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Resting-state functional MR imaging identifies cerebrovascular reactivity impairment in patients with arterial occlusive diseases: A pilot study.

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Abstract:	BACKGROUND: The development of non-invasive approaches for identifying hypoperfused brain tissue at risk is of major interest. Recently, the temporal-shift (TS) maps estimated from resting-state blood oxygenation level-dependent (BOLD) signals have been proposed for determining hemodynamic state. OBJECTIVE: To examine the equivalency of TS map versus cerebrovascular reactivity (CVR) map from acetazolamide-challenged single-photon emission computed tomography (SPECT) in identifying hemodynamic impairment in patients with arterial occlusive diseases. METHODS: Twenty-three patients with arterial occlusive diseases who underwent SPECT were studied. With a recursive TS analysis of low-frequency fluctuation of the BOLD signal, a TS map relative to the global signal was created for each patient. The voxel-by-voxel correlation coefficient was calculated to examine the image similarity between TS and SPECT-based cerebral blood flow (CBF) or CVR maps in each patient. Furthermore, simple linear regression analyses were performed to examine the quantitative relationship between the TS of BOLD signals and CVR in each cerebrovascular territory. RESULTS: The within-patient, voxel-by-voxel comparison revealed that the TS map was more closely correlated with SPECT-CVR map ([Z(r)] = 0.42 ± 0.18) than SPECT-CBF map ([Z(r)] = 0.058 ± 0.11) ($P < .001$, paired t test). The regression analysis showed a significant linear association between the TS of BOLD signals and CVR in the anterior circulation where the reduction of CVR was evident in the patient group. CONCLUSION: BOLD TS analysis has potential as a non-invasive alternative to current methods based on CVR for identification of the tissue at risk of ischemic stroke.
Suggested Reviewers:	Blaise deB Frederick McLean Imaging Center, Harvard Medical School bbfrederick@mclean.harvard.edu Great contributions to undestanding the low-frequency spontaneous oscillation in the

	systemic circulation and its effects on the brain fMRI signal.
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Additional Information:	
Question	**Response**
Significance of the Work: Please include a brief statement summarizing the significance of the work and in particular how it differs from and advances existing literature.	Spatial distribution of a time lag structure detected by time-shift (TS) analysis from the BOLD fMRI signal has recently been proposed as a non-invasive biomarker for cerebrovascular disease without need for exogenous contrast agents, vasodilatory stimuli, radiation exposure or patient cooperation. However, the technique has been validated only on the basis of temporal dynamics using perfusion MRI, another method dependent on perfusion delay. To provide a direct evidence for the capability of BOLD TS analysis in detecting brain tissue at risk of ischemic damage, it was compared with acetazolamide-challenged single photon emission computed tomography (SPECT) in 23 patients with arterial occlusive diseases, who required pre- or post-operative evaluation of cerebrovascular reactivity (CVR). BOLD TS map was found to have a higher correlation with CVR than cerebral blood flow map derived from SPECT, which was more prominent in advanced cases. There was even a moderate linear correlation between regional CVR and the perfusion delay from the TS map, both reflecting the severity of the hemodynamic impairment, but via different mechanisms. The results suggested that the BOLD TS map may substitute the current techniques as a non-invasive alternative for detecting tissue hypoperfusion in patients with arterial occlusive diseases.
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Please indicate which reporting guideline(s) the study adheres to (eg, STROBE, PRISMA, CONSORT). as follow-up to "**Compliance with Research Reporting Guidelines**: *Neurosurgery* endorses several reporting guidelines and requires authors to submit their research articles in accordance with the appropriate guideline statement(s) and checklist(s). Completed applicable checklists and flow diagrams must be included with submissions. Research articles that must be submitted according to the appropriate reporting guideline(s) include, but are not limited to: randomized trials, systematic reviews, meta-analyses of interventions, meta-analyses of observational studies, diagnostic accuracy studies, and observational epidemiological studies (eg, case series, cohort, case-control, and cross-sectional studies). Consult the EQUATOR Network, which maintains a useful, up-to-date list of guidelines as they are published, with links to articles and checklists: http://www.equator-network.org. Please confirm below that information is reported according to the relevant reporting guideline(s) and any required materials are included with the submission:"	STROBE
Statistical Analysis: For manuscripts that report statistics, the Editor requires that the authors provide evidence of statistical consultation or expertise. If your article includes statistics, has the information reported been evaluated by an expert?	Yes
IRB/Ethics Approval: Please indicate if your study has received institutional review board/ethics approval. If yes, these materials are readily available should the Editor request them.	Yes

March 9, 2018

Dr. Nelson M. Oyesiku

Editor-in Chief

NEUROSURGERY

Dear Dr. Nelson M. Oyesiku:

On behalf of the co-authors, I wish to submit an original article to the *NEUROSURGERY*, titled "Resting-state functional magnetic resonance imaging identifies cerebrovascular reactivity impairment in patients with arterial occlusive diseases: A pilot study," by Nishida S, Aso T, Takaya S, Takahashi Y, Kikuchi T, Funaki T, Yoshida K, Okada T, Kunieda T, Togashi K, Fukuyama H, and Miyamoto S.

Assessment of the hemodynamic state is essential for evaluating future stroke risk in patients with arterial occlusive diseases. Cerebrovascular reactivity (CVR) has been used in the pre- and post-surgical evaluation of arterial bypass surgery, to prevent future ischemic stroke in patients with arterial occlusive diseases. However, current techniques have limitations due to use of exogenous contrast agents, vasodilatory stimuli, radiation exposure or patient cooperation and hence a less invasive alternative is desirable.

A resting-state blood oxygenation level dependent (BOLD) signal-based blood-tracking method was recently reported as a biomarker for ischemic brain diseases (Lv Y et al., Ann. Neurol. 2013; Amemiya et al., Radiology 2014; Tong Y et al., JCBFM 2016). However, the clinical relevance of this technique has yet to be established, owing to a lack of inter-modality agreement study (i.e., with non-MRI and non-dynamic methods). Here, we examined whether the BOLD temporal-shift [TS] map has the potential to substitute ACZ-challenged SPECT in detecting impaired CVR in patients with arterial occlusive diseases. The results showed that the BOLD-TS map is comparable to the SPECT-based CVR map, despite different physiological bases of the techniques. Our results suggest that hemodynamic impairment with future stroke risk in patients with arterial occlusive diseases could be non-invasively assessed using the BOLD-TS map.

We believe that this work has an impact on the management of patients with chronic ischemia. We hope you will find the manuscript worthy of publication in the *NEUROSURGERY*.

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. All study participants provided informed consent, and the study design was approved by the appropriate ethics review board. We have read and understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare.

Thank you for your consideration. I look forward to hearing from you.

Sincerely yours,

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12. Miyamoto S: conception and design, acquisition of data, and revising the article.

All authors approved the final version of the manuscript and agree to be accountable for all aspects of this work.

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Resting-state functional magnetic resonance imaging identifies cerebrovascular reactivity impairment in patients with arterial occlusive diseases: A pilot study

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Resting-state functional MR imaging identifies cerebrovascular reactivity impairment in patients with arterial occlusive diseases: A pilot study.

Abstract

BACKGROUND: The development of non-invasive approaches for identifying hypoperfused brain tissue at risk is of major interest. Recently, the temporal-shift (TS) maps estimated from resting-state blood oxygenation level-dependent (BOLD) signals have been proposed for determining hemodynamic state.

OBJECTIVE: To examine the equivalency of TS map versus cerebrovascular reactivity (CVR) map from acetazolamide-challenged single-photon emission computed tomography (SPECT) in identifying hemodynamic impairment in patients with arterial occlusive diseases.

METHODS: Twenty-three patients with arterial occlusive diseases who underwent SPECT were studied. With a recursive TS analysis of low-frequency fluctuation of the BOLD signal, a TS map relative to the global signal was created for each patient. The voxel-by-voxel correlation coefficient was calculated to examine the image similarity between TS and SPECT-based cerebral blood flow (CBF) or CVR maps in each patient. Furthermore, simple linear regression analyses were performed to examine the quantitative relationship between the TS of BOLD signals and CVR in each cerebrovascular territory.

RESULTS: The within-patient, voxel-by-voxel comparison revealed that the TS map was more closely correlated with SPECT-CVR map ($[Z(r)] = 0.42 \pm 0.18$) than SPECT-CBF map ($[Z(r)] = 0.058 \pm 0.11$) ($P < .001$, paired t test). The regression analysis showed a significant linear

association between the TS of BOLD signals and CVR in the anterior circulation where the reduction of CVR was evident in the patient group.

CONCLUSION: BOLD TS analysis has potential as a non-invasive alternative to current methods based on CVR for identification of the tissue at risk of ischemic stroke.

Key Words: arterial occlusive diseases, cerebrovascular reactivity, functional magnetic resonance imaging, single-photon emission computed tomography

Running Title: BOLD detects abnormal cerebrovascular reactivity

Abbreviations

ACA, anterior cerebral artery; ACZ, acetazolamide; BOLD, blood oxygenation level dependent; CBF. cerebral blood flow; CO_2, carbon dioxide; CVR, cerebrovascular reactivity; FWHM, full width at half maximum; IMP, iodine-123 N-isopropyl-p-iodoamphetamine; MCA, middle cerebral artery; MRI, magnetic resonance imaging; MTT, mean transit time; ROI, region of interest; rs-fMRI, resting-state functional MRI; PCA, posterior cerebral artery; SPECT, single photon emission computed tomography; TS, temporal-shift; TTP, time to peak

Introduction

Assessment of hemodynamic impairment is essential for ischemic stroke risk prediction in patients with arterial occlusive diseases. Hemodynamic status in patients with chronic ischemia is evaluated through measurement of the vasodilatory reserve, which reflects compensatory responses to reduced cerebral perfusion pressure.[1, 2] The capacity for compensatory vasodilation is measured as cerebrovascular reactivity (CVR) using various techniques including nuclear medicine modalities, such as single-photon emission computed tomography (SPECT),[3, 4] and magnetic resonance imaging (MRI) [5], with the former still being considered the reference method. These tomographic imaging of CVR is useful in determining which patients with carotid stenosis [3] or moyamoya disease (MMD) would likely benefit from treatment. Especially in the latter, pre- and post-surgical evaluations of extracranial-intracranial arterial bypass surgery has been largely based on SPECT findings.[4, 6, 7] However, the procedure involves arterial blood sampling and ionizing radiation, in addition to the vasodilatory agents, such as acetazolamide (ACZ) or carbon dioxide, that impose additional burden on patients with a range of complications.[8, 9] Efforts are still underway to replace these techniques with new alternatives that are less invasive and demanding.

Recently, temporal-shift (TS) analysis on resting-state functional MRI (rs-fMRI), which involves generating a TS map from low-frequency fluctuation of blood oxygen level-dependent (BOLD) signals, has been introduced to evaluate the hemodynamic state. These studies have shown that the local time shift of the BOLD signal is correlated with the prolongation of perfusion parameters, such as the mean transit time (MTT) and time to peak (TTP), in patients with acute and chronic cerebral ischemia,[10-13] as well as in healthy subjects.[14] These lines of

evidence suggest that the TS of BOLD primarily reflects vascular structure[14-16] and that the local TS of BOLD and perfusion parameters exhibit the same behavior in cerebral ischemia. Observable changes in venous drainage with increases in age further supports the technique and its underlying principles as experiential evidence. [16] Given that these perfusion parameters mirror CVR impairment in chronic ischemia, via compromised hemodynamics such as reduced velocity of a collateral pathway [17-20], some degree of agreement is expected between the TS map from rs-fMRI and SPECT-based CVR in these patients. Assessing CVR impairment using non-invasive BOLD MRI without vasodilatory stimuli, such as carbon dioxide (CO_2) or ACZ, would have a clinical impact on the management of patients with chronic ischemia. In the present study, we aimed to examine the capability of the method in evaluating the hemodynamic impairment of the patients with arterial occlusive diseases via comparison with CVR calculated by ACZ-challenged SPECT.

Materials and Methods

Patients

From April 2014 to July 2016, we prospectively recruited 28 patients with arterial occlusive diseases (21 with MMD and seven with atherosclerotic diseases) who were diagnosed on routine magnetic resonance angiography and successfully underwent ACZ-challenged iodine-123 N-isopropyl-p-iodoamphetamine (^{123}I-IMP) SPECT scans. Patients with MMD were diagnosed according to the diagnostic criteria.[21] Patients with internal carotid artery stenosis/occlusion or middle cerebral artery (MCA) stenosis/occlusion were included in the atherosclerotic group. Since the hemodynamic change following acute stroke is a dynamic

process,[22, 23] we excluded patients who had a history of stroke events within a month before the SPECT scans. We also excluded three patients with MMD and two patients with atherosclerotic diseases who had large lesions involving one or more of the MCA division territories and/or the anterior or posterior cerebral artery (ACA or PCA), or neurological deficits that could have an effect on BOLD signal.[24, 25] Finally 23 patients were enrolled in this study. (nine men and 14 women; mean age, 40.2 ± 17.9 years). Among 18 patients with MMD, nine patients had undergone revascularization surgery 2 months or more before the current study. Cortical infarctions (<5 mL) were found in 4 patients during routine MRI scans. Cerebral angiography was performed according to the diagnostic criteria of MMD or for the evaluation of cerebral hemodynamics in patients who might have been candidates for surgical revascularization. The patient characteristics are summarized in **Table 1**.

This study was approved by our institutional review board/ethics committee (IRB C1002). The participants provided written informed consent in advance. To avoid the effect of ACZ on the TS map, rs-fMRI data was acquired before or one day after ACZ-challenged SPECT.

Imaging procedures

SPECT data acquisition and analysis

Dynamic SPECT data were acquired with a 2-head rotating gamma camera (Infinia, GE Medical Systems, Milwaukee, WI, USA) with an extended low-energy general-purpose collimator. For baseline SPECT, ^{123}I-IMP at 167 MBq was injected intravenously over 1 min when the data acquisition began. Arterial blood sampling was performed 10 min after data

acquisition was initiated. For ACZ-challenged SPECT, ACZ (17 mg/kg) was injected 10 min before ^{123}I-IMP was injected and the data acquisition was started. The data were acquired over a 28-min period through a 360° rotation at a rate of 180°/min. Images were reconstructed and the cerebral blood flow (CBF) value was calculated with the QSPECT software package using the Transmission Dependent Convolution Subtraction method.[26, 27] Each SPECT image was spatially normalized into 4-mm isotropic voxels using the SPECT template provided by SPM12 (Statistical parametric mapping, from the Wellcome Department of Cognitive Neurology, London, UK). CVR was calculated as follows: 100 × (ACZ scan - baseline scan)/baseline scan.

MR imaging data acquisition

A 3-T whole-body scanner (Tim-TRIO, Siemens, Erlangen, Germany) with a 32-channel phased-array head coil was used. BOLD rs-fMRI acquisition was performed using a multiband gradient-echo echo-planar imaging protocol from the University of Minnesota [28] with the following parameters: TR/TE = 1100/35 ms; flip angle = 60; matrix = 96 × 96 on a 192 × 192 mm^2 field of view; multiband factor = 6; and 72 2.0-mm-thick slices parallel to the anterior commissure-posterior commissure line. Only one run lasting 440 s (400 volumes, 7 min 20 s) was acquired, during which the patients were asked to stay still with their eyes open. A three-dimensional structural image was also acquired (MP-RAGE, TR/TI/TE = 1900/900/2.58 ms; 256 × 256 × 192 voxels over a 230 × 230 × 170 mm sagittal slab).

MR imaging analysis

Preprocessing

The data were preprocessed using FSL (http://www.fmrib.ox.ac.uk/fsl) and SPM12 on MATLAB (MathWorks, Natick, MA, USA). The volumes corresponding to the first 10 s were discarded to ensure stationarity. Head motion was compensated for through two steps: regressing out the parameters obtained in the motion correction procedure and data scrubbing.[29] The scrubbing procedure involved searching the realigned time series for either (1) a global signal change of more than 0.5% between consecutive acquisitions or (2) abrupt head motion exceeding ± 3 mm or ± 3° per 0.5 s. Those contaminated time points were replaced with linearly interpolated values.[30] Finally, a temporal band-pass filter (0.02–0.12 Hz) was applied.[14, 15, 31]

To conduct a group analysis, nonlinear warping to the Montreal Neurological Institute template brain[32] was performed on the T1 anatomical images and functional volumes were normalized by using these parameters and were re-sliced to result in 4-mm isotropic voxels to assure adequate temporal signal-to-noise ratio in each voxel. Spatial smoothing was applied to the volumes by using an 8-mm full width at half maximum (FWHM) Gaussian kernel.

Creating BOLD temporal-shift map (TS map)

The method for creating the TS map is described in detail elsewhere.[15] We created the TS map with a recursive procedure which was robust and might represent local blood circulation effectively.[33] A schematic diagram of the procedure is shown in **Figure 1A**. To create the initial reference time course, we used the global mean signal, which has commonly been used in previous studies [10-12] and would be more closely associated with arterial flow than other seeds, such as the superior sagittal sinus. Cross-correlations between this reference time course and

every brain voxel were calculated to identify those with the highest correlation at a time shift of zero. Thus, the global mean signal was used as the initial seed to identify the ± 0 s group of voxels. These voxels were used as the initial seed for the recursive procedure.

In each step of the recursive procedure, a cross-correlogram was calculated with the seed signal to obtain a set of voxels with a local peak at a time lag of ± 0.5 s. The reference time course was updated recursively at every step to the pooled signal from the voxels with the peak correlation at either 0.5 s or -0.5 s among three conditions: shifted by 0 s, ± 0.5 s, and ± 1 s. This procedure was repeated eight times for both the upstream and downstream directions to reach a ± 4 s tracking range. Thus, we created a TS map showing regions corresponding to -4 s, -3.5 s ...3.5 s, 4 s time shift relative to the global mean signal. The polarity of the TS was chosen so that the values represent phase advance and hence positive values indicate earlier arrival reflecting a "preferable" perfusion state. Peak correlation coefficients below 0.2 were ignored to prevent spurious correlations,[14] which allowed a considerable number of voxels to appear with no lag values. Such “holes” were filled by a Matlab script implementing a simple algorithm based on second-order partial differential equations (http://www.mathworks.com/matlabcentral/fileexchange/21214-inpainting-nan-elements-in-3-d). For voxel-wise analyses, in order to accomplish a smoothness comparable to that of the SPECT-based images, the resulting lag maps were further smoothed with an 8-mm FWHM box kernel.

Statistical analysis

To examine image similarity, a voxel-by-voxel Pearson’s correlation coefficient (*r*) between the TS map and the SPECT-based images (CBF and CVR maps) was calculated for each patient. We used the vascular territory brain template, covering the whole-brain gray matter

supplied by the anterior, middle, and posterior cerebral arteries (referred to as ACA, MCA, and PCA respectively) as a mask image to extract the values (**Fig. 1C**).[34] Using the z-transformed correlation coefficient [Z(*r*)], image similarity was evaluated with paired t-tests. To examine the association between the regional TS of BOLD signals and the SPECT-based CVR in each cerebrovascular territory, we performed region of interest (ROI)-based linear regression analyses, using the vascular territory brain template mentioned above (**Fig. 1C**). This template consists of three subregions (proximal, intermediate, and distal) in each vascular territory (ACA, MCA, and PCA). Among them, an intermediate template was chosen for the regression analyses so as to correctly represent each flow territory while minimizing the contribution from collateral circulation of other arterial trunks.[34, 35] CVR in each ROI was compared using repeated-measures ANOVA followed by a post hoc Tukey test. Statistical analyses were conducted using the SAS Software *JMP Version 12.2* and MATLAB and P-values less than 0.05 were considered to be significant.

Results

Voxel-based image similarity between the TS map and SPECT images

The SPECT images and TS map from each patient are displayed in **Supplementary Digital Contents**. Images from a representative patient are shown in **Figure 2**. In the TS map here, voxel values indicate the phase advance of BOLD signal time-series relative to the global signal, meaning that warm colors indicate relatively earlier arrival.[15] The TS map clearly exhibited higher similarity to the CVR map than to the CBF map. It was confirmed by the voxel-by-voxel correlation analysis showing higher correlation with the CVR map in 21 out of 23

patients (**Fig. 3**). A group comparison using paired t-tests showed a significantly higher correlation between the TS map and the CVR map ([Z(*r*)] = 0.42 ± 0.18) than between the TS map and the CBF map ([Z(*r*)] = 0.058 ± 0.11) (*P* < .001). There were no significant disease group differences, but we found a negative correlation between the image similarity of TS with the CVR map Z(*r*) and the mean CVR in the bilateral MCA ROIs (r = -0.54, P = 0.0074), suggesting high accuracy of the technique in severe cases.

ROI-based regression analysis between the TS of BOLD signals and CVR

The ROI-based regression analyses revealed a significant linear effect of the TS of BOLD signals on CVR in the bilateral ACA and MCA ROIs, but not in the PCA ROIs (**Fig. 4A**). The group comparison using ANOVA revealed a significant decrease in CVR among these ROIs [F (2, 111.8) = 46.0, *P* < .001]. The post hoc test showed that CVR was highest in the PCA ROIs than in the two anterior flow territories (ACA and MCA ROIs) (**Fig. 4B**, *P* < .001 by Tukey's test). Thus, a significant effect of TS on CVR was found in the area where CVR was relatively impaired.

Discussion

Voxel-by-voxel analyses demonstrated a good agreement of spatial distribution between the TS map from rs-fMRI and the CVR map calculated by ACZ-challenged SPECT in patients with arterial occlusive diseases. Although the interpretation of the TS of the BOLD signal time-series remains to be standardized, theoretically it tracks the propagation of a hemoglobin-related signal component that is thought to be intrinsic to blood.[14] Accordingly, studies have demonstrated an association of the TS map with perfusion delay parameters, such as MTT or

TTP,[10-13] but not with CVR per se.[17-19] This is the first study to confirm the clinical significance of the BOLD TS analysis via comparison with a technique not based on temporal properties of the blood flow.

The ROI analyses further revealed a linear association between the TS value and the CVR, but only in the anterior circulation (the ACA and MCA territories), not in the PCA territory where CVR was relatively preserved. In arterial occlusive diseases, a decrease in cerebral perfusion pressure induces protective mechanisms, such as compensatory vasodilation [1, 2] and collateral recruitment, both of which may affect the TS of BOLD signals.[11, 12] Among these changes, compensatory vasodilation is detected by CVR in SPECT while perfusion delay affects the TS map. Thus, a certain degree of severity of the ischemic condition should be present when a lesion is detected concomitantly by the TS and CVR maps. This would explain the observed negative correlation between the CVR in the whole MCA territory and image similarity of the TS map with the CVR map; the more severe the impairment, the better the TS map resembles the CVR map.

The present study confirmed that the BOLD TS analysis has potential for identification of the tissue at risk of ischemic stroke where CVR is impaired, without requiring radiation exposure or invasive procedures. CVR measured by BOLD and arterial spin labeling has been proposed as a less invasive alternative to CVR measured by ACZ-challenged SPECT.[36-39] Instead of ACZ, carbon dioxide (CO_2) is used as a vasodilator in this method. However, the manipulation of CO_2 requires patients to hold their breath or to inhale CO_2, which could cause transient complications such as headache and dizziness. Because of this, CVR measurement using CO_2 as a vasodilator occasionally fails to be completed in clinical practice.[40] In contrast, generating the TS map from

rs-fMRI does not pose these issues as repeatedly emphasized in earlier works. Furthermore, this method is, at least computationally, equivalent to tracking the contrast agent injected instantaneously to the initial seed region, both anteriorly and posteriorly in time, but without the need for an exogenous contrast agent. Good reproducibility of TS analysis of BOLD signals has been addressed previously,[11] which is further enhanced by the recursive approach.[15] Altogether, the TS map would serve as a substitute for the CVR map calculated by ACZ-challenged SPECT and may also provide additional information about hemodynamics while producing far less patient burden in those with chronic cerebral ischemia.

One major caveat of this study is the selection bias of patients. We recruited consecutive patients who needed ACZ-challenged SPECT for the pre- or post-surgical evaluation of the hemodynamic state. As a result, 18 out of 23 patients had MMD and nine had undergone surgical revascularization. Effect of revascularization surgery is also unclear because the sample size was insufficient for a subanalysis to draw any conclusion. On the other hand, our results showed a trend of higher similarity between the TS and CVR maps in patients with atherosclerotic diseases than in patients with MMD, suggesting that the TS of BOLD signals reflects CVR more accurately in atherosclerotic diseases. Further studies are thus warranted to examine the effect of the etiology of chronic cerebral ischemia on the TS map.

Conclusions

The present results confirm that the BOLD TS analysis is a promising alternative to the current techniques for detecting hemodynamic impairment in arterial occlusive diseases.

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1

Figure Legends

Figure 1. A schematic of the temporal-shift (TS) analysis and regions of interest (ROIs) used in the present study.

(A) A schematic diagram of the analysis workflow.

(B) ROIs used for the voxel-wise correlation and regression analyses. All colored voxels were used for the voxel-by-voxel correlation analyses. ROIs for the anterior (yellow), middle (violet), and posterior (cyan) cerebral artery intermediate flow territories were used for the regression analyses.

Figure 2. The TS map and single-photon emission computed tomography (SPECT) images in a representative patient (Patient No. 22, female, 65 years old) with middle cerebral artery (MCA) stenosis.

(A) Right internal carotid artery (ICA) angiogram (anteroposterior view) shows occlusion of the right ICA C1 segment.

(B) Left ICA angiogram (right anterior oblique view) shows no filling of distal left MCA branches and collateral flow via leptomeningeal anastomosis in the distal left MCA

(C) The fluid attenuation inversion recovery image shows no abnormalities in the territory of bilateral MCAs.

(D) In the 3D time-of-flight magnetic resonance angiography axial source image (top left), the signal of the branches of the right and left MCA is not observed (white arrows), whereas the

branch of the left MCA is preserved (white arrowhead). The cerebral blood flow (CBF) map measured by the baseline SPECT image (bottom left) shows no marked reduction in CBF in the MCA territories. In contrast, cerebrovascular reactivity (CVR) is decreased in the territories of the occluded MCAs (bottom right). The TS map (top right) and CVR map show similar distributions. The positive values in the TS map indicate phase advances relative to the global signal phase, reflecting early arrival of the blood.

Figure 3. Voxel-by-voxel correlation of the TS maps with SPECT images in each patient.

The light blue lines and blue lines indicate the patients with moyamoya disease who underwent or did not undergo surgery, respectively. The red line indicates the patients with atherosclerotic disease. TS maps from blood-oxygen-level-dependent (BOLD) signals are more closely correlated with CVR maps ([Z(r)] = 0.42 ± 0.18) than CBF maps ([Z(r)] = 0.058 ± 0.11).

*** = P < .001, paired-t test

Figure 4. ROI-based regression analyses between the TS of BOLD signals and CVR in each cerebrovascular territory.

(A) A significant effect of the TS of BOLD signals on CVR is observed in the anterior and middle cerebral artery ROIs. The light blue and blue circle plots indicate the patients without and with surgery, respectively. The red triangle plots indicate the patients with atherosclerotic diseases.

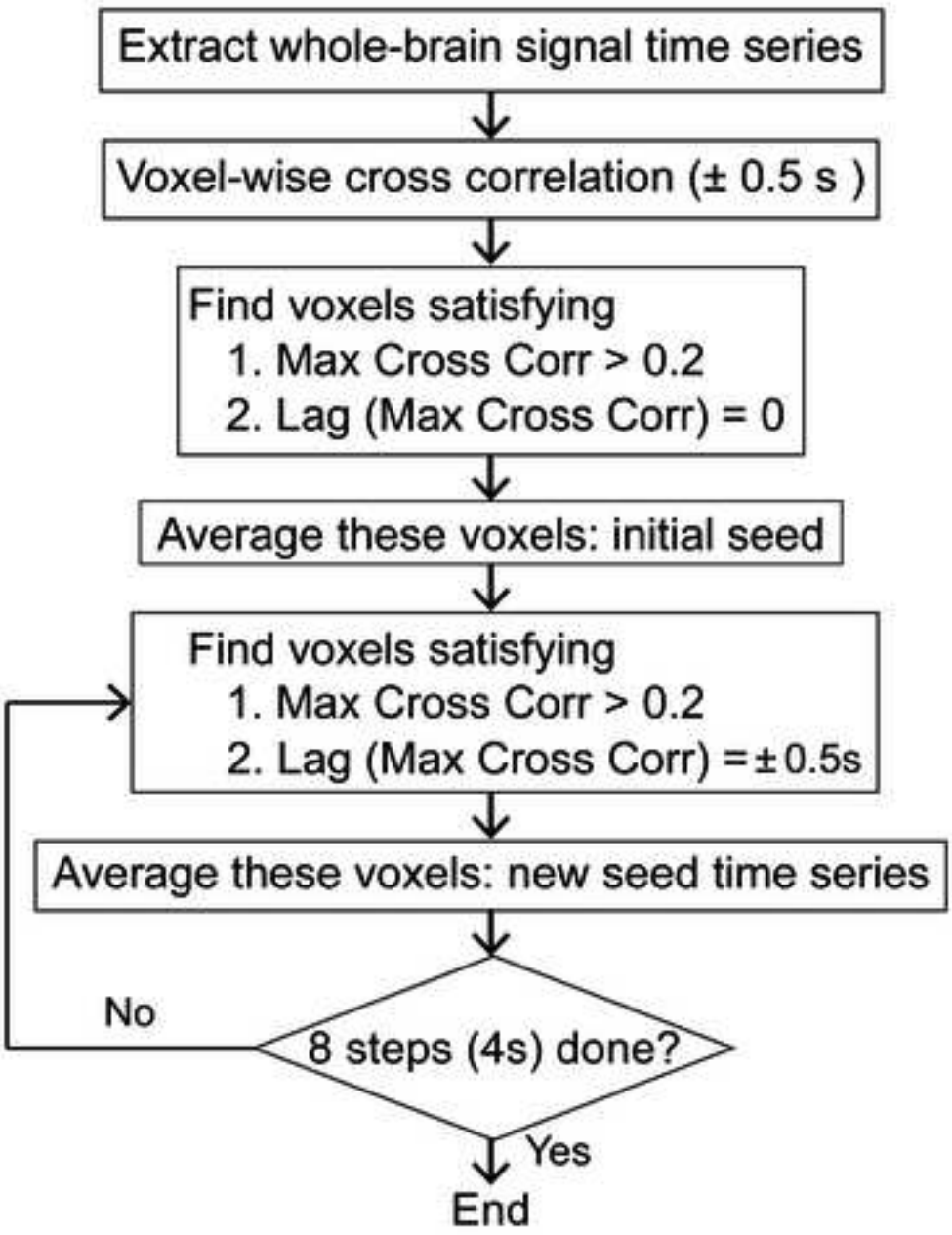
(B) Group comparison of mean CVR in each cerebrovascular territory of each hemisphere.

ACA = anterior cerebral artery, MCA = middle cerebral artery, PCA = posterior cerebral artery.

*** = P < .001

Supplementary Digital Contents. CBF map, CVR map, and temporal shift map from each patient.

A



B

ROIs used for statistical analysis

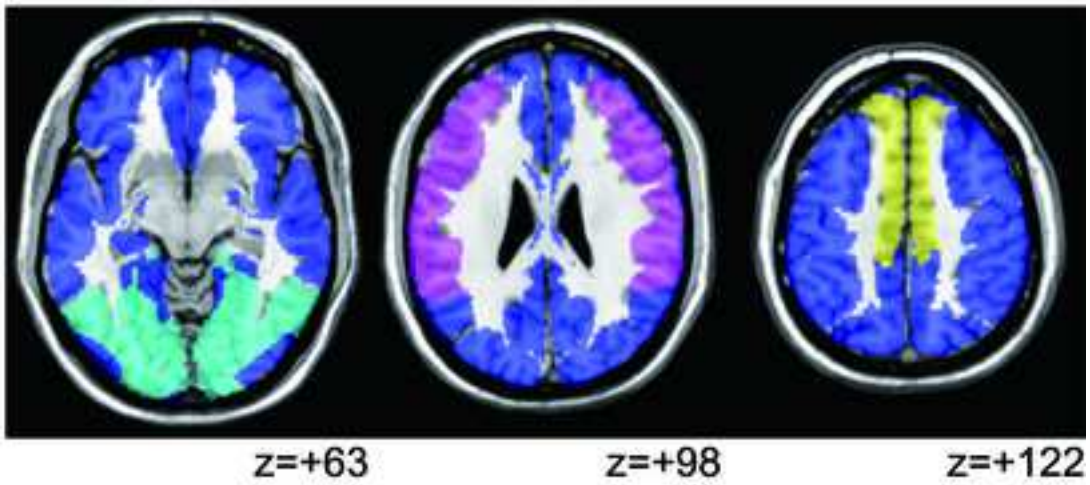


Figure2

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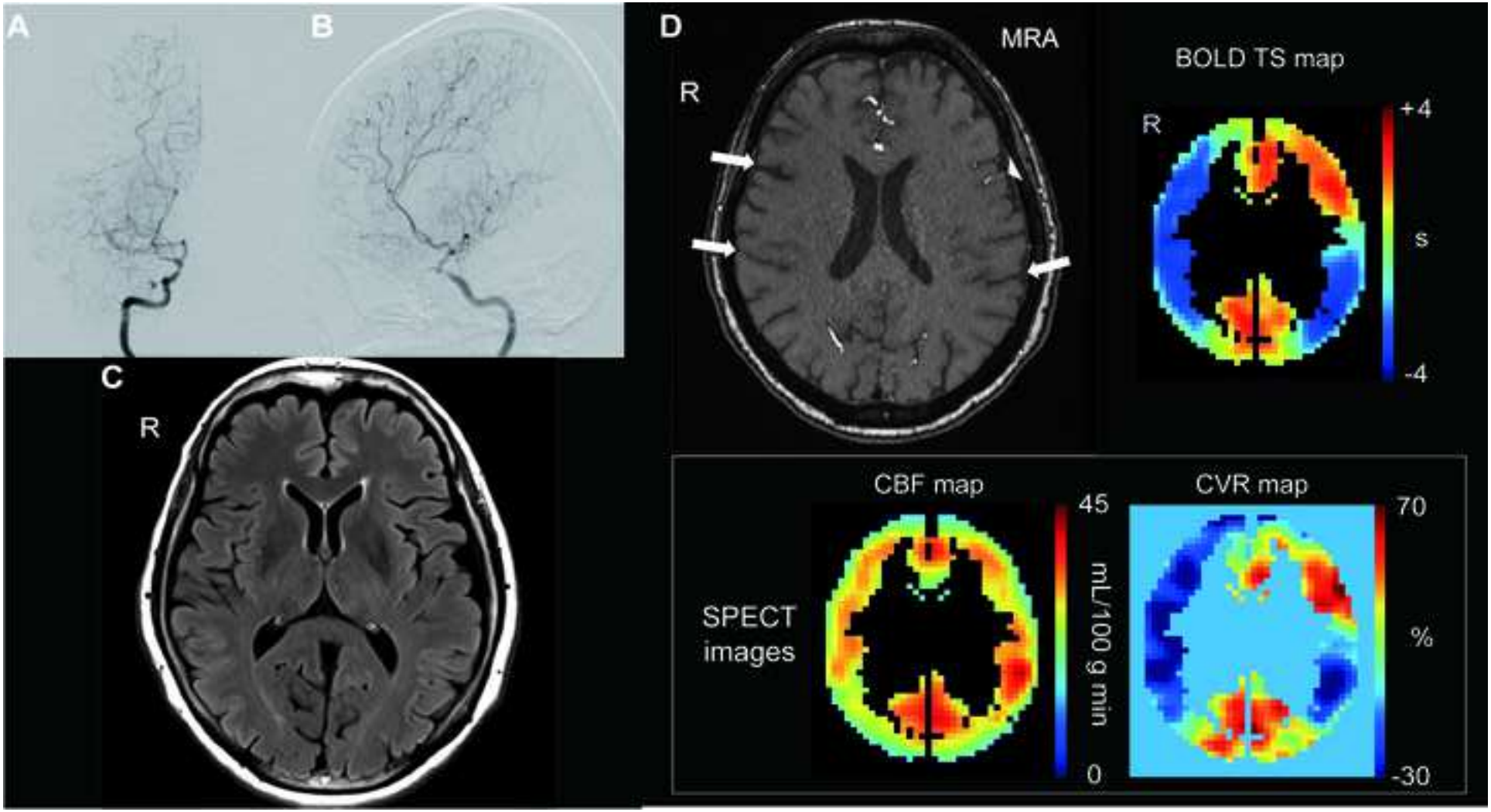

Figure3

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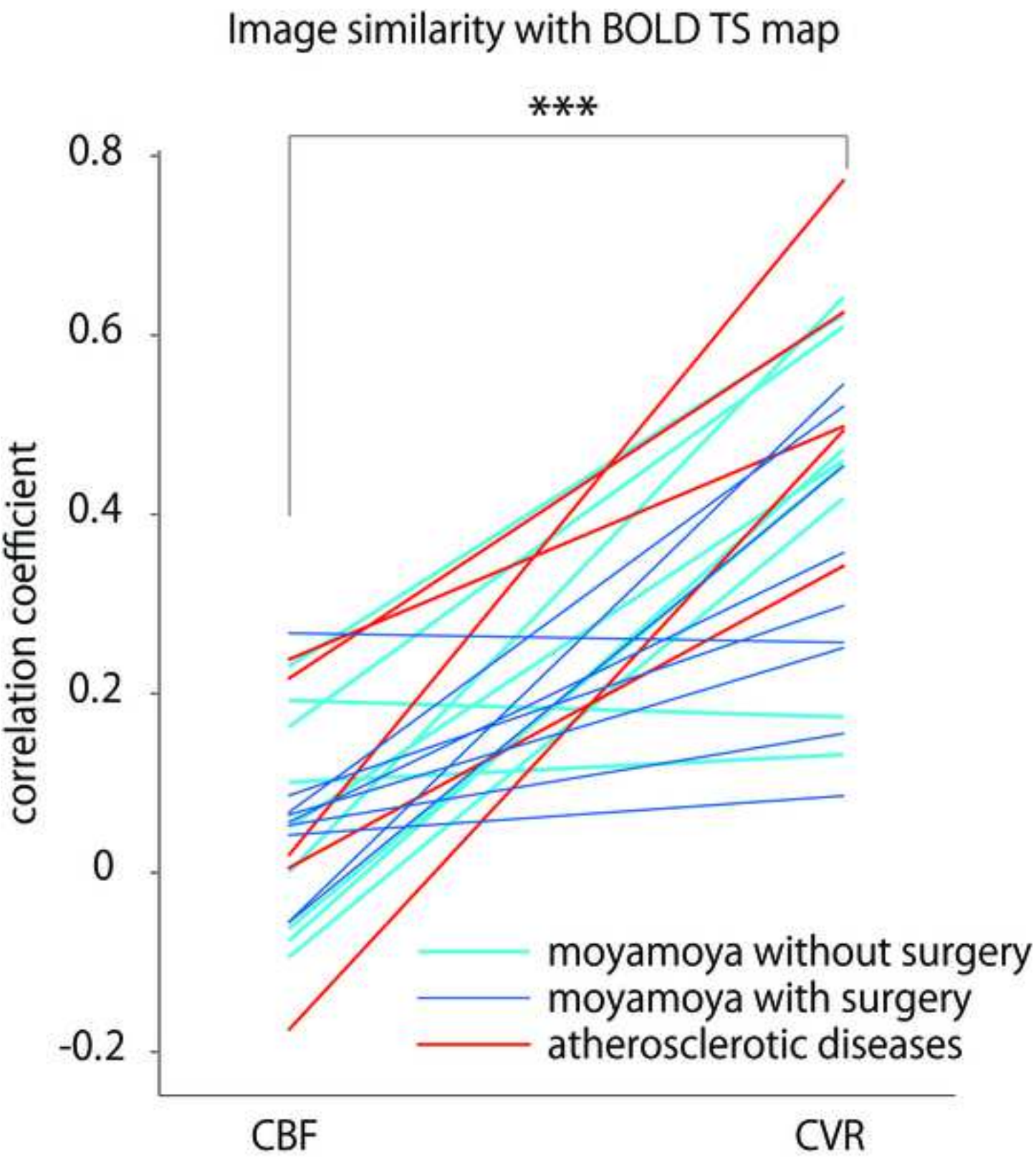

Figure4

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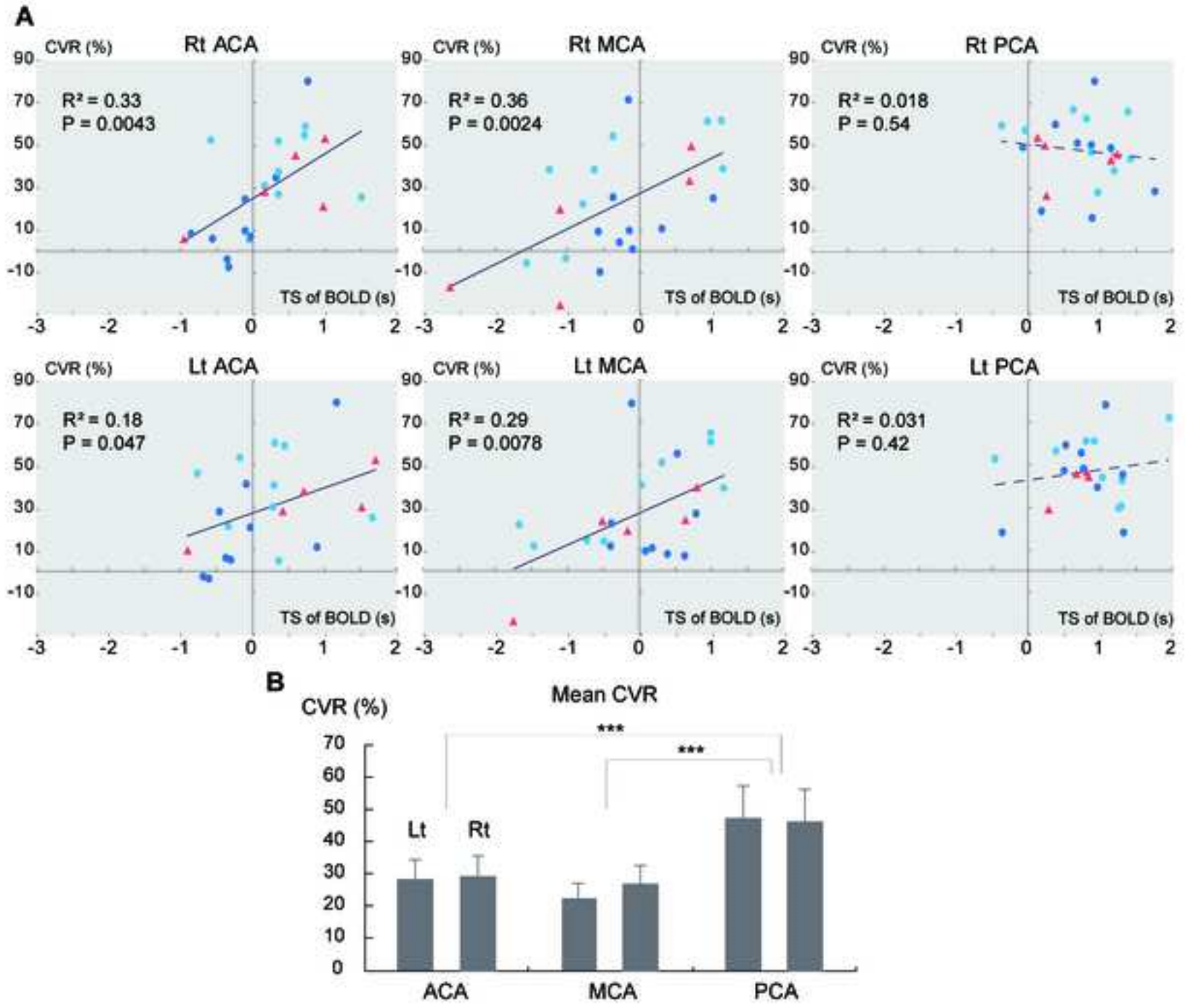

Table

Patient demographic data.

Disease	Patient No.	Sex	Age	Affected side	Onset	Structural damage	Operation (time)
Moyamoya disease	1	F	41	Right	- (post operation)	OCI (in the right parietal lobe)	right STA-MCA anastomosis (3 months prior)
	2	F	25	Right	TIA	none	
	3	F	15	Bilateral	- (post operation)	none	right EDAMS (3 years prior)
	4	F	29	Left	hemorrhage	none	
	5	M	17	Bilateral	- (post operation)	OCI (in the right frontal lobe)	left EMS (12 years prior) right EMS (6 years prior) right STA-MCA anastomosis (2 months prior)
	6	F	65	Bilateral	TIA	none	

7	F	43	Bilateral	- (post operation)	none	left STA-MCA anastomosis (3 months prior)
8	F	37	Right	None	none	
9	M	48	Bilateral	Infarct	none	
10	M	18	Bilateral	- (post operation)	none	right STA-MCA anastomosis (5 years prior)
11	M	41	Left	TIA	none	
12	F	16	Bilateral	- (post operation)	none	right STA-MCA anastomosis (7 years prior) right OA-PCA anastomosis (4 years prior) left STA-MCA anastomosis (6 months prior)
13	M	15	Bilateral	- (post operation)	none	right STA-MCA anastomosis (7 months prior)
14	F	41	Left	Infarct	OCI (in the left frontal lobe)	
15	M	35	Bilateral	- (post operation)	none	right STA-MCA anastomosis (4 years prior)

	16	M	36	Bilateral	hemorrhage	none	
	17	F	40	Bilateral	- (post operation)	none	right STA-MCA anastomosis (3 months prior)
	18	F	44	Right	TIA	none	
Middle cerebral artery stenosis	19	F	51	Bilateral	Infarct	none	
	20	M	62	Left	Infarct	OCI (in the left temporal lobe)	
Internal carotid occlusion	21	M	69	Right	TIA	None	
	22	F	65	left	TIA	None	
Internal carotid stenosis	23	F	72	Bilateral	None	none	

EDAMS, encephalo-duro-arterio-myo-synangiosis; EMS, encephalo-myo-synangiosis; MCA, middle cerebral artery; OA, occipital artery; OCI,; old cerebral infarction, PCA, posterior cerebral artery; STA, superficial temporal artery; TIA, Transient ischemic attack

Supplemental Digital Content1

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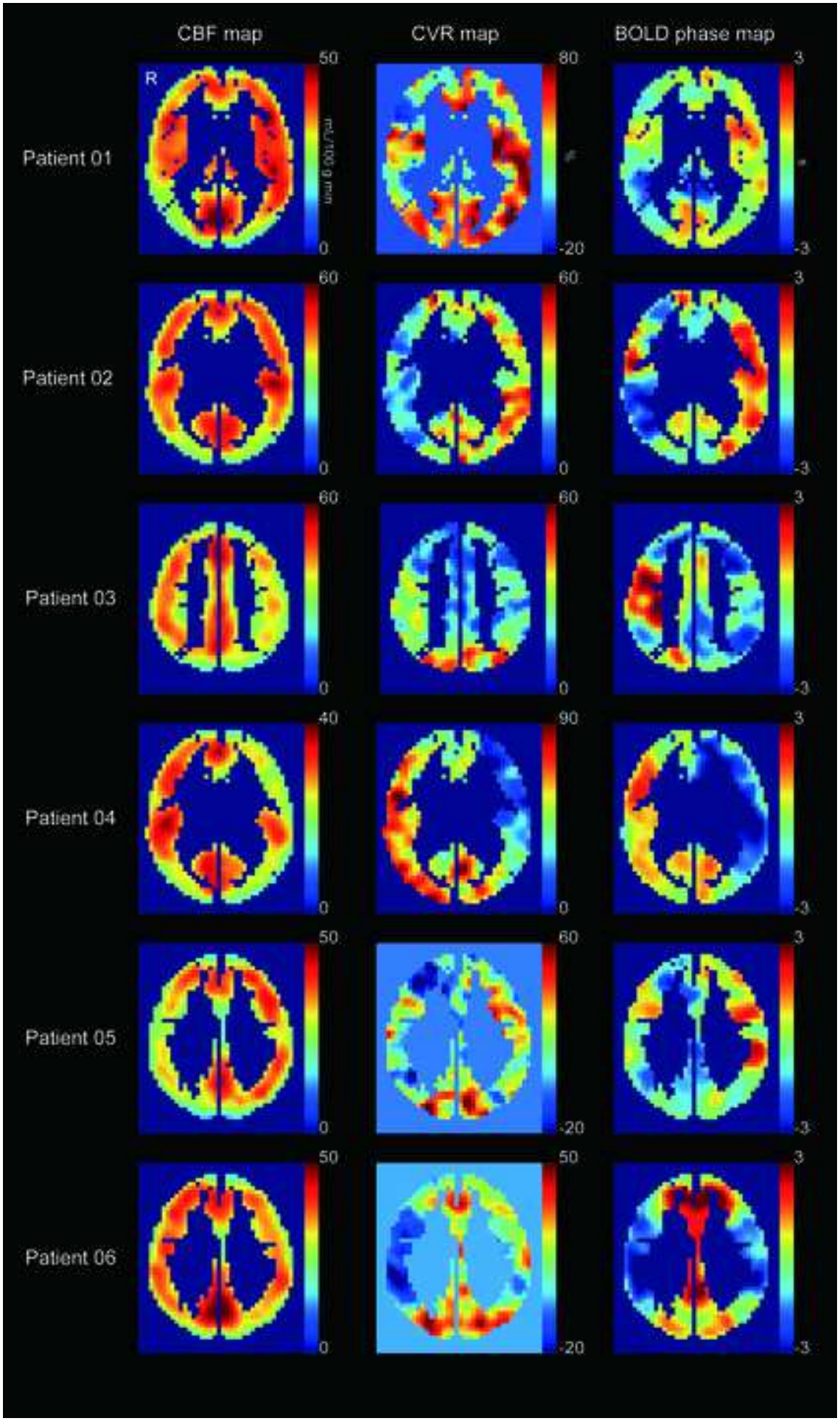

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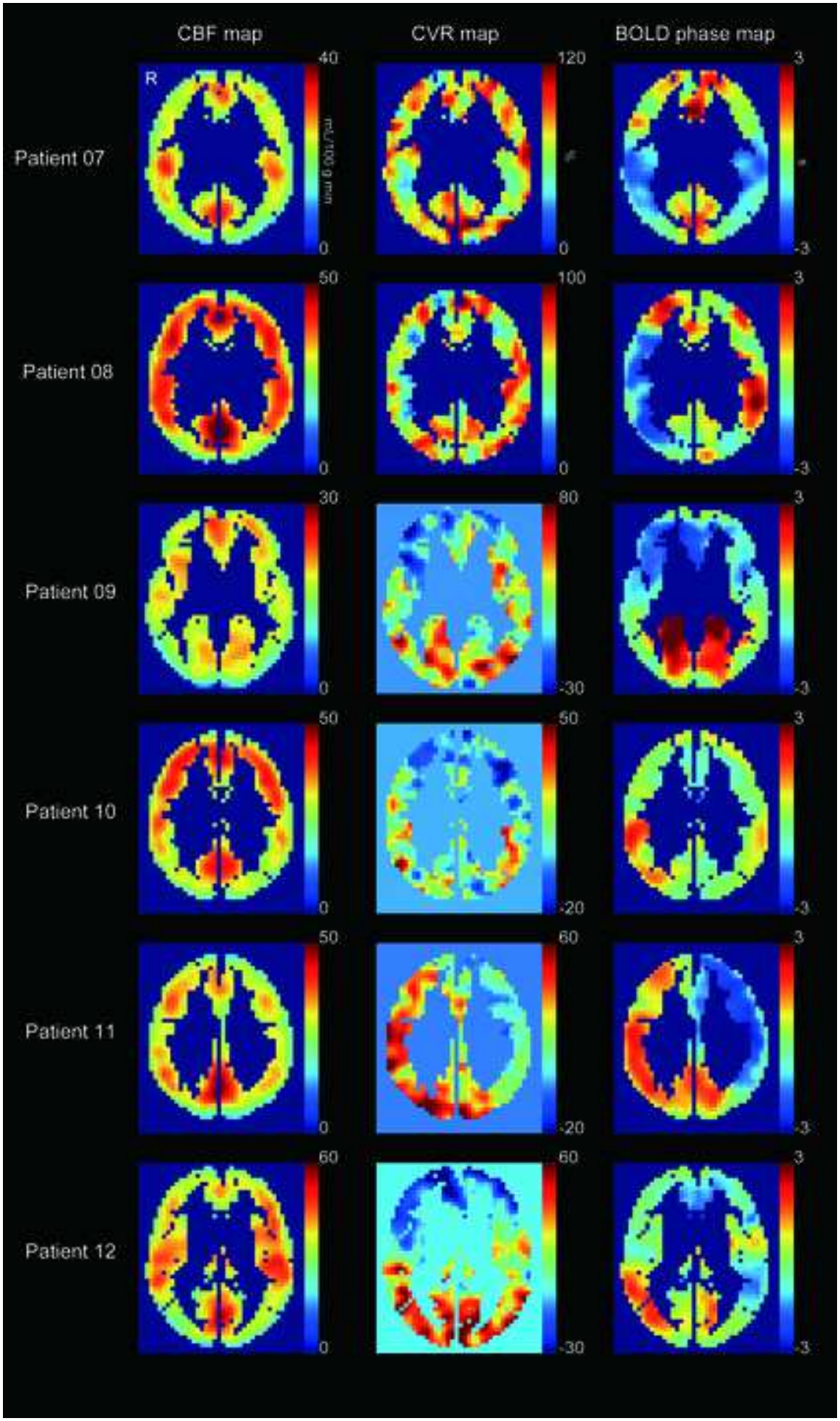

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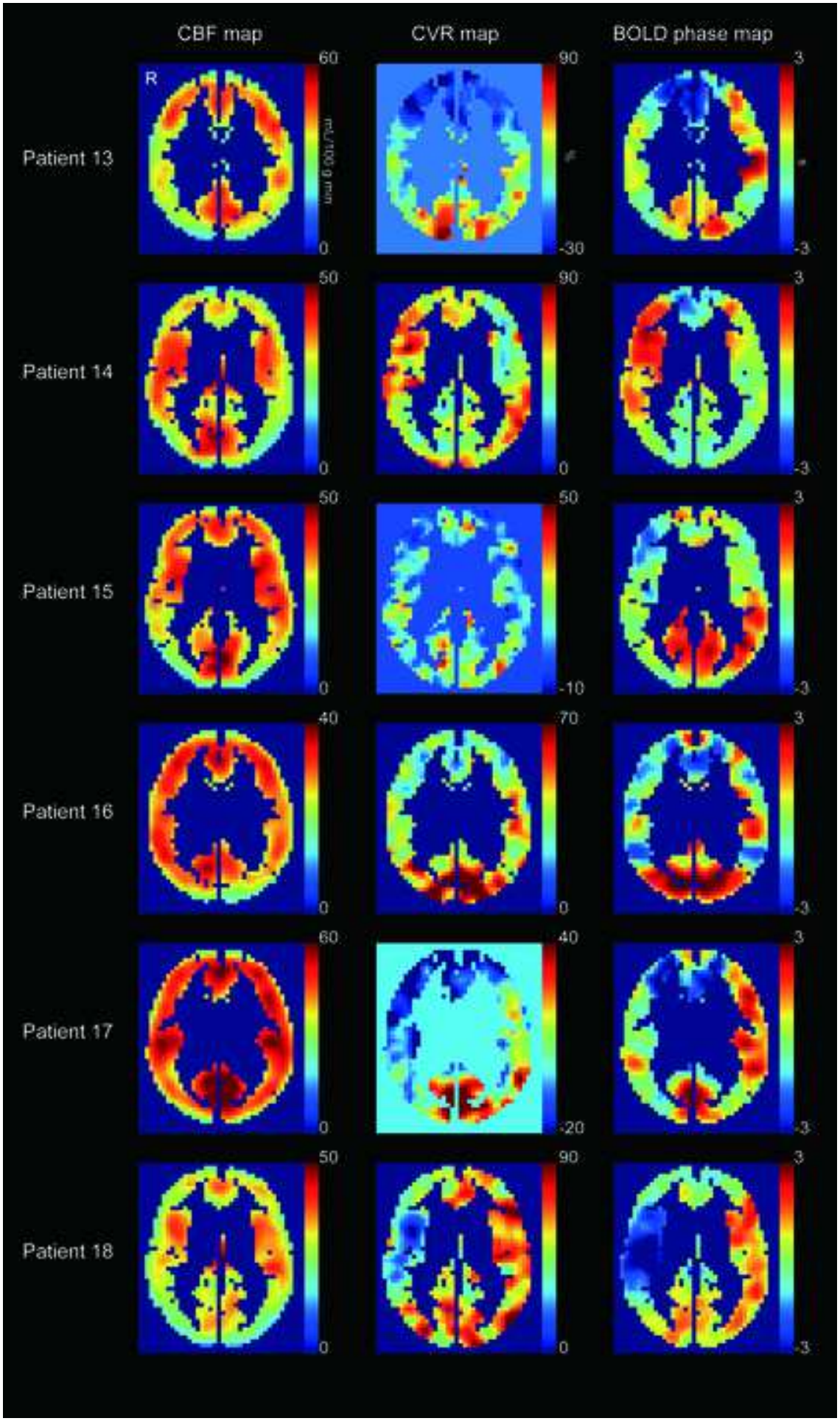

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