Reliability and sensitivity to altered hemodynamics measured with resting-state fMRI metrics: Comparison with $^{123}$I-IMP SPECT

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ABSTRACT

Blood oxygenation level-dependent (BOLD) contrast is sensitive to local hemodynamic changes and thus is applicable to imaging perfusion or vascular reactivity. However, knowledge about its measurement characteristics compared to reference standard perfusion imaging is limited. This study longitudinally evaluated perfusion in patients with steno-occlusive disease using resting-state functional MRI (rsfMRI) acquired before and within nine days of anterior circulation revascularization in patients with large cerebral artery steno-occlusive diseases. The reliability and sensitivity to longitudinal changes of rsfMRI temporal correlation (Rc) and time delay (Tdc) relative to the cerebellar signal were examined voxel-wise in comparison with single-photon emission CT (SPECT) cerebral blood flow (CBF) using the within-subject standard deviation (Sw) and intraclass correlation coefficients (ICCs). For statistical comparisons, the standard deviation (SD) of longitudinal changes within the cerebellum, the number of voxels with significant changes in the left middle cerebral artery territory ipsilateral to surgery, and their average changes relative to the cerebellar SD were evaluated. The test-retest reliability of the fMRI metrics was also similarly evaluated using the human connectome project (HCP) healthy young adult dataset. The test-retest time interval was 31 ± 18 days. Test-retest reliability was significantly higher for SPECT (cerebellar SD: $−2.59 \pm 0.20$) than for fMRI metrics (cerebellar SD: $R_c: −2.34 \pm 0.24$, $p = 0.04$; $T_{dc}: −2.19 \pm 0.21$, $p = 0.003$). Sensitivity to postoperative changes, which was evaluated as the number of voxels, was significantly higher for fMRI Tdc ($8.78 \pm 0.72$) than for Rc ($7.42 \pm 1.48$, $p = 0.03$) or SPECT CBF ($6.88 \pm 0.67$, $p < 0.001$). The ratio between the average Rc, Tdc, and SPECT CBF changes within the left MCA target region and cerebellar SD was also significantly higher for fMRI Tdc ($1.21 \pm 0.79$) than for Rc ($0.48 \pm 0.94$, $p = 0.006$) or SPECT CBF ($0.23 \pm 0.57$, $p = 0.001$). The measurement variability of time delay was also larger than that of temporal correlation in HCP data within the cerebellum ($t = −8.7$, $p < 0.001$) or in the whole-brain ($t = −27.4$, $p < 0.001$) gray matter. These data suggest that fMRI time delay is more sensitive to the hemodynamic changes than SPECT CBF, although the reliability is lower. The implication for fMRI connectivity studies is that temporal correlation can be significantly decreased due to altered hemodynamics, even in cases with normal CBF.

1. Introduction

Large cerebral artery steno-occlusive diseases are chronically progressive disorders (Gorelick et al., 2008). In patients suffering from these diseases, especially in cases undergoing revascularization surgery, cerebral blood flow (CBF) measurement is essential for evaluating the risk of future ischemic attack, selecting eligibility for revascularization therapy, and postoperative monitoring of changes (Andaluz et al., 2010; Juttukonda et al., 2021). Traditionally, most clinical perfusion imaging uses an exogenous contrast material or tracers such as iodium or xenon for computed tomography (CT) and gadolinium for magnetic resonance imaging (MRI), or radioactive tracers for positron emission tomography (PET) and single-photon emission CT (SPECT) (Wintermark et al., 2005). However, these studies are limited by the adverse effects of the contrast materials, higher costs, and radiation exposure, which are disadvantageous for managing diseases that often require follow-up. Non-invasive methods that exploit endogenous contrast materials, including blood oxygenation level-dependent (BOLD) imaging, could be a potential substitute to circumvent these limitations. Although it is most often used for functional MRI (fMRI) to infer neural activity, BOLD contrast is non-specifically sensitive to local hemodynamic changes (Nasrallah et al., 2015; Rostrup et al., 2000). Therefore, it is applicable for imaging perfusion or vascular reactivity under either task-controlled (Amemiya et al., 2012; Sierot et al., 2015; Tong et al., 2011) or resting-state (Amemiya et al., 2014; Christen et al., 2015a; Khalil et al., 2017; Lv et al., 2013; Siegel et al., 2016; Tong et al., 2017) conditions. In
resting-state fMRI (rsfMRI) studies, the temporal correlation of the time series is generally used to infer the strength of the functional "connectivity" between two regions (Biswal et al., 1995). However, the local hemodynamic status changes both the magnitude and time delay of fMRI signals (Amemiya et al., 2012; Qiao et al., 2017; Roc et al., 2006), thereby directly affecting their temporal correlation (Amemiya et al., 2014; Golestani et al., 2016; Siegel et al., 2016). The rsfMRI time delay measured using the global mean or similar signal as the reference signal has consistently confirmed that the delay is comparable to that in dynamic susceptibility contrast perfusion imaging in ischemic patients (Amemiya et al., 2014; Christen et al., 2015b; Lv et al., 2013) or in healthy controls (Amemiya et al., 2016; Tong et al., 2017), which most likely reflects the regional variance in the local hemodynamic responses (Amemiya et al., 2020). Theoretically, such fMRI metrics can be more sensitive to altered hemodynamics than CBF. This is because the blood transit time is delayed even under the condition where an increase in blood volume results in the successful preservation of normal CBF (Powers, 1991). Moreover, since BOLD contrast originates in the veins, the rs-fMRI time delay is amplified compared with the corresponding arterial transit time (Tong et al., 2017). However, due to a lack of studies examining the reliability of fMRI perfusion metrics or directly comparing them with a reference standard clinical examination, it remains unclear whether fMRI has an equivalent or even better reliability or sensitivity to longitudinal hemodynamic changes.

Understanding the characteristics of fMRI metrics, including the sources and patterns of measurement errors, not only helps improve fMRI perfusion imaging but would also contribute to improving fMRI methodology for assessing neural activity, since these share the same imaging and contrast mechanisms that rely on local hemodynamics. Therefore, this study examined the longitudinal characteristics of fMRI perfusion metrics, namely the temporal correlation coefficient and time delay computed voxel-wise by setting the average cerebellar time series as the reference signal, and compared with those of N-isopropyl-p-[123I]-iodoamphetamine (123I-Imp) SPECT-based CBF measurement during the perioperative period in patients undergoing anterior-circulation revascularization. Since there has been no study examining the reliability of these metrics, in addition to the main patient study, the test-retest reliability of the fMRI metrics was also assessed using the healthy subjects’ dataset acquired over consecutive days. We chose the HCP dataset that provides the highest quality data and is the subject of many studies so that the results can be related to those of other studies.

2. Methods

2.1. Theoretical simulation study

2.1.1. Dataset

To illustrate how the temporal correlation of two signals changes with altered hemodynamics that delay and decrease the magnitude of the signal, a simulation study was performed using an actual resting-state fMRI (rsfMRI) signal combined with a varied amount of simulated noise. The signal time course was originally from the WU-Minn HCP young healthy adults (ages 22–35) S1200 release data (https://www.humanconnectome.org/study/hcp-young-adult). The data of 100 runs from 50 subjects (32 women; average age: 29.4 ± 3.3 years) who underwent 15 min 3.0-T rsfMRI sessions (with a repetition time [TR] of 0.72 s) without quality control issues, whose mean framewise displacement was less than 0.2 mm, which had been minimally processed (Glasser et al., 2013), were subjected to the following analyses.

2.1.2. Simulation

After subject-level independent component analysis (ICA) noise reduction (sICA + FIX) (Griﬃanti et al., 2014; Salimi-Khorshidi et al., 2014), spatial smoothing with a Gaussian kernel with an 8 mm full-width at half-maximum, and linear trend removal and band-pass filtration at 0.01–0.1 Hz concatenated data having 120,000 time points (1200 frames × 50 subjects × 2 phase-encoding directions) were subjected to group-wise spatial ICA. The first ICA component, primarily representing the medial visual cortex’s time series $S(t)$, was used. The data were up-sampled to a resolution of 0.072 s (1/10 TR). A pair of random Gaussian noises, N1 and N2, with a mean of 0 and lasting for 1,200,000 time points, were generated and subjected to the band-pass filtering at 0.01–0.1 Hz. N1 and N2 were scaled to have a standard deviation of 1/5, 2/5, and 3/5 of the signal component, $S$. The time series were de-concatenated into 100 segments to perform the analysis for each run separately. Two time series, $X1$ and $X2$, having the same signal and different noise components, were prepared. The vascular effect was examined by changing the magnitude $m$ and time delay $\delta$ of the signal component $S$ only for $X1$ as follows:

$$X1 = m \cdot S(t - \delta) + k \cdot N1$$

$X2 = S(t) + k \cdot N2$

(1)

(2)

where $k$ represents the noise magnitude factor. $X1$ was arranged on a $60 \times 60$ grid, with the magnitude $m$ and time delay $\delta$ varied progressively along the $x$- and $y$-axes from 0 to −80% and 0 to 6 seconds in equal decrements and increments, respectively (Fig. 1). For each of the $n (= 100)$ runs, Pearson’s correlation coefficients $R$ between $X1$ and $X2$ were computed for $i \times j$ time series and averaged across $n$ runs for each noise factor $k$ as follows:

$$R_k(i, j) = \frac{1}{n} \sum_{i=1}^{n} \text{corr}(X1_{ij}, X2_{ijk})$$

$i, j = 1 \ldots 60, k = 1, 2, 3$ (3)

2.2. Imaging study

2.2.1. HCP dataset

The test-retest reliability of the fMRI metrics was also assessed using the minimally-processed HCP datasets (Glasser et al., 2013) acquired over consecutive days (HCP day 1 and 2) for the same 50 subjects as the simulation study. The fMRI metrics were measured by setting the average whole-brain gray matter signal time series as the reference signal and by computing the temporal correlation using Pearson’s correlation coefficient (R) and the time delay (TD) of each voxel’s time series, as in previous studies (Amemiya et al., 2014, 2016, 2019, 2020) (Fig. 2); briefly, after spatial smoothing with a Gaussian kernel with a full-width at half-maximum of 8 mm, linear trend removal, and band-pass filtering at 0.01-0.1 Hz, the TD was computed as the relative time lag $t$ that gives the best positive fit between each voxel’s time series and the time-shifted ($\pm$ 6 sec or ± 8.3 TR) reference signal using cross-correlation analysis (Amemiya et al., 2014, 2016, 2019, 2020). All data were up-sampled to a resolution of 0.14 sec (1/5 TR) for the analysis (Tong et al., 2017). For each fMRI dataset, mean frame-wise displacement was computed using the motion parameters following (Power et al., 2012).

2.2.2. Patient population

All procedures complied with the Declaration of Helsinki, and our university’s institutional review board approved the study. All patients provided written informed consent before the study. The eligible population included 12 consecutive patients (8 women; average age: 48.6 ± 14.1 years) with moyamoya disease ($n = 10$) or atherosclerotic steno-occlusive disease ($n = 2$) who were undergoing SPECT and MRI studies for surgical revascularization at our university hospital between February and July 2021. The inclusion criteria were a confirmed diagnosis of the disease based on an imaging study (Ihara et al., 2022; Kuroda et al., 2022) and availability of SPECT and fMRI data both before and within 14 days after surgery, which served as the test and retest data, respectively. The exclusion criteria were contraindications to the examinations. No patients were excluded. The test-retest time interval was $31 \pm 18$ days for fMRI and $37 \pm 23$ days for SPECT. The SPECT
dataset was the same as the one used in our previous studies comparing arterial spin labeling perfusion imaging protocols against SPECT CBF measurement (Amemiya et al., 2021, 2022).

2.2.3. SPECT acquisition

SPECT data were acquired starting from 25 min after intravenous injection of 222 MBq (6 mCi) N-isopropyl-p-[123]I-iodoamphetamine (123I-IMP) (Podreka et al., 1989) for 32 min using a triple-head gamma camera (GCA-9300R, Toshiba, Tokyo, Japan) equipped with low-energy high-resolution fan-beam collimators with 150 sec/cycle and 12 repeats. Image reconstruction was performed on a workstation (Vitrea Ver7.3, Toshiba, Tokyo, Japan) using the 3D ordered subset expectation maximization algorithm (Hudson and Larkin, 1994). Attenuation correction was performed using Chang’s method (Chang, 1978). The final images were reconstructed into 1.72-mm 3D-isotropic voxels using a 128 x 128 grid.

2.2.4. MR imaging

For rsfMRI, gradient-echo echo-planar images using a simultaneous multi-slice imaging technique and high-spatial-resolution T1-weighted images with an MP-RAGE sequence (repetition time [TR] = 9.5 ms, echo time [TE] = 3.8 ms, spatial resolution = 0.94 x 0.94 x 1 mm) were acquired with a whole-body 3.0-T MR unit (Signa Premier; GE Healthcare, Waukesha, WI) using a 48-channel phased-array head coil. The fMRI parameters were TR = 1000 ms; TE = 25.0 ms; flip angle = 53°; matrix size = 104 x 104; field of view (FOV) = 208 x 208 mm with 100% phase sampling and no interpolation; 3 mm thick sections with no gap; 48 sections; 305 frames; a multiband factor of 4; and a parallel imaging factor of 2. The choice of the multiband factor was based on a previous study comparing the temporal signal-to-noise ratio of the data (Todd et al., 2016). All subjects were instructed to lie still and remain awake during the fMRI scan with their eyes open.

2.2.5. Data processing

All fMRI data were processed using SPM12 (Wellcome Department of Cognitive Neurology, London, United Kingdom) and in-house scripts implemented in MATLAB 9.12.0 (MathWorks, Inc., Natick, MA, United States). After discarding the first five volumes to allow for T1 equilibration effects, the data were corrected for differences in acquisition time between slices, realigned to the first frame to account for movement artifacts, spatially aligned with anatomic T1-weighted images, and then normalized to the Montreal Neurological Institute (MNI) space via the unified segmentation approach (Ashburner and Friston, 2005) using the T1-weighted images and spatially smoothed with a Gaussian kernel with a full-width at half-maximum of 8 mm to obtain a smoothing radius comparable to that of the SPECT CBF as confirmed by 3dFWHMx of the AFNI software (https://afni.nimh.nih.gov/). After linear trend removal and band-pass filtering at 0.01-0.1 Hz, six rigid-body head motion parameters were regressed out from the data using the general linear model. The time delay and temporal correlation were computed as in the case.

Fig. 1. Resting-state fMRI Simulation Analysis. The top row (A–C) illustrates how the temporal correlation (Pearson’s correlation coefficient) between the two same signals changes with the time delay (y-axis) and magnitude decrease (x-axis) of the signal component in the presence of different levels of noise (x1, x2, and x3). The value represents the average correlation coefficients of the one-hundred runs. The middle row (D–F) shows examples of the two synthesized time series X1 and X2, while the bottom row (G–I) shows each component comprising the time series separately: Signal, N1, and N2. The green and cyan asterisks in the top row indicate the correlation coefficient of 0.85 and 0.72 obtained with 2.2- and 3.4-second delays or a 63% and 79% decrease of the signal magnitude (A), respectively. The same effect was obtained by doubling (B) and tripling (C) the noise of the two time series, respectively.
of the HCP data, but with the reference signal set as the average of the cerebellar time series and thus referred to as TDC and Rc. The mean frame-wise displacement of the fMRI scans (Power et al., 2012) was also computed.

SPECT images were also normalized to the MNI template by using SPM12. All fMRI and SPECT data were resampled to 2-mm isotropic voxels. Since the MNI template is not horizontally symmetrical, all normalized fMRI and SPECT data were further subjected to symmetrization using a symmetric template constructed by averaging the original and horizontally flipped MNI templates. Using the original MNI template as the source image and the symmetrized MNI template as the target image, spatial transformation parameters were computed and applied to the normalized fMRI and SPECT data for the symmetrization. For participants who underwent surgery on the right side, all symmetrized data were flipped in a left-to-right direction so that the left hemisphere was used to examine sensitivity to postoperative changes (Fig. 2). All SPECT CBF maps were scaled to the average value within the cerebellar mask created by thresholding the individual tissue map with a ≥ 10% probability of being gray matter. In order to compare differently measured data, all fMRI and SPECT data were scaled with the proportion of maximum scaling method (Little, 2013), which transforms each scale to a metric from 0 to 1 without changing the relative distribution of each value X, by setting the minimum and maximum values of the observations \( X_{\text{min}} \) and \( X_{\text{max}} \) to 0 and 1, respectively, and by setting the new value \( X' \) as follows:

\[
X' = \frac{X - X_{\text{min}}}{X_{\text{max}} - X_{\text{min}}}
\]  

Unlike Z-scoring, it transforms each scale without distorting the ratio of the longitudinal difference as long as the minimum and maximum values are fixed. Thus, we employed fixed max and minimum values for each metrics as follows: -1 and 1 for correlation coefficients, -6 and 6 for time lag, and 0 and 2.1 (maximum value of all data) for SPECT relative CBF.

2.2.6. Statistical analyses

For each measurement of fMRI and SPECT, the within-subject standard deviation (Sw) (Bland and Altman, 1996) representing the average group variability of each subject’s values on repeated testing was computed voxel-wise:

\[
Sw^2 = \frac{1}{2n} \sum d_i^2
\]  

where \( n \) is the number of subjects, and \( d_i \) is the difference between pre- and postoperative measurements for each subject. As another reliability index, intraclass correlation coefficients (ICCs) based on a
single-measurement, absolute-agreement, two-way mixed-effects model were also computed using the following formula:

$$ICC = \frac{MS_R - MS_E}{MS_R + (k - 1)MS_E + \frac{2k}{n}(MS_C - MS_E)}$$ (6)

where $MS_R$ is the mean square for rows (between-subjects mean square), $MS_E$ is the mean square for error, $MS_C$ is the mean square for columns (within-subjects mean square), $n$ is the number of subjects, and $k$ is the number of repeated measurements (Shrout and Fleiss, 1979). Histogram analyses were performed for each ICC map within the cerebellum and whole-brain gray matter for HCP data with a histogram bin width of 0.005 and a range of −1.0 to 1.0. The ICCs were interpreted using the criteria proposed by Cicchetti (1994), where an ICC of < 0.40 is considered poor, 0.40–0.59 is fair, 0.60–0.74 is good, and 0.75–1.00 is excellent.

As the reliability metric, the standard deviation of pre- and postoperative difference within the cerebellum (or day 1 and day 2 difference within the cerebellum or whole-brain gray matter for the HCP study) was calculated for each subject for each measurement. For the patient data, sensitivity to postoperative changes was examined in the left middle cerebral artery (MCA) territory by counting the number of voxels with a postoperative difference 2.77 times larger than the average cerebellar Sw (Bland and Altman, 1996). The ratio between the average changes within the left MCA target region and the standard deviation within the cerebellum was also used for statistical comparison. The multiple metrics were compared using a one-way repeated measures ANOVA followed by Bonferroni-corrected paired t-tests.

The across-subjects correlation of the standard deviations of Rc and TDC postoperative changes within the MCA territory (or day 1 and day 2 difference of R and TD within the whole-brain gray matter for HCP study) was evaluated. Correlation between the changes of the two metrics was tested by computing the Pearson’s correlation coefficients for each subject that was Fisher’s Z transformed to be subjected to the across-subjects one-sample t-test against the null hypothesis of no correlation. The effect of motion on the measurement reliability and sensitivity to longitudinal CBF changes was also examined using the motion index, defined as the larger of the pre- and postoperative (or day 1 and day 2) mean frame-wise displacement of the fMRI scans.

Statistical analyses were performed using MATLAB version 9.12.0 (MathWorks, Natick, MA) and SPSS 22 software (IBM Corp., Armonk, NY). $P$ values less than 0.05 were considered statistically significant. The Shapiro–Wilk test was used to test the normality of the measured variables. If a distribution deviated from normal, statistical analyses were performed based on log-transformed data.

3. Results

3.1. Simulation study

The simulation demonstrates how the correlation coefficient between the same two signals decreases with varying degrees of hemodynamic changes under the three conditions with different noise levels (Fig. 1). TDS of 2.2 and 3.4 s alone decreases the Pearson’s correlation coefficient from 0.96 ± 0.03 (noise level 1 without delay or magnitude decrease) to 0.85 ± 0.03 and 0.72 ± 0.06, which is equivalent to reducing the magnitude of the signal by 63% and 79%, or to doubling and tripling the noise of the two time series, respectively.

![Fig. 3. Test-retest reliability of the HCP resting-state fMRI Metrics. As an index of the test-retest reliability, the average standard deviation (SD) of the day 1 and day 2 fMRI metrics, temporal correlation (R) and time delay (TD), were measured within the cerebellum (A) and the whole-brain (B) gray matter. The reliability of R was significantly higher than that of TD (A and B). The average frame-wise displacement of the day 1 and day 2 data did not significantly differ (C). Intraclass correlation coefficients (ICCs) measured within the cerebellum (D) and whole-brain (E) gray matter showed that, on average, R’s ICCs were higher. There was a negligible correlation between the variance of R and TD (F).](image-url)
3.2. Reliability of HCP normal subject datasets

The mean frame-wise displacement of the scans from day 1 (0.13 ± 0.02 mm) and day 2 (0.13 ± 0.02 mm) did not differ significantly \((t = -1.63, p = 0.11)\) (Fig. 3). The voxel-wise Sw, the average measurement difference, the ICC maps, and the average of each fMRI measurement are shown in Fig. 4. The average non-scaled R and TD within the whole-brain gray matter were as follows: R \((\text{day 1}, r = 0.51 ± 0.08; \text{day 2}, r = 0.52 ± 0.09, t = -1.75, p = 0.089)\), TD \((\text{day 1}, -0.098 ± 0.10 \text{ sec}; \text{day 2}, -0.11 ± 0.089 \text{ sec}, t = 1.35, p = 0.18)\). Variability of the fMRI metrics within the cerebellum or in the whole-brain gray matter (scaled, log-transformed SD) showed significantly smaller inter-individual variability for R \((\text{cerebellum}, -2.59 ± 0.24; \text{whole brain}, -2.64 ± 0.18)\) compared to TD \((\text{cerebellum}, -2.39 ± 0.36, \text{whole brain}, -2.15 ± 0.25)\) \((\text{cerebellum} t = -8.7, p < 0.001; \text{whole brain}, t = -27.4, p < 0.001)\) (Figs. 3 and 4, Table 1). The ICCs also showed a wider distribution of TD, which centered on a lower value than that of R (Figs. 3 and 4, Table 1). A statistically significant but negligible level of correlation was seen between R and TD \((\text{day 1}, Z = -0.070 ± 0.055, t = -12.9, p < 0.001; \text{day 2}, Z = -0.077 ± 0.051, t = -14.9, p < 0.001)\). The correlation between R and TD’s test-retest variance was also statistically significantly but at the negligible levels \((\text{whole brain}, Z = -0.039 ± 0.16, t = -2.51, p = 0.014)\) (Fig. 3). No significant correlation was found between the motion index and the measurement variability of the fMRI metrics for R \((\text{cerebellum} r = 0.027, p = 0.79; \text{whole brain}, r = 0.082, p = 0.42)\) or TD \((\text{cerebellum} r = 0.077, p = 0.45; \text{whole brain}, r = 0.064, p = 0.52)\).

3.3. Patient study

3.3.1. Patient demographics

Patient demographics and a summary of the data are provided in Table 2. Postoperative fMRI and SPECT scans were performed 5.5 ± 1.6 (range: 3–9) days after the surgical procedure. Postoperative SPECT and fMRI studies were performed on the same day for all patients.

![Fig. 4. Voxel-wise Sw, Average Measurement Difference, and ICC Maps of the HCP resting-state fMRI. Voxel-wise within-subject standard deviation (Sw) images showed that test-retest variability was smaller in the gray matter compared with that of the white matter for both temporal correlation (R) and time delay (TD). Day 2 minus day 1 images (Delta) also showed that the measurement difference was generally small within the gray matter. The intraclass correlation coefficients (ICCs) showed that measurement reliability was higher for TD than R near the larger veins and venous sinuses but lower in the other regions. Average day 1 and day 2 R images showed a positive correlation across the gray matter, while TD showed a spatiotemporal pattern similar to that of perfusion time delay. Data are not scaled. The numbers within the parentheses for Sw and Delta images correspond to the values scaled using the proportion of the maximum scaling method. All data are shown in the radiological view.](image-url)
Preoperative SPECT and fMRI studies were performed on the same day in 7 patients and within 1 day (n = 1), 2 days (n = 2), 5 days (n = 1), and 2 months (n = 1) in the others. There were no postoperative signs of hyperperfusion syndrome or neurological complications.

3.3.2. Characteristics of fMRI and SPECT measurement in patient study

The mean frame-wise displacement of the fMRI scans was as follows: pre, 0.15 ± 0.04 mm; post, 0.16 ± 0.06 mm. The two measurements did not significantly differ (t = 0.57, p = 0.58) (Fig. 5). Compared with the HCP data, motion was larger for the patient data (scan1, t = 4.99, p < 0.001; scan 2, t = 4.10, p < 0.001). The pre- and postoperative average non-scaled Rc and TDc values within the whole-brain gray matter were as follows: pre, 0.36 ± 0.16; post, 0.36 ± 0.15. TDc, pre, 1.67 ± 0.96 s, post, 1.41 ± 0.92 s or SPECT CBF, pre 0.97 ± 0.21; post, 0.97 ± 0.22. Pre- and postoperative average non-scaled TDc values within the left MCA territory (non-scaled) significantly differed (pre, 2.53 ± 1.90; post, 1.10 ± 1.47, t = 4.47, p = 0.001), while they did not significantly differ for Rc (pre, 0.26 ± 0.22, post, 0.33 ± 0.14, t = −0.17, p = 0.19) or SPECT CBF (pre 0.97; post, 0.97, t = 1.22, p = 0.25). The average maps of pre- and postoperative fMRI measurements and their difference are shown in Figs. 6 and 7 and Table 2. Pre-operative average Rc and TDc maps showed reduced temporal correlation and signal delay in the bilateral anterior circulation territory (Fig. 6, Pre). After unilateral revascularization, Rc increased and TDc decreased primarily in the left MCA territory. Similar changes were also observed in the contralateral watershed areas (Fig. 6, Delta). The SPECT CBF maps showed subtle changes between the pre- and postoperative measurements in the left MCA territory, but not in the other regions (Fig. 6, Delta).

3.3.3. Reliability and sensitivity to postoperative changes

Voxel-wise Sw and ICC maps of fMRI and SPECT measurements are shown in Figs. 6 and 7, respectively. The test-retest variability within the cerebral was significantly lower for SPECT CBF (−2.59 ± 0.20) than the fMRI temporal correlation (Rc, −2.34 ± 0.24, p = 0.04) or time delay (TDc, −2.19 ± 0.21, p = 0.003) (Fig. 5, Table 2). A significant difference was also observed between the variability of TDc and Rc (p = 0.03) (Fig. 5, Table 2). The cerebellar variability of Rc was significantly larger than that of the HCP data (t = 3.64, p < 0.001). In contrast, the variability of TDc was not significantly different between the two groups (t = 1.43, p = 0.15) (Fig. 5, Table 2).

Sensitivity to postoperative changes in the left MCA territory evaluated as the number of voxels with significant postoperative change, was significantly higher for fMRI TDc (8.78 ± 0.72) than Rc (7.42 ± 1.48, p = 0.03) or SPECT CBF (6.88 ± 0.67, p = 0.001) (Fig. 5, Table 2). The ratio between the average Rc, TDc, and SPECT CBF changes within the left MCA target region and cerebellar SD was also significantly higher for fMRI TDc (1.21 ± 0.79) than Rc (0.48 ± 0.94, p = 0.006) or SPECT CBF (0.23 ± 0.57, p = 0.001). The ICC maps and histogram analyses showed more voxels with higher ICs in fMRI Rc and SPECT CBF than in fMRI TDc, indicating higher reliability for fMRI Rc and SPECT CBF measurements than those of fMRI TDc (Fig. 5, Table 2). TDc and Rc variability within the cerebellum was significantly correlated (Pearson’s R = 0.72, p = 0.008). Postoperative changes in TDc and Rc values within the left MCA territory were also significantly correlated (Z = −0.23 ± 0.14, p < 0.001).

3.3.4. Effect of motion on reliability and sensitivity to postoperative changes

The motion index was significantly positively correlated with the variability of Rc in the cerebellum (R = 0.60, p = 0.04), but not with
that of TDC ($R = 0.46$, $p = 0.14$). The motion index was significantly negatively correlated with the sensitivity of Rc to postoperative changes, which was measured as the relative mean value changes ($R = -0.64$, $p = 0.024$), but not with that of TDC ($R = -0.32$, $p = 0.31$) or the number of voxels with significant changes of Rc ($R = -0.43$, $p = 0.16$) and of TDC ($R = -0.32$, $p = 0.31$).

4. Discussion

In this study, we examined the test-retest reliability and sensitivity to hemodynamic changes of the two fMRI metrics in patients undergoing a revascularization surgery and compared the results with those of SPECT CBF. Using the measurement within the cerebellum as the reference signal, we showed that while the reliability was significantly lower for fMRI than SPECT, the sensitivity to postoperative changes was higher for fMRI TDC and equivalent for fMRI Rc.

Consistent with previous studies, the global mean signal of the rsfMRI showed a positive correlation with each voxel’s signal throughout the cerebral gray matter in healthy subjects, with a time delay similar to that of vascular perfusion (Amemiya et al., 2016, 2019, 2020; Tong et al., 2017, 2019). Although the source of this widespread ubiquitous signal is still controversial (Amemiya et al., 2020; Drew, 2019; Liu et al., 2017; Tong et al., 2019), these findings suggest that the low-frequency fluctuations mainly result from a phenomenon triggering the vascular response throughout the brain, rather than a locally confined event or motion artifact. Therefore, it can serve as an ideal reference signal to measure the effect of hemodynamic changes throughout the whole brain. In the patient study, we used the average cerebellar time series as the reference signal, since the patients were suffering from a steno-occlusive disease of the anterior circulation. This might have introduced some measurement errors due to a larger noise in the reference signal expected to reside in the average cerebellar signal than in the global mean signal. Nevertheless, both the temporal correlation and time delay could indicate the hemodynamic changes within the target area of the left MCA territory. The several seconds of BOLD signal delay seen in the MCA territory significantly decreased postoperatively, with a moderate recovery of temporal correlation.

As the simulation study showed, several seconds of signal delay could significantly decrease the time series correlation, even if the signal magnitude remained the same. Therefore, in theory, BOLD fMRI signal correlation can also reflect hemodynamic impairment, even when autoregulatory vasodilatation or increases in tiny collaterals maintain normal blood flow by increasing the blood volume. This is known as the Powers Stage I (Powers, 1991) condition, which describes the state of hemodynamic changes often found in patients suffering from chronic large cerebral artery steno-occlusive diseases. Indeed, although not statistically significant, Rc within the left MCA territory increased postoperatively, which was significantly correlated with the decrease in delay. However, the sensitivity of Rc to the postoperative hemodynamic changes was significantly lower than that of TDC and equivalent to that of SPECT CBF. As we confirmed in this study, it is likely that the larger variability of Rc compared to SPECT CBF prevented the former from being more sensitive than the latter. One important factor causing the variability in the patient data was the effect of motion. For the HCP data, the effect of
Fig. 6. Voxel-wise Sw, Average Measurement Difference, and ICC Maps of the Patient Data. Voxel-wise within-subject standard deviation (Sw) images showed a larger variability of fMRI time delay (TDC) than that of temporal correlation (Rc) or single-photon emission CT (SPECT) cerebral blood flow (CBF) not only within the target, left middle cerebral artery (MCA) perfusion territory but in other regions. Post- minus pre-operative images (Delta) showed an increase of Rc and shortening of TDC within the left MCA territory, while the corresponding change was less clear for SPECT CBF. The intraclass correlation coefficients (ICCs) showed higher measurement reliability in the gray matter for all three data groups. Average pre- and postoperative Rc images (Pre and Post) showed a positive correlation across the gray matter, while TD showed a prominent signal delay within the bilateral MCA. Data are not scaled. The numbers within the parentheses for Sw and Delta images correspond to the values scaled using the proportion of the maximum scaling method. All data are shown in the radiological view.
motion was not significantly correlated with the reliability of the R and TD, which agrees with a previous study comparing the effect of motion between groups of data with a mean framewise displacement larger and smaller than 0.1 mm (Noble et al., 2017). Although the mean framewise displacement was less than 0.2 mm in the patient data, they were still larger than those of the HCP data and had a significant positive correlation with the cerebellar variability of the fMRI metrics. The intersession reliability of rsfMRI has been shown to increase with increasing scan length, plateauing at 9–12 min or longer in a healthy-subject study (Birn et al., 2013). This was due to the increases in both the number of time points and the scanning duration (Birn et al., 2013). For the present patient study, although the number of the time points could be increased by using a simultaneous multi-slice imaging technique, a longer scan time for rsfMRI in the perioperative patients was practically difficult. Therefore, the shorter scan time of five minutes was likely another reason for its reduced reliability compared with that of the HCP data acquired in fifteen minutes. Other possible factors are artifacts from the metal plate and air bubbles near the surgical site in the postoperative images that could have attenuated the signal magnitude, thereby directly decreasing the temporal correlation.

As for the time delay, although both the patients’ and the healthy subjects’ data showed that TD’s variability was significantly higher than that of R, TD’s sensitivity was even higher compared with R and SPECT, indicating that the effect of the hemodynamic changes on signal delay was large enough to overcome its larger measurement variability. Empirically, the temporal parameters of perfusion imaging are known to provide higher sensitivity than CBF to altered hemodynamics associated with a higher vulnerability to future infarction (Zaroweb et al., 2019). They also have a high concordance even among the different imaging methods (Campbell et al., 2012). Therefore, it is usually the temporal parameters, such as the time-to-maximum of contrast-enhanced perfusion imaging, that are used to indicate the perfusion deficits corresponding to the penumbra in acute stroke studies (Campbell et al., 2019; Demeestere et al., 2020). The highest sensitivity of TDc in this study is in line with these findings and those of a previous task fMRI study, confirming that the BOLD signal time delay provides a higher specificity to indicate the hemodynamic impairment than the BOLD signal magnitude (Amemiya et al., 2012). This likely reflects the physiological mechanism of the metrics. While CBF is determined by the combination of the transit time, vessel diameter, and vascular density (i.e., blood flow = blood volume/mean transit time), whose stability is maintained via cerebral autoregulation (Paulson et al., 1990), the blood transit time is solely dependent on the diameter of the arteries, which increase resistance as they become smaller, as long as the perfusion pressure remains the same.

To enhance the temporal correlation between the reference signal and each voxel’s time series, we avoided applying regression of any type of BOLD signal for this study. As a previous study confirmed, the BOLD signal time delay has a similar spatiotemporal pattern regardless of the cause of the hemodynamic response (Amemiya et al., 2020). Regression of the BOLD signal was, therefore, expected not only to reduce the temporal correlation but also affect the time delay computation. Indeed, the subject-level ICA noise reduction (siCA + FIX) applied to the same dataset significantly decreased the temporal correlation R, the measurement reliability of R and TD, and the ICC of R and TD (Supplementary Material). These findings are consistent with previous studies showing that the global signal regression decreased the test-retest reliability of the rsfMRI studies (Guo et al., 2012; Noble et al., 2019; Parkes et al., 2018; Shirer et al., 2015; Song et al., 2012), presumably because of the loss of the shared component. While such a denoising step might be indispensable depending on the aim of the study, it is important to note that it can mask the effect of the hemodynamics rather than get rid of it. The resultant signals might appear to have a more negligible effect from the changes in hemodynamics, as the FIX-denoised data in this study showed. However, simple regression of a signal component never eliminates the hemodynamic effect embedded in each component. On the contrary, it might be further complicated by the fact that regression of the shared component artificially distorts
the connectivity measurement (Murphy et al., 2009). Even in healthy subjects, such an effect is exacerbated in the presence of the signal time lag (Erdogan et al., 2016), which could be another possible reason accounting for the reduced measurement reliability of the FIX-denosed data in this study or the heterogenous and incongruent results of the rsfMRI studies in ischemic patients (Fischer et al., 2022).

There are some technical considerations to be taken into account when interpreting the results. Firstly, to compare data with different measurement units, we used the proportion of the maximum scaling method. This was to avoid introducing a bias in the longitudinal comparison (Moeller, 2015). Although the choice of scaling method might affect the comparison of the reliability, the sensitivity analysis using the patient data does not depend on the scaling method. Secondly, the sample size of the patient study was small due to the limited number of patients undergoing revascularization surgery. Nevertheless, the significant difference between rsfMRI TD and SPECT was confirmed. This is likely due to the effect size, which was large enough to provide visible changes in postoperative rsfMRI metrics even at the single-patient level. Finally, the interval between pre- and postoperative scans was longer for SPECT in two patients. Nevertheless, the results remained the same without these two for both the test-retest variability and sensitivity analyses.  

5. Conclusions

While the test-retest reliability of rsfMRI perfusion metrics was smaller than that of SPECT CBF, the sensitivity to subtle postoperative hemodynamic changes in asymptomatic patients suffering from large cerebral artery steno-occlusive diseases was larger for fMRI TD and equivalent for fMRI R compared with SPECT CBF. The implication for fMRI connectivity studies is that temporal correlation can be significantly decreased due to altered hemodynamics, even in cases with normal CBF.

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Code and data availability statement

Code is available on GitHub (https://github.com/amemiyas/ 
rsfMRI). Raw patient data that support the findings of this study are available from the corresponding author, S.A., upon reasonable request due to requirements of formal permission from the institutional review board. The healthy subjects’ data used in this study are openly available at https://www.humanconnectome.org/.

Declarations of Competing Interest

none.

Credit authorship contribution statement

Shiori Amemiyas: Conceptualization, Methodology, Software, Formal analysis, Writing – original draft. Hidemasa Takao: Resources, Writing, review & editing. Yusuke Watana: Data curation, Writing – review & editing. Satoru Miyawakis: Resources, Writing – review & editing. Satoshi Koizumi: Resources, Writing – review & editing. Nobuhito Saito: Resources, Writing – review & editing. Osamu Abe: Resources, Writing – review & editing.

Data Availability

Data will be made available on request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.116/j.neuroimage.2022.119654.

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