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Gradient synchronization for multivariate functional data, with application to brain connectivity

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Abstract

Quantifying the association between components of multivariate random curves is of general interest and is a ubiquitous and basic problem that can be addressed with functional data analysis. An important application is the problem of assessing functional connectivity based on functional magnetic resonance imaging (fMRI), where one aims to determine the similarity of fMRI time courses that are recorded on anatomically separated brain regions. In the functional brain connectivity literature, the static temporal Pearson correlation has been the prevailing measure for functional connectivity. However, recent research has revealed temporally changing patterns of functional connectivity, leading to the study of dynamic functional connectivity. This motivates new similarity measures for pairs of random curves that reflect the dynamic features of functional similarity. Specifically, we introduce gradient synchronization measures in a general setting. These similarity measures are based on the concordance and discordance of the gradients between paired smooth random functions. Asymptotic normality of the proposed estimates is obtained under regularity conditions. We illustrate the proposed synchronization measures via simulations and an application to resting-state fMRI signals from the Alzheimer's Disease Neuroimaging Initiative and they are found to improve discrimination between subjects with different disease status.

Keywords: Alzheimer's disease, concordance, fMRI, functional connectivity, functional data analysis, Pearson correlation

1 Introduction

In many applications, data are collected in the form of curves or signals over time. In the context of functional data analysis (FDA), such curve data are modelled as realizations of an underlying smooth stochastic process. Although a variety of approaches have been proposed for univariate functional data (Cai & Yuan, 2012; Cardot et al., 2003; Chiou & Müller, 2014; Chiou et al., 2016; Crambes et al., 2009; Fan & Zhang, 1999; Hall & Horowitz, 2007; Hoover et al., 1998; Huang et al., 2002; Ramsay & Dalzell, 1991; Shin, 2009; Yao et al., 2005; Zhu et al., 2014), the statistical modelling of dependency between the components of multivariate functional data has received less attention.

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Generally, a problem of continuing interest in FDA is the construction of measures of correlation and association between components of multivariate random curves (He et al., 2000). A classical correlation measure is the Pearson product-moment correlation coefficient (Pearson, 1895) which describes the linear dependence between two random variables. It can be viewed as the cosine of the angle between two centred vectors of a sample. The notion of an angle has been extended to random functions in a Hilbert space (Dubin & Müller, 2005), providing a theoretically supported dynamic functional correlation. A traditional approach to describe the correlation between random vectors is canonical correlation (Hotelling, 1936), which has been extended to multivariate time series (Brillinger, 1975) under the stationarity assumption and to bivariate functional data (Leurgans et al., 1993) under the rubric functional canonical correlation. Functional canonical correlation requires delicate regularization as it involves inverse operators (Cupidon et al., 2008; Eubank & Hsing, 2008; He et al., 2003, 2004). To avoid the inverse problem, several alternative notions of functional correlation have been proposed, including dynamic correlation (Dubin & Müller, 2005), which is an extension of Pearson correlation (PC) to the case of functional data, and also a functional correlation based on functional singular decomposition (Yang et al., 2011).

Measures of functional correlation and association are at the core of the quantitative analysis of functional connectivity in neuroscience for time-course data obtained from functional magnetic resonance imaging (fMRI). The fMRI time courses are referred to as blood oxygenation level dependent (BOLD) signals, where an increase in blood flow caused by neuronal activity is thought to lead to a surplus in local blood oxygen (Poldrack et al., 2011), and one measures local changes in deoxyhaemoglobin concentration in the brain, which serves as a proxy for neural activity (Lindquist, 2008). Functional connectivity as used in neuroimaging corresponds to the temporal correlation of a neurophysiological index measured in different brain areas (Friston et al., 1993). The temporal PC was first applied in resting-state fMRI functional connectivity studies by Biswal et al. (1995) and remains one of the predominant tools to measure temporal correlation in the fMRI literature. Other commonly used measures include coherence (Ombao et al., 2008; Sun et al., 2004), which goes back to Wiener (1930), and partial coherence (Tick, 1963) to evaluate the linear relationship between fMRI time series in the frequency domain under various versions of stationarity. Resting-state fMRI is a common method to study brain functional connectivity when subjects are not performing an explicit task (Biswal, 2012; Greicius et al., 2003; Shehzad et al., 2009).

As the temporal variability of signals may exhibit changes across time during the period of data collection, it is of interest to study association measures that can reflect the dynamic characteristics of time courses, especially as the study of variability of connectivity over time has become more popular in recent years (Allen et al., 2014; Chang & Glover, 2010; Hutchison et al., 2013; Lindquist et al., 2014; Patel et al., 2006; Xue et al., 2015), leading to novel approaches to measure functional connectivity in the context of brain diseases such as Alzheimer's disease (AD) (Bijsterbosch et al., 2017; van den Heuvel & Pol, 2010). This motivated us to study the application of the proposed measures of synchronization to resting-state fMRI signals from Alzheimer's patients. While we highlight fMRI signals as a major application area, the relevance and impact of the proposed methodology is not limited to this specific application. Indeed, Leurgans et al. (1993) and Dubin and Müller (2005) demonstrated how their respective versions of functional correlation led to new insights for the gait data (Ramsay & Silverman, 2005) and multivariate physiological data in nephrology (Kaysen et al., 2000), respectively, in addition to applications to longitudinal medical studies such as the Baltimore Longitudinal Study of Aging (Yang et al., 2011).

To study association in the presence of complex time variability, we propose new association measures for paired functional data that emphasize dynamics and are shown to be useful for assessing fMRI-based brain connectivity. The proposed measures differ in essential ways from the commonly used sliding window method (Chang & Glover, 2010) for the analysis of functional connectivity, where one computes temporal PCs over sliding windows. They include *gradient synchronization* and *gradient synchronization fluctuation* and are based on the sign of the product of the derivatives of the two random functions, which is used to track time dynamic synchronicity between two signals. We show that this concept can be interpreted as a limit of temporal PCs that are constructed over sliding windows when the window size shrinks

to zero. Gradient synchronization provides a measure of similarity at the individual level which is readily extended to samples by averaging across subjects. A second measure, gradient synchronization fluctuation, is the number of sign changes of the product of the empirical derivatives of the signals and serves as an additional useful measure. Previous measures to describe changing patterns of connectivity include a dynamic connectivity regression algorithm to detect change points in connectivity (Cribben et al., 2012, 2013) and temporal independent component analysis to obtain temporal functional modes (Smith et al., 2012). In an application to fMRI signals from 11 brain regions (Andrews-Hanna et al., 2010), we find that the proposed gradient synchronization is more closely associated with disease status than traditional PC-based measures.

The remainder of the paper is organized as follows. We define the concepts of gradient synchronization and gradient synchronization fluctuation and the proposed estimators in Section 2. Theoretical results that include asymptotic normality for the proposed estimators are given in Section 3. Simulation results are presented in Section 4, followed by an application to resting-state fMRI data described in Section 5. A discussion follows in Section 6 and the proofs can be found in Section S1 in the online supplementary material.

2 Gradient synchronization

2.1 From segmented correlation to gradient synchronization

Let (X, Y) be a pair of centred random functions on an interval D, assumed to be $[0, 1]$ without loss of generality. We assume that X and Y are both in the Hilbert space L_2 endowed with the inner product $\langle X, Y\rangle = \int_D X(t)Y(t)\mathrm{d}t$. Then, $\langle X, Y\rangle/(\|X\|\|Y\|)$ may be viewed as the cosine of the angle between X and Y, where $\|X\|^2 = \langle X, X\rangle$.

To introduce the proposed time-varying measure of association between pairs of random curves, we first partition D into many small segments and then calculate the cosine of the angles of the two centred curves on each of the segments induced by the partition. Specifically, let $\mathcal{P} = \{A_1, \ldots, A_{K_\mathcal{P}}\}$ be a collection of disjoint intervals of which the union is $[0, 1]$ and $\delta_\mathcal{P} = \max_{1\le k\le K_\mathcal{P}}\{\mu(A_k)\}$, where μ stands for the Lebesgue measure on $\mathbb{R}$. Given a random curve X, the temporally centred curve on A_k is $X(t) - \int_{A_k} X(s)\mathrm{d}s/\mu(A_k)$, for $t \in A_k$, and analogously for Y. The cosine of the angle between the centred curves on the segment A_k is then

$$r_{A_k}(X, Y) = \frac{\int_{A_k}\left\{X(t) - \frac{1}{\mu(A_k)}\int_{A_k} X(s)\mathrm{d}s\right\}\left\{Y(t) - \frac{1}{\mu(A_k)}\int_{A_k} Y(s)\mathrm{d}s\right\}\mathrm{d}t}{\sqrt{\left[\int_{A_k}\left\{X(t) - \frac{1}{\mu(A_k)}\int_{A_k} X(s)\mathrm{d}s\right\}^2\mathrm{d}t\right]\left[\int_{A_k}\left\{Y(t) - \frac{1}{\mu(A_k)}\int_{A_k} Y(s)\mathrm{d}s\right\}^2\mathrm{d}t\right]}}. \quad (1)$$

We observe that r_{A_k} is closely connected to the classical PC for paired data observed during the time interval A_k, which is the customary measure of connectivity in fMRI research. To see this, approximate the integrals in equation (1) by Riemann sums over a set of M time points, $t_{1k} < t_{2k} < \cdots < t_{Mk}$, in A_k. Then, the right-hand side of equation (1) is approximately the PC of the M data pairs $(X(t_{mk}), Y(t_{mk}))$, $m = 1, \ldots, M$. Thus, for each pair of curves $(X(t), Y(t))$, their similarity or association can be quantified by a sequence of local similarities $r_{A_k}(X, Y)$ that quantify the similarity between X and Y along the time segments A_k. This similarity measure is time dynamic and can be characterized by

$$S_{XY,\mathcal{P}}(t) = \sum_{k=1}^{K_\mathcal{P}} r_{A_k}(X, Y)\mathcal{I}_{A_k}(t), \quad (2)$$

where $\mathcal{I}$ is the indicator function.

Under the following standard assumption (A1),

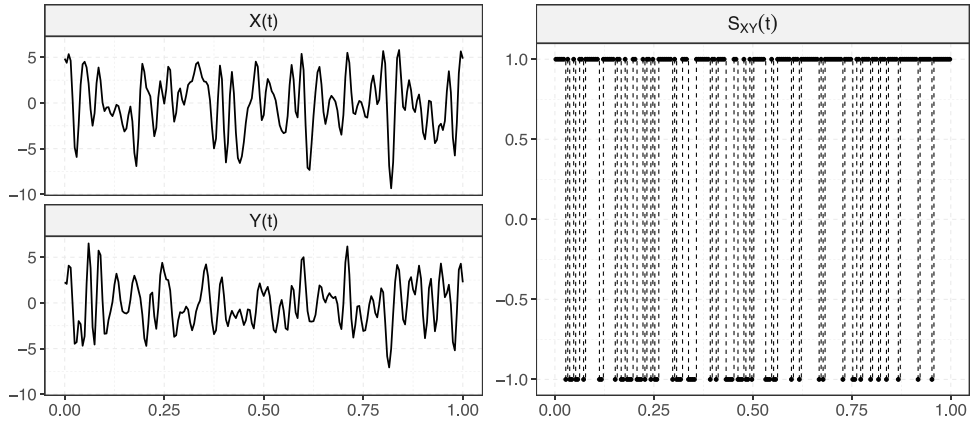

Figure 1. One randomly selected realization of the paired functions $(X(t), Y(t))$ and the corresponding gradient synchronization function $S_{XY}(t)$ (3) generated according to the simulations described in Section 4 with $L = 91$.

(A1) $X(\cdot)$ and $Y(\cdot)$ are continuously differentiable on $[0, 1]$ almost surely, $X(\cdot)$ and $Y(\cdot)$ are continuously differentiable on $[0, 1]$ almost surely.

One finds that as the partition $\mathcal{P}$ gets finer, $S_{XY,\mathcal{P}}(t)$ converges to the gradient synchronization (GS) function

$$S_{XY}(t) = \text{sign}\{X'(t)Y'(t)\}, \tag{3}$$

where $\text{sign}(u) = -1, 0, 1,$ if $u < 0, u = 0, u > 0,$ respectively.

Theorem 1 If Assumption (A1) holds, then for any $t \in (0, 1)$ with $\mathbb{P}\{X'(t)Y'(t) = 0\} = 0$, $S_{XY,\mathcal{P}}(t)$ converges to $S_{XY}(t)$ almost surely as $\delta_{\mathcal{P}} \to 0$.

We refer to $S_{XY}(\cdot)$ as the gradient synchronization function of X and Y since it captures the synchronization of the derivatives or gradients of X and Y. This is illustrated in Figure 1 for a realization of the paired random functions (X, Y) generated according to simulations in Section 4. The oscillations of the random functions result in frequent jumps of $S_{XY}(\cdot)$ between the values 0 and 1, motivating a simple summary measure.

Let $\#A$ be the cardinality of a set A. For any interval $I \subseteq (0, 1)$, we denote the cardinalities of the random sets of zero crossings for X' and Y' by

$$N_{X'}(I) = \#\{t \in I \mid X'(t) = 0\} \quad \text{and} \quad N_{Y'}(I) = \#\{t \in I \mid Y'(t) = 0\}, \tag{4}$$

respectively, and for $I = (0, 1)$ write $N_{X'} = N_{X'}((0, 1))$ and $N_{Y'} = N_{Y'}((0, 1))$. We need an additional assumption, which is not overly restrictive if (A1) is satisfied.

(A2) Almost surely, $N_{X'}$ and $N_{Y'}$ are finite.

We note that Assumption (A2) guarantees that $S_{XY}(\cdot)$ is Riemann integrable almost surely (Theorem 8 in Section 5.3 of Royden & Fitzpatrick, 2010). This leads to

Definition 1 The GS R and the population GS (pGS) ρ of random functions X and Y are defined as

$$R = \int_0^1 S_{XY}(t)\mathrm{d}t \quad \text{and} \quad \rho = \mathbb{E}(R). \tag{5}$$

Obviously, the pGS ρ is always between -1 and 1 and is a measure of similarity as the population mean of the aggregated concordance and discordance of the gradients of the random curves X and Y. It is positive if both trajectories tend to jointly increase or decrease so that their derivatives have the same sign and is negative if the signals tend to head in opposite directions. With $\rho_+ = \mathbb{E}[\mu\{t \in D{:}X'(t)Y'(t) > 0\}]$ and $\rho_- = \mathbb{E}[\mu\{t \in D{:}X'(t)Y'(t) < 0\}]$ representing, respectively, the proportion of the time domain where concordance and discordance of the derivatives of X and Y occurs, under the assumption that $\mathbb{E}[\mu\{t \in D{:}X'(t)Y'(t) = 0\}] = 0$, we have $\rho_+ + \rho_- = 1$, whence $\rho_+ = (1+\rho)/2$ and $\rho_- = (1-\rho)/2$ follow in conjunction with $\rho = \rho_+ - \rho_-$. The extreme scenario $\rho = 1$ occurs when X and Y are both monotonically strictly increasing or both monotonically strictly decreasing, and $\rho = -1$ occurs when one of them is monotonically strictly increasing, while the other is monotonically strictly decreasing over the entire domain. In all other scenarios, one has $-1 < \rho < 1$, where $\rho = 0$ indicates that the aggregated areas of concordance and discordance balance each other out; that is, for half of the time period, there is concordance and for the other half there is discordance.

For a simple example, consider two random functions $X(t) = -V\cos(7\pi t/4)$, $Y(t) = V\sin(7\pi t/4)$, $t \in [0, 1]$, where $V \sim N(0, 1)$. Then,

$$\begin{aligned}
\mathbb{E}\left[\int_0^1 \operatorname{sign}\{X'(t)Y'(t)\}\mathrm{d}t\right] &= \int_0^1 \mathbb{E}[\operatorname{sign}\{X'(t)Y'(t)\}]\mathrm{d}t \\
&= \int_0^1 \mathbb{E}[\operatorname{sign}\{(7\pi V/4)^2 \sin(7\pi t/2)/2\}]\mathrm{d}t \\
&= \int_0^1 \operatorname{sign}\{\sin(7\pi t/2)\}\mathrm{d}t \\
&= \int_0^{2/7} 1\mathrm{d}t - \int_{2/7}^{4/7} 1\mathrm{d}t + \int_{4/7}^{6/7} 1\mathrm{d}t - \int_{6/7}^1 1\mathrm{d}t \\
&= 1/7.
\end{aligned}$$

Thus, $\rho = 1/7$ and therefore $\rho_+ = 4/7$ and $\rho_- = 3/7$.

It is also of interest to investigate the expected number of sign changes of $S_{XY}(\cdot)$ from 1 to -1 or -1 to 1 over time. These sign changes quantify the fluctuation of concordance and discordance between the signals X and Y and thus provide a measure for the stability of gradient synchronization over time. For a piece-wise continuous function $f{:}[0, 1] \to \mathbb{R}$, denote by $f(t^-) = \lim_{s \to t^-} f(s)$ and $f(t^+) = \lim_{s \to t^+} f(s)$ the left and right limits, respectively. Fluctuations in gradient synchronization can be quantified by counting the sign changes of $S_{XY}(\cdot)$, motivating the following definition of gradient synchronization fluctuation at the population level.

Definition 2 The gradient synchronization fluctuation (GSF) Z and the population GSF (pGSF) ζ for random functions X and Y are

$$Z = \#\{t \in (0, 1) \mid S_{XY}(t^-)S_{XY}(t^+) = -1\} \quad \text{and} \quad \zeta = \mathbb{E}(Z). \tag{6}$$

We note that the GSF Z is finite almost surely since it is bounded by $N_{X'} + N_{Y'}$ which is finite under Assumption (A2). To guarantee that ζ is well defined, we further require the following regularity condition for the cardinalities $N_{X'}$ and $N_{Y'}$ of random sets of zero crossings for X' and Y' as defined in equation (4).

(A3) $\mathbb{E}(N_{X'}) < \infty$ and $\mathbb{E}(N_{Y'}) < \infty$.

Assumption (A3) requires that the expectations of $N_{X'}$ and $N_{Y'}$ exist and is a stronger condition than (A2). This condition is related to the study of the expected number of roots of a smooth random function with the Kac–Rice formula (Kac, 1948; Rice, 1944). For a random process $U(\cdot)$ defined on an interval I, with $N_U = \#\{t \in I \mid U(t) = 0\}$, these formulas provide certain integrals to calculate $\mathbb{E}(N_U)$ under regularity conditions (Adler & Taylor, 2009; Azaïs & Wschebor, 2009). For a Gaussian random function $U(\cdot)$ taking values in $C^1([0, 1])$, a sufficient condition for $\mathbb{E}(N_U) < \infty$ is that the distribution of $U(t)$ is not degenerate for any $t \in [0, 1]$ (Azaïs & Wschebor, 2009,

Theorem 3.2). An example is given by $U(t) = \sum_{k=1}^{K} A_k \phi_k(t)$, where the A_k are Gaussian random variables and $\{\phi_k(\cdot)\}$ is a polynomial basis or trigonometric basis. Conditions (A2) and (A3) are satisfied if X and Y are Gaussian processes with $C^2([0, 1])$ sample paths and $X'(t)$ and $Y'(t)$ are non-degenerate random variables for any $t \in [0, 1]$. For non-Gaussian processes, sufficient conditions for $\mathbb{E}(N_U) < \infty$ are in Theorem 3.4 of Azaïs and Wschebor (2009).

2.2 Estimation

In practice, data are only available as discrete measurements taken at a grid of time points. For independent copies $\{(X_i, Y_i)\}_{i=1}^n$ of the underlying random processes (X, Y), we assume that $X_i(\cdot)$ and $Y_i(\cdot)$ are observed on $J + 1$ time points $0 = t_0 < t_1 < \cdots < t_J = 1$, which form a partition $\mathcal{J} = \{t_j\}_{j=0}^J$ of $[0, 1]$. For the ith subject, the corresponding GS, as per (5), is given by

$$R_i = \int_0^1 S_{X_i Y_i}(t)\mathrm{d}t = \int_0^1 \mathrm{sign}\{X_i'(t)Y_i'(t)\}\mathrm{d}t. \tag{7}$$

An empirical derivative for X_i and Y_i can be obtained by difference quotients

$$\widehat{X}_{i\mathcal{J}}'(t) = \sum_{j=1}^{J} D_{j,X_i}\mathcal{I}_{[t_{j-1},t_j)}(t) \quad \text{and} \quad \widehat{Y}_{i\mathcal{J}}'(t) = \sum_{j=1}^{J} D_{j,Y_i}\mathcal{I}_{[t_{j-1},t_j)}(t), \tag{8}$$

where $D_{j,X_i} = \{X_i(t_j) - X_i(t_{j-1})\}/(t_j - t_{j-1})$ and D_{j,Y_i} is defined analogously. Then, a plug-in estimate for R_i is

$$\widehat{R}_{\mathcal{J},i} = \sum_{j=1}^{J} (t_j - t_{j-1})\mathrm{sign}(D_{j,X_i}D_{j,Y_i}). \tag{9}$$

Naturally, the empirical estimate for the pGS ρ is then

$$\widehat{\rho}_{\mathcal{J}} = \frac{1}{n}\sum_{i=1}^{n} \widehat{R}_{\mathcal{J},i}. \tag{10}$$

The asymptotic normality of the estimate $\widehat{\rho}_{\mathcal{J}}$ is provided in Theorem 2 in Section 3.

For $i = 1, \ldots, n$, as per equation (6), the subject-specific GSF Z_i is

$$Z_i = \#\{t \in (0, 1) \mid S_{X_i Y_i}(t^-)S_{X_i Y_i}(t^+) = -1\}. \tag{11}$$

Since the observable time grid $\mathcal{J} = \{t_j\}_{j=0}^J$ is often pre-determined by a measurement device or sampling plan, a variant of the pGSF ζ in (6) that reflects the time grid $\mathcal{J}$ is also useful. Specifically, a grid-dependent variant $\zeta_{\mathcal{J}}$ of the pGSF is defined as

$$\zeta_{\mathcal{J}} = \mathbb{E}(\widehat{Z}_{\mathcal{J},i}), \tag{12}$$

where $\widehat{Z}_{\mathcal{J},i}$ is an estimate for Z_i by simply counting the sign changes in terms of whether adjacent intervals have the same or different signs of the empirical gradients, i.e.

$$\begin{aligned}\widehat{Z}_{\mathcal{J},i} = &\#\{2 \le j \le J \mid D_{j-1,X_i}D_{j,X_i}D_{j-1,Y_i}D_{j,Y_i} < 0\} \\ &+ \#\{1 \le j \le J \mid D_{j,X_i}D_{j,Y_i} = 0\},\end{aligned} \tag{13}$$

where D_{j,X_i} and D_{j,Y_i} are defined as after equation (8). Hence, a sample estimate of ζ can be obtained by

$$\widehat{\zeta}_{\mathcal{J}} = \frac{1}{n}\sum_{i=1}^{n} \widehat{Z}_{\mathcal{J},i}. \tag{14}$$

We establish the asymptotic normality of $\widehat{\zeta}_{\mathcal{J}}$ in Theorem 3 below, where we consider the pGSF ζ in (6) and the grid-dependent variant $\zeta_{\mathcal{J}}$ in (12) as the targets, respectively.

3 Asymptotic properties

For the partition $\mathcal{J}$ of $[0, 1]$, let $\delta_{\mathcal{J}} = \max_{1\le j\le J}\{t_j - t_{j-1}\}$. To derive the asymptotic properties of the proposed estimators, we assume $\delta_{\mathcal{J}} \to 0$ as $n \to \infty$, which requires the grid to get denser as the sample size increases. Although the partition $\mathcal{J} = \mathcal{J}_n$ depends on the sample size n, we keep the notation $\mathcal{J}$ instead of $\mathcal{J}_n$ if no confusion arises. Based on Assumptions (A1)–(A3), we obtain the consistency and asymptotic normality of $\widehat{\rho}_{\mathcal{J}}$.

Theorem 2
(a) If Assumptions (A1) and (A2) hold, then $\widehat{\rho}_{\mathcal{J}}$ converges to ρ (5) in probability.
(b) If Assumptions (A1) and (A3) hold and $\delta_{\mathcal{J}} = o(n^{-1/2})$, then $\sqrt{n}(\widehat{\rho}_{\mathcal{J}} - \rho)/\widehat{\sigma}_{R,\mathcal{J}}$ converges in distribution to $N(0, 1)$, where $\widehat{\sigma}_{R,\mathcal{J}}$ is the square root of the empirical estimate of the variance of R, i.e. $\widehat{\sigma}_{R,\mathcal{J}} = \{(n-1)^{-1}\sum_{i=1}^{n}(\widehat{R}_{\mathcal{J},i} - \widehat{\rho}_{\mathcal{J}})^2\}^{1/2}$.

To obtain the asymptotic normality of $\widehat{\zeta}_{\mathcal{J}}$, we need the following conditions:

(A4) $\mathbb{E}(N_{X'}^2) < \infty$ and $\mathbb{E}(N_{Y'}^2) < \infty$.
(A5) $\mathbb{P}(\exists t \in (0, 1)$ such that $X'(t) = Y'(t) = 0) = 0$.
(A6) There exist constants $C > 0$ and $\epsilon > 0$ such that for all $\delta_{\mathcal{J}} < \epsilon$, the following holds: (a) $\mathbb{P}(N_{X'}(I) = k) \le C|I|^k$ and $\mathbb{P}(N_{Y'}(I) = k) \le C|I|^k$, for all $k \in \mathbb{N}$ and $I \in \{[t_0, t_1), [t_{J-1}, t_J]\}$, as well as for all $k \in \mathbb{N} \cap [2, \infty)$ and $I \in \{[t_{j-2}, t_j) : j = 2, \ldots, J\}$ and (b) $\mathbb{P}(N_{X'}(I) = 1, N_{Y'}(I) = 1) \le C|I|^2$, for $I \in \{[t_0, t_1), [t_{J-1}, t_J]\}$. Here $N_{X'}(I)$ and $N_{Y'}(I)$ are defined in equation (4), and $|I|$ denotes the length of I.

Assumption (A4) is needed to obtain the asymptotic normality of $\widehat{\zeta}_{\mathcal{J}}$ when the target is the grid-dependent $\zeta_{\mathcal{J}}$ in (12). It is a stronger condition than (A3). Fortunately, we can tap into known results on the second moments of N_U for a random process $U(\cdot)$. For a Gaussian random function $U(\cdot)$ in $C^1([0, 1])$, $\mathbb{E}(N_U^2) < \infty$ holds if the joint distribution of $(U(s), U(t))$ is non-degenerate for any $0 \le s < t \le 1$, see Theorem 3.2 of Azaïs and Wschebor (2009). Thus, a sufficient condition for Assumption (A4) is that X is a Gaussian process having $C^2([0, 1])$ sample paths and the joint distribution $(X'(s), X'(t))$ is non-degenerate for any $0 \le s < t \le 1$ and analogously for Y; for non-Gaussian processes see Theorem 3.4 of Azaïs and Wschebor (2009) and Chapter 11 of Adler and Taylor (2009).

Assumptions (A5) and (A6) are needed to obtain the asymptotic normality of $\widehat{\zeta}_{\mathcal{J}}$ when targeting the grid-independent pGSF ζ in (6). Specifically, Assumption (A5) implies that X' and Y' cannot be zero at the same t almost surely; it does not preclude that there are times t where X' or Y' are zero. This assumption guarantees that $\widehat{Z}_{\mathcal{J},i}$ converges almost surely as $\delta_{\mathcal{J}} \to 0$ and it holds under some regularity conditions as discussed in Chapter 3 of Azaïs and Wschebor (2009). In particular, Assumption (A5) holds if (X, Y) is a bivariate Gaussian process with $C^2([0, 1])$ sample paths and $X'(t)$ and $Y'(t)$ are non-degenerate random variables for any $t \in [0, 1]$. Assumption (A6) is a restriction on the frequency of zero crossings of X' and Y', which implies Assumption (A4), and is needed to ensure $\zeta_{\mathcal{J}} - \zeta = O(\delta_{\mathcal{J}})$ as $\delta_{\mathcal{J}} \to 0$. Assumption (A6) is satisfied, for example, in the case where X and Y are random polynomials such that the distance between any two zero crossings of X' and Y' is at least ε, where $\varepsilon > 0$ is a constant.

Theorem 3
(a) If Assumptions (A1) and (A4) hold, then $\sqrt{n}(\widehat{\zeta}_{\mathcal{J}} - \zeta_{\mathcal{J}})/\widehat{\sigma}_{Z,\mathcal{J}}$ converges in distribution to $N(0, 1)$, where $\widehat{\sigma}_{Z,\mathcal{J}}$ is the square root of the empirical estimate of the variance of Z, i.e. $\widehat{\sigma}_{Z,\mathcal{J}} = \{(n-1)^{-1}\sum_{i=1}^{n}(\widehat{Z}_{\mathcal{J},i} - \widehat{\zeta}_{\mathcal{J}})^2\}^{1/2}$.
(b) If Assumptions (A1), (A5), and (A6) hold and $\delta_{\mathcal{J}} = o(n^{-1/2})$, then $\sqrt{n}(\widehat{\zeta}_{\mathcal{J}} - \zeta)/\widehat{\sigma}_{Z,\mathcal{J}}$ converges in distribution to $N(0, 1)$.

Table 1. Bias, variance, and mean squared error of the proposed estimator $\widehat{\rho}_{\mathcal{J}}$ with respect to the target ρ

		$J = 100$	$J = 200$	$J = 500$
Bias$(\widehat{\rho}_{\mathcal{J}})$	$n = 50$	11.714	4.832	3.620
	$n = 200$	7.710	2.067	2.944
	$n = 1{,}000$	7.088	0.732	0.952
Var$(\widehat{\rho}_{\mathcal{J}})$	$n = 50$	2.059	1.730	1.556
	$n = 200$	0.481	0.415	0.363
	$n = 1{,}000$	0.102	0.084	0.076
MSE$(\widehat{\rho}_{\mathcal{J}})$	$n = 50$	2.073	1.732	1.557
	$n = 200$	0.487	0.415	0.364
	$n = 1{,}000$	0.107	0.084	0.076

Note. Based on $M = 1{,}000$ simulation runs, the first row provides the bias $\text{Bias}(\widehat{\rho}_{\mathcal{J}}) = \sum_{m=1}^{M} (\widehat{\rho}_{\mathcal{J}}^{[m]} - \rho)/M$, where $\widehat{\rho}_{\mathcal{J}}^{[m]}$ is the proposed estimator of ρ for the mth simulation run. The second row provides the variance $\text{Var}(\widehat{\rho}_{\mathcal{J}}) = \sum_{m=1}^{M} (\widehat{\rho}_{\mathcal{J}}^{[m]} - M^{-1} \sum_{m'=1}^{M} \widehat{\rho}_{\mathcal{J}}^{[m']})^2/M$ of the proposed estimator. The third row shows the mean squared error $\text{MSE}(\widehat{\rho}_{\mathcal{J}}) = \sum_{m=1}^{M} (\widehat{\rho}_{\mathcal{J}}^{[m]} - \rho)^2/M$. All values in the table have been divided by 10^{-4}.

The asymptotic normality of $\widehat{\rho}_{\mathcal{J}}$ and $\widehat{\zeta}_{\mathcal{J}}$ can be utilized for inference such as the construction of asymptotic confidence intervals for ρ and ζ. Let z_α denote the upper α-quantile of $N(0, 1)$, i.e. $\mathbb{P}(V > z_\alpha) = \alpha$ where $V \sim N(0, 1)$. By Theorems 2 and 3, $\widehat{\rho}_{\mathcal{J}} \pm z_{\alpha/2}\widehat{\sigma}_{R,\mathcal{J}}/\sqrt{n}$ and $\widehat{\zeta}_{\mathcal{J}} \pm z_{\alpha/2}\widehat{\sigma}_{Z,\mathcal{J}}/\sqrt{n}$ are $100(1-\alpha)\%$ asymptotic confidence intervals for the pGS ρ and the pGSF ζ.

4 Simulation studies

To demonstrate the finite sample performance of the proposed estimators, our simulation design included $M = 1{,}000$ simulation runs and $n = 50$, 200, and 1,000 independent and identically distributed (i.i.d.) pairs of random functions (X_i, Y_i), $i = 1, \ldots, n$. The grid points $\{0 = t_0 < \cdots < t_J = 1\}$ were located equidistantly on $[0, 1]$, with the number of grid points chosen as $J = 100$, 200, and 500. Paired functional data (X_i, Y_i) were generated from the trigonometric basis as follows:

$$X_i(t_j) = \sum_{l=1}^{L} A_{i,l}\phi_l(t_j) \quad \text{and} \quad Y_i(t_j) = \sum_{l=1}^{L} B_{i,l}\phi_l(t_j),$$

where $L = 91$, $\phi_1(t) \equiv 1$, $\phi_l(t) = \sqrt{2}\cos((l-1)\pi t)$ for odd $l > 1$ and $\phi_l(t) = \sqrt{2}\sin(l\pi t)$ for even l, $A_i = (A_{i,1}, \ldots, A_{i,L})^\top$ are i.i.d. random vectors from $N(0, D)$ with the covariance matrix D a diagonal matrix with elements $D_{ll} = \exp(-|l - 35|/50)/8$ for $l = 1, \ldots, L$ and $B_i = (B_{i,1}, \ldots, B_{i,L})^\top = aA_i + VC_i$, with C_i independent copies of A_i, V an $L \times L$ matrix with (i, j)th entry $V_{ij} = 0.8 \times 0.3^{|i-j|}$, and a such that $\int_0^1 \text{Var}\{X_i(t)\}\text{d}t = \int_0^1 \text{Var}\{Y_i(t)\}\text{d}t$, i.e. $\sum_{l=1}^{L} D_{ll} = a^2 \sum_{l=1}^{L} D_{ll} + \text{trace}(VDV^\top)$, whence $a = 0.48414$. The value of pGS is $\rho = 0.34253$, obtained numerically by averaging the values for 10^6 paired random functions, recorded on a regular grid with increment 10^{-6} on $[0, 1]$. Similarly, the value of pGSF is $\zeta = 130.67$ and its grid-dependent variant $\zeta_{\mathcal{J}}$ equals 42.567, 77.472, and 107.67 for $J = 100$, 200, and 500, respectively, where J determines the segmentation scheme.

Table 1 contains the numerical results for the estimates of pGS and Table 2 the coverage rate of the 95% confidence interval $\widehat{\rho}_{\mathcal{J}} \pm z_{0.025}\widehat{\sigma}_{R,\mathcal{J}}/\sqrt{n}$. We find that the proposed estimator $\widehat{\rho}_{\mathcal{J}}$ converges to the true target ρ as sample size n increases and the coverage rate of the confidence interval is close to the nominal level 95%. The corresponding results for the estimate of pGSF are in

Table 2. Coverage rates for 95% confidence intervals $\widehat{\rho}_{\mathcal{J}} \pm z_{0.025}\widehat{\sigma}_{R,\mathcal{J}}/\sqrt{n}$

	$J = 100$	$J = 200$	$J = 500$
$n = 50$	0.944	0.937	0.930
$n = 200$	0.954	0.943	0.949
$n = 1{,}000$	0.945	0.956	0.947

Table 3. Bias, variance, and mean squared error of the proposed estimator $\widehat{\zeta}_{\mathcal{J}}$ with respect to the target $\zeta_{\mathcal{J}}$

		$J = 100$	$J = 200$	$J = 500$
$\text{Bias}_{\mathcal{J}}(\widehat{\zeta}_{\mathcal{J}})$	$n = 50$	−0.023	−0.013	−0.057
	$n = 200$	−0.013	0.011	−0.042
	$n = 1{,}000$	−0.009	0.005	−0.025
$\text{Var}(\widehat{\zeta}_{\mathcal{J}})$	$n = 50$	0.660	1.468	1.222
	$n = 200$	0.158	0.342	0.300
	$n = 1{,}000$	0.030	0.067	0.059
$\text{MSE}(\widehat{\zeta}_{\mathcal{J}})$	$n = 50$	0.660	1.468	1.225
	$n = 200$	0.159	0.342	0.302
	$n = 1{,}000$	0.030	0.067	0.060

Note. Based on $M = 1{,}000$ simulation runs, the first row provides the bias $\text{Bias}_{\mathcal{J}}(\widehat{\zeta}_{\mathcal{J}}) = \sum_{m=1}^{M}(\widehat{\zeta}_{\mathcal{J}}^{[m]} - \zeta_{\mathcal{J}})/M$, where $\widehat{\zeta}_{\mathcal{J}}^{[m]}$ is the proposed estimator of ζ for the mth simulation run. The second row provides the variance $\text{Var}(\widehat{\zeta}_{\mathcal{J}}) = \sum_{m=1}^{M}(\widehat{\zeta}_{\mathcal{J}}^{[m]} - \bar{\zeta}_{\mathcal{J}})^2/M$ of the proposed estimator, where $\bar{\zeta}_{\mathcal{J}} = \sum_{m=1}^{M}\widehat{\zeta}_{\mathcal{J}}^{[m]}/M$. The third row shows the mean squared error $\text{MSE}_{\mathcal{J}}(\widehat{\zeta}_{\mathcal{J}}) = \sum_{m=1}^{M}(\widehat{\zeta}_{\mathcal{J}}^{[m]} - \zeta_{\mathcal{J}})^2/M$.

Table 4. Coverage rates for the 95% confidence intervals $\widehat{\zeta}_{\mathcal{J}} \pm z_{0.025}\widehat{\sigma}_{Z,\mathcal{J}}/\sqrt{n}$

	$J = 100$	$J = 200$	$J = 500$
$n = 50$	0.936	0.932	0.942
$n = 200$	0.953	0.950	0.949
$n = 1{,}000$	0.956	0.957	0.948

Tables 3 and 4, where the target is the grid-dependent variant $\zeta_{\mathcal{J}}$. It can be seen that $\widehat{\zeta}_{\mathcal{J}}$ moves closer to $\zeta_{\mathcal{J}}$ for increasing sample size and the coverage of the confidence intervals is satisfactory.

Often the observable time grid $\mathcal{J}$ is pre-determined by the measurement device and the fluctuation of the gradient synchronization inside intervals (t_{j-1}, t_j) is not detectable. This leads to a natural bias so that $\widehat{\zeta}_{\mathcal{J}}$ underestimates the grid-independent pGSF ζ in general. We demonstrate this phenomenon in simulations. Table 5 provides the bias, variance, and mean squared error of the proposed estimator $\widehat{\zeta}_{\mathcal{J}}$ with respect to the target ζ. The bias decreases as the partition gets finer and the estimating error is seen to be dominated by the bias. Bias correction will be a relevant topic for future research.

In addition, we evaluated the performance of the proposed estimators of pGS and pGSF obtained from samples of smaller size starting from $n = 1$ for functions observed on various time grids with different numbers of time points $J \in \{100, 200, 500\}$. As shown in the boxplots for estimated pGS and pGSF in Figures S1 and S2 in Section S2 in the online supplementary material, for sample sizes n as small as 25, the estimation accuracy is quite satisfactory.

Table 5. Bias, variance, and mean squared error of the proposed estimator $\widehat{\zeta}_{\mathcal{J}}$ with respect to the target ζ

		$J = 100$	$J = 200$	$J = 500$
$\text{Bias}(\widehat{\zeta}_{\mathcal{J}})$	$n = 50$	−88.130	−53.215	−23.060
	$n = 200$	−88.120	−53.191	−23.044
	$n = 1{,}000$	−88.116	−53.197	−23.027
$\text{Var}(\widehat{\zeta}_{\mathcal{J}})$	$n = 50$	0.660	1.468	1.222
	$n = 200$	0.158	0.342	0.300
	$n = 1{,}000$	0.030	0.067	0.059
$\text{MSE}(\widehat{\zeta}_{\mathcal{J}})$	$n = 50$	7767.515	2833.317	532.969
	$n = 200$	7765.237	2829.607	531.344
	$n = 1{,}000$	7764.427	2830.023	530.322

Note. Based on $M = 1{,}000$ simulation runs, the first row provides the bias $\text{Bias}(\widehat{\zeta}_{\mathcal{J}}) = \sum_{m=1}^{M} (\widehat{\zeta}_{\mathcal{J}}^{[m]} - \zeta)/M$, where $\widehat{\zeta}_{\mathcal{J}}^{[m]}$ is the proposed estimator obtained for the mth simulation run. The second row provides the variance $\text{Var}(\widehat{\zeta}_{\mathcal{J}}) = \sum_{m=1}^{M} (\widehat{\zeta}_{\mathcal{J}}^{[m]} - M^{-1} \sum_{m'=1}^{M} \widehat{\zeta}_{\mathcal{J}}^{[m']}/M)^2/M$ of the proposed estimator. The third row shows the mean squared error $\text{MSE}(\widehat{\zeta}_{\mathcal{J}}) = \sum_{m=1}^{M} (\widehat{\zeta}_{\mathcal{J}}^{[m]} - \zeta)^2/M$.

As in reality data may be noisy, in addition we considered scenarios where the simulated curves are contaminated with different levels of random noise. To study the case of error contaminated data, we generated the observations of X_i and Y_i as

$$X_{ij} = X_i(t_j) + \epsilon_{ij} \quad \text{and} \quad Y_{ij} = Y_i(t_j) + \varepsilon_{ij},$$

where ϵ_{ij} and ε_{ij} for $i = 1, \ldots, n$ and $j = 1, \ldots, J$ are i.i.d. random noise generated from $N(0, \sigma^2_{\text{err},X})$ and $N(0, \sigma^2_{\text{err},Y})$, respectively. We define the signal-to-noise ratio (SNR) as the integrated variance of the random functions divided by the noise variance, i.e.

$$\text{SNR} = \sqrt{\frac{\int_0^1 \text{Var}\{X_i(t)\}\text{d}t}{\sigma^2_{\text{err},X}}}$$

for functions X and analogously for functions Y.

This definition quantifies the contrast of the variability of signal and noise and is also commonly used in fMRI analyses (Frässle et al., 2017; Stephan et al., 2008; Welvaert & Rosseel, 2013), which is sometimes referred to as contrast-to-noise ratio alternatively. The signal-to-noise ratios considered were 20, 5, and 2, similar to the values taken in simulations of fMRI studies and corresponding to three levels of contamination in the observed data, which in what follows are referred to as low-, medium-, and high-contamination scenarios, respectively. We also compared the estimation of pGS and pGSF based on raw noisy data with the estimation based on band-pass filtered data. For the latter, the band-pass filtering was applied to only preserve frequency components between 0.01 and 0.1 Hz assuming that the recording for an entire function takes 600 s, mimicing the Alzheimer's Disease Neuroimaging Initiative (ADNI) fMRI data in Section 5 with around 200 measurements per scan recorded with repetition time (TR) 3,000 ms. As shown in Tables S1–S6 in Section S2 in the online supplementary material, pGS and pGSF are not well estimated based on unfiltered noisy data, especially when the observed time grid $\mathcal{J}$ is relatively dense (e.g. $J = 200$ and $J = 500$). Yet for the band-pass filtered data, the performance of the proposed estimators is found to be much better—both the size of bias and variance shrink overall and the shrinkage is more remarkable as the observed time grid $\mathcal{J}$ gets denser.

5 Application to resting-state fMRI data

Resting-state fMRI data consisting of BOLD signals, while subjects relax were obtained from the ADNI database (http://adni.loni.usc.edu). The ADNI fMRI data have different numbers of temporal volumes and we took those scans that have 197 time points so that the sample size is the largest across different time points. Each subject was assigned to one of six cognitive groups: cognitively normal (CN, 279 subjects), subjective memory concerns (SMC, 24 subjects), early mild cognitive impairment (EMCI, 54 subjects), mild cognitive impairment (MCI, 120 subjects), late mild cognitive impairment (LMCI, 20 subjects), and AD dementia (36 subjects). From each subject, we considered their earliest available fMRI scans for those with repeated scans. The BOLD signals are measured with repetition time (TR) 3,000 ms.

Pre-processing of the BOLD signals followed standard procedures, including head motion correction, slice-timing correction, co-registration, normalization, and spatial smoothing. The first four time points were removed to eliminate non-equilibrium effects of magnetization. Subsequently, average signals of voxels within each seed region were extracted, where linear detrending and band-pass filtering were performed to account for signal drift and global cerebral spinal fluid and white matter signals, including only frequencies between 0.01 and 0.1 Hz, respectively. These steps were performed in MATLAB using the Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm) and Resting-State fMRI Data Analysis Toolkit V1.8 (REST1.8, http://restfmri.net/forum/?q=rest).

Our analysis focused on the default network, a set of regions that activate when there is no external stimulus (Mazoyer et al., 2001; Raichle et al., 2001; Shulman et al., 1997). Functional connectivity within the default network has been shown to be deficient in a number of neurological diseases including Alzheimer's (Buckner et al., 2008; Greicius et al., 2004). Our analysis focused on the 11 regions of interest (ROIs) within the default network identified in Andrews-Hanna et al. (2010, Table S1, replicated in Table S7 in Section S3 in the online supplementary material). To quantify the strength of inter-regional functional connectivity, we considered the average signals of spherical seed regions of diameter 8 mm centred at the seed voxels of these regions. This yielded 55 paired combinations for the 11 ROIs. To investigate the differences between cognitive groups, we carried out Kruskal–Wallis tests and two-sample Wilcoxon rank sum tests for the equality of the distributions for connectivity measures. Specifically, we first considered a summary statistic of connectivity measures aggregating all 55 pairs of ROIs, the mean of the absolute values (mean size) of pair-wise connectivity measures over all 55 ROI pairs, as a single quantity summarizing the magnitude of average hub connectivity.

We considered three connectivity measures: The proposed GS R_i in (7) with an estimate $\widehat{R}_{\mathcal{J},i}$ in (9) and the proposed GSF Z_i in (11) with an estimate $\widehat{Z}_{\mathcal{J},i}$ in (13), based on centred signals, as well as the (static) temporal PC, which for the ith subject with data (X_i, Y_i) is defined as

$$P_{\mathcal{J},i} = \frac{\sum_{j=1}^{J} \{X_i(t_j) - \bar{X}_i\}\{Y_i(t_j) - \bar{Y}_i\}}{\sqrt{\sum_{j=1}^{J} \{X_i(t_j) - \bar{X}_i\}^2} \sqrt{\sum_{j=1}^{J} \{Y_i(t_j) - \bar{Y}_i\}^2}}, \tag{15}$$

with $\bar{X}_i = J^{-1} \sum_{j=1}^{J} X_i(t_j)$ and $\bar{Y}_i = J^{-1} \sum_{j=1}^{J} Y_i(t_j)$. We note that the temporal PC is the standard functional connectivity measure used in brain imaging studies and for our analysis is computed based on all the temporal measurements during the screening session with the first four measurement times discarded, as described above. Results of Kruskal–Wallis tests in Table 6 demonstrate that the proposed measures GS and GSF discriminate the six cognitive groups, whereas no significant difference is found among the six groups for temporal PC. Furthermore, when applying two-sample Wilcoxon rank sum tests for each pair of cognitive groups (Table 7), temporal PC does not significantly distinguish between any groups, while all pairs of groups except for the pair (MCI, AD) are significantly distinguished by GS and all are distinguished by GSF except for the pairs (CN, LMCI) and (SMC, MCI). When considering simultaneous pair-wise comparisons between the 15 pairs formed by the 6 groups, GSF still significantly discriminates 10 pairs of groups and GS 14 pairs.

Table 6. *P*-values of the Kruskal–Wallis tests to compare mean sizes over the 55 pairs of ROIs of (static) temporal PC (15), GS (9), and GSF (13) among the six cognitive groups

PC	GS	GSF
0.63	2.1×10^{-61}	2.3×10^{-36}

Note. GS = gradient synchronization; GSF = gradient synchronization fluctuation; PC = Pearson correlation; ROIs = regions of interest.

Table 7. *P*-values of the two-sample Wilcoxon rank sum tests to compare mean sizes over the 55 pairs of ROIs of (static) temporal PC (15), GS (9), and GSF (13) between the six cognitive groups

Pair of groups	PC	GS	GSF
(CN, SMC)	0.65	1.3×10^{-12}**	0.021*
(CN, EMCI)	0.22	1.1×10^{-23}**	7.0×10^{-22}**
(CN, MCI)	0.71	1.5×10^{-33}**	0.027*
(CN, LMCI)	0.41	3.2×10^{-9}**	0.72
(CN, AD)	0.43	3.0×10^{-16}**	3.3×10^{-19}**
(SMC, EMCI)	0.22	1.6×10^{-5}**	3.8×10^{-10}**
(SMC, MCI)	0.77	6.8×10^{-10}**	0.11
(SMC, LMCI)	0.36	3.6×10^{-6}**	0.0012 **
(SMC, AD)	0.33	2.6×10^{-7}**	8.1×10^{-11}**
(EMCI, MCI)	0.18	1.7×10^{-16}**	1.0×10^{-17}**
(EMCI, LMCI)	0.96	1.4×10^{-8}**	6.1×10^{-9}**
(EMCI, AD)	0.80	3.4×10^{-10}**	1.7×10^{-4}**
(MCI, LMCI)	0.35	9.8×10^{-9}**	0.047*
(MCI, AD)	0.36	0.35	1.5×10^{-16}**
(LMCI, AD)	0.86	1.4×10^{-7}**	4.0×10^{-9}**

Note. Significance at level 0.05 for individual tests is marked by '*' and for multiple comparisons after the Bonferroni correction (i.e. less than $0.05/15 \approx 0.0033$) by ' **'. AD = Alzheimer's disease; CN = cognitively normal; EMCI = early mild cognitive impairment; GS = gradient synchronization; GSF = gradient synchronization fluctuation; LMCI = late mild cognitive impairment; MCI = mild cognitive impairment; PC = Pearson correlation; ROIs = regions of interest; SMC = subjective memory concerns.

Another question of interest is whether subjects in different cognitive groups exhibit differences in connectivity among specific pairs of brain regions. To address it, we performed Kruskal–Wallis tests for the 55 combinations of paired ROIs, with comparisons based on temporal PC and the proposed GS and GSF. To account for multiple comparisons, *p*-values were adjusted by Bonferroni correction. As illustrated in Figure 2, significant differences among the six cognitive stages were found using GS and GSF for all 55 pairs of ROIs, while no pervasive differences were found when using temporal PC. When employing two-sample Wilcoxon rank sum tests to compare 55 pairs of ROIs simultaneously in terms of (static) temporal PC (15), GS (9), and GSF (13) between subjects in different cognitive groups, again GSF was found to discriminate much better between the various cognitive groups than temporal PC and GS (see Figures S3–S17 in the online supplementary material).

Beyond static functional connectivity, the proposed synchronicity measures GS and GSF can also be leveraged for the analysis of dynamic functional connectivity. To study the dynamics in resting-state functional connectivity, one of the most commonly used approaches is sliding windows (Hutchison et al., 2013). Specifically, functional connectivity metrics are calculated using data points falling within windows of fixed length that are shifted across the time domain. Accordingly, we compared the performance of the dynamic temporal PC with dynamic counterparts of the proposed GS and GSF.

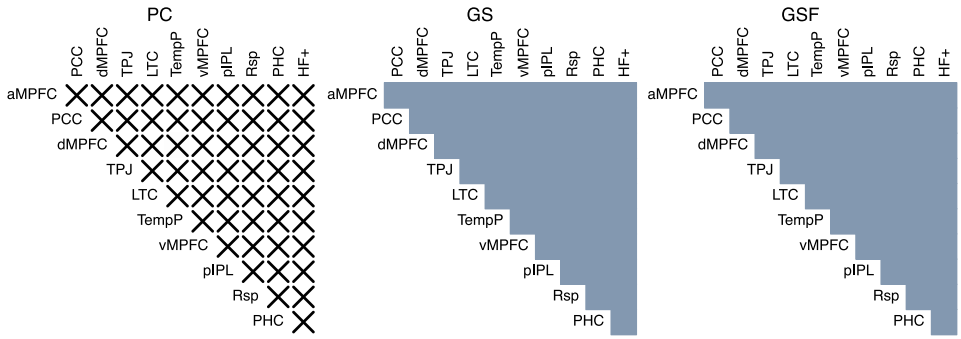

Figure 2. Kruskal–Wallis tests to compare 55 pairs of ROIs simultaneously in terms of (static) temporal PC (15) (left), GS (9) (middle), and GSF (13) (right) among the six cognitive groups, where significance at level 0.05 after Bonferroni adjustment is shown by filled squares and insignificance by crosses. GS = gradient synchronization; GSF = gradient synchronization fluctuation; PC = Pearson correlation; ROIs = regions of interest.

Table 8. *P*-values of Kruskal–Wallis tests to compare the averages over the 55 pairs of the 11 ROIs in Andrews-Hanna et al. (2010) of standard deviations of dynamic temporal PC (16), GS and GSF (17) among the six cognitive groups

Dynamic PC	Dynamic GS	Dynamic GSF
1.2×10^{-4}	5.2×10^{-72}	2.0×10^{-60}

Note. GS = gradient synchronization; GSF = gradient synchronization fluctuation; PC = Pearson correlation; ROIs = regions of interest.

The dynamic temporal PC of the pair (X_i, Y_i) is defined as

$$P^{\mathrm{dyn}}_{\mathcal{J},i}(s,\Delta) = \frac{\sum_{j=s}^{s+\Delta-1}\{X_i(t_j) - \bar{X}_i(s,\Delta)\}\{Y_i(t_j) - \bar{Y}_i(s,\Delta)\}}{\sqrt{\sum_{j=s}^{s+\Delta-1}\{X_i(t_j) - \bar{X}_i(s,\Delta)\}^2}\sqrt{\sum_{j=s}^{s+\Delta-1}\{Y_i(t_j) - \bar{Y}_i(s,\Delta)\}^2}}, \tag{16}$$

for $s = 1, \ldots, J - \Delta + 1$, where Δ is the window size, $\bar{X}_i(s,\Delta) = \Delta^{-1}\sum_{j=s}^{s+\Delta-1} X_i(t_j)$, and $\bar{Y}_i(s,\Delta) = \Delta^{-1}\sum_{j=s}^{s+\Delta-1} Y_i(t_j)$. The empirical dynamic GS $\widehat{R}^{\mathrm{dyn}}_{\mathcal{J},i}$ and dynamic GSF $\widehat{Z}^{\mathrm{dyn}}_{\mathcal{J},i}$ can be analogously defined over sliding windows as

$$\begin{aligned}
\widehat{R}^{\mathrm{dyn}}_{\mathcal{J},i}(s,\Delta) &= \sum_{j=s}^{s+\Delta-1}(t_j - t_{j-1})\mathrm{sign}(D_{j,X_i}D_{j,Y_i}),\\
\widehat{Z}^{\mathrm{dyn}}_{\mathcal{J},i}(s,\Delta) &= \#\{s+1 \le j \le s+\Delta-1 \mid D_{j-1,X_i}D_{j,X_i}D_{j-1,Y_i}D_{j,Y_i} < 0\}\\
&\quad + \#\{s \le j \le s+\Delta-1 \mid D_{j,X_i}D_{j,Y_i} = 0\},
\end{aligned} \tag{17}$$

where D_{j,X_i} and D_{j,Y_i} are defined as after equation (8). We adopt $\Delta = 15$, which represents measurements during a time interval of 45 s and quantify the variability of dynamic functional connectivity for (X_i, Y_i) by the standard deviations of $P^{\mathrm{dyn}}_{\mathcal{J},i}(s,\Delta)$, $\widehat{R}^{\mathrm{dyn}}_{\mathcal{J},i}(s,\Delta)$, and $\widehat{Z}^{\mathrm{dyn}}_{\mathcal{J},i}(s,\Delta)$, over $s \in \{1, \ldots, J - \Delta + 1\}$ (Choe et al., 2017; Hindriks et al., 2016).

Based on the averages over the 55 hub pairs of standard deviations of the three dynamic functional connectivity metrics, we performed Kruskal–Wallis tests and two-sample Wilcoxon rank sum tests to compare the various cognitive groups. Significant differences between the six cognitive groups were found for dynamic PC and dynamic GS as well as dynamic GSF (Table 8).

Table 9. *P*-values of two-sample Wilcoxon rank sum tests to compare the averages over the 55 pairs of the 11 ROIs in Andrews-Hanna et al. (2010) of standard deviations of dynamic temporal PC (16), GS and GSF (17) between the six cognitive groups

Pair of groups	Dynamic PC	Dynamic GS	Dynamic GSF
(CN, SMC)	0.50	$1.1 \times 10^{-12**}$	$2.0 \times 10^{-13**}$
(CN, EMCI)	0.042^{*}	$5.3 \times 10^{-25**}$	$1.4 \times 10^{-21**}$
(CN, MCI)	0.032^{*}	$3.6 \times 10^{-37**}$	$1.3 \times 10^{-20**}$
(CN, LMCI)	0.089	$5.2 \times 10^{-11**}$	$4.9 \times 10^{-13**}$
(CN, AD)	$5.5 \times 10^{-6**}$	$6.8 \times 10^{-22**}$	$1.1 \times 10^{-20**}$
(SMC, EMCI)	0.43	$1.8 \times 10^{-8**}$	$1.8 \times 10^{-6**}$
(SMC, MCI)	0.70	$5.5 \times 10^{-8**}$	$6.7 \times 10^{-10**}$
(SMC, LMCI)	0.27	$3.0 \times 10^{-4**}$	$2.7 \times 10^{-4**}$
(SMC, AD)	0.0041^{*}	$5.5 \times 10^{-17**}$	$2.5 \times 10^{-4**}$
(EMCI, MCI)	0.70	$4.3 \times 10^{-16**}$	$1.4 \times 10^{-14**}$
(EMCI, LMCI)	0.67	$7.1 \times 10^{-7**}$	$1.9 \times 10^{-8**}$
(EMCI, AD)	0.016^{*}	$3.9 \times 10^{-14**}$	$6.0 \times 10^{-10**}$
(MCI, LMCI)	0.57	$2.6 \times 10^{-6**}$	$7.1 \times 10^{-11**}$
(MCI, AD)	0.0021^{*}	$1.9 \times 10^{-19**}$	$4.5 \times 10^{-17**}$
(LMCI, AD)	0.20	$8.8 \times 10^{-10**}$	0.011^{*}

Note. Significance at level 0.05 for individual tests is marked by '*' and for multiple comparisons after the Bonferroni correction (i.e. less than $0.05/15 \approx 0.0033$) by ' **'. AD = Alzheimer's disease; CN = cognitively normal; EMCI = early mild cognitive impairment; GS = gradient synchronization; GSF = gradient synchronization fluctuation; LMCI = late mild cognitive impairment; MCI = mild cognitive impairment; PC = Pearson correlation; ROIs = regions of interest; SMC = subjective memory concerns.

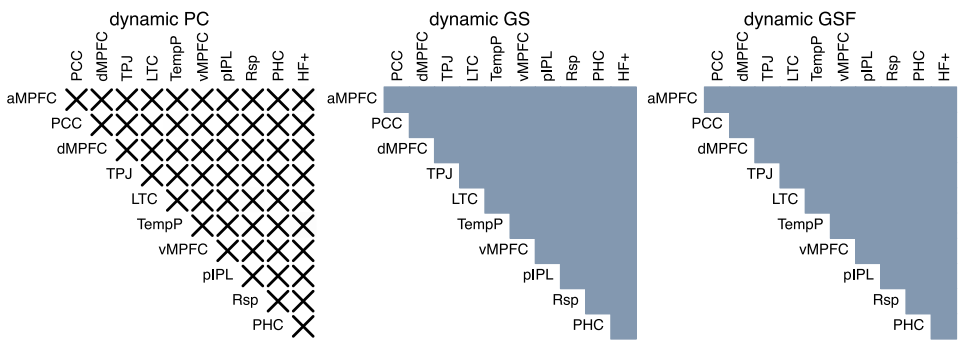

Figure 3. Kruskal–Wallis tests to compare 55 pairs of the 11 ROIs in Andrews-Hanna et al. (2010) simultaneously in terms of the standard deviations of dynamic temporal PC (16) (left), GS (middle), and GSF (right) (17) for the six cognitive groups, where significance at level 0.05 after Bonferroni adjustment is shown by coloured squares and insignificance by crosses. GS = gradient synchronization; GSF = gradient synchronization fluctuation; PC = Pearson correlation; ROIs = regions of interest.

Furthermore, dynamic GS and GSF distinguish many more pairs of ROIs than dynamic PC does (Table 9).

We also performed pair-wise Kruskal–Wallis tests and two-sample Wilcoxon rank sum tests for all 55 pairs with Bonferroni correction for multiple comparisons and found significant differences in terms of the variability of dynamic GS and GSF between the six cognitive groups, while dynamic PC found none (Figure 3). It emerged that variability of dynamic functional connectivity between many more pairs of ROIs differs significantly between subjects in different cognitive groups in

terms of GS and GSF but not for temporal PC (Figures S18–S32 in the online supplementary material). We repeated this analysis for the 20 ROIs identified by Buckner et al. (2009, Table 4, replicated in Table S8 in Section S4 in the online supplementary material), where similar findings emerged as for the analysis of the 11 ROIs in Andrews-Hanna et al. (2010). Results are provided in Tables S9–S12 and Figures S33–S64 in the online supplementary material. In addition, we constructed networks based on the proposed pGS and pGSF; see Section S5 in the online supplementary material.

6 Discussion

The proposed new measures, gradient synchronization (GS), and gradient synchronization fluctuation (GSF), measured as integrals and sign changes of $X'(t)Y'(t)$, complement established similarity measures such as PC, partial correlation (e.g. Marrelec et al., 2006), mutual information, and partial/conditional mutual information (e.g. Cassidy et al., 2014; Gretton et al., 2006; Salvador et al., 2010, 2007, 2005). In brain connectivity studies, mutual and partial mutual information are often applied in the frequency domain and hence reflect the dependence/similarity of paired random functions across different frequencies (e.g. Cassidy et al., 2014; Salvador et al., 2010, 2007, 2005), while the proposed measures focus on the similarity of temporal dynamics. Specifically, GS captures the average aggregated concordance and discordance of the change rates between random curves, while GSF provides a complementary measure of the stability of the gradient synchronization.

6.1 Application to fMRI data

The proposed measures were found to better distinguish different cognitive groups in the AD spectrum for the ADNI data compared to standard PC-based measures. Reduced connectivity between the posterior cingulate cortex (PCC) and the medial temporal lobe (MTL) structures was previously found for AD patients compared to normal controls (Greicius et al., 2004). Among the eleven regions in the default network identified in Andrews-Hanna et al. (2010), five belong to the MTL subsystem, namely ventral medial prefrontal cortex (vMPFC), posterior inferior parietal lobule (pIPL), retrosplenial cortex (Rsp), parahippocampal cortex (PHC), and hippocampal formation (HF^+). In contrast to temporal PC, GSF and variance of dynamic GS were found to significantly differ between PCC and MTL regions among the six groups (Figures 2 and 3) and also between CN and other groups (Figures S7, S19, and S21 in the online supplementary material). Reduced metabolism and perfusion in parietal lobes, medial temporal structures and the PCC in Alzheimer's (Bradley et al., 2002; Matsuda, 2001) may also be related to the deficient connectivity between these regions. Reduced connectivity between the temporal parietal junction and the PCC as well as the five MTL regions is partly identified by GSF and more fully by dynamic GS, but not by temporal PC (Figures 2 and 3; Figures S7, S19, and S21 in the online supplementary material).

6.2 Consistency, reliability, and comparison of different fMRI measures

Following other fMRI studies (e.g. Zhao et al., 2023), we evaluated the individual stability of the proposed GS and GSF as well as temporal PC based on first two consecutive fMRI scans taken from CN subjects such that second scans are taken within 12 months of the first scans. To measure individual stability, we computed the intra-class correlation (ICC) (Shrout & Fleiss, 1979). Considering a set of measures obtained from scan j and subject i for $j = 1, \ldots, k$ and $i = 1, \ldots, n$, denoted by $\{x_{ij}\}$, ICC is defined as

$$\mathrm{ICC} = \frac{\mathrm{BMS} - \mathrm{WMS}}{\mathrm{BMS} + (k-1)\mathrm{WMS}}.$$

Here, the between-target mean square (BMS) $\mathrm{BMS} = \sum_{i=1}^{n} k(\bar{x}_{i\cdot} - \bar{x}_{\cdot\cdot})^2/(n-1)$ and the within-target mean square (WMS) $\mathrm{WMS} = \sum_{i=1}^{n}\sum_{j=1}^{k}(x_{ij} - \bar{x}_{i\cdot})^2/\{n(k-1)\}$, and in our case, $k = 2$. Higher values of ICC imply that variability in the corresponding measure is primarily driven by the variation of subjects and that the measure is more stable for each subject. We computed ICC for each of the 55 pairs of ROIs in the default network identified in Andrews-Hanna et al. (2010)

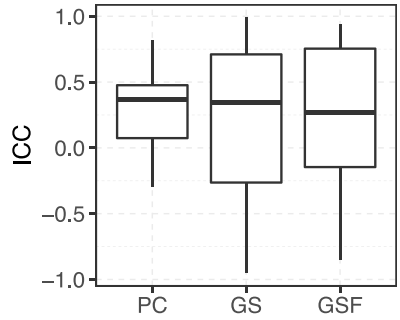

Figure 4. Boxplots of ICCs of temporal PC (15) (left), GS (9) (middle), and GSF (13) (right) evaluated over the 55 pairs of ROIs in the default network identified in Andrews-Hanna et al. (2010, Table S1). GS = gradient synchronization; GSF = gradient synchronization fluctuation; ICC = intra-class correlation; PC = Pearson correlation; ROIs = regions of interest.

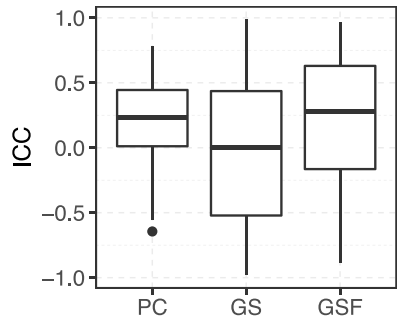

Figure 5. Boxplots of ICCs of temporal PC (15) (left), GS (9) (middle), and GSF (13) (right) evaluated over the 190 pairs of ROIs identified in Buckner et al. (2009, Table 4). GS = gradient synchronization; GSF = gradient synchronization fluctuation; ICC = intra-class correlation; PC = Pearson correlation; ROIs = regions of interest.

for each measure, temporal PC (15), GS (9), and GSF (13), respectively. As seen in in Figure 4, the three measures yield similar ICCs and hence have comparable subject stability, while the ICCs of GS and GSF have higher variation among pairs of ROIs. We repeated the analysis on the 190 pairs of ROIs identified in Buckner et al. (2009, Table 4) and found that subject stability of GSF is as good as that of PC, while the subject stability of GS is slightly inferior (Figure 5). Comparing ICCs of different functional connectivity measures evaluated over different sets of ROIs in Figures 4 and 5, we find that, similar to Zhao et al. (2023), within-network individual stability of PC and GS is higher than across-network individual stability, noting that the 11 ROIs identified in Andrews-Hanna et al. (2010) all lie in the default network, while the 20 ROIs identified in Buckner et al. (2009, Table 4) fall in multiple networks including the default network. For GSF, both within-network and across-network individual stability are high.

6.3 General applicability

While our approach was motivated by a study of functional connectivity of the human brain and we illustrate our methods in this paper with resting-state BOLD fMRI signals, the proposed methods are broadly applicable to multivariate functional data. Such data are increasingly encountered, for example in longitudinal studies with densely measured multivariate outcomes. One advantage of the segmentation technique is that it keeps track of local dynamic behaviour and both the average behaviour as well as the stability of synchronization over time can be quantified and studied. A noteworthy feature is that no smoothing parameter selection is required. By exploiting the functional features of the data, we avoid assumptions of temporal stationarity that have been imposed for signals in fMRI studies. The proposed methods are also suitable to quantify the temporal

variability of signals, including changes of synchronization patterns over time, e.g. in task-based fMRI studies.

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Data availability

Code for the implementation of the proposed methods is available at https://github.com/yqgchen/GS. Data used in preparation of this article were obtained from the ADNI database (https://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete list of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-conten/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Supplementary material

Supplementary material is available online at *Journal of the Royal Statistical Society: Series B*.

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