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Multi-echo Functional Connectivity as an Evaluation Metric for Denoising

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INTRODUCTION

Several quality control (QC) metrics exist for fMRI (e.g., temporal signal-to-noise ratio (TSNR), test-retest reliability), yet their interpretation and usefulness remain challenging[1]. For example, higher TSNR suggests better data, yet removal of neuronally-driven BOLD signal would also increase it. Also, perfect reliability across sessions can obscure relevant changes in functional connectivity (FC) over time. To overcome this, we propose a new QC metric for multi-echo (ME) fMRI[2] that quantifies the likelihood of data being dominated by BOLD effects, and show its ability to reveal pre-processing issues not evident with classical QC metrics.

THEORY

Multi-Echo fMRI Signal Model

BOLD Signal at location 'x', time 't' and echo 'TE_k'

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

Net Magn. fluctuations: $S_o(x,t) = \overline{S_o(x)} + \Delta S_o(x,t)$ $\quad \Delta S_o(x,t) \ll \overline{S_o(x)}$ $\quad \Delta\rho(x,t) = \Delta S_o(x,t) / \overline{S_o(x)}$

BOLD fluctuations: $R_2^*(x,t) = \overline{R_2^*(x)} + \Delta R_2^*(x,t)$ $\quad \Delta R_2^*(x,t) \ll \overline{R_2^*(x)}$

Mean Signal: $\overline{S(x,TE_k)} = \overline{S_o(x)} \cdot e^{-\overline{R_2^*(x)}\cdot TE_k}$

Assuming n(x,t) [thermal noise] is negligible

Fluctuations from the mean in percent change units

$$\frac{S(x,t,TE_k) - \overline{S(x,TE_k)}}{\overline{S(x,TE_k)}} \approx \Delta\rho(x,t) - \Delta R_2^*(x,t)\cdot TE_k$$

$$s_{x,k} \approx \Delta\rho_x \quad -\Delta R_x \cdot TE_k$$

Signal fluctuation at location 'x', time 't' and echo 'TE_k' — Fluctuations in Net Magnetization — BOLD Fluctuations

Across-Echoes FC (Pearson's Correlation)

$s_{x,i} \approx \Delta\rho_x - \Delta R_x \cdot TE_i$ ← Signals at two ROIs [x and y] acquired at two different TEs [i and j] → $s_{y,j} \approx \Delta\rho_y - \Delta R_y \cdot TE_j$

$$R(s_{x,i}, s_{y,j}) = \frac{\sum(s_{x,i} - \overline{s_{x,i}})\cdot(s_{y,j} - \overline{s_{y,j}})}{\sqrt{\sum(s_{x,i} - \overline{s_{x,i}})^2 \cdot \sum(s_{y,j} - \overline{s_{y,j}})^2}} \underset{\overline{s_{y,j}}=0}{\overset{\overline{s_{x,i}}=0}{=}} \frac{\sum s_{x,i}\cdot s_{y,j}}{\sqrt{\sum(s_{x,i})^2 \cdot \sum(s_{y,j})^2}} = \frac{\sum(\Delta\rho_x - \Delta R_x \cdot TE_i)\cdot(\Delta\rho_y - \Delta R_y \cdot TE_j)}{\sqrt{\sum(\Delta\rho_x - \Delta R_x \cdot TE_i)^2} \cdot \sqrt{\sum(\Delta\rho_y - \Delta R_y \cdot TE_j)^2}}$$

BOLD DOMINATED REGIME

$\Delta\rho_x \ll \Delta R_x$ & $\Delta\rho_y \ll \Delta R_y$

$$R_{xi,yj} = \frac{TE_i \cdot TE_j \cdot \sum(\Delta R_x \cdot \Delta R_y)}{TE_i \cdot TE_j \cdot \sqrt{\sum(-\Delta R_x)^2} \cdot \sqrt{\sum(-\Delta R_y)^2}}$$

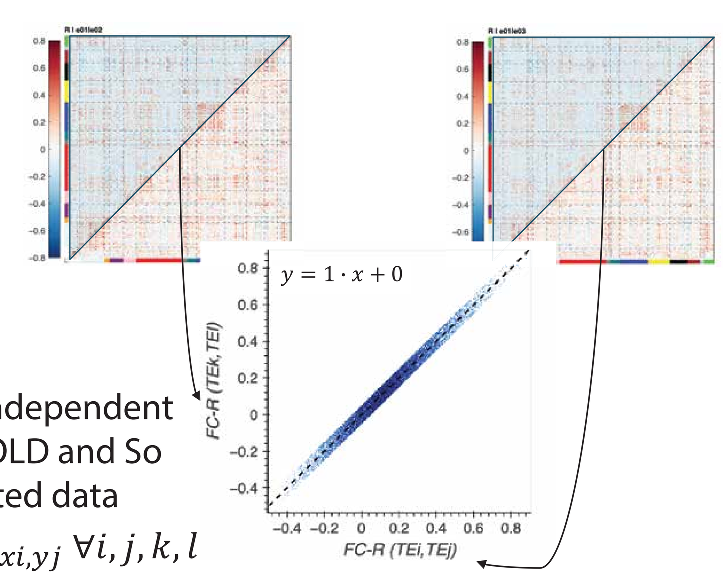
R is TE-independent

So DOMINATED REGIME

$\Delta\rho_x \gg \Delta R_x$ & $\Delta\rho_y \gg \Delta R_y$

$$R_{xi,yj} = \frac{\sum \Delta\rho_x \cdot \Delta\rho_y}{\sqrt{\sum(\Delta\rho_x)^2} \cdot \sqrt{\sum(\Delta\rho_y)^2}}$$

R is TE-independent



FC-R is TE-independent both for BOLD and So dominated data

$R_{xk,yl} = R_{xi,yj} \; \forall i,j,k,l$

Across-Echoes FC (Covariance)

$$C_{xi,yj} = \frac{1}{N_t - 1}\sum(s_{x,i} - \overline{s_{x,i}})\cdot(s_{y,j} - \overline{s_{y,j}}) \underset{\overline{s_{y,j}}=0}{\overset{\overline{s_{x,i}}=0}{=}} \frac{1}{N_t - 1}\sum s_{x,i}\cdot s_{y,j} = \frac{1}{N_t - 1}\sum(\Delta\rho_x - \Delta R_x \cdot TE_i)\cdot(\Delta\rho_y - \Delta R_y \cdot TE_j)$$

BOLD DOMINATED REGIME

$\Delta\rho_x \ll \Delta R_x$ & $\Delta\rho_y \ll \Delta R_y$

$$C_{xi,yj} = \frac{TE_i \cdot TE_j}{N_t - 1}\sum \Delta R_x \cdot \Delta R_y$$

C is a function of contributing echoes

So DOMINATED REGIME

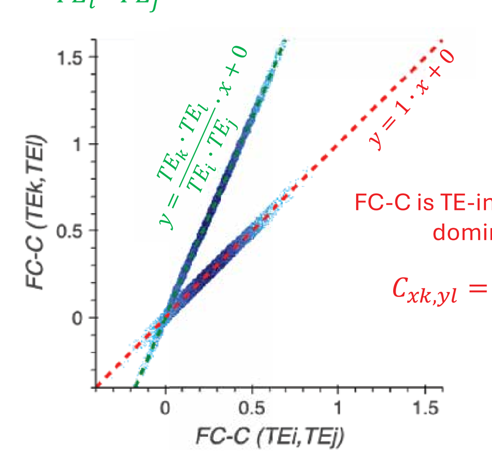
$\Delta\rho_x \gg \Delta R_x$ & $\Delta\rho_y \gg \Delta R_y$

$$C_{xi,yj} = \frac{1}{N_t - 1}\sum \Delta\rho_x \cdot \Delta\rho_y$$

C is TE-independent

FC-C is TE-dependent for BOLD dominated data

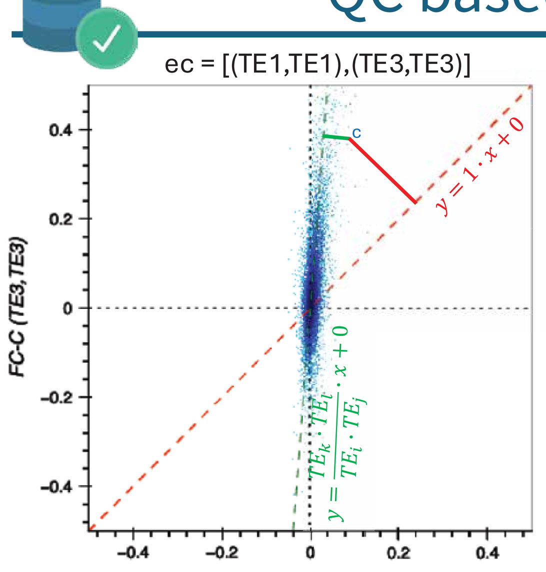
$$C_{xk,yl} = \frac{TE_k \cdot TE_l}{TE_i \cdot TE_j}\cdot C_{xi,yj}$$



FC-C is TE-independent for So dominated data

$C_{xk,yl} = C_{xi,yj} \; \forall i,j,k,l$

QC based on across-echo inter-regional covariance



1) For each TE combination 'ec' compute the root mean square of euclidean distance of all connections (N_c) to the theoretical BOLD line:

$$d_{BOLD,ec} = \frac{1}{N_c}\sum_{c=1}^{N_c} dist(c, BOLD\ line)^2$$

2) Do the same for the theoretical So line:

$$d_{So,ec} = \frac{1}{N_c}\sum_{c=1}^{N_c} dist(c, So\ line)^2$$

3) Transform distances to probabilities using softmax:

$$p_{BOLD,ec} = \frac{e^{d_{BOLD,ec}}}{e^{d_{BOLD,ec}} + e^{d_{So,ec}}}$$

4) Average p_{BOLD} across all available 'ec'

$$p_{BOLD} = \sum_{\forall ec} p_{BOLD,ec}$$

METHODS: Test Dataset

Objective: Evaluate theoretical derivations on real fMRI data.

Dataset: Two ME resting-state scans with the following distinct noise profiles[3]:

- Non-BOLD Dominated Data: minimally pre-processed data with strong S_o fluctuations due to the use of an irregular repetition time (TR).
- BOLD Dominated Data: low motion, regular TR data denoised with tedana.

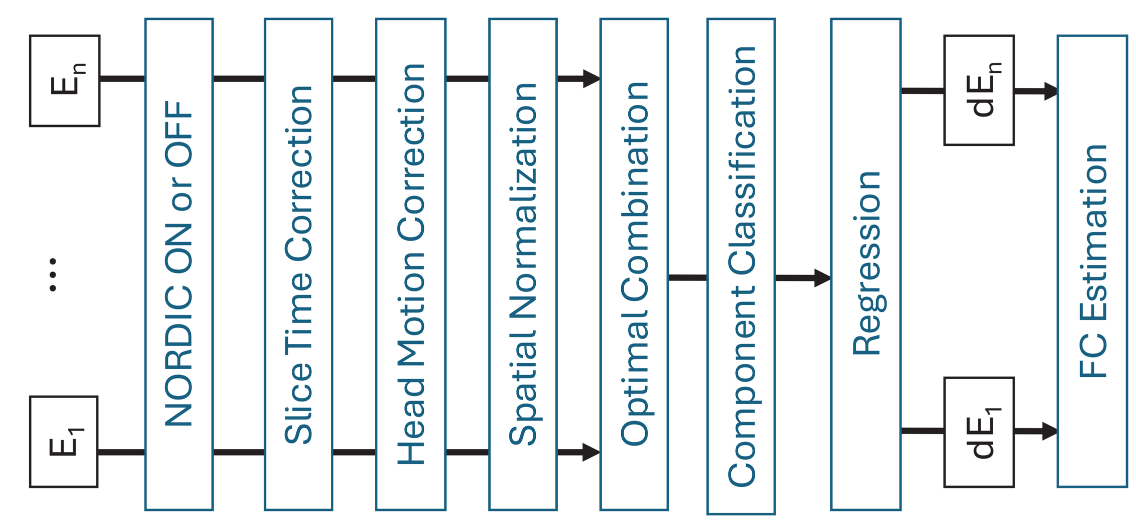
Analysis: Extract ROI timeseries for Powers 264 ROI atlas[4] for all TEs, generate scatter plots for different echo combinations, compute p_{BOLD}.

METHODS: Evaluation Dataset

Objective: evaluate denoising methods using pBOLD and TSNR

Dataset: 436 publicly available Multi-echo (TE=13.7/30/47ms) resting-state scans[5]

Pre-processing:

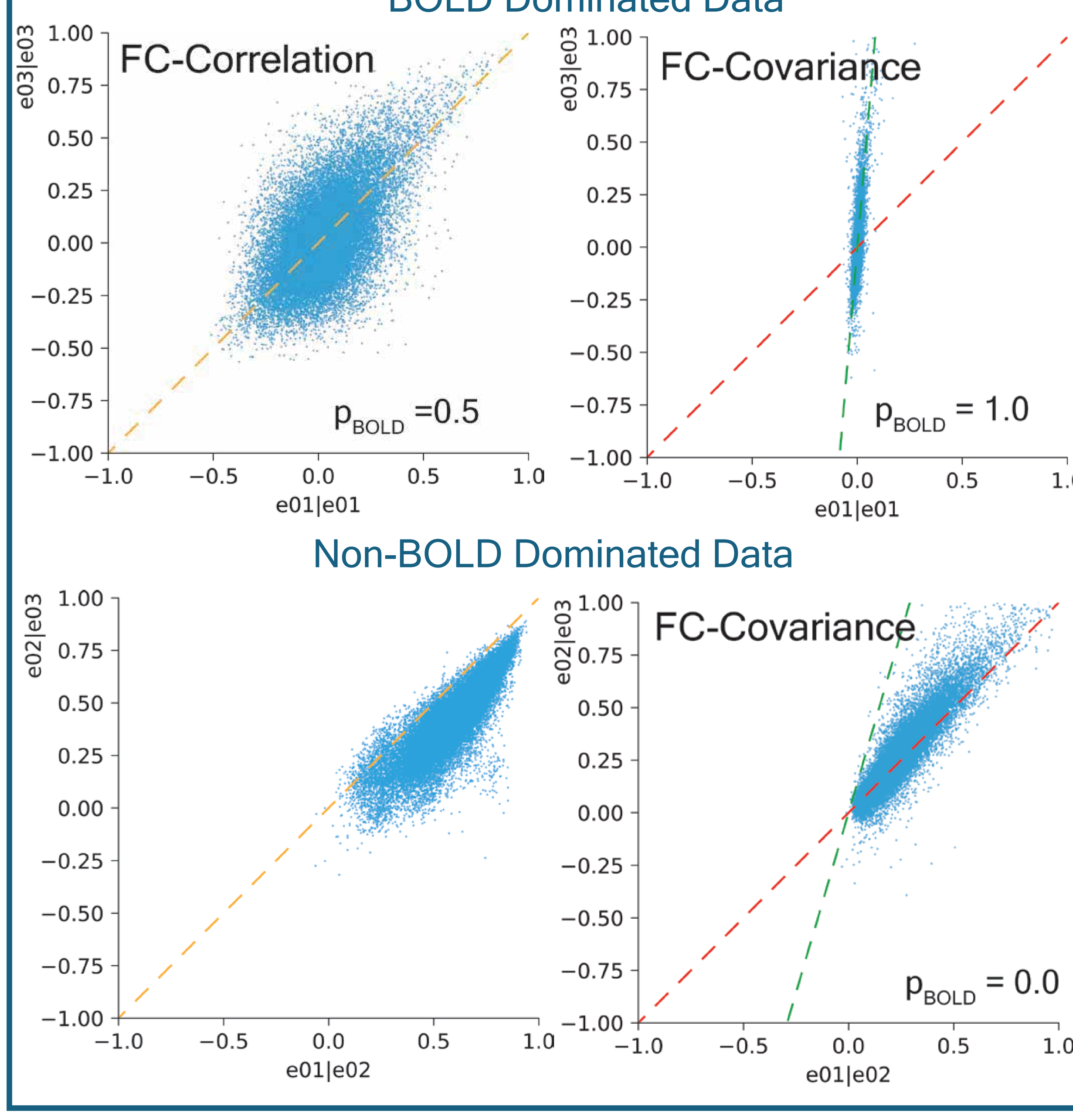


Regression Alternatives

- Basic: slow drifts, motion and its 1st derivative, aComCorr.
- Global Signal (GSR)[6]: basic regressors + global signal.
- Tedana[7]: basic regressors + tedana 'reject' components

Quality Assurance: we computed TSNR and pBOLD for all pipelines.

RESULTS: Test Dataset

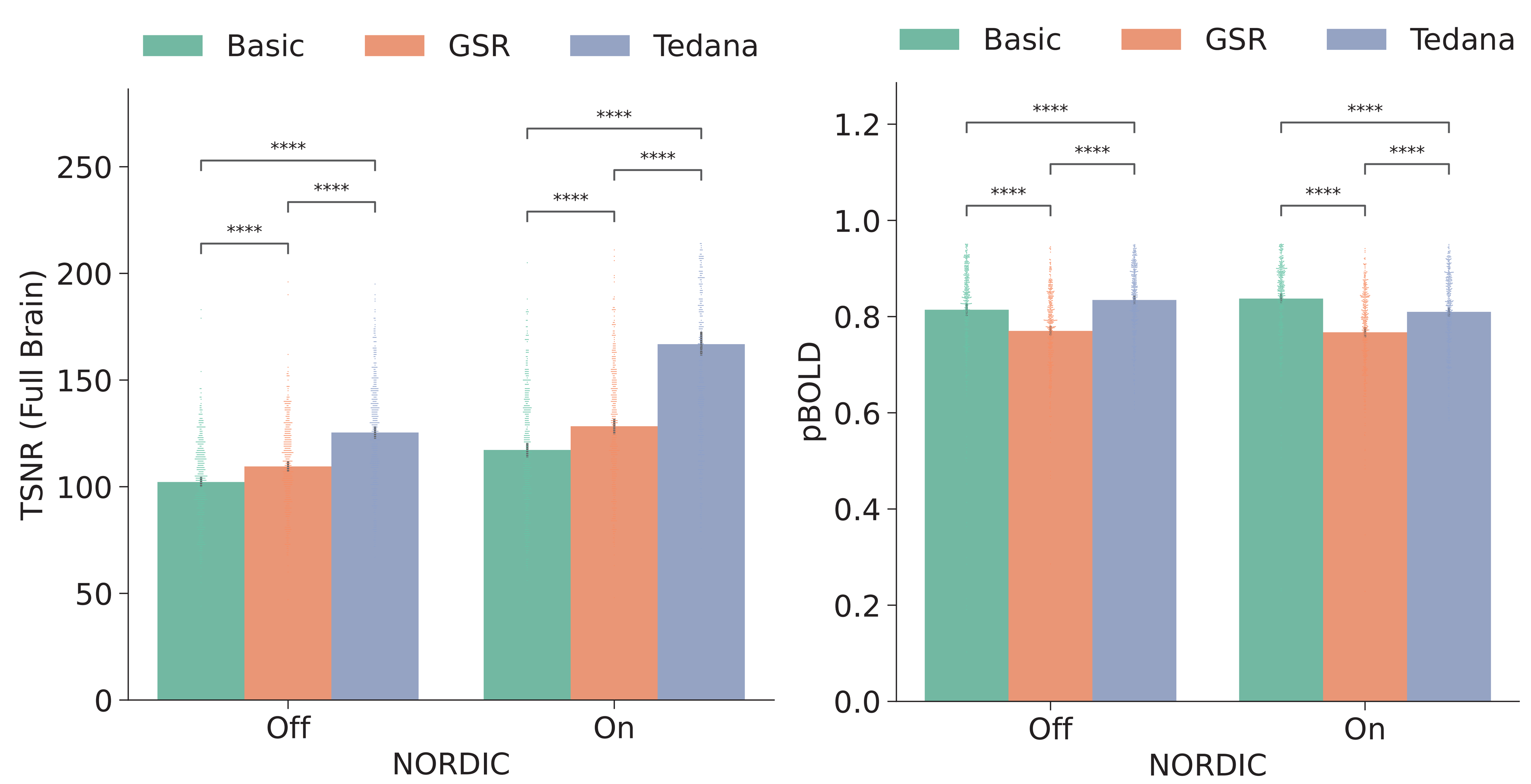


Representative scatter plots of FC (left as Correlation | right as Covariance) for data dominated by BOLD (top) and So flutuations (Bottom) computed using different TE pairs.

Dots represent individual connections, and dashed lines expected theoretical behaviors: orange = identity line and expected behavior for correlation irrespective of noise; red = identity line and expected behavior for covariance when data is not dominated by BOLD; green = line with TE-dependent slope that identified expected behavior for BOLD dominated data when FC is estimated via covariance.

p_{BOLD} for FC as correlation is not informative as expected. Importantly, p_{BOLD} for FC as covariance clearly captures the differential noise profiles of the test data and clearly follows theoretical expectations.

RESULTS: Evaluation Dataset



(LEFT) TSNR significantly increased for GSR and Tedana relative to Basic denoising. It did also for Tedana relative to GSR. This is true independently of whether NORDIC is applied. Finally applying NORDIC always left to increases in TSNR. Based on TSNR one would conclude that it is always beneficial to apply NORDIC, that Tedana is the optimal denoising approach,and that GSR ouperforms Basic denoising.

(RIGHT) When NORDIC is not applied, p_{BOLD} significantly increased for Tedana relative to Basic denoising. Yet, that is not the case for GSR which leads to lower p_{BOLD} than Basic denoising. When NORDIC is applied, both GSR and Tedana perform worse than basic denoising. Based on p_{BOLD}, one would conclude that in absence of NORDIC, Tedana is the best approach. Also that there is some issue when NORDIC and Tedana are combined. Finally, the last conclusion based on pBOLD is that GSR might not be as beneficial as TSNR seems to indicate.

DISCUSSION/CONCLUSIONS

Across-echo covariance alerts to less R_2^* & BOLD sensitivity where TSNR suggests otherwise:

- pBOLD signaled an issue with combining NORDIC and Tedana. Further exploration revealed that when NORDIC is on, tedana fails at estimating number of components.
- pBOLD indicates that GSR results in less BOLD-dominated data. As the global signal contains both arifactual (e.g., respiration) and neurally induced fluctuations[8]; to correctly interpret this decrease in pBOLD future work should evaluate the relative contributions of these two BOLD flucutation types to the global signal.

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