What is fMRI's full potential?

Multi-echo denoising and ways to improve our research

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*“My current interests are in the uses of fMRI to study the brain. I believe fMRI has barely begun to reach its **full potential** and I hope that, in my future research, I can both use and improve on existing technology.”*
--me (graduate school application)

- fMRI has changed science
- fMRI has still not reached its full potential/hype

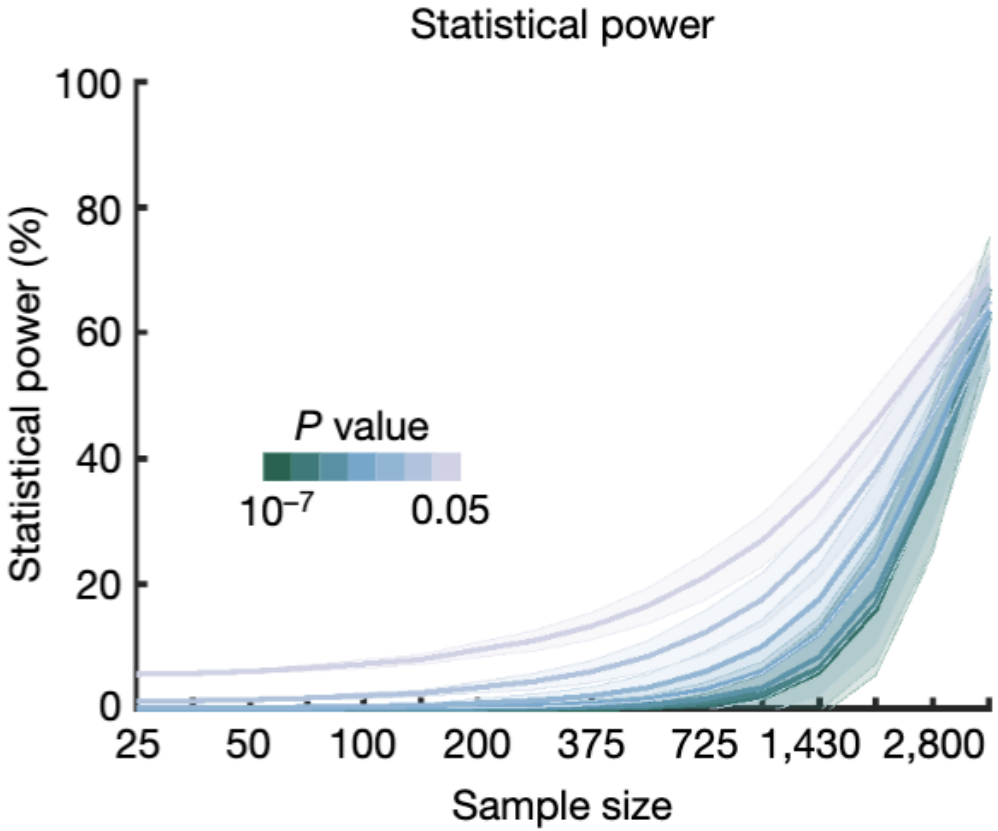
It is still not sufficiently practical and
reliable for many research applications
and clinical prognosis & diagnosis

Overview

- What do we mean by better fMRI?
- An example of work and challenges for improving fMRI from:
  - Hemodynamic variation to
  - Deep sampling and the limits of voxel-wise statistical significance to
  - Multi-echo fMRI to support smaller samples
- Background on multi-echo fMRI
- Improving research and building community through tedana
- Advancing multi-echo & work-in-progress

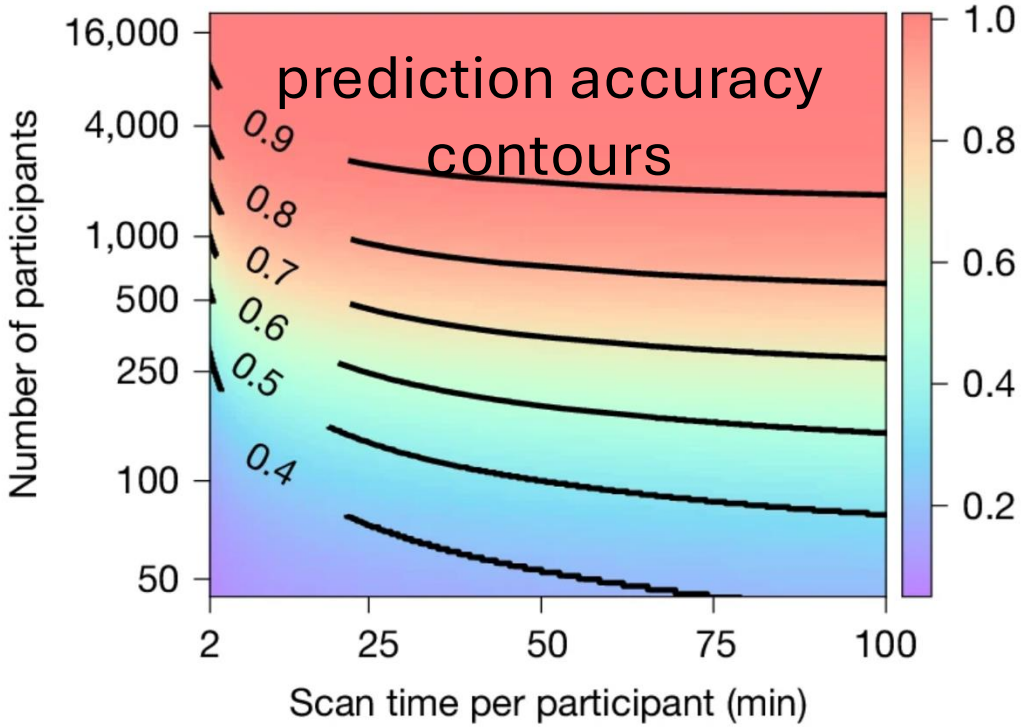
What does better fMRI look like?

How many participants?



Marek, Tervo-Clemmens, et. al. *Nature* 2022
Reproducible brain-wide association studies require thousands of individuals

Scan time per participant?

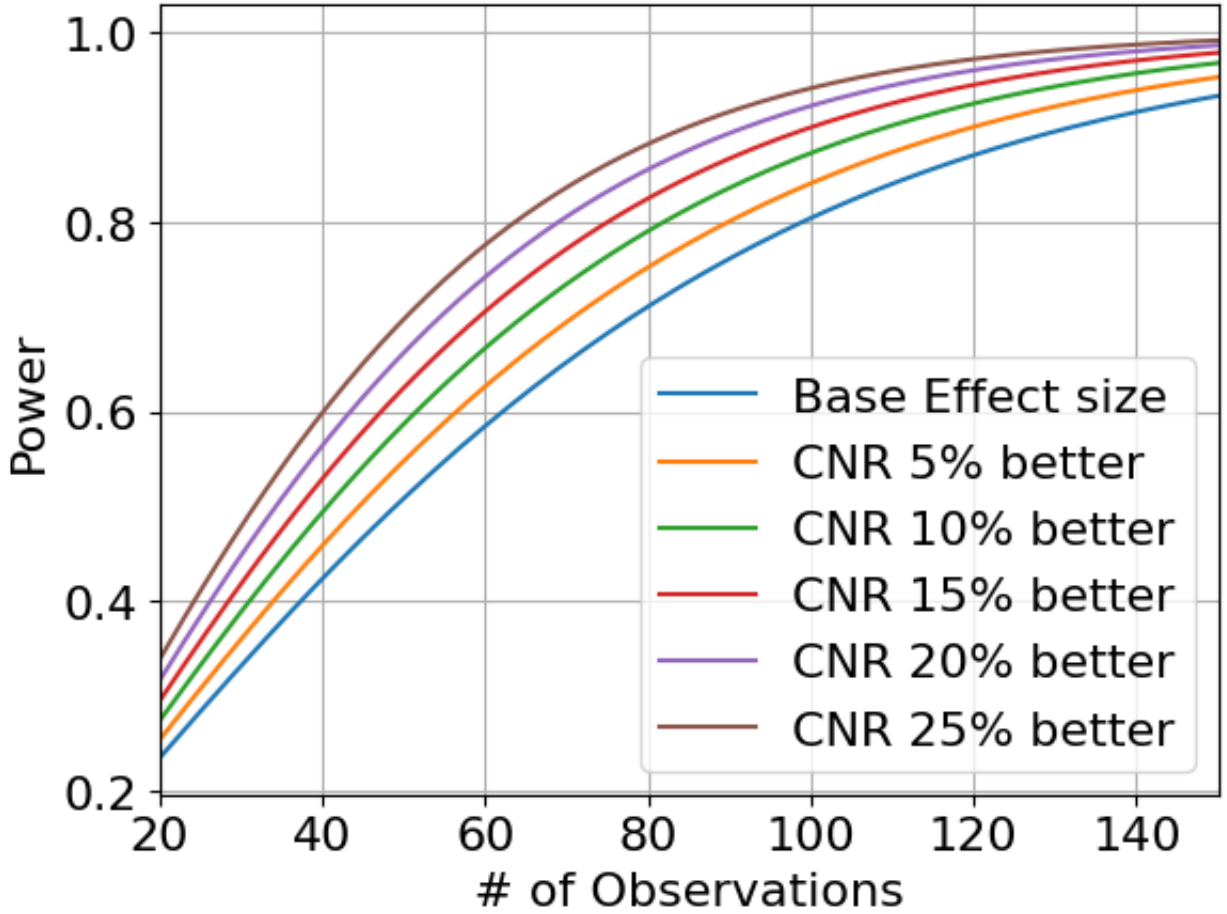


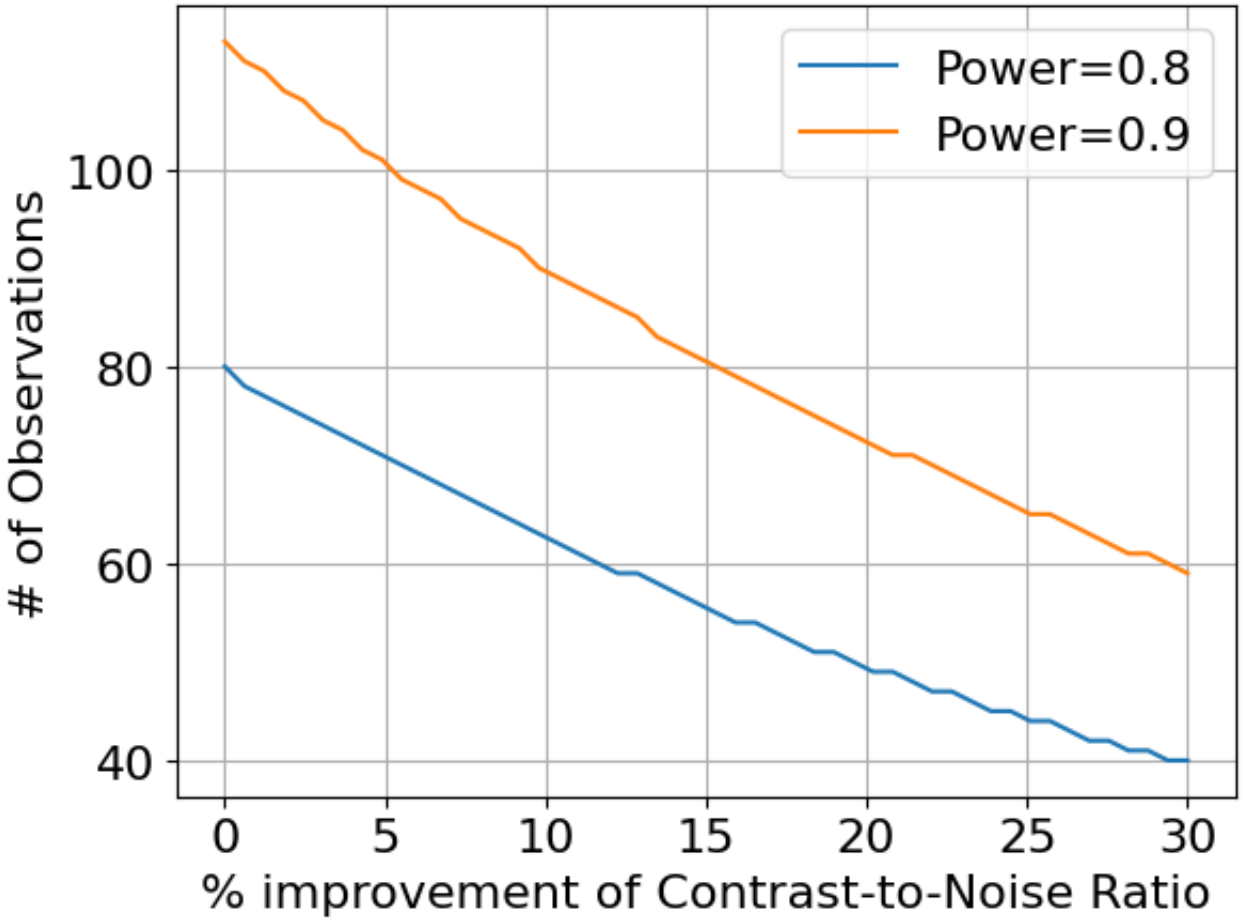
Ooi, Orban, et. al. *Nature* 2024
Longer scans boost prediction and cut costs in brain-wide association studies

Scan duration is one of multiple ways to improve intra-subject data quality

Power for a paired t-test

baseline effect size = 0.4



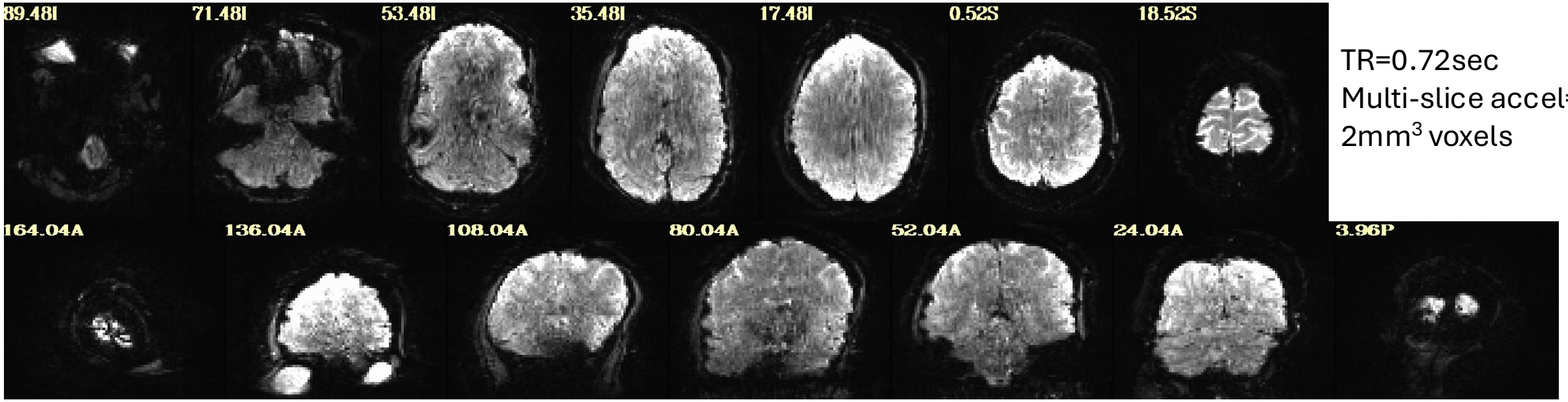


Stat power of 0.8

Baseline = 80 people
↑ 5% CNR = 70 people
↑10% CNR = 62 people
↑20% CNR = 49 people
↑30% CNR = 40 people

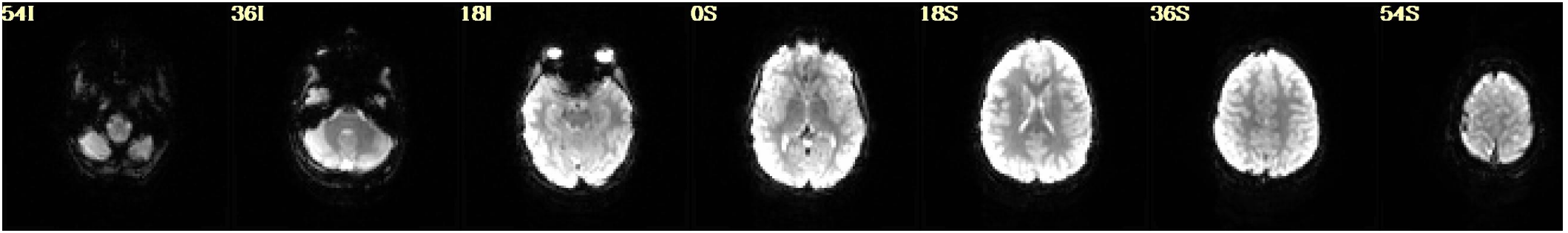
A (mildly provocative) case study

Arbitrary volunteer from the original Human Connectome Project



TR=0.72sec
Multi-slice accel=8
2mm^3 voxels

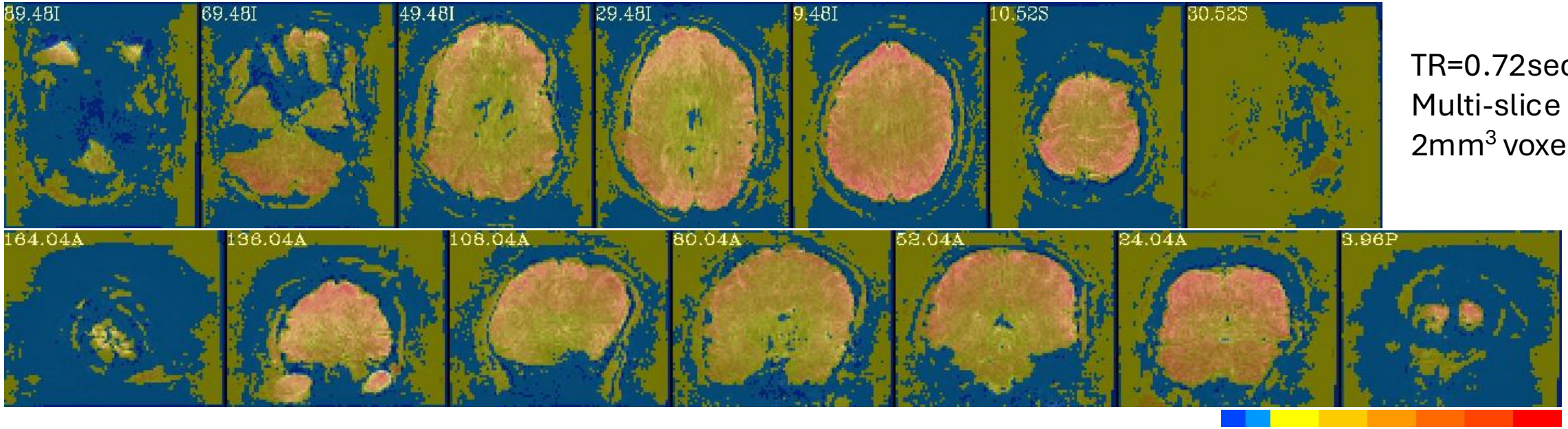
Arbitrary volunteer from ABIDE



TR=2.5sec
In-slice accel=3
~3mm^3 voxels

A (mildly provocative) case study

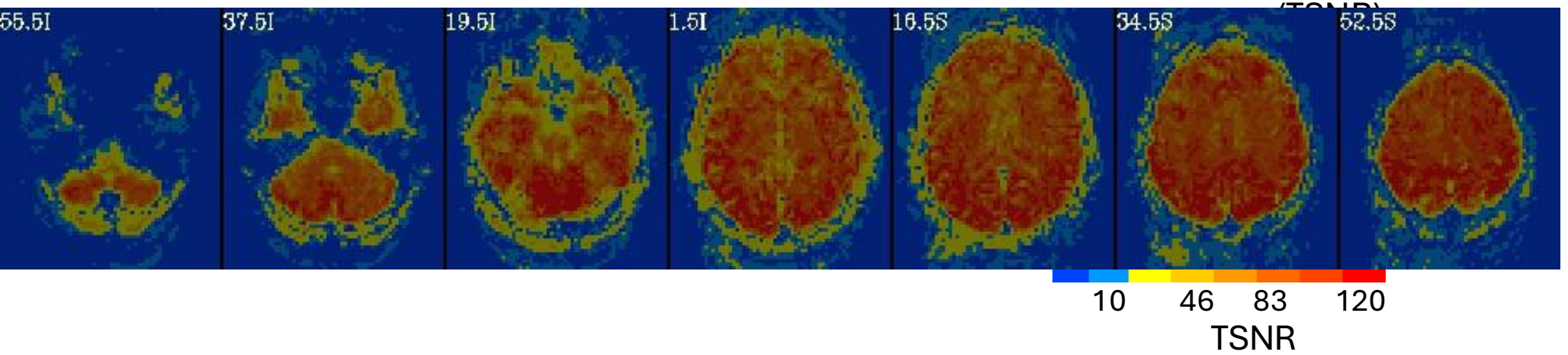
Arbitrary volunteer from the original Human Connectome Project



TR=0.72sec
Multi-slice accel=8
2mm^3 voxels

Temporal Signal to noise ratio (TSNR)

Arbitrary volunteer from ABIDE



TR=2.5sec
In-slice accel=3
~3mm^3 voxels

What we optimize our data for matters

- Successful Research using HCP data
  - ROIs that average across many voxels
  - Correlation or task studies that summarize data across time
  - Averages across the large population
- HCP weaknesses
  - Studies that fully take advantage of the short TR **and** smallish voxel size
  - Brain-wide association studies (BWAS) that require robust signal in individuals' data
- **Note:** This is a broad & not completely fair generalization.

What improves data quality?
Increase Contrast to Noise Ratio

Noise ↓

- Noise removal through averaging
  - More participants
  - More data per participant
  - Averaging across space (ROIs)
- Better MRI hardware, pulse sequences, & reconstruction
- Tuning acquisition parameters
- Human factors
  - Experimental design
  - Participant behavior/variation
- Noise removal using defined models of noise
  - Motion, respiration, pulsation regressors
  - Multi-echo fMRI

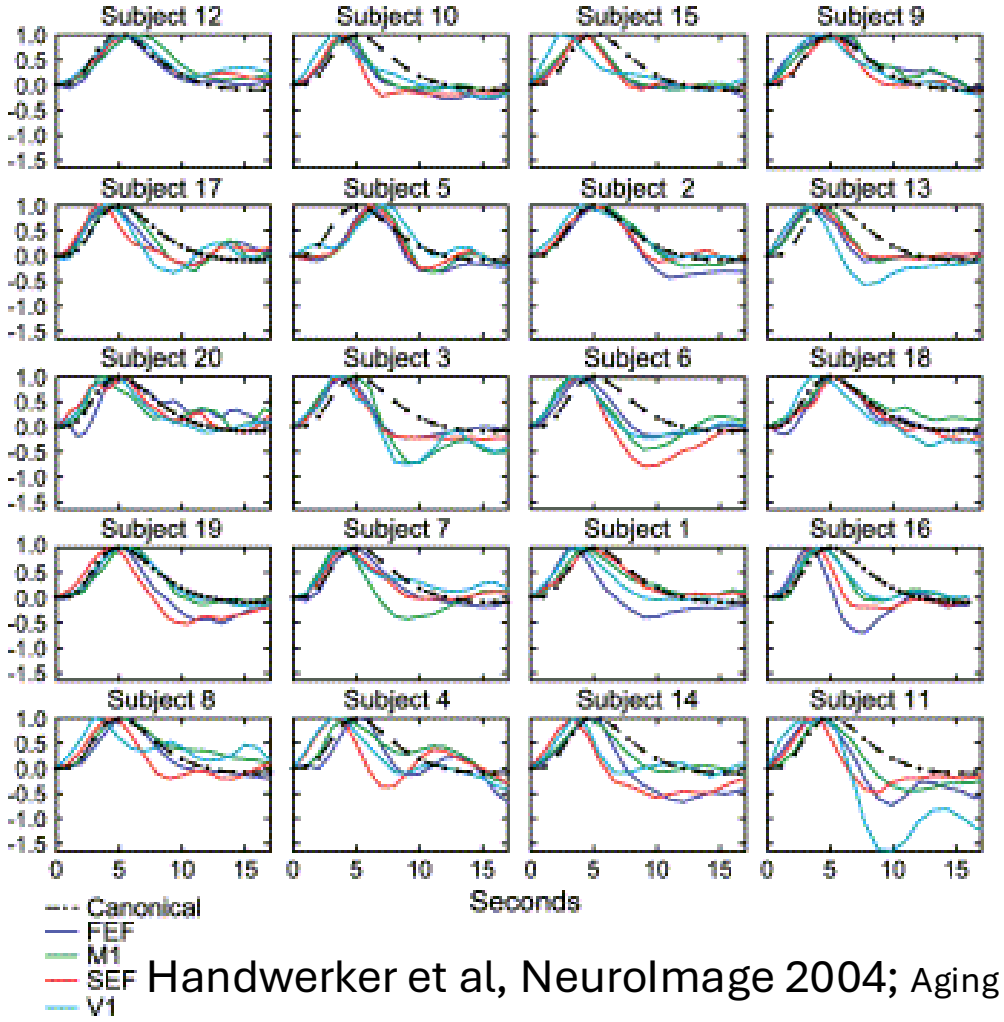
Contrast ↑

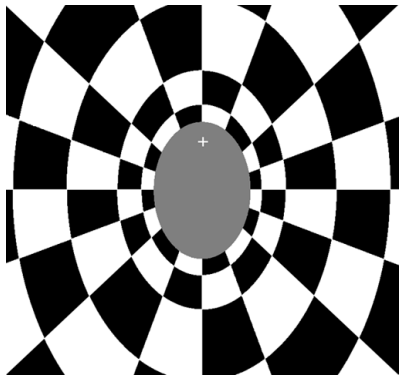
- Pulse sequences
- Tuning acquisition parameters
- Human factors
- Better specification of the effect of interest
- Better modeling of effect of interest

Better modeling of the effect of interest

Vasculature changes with aging.
How does that affect fMRI measurements?

Hemodynamic responses vary across individuals & regions

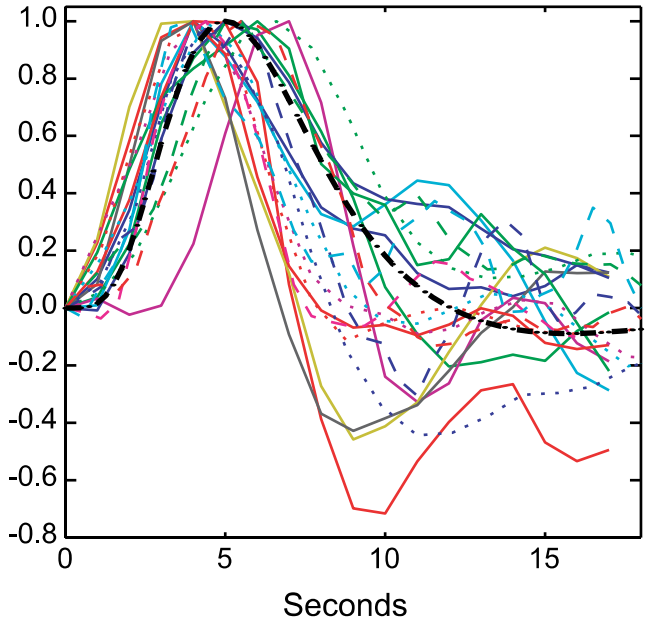




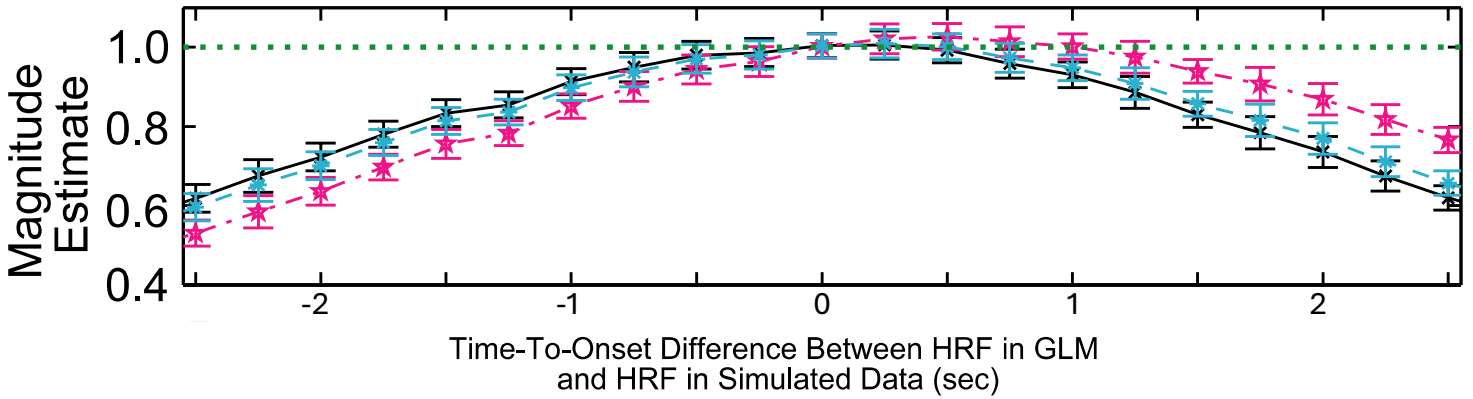
Present a 200ms flickering checkerboard every 18-24s

Volunteers press a button and move their eyes

Primary Motor HRFs across individuals



HRF model affects magnitude estimates



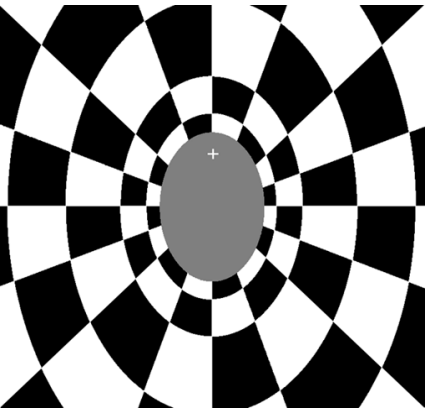
Handwerker et al, NeuroImage 2004; Aging part: Handwerker et al, HBM 2007

Possible Improvements

- Better modeling of HRF shape
  - Person-specific HRF estimates
  - Flexible HRF models
- Study designs that are less sensitive to 1-3s of temporal variation
  - Block design
  - Some multi-voxel pattern analysis designs
- Analyses that are less sensitive to temporal variation
  - Not using magnitude estimate alone in group analysis
  - Frequency-based analyses

The unpublished part

Defined models of noise



Present a 200ms flickering checkerboard every 18-24s

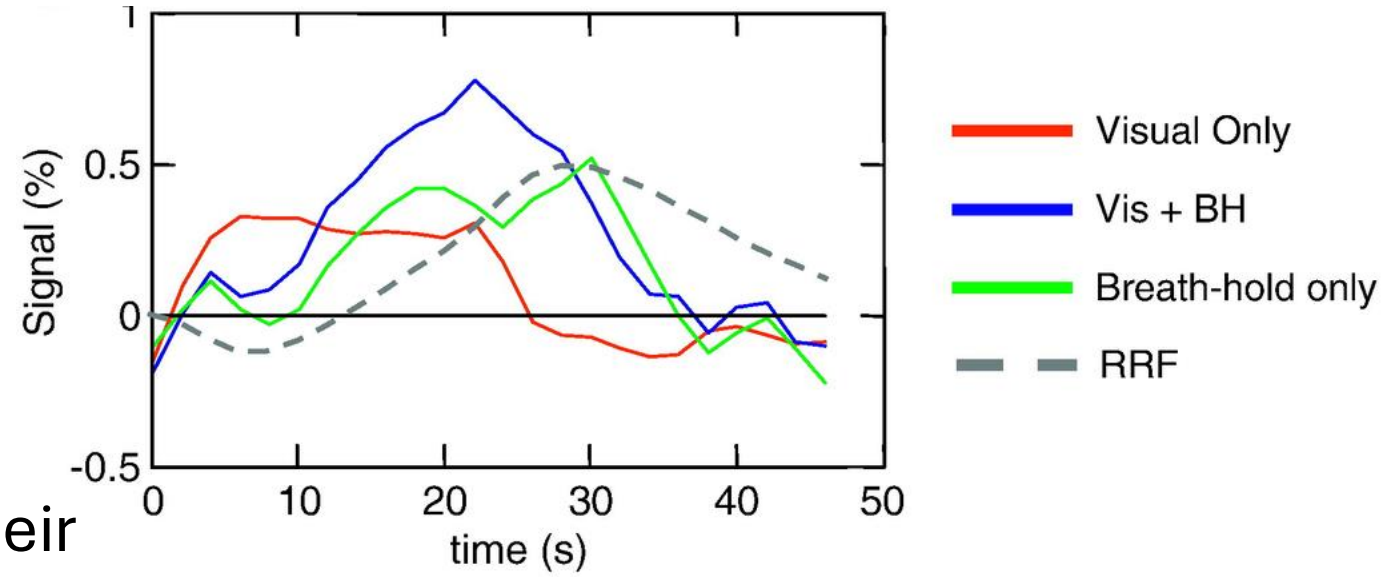
Volunteers press a button and move their eyes

- Stimuli presented for 3s, 6s & 12s durations
- A non-trivial # of volunteers held their breath for the stimulus duration
  - Breath holding causes a robust, brain-wide BOLD response
- No respiration data →

  Visually appealing results →

  Misinterpreted results

fMRI in the presence of task-correlated breathing variations

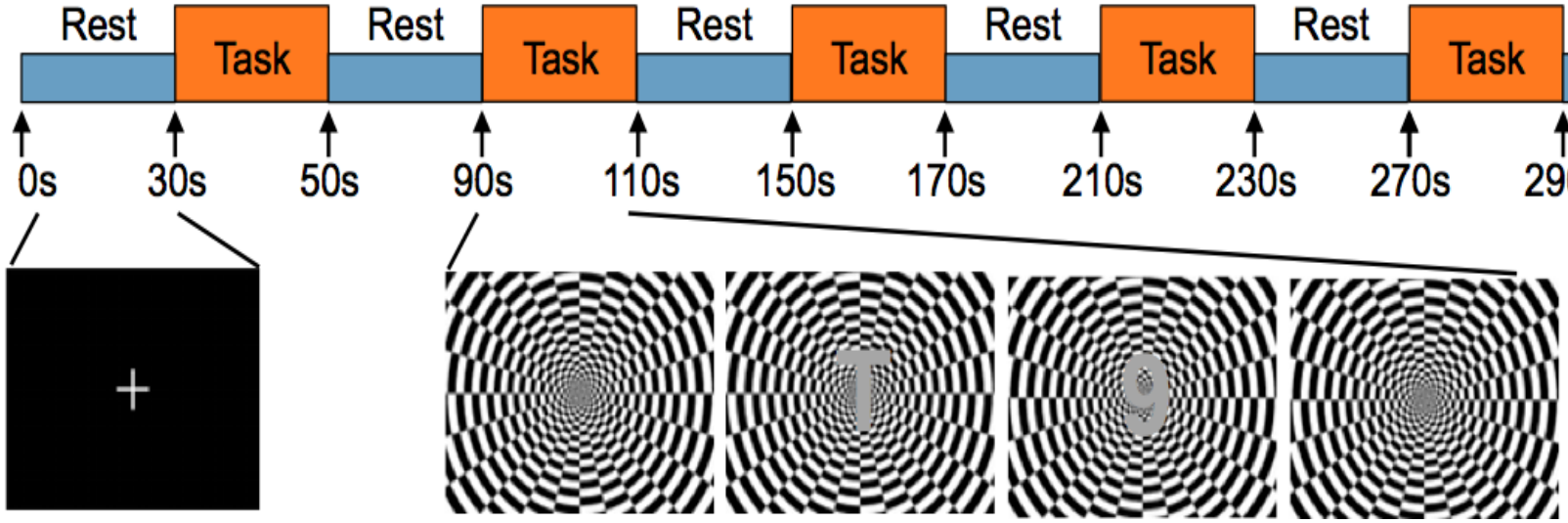


Birn, Murphy, Handwerker, Bandettini NeuroImage 2009

Even with good HRF modeling, how much should we focus on thresholds?

Better specification of the effect of interest

Noise removal through averaging

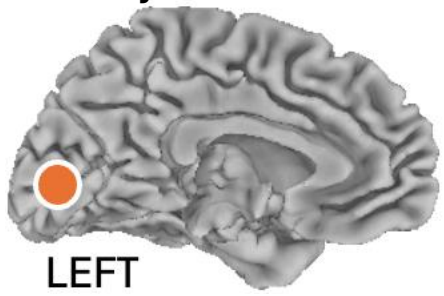


3 volunteers

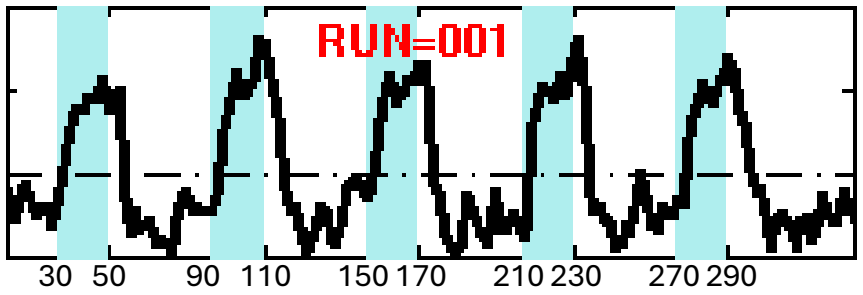
100 five minute runs

9 hours of data/volunteer

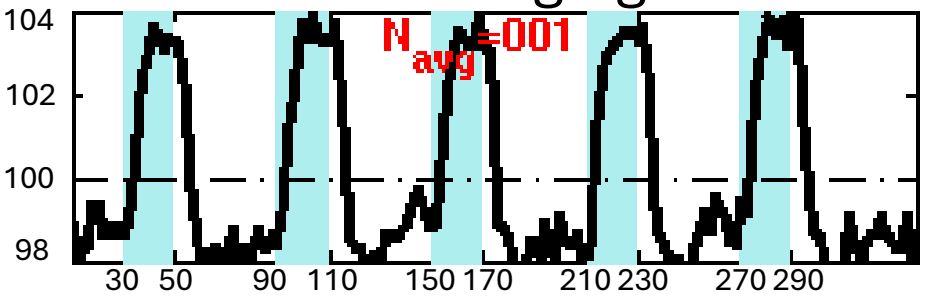
Primary visual cortex



Individual Runs



Averaging

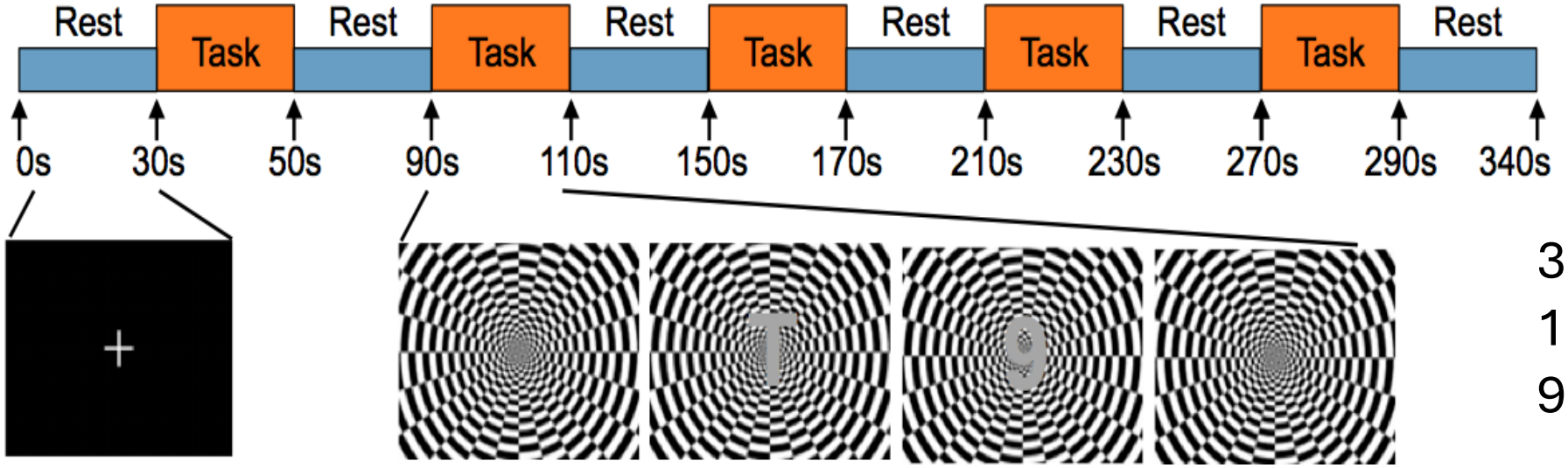


Gonzalez-Castillo, Saad, Handwerker, Bandettini PNAS 2012

How much should we focus on thresholds?

Better specification of the effect of interest

Noise removal through averaging

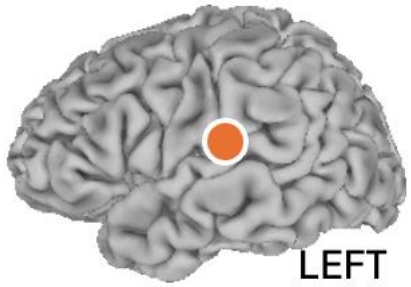


3 volunteers

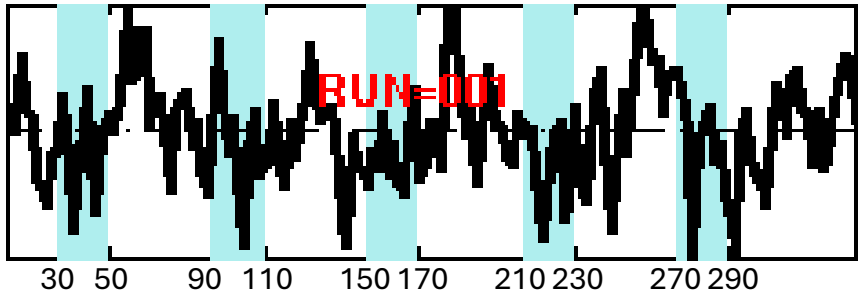
100 five minute runs

9 hours of data/volunteer

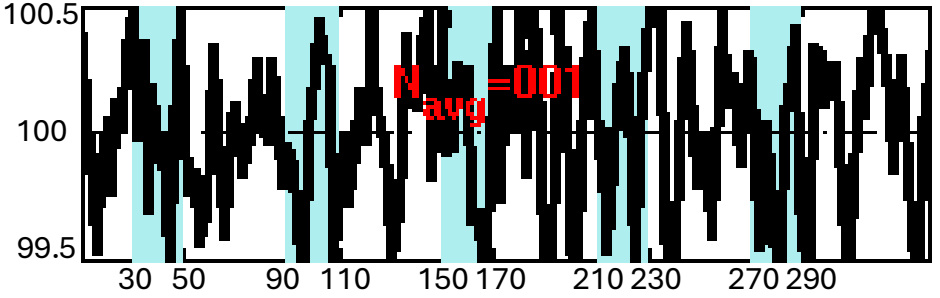
Primary **auditory** cortex



Individual Runs

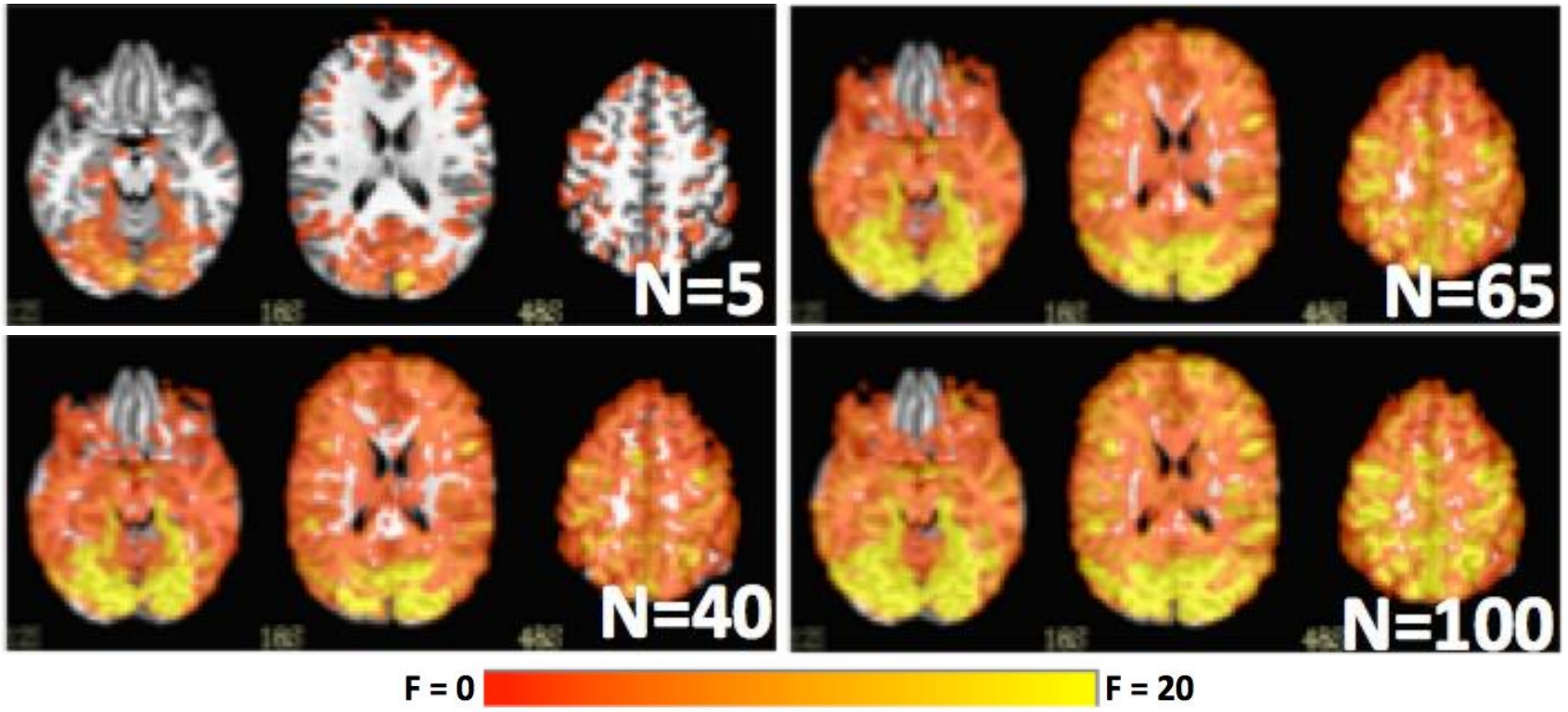


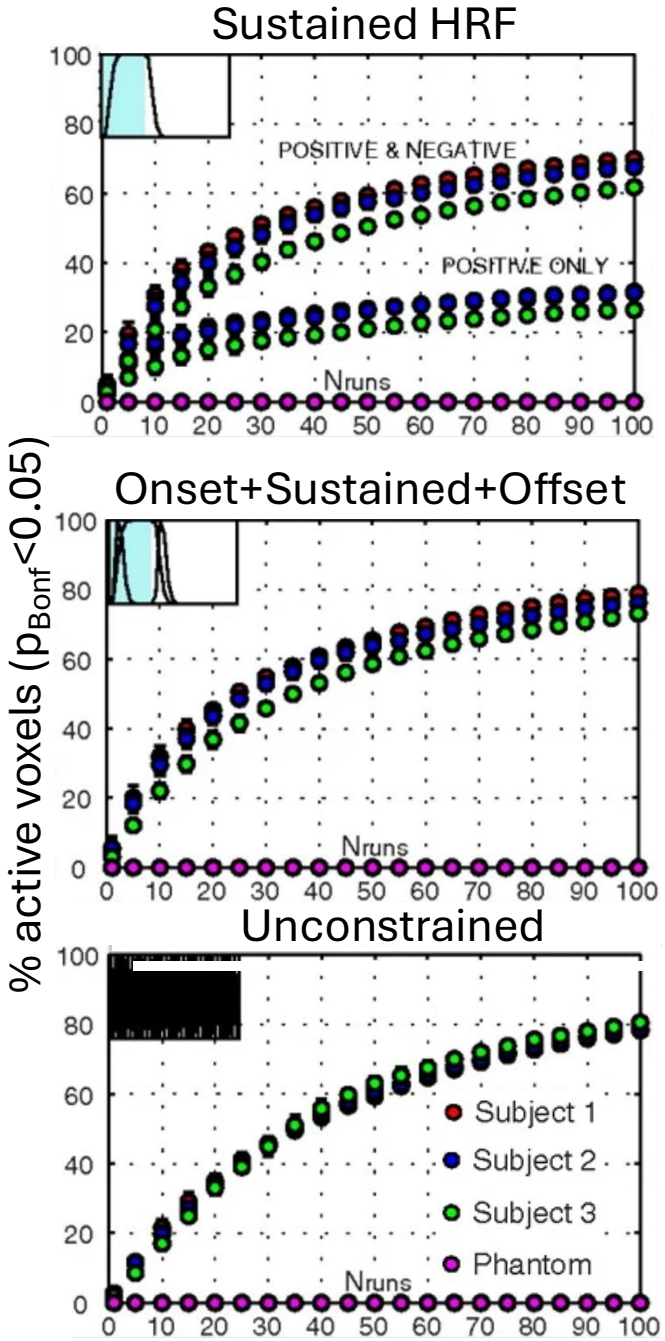
Averaging



Gonzalez-Castillo, Saad, Handwerker, Bandettini PNAS 2012

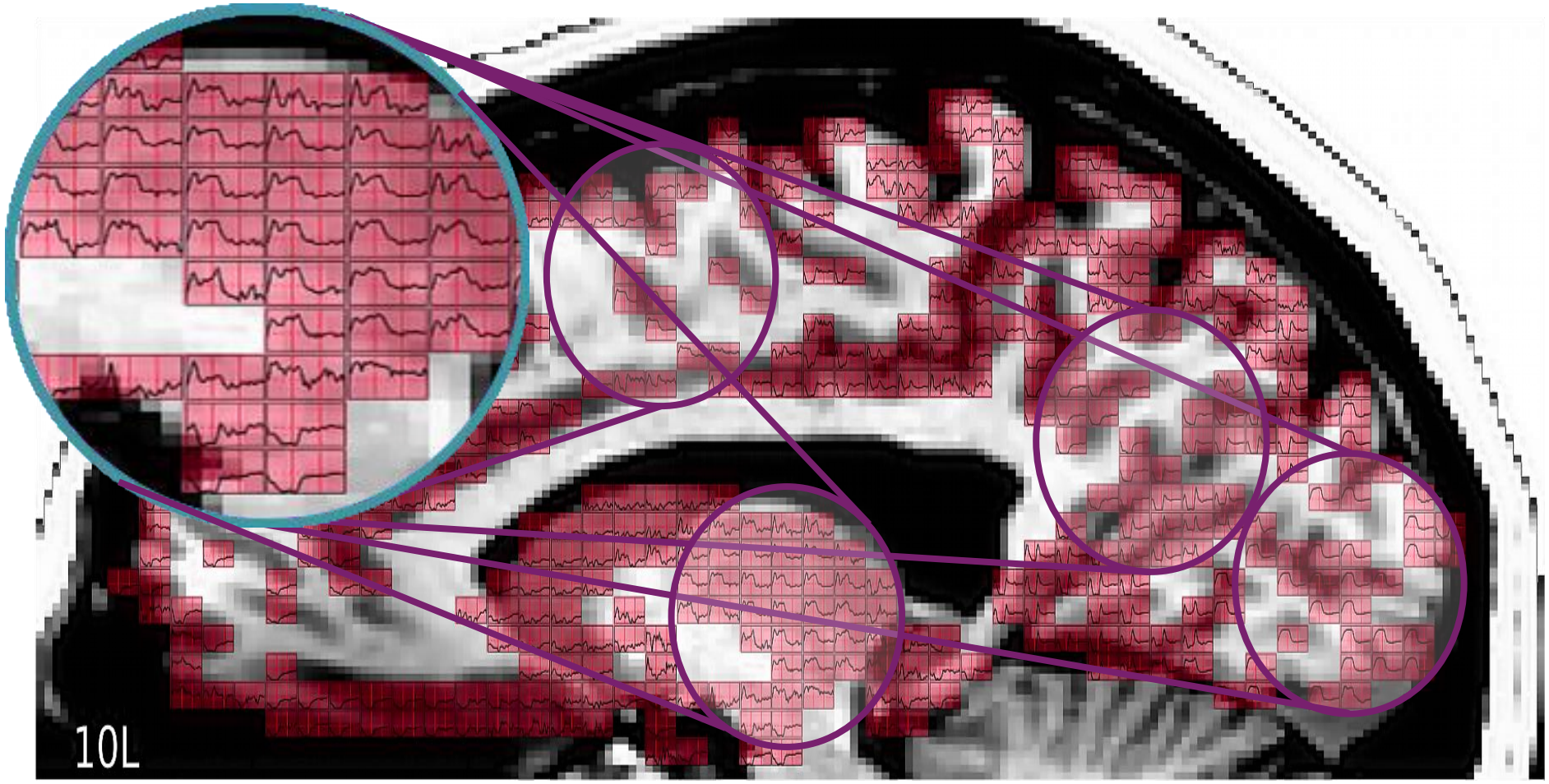
More data means more of the brain is significantly modeled by the task





Gonzalez-Castillo, Saad, Handwerker, Bandettini PNAS 2012

Model-based activation maps only tell part of the story



More data → More signif voxels; Small threshold changes shouldn't affect interpretation

Intervoxel relationships and response shapes have meaning

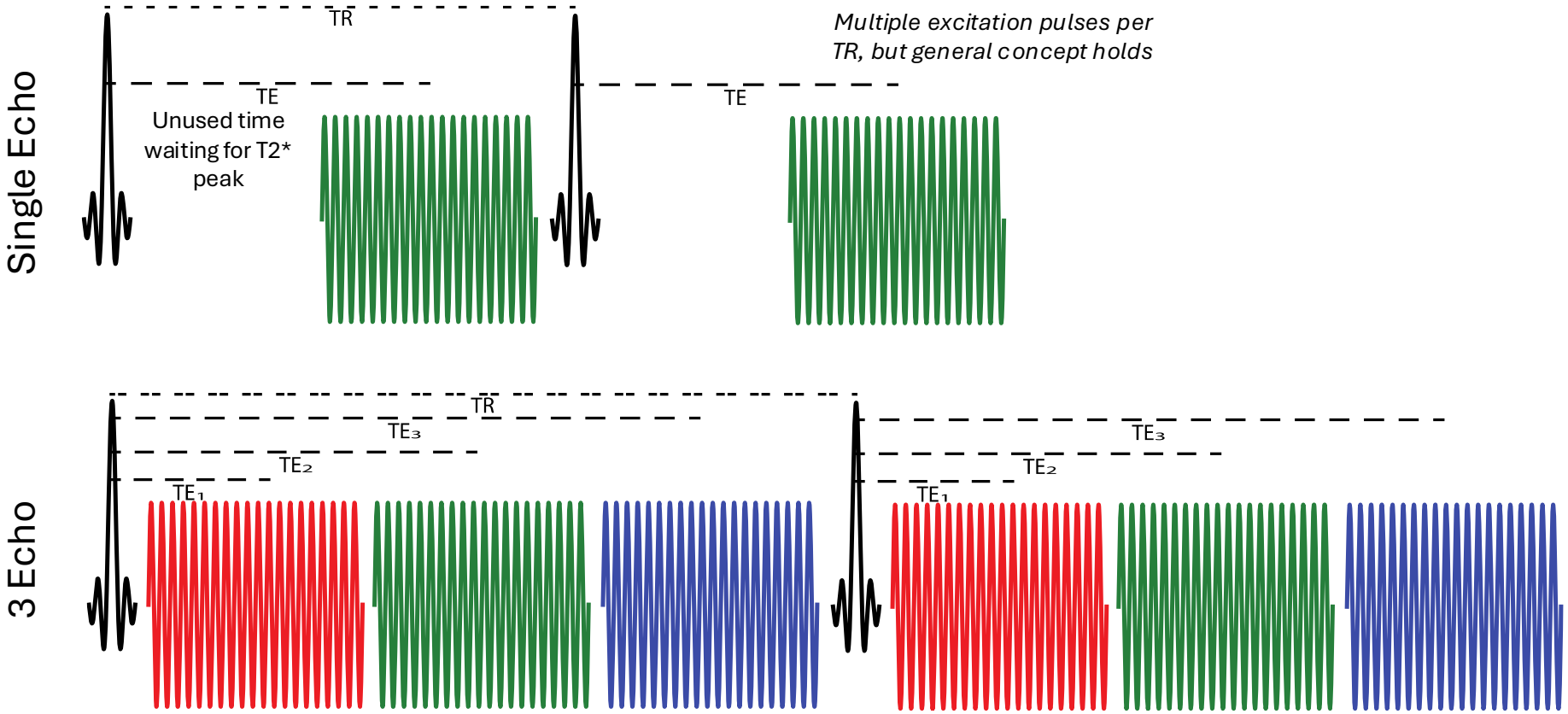
Gonzalez-Castillo, Saad, Handwerker, Bandettini PNAS 2012

Follow up with 7T & more response shape modeling:
Gonzalez-Castillo, Hoy, Handwerker, et al Cereb Cortex 2015

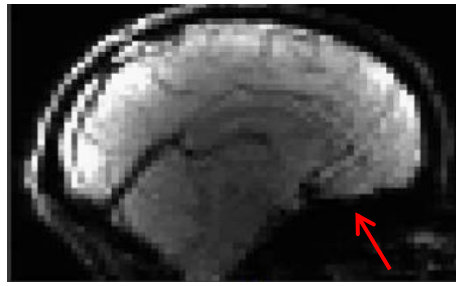
Paths forward

- More data = More interesting
  - Deep scanning / Precision Imaging
  - Awesome, but hard to scale
- Better data → More interesting with less data
  - Can we get similar results with less than 9h per volunteer?
  - **Multi-echo fMRI is one tool for this**

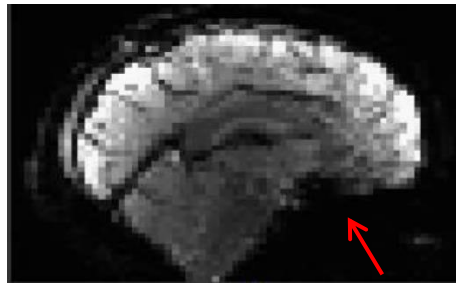
What is multi-echo fMRI?



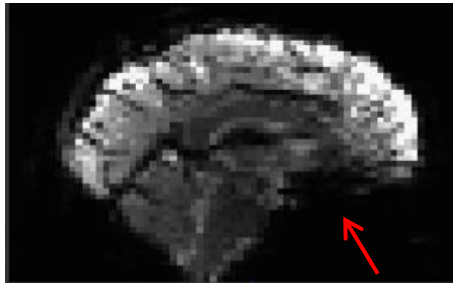
Echo 1



Echo 2



Echo 3

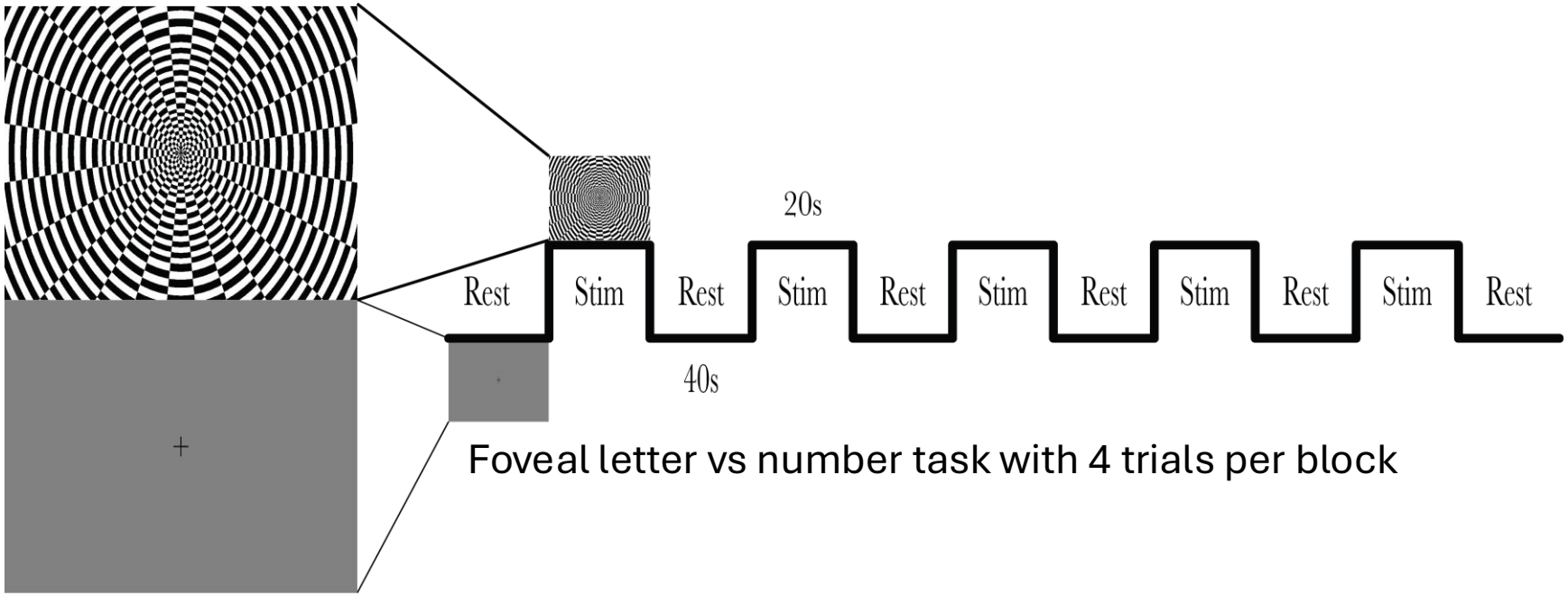


- Can process just middle echo (similar to single echo fMRI)
- Take a weighted average “optimal combination” of the echoes
- Use an ICA-based denoising method (MEICA or tedana)

Can we get such data in less than 9 hours?

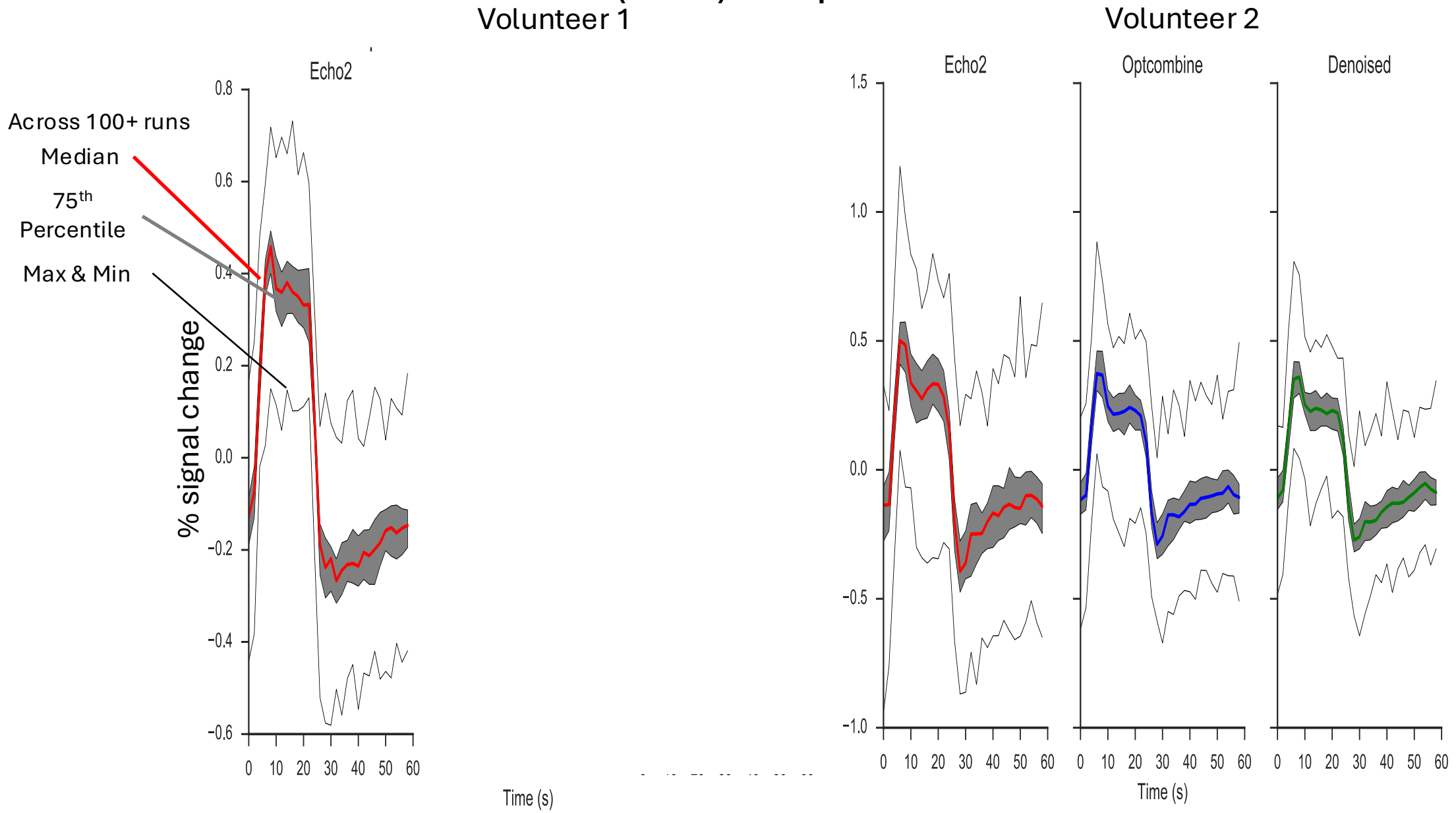
Evaluating Contrast-to-noise changes from multi-echo fMRI

- 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)



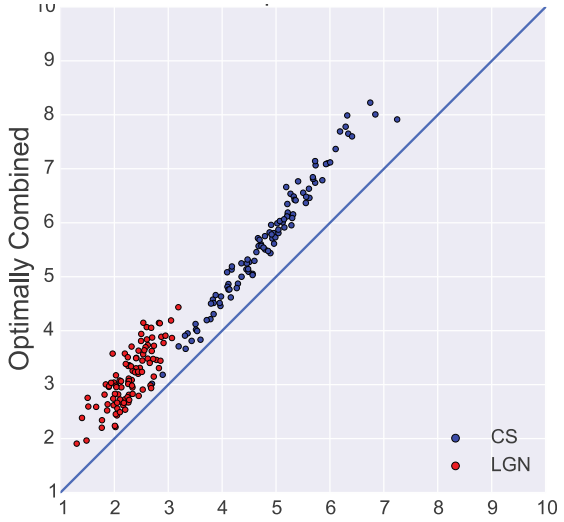
Foveal letter vs number task with 4 trials per block

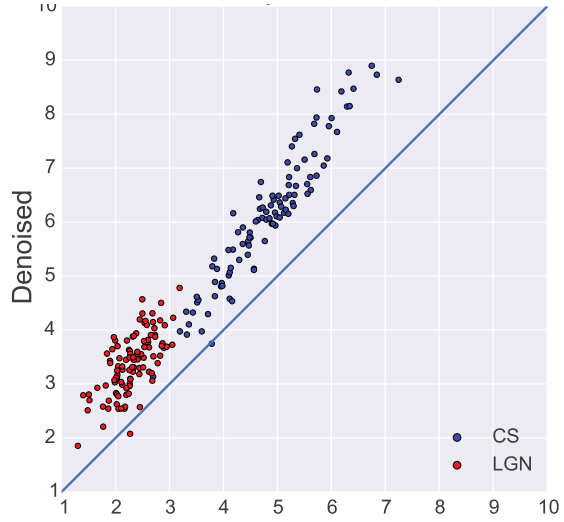
Lateral Geniculate Nucleus (LGN) Responses

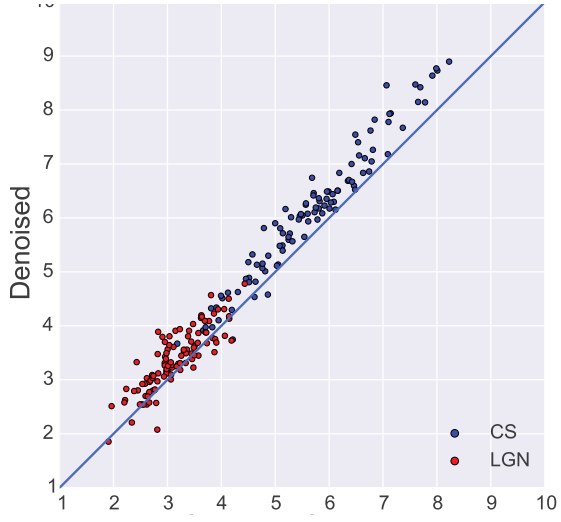


Contrast-to-Noise By Run

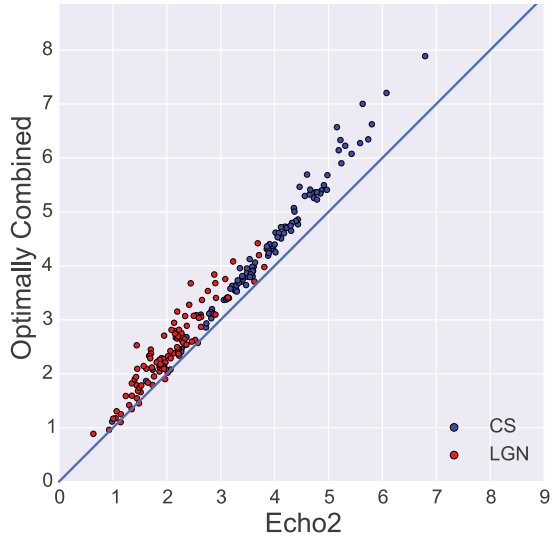
CNR Comparison for Volunteer 1

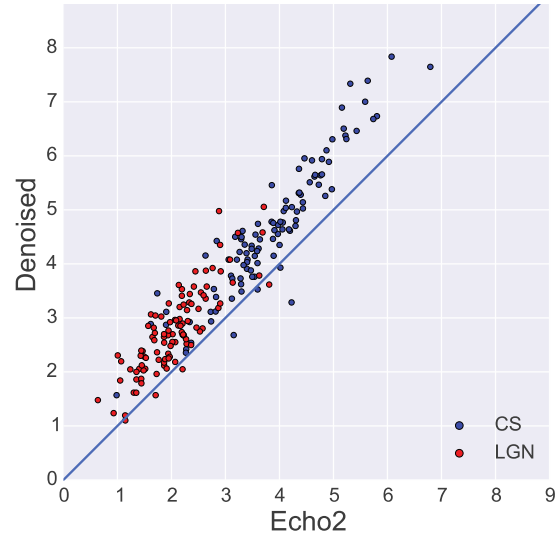


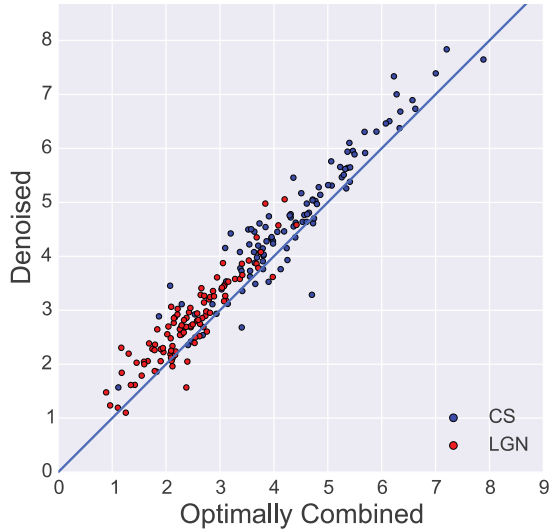




CNR Comparison for Volunteer 2







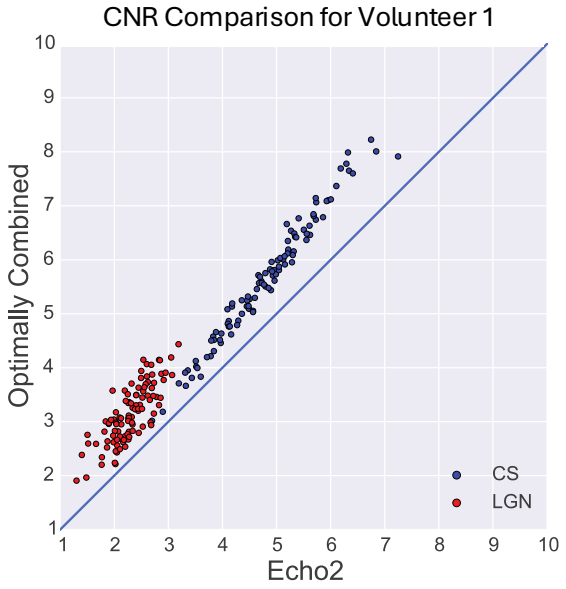
Regions of Interest

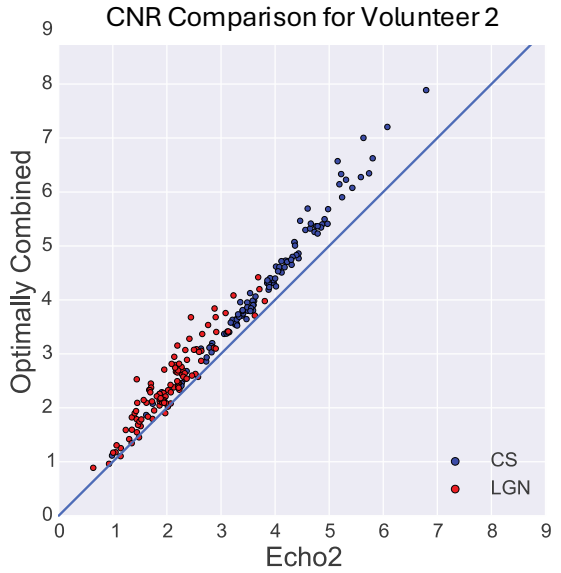
CS
Calcarine Sulcus

LGN
Lateral Geniculate Nucleus

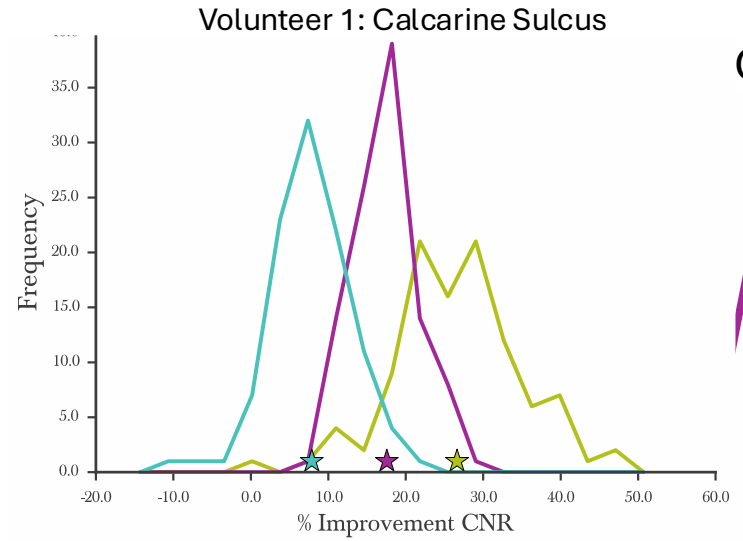
Each dot is the CNR values from 1 run

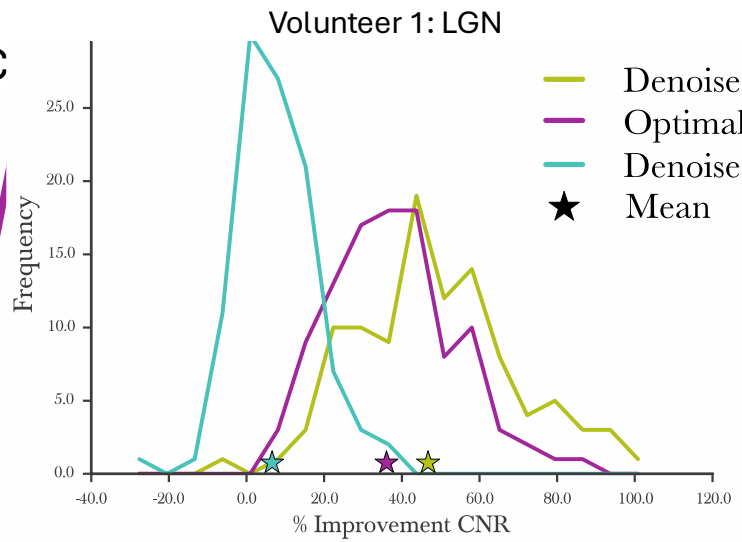
Contrast-to-Noise By Run

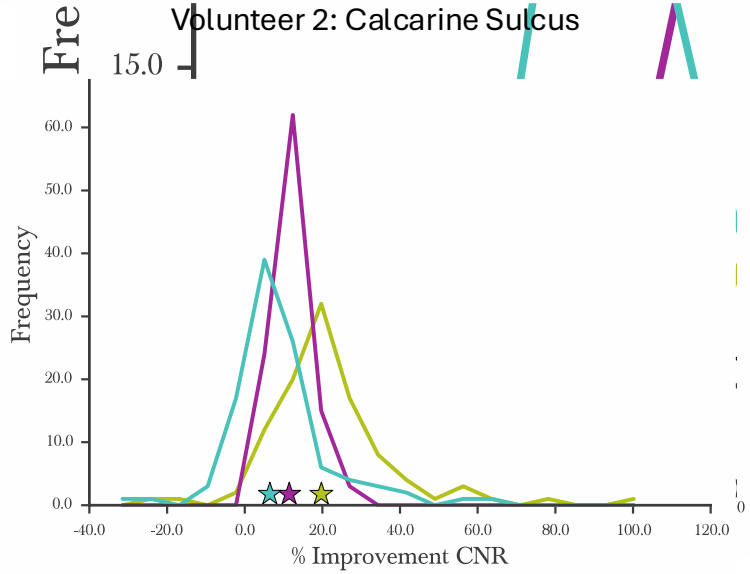


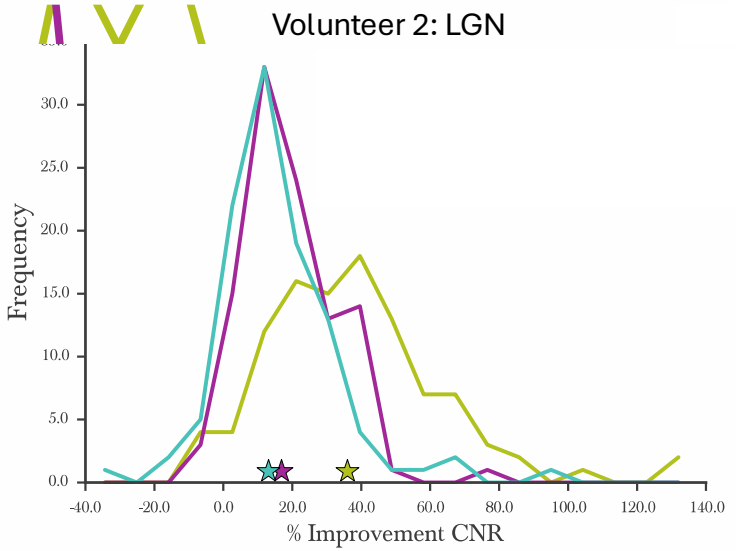


CNR % Improvement Between Preprocessing Methods



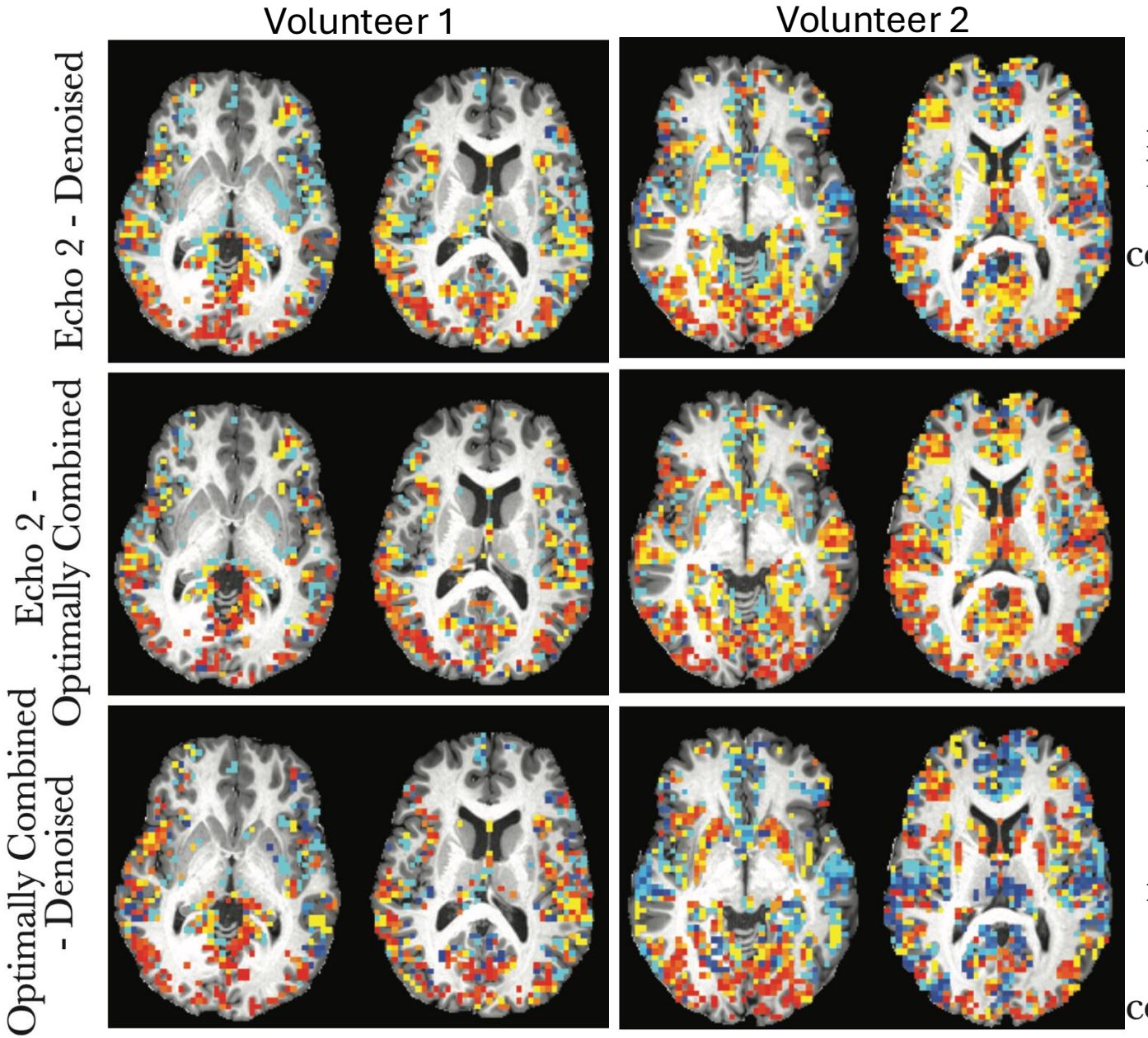






Denoised/Echo 2
Optimally Combined/Echo 2
Denoised/Optimally Combined
★ Mean

Difference in runs needed for consistent activity

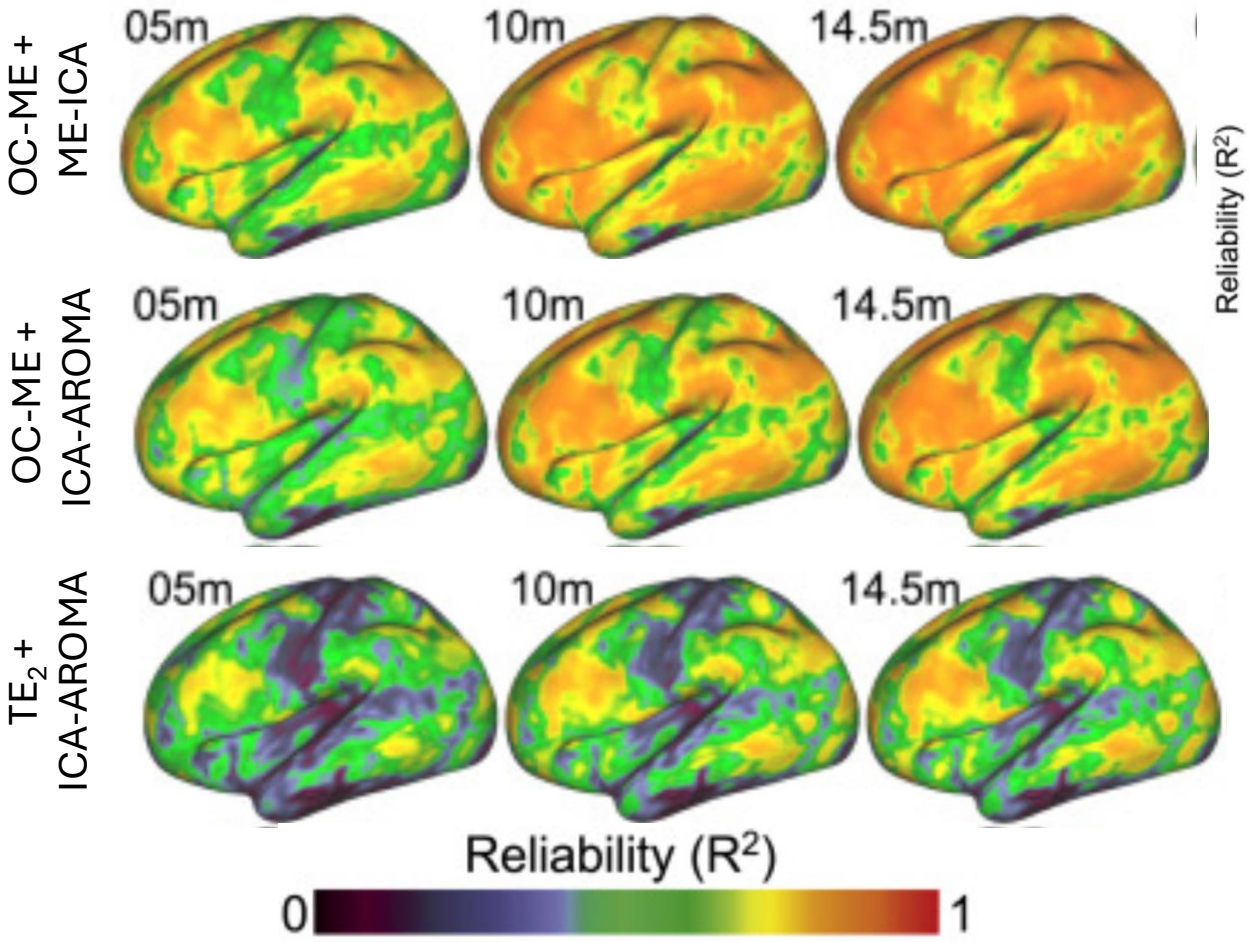


Consistent = 95% of permutations significant ($p_{Bonf}<0.05$)

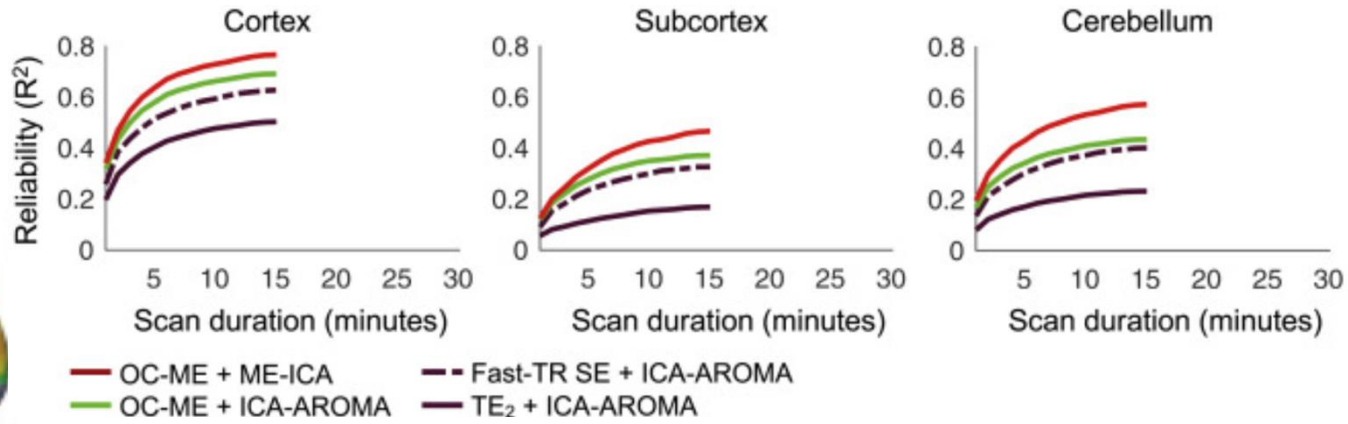
- 10 runs fewer is 50 minutes less fMRI data
- Optimal combination uses consistently fewer runs
- Denoising can result in even more improvement, but is less consistent
  - More to understand & improve on denoising methods
- Limits of presented data
  - Awesome volunteers: <1.5mm max head motion in 204/206 runs
  - Single, stable scanner with a regular Quality Assurance testing
  - Benefits of denoising may be greater with more noise to remove

Multi-echo fMRI improves reliability

Reliability map, sbj ME01



Time x reliability, sbj ME01

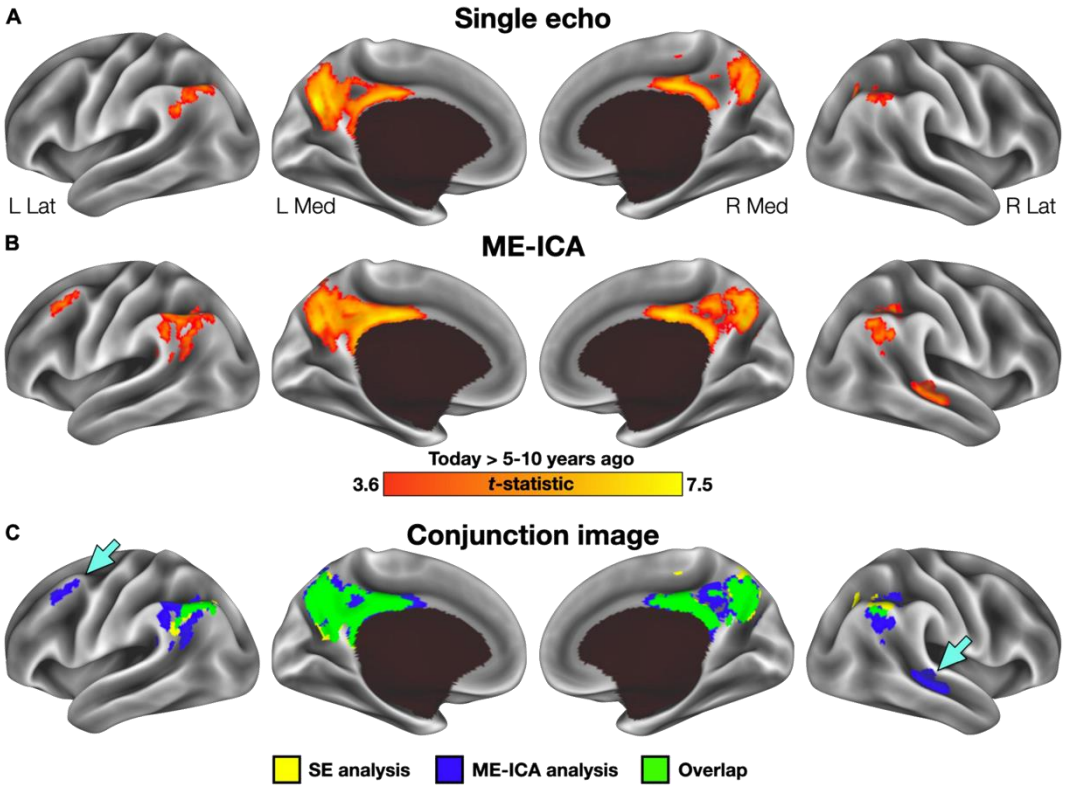


Collecting Multi-echo data + multi-echo denoising is better than multi-echo data without denoising and single-echo data with a shorter-TR

Lynch et al “Rapid Precision Functional Mapping of Individuals using multi-echo fMRI” Cell Reports 2022

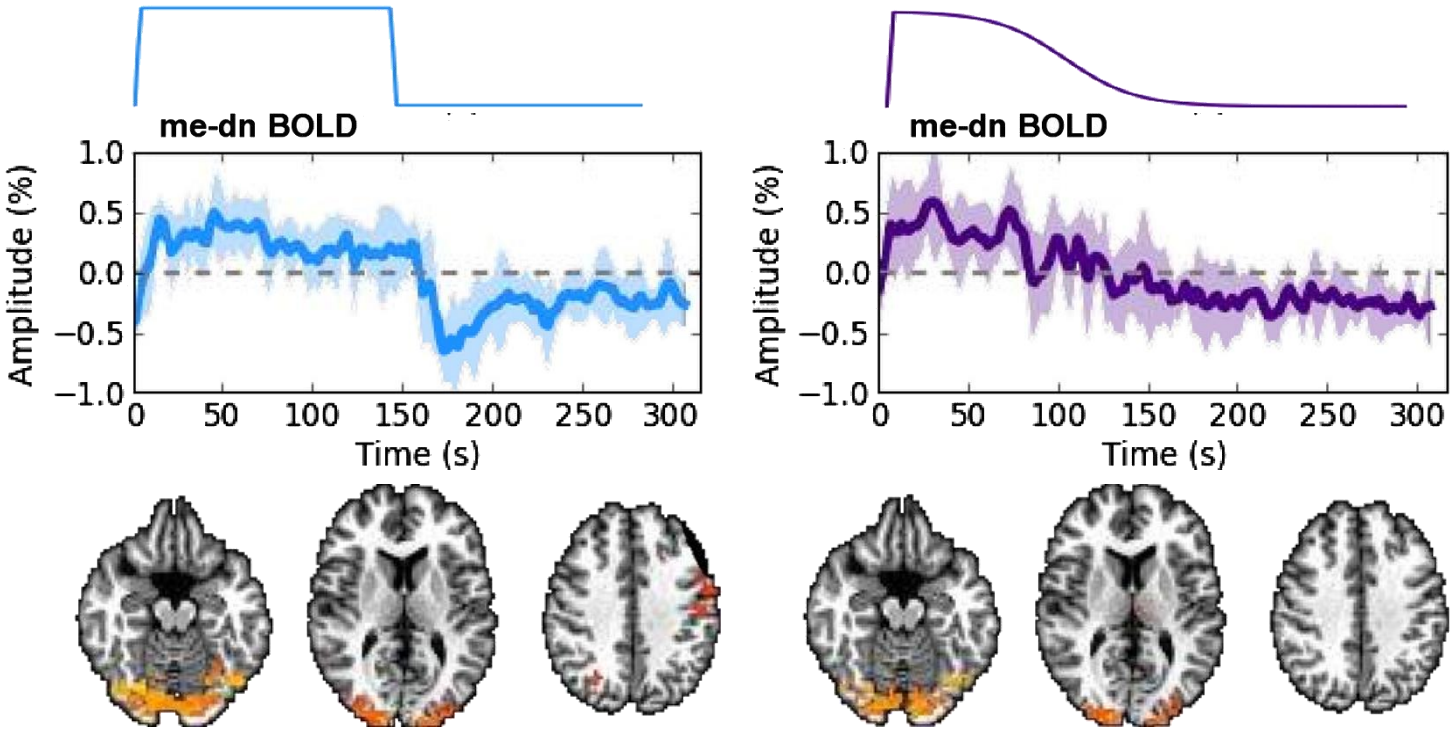
Multi-echo fMRI improves data

Overt Speech



Gilmore et al. "A comparison of single- and multi-echo processing of fMRI Data during autobiographical recall" Front. Neurosc. 2022

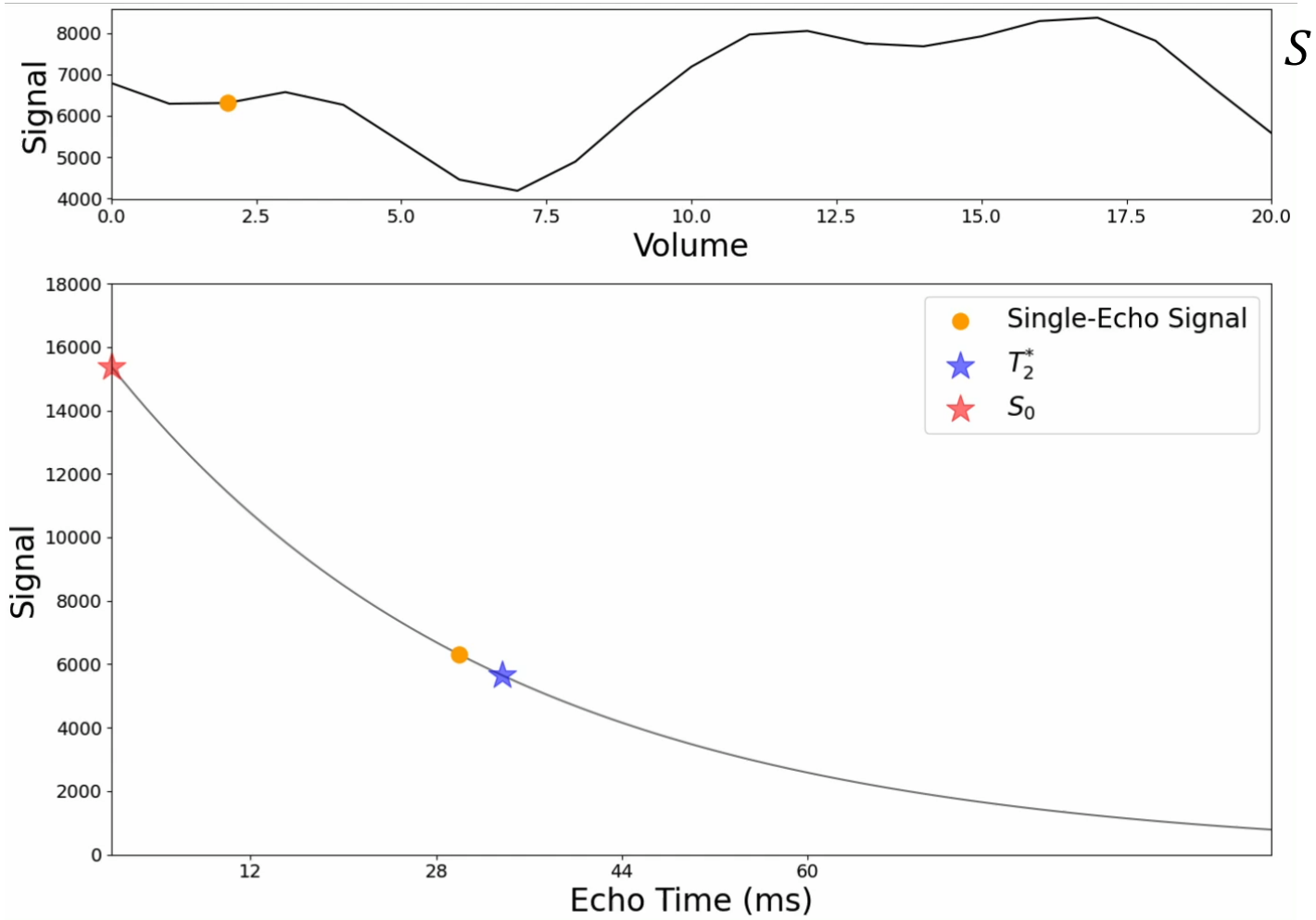
Temporally slow changes



Evans et al. "Separating Slow BOLD from non-BOLD baseline…" NeuroImage 2015

Why multi-echo information is useful

Separating Contrast from Noise



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

The signal decays with echo time

S_0

- The y-intercept at TE=0
- Non-neural signals including head motion & scanner artifacts

$R_2^* = 1/T_2^*$

- The rate of decay
- Altered by several factors including changes in blood oxygenation (BOLD)

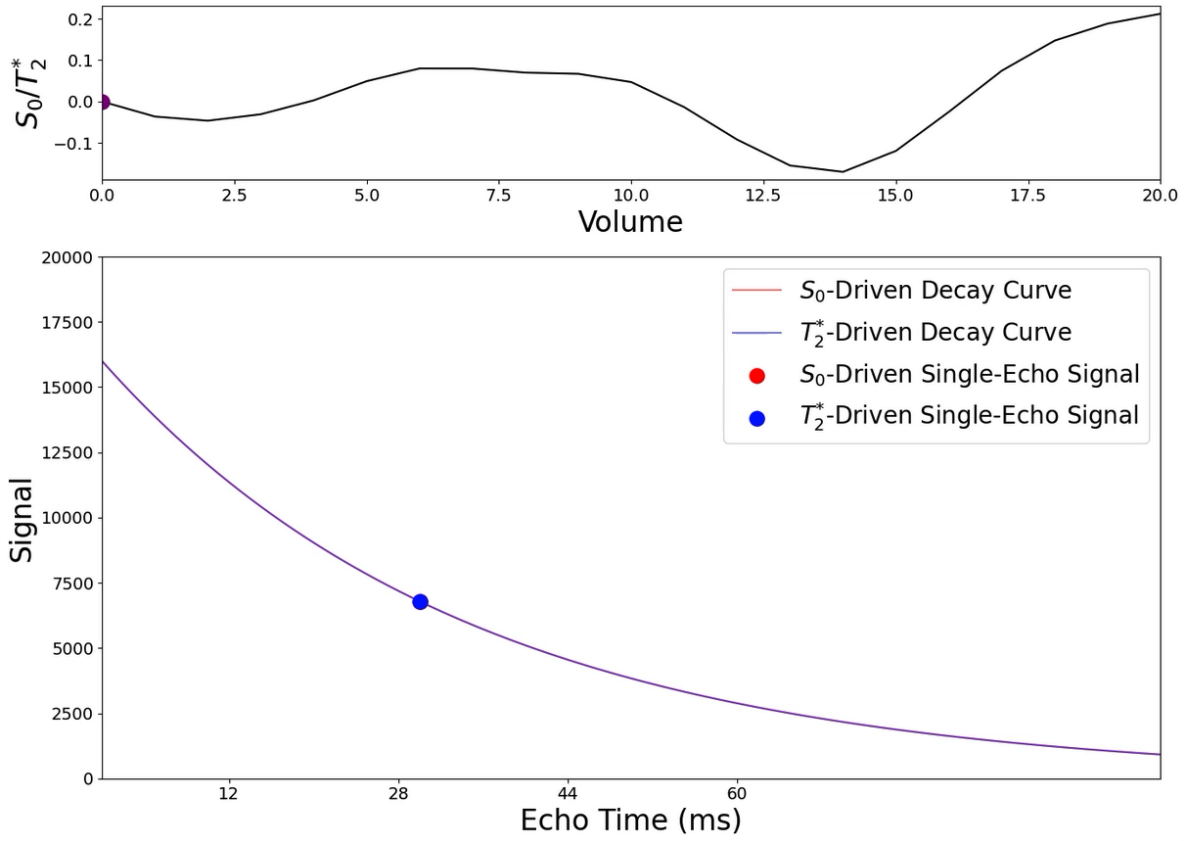
n = thermal noise

- Rician for magnitude only data
- Gaussian for complex data
- Echo time independent

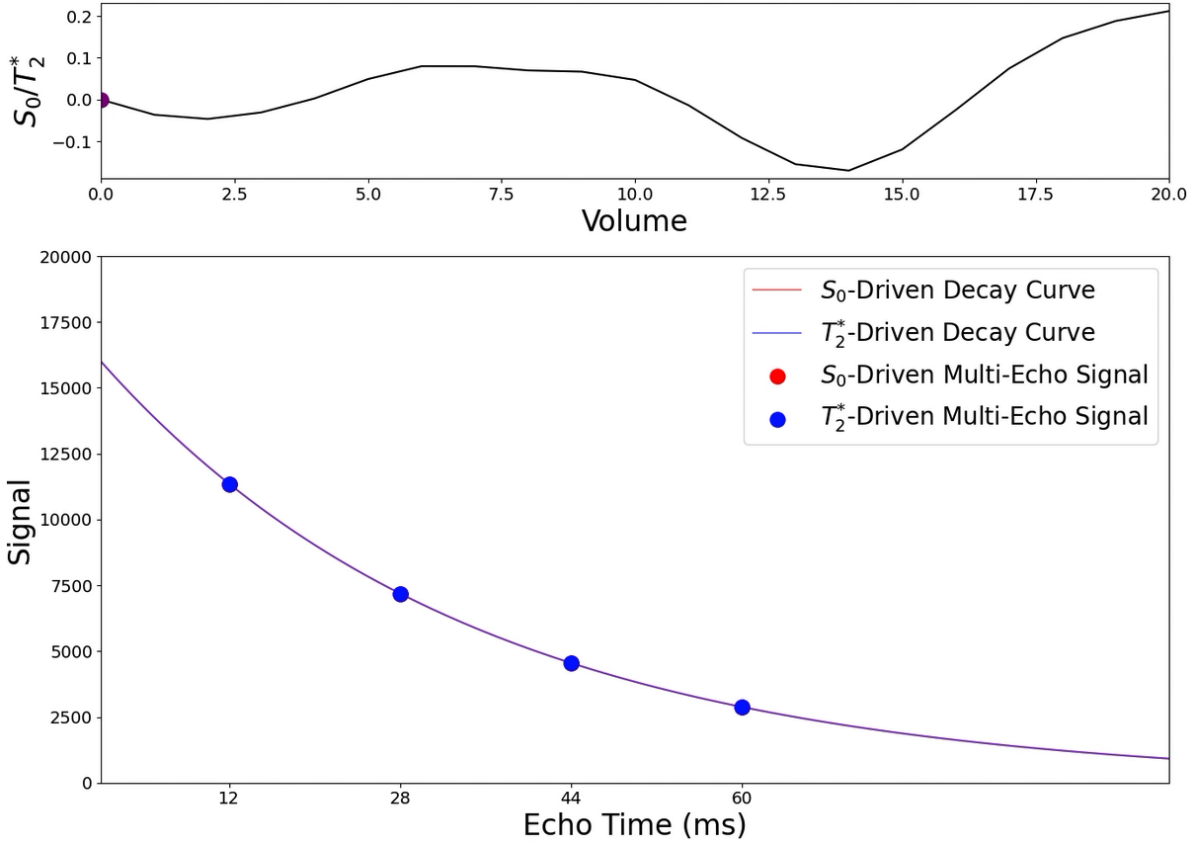
https://me-ica.github.io/multi-echo-data-analysis/content/Signal_Decay.html

Distinguishing T_2^* and S_0

What we measure with single-echo fMRI



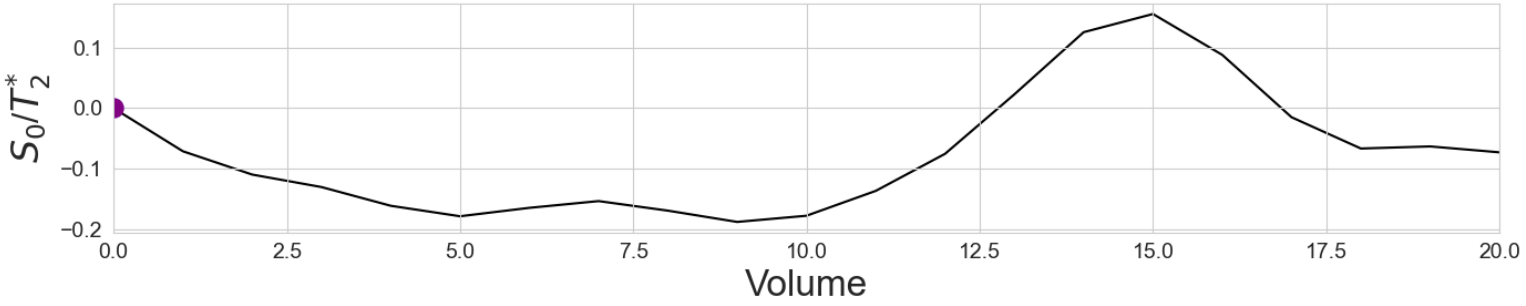
What we measure with multi-echo fMRI

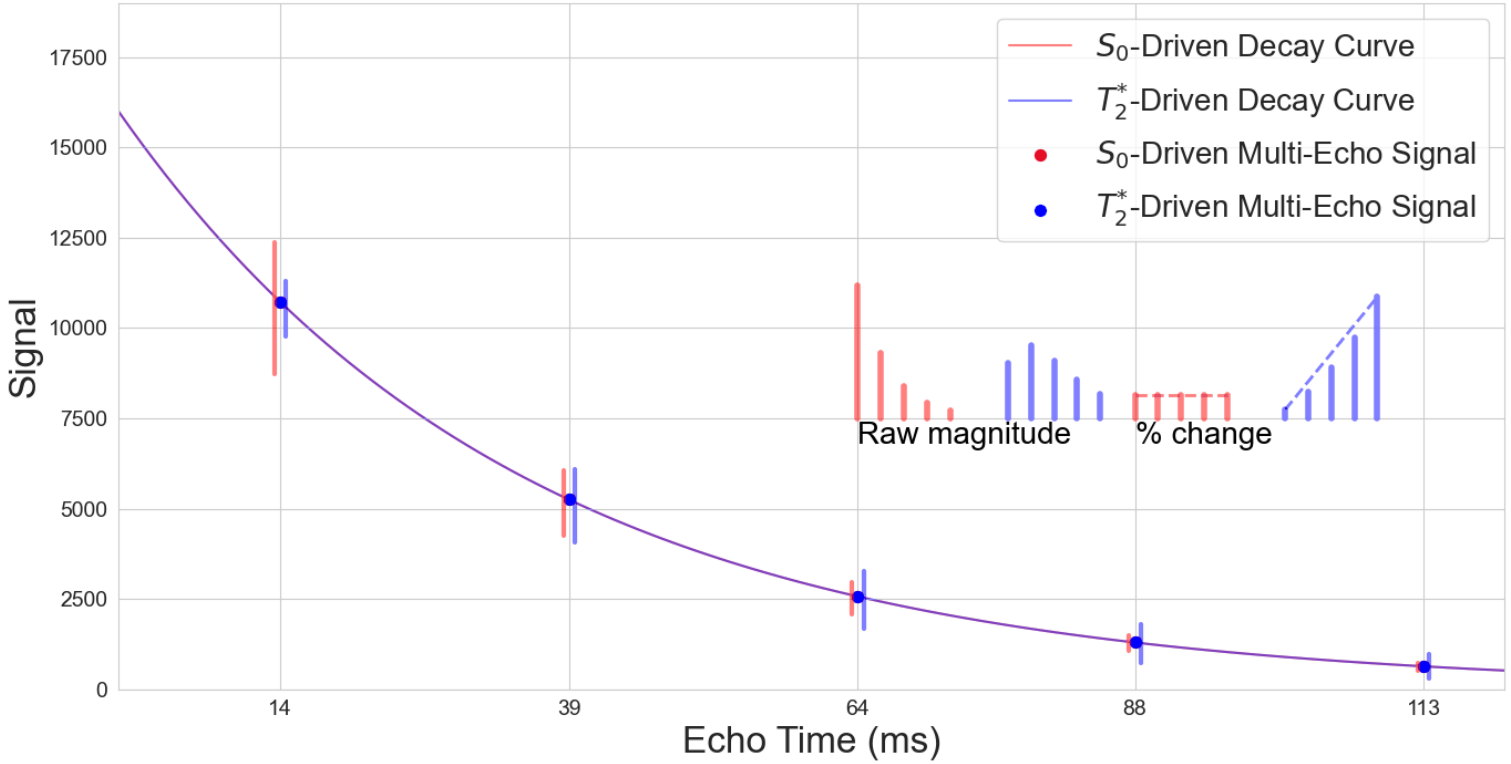


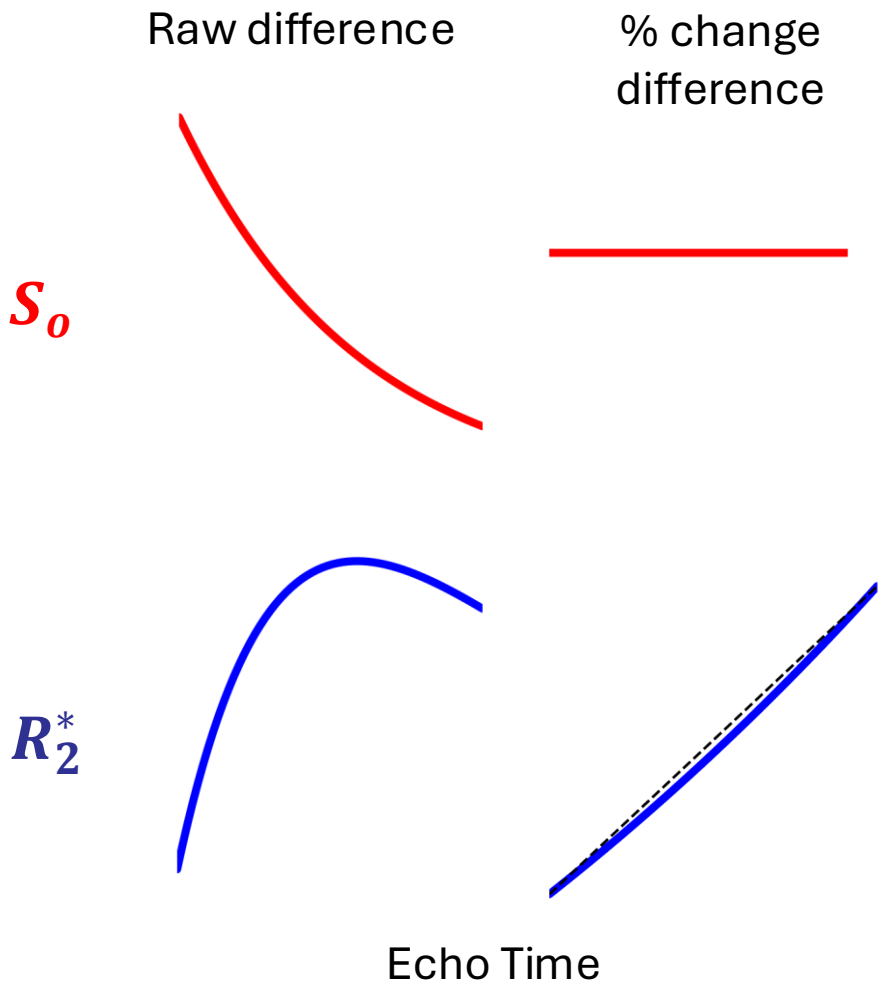
$$S(x,t,TE_k) = \boldsymbol{S_o(x,t)} \cdot e^{-\boldsymbol{R_2^*(x,t)}\cdot TE_k} + n(x,t)$$

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

Distinguishing T_2^* and S_0



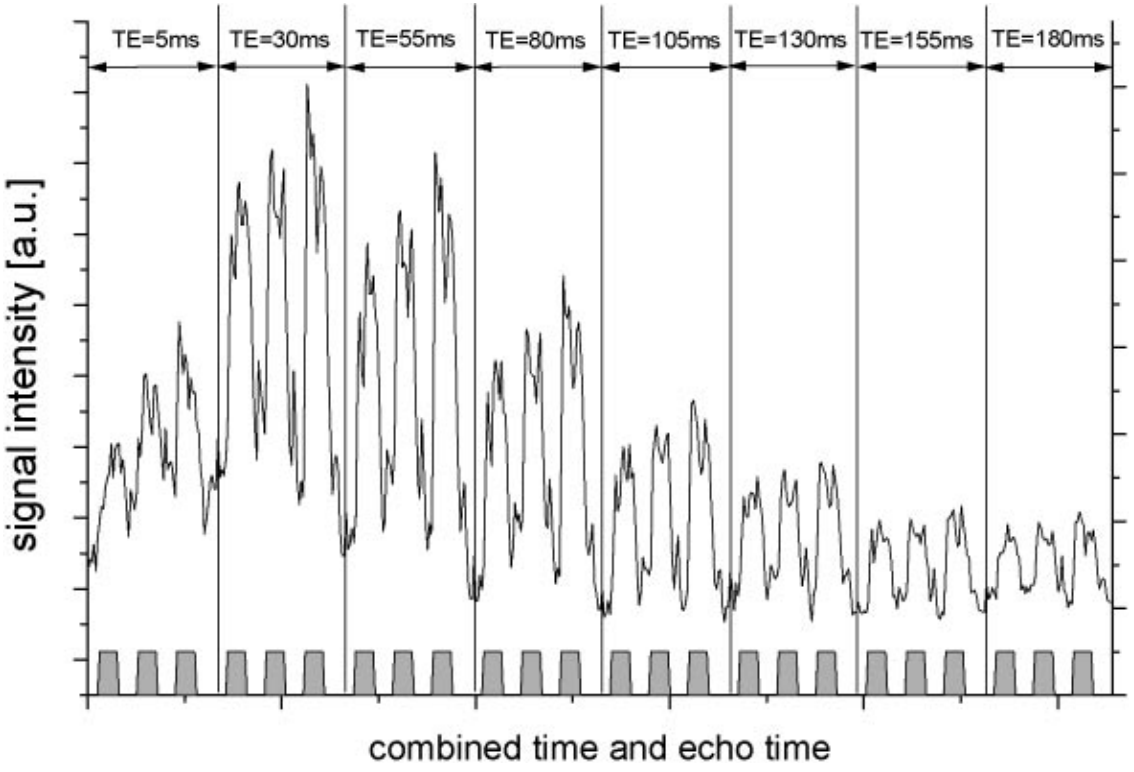




$$S(x,t,TE_k) = \boldsymbol{S_0(x,t)} \cdot e^{-\boldsymbol{R_2^*(x,t)} \cdot TE_k} + n(x,t)$$

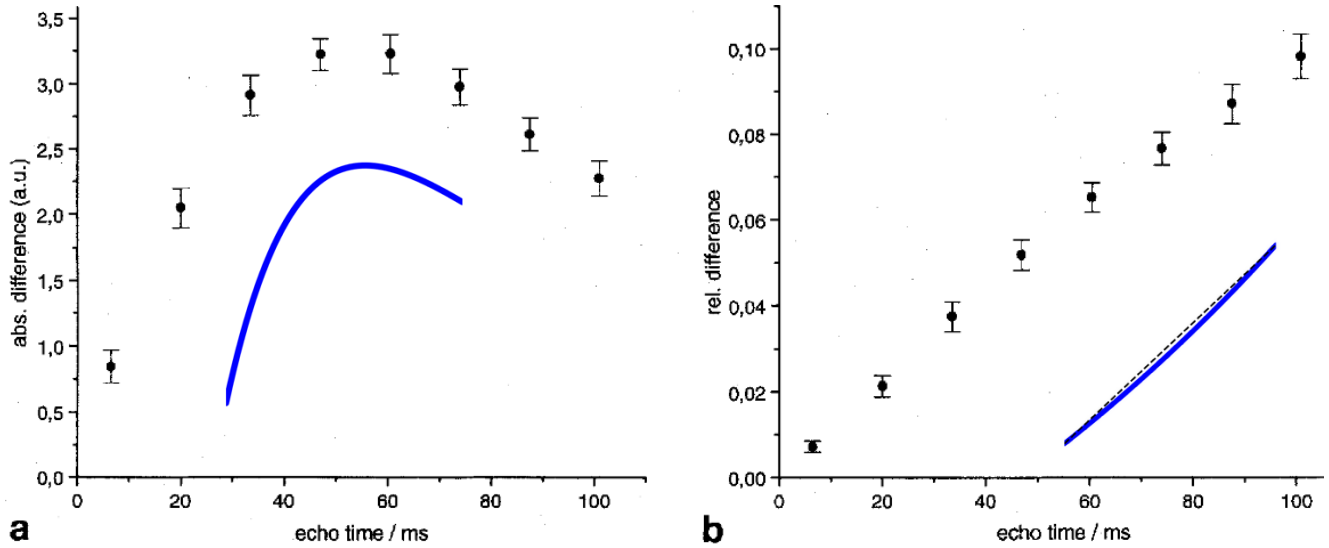
Response magnitudes by echo time

Finger tapping task at 3T



Barth et al NMR Biomed 2001

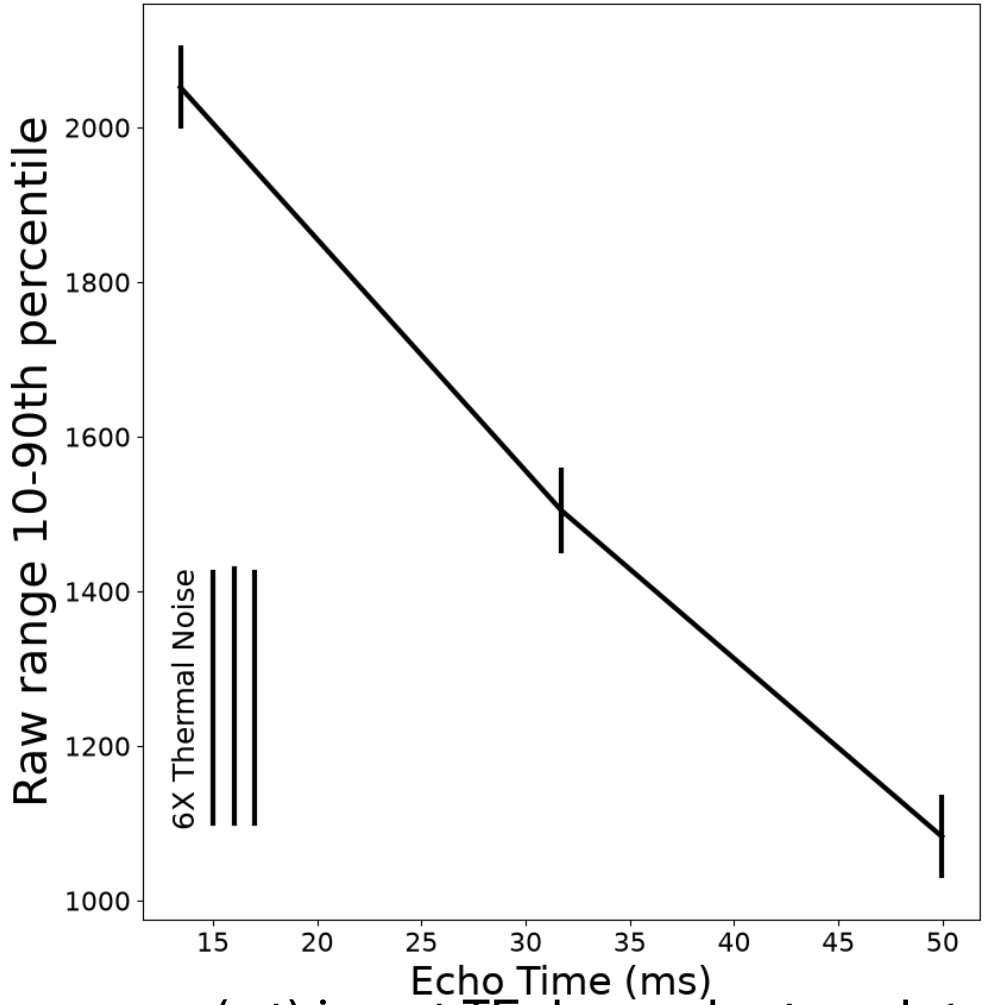
8Hz flashing checkerboard at 2T

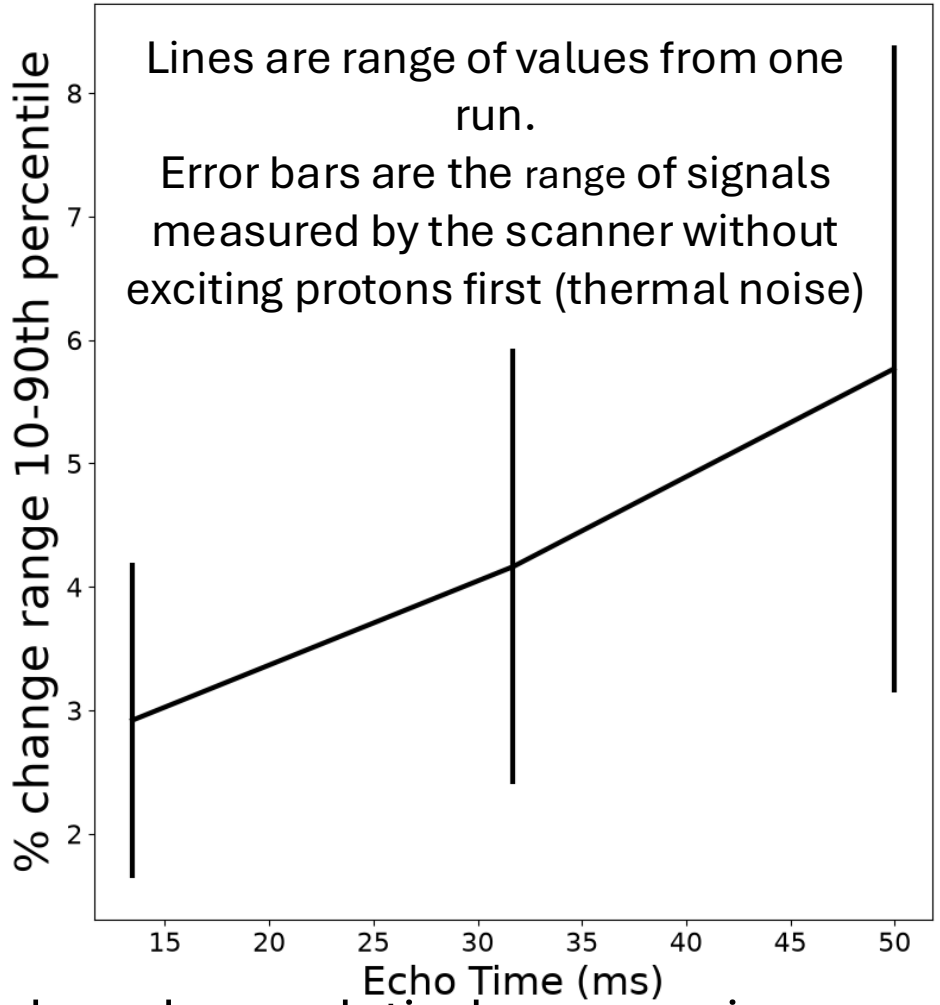


Speck & Hennig 1998

Without ignoring thermal noise

$$S(x,t,TE_k) = \boldsymbol{S_o(x,t)} \cdot e^{-TE_k \cdot \boldsymbol{R_2^*(x,t)}} + n(x,t)$$





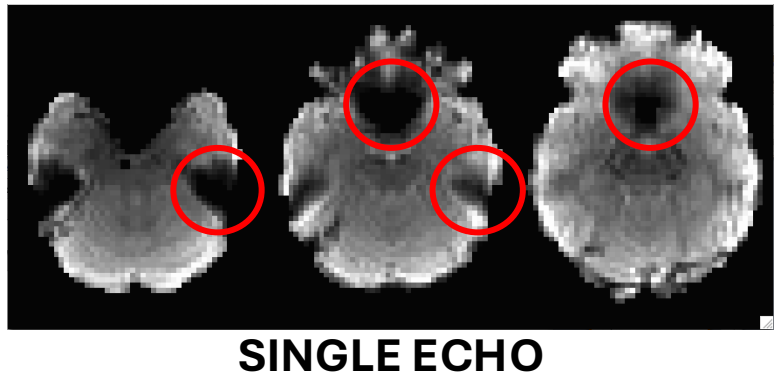
n(x,t) is not TE dependent, so later echoes have relatively more noise

A linear fit across ≧3 noisy data points is… challenging

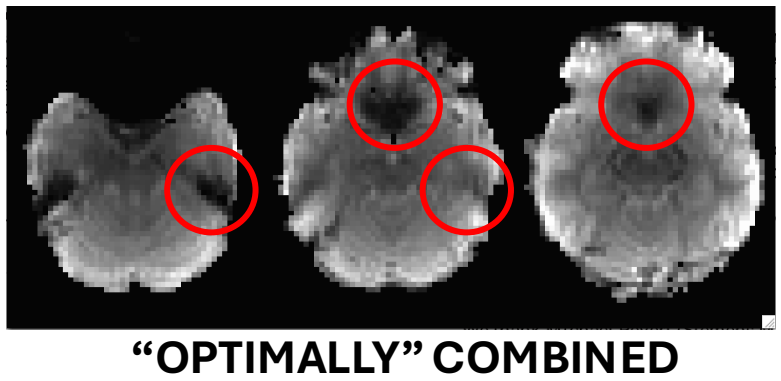
Weighted average of the echoes

T_2^*-Combined Method

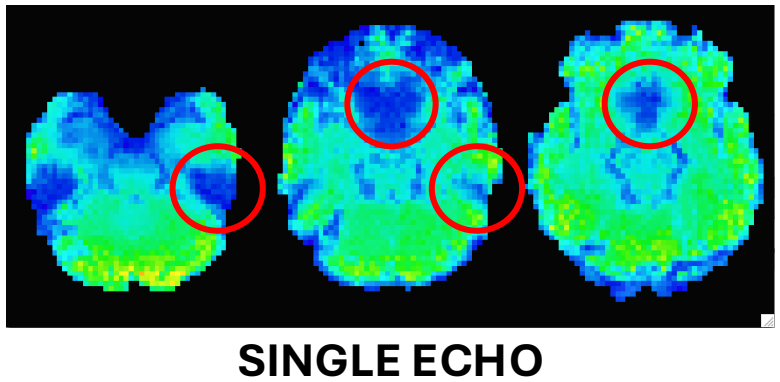
$$w_n = \frac{TE_n \cdot e^{-TE_n / T_2^*}}{\sum_{i=1}^{N} TE_i \cdot e^{-TE_i / T_2^*}}$$



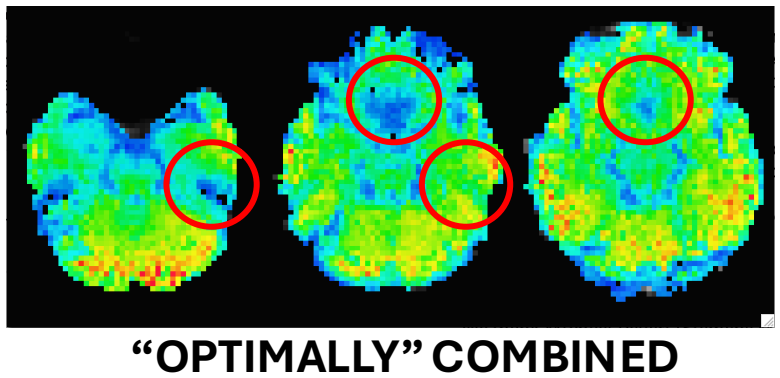
SINGLE ECHO



"OPTIMALLY" COMBINED



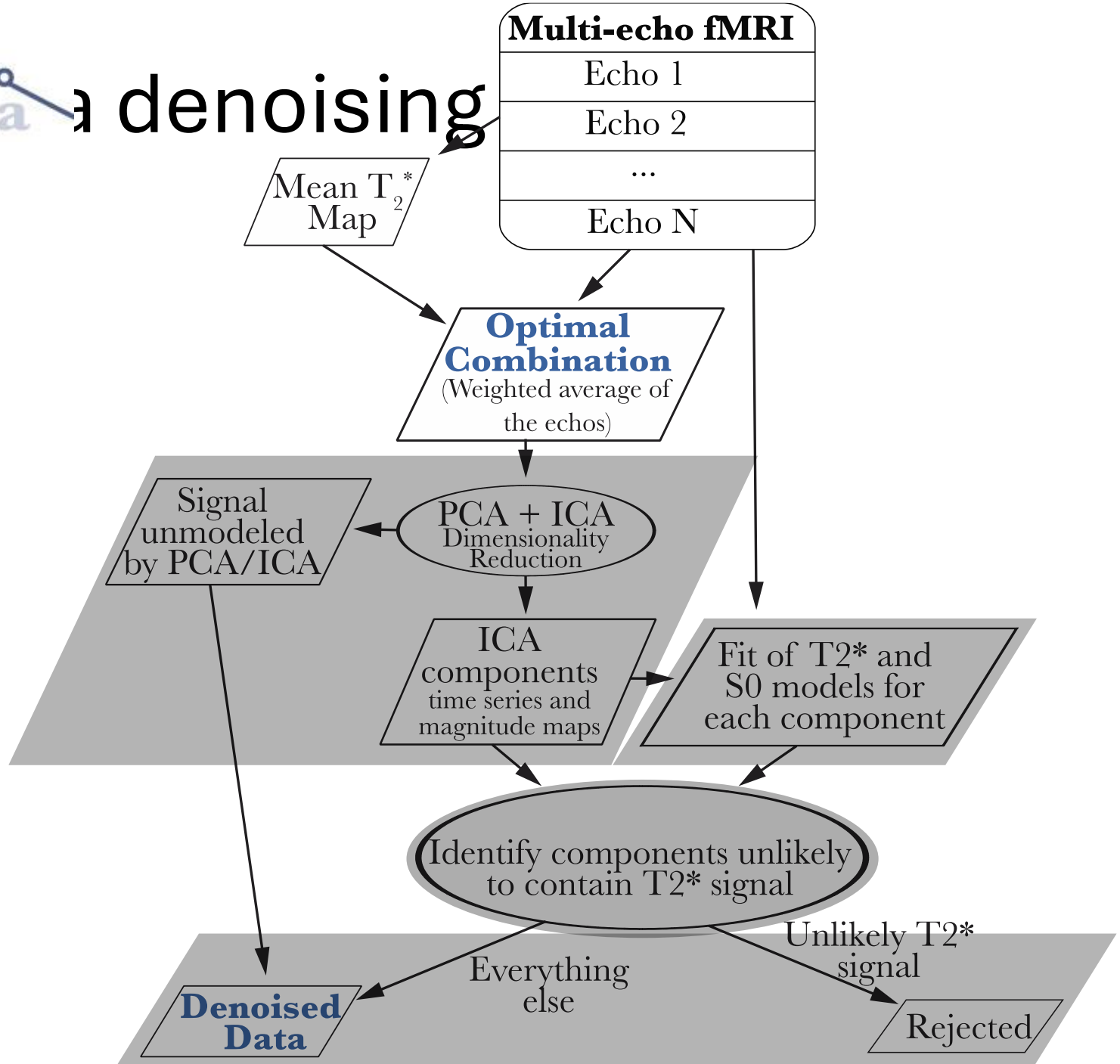
SINGLE ECHO



"OPTIMALLY" COMBINED

- Average of echoes weights towards voxelwise mean T_2^*
- Recovers signal in *some* dropout regions
- Straightforward math
- T_2^* fit is on a lower-noise average across time
- Automatically calculated in AFNI, fMRIPrep, tedana, +
- Reliable improvements
  - Improvement should be equal or better than SNR loss from a small increase in acquisition acceleration to acquire multi-echo

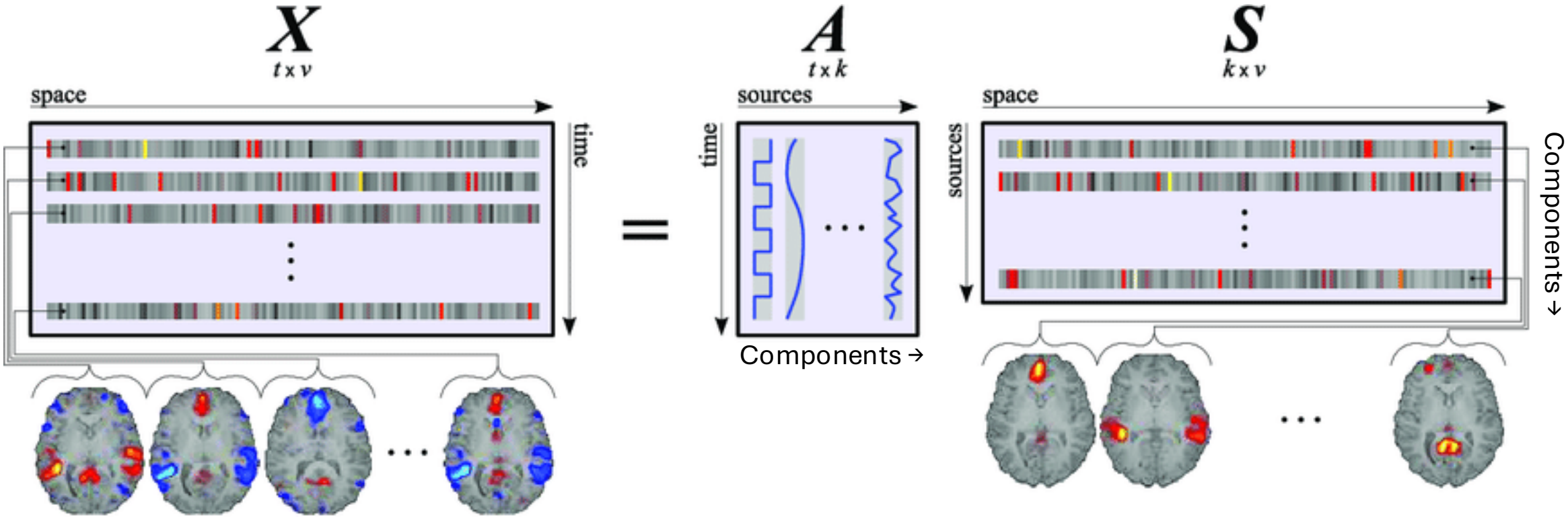
MEICA or tedana denoising



Hand waving explanation of ICA

Weighted average reduces noise in model fit by averaging across time

ICA reduces noise in model fit by averaging across spatio-temporal components



Ylipaavalniemi, *Variability of Independent Components in functional Magnetic Resonance Imaging*

Originally applied to multi-echo denoising by Buur, *IEEE J. Sel. Top. Signal Process* (2008)

Method in ME-ICA and tedana software initially developed in Kundu, *NeuroImage* (2012)

ICA component report in tedana

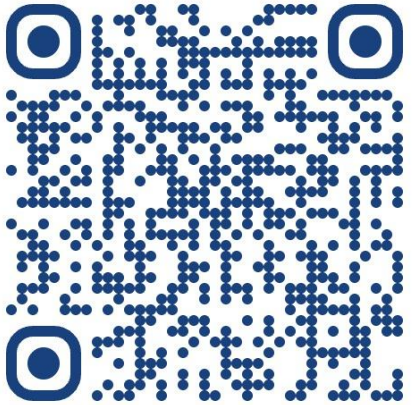
Component	Kappa	Rho	Variance %	κ Rank	ρ Rank	Dice FT2	Dice FS0	S/N t	Classification	Tags
ICA 29	105.57	18.36	0.54	7.00	16.00	0.79	0.67	13.35	accepted	Likely BOLD
ICA 30	68.46	17.99	0.37	14.00	18.00	0.75	0.64	17.81	accepted	Likely BOLD
ICA 31	136.49	28.57	9.08	1.00	2.00	0.72	0.63	5.96	accepted	Likely BOLD

Interactive component browser in RICA
rica-fmri.netlify.app

https://me-ica.github.io/ohbm-2026-multiecho/tedana_processed/tedana_report.html

Running tedana

Code & Interactive Reports



```
pip install tedana
tedana -d data_e1.nii data_e2.nii data_e3.nii \
  -e 15 30 45 \
  -tree minimal \
  --mask mask_file.nii \
  --convention bids
```

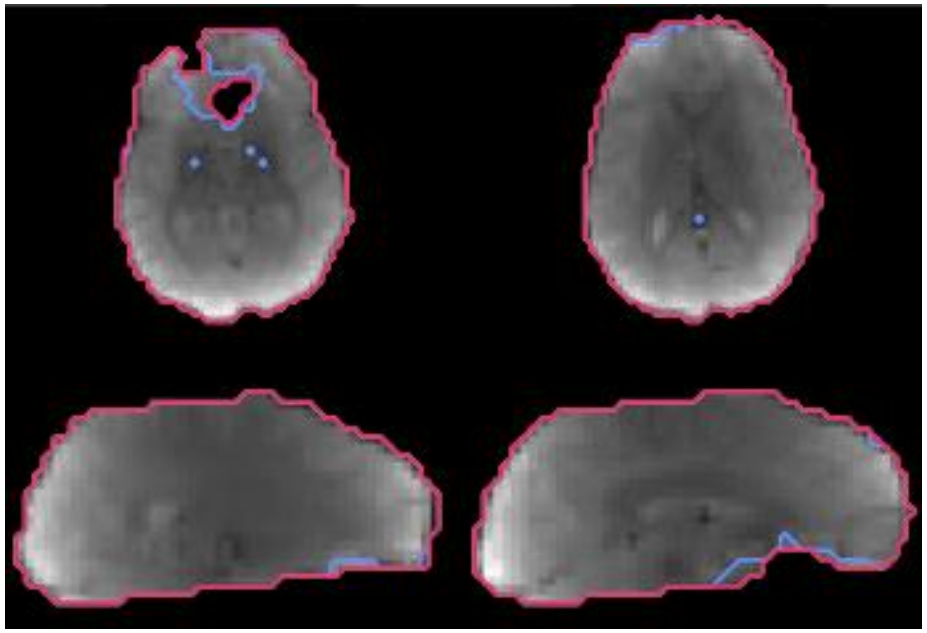
Built into AFNI & fMRIPrep pipelines

tedana.readthedocs.io includes:

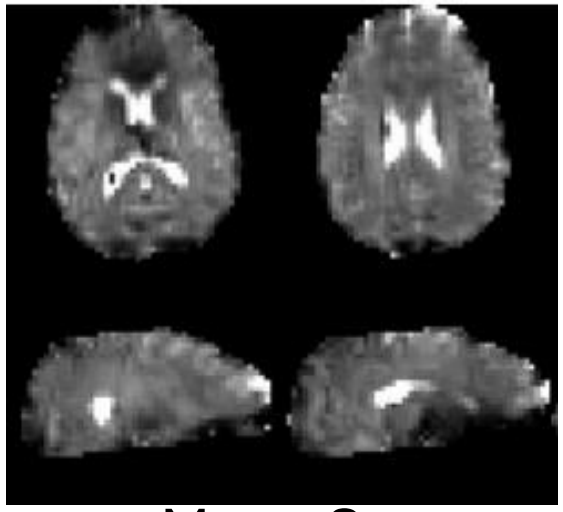
- Instructions on expected preprocessing steps
- Descriptions of options, output files, and visualizations
- Can also run from within python

Tools to assess quality are central to analysis

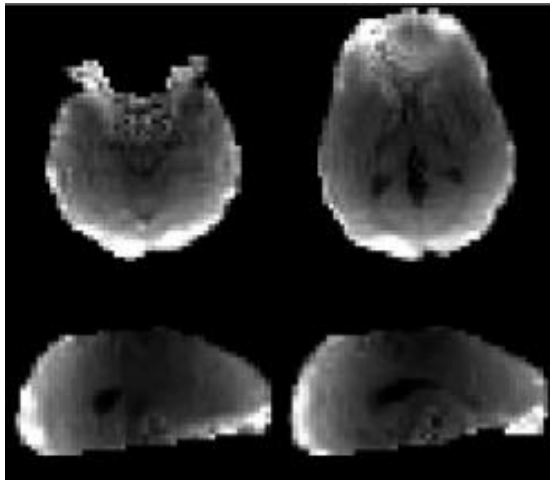
Initial & mask with 3 good echoes



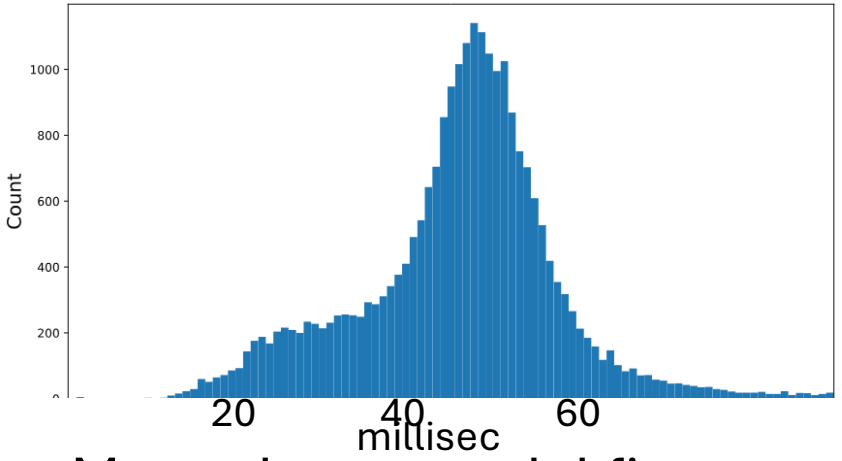
Mean T_2^*



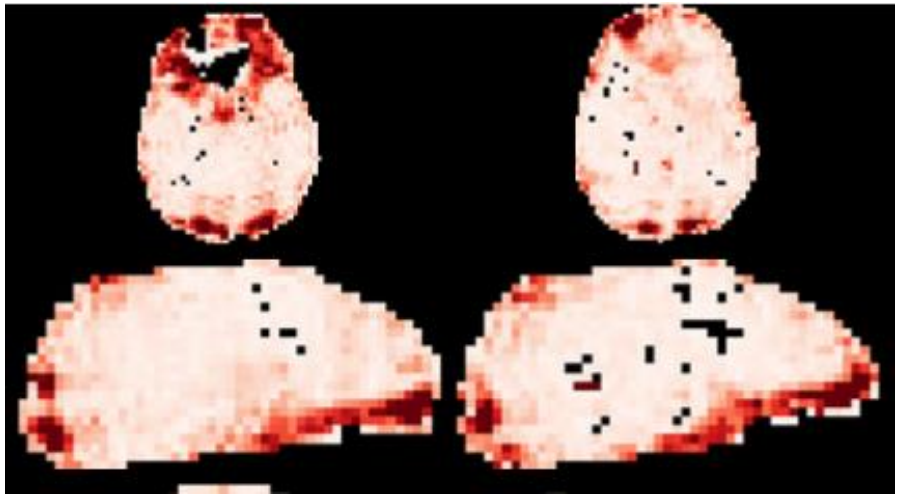
Mean S_0



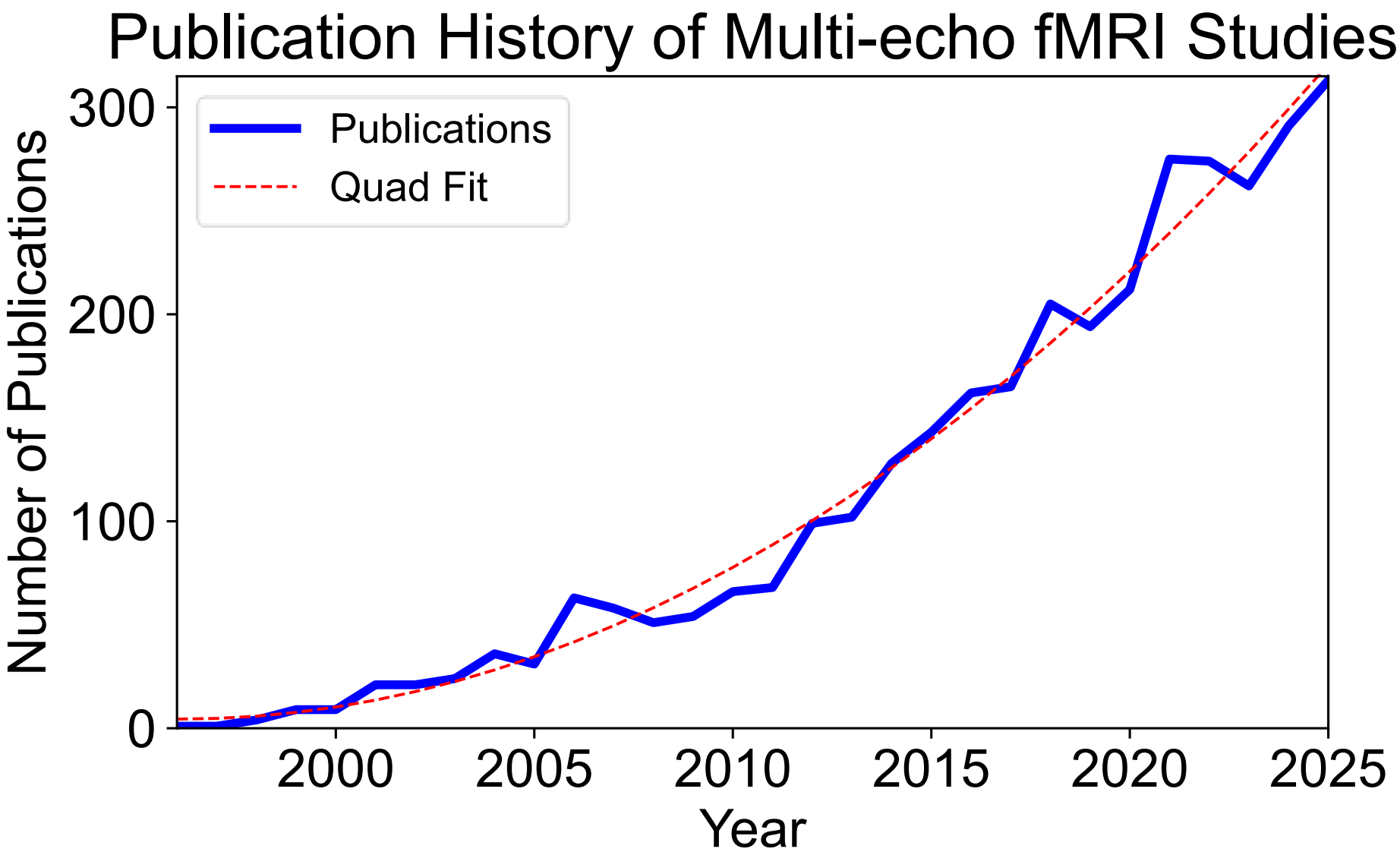
T_2^* Distribution



Mean decay model fit error



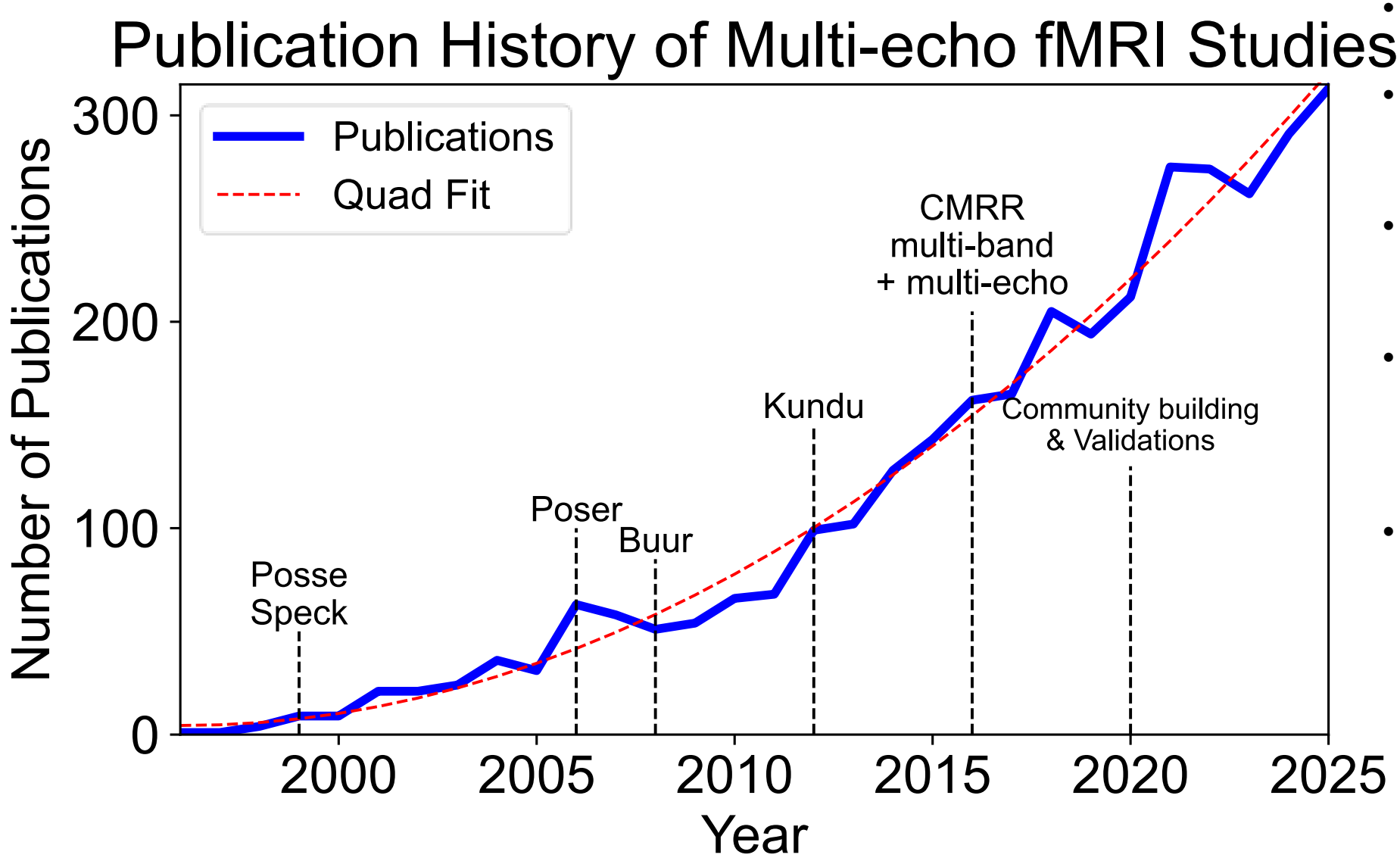
Just creating a method isn't enough



Scopus query: ((ALL(multi-echo) OR ALL(multiecho)) AND ALL(FMRI) AND PUBYEAR > 1991 AND PUBYEAR < 2027)

Reading list & more history

Just creating a method isn't enough



- 1999-2008: Developed of key theories for noise reduction
- 2008-2015: Accessible hardware & pulse sequences limited practical ME usage
- 2012-3: Kundu developed ME-ICA, showed practical benefits. Generated wider interest
- 2016: First widely available multi-band + ME sequence made ME possible with minimal compromises
- **2018: Software devel community + large validations of ME benefits start to get published**

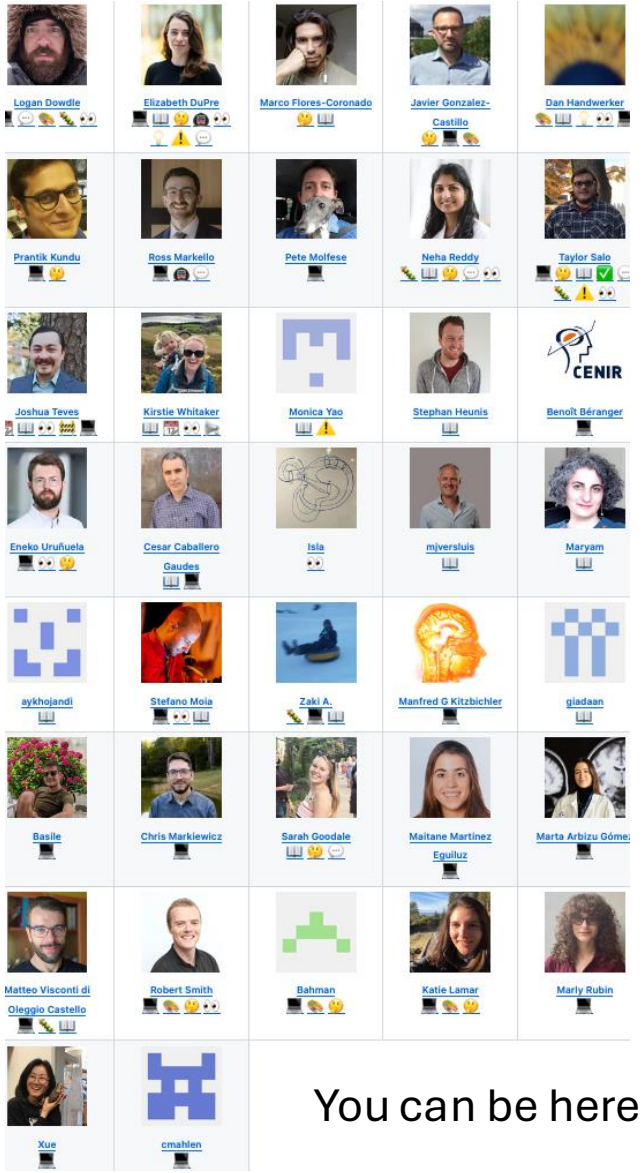
Reading list & more history

Scopus query: ((ALL(multi-echo) OR ALL(multiecho)) AND ALL(FMRI) AND PUBYEAR > 1991 AND PUBYEAR < 2027)

Software & Community

- Tedana started in May 2018 by Elizabeth DuPre et al to advance MEICA by Kundu et al
- Processing code
- Multi-echo education
- Approx 37 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



You can be here too!

Discussions are open

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

16 Open ✓ 751 Closed Author ▾ Label ▾ Projects ▾ Milestones ▾ Reviews ▾

Parallelize component figure creation ✓ refactoring reports
#1356 opened on Feb 9 by tsalo Member • Review required

Refer to unstandardized PEs as PEs and standardized PEs as betas ✓ breaking-change documentation refactoring ⊙ 1
#1338 opened on Jan 29 by tsalo Member • Review required

Use standardized parameter estimates for metrics instead of unstandardized ones ✓ breaking-change TE-dependence ⊙ 1
#1337 opened on Jan 29 by tsalo Member • Approved

Allow simultaneous estimation of TE-(in)dependence metrics ✓ enhancement TE-dependence ⊙ 1
#1357 opened on Feb 9 by tsalo Member • Draft

Calculate dependence metrics for modified mixing matrices and confounds ✓ enhancement ⊙ 2
#1350 opened on Feb 6 by tsalo Member • Review required

Add tree argument to ica_reclassify ✗ enhancement ⊙ 1
#1360 opened on Feb 11 by tsalo Member • Draft

Expand interpolation option to perform two-stage interpolation+fitting ✓ enhancement T2*/S0 estimation
#1459 opened last week by tsalo Member • Approved

ENH: Modularize tedana.py workflow into pipeline stages ✓ refactoring
#1280 opened on Dec 18, 2025 by eurunuela Member • Draft 4 of 6 tasks

Refactor workflows with shared module architecture ✓ refactoring
#1281 opened on Dec 18, 2025 by eurunuela Member • Draft 1 of 5 tasks

Support for new contributors

https://github.com/ME-ICA/tedana/blob/main/CONTRIBUTING.md 80%

ines (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:

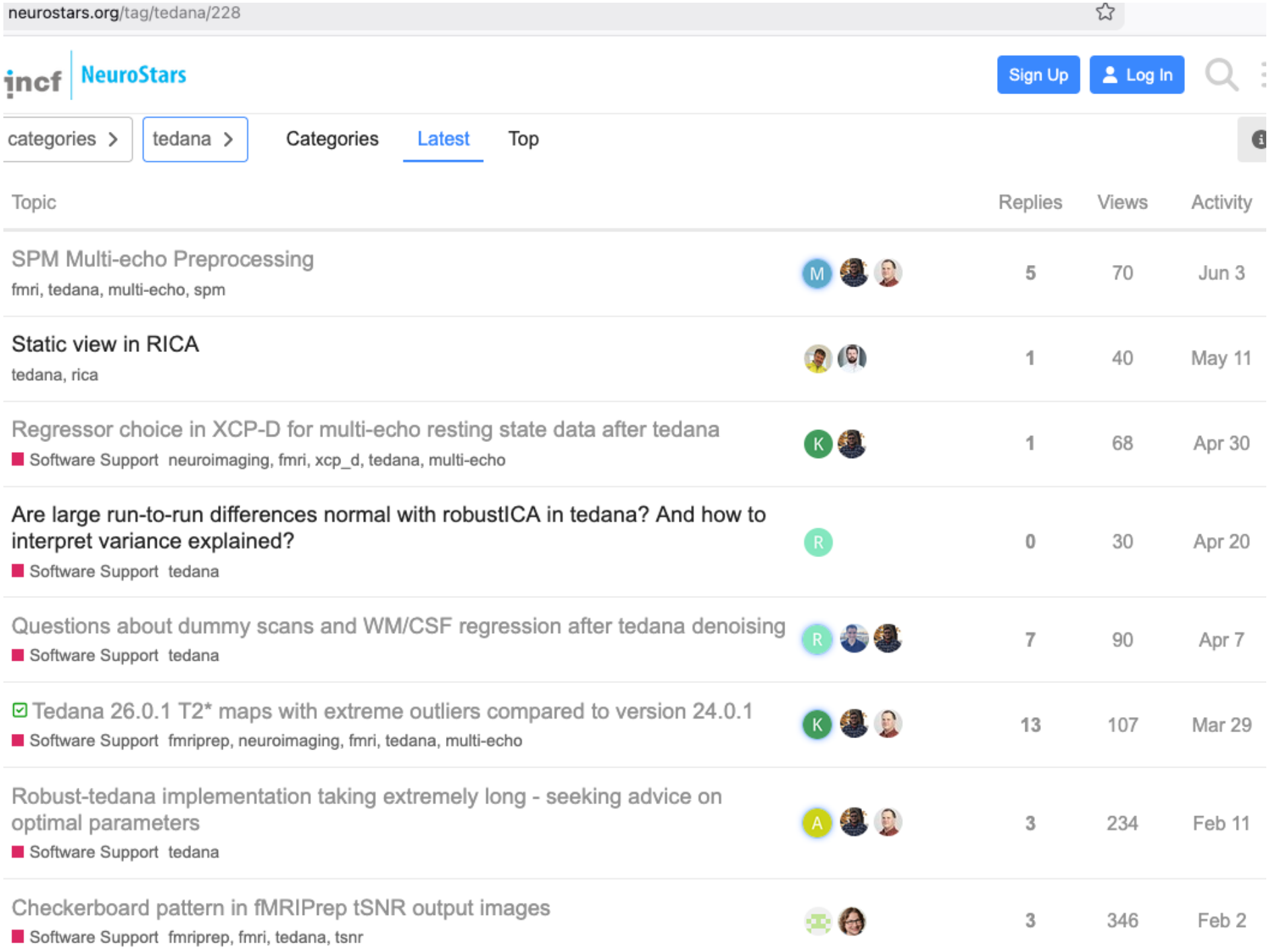
Don't know where to get started? Read Joining the conversation and pop into Mattermost to introduce yourself! Let us know what your interests are and we will help you find an issue to contribute to. Thanks so much!

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



Multi-echo book

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

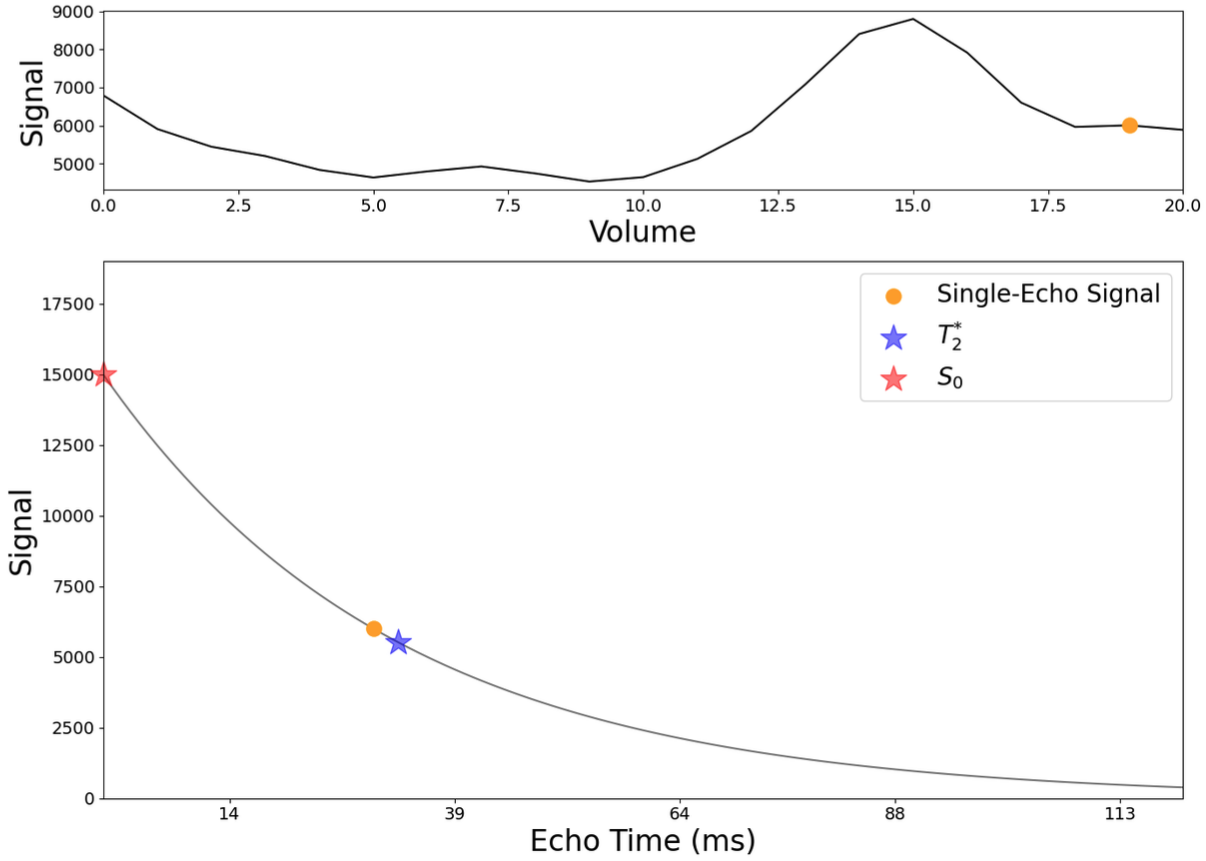
80%

tedana

Search ⌘ + K

Both factors of the product - S_0 and the exponential with T_2^* - capture local fluctuations happening during MRI acquisition, but from different origins. The figure represents how the signal of a voxel is associated to S_0 and T_2^*, showing how changes in fMRI data can be driven by both factors.

▸ **Show code cell content**



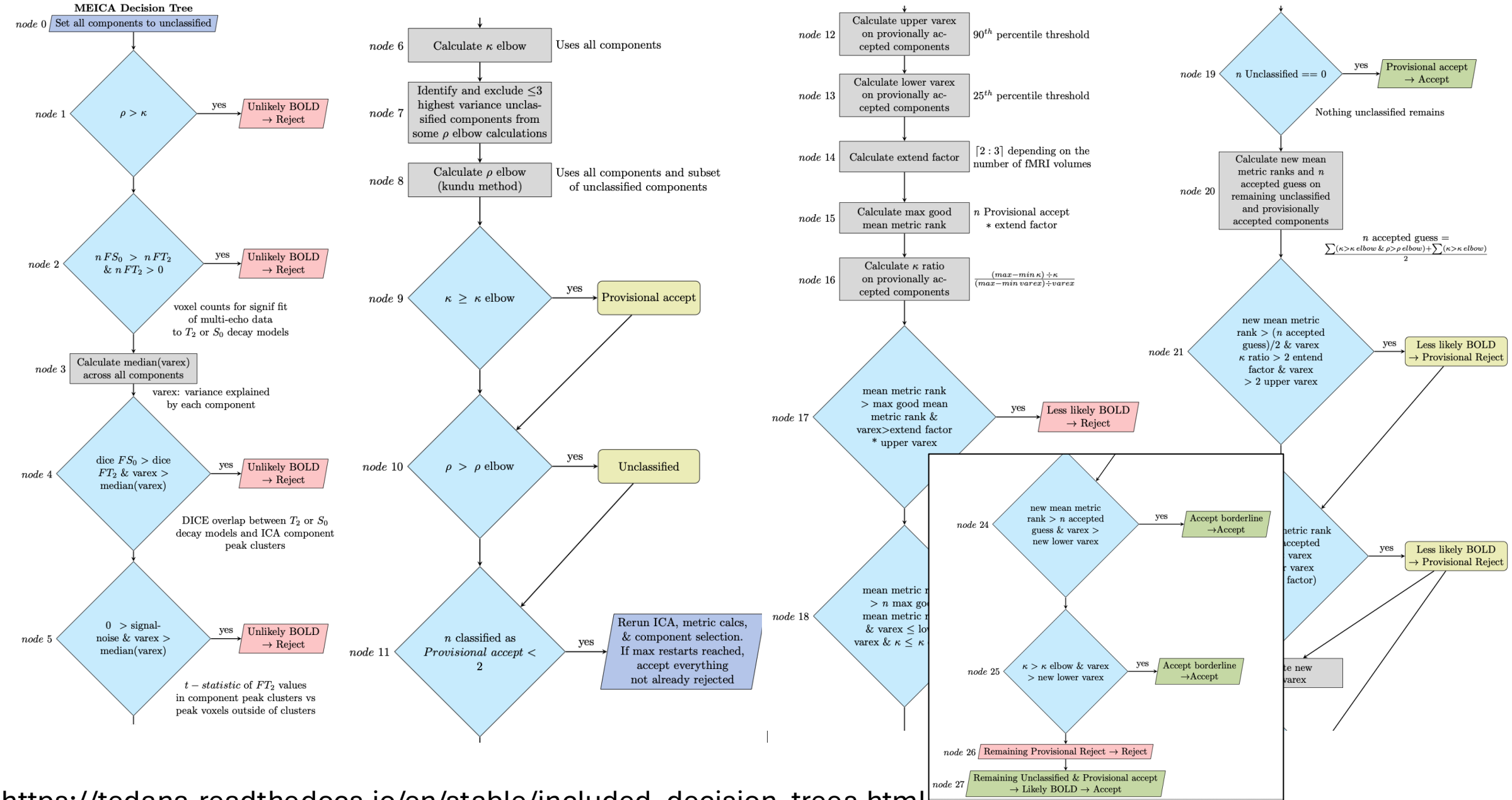
More contributors are welcome!

- 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 help validate methods & potential improvements

Community is essential

- Theory wasn’t enough
- Methods weren’t enough
- Software wasn’t enough
- Connecting them all with community & resources is helping turn multi-echo into a standard tool.
- Methods development must be connected to community interest and needs continues

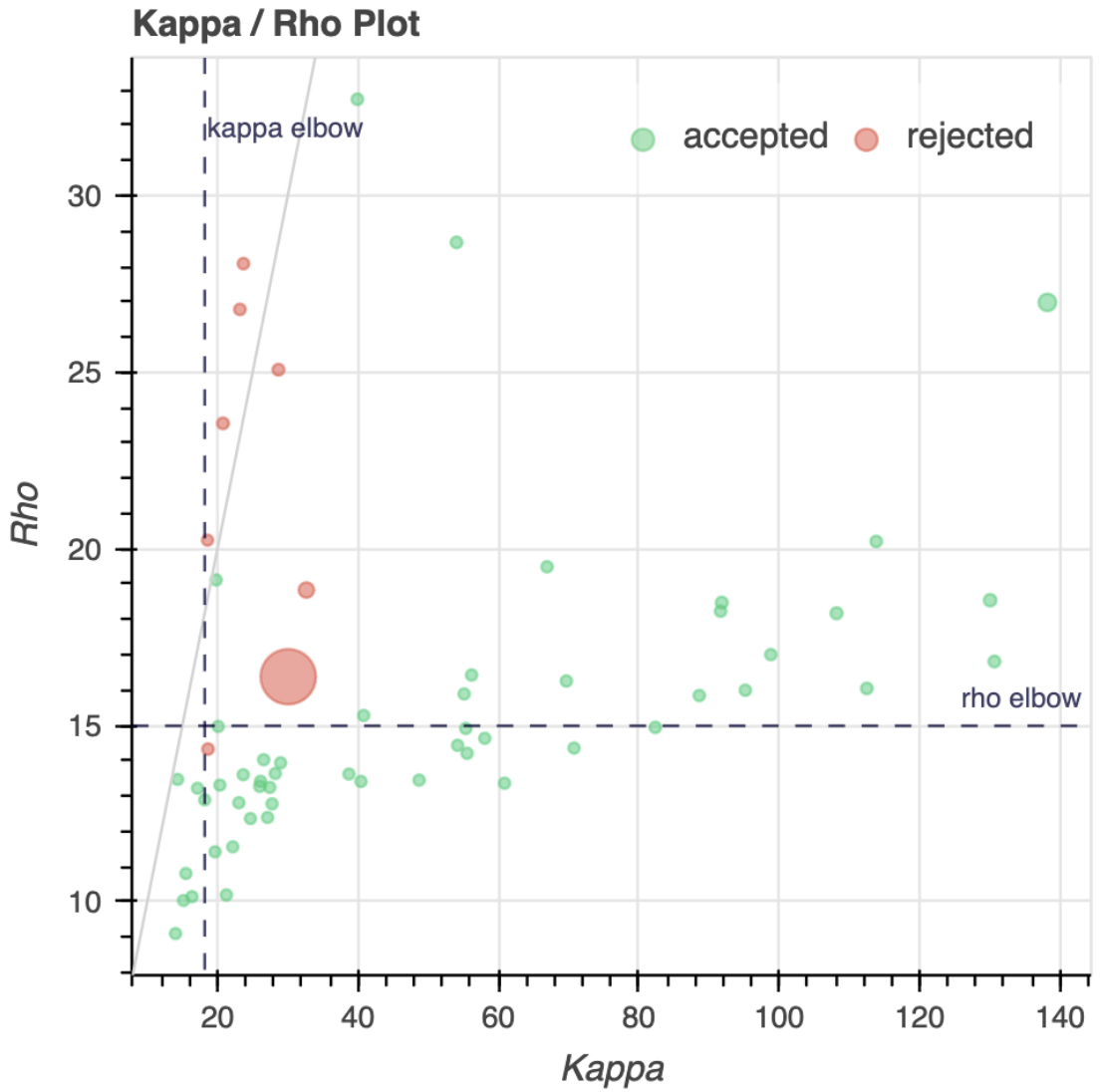
The MEICA decision process is... quirky



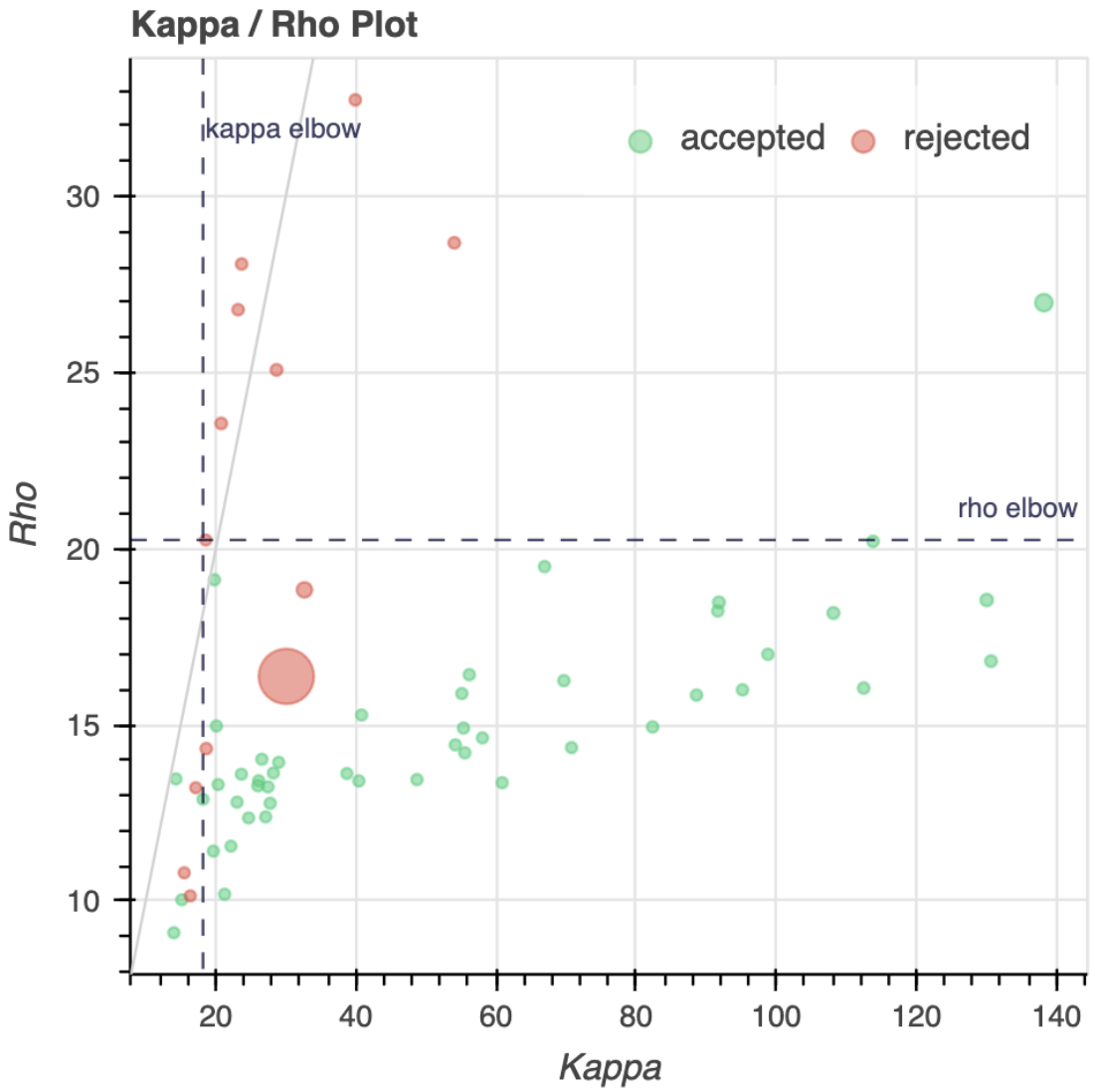
https://tedana.readthedocs.io/en/stable/included_decision_trees.html

Where to “cut” for good vs bad?

MEICA ”decision tree”

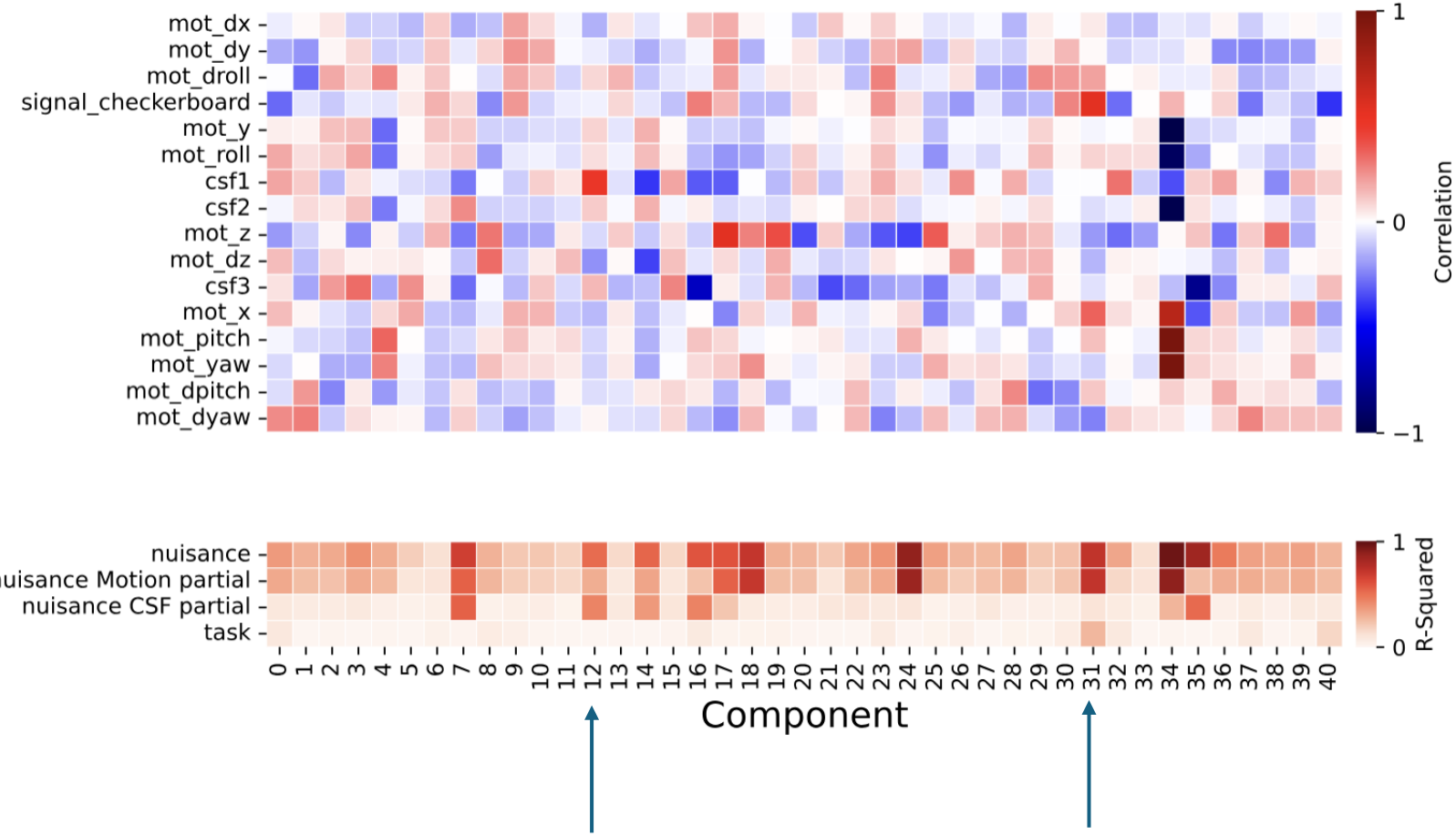


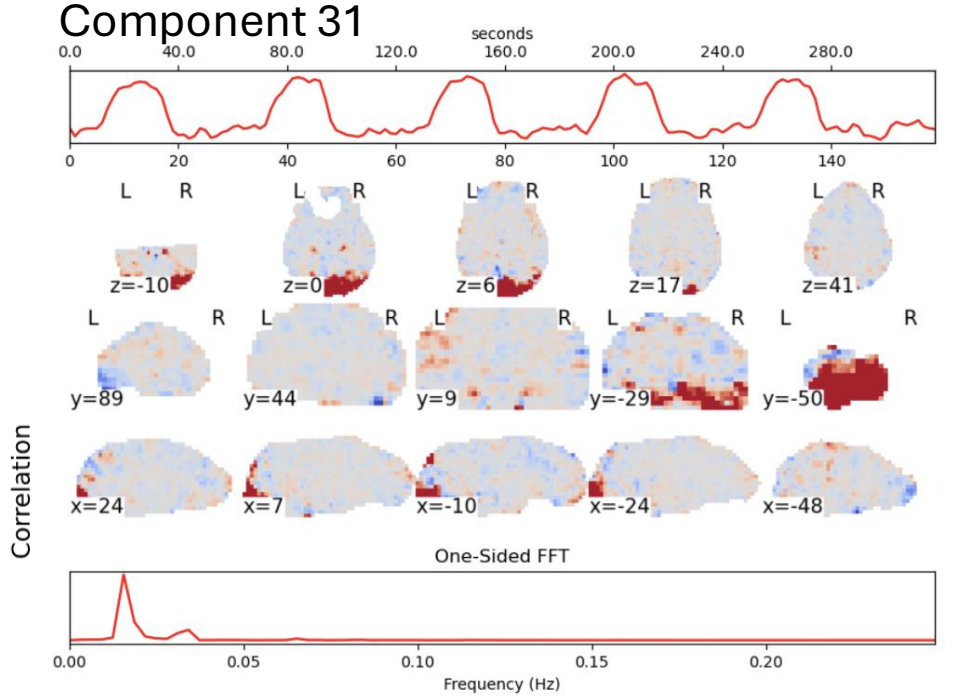
Tedana minimal “decision tree”

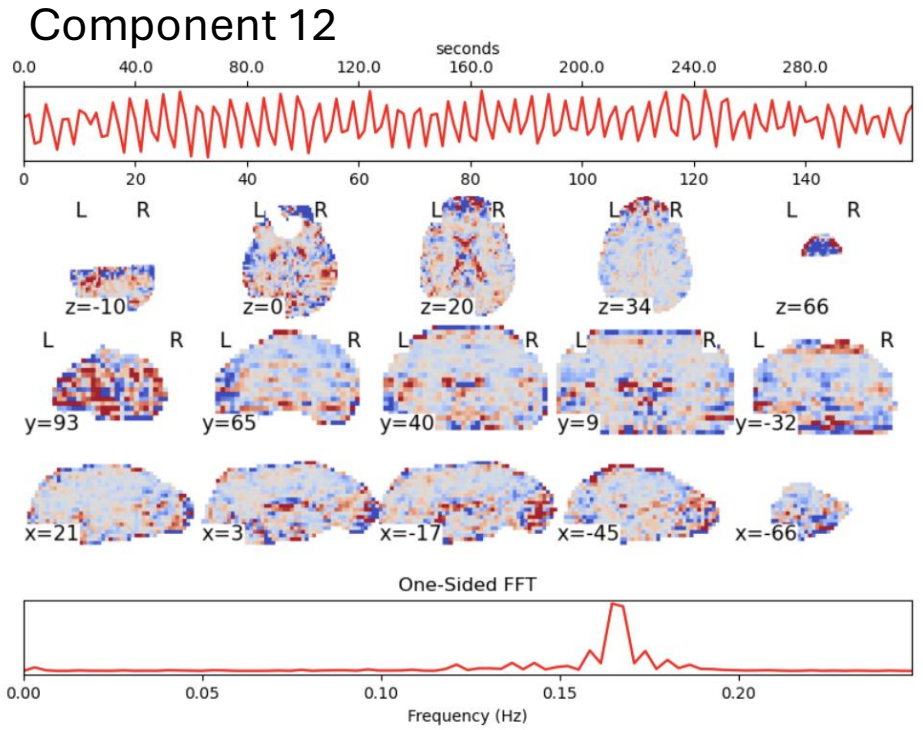


Functionality to let uses alter, test, and understand decision trees

Integrating external regressors



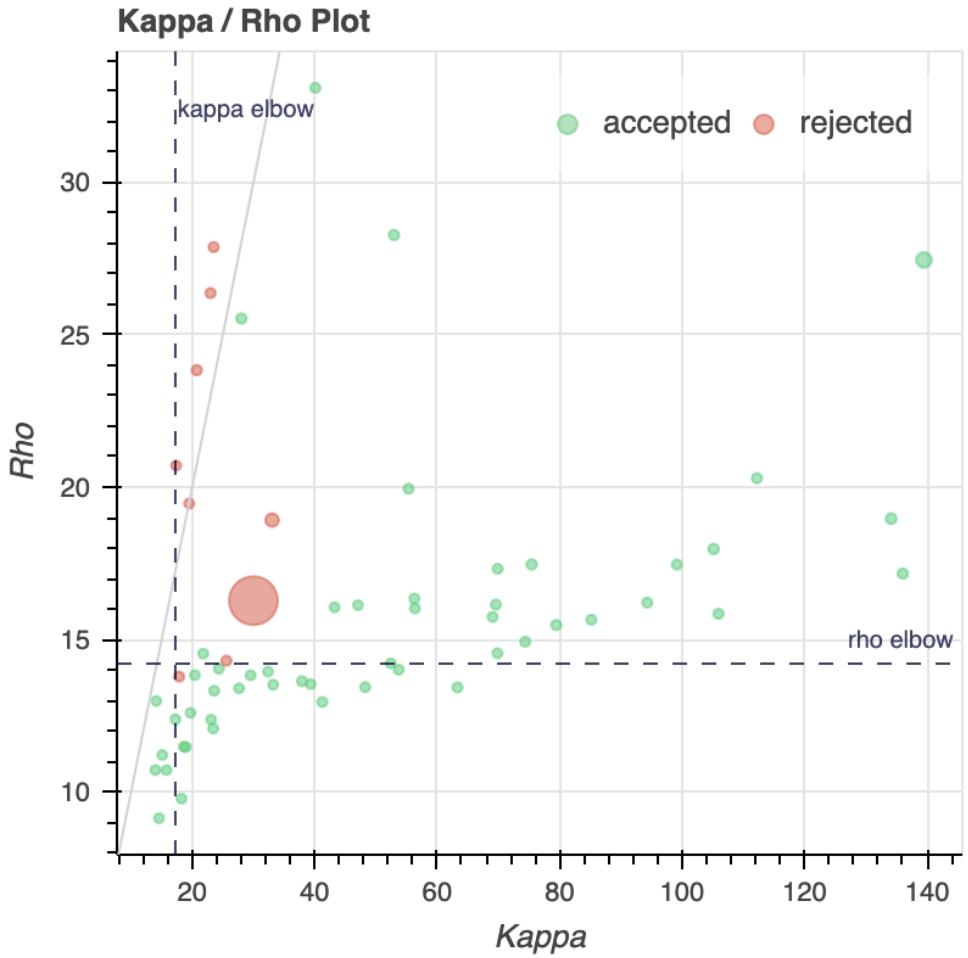


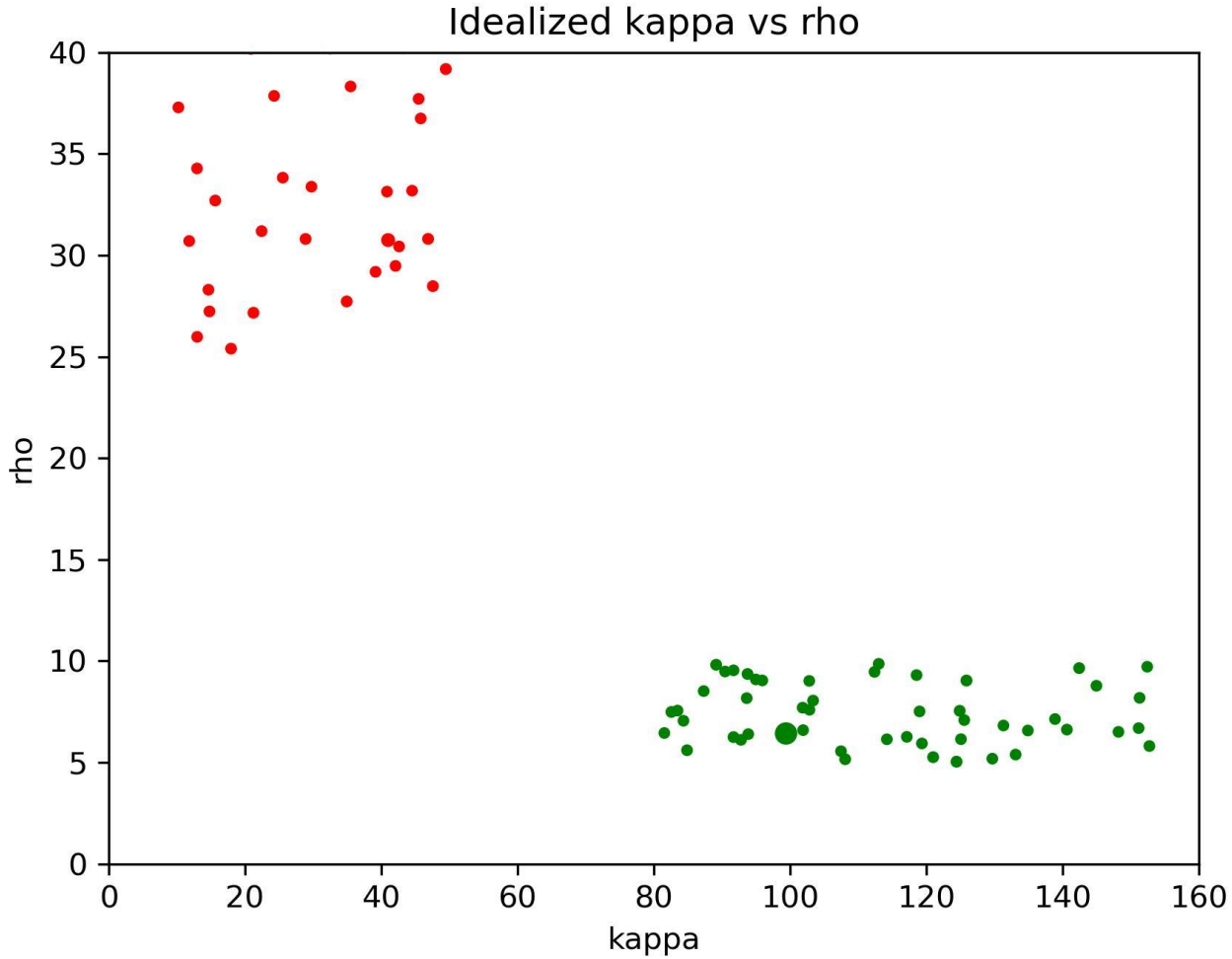


https://me-ica.github.io/ohbm-2026-multiecho/tedana_external_regress_processed/tedana_report.html

Why is the decision process unclear?

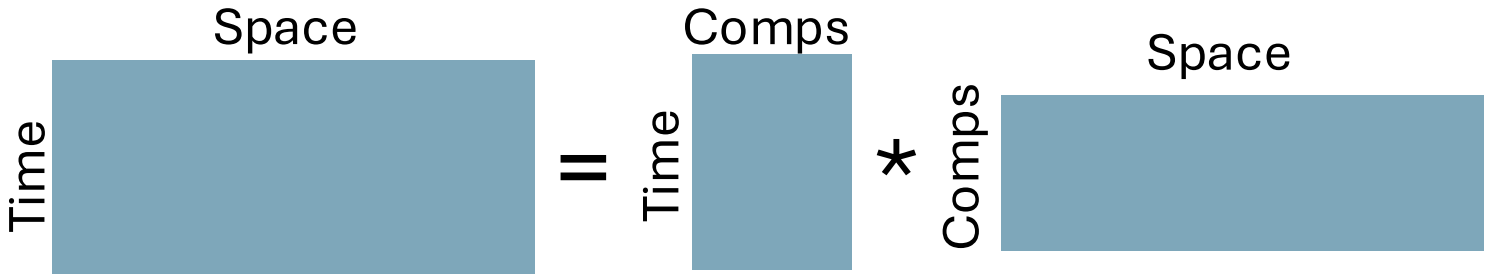
Very early work-in-progress



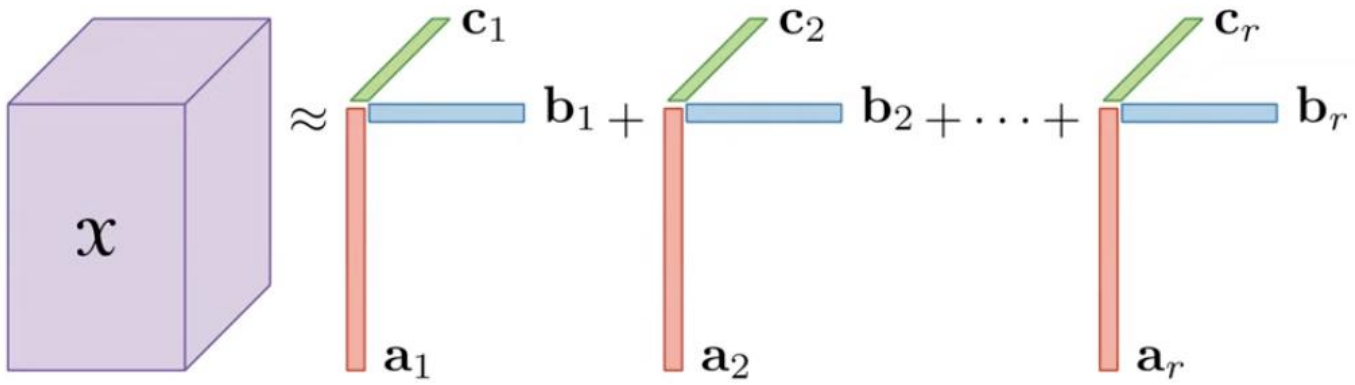


Everything far from the extremes is not only imprecise to classify,
but is inherently a mix of signal we want and don't want

Standard ICA



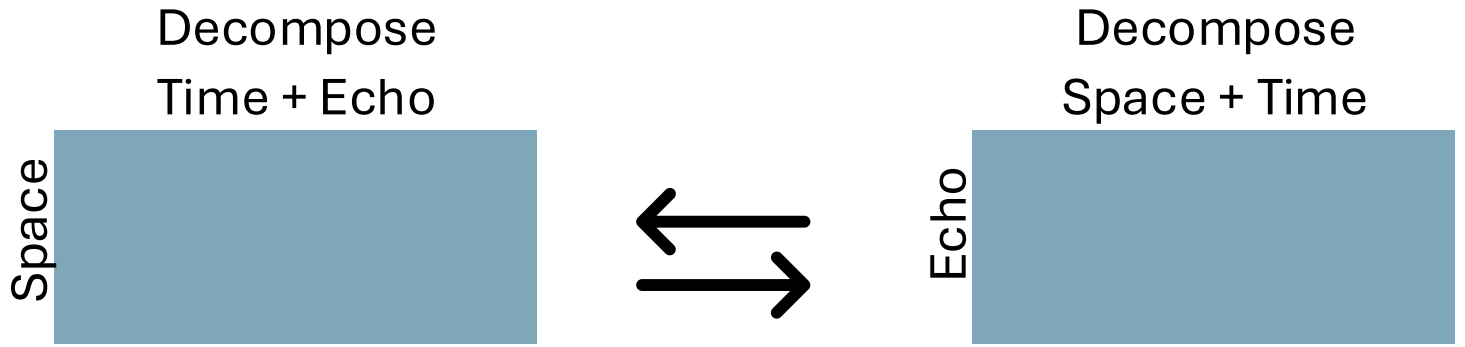
Tensorial ICA



Modeling separately across space, time, & echoes

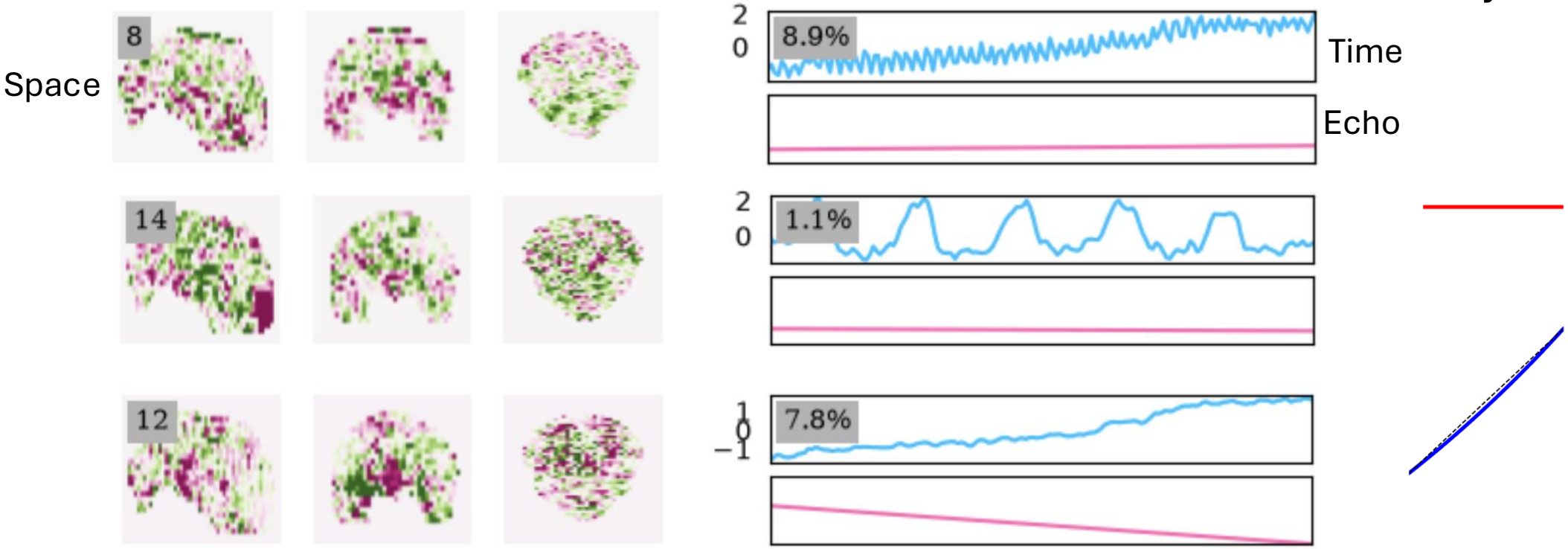
https://www.youtube.com/watch?v=V_ugq2iIjxE

Tensorial ICA



Iterate back & forth until changes are small enough to be called convergence

Alternate solving for ICA iterations with solving for the physics-informed echo decay curve



Additional uses of multi-echo information

- Validation any denoising pipeline is isolating T_2^*
  - “A new fMRI quality metric using multi-echo information: Theory, validation and implications” bioRxiv 2026
    Gonzalez-Castillo, Caballero-Gaudes, Handwerker, Bandettini
- Paradigm Free Mapping (Caballero-Gaudes, *NeuroImage*, 2019)
  - For finding sparse events in time
  - https://me-ica.github.io/multi-echo-data-analysis/content/05_3dMEPFM.html

Take-home messages

- We work towards the full potential of fMRI by optimizing improvements in design, acquisition, and analysis for specific application
- Multi-echo fMRI is one tool that is benefiting some applications and has the potential to benefit more
- These types of improvements require collaboration and community building between methods research and applications

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