Title: On time delay estimation and sampling error in resting-state fMRI

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ABSTRACT

Accumulating evidence indicates that resting-state functional magnetic resonance imaging (rsfMRI) signals correspond to propagating electrophysiological infra-slow activity (<0.1 Hz). Thus, pairwise correlations (zero-lag functional connectivity (FC)) and temporal delays among regional rsfMRI signals provide useful, complementary descriptions of spatiotemporal structure in infra-slow activity. However, the slow nature of fMRI signals implies that practical scan durations cannot provide sufficient independent temporal samples to stabilize either of these measures. Here, we examine factors affecting sampling variability in both time delay estimation (TDE) and FC. Although both TDE and FC accuracy are highly sensitive to data quantity, we use surrogate fMRI time series to study how the former is additionally related to the magnitude of a given pairwise correlation and, to a lesser extent, the temporal sampling rate. These contingencies are further explored in real data comprising 30-minute rsfMRI scans, where sampling error (i.e., limited accuracy owing to insufficient data quantity) emerges as a significant but underappreciated challenge to FC and, even more so, to TDE. Exclusion of high-motion epochs exacerbates sampling error; thus, both sides of the bias-variance (or data quality-quantity) tradeoff associated with data exclusion should be considered when analyzing rsfMRI data. Finally, we present strategies for TDE in motion-corrupted data, for characterizing sampling error in TDE and FC, and for mitigating the influence of sampling error on lag-based analyses.

Keywords: time delay estimation, functional connectivity, lag, sampling error, head motion, reliability

1. INTRODUCTION

Since the seminal observations of Biswal and colleagues (Biswal *et al.*, 1995), interest in resting-state functional magnetic resonance imaging (rsfMRI) for the study of spontaneous brain activity has increased exponentially (Snyder and Raichle, 2012). Studying the zero-lag temporal correlation structure of spontaneous fluctuations in the blood oxygen level-dependent (BOLD) signal (i.e., "functional connectivity (FC)" analysis) provides an efficient means for mapping the large-scale spatial organization of brain function (Fox *et al.*, 2005; Damoiseaux *et al.*, 2006; Fox and Raichle, 2007; Power *et al.*, 2011; Yeo *et al.*, 2011). Although FC is the standard mode of rsfMRI analysis, spontaneous BOLD fluctuations additionally exhibit spatiotemporal dynamics not captured by zero-lag FC (i.e., processes whose measurement is contingent upon the temporal ordering of BOLD time points) (Liégeois *et al.*, 2017). In particular, rsfMRI signals reflect infra-slow (<0.1 Hz) electrophysiological activity (Hiltunen *et al.*, 2014; Palva and Palva, 2012; Pan *et al.*, 2013), which exhibits stereotyped propagation patterns across the brain; this widespread propagation leads to reliable interregional time delays on the order of one second between BOLD signals (MatsuiMurakami and Ohki, 2016; Mitra *et al.*, 2018). The resultant temporal latency structure comprises multiple reproducible propagation sequences (Mitra *et al.*, 2015a), is dramatically rearranged across arousal states (Mitra *et al.*, 2015b; Mitra *et al.*, 2016; Mitra *et al.*, 2018), and is sensitive to behavior (Mitra *et al.*, 2014) and pathology (Mitra *et al.*, 2017) even in the absence of significant changes in FC. Thus, time delay estimation (TDE) provides a useful complement to zero-lag FC for characterizing spatiotemporal structure in rsfMRI.

Importantly, the predominance of very low frequencies (<0.1 Hz) in infra-slow activity and BOLD signals means that practical scan durations do not provide sufficient independent temporal samples to stabilize second-order statistical measures (Laumann *et al.*, 2015). These include cross-correlation among pairs of regional BOLD signals, from which both FC and time

delays can be derived (Fig. 1). There is growing appreciation for the consequences of such sampling variability on FC (Hlinka and Hadrava, 2015; Laumann *et al.*, 2015; Laumann *et al.*, 2016; Hindriks *et al.*, 2016), although the effects of rsfMRI artifacts such as those arising from head motion have received more attention. Crucially, procedures such as temporal censoring (i.e., the exclusion of high-motion time points) are effective for mitigating artifact (Power *et al.*, 2012) but at the cost of increased sampling error. Thus, it is important to consider both sides of the tradeoff between data quality and quantity, or between *bias* associated with specific artifacts and *variance* arising from reduced data quantity. Although the "correct" balance depends on the question of interest, in general, the latter becomes increasingly problematic the less stable a statistical measure is. Hence, sampling variability is a significant concern for correlations, and even more so for lag-based measures (Smith *et al.*, 2011). Further, temporal censoring complicates TDE, which generally requires contiguous data.

The primary goals of this work are to examine factors impacting TDE (and FC) sampling variability in fMRI, to address the integration of motion censoring with TDE, and to examine bias-variance tradeoffs in both TDE and FC. We begin with analyses of surrogate fMRI time series pairs with modeled time delays; these allow us to quantify, as a function of multiple factors, TDE and FC error with respect to "true" delays and correlations, respectively. Next, we use insights from these simulations to demonstrate how the effects of sampling variability in both TDE and FC can be easily observed in real data. Finally, we conclude with strategies to reduce the influence of sampling error on inferences drawn from TDE. Importantly, although interregional TDE is perhaps the most straightforward approach for quantifying BOLD propagation (Fig. 1), results are pertinent to the variety of approaches that have been used to detect or exploit temporal offsets among fMRI signals (Goebel *et al.*, 2003; SunMiller and D'Esposito, 2005; GargCecchi and Rao, 2011; Majeed *et al.*, 2011; Friston *et al.*, 2014; Mitra *et*

al., 2014; Amemiya *et al.*, 2016; Gilson *et al.*, 2016; Raatikainen *et al.*, 2017) (see Friston et al. (FristonMoran and Seth, 2013; Friston *et al.*, 2014) for taxonomy of these approaches).

2. TIME DELAY ESTIMATION

2.1. Theory

The Pearson correlation coefficient, r, for zero-lag correlation (i.e., FC) between continuous signals, $x_1(t)$ and $x_2(t)$, is given by:

$$r_{x_1x_2} = \frac{1}{\sigma_{x_1}\sigma_{x_2}}\frac{1}{T}\int x_1(t)\cdot x_2(t)dt\,, \tag{1}$$

where σ_{x_1} and σ_{x_2} are the temporal standard deviations of the zero-mean signals x_1 and x_2 and T is the interval of integration. By generalizing this equation to accommodate temporal delays, τ, between the signals, correlation (or covariance, for simplicity, where $r_{x_1x_2}$ is not normalized by the signal standard deviations) can be computed as a function of delay in seconds. Thus,

$$c_{x_1x_2}(\tau) = \frac{1}{T}\int x_1(t+\tau)\cdot x_2(t)dt \tag{2}$$

defines the cross-covariance function (CCF). The lag between x_1 and x_2, $\tau_{1,2}$, is then determined to be the value of τ at which $c_{x_1x_2}(\tau)$ exhibits an extremum. Thus,

$$\tau_{1,2} = \arg\max_{\tau}\left(\left|c_{x_1x_2}(\tau)\right|\right). \tag{4}$$

While the CCF of periodic time series is likely to feature multiple extrema, BOLD signals are aperiodic (He *et al.*, 2010; ZarahnAguirre and D'Esposito, 1997) and almost always produces a single, well-defined cross-covariance extremum for a given pair of time series, typically in the range of ±1 s.

2.2. Implementation

In practice, we first construct the CCF in the time domain at discrete multiples of the TR (i.e., at the sampling interval). A single CCF for each session is obtained by summing unnormalized cross-covariance over blocks (b) of contiguous frames, and subsequently normalizing based on the entire time series. (Variations of this approach are discussed in the next section). Thus,

$$c_{x_{1_b}x_{2_b}}(\Delta) = \sum_{t=1}^{N_b} x_{1_b}(t+\Delta) \cdot x_{2_b}(t)\,, \tag{5}$$

$$c_{x_1x_2}(\Delta) = \frac{1}{N_{\Delta=0}} \sum_{b=1}^{B} c_{x_{1_b}x_{2_b}}\,, \tag{6}$$

where Δ is the temporal shift in units of TRs, t indexes frames, N_b is the total number of frames within the block, $N_{\Delta=0}$ is the total number of frames contributing to the zero-lag CCF estimate, and B is the total number of blocks. Because BOLD signals are best understood as stationary random processes (Liégeois *et al.*, 2017), we set time series to zero-mean prior to Equation (5) by subtracting the mean computed over the maximum number of realizations (i.e., all non-censored frames from the time series), rather than de-meaning each block separately, which would also increase the bias associated with CCF estimation (Marriott and Pope, 1954; Kendall, 1954).

We subsequently use three-point parabolic interpolation among the empirical peak of $c_{x_1x_2}$ (c_{peak}) and the values immediately preceding (c_{peak-1}) and succeeding (c_{peak+1}) it in order to approximate the extremum and its associated abscissa, $\hat{\tau}_{1,2}$, at a temporal resolution finer than the sampling rate (Fig. 1A-B) (Mitra *et al.*, 2014):

$$\hat{\tau} = \mathrm{TR}\frac{c_{peak-1} - c_{peak+1}}{2\left(c_{peak-1} - 2c_{peak} + c_{peak+1}\right)}\,. \tag{7}$$

We currently discount delays longer than four seconds ($\hat{\tau}_{max}$= 4 s) as, in our experience, such results appear to reflect sampling error or artifact. Because a given time delay will typically

result in a peak in the empirical CCF at the nearest multiple of the TR, a true time delay at the maximum allowable ($\tau = \hat{\tau}_{max}$) can be resolved by allowing at least that number of time shifts, plus an additional time shift for parabolic interpolation ($\Delta_{max} = \mathrm{round}(\hat{\tau}_{max}/\mathrm{TR}) + 1$), where $\mathrm{round}()$ evaluates to the nearest integer. In the present case (TR = 2.2 s), three time shifts (Δ_{max} = 3) were needed in each direction to estimate $\tau = \hat{\tau}_{max}$. Hence, $c_{x_1 x_2}(\Delta)$ was computed over $\Delta \in$ [-3, 3].

The above approach can be generalized to a set of n time series $[x_1(t), x_2(t), \ldots, x_n(t)]$. Thus, $C_{x_i x_j}(\Delta)$ will be an $n \times n \times \Delta$ cross-covariance matrix from which $\hat{\tau}_{x_i x_j}$ can be obtained for every pair of time series, $x_i x_j$ $(i, j \in 1, 2, \ldots, n)$, yielding an $n \times n$ time delay matrix:

$$TD = \begin{bmatrix} \hat{\tau}_{1,1} & \cdots & \hat{\tau}_{1,n} \\ \vdots & \ddots & \vdots \\ -\hat{\tau}_{n,1} & \cdots & \hat{\tau}_{n,n} \end{bmatrix}. \quad (8)$$

The diagonal entries of TD are 0 by definition, given that a time series is perfectly correlated with itself at zero-lag. Moreover, TD is anti-symmetric ($\hat{\tau}_{i,j} = -\hat{\tau}_{j,i}$): if the time series x_i is determined to precede x_j by a certain magnitude, then x_j can equivalently be said to succeed x_i by the same magnitude, yielding the opposite sign.

Here we compute $\hat{\tau}_{i,j}$ as the temporal delay of x_j relative to x_i, such that a negative value implies that x_j precedes x_i. Thus, in accord with Nikolic et al. (SchneiderHavenith and Nikolić, 2006; Nikolić, 2007), a column-wise mean will yield a one-dimensional projection of TD, which we refer to as a "lag projection" (TD_P), reflecting the mean latency of each region of interest (ROI), n, with respect to all other ROIs. Hence,

$$TD_P = \frac{1}{n}\left[\sum_{j=1}^{n} \hat{\tau}_{1,j} \ldots \sum_{j=1}^{n} \hat{\tau}_{n,j}\right]. \quad (9)$$

Further, for a given "seed" region comprising one or multiple ROIs, the entire rows of TD corresponding to these ROIs can be averaged to give a seed-based lag map – a one-dimensional map of each voxel's temporal delay with respect to the seed. The majority of real data presented here utilize a widely used set of 264 ROIs (Power *et al.*, 2011) for simplicity. Exceptions are Figures 1E, 5, and 10, which utilize 6 mm cubic gray matter voxels (Mitra *et al.*, 2014) to provide uniform spatial coverage.

2.3. TDE and motion censoring

Unlike surrogate data, real fMRI data are contaminated by artifact generated by head motion, cardio-pulmonary pulsations and fluctuating arterial pCO_2, which poses challenges to accurately estimating time delays of interest. Rather than individually examining each of these artifact sources, we reason that existing denoising strategies (PowerSchlaggar and Petersen, 2015; Liu, 2016; Caballero-Gaudes and Reynolds, 2017; Satterthwaite *et al.*, 2017) should improve TDE. However, one such technique, motion censoring (Power *et al.*, 2012), is worth revisiting in detail in the context of TDE.

Removal of high-motion time points (censoring or scrubbing) from rsfMRI data reduces motion artifact (Power *et al.*, 2012) but integration of censoring into TDE is not straightforward. Zero-lag correlation is invariant to re-ordering of data points within a time series, provided that the new ordering is common to both time series (Liégeois *et al.*, 2017). This means that, within each time series, time points on either side of flagged high-motion frames can be directly concatenated. However, when computing pairwise correlation or covariance as a function of time delay (i.e., $c_{i,j}(\Delta)$ where $\Delta \neq 0$), the flagged frames of the shifted time series will be misaligned with those of the first time series (Fig. 2a). In this case, concatenation would lead to erroneous results (Scargle, 1989). Instead, at each time shift, Δ, a proper "temporal mask" of flagged frames will be the intersection of the temporal mask at zero-lag and the shifted temporal mask. This implies that, for each time shift, the number of frames excluded from the covariance

computation exceeds the number of high-motion frames. Theoretically, this temporal masking strategy can lead to data loss by as much as a factor of two; however, in practice, the loss is less because high-motion frames tend to cluster together (PowerSchlaggar and Petersen, 2015).

There are several ways to incorporate censoring into TDE (Fig. 2). One straightforward approach is simply to include, for each lag, all valid pairs of temporal samples as defined by the intersection temporal mask. Although this strategy makes use of all non-flagged frames, it can produce large differences in the number of frames contributing to each Δ of the CCF (Fig. 2a, black). Consequently, the variance of each CCF point can differ substantially. Another concern is that motion artifacts may have temporally extended effects. Thus, while a pair of frames separated by a single high-motion time point may be valid, including them may corrupt the CCF at that Δ.

An alternative strategy is to compute CCFs only over blocks of contiguous data (Fig. 2A, dark and light green), which avoids both above discussed limitations. We refer to this strategy as the "block approach." Summing (unnormalized) cross-covariance estimates across such blocks yields a single CCF for the time series (Eq. (6)). In prior analyses, we have used a conservative version of this approach, retaining only blocks of low-motion data at least 60 seconds in duration (Mitra *et al.*, 2014). Head movements often are followed by prolonged signal changes (Power *et al.*, 2018). However, global signal regression (GSR) effectively limits motion artifacts to the epoch of movement (Power *et al.*, 2014; Byrge and Kennedy, 2018; Power *et al.*, 2018), which suggests that a 60-second minimum may be overly conservative *when using GSR*. Therefore, it is worthwhile to determine the degree to which including shorter blocks can reduce sampling error. To limit the degree to which different points of the CCF have unequal numbers of samples, a reasonable lower limit for block duration would be one that

allows for at least one sample per block to contribute to every point of the CCF (i.e., $(\Delta_{max} + 1) \times$ TR) (Fig. 2A, light green).

Given contiguous data, computing lagged CCFs raises the choice of normalizing the estimate at all lags by a constant (number samples at zero lag, as in Eq. 6) vs. normalizing by the number of samples at each lag. The first option leads to biased but lower variance estimates (Jenkins and Watts, 1968). Given non-contiguous data, as in the present case, the situation is more complicated as the number of samples at each lag may vary widely. Figure 2B illustrates this issue using surrogate data combined with the real temporal mask obtained from moderately censored data. This toy case demonstrates that normalization strategy can lead to markedly different TD estimates.

Finally, if the block approach (see above) is used, a single high-motion time point will result in the loss of several surrounding frames. Because BOLD fluctuations are very slow (<0.1 Hz), it is possible that a reasonably accurate value for a contaminated frame may be estimated from its surrounding frames. Thus, interpolation is another viable strategy for reducing excessive data loss, and hence, sampling error. Alternatively, this strategy assumes that surrounding frames are free of artifact, which is not necessarily true. As with small blocks, determining the utility of interpolation requires quantitative comparisons using real data.

3. METHODS

3.1. Subjects

We used the recently published Midnight Scan Club (MSC) dataset comprising ten 30-minute eyes-open rsfMRI sessions from each of ten individuals (Gordon *et al.*, 2017).

3.2. MRI acquisition

Details for acquisition of the MSC dataset have been described previously (Gordon *et al.*, 2017). All imaging was performed on a Siemens TRIO 3T MRI scanner. For each subject,

anatomical scans included four T1-weighted sagittal magnetization-prepared rapid gradient-echo (MP-RAGE) images as well as four T2-weighted sagittal images. Functional, T2*-weighted imaging (gradient-echo, 36 slices, TR = 2.2 s, TE = 27 ms, flip angle = 90°, voxel size = 4 mm isotropic) included 30 contiguous minutes of resting-state fMRI, collected during each of ten sessions performed at midnight, giving each subject five hours of resting-state data. During resting-state data acquisition, subjects fixated a white crosshair against a black background. An EyeLink 1000 eye-tracking system (http://www.sr-research.com) indicated that one subject (MSC08) exhibited prolonged eye closures, likely indicating sleep (Gordon *et al.*, 2017).

3.3. fMRI preprocessing

For each subject a mean of field maps collected over multiple sessions was applied to images from all sessions for distortion correction, as described in detail elsewhere (Laumann *et al.*, 2015; Laumann *et al.*, 2016).

Functional data were next preprocessed to reduce artifact, maximize cross-session registration, and transform to an atlas space. All sessions underwent correction for odd-even slice intensity differences stemming from interleaved acquisition of slices within a volume, correction for within-volume slice-dependent time shifts, intensity normalization to a whole brain mode value of 1000, and within- and between-run rigid body correction for head movement. Transformation to Talairach atlas space (Talairach and Tournoux, 1988) was computed by registering the mean intensity image from a single BOLD session via the average T1-weighted image and average T2-weighted image, and subsequent BOLD sessions were linearly aligned to this first session. This atlas transformation was combined with mean field distortion correction and resampling to 3 mm isotropic atlas space in a single step.

Subsequent processing was performed on the atlas-transformed, volumetric time series to further reduce artifact. First, temporal masks were created to flag motion-contaminated

frames. Such frames were identified by outlying values of framewise displacement (FD), a scalar index of instantaneous head motion, computed as the sum of the magnitudes of the differentiated translational (three) and rotational (three) motion parameters (Power *et al.*, 2012). Several subjects exhibited high-frequency peaks in the power spectrum of the *y* motion parameter, which captured the phase-encoding direction (anterior-to-posterior) (Gordon *et al.*, 2017); because this did not have an obvious influence on the data, nor an obvious relationship to typical head movements, and occurred above frequencies of interest (>.1 Hz), we low-pass filtered the *y*-motion time course at 0.1 Hz in all subjects prior to computing FD to prevent inflation of FD values and superfluous data loss (Siegel *et al.*, 2017). Frames with FD exceeding 0.2 mm (Power *et al.*, 2014) were replaced via linear interpolation to yield continuous time series that could be filtered while mitigating the spread of motion artifact to surrounding frames (Carp, 2013). Interpolated BOLD time series, as well as motion parameters (HallquistHwang and Luna, 2013), were subsequently passed through a zero-phase second-order Butterworth band-pass filter (0.005 Hz < f < 0.1 Hz) to mitigate scanner drift and high-frequency artifact. Note that the extended duration of MSC scans gives the opportunity to capitalize on lower frequencies than typically analyzed with fMRI.

3.4. Component-based nuisance regression

Next, the filtered BOLD time series underwent a component-based nuisance regression approach incorporating elements of previously published methods (Behzadi *et al.*, 2007; PatriatMolloy and Birn, 2015). Substantial variance in cerebrospinal fluid (CSF) and white matter corresponds to physiological noise (e.g., CSF pulsations), arterial pCO_2-dependent changes in T2*-weighted intensity (Power *et al.*, 2018), and motion artifact. Because such spurious variance is widely shared with regions of interest in gray matter, time series extracted from these regions are often used for nuisance regression. While the mean signals from white matter and CSF are typically regressed from gray matter BOLD time series, regression of multiple

components comprising the nuisance signals has the potential to remove additional physiological variance (Behzadi *et al.*, 2007) and motion artifact (Muschelli *et al.*, 2014; PatriatMolloy and Birn, 2015) that has spatiotemporal structure differing from the mean signal.

Generation of component-based nuisance regressors proceeded as follows. Masks of white matter and ventricles were segmented using FreeSurfer (Fischl, 2012; DaleFischl and Sereno, 1999) and spatially resampled in register with the fMRI data. Voxels surrounding the edge of the brain are particularly susceptible to motion artifacts (Satterthwaite *et al.*, 2013; Yan *et al.*, 2013a); hence, a third nuisance mask was created for extra-axial (or "edge" (PatriatMolloy and Birn, 2015)) voxels by thresholding a temporal standard deviation image (tSD > 2.5%) (Behzadi *et al.*, 2007) that excluded the eyes and a dilated whole brain mask. Voxel-wise nuisance time series were dimensionally reduced as in CompCor (Behzadi *et al.*, 2007), except that the number of retained regressors, rather than being a fixed quantity, was determined independently for each of the three nuisance masks by orthogonalization of the covariance matrix and retaining components ordered by decreasing eigenvalue up to a condition number of 30 (i.e., λ_{min} must satisfy $\lambda_{max}/\lambda_{min} > 30$). The retained components across all compartments formed the columns of a design matrix, X, along with six motion parameter time series.

The columns of X are likely to be substantially collinear. To prevent numerical instability owing to rank-deficiency during nuisance regression, a second-level singular value decomposition was applied to XX^T to impose an upper limit of 250 on the condition number. This strategy yielded on average 29.6 ± 8.5 (mean ± standard deviation) regressors per 30 minute session (range = 16-55 regressors), to which the mean signal averaged over the whole brain (global signal), along with its first derivative, were added. Although global signal variance is in part neural in origin (Schölvinck *et al.*, 2010; Wong *et al.*, 2013; Liu *et al.*, 2018; Turchi *et al.*, 2018), global signal regression is a highly effective strategy to reduce spatially distributed artifact from myriad sources (Satterthwaite *et al.*, 2013; Power *et al.*, 2014; Ciric *et al.*, 2017;

Power *et al.*, 2017; Power *et al.*, 2018) as well as the temporally extended effects of such artifacts (Byrge and Kennedy, 2018; Satterthwaite *et al.*, 2013; Power *et al.*, 2014; Power *et al.*, 2017), which could lead to spurious time delays.

The final set of regressors was applied in a single step to the filtered, interpolated BOLD time series. Finally, the interpolated time points were re-censored using a temporal mask. Time series were averaged within ROIs, which were either 264 10 mm diameter spheres (Power *et al.*, 2011) for TD and FC distributions or 6 mm gray matter cubes (Mitra *et al.*, 2014) for time delay matrices and lag projections maps (Fig. 1, 5 & 10).

3.5. Surrogate fMRI time series

Determination of TDE accuracy requires knowledge of the true delay between a pair of time series, which is not known in real fMRI data. Therefore, we simulated pairs of fMRI time series with modeled time delays. Characteristics of fMRI signals, such as their $1/f$-like behavior (ZarahnAguirre and D'Esposito, 1997; He *et al.*, 2010), very low frequencies of interest (< 0.1 Hz), and comparatively small time delays (±1 s), make TDE in fMRI a unique challenge. The creation of time series with these features proceeded as follows: First, two $1/f^{\alpha}$ Gaussian noise time series of the desired length and temporal sampling rate were generated using a previously published algorithm for the frequency domain generation of power law noise signals (Kasdin, 1995; Kasdin and Walter, 1992), as implemented in MATLAB (StoyanovGunzburger and Burkardt, 2011). We used $\alpha = 0.7$ for all simulations, which is a typical value for this parameter in fMRI data despite small variations across the brain (He *et al.*, 2010; He, 2011). Next, these time series were put through the same bandpass filter as the BOLD data (i.e., $0.005 < f < 0.1$, 2nd order Butterworth). To precisely specify the desired correlation, these time series were standardized (made zero-mean, unit-variance), orthogonalized by projection onto the eigenvectors of the desired 2×2 correlation matrix R, standardized once more, and finally multiplied by an upper-triangular matrix U satisfying $R = U^T U$ (obtained by the Cholesky

factorization of R). This resulted in two zero-mean time series of unit variance that duplicated the spectral content of BOLD time series and had the specified correlation at zero-lag. Finally, one of the time series, x_1, was shifted in the frequency domain representation to precisely model the desired time delay, τ. Thus,

$$x_{1,\Delta=\tau} = F^{-1}\left(F\left(x_{1,\Delta=0}\right) \cdot e^{-i2\pi f\tau}\right) \quad (10)$$

where $F(x)$ and $F^{-1}(x)$ are the Fourier and inverse Fourier transforms of x, Δ is the time shift, f is the equal-length sequence of frequency-domain samples, and multiplication is performed elementwise. TDE was performed between the resulting time domain signal, $x_{1,\Delta=\tau}$, and its unshifted signal pair, $x_{2,\Delta=0}$.

Except where noted, simulated time series were constructed with the following parameters: r = 0.9 (before time shifting), τ = 0.5 s, duration = 60 min. An unrealistically high r was used to visually enhance relationships between TDE error and other factors. Each data point in Figures 3, S1, and S2 represents 2,000 simulations.

TDE accuracy was evaluated in terms of bias, variance, and root-mean-square error (RMSE). Over n = 2,000 simulations, these were computed as follows:

$$Bias(\hat{\tau}) = \frac{1}{n}\sum_{i=1}^{n}\hat{\tau}_i - \tau \quad (11)$$

$$Variance(\hat{\tau}) = \frac{1}{n}\sum_{i=1}^{n}(\hat{\tau}_i - \bar{\tau})^2 \quad (12)$$

$$RMSE(\hat{\tau}) = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(\hat{\tau}_i - \tau)^2} = \sqrt{Bias^2(\hat{\tau}) + Variance(\hat{\tau})}\,, \quad (13)$$

where τ, $\hat{\tau}_i$ and $\bar{\tau}$ signify the true time delay, the time delay measured on a given simulation i, and the mean time delay over n observations, respectively.

We additionally used zero-lag surrogate time series to evaluate FC accuracy. For these simulations, the "true" correlation r was set in the above manner but for extended duration time series (5,000 minutes). This allowed us to estimate the accuracy of $\hat{r}$ computed over a range of smaller data durations and a range of true correlation (r) values. Accuracy was evaluated in terms of RMSE:

$$RMSE(\hat{r}) = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(z(\hat{r}_i) - z(r))^2}\ , \tag{14}$$

where $z()$ signifies Fisher z-transformation (Fisher, 1915; Fisher, 1921).

Finally, surrogate data were used to isolate the effects of censoring-induced sampling variability (i.e., variable data *quantity*) from variable data *quality* and true intra- and inter-subject variability (Figure 8C-D only). For this analysis, surrogate time series were generated as above but were projected onto the eigenvectors of the real, group average 264 × 264 correlation matrix.

MATLAB code for comparing TDE strategies in surrogate time series and computing TD matrices and weighted lag projections as in this paper has been made publicly available at [link will be provided upon acceptance].

3.6. Outcome metrics and statistical analysis

TDE strategies (discussed in Section 2) may have opposing impacts on bias and variance, making it difficult to determine whether one strategy is superior to another. However, because the effects on bias and variance disproportionately impact high-motion data, our primary outcome measures were 1) correspondence between low- and high-motion sessions within each subject, and 2) correspondence between each session and the group average. Correspondence was computed over all unique ROI pairs for both TD and FC matrices (i.e., vectorized upper triangular of the 264 × 264 TD or FC matrix). TD pairs corresponding to |FC| <

.2 (as determined by the censored group average FC matrix) were excluded in these comparisons to focus reliability analyses on more robust relationships. Correspondence was determined by Spearman's ρ for TD and Pearson's r for FC distributions.

Sampling error tends to result in larger magnitude correlations (PowerSchlaggar and Petersen, 2015), which increases the probability of the CCF (erroneously) exhibiting a maximum at some offset from zero-lag. Consequently, sampling error also tends to result in larger time delays. Therefore, we used the width of a given TD or FC distribution as a proxy for sampling error, which we computed as the standard deviation, σ, across the distribution. We also used QC:FC (Power *et al.*, 2012) and QC:TD correlation distributions to visualize the impacts of head motion and sampling error on correlations and time delays, respectively. Each data point in these distributions reflects the correlation between mean FD (quality control metric) and a specific ROI:ROI pair FC (or TD) value, across all 100 MSC sessions. We use the FC or TD absolute value (|FC| and |TD|) in order to focus on the impact of sampling error on the magnitude of these statistics. While mean FD reflects the degree of head motion prior to censoring, it also provides an approximation for the relative amount of data loss following censoring (i.e., subjects with higher mean FD will generally lose more data due to censoring). Thus, because we are primarily interested in the effects of sampling variability due to data loss, we use mean FD computed *prior* to censoring throughout the paper. This is favorable to FD computed *after* censoring, which will be less correlated with data loss, and the actual quantity of data loss, which will differ depending on the strategy used for TDE. Nonetheless, FD computed before and after censoring correlated well ($r = .71$). Moreover, across different strategies, FD computed prior to censoring correlated well with the number of frames used for TDE ($r > -.75$ in all cases; $r = -.92$ with minimum allowable block duration). Further information related to motion and censoring can be found in Supplementary Tables 1-4.

Statistical significance of differences between TDE methods was assessed with Student's paired t-tests performed on the Fisher-z transformed ρ or r values, or σ values corresponding to the TD or FC distributions.

4. RESULTS

4.1. Factors influencing TDE (and FC) accuracy: insights from surrogate time series

We used data simulations to explore the dependence of BOLD TDE accuracy on data quantity, correlation magnitude, and temporal sampling interval (Fig. 3). Figure 3A shows a roughly linear relationship between data quantity and RMSE extending over multiple decades on a log-log plot, underscoring the sensitivity of TDE accuracy to the quantity of data. Note that an unrealistically high correlation (r = 0.9) was used to make the pattern clear; as is evident in Figure 3B, TD RMSE exhibits a strong dependence on correlation magnitude. In particular, as correlation magnitude falls below ~0.2, RMSE markedly increases. An algebraic model of this effect is given below in section 4.4. Thus, in real (GSR) data, where the mean pairwise correlation magnitude may be as low as ~0.1 (as in the present study), the pattern in Figure 3A would be substantially shifted rightward (see Fig. S1 for RMSE plots at weaker correlation magnitudes). Note that Figure 3B explores TD RMSE as function of correlation magnitude in 60-minute time series; see Figure S1 for this dependence in typical session- (10 minutes) and group-level (250 minutes) data quantities.

In comparison to data quantity and correlation magnitude, the effect of TR is relatively minor but is most apparent given large quantities of data, where higher TRs (lower sampling rate) asymptote at greater RSME (Fig. 3A & S1). Thus, coarse sampling leads to poorer TDE resolution, even after parabolic interpolation. The improved detection of directionality in fMRI with increased sampling rate has previously been demonstrated in real data (Lin *et al.*, 2014).

As pointed out in Equation (13), RMSE can be expressed in terms of bias, which refers to the difference between the expected value of an estimator and the true value of the parameter being estimated, and variance, which reflects the expected (squared) deviation of a single estimate from the mean estimate across a given number of observations. In Figures 3A and B, separate bias and variance plots are not shown because RMSE is largely determined by the latter (i.e., there is no systematic bias in TDE associated with specific data quantities or correlation magnitudes). However, it is useful to visualize all three properties when exploring dependence of TDE accuracy on the true time delay relative to the sampling interval, which is shown in Figure 3C for multiple TRs. The sinusoidal bias pattern (Fig. 3C, left) is a well-known characteristic of parabolic interpolation (Boucher and Hassab, 1981; Céspedes *et al.*, 1995) and effectively biases estimates toward the nearest TR. This bias progressively worsens with increasing temporal distance from (roughly) the nearest half-multiple of the TR. Thus, for time delays in the range of 0 s up to 2 s for TR = 2 s, delays closer to 2 s are overestimated, and there is no bias at exactly 1 s. Bias is most severe when τ/TR ≈ 0.3 and ≈ 0.7, as reported previously (Boucher and Hassab, 1981; Céspedes *et al.*, 1995). This is yet another instance of a bias-variance tradeoff, as other TDE approaches (e.g., in the frequency domain) are free of this bias but exhibit greater variance.

A complementary pattern is observed for variance, which peaks halfway between samples (Boucher and Hassab, 1981; Céspedes *et al.*, 1995) (Fig. 3C, right). Combining these bias and variance effects yields an RMSE pattern that exhibits peaks around the quarter-interval marks and a local trough halfway between samples (Fig. 3C, lower). Note also that RMSE in seconds scales with TR without change in pattern (Céspedes *et al.*, 1995).

Like TDE, FC accuracy is highly dependent on data quantity and continues to decrease linearly on a log-log plot up to the maximum measured duration (1000 minutes). However, FC sampling variability is not obviously sensitive to the true correlation of a given time series pair,

425 nor the temporal sampling rate, making it a simple reflection of data quantity measured in units
426 of time (Fig. S2).

427 *4.2. Manifestations of bias and variance in real data (prior to censoring)*

428 We next sought to determine whether the above relationships are apparent in real data.
429 Figure 4A displays histograms of all possible pairwise time delay estimates among 264 ROIs
430 (Power *et al.*, 2011) using our published approach for TDE (Mitra *et al.*, 2014): data is from
431 either one session (MSC01 session 1; red), one subject (MSC01, time delays averaged over all
432 10 sessions; green), or all 10 subjects (MSC01-MSC10, time delays averaged across sessions
433 within subject and subsequently across subjects; black). Decreasing variance associated with
434 increasing data quantity is apparent in the widths of the distributions.

435 Figure 4B displays histograms of all unique pairwise time delays from all 100 MSC
436 sessions. The blue trace reflects only those time delays corresponding to ROI pairs with zero-
437 lag correlation magnitude ≥ 0.2, while pairs with correlation < 0.2 are represented by the pink
438 trace. Several inferences can be made from these histograms. First, there are far more pairwise
439 correlations below rather than above 0.2. Second, parabolic interpolation bias is much more
440 apparent for weaker as opposed to stronger correlations. Structure in the pink trace (slope
441 discontinuity at $\pm$1.1 sec in data acquired at TR = 2.2 sec) reflects bias associated with
442 parabolic interpolation (Moddemeijer, 1991) (Fig. 3C, left). The pattern is less obvious (but
443 nonetheless present) for more strongly correlated pairs (blue) because they exhibit less
444 sampling error, hence, relatively few delays far from zero.

445 We next consider how TD error can obscure spatiotemporal patterns of interest. Figure
446 1D shows the MSC-average TD matrix, masked to include only cortical $(6\ mm)^3$ cubes with
447 high-probability (≥ 90%) affiliation with one of seven functional networks (Hacker *et al.*, 2013).
448 The rows and columns of this matrix have been sorted from early-to-late by their mean values,

and by functional network, to demonstrate delays on the order of ~1 s in both on- and off-diagonal blocks. Note that the well-ordered, early-to-late progression within each block, as well as the consistency with which certain voxels appear as early or late across rows/columns, is not imposed; rather, this latency structure suggests that infra-slow activity is well-organized both within and between networks. Importantly, this matrix represents 3000 minutes of data and recapitulates prior findings obtained from similarly large data quantities (Mitra *et al.*, 2014). In contrast, Figure 5A shows a TD matrix from one MSC subject (MSC01, averaged across all 10 sessions; 300 minutes) following the same sorting procedure as in Figure 1D, along with the zero-lag, absolute value FC matrix from the same subject. Structure in the off-diagonal blocks is less evident in Figure 5A in comparison to Figure 1D. In general, the degree to which a block in the TD matrix of Figure 5A is structured appears to correspond to the strength of absolute value FC within the block.

To quantify the relationship between TD matrix structure and correlation magnitude, we first created a measure that approximately reflects temporal structure. Specifically, because well-structured blocks of the sorted TD matrix appear to comprise roughly iso-latent diagonals, we defined “error” in the latency structure of each block as the RMSE of all time delays in the block relative to the mean delay of their respective diagonals (Fig. 5B). Next, we averaged |FC| within each of the blocks (Fig. 5C). These procedures resulted in block-wise values of both error and mean |FC| (Fig. 5D), which we correlated with each other using session-, subject-, and group-level matrices. As expected, error in latency structure decreased with increasing data. Moreover, there was a strong inverse correlation between error and mean |FC| at the session (r = -.87, p < .0001) and subject (r = -.81, p < .0001) levels, but not at the group level (r = .26, p = .18) (N = 28 blocks for each correlation) (Fig. 5E). This pattern is understandable as a consequence of Figure 3A-B: while data quantity at the group-level was sufficient for a majority of ROI pairs (e.g., Fig. 1D), data quantity contributing to session- and subject-level TD matrices

was sufficient for only those ROI pairs with relatively strong FC. Once sampling error is largely mitigated, there is little dependence of latency structure on the underlying correlations.

4.3. Sampling error incurred from motion censoring

As TDE sampling error can be readily observed prior to censoring, removing time points necessarily increases this source of error, even while mitigating error stemming from artifact. Accordingly, we sought to determine how censoring contributes to sampling error. Because sampling error tends to increase the magnitude of correlations (Yan *et al.*, 2013a; PowerSchlaggar and Petersen, 2015), and thus, cross-correlation derived time delays (e.g., Fig. 4), we focused on TD and FC magnitudes and distribution widths in relation to head motion and data loss.

Results pertaining to head motion artifact and data loss are shown in Figure 6. Prior to motion censoring, the standard deviation of a single session's TD distribution was positively correlated with mean FD across all 100 MSC sessions ($r = .32$, $p < .001$) (Fig. 6A left). This result implies that head motion introduces spurious time delays that tend to be longer than those arising from neurophysiology (Byrge and Kennedy, 2018). After censoring FD > 0.2 mm frames (Power *et al.*, 2014) and using our original strategy of discarding segments of data < 60 s in duration (Mitra *et al.*, 2014), the mean distribution width (as measured by the standard deviation) across all sessions was greatly increased ($\sigma_{pre} = 1.60 \pm 0.07$, $\sigma_{post} = 1.67 \pm 0.15$; $p_{post\text{-}pre} < .0001$) and the correlation between TD distribution width and mean FD increased to .72 ($p < .0001$) (Fig. 6A right). Although the standard deviation of the FC distribution was inversely correlated with mean FD prior to censoring ($r = -.44$, $p < .0001$), perhaps owing largely to stronger negative correlations in low-motion sessions, FC σ, like TD σ, also became strongly correlated with mean FD after censoring ($r = .43$, $p < .0001$) ($\sigma_{pre} = 0.18 \pm 0.01$, $\sigma_{post} = 0.20 \pm 0.03$; $p_{post\text{-}pre} < .0001$) (Fig. 6B).

Relating distribution widths to FD before versus after censoring, as above, permits quantification of the influence of head motion and data loss, respectively, on TD (and FC) at the session level. These relationships can be further examined at the level of individual ROI pairs. Accordingly, a histogram may be constructed in which each observation reflects one ROI pair, and its value corresponds to the correlation, across 100 sessions, between mean FD and the TD of that ROI pair. A similar histogram can be constructed for FC for all ROI pairs. Such "QC:FC" (quality control:functional connectivity) correlation distributions have previously been used to visualize the impact of head motion on FC, where head motion generally shifts the QC:FC distribution rightward (Power *et al.*, 2014; Ciric *et al.*, 2017). Here, we extend this strategy to studying how head motion (and data loss) impacts TD as well as FC. We computed QC:TD (QC:FC) by taking the absolute value of the TD (FC). pair to focus specifically on sampling error. A null model was generated by randomly permuting mean FD over sessions. Prior to censoring, the QC:|TD| distribution was shifted slightly rightward compared to the null model (Fig. 6C) while the QC:|FC| distribution was shifted leftward (Fig. 6D). Thus, as observed at the session level (Fig. 6A-B), head motion leads to inflated estimates of TD while tending to reduce FC magnitude. After censoring, both QC:|TD| and QC:|FC| distributions were shifted rightward, suggesting, once again, that increased data loss leads to inflated TD and FC estimates. Altogether, these findings point to a strong increase in sampling error associated with censoring under the 60-second block requirement.

We next explored the ramifications of censoring-induced sampling error. Because high-motion sessions are more severely impacted, we assessed correspondence between the five lowest- and highest-motion sessions within each of the 10 MSC subjects, as well as the correspondence of each session to the group average. Importantly, the latter metric is also sensitive to head motion and is significantly inversely correlated with mean FD across all 100 sessions before motion censoring (r = -.39, p < 0.0001 for TD; r = -0.39, p < 0.0001 for FC).

Comparing TDE results with and without motion censoring, using an FD threshold of 0.2 mm with the 60 second block requirement, resulted in greater divergence between low- versus high-motion sessions (N = 10 subjects, $p < .05$) and consistently decreased session-to-group correspondence (N = 100, $p < .001$) (Fig. 6D). This was true of FC as well (low:high-motion, $p < 0.1$; session:group, $p < 0.001$) (Fig. 6E). Thus, an overly stringent approach to motion censoring (FD < 0.2mm and 60 sec blocks) yields poorer results for both TD and FC than simply retaining the high-motion time points.

4.3. Comparing strategies for TDE among discontinuous time series

The 60-second block duration was originally adopted to avoid TDE errors generated by temporally extended artifact associated with head motion. However, it has since been shown that GSR (which we use) effectively reduces such artifacts (Power *et al.*, 2014; Byrge and Kennedy, 2018), Accordingly, we next determined how including relatively short epochs impacts our outcome metrics. Outcome was again assessed as the correlation between vectorized TD and FC matrices (correspondence). We found that low:high-motion correspondence as well as session:group correspondence monotonically increased as the imposed minimum block duration was reduced down to the limit consistent with at least one data point from each block contributing to each CCF lag ("minimum allowable" block duration) (Fig. 7A). Similar results were observed for FC (Fig. 7B).

Results so far have been reported for the unbiased CCF estimator, i.e., normalized by the number of sampled frames at each lag. Since the minimum allowable block approach ("min") proved optimal, we compared it against three alternatives: (i) biased CCF estimator (i.e., normalized by the number of sampled frames at zero-lag) with the minimum allowable block duration ("biased"), (ii) enforcing equal samples at each time point in an unbiased CCF estimator (as in Figure 2A, light green; “equal”), and (iii) unbiased estimator using all valid frames at a given time shift (as in Figure 2A, black; “all”). Of these 4 approaches, the unbiased

548 CCF estimator with minimum allowable block requirement performed best (Fig. S3). However,
549 the differences between these approaches were minimal in comparison to relaxing the imposed
550 minimum block duration requirement.

551 We additionally investigated whether interpolating over censored frames could further
552 improve the unbiased, minimum allowable block approach. Given the degree of sampling error
553 present at the single-session level, even with 30-minute sessions, it might be expected that
554 interpolation would improve outcome metrics by salvaging data, even if that data is of poor
555 quality. Accordingly, the effects of linear interpolation were compared against an approach in
556 which interpolated frames were replaced with the original (post-regression), potentially
557 contaminated values. Although both of these approaches improved group correspondence for
558 both TD and FC, interpolation did not outperform the alternative for FC and, for TDE, performed
559 significantly worse (Fig. S4).

560 Finally, because the minimum allowable block duration approach is far more lenient than
561 the imposed 60-second minimum and is comparable with conventional FC data constraints
562 (e.g., (Power *et al.*, 2014)), we repeated the analyses in Figure 6A-D using the minimum
563 allowable block duration approach. We found that both TD distribution widths and magnitudes
564 remained positively correlated with mean FD, though these relationships were no longer
565 apparent for FC (Fig. 8). In order to aid interpretation of this result, we repeated these analyses
566 in surrogate time series; doing so enabled us to isolate potential consequences of censoring-
567 induced sampling error, when using the minimum allowable block duration, from effects related
568 to data quality or biology. We generated a single set of 264 surrogate time series based on the
569 real group average correlation matrix (and assumption of zero lag among all time series). Next,
570 we censored these time series according to the real temporal censoring masks (FD > 0.2) from
571 each of the 100 MSC sessions. Hence, any differences in correlation or lag structure computed
572 from these time series would be attributable to censored-induced sampling error.

We found TD and FC relationships with FD to be outstanding in the surrogate data (Fig. 9), demonstrating that censoring-induced sampling variability remains a significant source of error for both TD and FC when using the minimum allowable block duration approach, despite 30-minute sessions. Taking these findings into account, it can be concluded from the real data (Fig. 8) that 1) sampling variability still has a considerable influence on observed time delays when using minimum allowable block duration, and 2) absence of a prominent FC:FD relationship when using the minimum block approach does not indicate the absence of sampling error, but rather that the influence of sampling error is less salient in comparison to other factors (e.g., data quality and inter-session or inter-subject variability). Thus, sampling error remains an issue for TD and FC when using 30-minute sessions.

4.4. Weighting lag projections against sampling error

We use "lag projections" to visualize each region's mean temporal relationship with the rest of the brain (Fig. 1E). Lag projections are computed by averaging a region's temporal lag with respect to all other regions (columns of TD matrices; Eq. 9). Given the dependence of TDE accuracy on correlation, we asked whether this relation could be used to obtain more reliable lag projections. Inspection of the relation between RMSE and $|r|$ (e.g., Fig. 3B) suggested the following functional form:

$$f(r) = \beta \tan\left(\frac{\pi}{2}(1 - |r|)\right), \tag{15}$$

which accurately describes TD RMSE in surrogate time series with β fit by conventional regression (Fig. 10A). This expression explains >.99 of the variance in data quantities that are typical in group-level analyses.

Equation (15) can be used to reduce the sampling error of lag projections by down-weighting high-variance lag estimates. Thus, weighted lag projections, (wTD_P) are computed by inversely weighting TD pairs in proportion to modeled squared error. Thus,

$$wTD_P = \left[\frac{1}{\sum w_j}\right] \cdot \left[\sum_{j=1}^{n} w_{1,j} \cdot \hat{\tau}_{1,j} \ldots \sum_{j=1}^{n} w_{n,j} \cdot \hat{\tau}_{n,j}\right], \quad \text{where } w_{i,j} = \frac{1}{f^2(\hat{r}_{i,j})}. \tag{16}$$

In Equation (16), the correlation used to compute $w_{i,j}$ is the conventional zero-lag FC metric ($\hat{r}_{i,j}$). In principle, the peak correlation at $\hat{\tau}_{1,j}$ could have been used instead. However, this measure is more susceptible to spurious inflation (BrightTench and Murphy, 2017). Given the predominance of frequencies below 0.1 Hz in BOLD signals, zero-lag correlation differs only slightly from peak correlations obtained within the range of lags studied here.

The effect of weighting in real data is examined in Figure 10B-D. Panel B shown voxel-wise lag projections at the session-, subject- and group-levels. Weighting generally increases the magnitude of projection values. This effect is quantitatively demonstrated in panel C as an increase in session-level lag projection distribution widths. Weighting disproportionately impacts sessions with less data (i.e., those with the higher mean FD), which manifests as greater correlation between lag projection σ and FD (unweighted $r = .75$, weighted $r = .37$). Despite this effect, weighting drastically improved individual correspondence with the group average *unweighted* lag projection (panel D). Thus, weighting effectively reduces the impact of sampling error on the spatiotemporal patterns reflected in lag projections.

5. DISCUSSION

Here we have investigated factors contributing to sampling variability in fMRI time delay estimation (TDE). The overarching result is that sampling error is a critical issue in both TDE and zero-lag functional connectivity (FC) analyses. Below we discuss the implications of these findings for rsfMRI research.

5.1. Motion censoring and TDE

We compared multiple strategies for TDE in the presence of discontinuities introduced from motion censoring (Fig. 2). Several of these strategies involve tradeoffs between bias and variance that more strongly impact high-motion sessions, i.e., sessions with less useable data. Therefore, to examine bias-variance tradeoffs, we used correspondence between low- and high-motion sessions as well as session-level correspondence with the motion-censored group data as outcome measures.

We found that including small blocks of contiguous data greatly reduces sampling error, down to the minimum allowable duration at which each block still contributes at least one temporal sample to all CCF lags (Fig. 7). Hence, in order to minimize data loss, the smallest possible number of time shifts should be used to estimate the CCF. Because the spectral content of BOLD signals is weighted towards very low frequencies, CCF peaks on the order ~10 sec or more may be expected. However, we currently exclude delays longer than four seconds as, in our experience, such latencies seem to reflect sampling error or artifact. Thus, in the MSC data, we were able to compute each CCF over just seven time shifts (Δ_{max} = 3), making the minimum allowable block duration (Δ_{max} + 1) × TR = 8.8 s (see Section 2.2 and Fig. 2A).

Including all valid frames at a given time shift makes maximal use of data, hence minimized sampling error. However, this approach did not improve outcome measures, possibly owing to artifact in extremely short segments of data (i.e., here, < 5 frames) that are surrounded by high-motion epochs, or spurious time delays associated with data samples on opposite sides of high-motion epochs. Because the “all” valid frames approach yields results comparable to the minimum allowable block approach ("min"), we favor the latter to avoid large disparities in the number of frames contributing to (and thus, the variance of) each lag of the CCF. Using a block approach, temporal interpolation also salvages substantial data, that is, frames surrounding the censored artifact. However, interpolation failed to improve outcome metrics beyond simply

including the original high-motion time points. Therefore, replacing potentially contaminated frames with interpolated data is not advisable. However, we did not account for the level of head motion in the frames that were interpolated. It remains possible that interpolation is useful in specific situations, for example, when a long block of data is interrupted by a single large head movement. Nonetheless, because we find that the minimum imposed block duration can be brief, interpolation, even if effective, has only limited potential to salvage data. Finally, we found that, while the biased CCF is associated with reduced variance, in our case, the unbiased CCF estimator yielded more favorable outcome metrics, although these differences were small. Based on these findings, the unbiased, minimum allowable block approach with no interpolation was the most effective of the examined TDE strategies.

We note that the purpose of these comparisons is primarily to outline the nuances of motion censoring in the context of TDE and to assess the involved bias-variance tradeoffs. In practice, the nature of the dataset (e.g., TR, degree and pattern of head motion, pre-processing strategies) will likely affect which approaches appear “optimal.” For example, interpolation may be more useful in datasets with shorter TR. Further, even micro-movements (i.e., FD below 0.2) can still have a detectable influence on rsfMRI data (Power *et al.*, 2014), and are likely to be more prevalent in temporal proximity to larger movements. Therefore, in very large datasets in which sampling error has been minimized, more aggressive data exclusion (e.g., stricter criteria for censoring and/or minimum block duration) may prove beneficial. Our findings may provide a useful guideline but are not guaranteed to be optimal in all cases. To aid in the evaluation and application of TDE in diverse fMRI datasets, we have made publicly available MATLAB code for lag computation in real and surrogate data as described here ([link will be made available upon acceptance]).

5.2. Using correlation to inform lag analysis

The accuracy of TDE between two signals is highly dependent on the strength of correlation between them (Walker and Trahey, 1995; CéspedesOphir and Alam, 1997) (Fig. 3B). TD matrices comprise both intra- (on-diagonal) and inter-network (off-diagonal) relationships (e.g., Fig. 5), the latter of which correspond (by definition) to comparatively weak correlations prone to sampling error. Even so, large quantities of data reveal structure in off-diagonal blocks (Fig. 1D), suggesting that the activity shared between networks, albeit comparatively minor, is well-organized and may be biologically important (Mitra and Raichle, 2016; Mitra and Raichle, 2018). Indeed, inter-network lag relationships may reflect integrative aspects of spontaneous brain activity complementary to the segregated functional networks revealed by zero-lag FC. Unfortunately, inter-network lag relationships require large quantities of data to estimate accurately (Fig. 5). Nonetheless, informative lag analyses can be performed with data quantities that may not be sufficient to stabilize the full TD matrix. For example, time delays among highly correlated ROI pairs can be estimated to reasonable accuracy with far less data than that required to study brain-wide propagation. Correlations may also be used to threshold seed lag maps, providing a more reliable visualization of the seed's temporal relationships with regions exhibiting closely shared activity.

TD matrices exhibit significant transitivity (Mitra *et al.*, 2014), as defined by the high proportion of all possible triples whose time delays sum to 0 (Nikolić, 2007), despite high dimensionality (Mitra *et al.*, 2015a). Thus, one-dimensional lag projections provide a useful spatiotemporal representation of propagation structure. Moreover, unlike full TD matrices, stable lag projections can be computed with relatively limited quantities of data (Fig. 10D). Further, statistical testing performed between lag projections from different groups or conditions is a useful low-dimensional approach to identifying regions whose spatiotemporal relationships may be altered (Mitra *et al.*, 2015b; Mitra *et al.*, 2017). By using correlation magnitude to give weight

690 to stronger pairwise relationships, weighted lag projections offer increased reliability and may
691 prove more sensitive to group differences in spatiotemporal patterns.

692 We show above that sampling error increases the distribution widths of both measured
693 TDs and correlations. Perhaps counterintuitively, weighting also increased the distribution width
694 of lag projection values (Fig. 10C). Weighting likely increases sampling error by reducing the
695 effective number of ROIs over which the mean temporal delay is computed, which leads to
696 increased correlation between distribution width and data loss. However, this effect appears to
697 be less important than down-weighting sampling error from weak correlations. Accordingly, the
698 overall effect of weighting is improved reliability. We conclude that weighting usefully mitigates
699 the adverse impact of sampling error on observed spatiotemporal topographies.

700 Finally, in addition to their statistical relation, TD and FC are phenomenologically related.
701 Therefore, statistical differences in TD cannot be properly interpreted without comparison of
702 underlying correlation structure. Likewise, interpretation of a given TD is greatly informed by
703 knowledge of FC. Statistical significance of TD may be established by comparison with TD
704 computed from appropriate null data: surrogate time series matching the quantity, correlation
705 magnitude(s), TR, and auto- and cross-spectral content of the real data, but with peak
706 correlation at zero-lag (i.e., devoid of latencies). This can be achieved, for example, by
707 destroying phase information from the original time series (Hindriks *et al.*, 2018). Null data may
708 also be used to construct confidence intervals for empirical TD. Nonetheless, the biological
709 interpretation of a significant TD or significant between-group difference in TD may differ widely
710 depending on the underlying FC, or the presence and/or nature of a change in FC.

711 *5.3. Motion censoring and sampling error in rsfMRI*

712 Limited data quantity is among the most significant challenges in rsfMRI research. The
713 slow nature of fMRI signals (<0.1 Hz) necessitates large quantities of data to obtain sufficient

independent temporal samples. Even after reducing the minimum imposed block duration to that of conventional FC analysis (e.g., (Power *et al.*, 2014)), across 100 scans, the width of both the TD (in real and simulated data) and zero-lag FC (in simulated data) distributions following censoring remained positively correlated with head motion (i.e., data loss) (Fig. 8-9). Yan et al. previously demonstrated an increase in observed FC magnitude with excessive censoring (Yan *et al.*, 2013a); we show that this manifestation of FC sampling error is observable even in atypically long (30 minutes before censoring) rsfMRI time series.

We additionally found that QC:|TD| (in real and simulated data) and QC:|FC| (primarily in simulated data) distributions were shifted rightward after censoring, again reflecting the tendency of sampling error to inflate TD and FC estimates (Fig. 6C-D, Fig. 8B & Fig. 9B). Why have these patterns not been apparent in prior studies? One reason is that the range of data quantities in the present study is larger than typical. Thus, if 10 minutes typically are acquired, and censoring removes as much as half, the range of retained data quantities in a given dataset remains relatively limited. This potential for censoring to introduce large discrepancies in retained data quantity among long scans was previously discussed by Satterthwaite et al. (Satterthwaite *et al.*, 2013). Computing QC:|FC| rather than QC:FC, as in prior work, also is crucial. In our analysis, the QC:|FC| distribution was left-shifted (relative to the null) prior to censoring and right shifted after censoring (Fig. 6D). In contrast, the QC:FC distribution was zero-centered and minimally impacted by censoring (Fig. S5), which is typical of GSR data (Power *et al.*, 2014; Ciric *et al.*, 2017).

How does unequal sampling error impact statistical comparisons across groups? Welch's *t*-test and non-parametric tests for group differences in mean value take sampling variability into account. Thus, unequal sampling error is not a significant barrier in most group comparisons when group differences in mean value is at issue. The possibility of adjusting censoring (or discarding data) to ensure uniform number of frames in all subjects has been

discussed (Ciric *et al.*, 2017; Power *et al.*, 2014). However, we see no reason to deliberately introduce sampling error in this manner except when unequal variance biases outcomes, as in analyses based on machine learning (Power *et al.*, 2014). Of greater consequence is that sampling error is not fully eliminated in 30-minute rsfMRI sessions, let alone conventional five-minute sessions. This point is evident in recent reports on highly-sampled individuals, in which it is shown that single-subject FC matrix reliability plateaus only after more than an hour of data is analyzed (Laumann *et al.*, 2015; Gordon *et al.*, 2017).

Corruption of FC by head motion artifact and denoising strategies (e.g., nuisance regression, filtering) for reducing this motion-related bias have been well-described (PowerSchlaggar and Petersen, 2015; Satterthwaite *et al.*, 2017). However, these strategies currently fall short of completely removing motion artifact; hence, excluding high-motion time points further improves data quality (Power *et al.*, 2012; Power *et al.*, 2014; Satterthwaite *et al.*, 2013; Yan *et al.*, 2013a; Yan *et al.*, 2013b; Burgess *et al.*, 2016; Ciric *et al.*, 2017; Siegel *et al.*, 2017). But, motion censoring exacerbates sampling error (Ciric *et al.*, 2017). Although in principle sampling error (variance) is preferable to a systematic bias, sampling error increases the likelihood of spurious findings, reduces statistical power for detecting true effects, and produces artificially inflated estimates of TD and FC under the limited data conditions typical of most fMRI studies. Thus, censoring necessarily involves a bias-variance tradeoff, both sides of which should be considered when determining censoring criteria and when interpreting reported outcomes.

We used reliability to assess the tradeoff between bias reduction versus increased variance associated with censoring. Theoretically, reliability as an outcome measure can be confounded by reliable artifact. However, this is unlikely a significant concern in the present study for the following reasons: (1) We examined reliability following extensive nuisance regression. (2) Reliability was assessed as correspondence between low- and high-motion

764 sessions. (3) Reliability additionally was assessed as correspondence between individual
765 sessions and the censored group average, and this measure inversely correlated with head
766 motion. Thus, these measures were unlikely to have reflected reliability of artifact.

767 That said, we observed only modest and mixed effects of censoring on TD and FC
768 reliability, provided that the analyses used the minimum allowable block duration strategy
769 (compare Fig. 7 with Fig. 6E-F). The small magnitude of these effects may be attributable to
770 effective denoising, including component-based regression (Behzadi *et al.*, 2007; PatriatMolloy
771 and Birn, 2015) and GSR (Power *et al.*, 2014), and to the present dataset being relatively low-
772 motion (Tables S1-4). The impact of censoring on reliability likely depends on both data quantity
773 and quality, including the efficacy of pre-processing and the type and pattern of motion artifact
774 (e.g., small vs. large, sparse vs. frequent; see Supplementary Tables 1-4 for session-specific
775 information related to motion and censoring from the present dataset). More work is needed to
776 better define these dependencies.

777 More generally, while many of the analyses herein suggest that maneuvers increasing
778 data quantity are preferable, this was not always the case. As described above, neither the “all”
779 condition nor temporal interpolation improved outcome measures despite increased data
780 quantity. It is likely that an increase in bias associated with these approaches counteracted any
781 benefits of decreased variance. Moreover, the present results focus on single sessions (albeit
782 30 minutes); in larger group analyses, researchers can afford to sacrifice more potentially-
783 biased data without substantially increased variance. Our analyses bring attention to the
784 perhaps underappreciated influence of sampling error. In all cases, both artifact-related bias
785 (Power *et al.*, 2012; Satterthwaite *et al.*, 2012; Van DijkSabuncu and Buckner, 2012; Siegel *et*
786 *al.*, 2017) and sampling variability warrant careful consideration in fMRI analyses.

787

788 **6. CONCLUSIONS**

TDE is a useful complement to zero-lag FC for studying the spatiotemporal organization of spontaneous infra-slow brain activity, as manifest in rsfMRI signals. However, sampling error presents a significant hurdle to TDE in fMRI and, as we show here, is an underappreciated challenge to FC analysis as well. Different research questions will warrant different tolerances for artifact-related bias and for sampling variability, each of which can often be reduced at the cost of increasing the other. In general, more data is needed for TDE as compared to zero-lag FC analysis, which itself requires more data than task-based fMRI analyses. Nonetheless, while large datasets will permit the most informative studies of propagation throughout the brain, useful lag projection comparisons and time delays between strongly-correlated time series can be computed with more limited quantities of data. Surrogate time series may be useful to gauge the data requirements for a specific question given the nature of the data.

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FIGURE LEGENDS

Figure 1. Computation and visualization of time delays from cross-covariance functions. **(A)** Two exemplar ROI time series from the default mode network over ~200 s. **(B)** The corresponding CCF (Eq. (5)) is computed here over ± 6.6 s, which is equivalent to ± 3 frames as the repetition time was 2.2 s. The time delay (TD; $\tau_{i,j}$) between these time series is the value at which the absolute value of the CCF is maximal. TD can be determined at a resolution finer than the temporal sampling density by parabolic interpolation (red) through the empirical extremum and the points on either side of it (blue) (Eq. (7)). Zero-lag correlation (FC; $r_{i,j}$) is computed from the normalized CCF at zero-lag. **(C)** Toy case illustration of a TD matrix (Eq. (8)) comprising 3 voxels. TD matrices contain time delays between every pair of analyzed ROIs and are anti-symmetric by definition. Computing the mean over each column of a TD matrix generates a lag projection map (Eq. (9)), a one-dimensional projection of lag structure **(D)** TD matrix from real rsfMRI data (MSC group average). The rows and columns of this matrix have been sorted from early-to-late and by functional network affiliation. Doing so reveals a range of delays on the order of 1 s both within (on-diagonal) and between (off-diagonal) networks. See text for description of ROIs. **(E)** Example lag projection map computed from the full MSC average TD matrix. The projection identifies regions whose spontaneous activity on average tends to be early (blue) or late (red) with respect to ongoing activity in the rest of the brain (Mitra *et al.*, 2014). DAN, dorsal attention network; VAN, ventral attention network; SMN, sensorimotor network; VIS, visual network; FPC, frontoparietal control network; LAN, language network; DMN, default mode network.

Figure 2. Cross-covariance among discontinuous time series. (A) x_1 and x_2 are two surrogate time series. An example temporal mask shows censored time points in red (zeros). Although x_1 and x_2 share a temporal mask at zero-lag, computing cross-covariance requires that the time series be shifted with respect to one another, and with them, their associated temporal masks. Several shifts of the temporal masks are shown. To compute covariance at a given CCF lag, Δ, one could use all pairs of valid frames that align at that lag (all frames in black). This approach maximizes data usage but results in a substantially different number of samples (N) at each shift. Alternatively, one could restrict the minimum size of a block of non-censored data at zero-lag such that each block contributes at least one sample to every CCF lag (dark green). The minimum allowable block duration satisfying this requirement, is equal to the total number of lags (i.e., $\Delta_{max} + 1 = 4$ frames). This approach would limit (but not eliminate) uneven samples, at the cost of using less data. Note the symmetry of positive and negative CCF lags. Finally, a restriction may be imposed such that an equal number of samples contribute to each CCF lag, although this leads to still further data loss (light green). **(B)** CCFs for two surrogate time series, modeled at r = 0.9 and τ = 1 s, following censoring with a real temporal mask from a moderate-motion scan (MSC10 session 1). The black and pink CCFs represent the unbiased and biased CCF estimators, respectively. Note the triangular bias in the pink CCF, resulting in a $\hat{\tau}$ value much lower than the true delay. Although the black CCF is quite accurate in this case, the unbiased estimator leads to $\hat{\tau}$ values that have comparatively higher variance and may often exceed the true delay.

Figure 3. TDE dependence on data quantity, correlation magnitude, and temporal sampling interval. Surrogate time series (τ = 0.5 s) reveal strong inverse relationships between TDE accuracy and both **(A)** data quantity (shown for r = 0.9 on a log-log plot spanning several decades) and **(B)** correlation magnitude (shown for 60 minutes of data). Note that longer TRs asymptote at higher RMSE, limiting their precision relative to shorter TRs. **(C)** TDE bias (left) reflects parabolic interpolation bias. $\hat{\tau}$ values tend to cluster at ½ multiples of the TR. The variance pattern (right) is attributable to the subsample TDE that is required in fMRI analysis and thus peaks halfway between samples. Combining these two trends yields a pattern in which RMSE increases with increasing temporal distance between τ and the nearest TR multiple, save for a trough midway between samples owing to the lack of bias in this region. In all cases, lower TRs yield more favorable results; however, TDE dependence on TR is small relative to data quantity and correlation magnitude. Each data point in the Figure represents a mean across 2,000 simulations.

Figure 4. Manifestations of sampling error in real rsfMRI data without censoring. (A) Distributions of pairwise time delays among 264 ROIs (upper triangular of TD matrix) at the session (red), subject (green) and group (black) levels in the MSC dataset Increasing data quantity reduces sampling error, as indicated by the width of the TD distributions. **(B)** Distributions of all MSC session-level pairwise time delays corresponding to zero-lag correlation magnitudes < .2 (pink) or ≥ .2 (blue), as determined by the MSC average correlation matrix. The increased width of the pink distribution results from sampling error associated with weaker correlations. The wide distribution also makes the bias of parabolic interpolation readily observable: time delay estimates cluster around the TR (here, 2.2 s) and slope discontinuities appear at every ½ TR.

Figure 5. Temporal structure in intra- and inter-network relationships is obscured by sampling error. (A) Subject-level (MSC01) TD (left) and |FC| (right) matrices comprising 6 mm gray matter cube ROIs grouped by functional network (as in Fig. 1D). **(B)** Toy case illustrating computation of blockwise diagonal "error" (non-square blocks are first interpolated to yield square blocks). TD matrix blocks in (A) that appear more organized seem to comprise (roughly) iso-latent diagonals. Thus, temporal structure of a given block (submatrix) can be estimated as the RMSE of all time delays in the block relative to the mean delay of their respective diagonals. Error of the perfectly structured toy submatrix amounts to 0. Repeating this process for each unique block yields an error matrix. **(C)** Toy case illustrating computation of the mean |FC| matrix. **(D)** MSC01 error and mean |FC| matrices computed from the TD and |FC| matrices shown in (A). Submatrices were interpolated to be square before computing diagonals. (The main diagonal is all zeroes by definition and therefore excluded in error computations). **(E)** Error in temporal structure as a function of mean |FC|, computed for the 28 unique network blocks at the session (MSC01 session 1), subject (MSC01) and group (MSC average) levels. Error is strongly inversely correlated with FC magnitude at the session and subject levels. At the group level (3,000 minutes of data), this correlation is not significant. Note overall decrease in error and leftward shift of $|\hat{r}|$ values associated with increasing data. (****p <.0001; N = 28 blocks). DAN, dorsal attention network; VAN, ventral attention network; SMN, sensorimotor network; VIS, visual network; FPC, frontoparietal control network; LAN, language network; DMN, default mode network.

Figure 6. Sampling error arising from aggressive data exclusion. (A) Scatter plots illustrating the relationship between TD distribution width, as measured by the standard deviation (σ_{TD}), and head motion/data loss, as measured by mean FD. Each point represents one MSC session, color-coded by subject. Pre-censoring plots reflect a relationship with head motion, while post-censoring plots predominantly reflect sampling error. Censoring exacerbates an already positive relationship between mean FD and σ_{TD}. **(B)** Same as in (A), but for FC. Following censoring, the relationship between σ_{FC} and mean FD changes from significantly negative to significantly positive. **(C)** Distribution of correlations between |TD| and mean FD, across all 100 sessions. Each data point included in the QC:|TD| histogram corresponds to a single ROI pair. Null distributions, computed by randomly permuting mean FD values, are centered near zero (black). Higher motion sessions show modestly greater magnitude time delays (left) before censoring (red); this effect is exacerbated after data exclusion (blue) due to increased sampling error in higher-motion sessions. **(D)** Same as in (C), but for |FC|. Censoring leads to inflated |FC| (blue). **(E)** The left panel shows intra-subject correspondence (Spearman's rho) of the vectorized TD matrix averaged across the five lowest- and highest-motion sessions for each subject. The right panel shows, for each subject, mean correspondence between each session's TD matrix and the censored group average. Error bars denote standard deviation. **(F)** Same as in (E), but for FC, and correspondence is measured as Pearson's *r*. In both (D) and (E), stringent motion criteria adversely impact reliability (*p <.05; **p < .01; ***p < .001; N = 10 for Low:High motion correspondence, N = 100 for Group correspondence).

Figure 7. Including small blocks of clean data improves intra- and inter-subject reliability of TD and FC. (A) Same plots as in Figure 6E-F, but for different minimum imposed block durations. The minimum allowable block duration (min) is 8.8 s ($(\Delta_{max} + 1) \times$ TR). **(B)** Same as in (A), but for FC.

Figure 8. Censoring-induced sampling error in TD, but not FC, remains observable with minimum allowable block duration. (A) Post-censoring σ:FD scatter plots as in the right panels of Figure 6A-B, but for minimum imposed block duration equivalent to the minimum allowable (rather than 60 seconds, as in Fig. 6). **(B)** Same distributions as in Figure 6C-D, but only post-censoring and for minimum allowable block duration. Censoring-induced sampling error inflates |TD| even with minimum allowable block duration, but this is less apparent for FC.

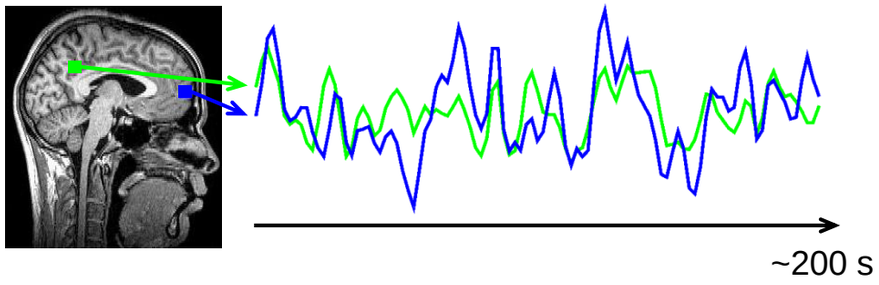
Figure 9. Censoring-induced sampling error in TD and FC computed from surrogate data remains substantial with minimum allowable block duration. (A) Post-censoring σ:FD scatter plots as in Figure 8A, but for TD and FC distributions computed from surrogate data. The 100 real, session-specific temporal censoring masks were applied to a single set of surrogate time series, which was constructed from the MSC average 264 x 264 FC matrix (no lags were built in). Note that the group average correlation distribution is narrower than that obtained from single sessions; thus σ_{TD} values are somewhat larger than in Figure 8A (more sampling error) and σ_{FC} values are generally smaller than in Figure 8A. **(B)** Same distributions as in Figure 8B, but for TD and FC computed from surrogated data as described above. Effects of censoring-induced sampling error are still present with minimum allowable block duration.

Figure 10. |FC|-weighted lag projections improve reliability. (A) Modeling the relationship between TDE error and zero-lag correlation magnitude. By adjusting a single parameter, β, Eq.

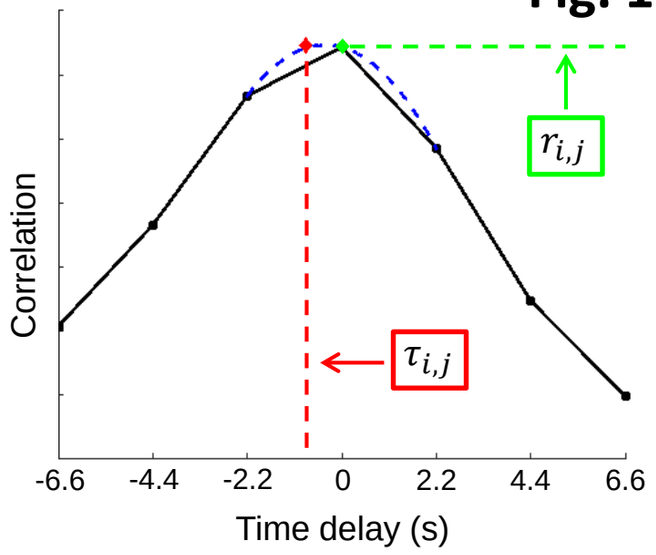
(15) (red) captures this relationship well for a range of data quantities and TRs. For each data quantity, β and R^2 values are based on fit to 2 s TR. **(B)** Example unweighted (top) and weighted (bottom) lag projections for MSC01 session 1 (left), MSC01 (middle; TD averaged over all 10 sessions prior to lag projection computation), and MSC01-10 (right; TD first averaged over all 100 sessions). **(C)** σ:FD plots depicting the width of the distributions of lag projection values for each MSC session as a function of mean FD. Weighting increases distribution widths as well as the relationship between distribution width and data loss. **(D)** Correspondence of session-level unweighted and weighted lag projections with group *unweighted* lag projection. Weighting strongly improves reliability. (***$p < .001$).

Fig. 1

A



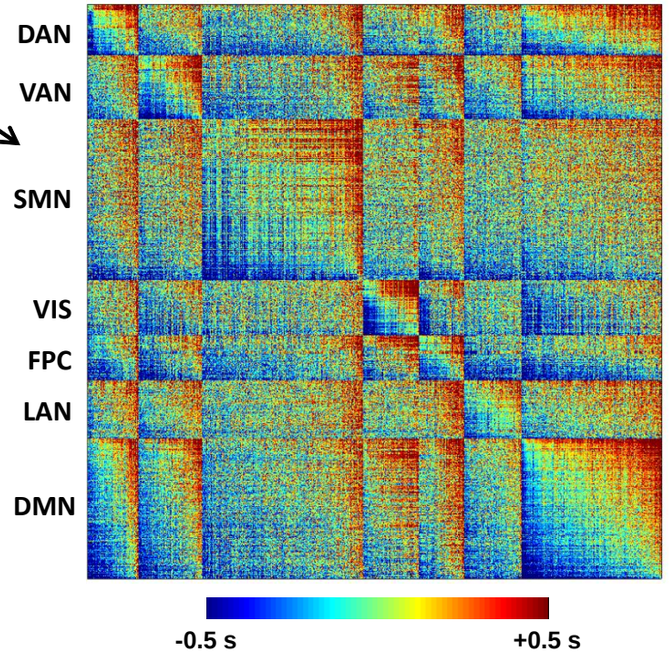
B



C

ROI	1	2	3
1	0	$\tau_{1,2}$	$\tau_{1,3}$
2	$-\tau_{1,2}$	0	$\tau_{2,3}$
3	$-\tau_{i,3}$	$-\tau_{2,3}$	0
Mean	$-\frac{1}{3}(\tau_{1,2}+\tau_{1,3})$	$\frac{1}{3}(\tau_{1,2}-\tau_{2,3})$	$\frac{1}{3}(\tau_{1,3}+\tau_{2,3})$

D



E

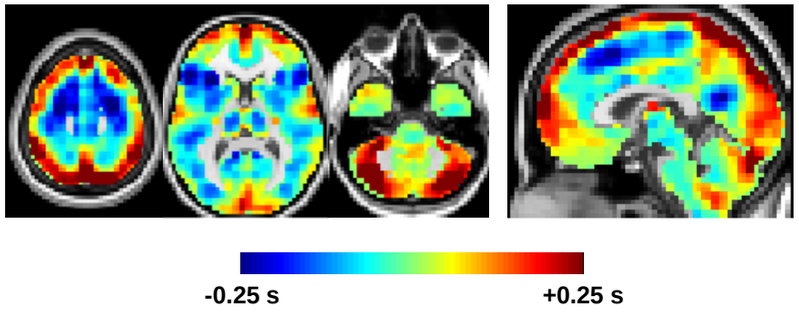
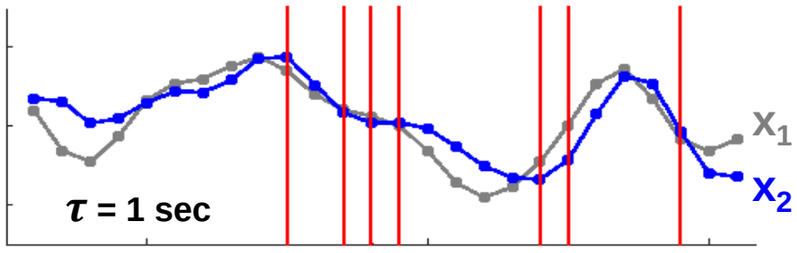


Fig. 2

A



temporal mask: 1 1 1 1 1 1 1 1 1 0 1 0 0 0 1 1 1 1 0 0 1 1 1 0 1 1

Δ = 0		N = 19
mask 1	1 1 1 1 1 1 1 1 1 0 1 0 0 0 1 1 1 1 0 0 1 1 1 0 1 1	N = 14
mask 2	1 1 1 1 1 1 1 1 1 0 1 0 0 0 1 1 1 1 0 0 1 1 1 0 1 1	N = 8
Δ = +1		N = 14
mask 1	1 1 1 1 1 1 1 1 1 0 1 0 0 0 1 1 1 1 0 0 1 1 1 0 1 1	N = 12
mask 2	1 1 1 1 1 1 1 1 1 0 1 0 0 0 1 1 1 1 0 0 1 1 1 0 1 1	N = 8
Δ = +2		N = 12
mask 1	1 1 1 1 1 1 1 1 1 0 1 0 0 0 1 1 1 1 0 0 1 1 1 0 1 1	N = 10
mask 2	1 1 1 1 1 1 1 1 1 0 1 0 0 0 1 1 1 1 0 0 1 1 1 0 1 1	N = 8
Δ = +3		N = 11
mask 1	1 1 1 1 1 1 1 1 1 0 1 0 0 0 1 1 1 1 0 0 1 1 1 0 1 1	N = 8
mask 2	1 1 1 1 1 1 1 1 1 0 1 0 0 0 1 1 1 1 0 0 1 1 1 0 1 1	N = 8
Δ = -3		N = 11
mask 1	1 1 1 1 1 1 1 1 1 0 1 0 0 0 1 1 1 1 0 0 1 1 1 0 1 1	N = 8
mask 2	1 1 1 1 1 1 1 1 1 0 1 0 0 0 1 1 1 1 0 0 1 1 1 0 1 1	N = 8

B

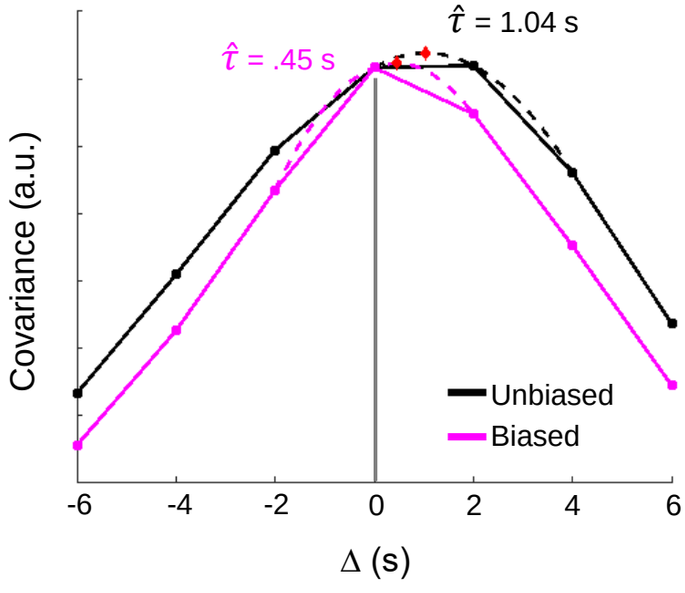
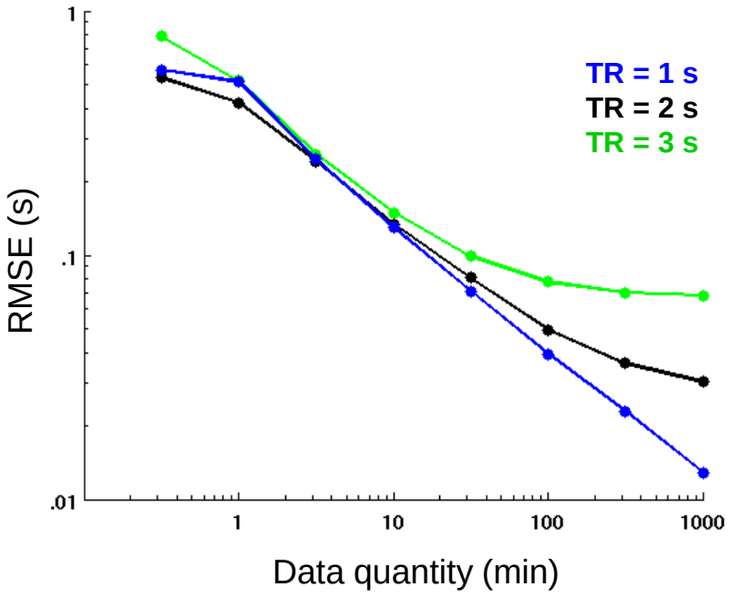
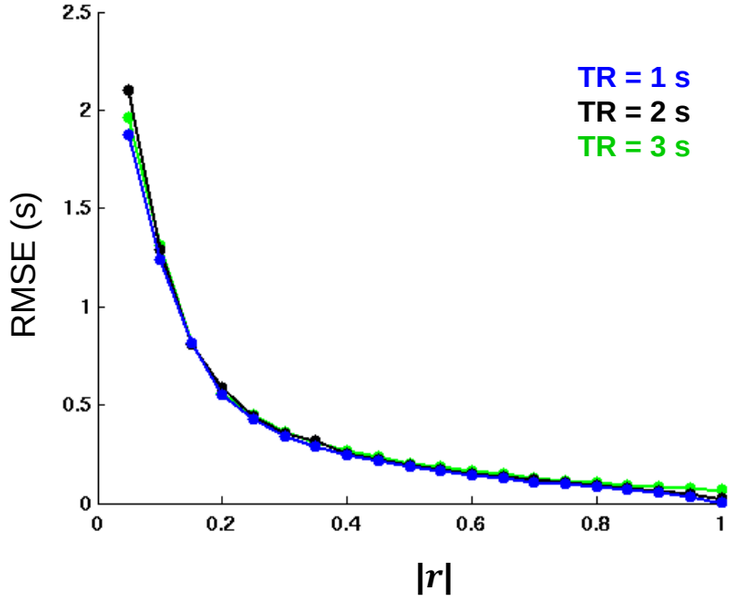


Fig. 3

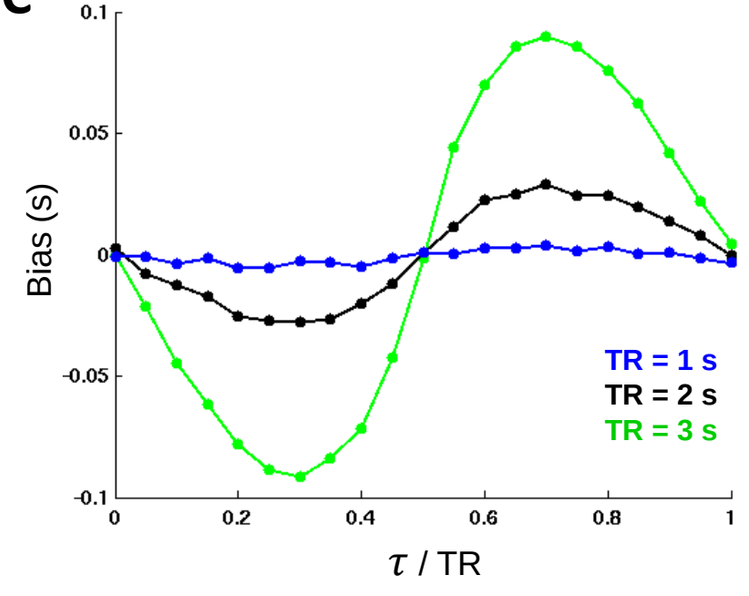
A

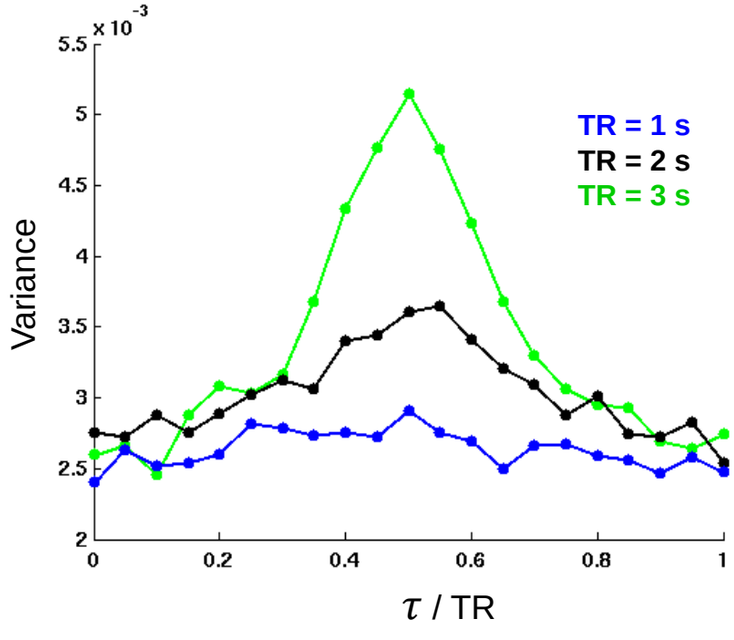

RMSE (s)
Data quantity (min)
TR = 1 s
TR = 2 s
TR = 3 s

B


RMSE (s)
|r|
TR = 1 s
TR = 2 s
TR = 3 s

C


Bias (s)
τ / TR
TR = 1 s
TR = 2 s
TR = 3 s


x 10^-3
Variance
τ / TR
TR = 1 s
TR = 2 s
TR = 3 s

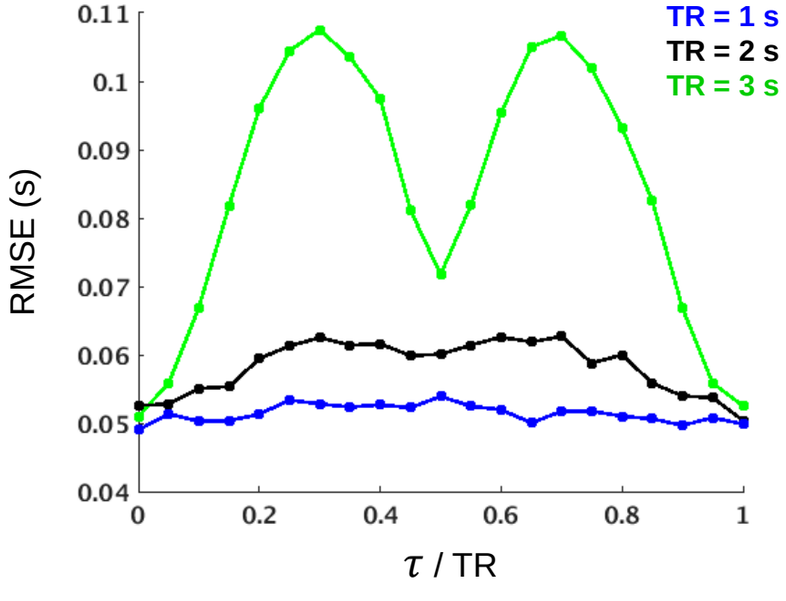
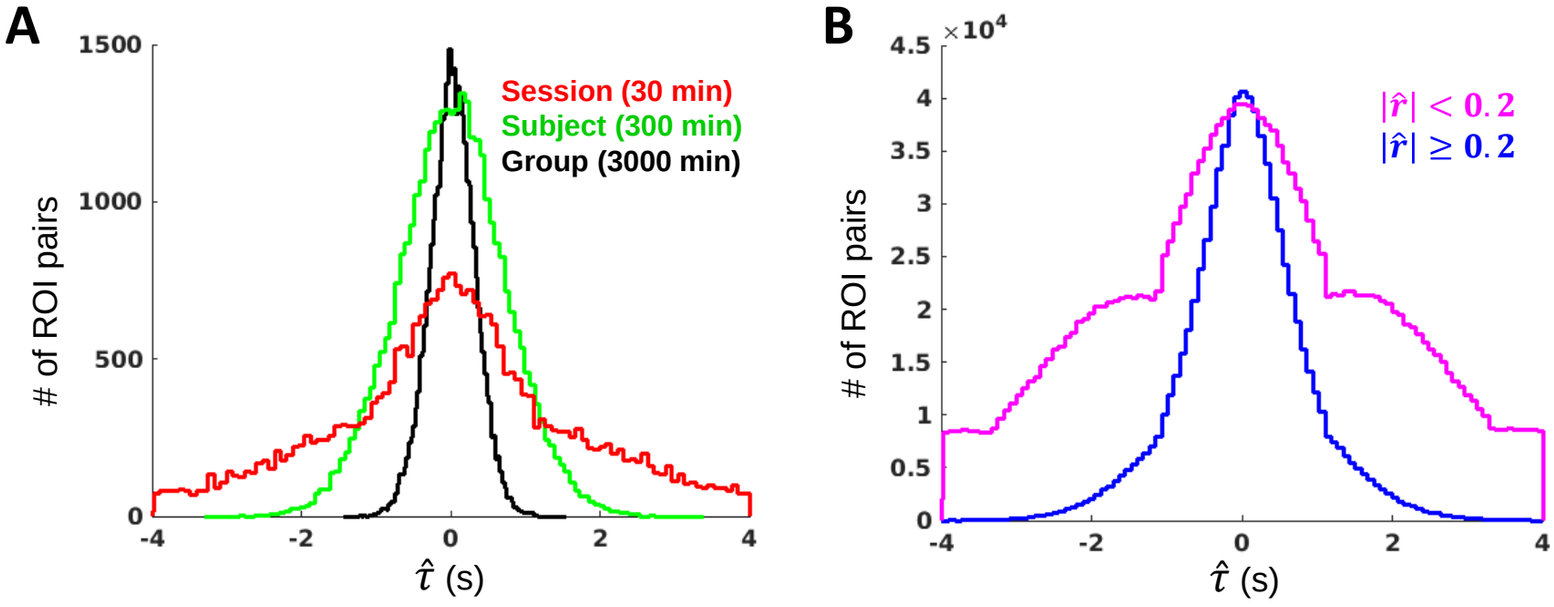

RMSE (s)
τ / TR
TR = 1 s
TR = 2 s
TR = 3 s

Fig. 4


A
1500
1000
500
0
# of ROI pairs
-4
-2
0
2
4
$\hat{\tau}$ (s)
Session (30 min)
Subject (300 min)
Group (3000 min)
B
$\times 10^4$
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
# of ROI pairs
-4
-2
0
2
4
$\hat{\tau}$ (s)
$|\hat{r}| < 0.2$
$|\hat{r}| \geq 0.2$

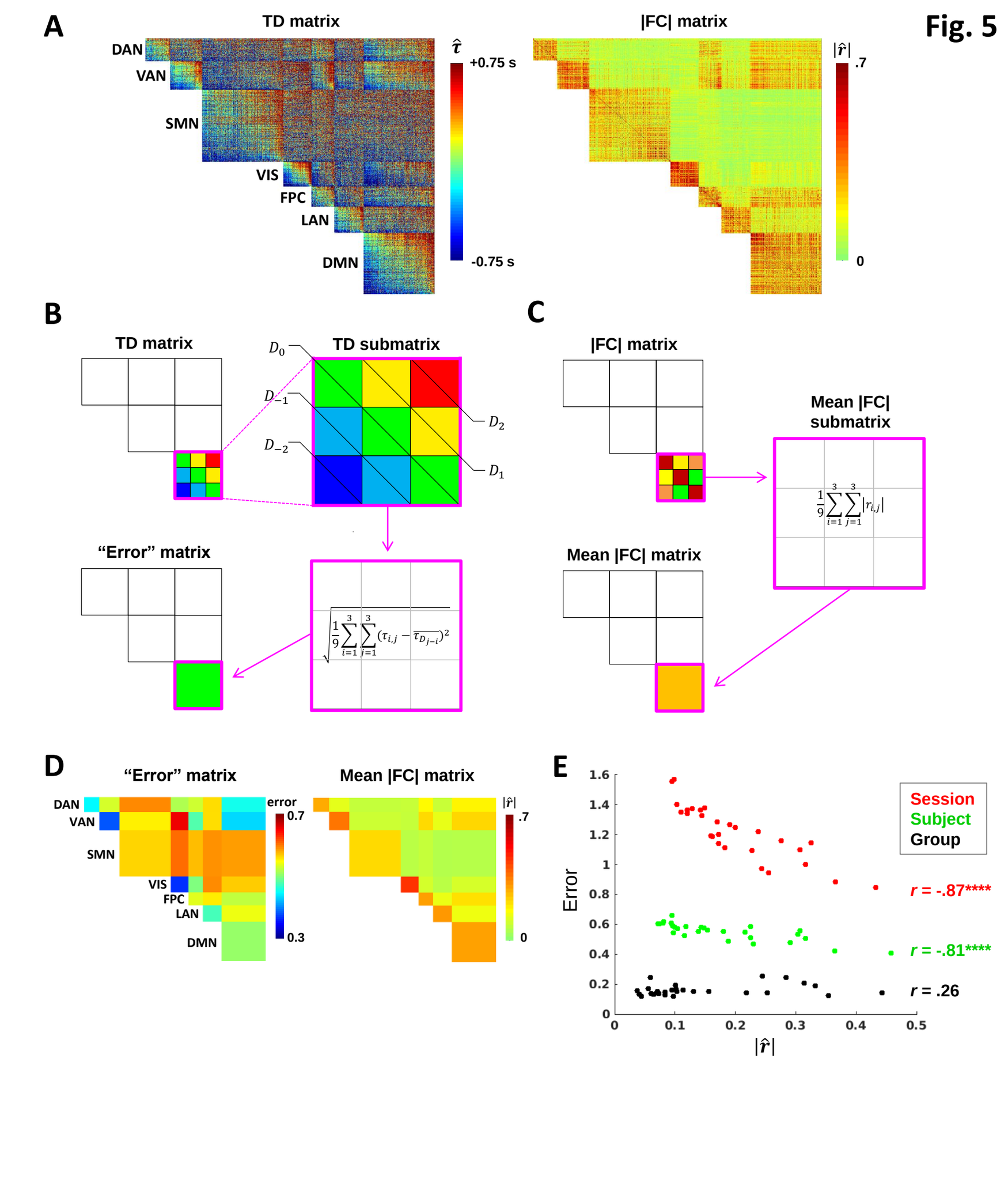

A
TD matrix
DAN
VAN
SMN
VIS
FPC
LAN
DMN
$\hat{\tau}$
+0.75 s
-0.75 s
|FC| matrix
$|\hat{r}|$
.7
0
B
TD matrix
TD submatrix
D_0
D_{-1}
D_{-2}
D_2
D_1
"Error" matrix
$\sqrt{\frac{1}{9}\sum_{i=1}^{3}\sum_{j=1}^{3}(\tau_{i,j}-\overline{\tau_{D_{j-i}}})^2}$
C
|FC| matrix
Mean |FC| submatrix
$\frac{1}{9}\sum_{i=1}^{3}\sum_{j=1}^{3}|r_{i,j}|$
Mean |FC| matrix
D
"Error" matrix
Mean |FC| matrix
DAN
VAN
SMN
VIS
FPC
LAN
DMN
error
0.7
0.3
$|\hat{r}|$
.7
0
E
Error
$|\hat{r}|$
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.1
0.2
0.3
0.4
0.5
Session
Subject
Group
r = -.87****
r = -.81****
r = .26
Fig. 5

Fig. 6

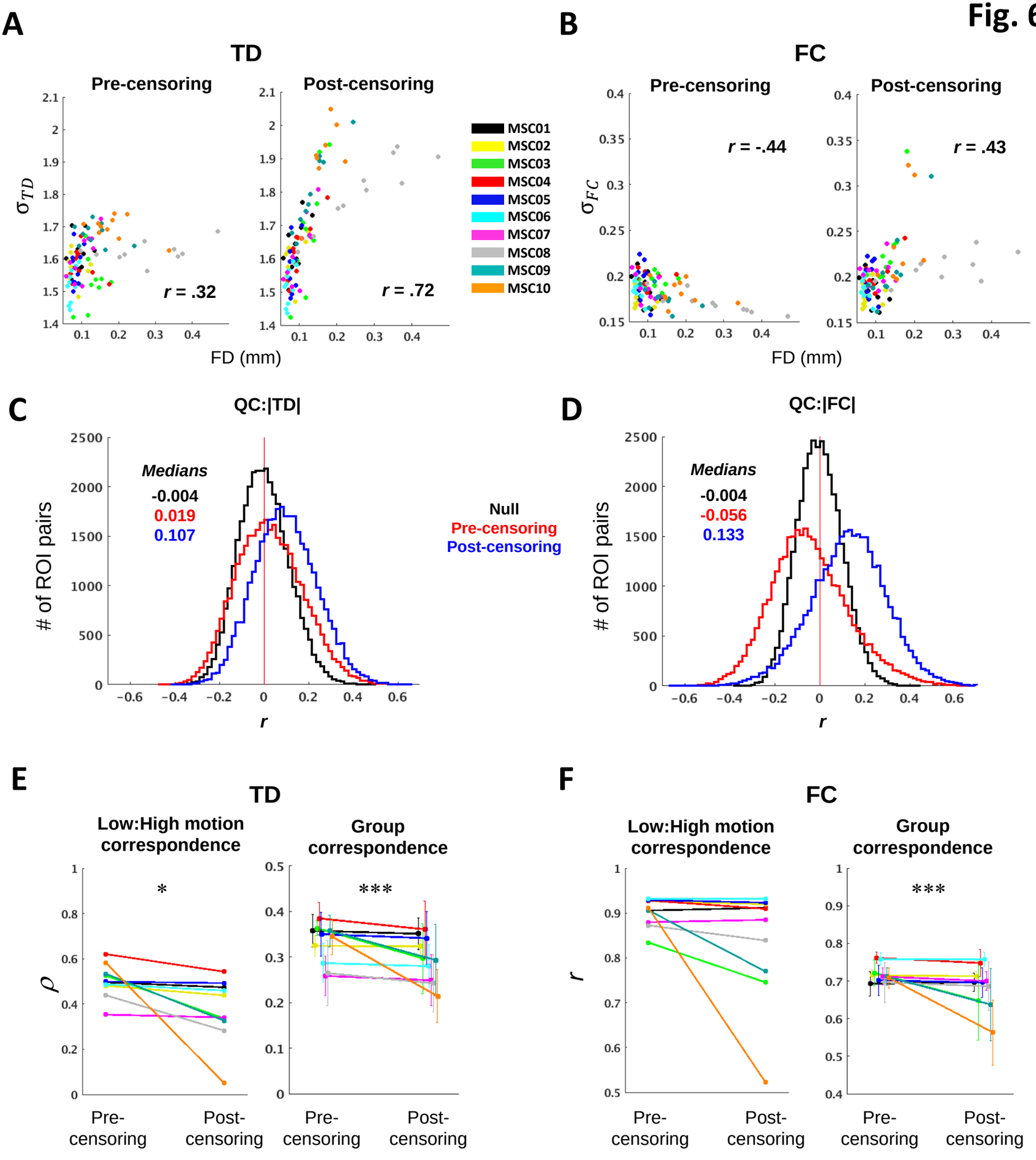

A
TD
Pre-censoring
Post-censoring
σ_{TD}
r = .32
r = .72
FD (mm)
MSC01
MSC02
MSC03
MSC04
MSC05
MSC06
MSC07
MSC08
MSC09
MSC10
B
FC
Pre-censoring
Post-censoring
σ_{FC}
r = -.44
r = .43
FD (mm)
C
QC:|TD|
# of ROI pairs
Medians
-0.004
0.019
0.107
Null
Pre-censoring
Post-censoring
r
D
QC:|FC|
# of ROI pairs
Medians
-0.004
-0.056
0.133
r
E
TD
Low:High motion correspondence
Group correspondence
ρ
*
***
Pre-censoring
Post-censoring
F
FC
Low:High motion correspondence
Group correspondence
r
***
Pre-censoring
Post-censoring

Fig. 7

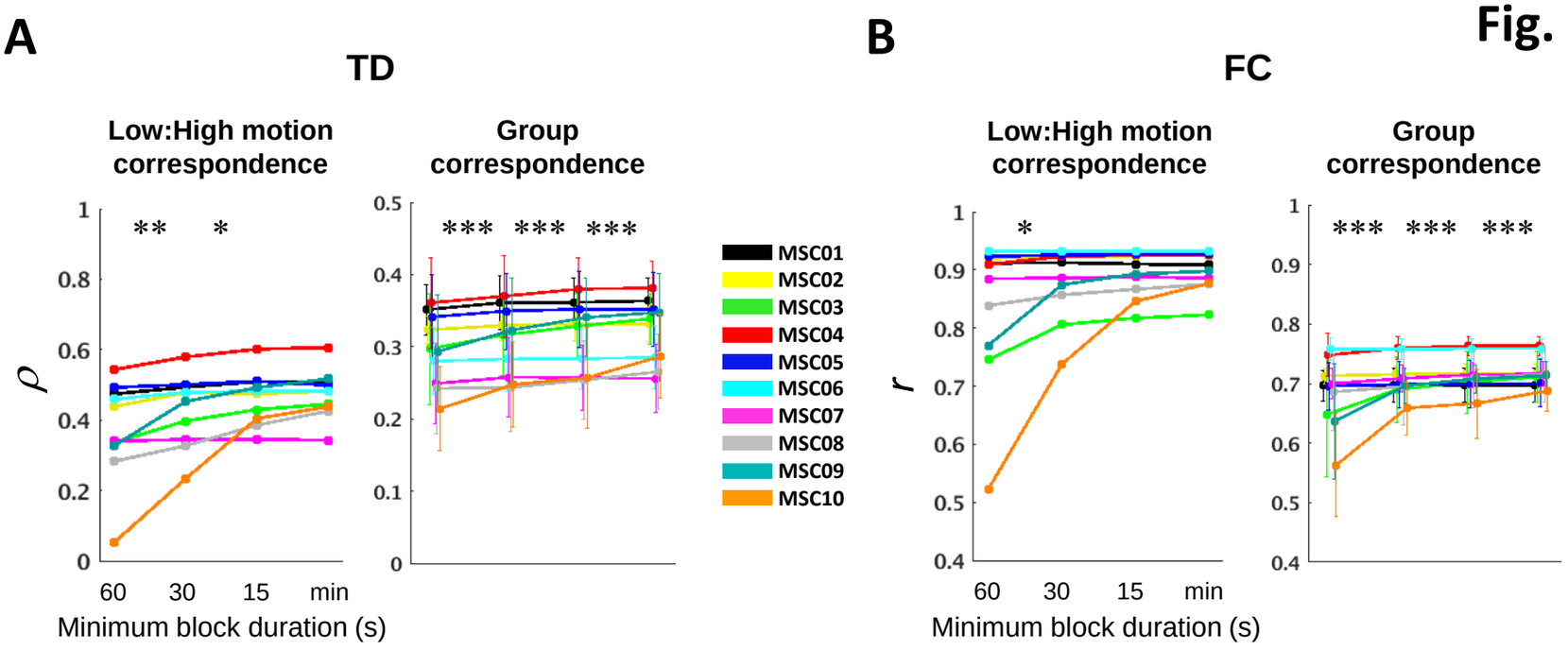
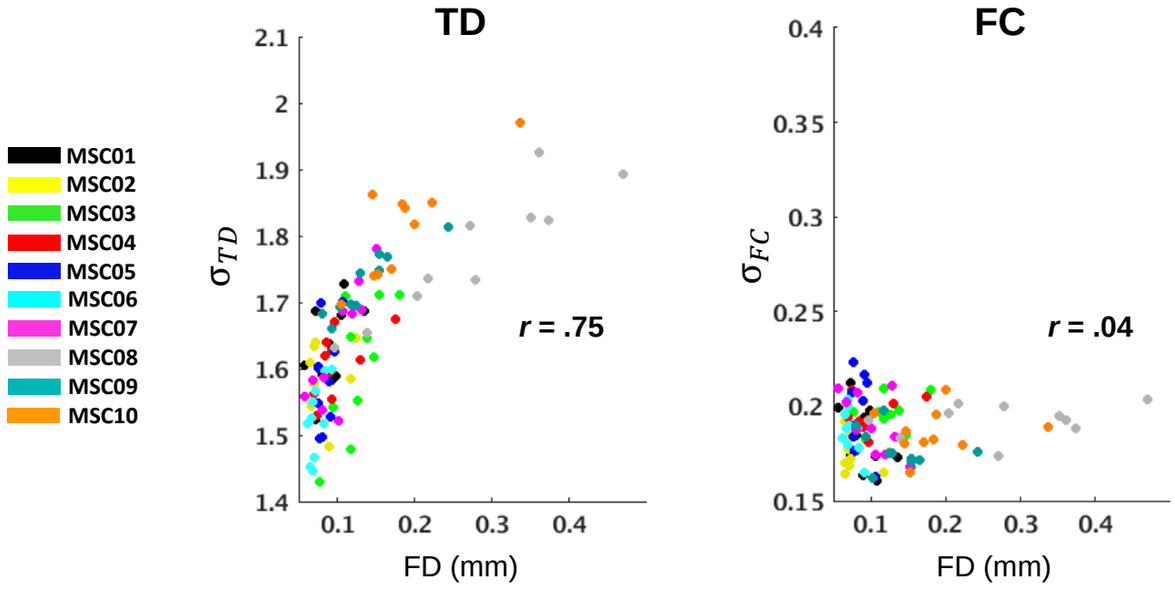

A
TD
Low:High motion correspondence
Group correspondence
**
*
***
***
***
ρ
1
0.8
0.6
0.4
0.2
0
0.5
0.4
0.3
0.2
0.1
0
60
30
15
min
Minimum block duration (s)
MSC01
MSC02
MSC03
MSC04
MSC05
MSC06
MSC07
MSC08
MSC09
MSC10
B
FC
Low:High motion correspondence
Group correspondence
*
***
***
***
r
1
0.9
0.8
0.7
0.6
0.5
0.4
60
30
15
min
Minimum block duration (s)

Fig. 8

A


MSC01
MSC02
MSC03
MSC04
MSC05
MSC06
MSC07
MSC08
MSC09
MSC10
TD
FC
σ_{TD}
σ_{FC}
r = .75
r = .04
FD (mm)
FD (mm)

B

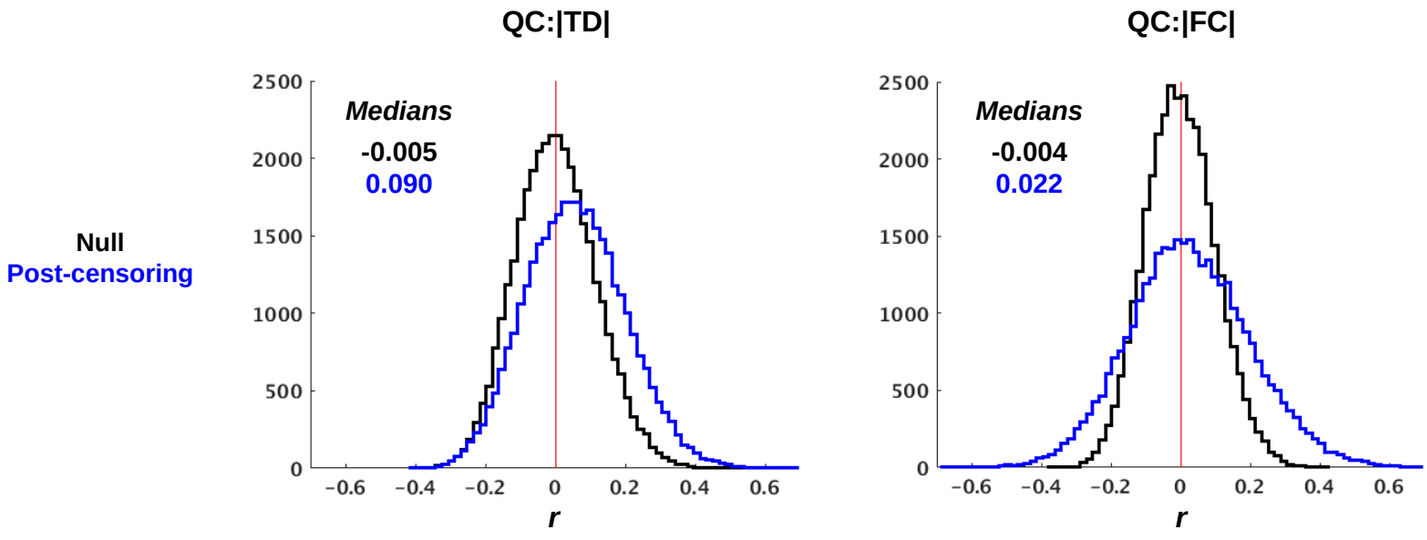
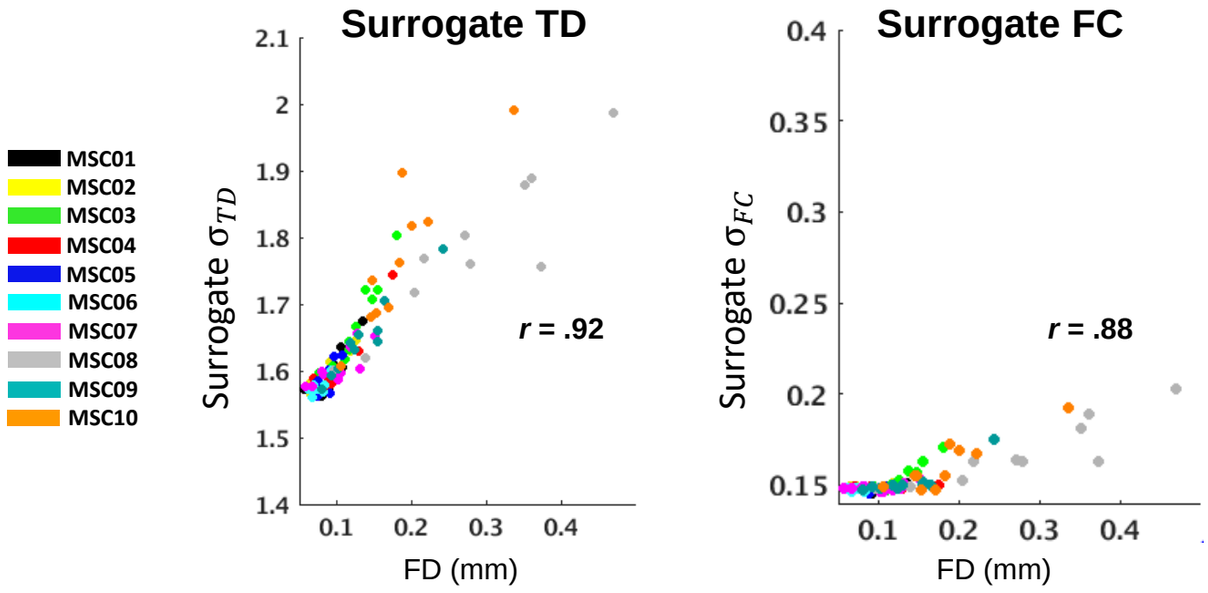

Null
Post-censoring
QC:|TD|
QC:|FC|
Medians
-0.005
0.090
Medians
-0.004
0.022
r
r

Fig. 9

A


MSC01
MSC02
MSC03
MSC04
MSC05
MSC06
MSC07
MSC08
MSC09
MSC10
Surrogate TD
Surrogate σ_TD
r = .92
FD (mm)
Surrogate FC
Surrogate σ_FC
r = .88
FD (mm)

B

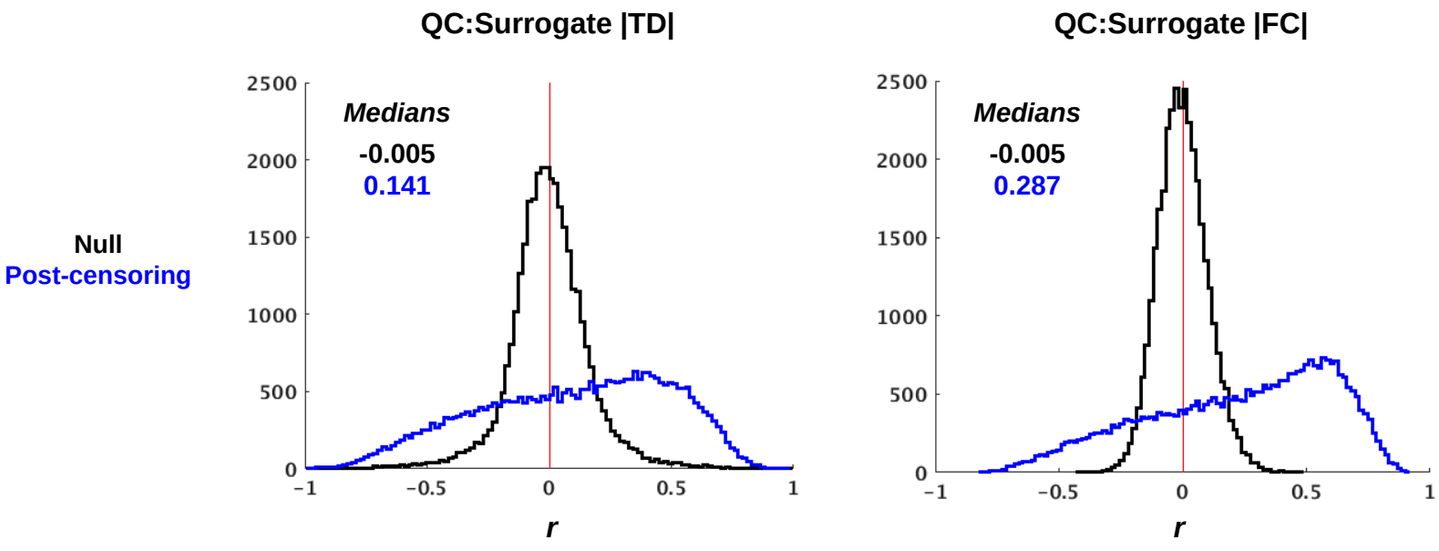
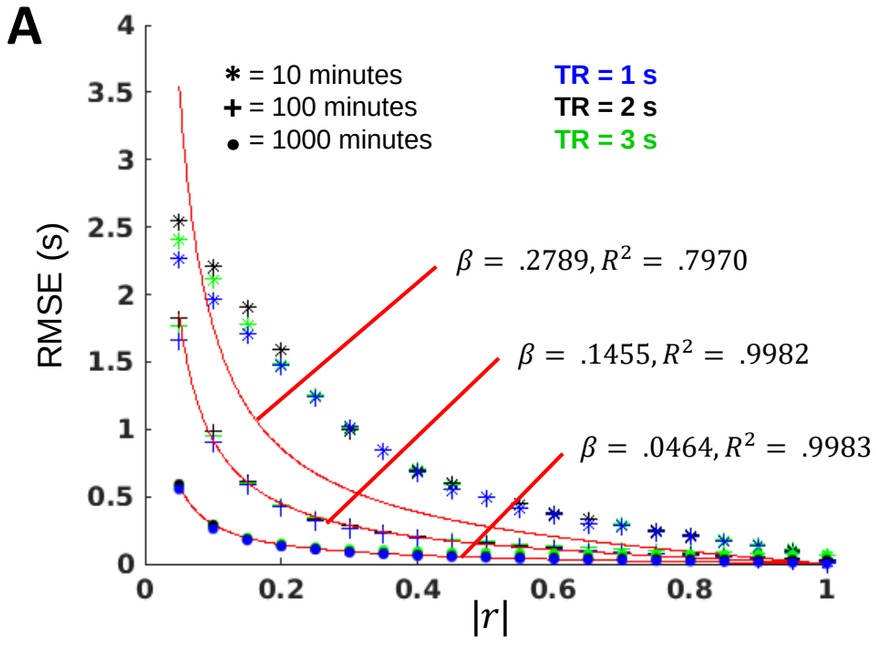
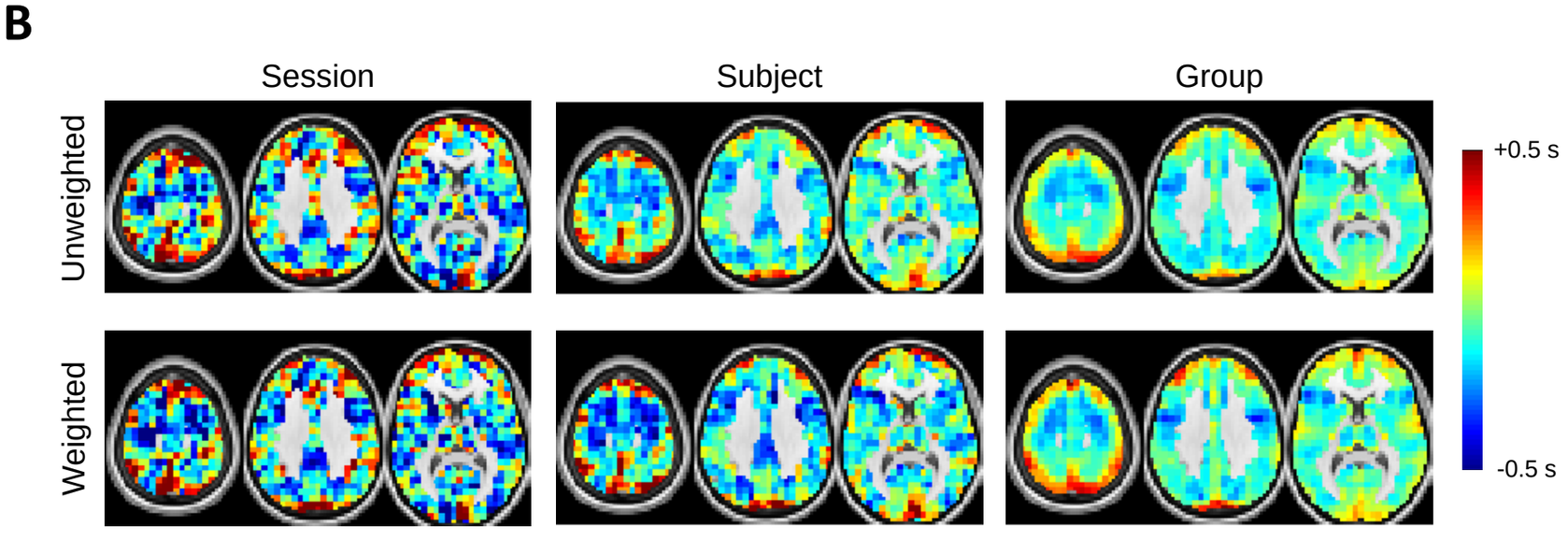
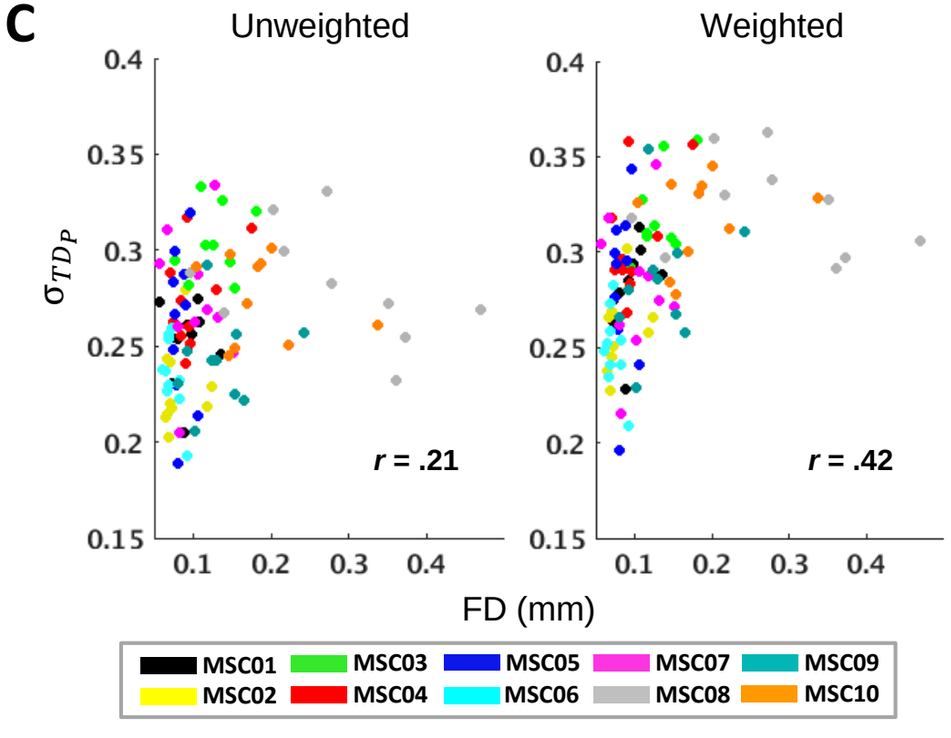
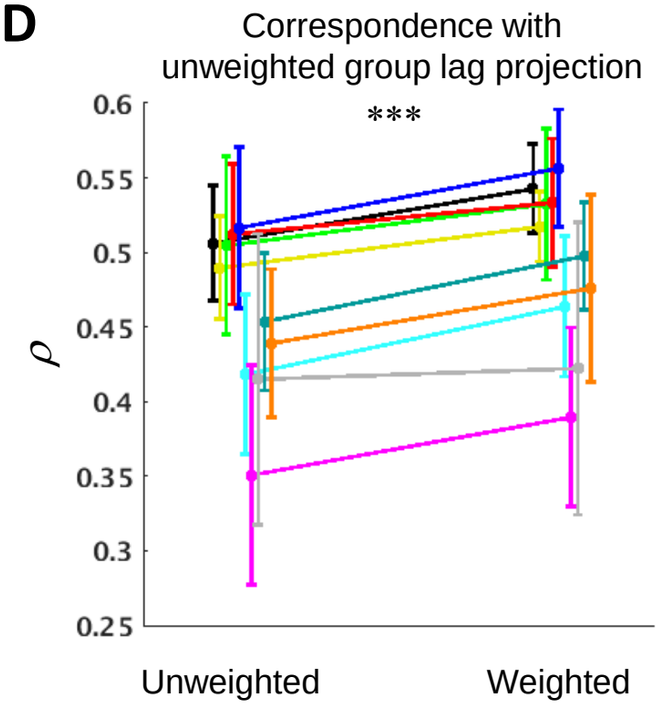

Null
Post-censoring
QC:Surrogate |TD|
Medians
-0.005
0.141
r
QC:Surrogate |FC|
Medians
-0.005
0.287
r

Fig. 10


A
* = 10 minutes
+ = 100 minutes
• = 1000 minutes
TR = 1 s
TR = 2 s
TR = 3 s
RMSE (s)
$\beta = .2789, R^2 = .7970$
$\beta = .1455, R^2 = .9982$
$\beta = .0464, R^2 = .9983$
$|r|$


B
Session
Subject
Group
Unweighted
Weighted
+0.5 s
-0.5 s


C
Unweighted
Weighted
σ_{TD_P}
r = .21
r = .42
FD (mm)
MSC01
MSC02
MSC03
MSC04
MSC05
MSC06
MSC07
MSC08
MSC09
MSC10


D
Correspondence with
unweighted group lag projection
***
ρ
Unweighted
Weighted

Supplementary figures