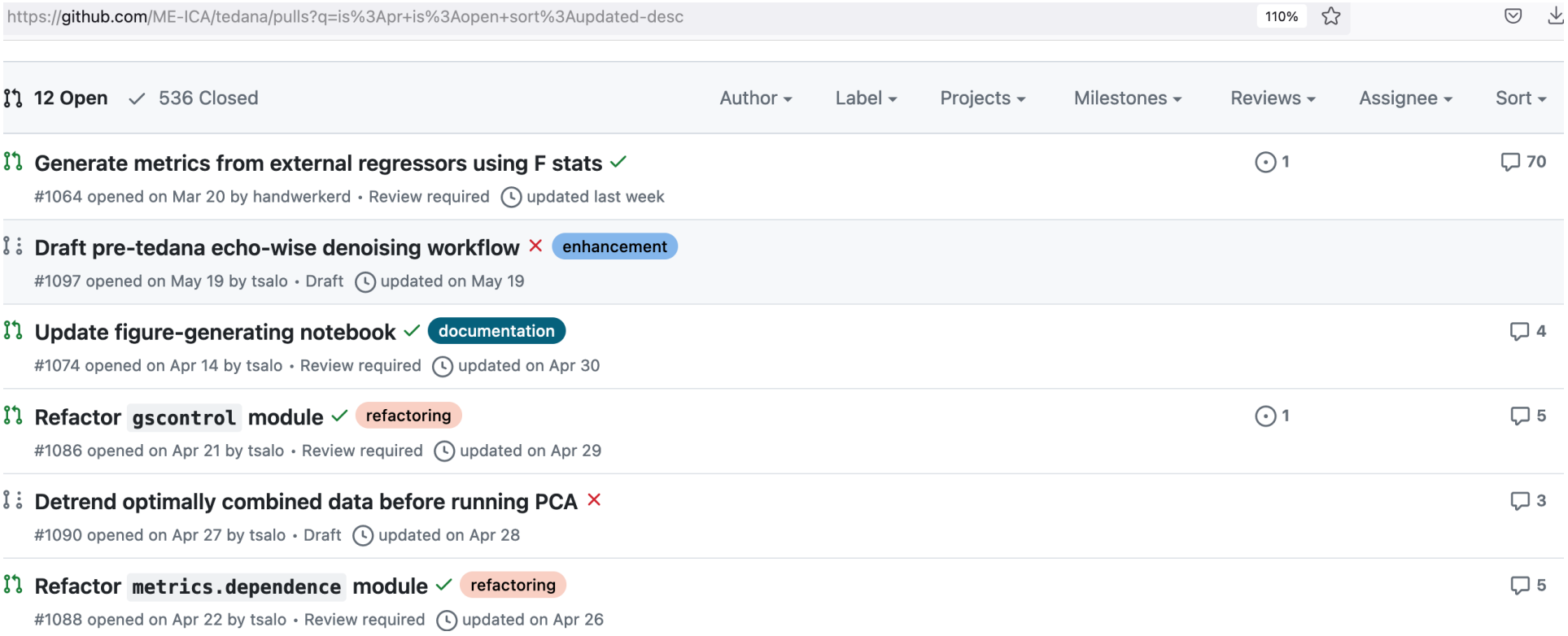
Multi-echo Jupyter Book!

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

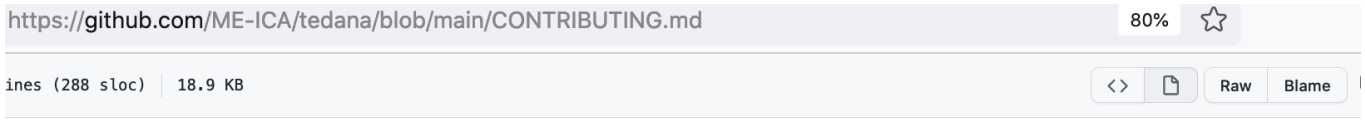
Jupyter Books have both the code to generate figures and the text in one place



Discussions are open



Support for new contributors



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

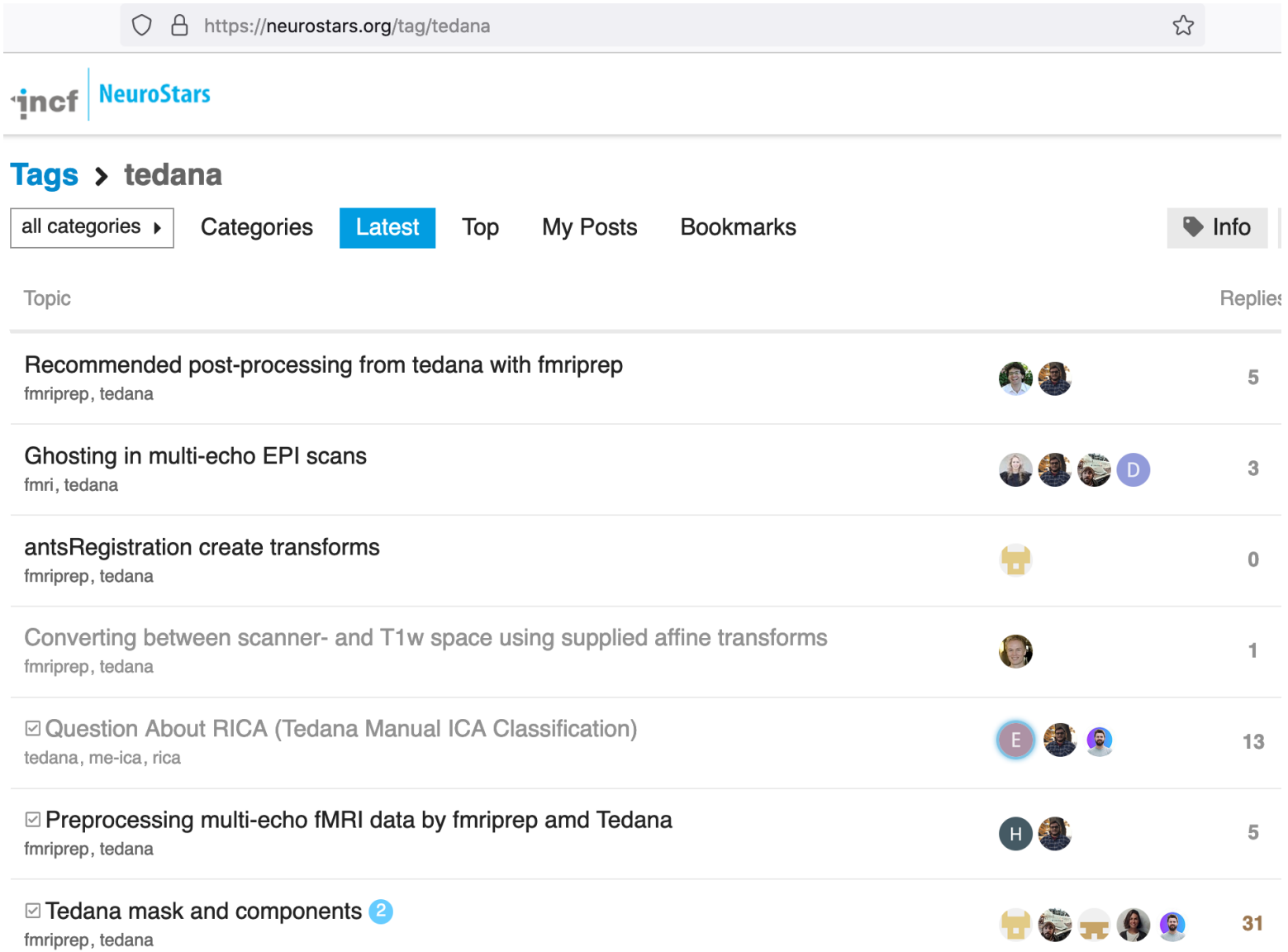
Don't know where to get started? Read Joining the conversation and pop into Mattermost to introduce yourself! Let us know what your interests are and we will help you find an issue to contribute to. Thanks so much!

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.

neurostars message board for users



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