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Regional Impairment of Cerebrovascular Reactivity and BOLD Signal in Adults After Stroke

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Background and Purpose—Comparative studies across populations using functional magnetic resonance imaging (fMRI) rely on a similar relationship between blood oxygen level-dependent (BOLD) signal and neural activity. However, in elderly and patients with cerebrovascular disease, impaired cerebrovascular dynamics and neurovascular coupling may explain differences in BOLD contrast across populations and brain regions. The purpose of the study was to determine whether poststroke patients have regional heterogeneities of cerebrovascular reactivity (CVR) and their potential influence on voxel-wise motor-related BOLD signal.

Methods—Using fMRI, 8 fully recovered patients from stroke in the frontal lobe without cortical lesion in the regions of interest located in the primary sensorimotor cortex (SMC), supplementary motor area (SMA), and cerebellum (CRB) were compared with 8 healthy subjects. Motor-related BOLD signal changes (%SC) were evaluated during simple unimanual and bimanual tasks, and CVR was evaluated during hyperventilation (HV). Analyses were performed using Lipsia software in SMC, SMA, and CRB.

Results—In controls, amplitudes of BOLD signal were symmetrical in all regions of interest during all motor tasks and HV. In patients, %SC was decreased in SMC and SMA of the lesioned hemisphere despite their apparent anatomical integrity for all tasks. Impaired CVR was a predictor of impaired motor-related BOLD response in the SMC during contralateral movements ($\beta = -1.87$; $R = -0.75$; $P = 0.03$).

Conclusions—These preliminary findings suggest that CVR heterogeneities may account for task-related BOLD signal changes in patients after stroke. **(*Stroke*. 2005;36:1146-1152.)**

Key Words: hyperventilation ■ magnetic resonance imaging, functional ■ motor activity ■ stroke, ischemic

To investigate mechanisms of recovery and cortical reorganization related to stroke, functional magnetic resonance imaging (fMRI) has become a widely used noninvasive neuroimaging technique based on blood oxygen level-dependent (BOLD) signal. Although the neurovascular coupling remains incompletely understood, several studies performed in steady-state animal preparations and in healthy human volunteers reported a linear relationship between neural activity and the BOLD signal.[1] However, the hemodynamic response can vary across populations, cortical areas, and stimuli duration.[2–5] Clinical investigations brought evidence that BOLD signal was impaired in patients.[3,6–11] Hence, in comparative studies between populations and regions of interest, the assumption of a constant neurovascular coupling is highly questionable under pathological conditions, and inferences on neural activity have to be conducted cautiously.[3] A careful selection of subjects is required to control for relevant cofactors of the BOLD response and cerebrovascular reactivity (CVR) should be evaluated regionally to define individual and population baselines to conduct further comparisons.[3] Rossini et al[11] showed that impaired sensory-induced BOLD contrast was mostly related to impaired CVR.

A number of methods has been proposed to evaluate CVR using different imaging techniques such as transcranial Doppler ultrasonography,[11] positron emission tomography,[12] and fMRI[13] and vasoactive agents such as acetazolamide or CO_2 challenge (CO_2 inhalation or hyperventilation). Hyperventilation (HV) is used as a simple and reliable task to map individual CVR.[13,14] HV induces hypocapnia that reduces cortical MR intensity, which is thought to reflect increased oxygen extraction related to cerebral vasoconstriction and reduced cerebral blood flow (CBF).[14] fMRI BOLD signal is mainly related to small cortical vessels reactivity, and may reveal regional CVR heterogeneities.[13]

To determine whether patients have particular regional CVR heterogeneities and their potential influence on motor-related BOLD signal, we compared fully recovered patients from stroke to healthy subjects during simple motor tasks and hyperventilation using fMRI.

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Clinical Characteristics of the Patients

Patient No./Age*/Sex	Ischemic Infarct				Clinical Features	
	Side	Topography	Volume, cm^3	Time to Stroke†	Initial Motor Deficit‡	Additional Disease
1/72/M	Left	Frontal	40.20	32	4/5	HBP
2/56/W	Right	Frontal	4.50	71	3/5	...
3/42/M	Right	Frontotemporoparietal	61.50	56	3/5	...
4/43/W	Right	Frontal	27.60	85	3/5	...
5/63/W	Right	Frontal	39.60	58	4/5	...
6/52/M	Left	Frontal	23.20	11	4/5	...
7/58/M	Right	Frontotemporoparietal	96.00	60	3/5	HBP
8/34/W	Right	Frontotemporoparietal	23.80	33	3/5	...

*In years.
†In months.
‡According to Mathew Stroke Scale.
HBP indicates high blood pressure; M, man; W, woman.

Subjects and Methods

Subjects

Patients were identified from review of admitting records to Daycare Clinic of Cognitive Neurology, University of Leipzig. Inclusion criteria were: (1) stroke history with full clinical recovery[15] and normal electromyogram recordings from 2 hand muscles (M. flexor pollicis longus, M. extensor digitorum communis); (2) brain infarction of, at least, the frontal lobe without hemorrhage; (3) no macroscopic lesion of the hand representation in primary sensorimotor cortex, SMA, CRB, basal ganglia, or thalamus on 3-dimensional (3D) T1-weighted images; (4) no severe cerebral small-vessels disease on T2-weighted images defined by a score >12 based on MR structural abnormalities;[16] and (5) no significant cerebrovascular stenosis (≥70% based on NASCET measurement) assessed by Doppler and duplex sonography. Exclusion criteria of the study were: (1) excessive blood pressure >140/90 mm Hg at the time of examination; (2) tachycardia (pulse >120/min); (3) hypoxemia (PaO_2 <90 mm Hg); and (4) inappropriate task performance (see HV subsection).

Thus, 8 patients (4 women and 4 men; mean age±SD=52.5±12.4 years) were compared with 8 age-matched healthy volunteers (3 women and 5 men; age=57.8±5.1 years) without neurological or vascular history. Clinical and imaging details of the enrolled patients are presented in the Table and Figure I (available online only at http://www.strokeaha.org). All subjects were nonsmokers and right-handed according to the Edinburgh Handedness Inventory.[17] All subjects gave their informed consent according to the Declaration of Helsinki.

MR Imaging

The protocol was performed on a 3-T whole-body MR scanner (Medspec 300/100; Brucker Medizintecknik). Functional images consisted in acquiring 20 axial planes (field of view: 19.2 cm; matrix: 64×64; slice thickness: 4 mm, gap: 1 mm) parallel to the anterior commissure–posterior commissure plane covering the whole brain and cerebellum using a single-shot gradient-recalled echo-planar imaging sequence (EPI) (time of repetition [TR]/time of echo [TE]: 2000/30 ms; flip angle: 90°). Before functional images, acquisition of anatomical images consisted of a high-resolution 3D T1-weighted MDEFT[18] volume with 116 axial planes (matrix: 256×256; TR/TE: 1200/10 ms; thickness: 1.5 mm, no gap) for anatomical study and coregistration of the functional data, 20 axial T1-weighted MDEFT images (matrix: 256×256; TR/TE: 1300/10 ms; thickness: 4 mm, gap: 1 mm) and 20 axial T1-weighted inversion recovery EPI with identical geometrical parameters as the functional images for coregistration, and 20 axial T2-weighted images (matrix: 512×512; TR/TE: 8500/80 ms; thickness: 4 mm, gap: 1 mm) to determine cerebral small-vessel disease.[16]

Tasks

Before MR examination, all subjects were clinically examined and trained for 15 minutes to perform the tasks correctly. Instructions were visually cued.

Motor Tasks

Three manual tasks were successively performed and consisted of simple hand grip at 1 Hz of the right hand, the left hand, and both hands. Each task was composed of 6 seconds of rest (secondarily discarded of the analysis to allow magnetic field to reach equilibrium), followed by 6 successive blocks (each block alternating 24 seconds of rest and 24 seconds of movement; total duration: 4 minutes and 54 seconds).

Hyperventilation

After motor tasks, subjects were instructed to perform HV at 1 Hz. The task was composed of 3 blocks (each block alternating 1 minute of rest, 2 minutes of HV, 1 minute of rest; total duration=12 minutes). Using a Maglife device (Brucker Medizintecknik), the end-tidal CO_2 partial pressure ($EtCO_2$), respiratory rate, arterial pulse, and O_2 blood saturation were monitored. Appropriate HV was defined by $EtCO_2$ <25 mm Hg.[13]

Data Analysis

Anatomical and functional images were processed using LIPSIA, dedicated software of preprocessing, registration, signal analysis, statistical evaluation, and visualization.[19] Before signal analysis and statistical evaluation, functional data were preprocessed using successively: (1) in-plane motion correction; (2) slice–time correction to compensate for the temporal offset between slices acquired within the same scan using a cubic–spline interpolation; (3) baseline drift correction by using a voxel-wise high-pass filter in the temporal domain (cutoff period of 1.5-times of the stimulation frequency); and (4) spatial Gaussian filter with a kernel size of 5.65 mm full-width half-maximum.

The 3D anatomical data set (3D-MDEFT) was standardized to a stereotactic reference space.[20] A transformation matrix was calculated by mapping the 2-dimensional anatomical slices (2D-MDEFT) onto the 3D-MDEFT images by using a rigid linear registration with 6 degrees of freedom (3 rotational, 3 translational). The inversion recovery EPI data were applied to refine the transformation matrix for EPI functional images. The rotational and translational parameters were subsequently transformed by linear scaling to a standard size. The resulting parameters were then used to transform the

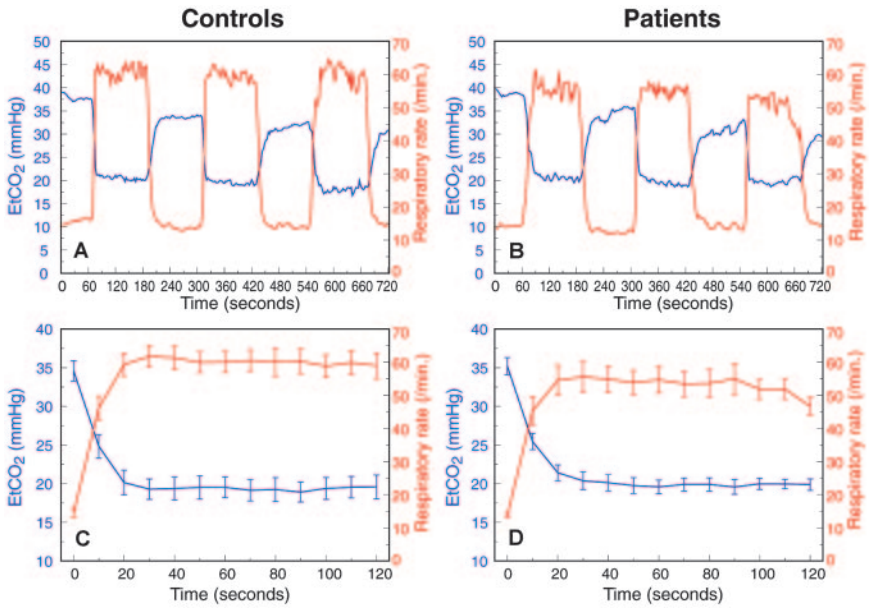

Figure 1. Monitoring of end-tidal P_{CO_2} and respiratory rate during hyperventilation. Time courses for the whole task (A, B), and for stimulus block (mean±SEM); (C, D) showed similar performances in both group, despite a small decrease of respiratory rate over the last seconds of the block in patients.

functional slices using tri-linear interpolation, so that the resulting functional slices were aligned with the stereotactic coordinate system.

For each subject, signal time courses were extracted from 3 different anatomical regions in each hemisphere: primary SMC, SMA, and the quadrangular lobule of the CRB. In each anatomical region, the voxel corresponding to the maximum z value during the bimanual task for z value >3.09 ($P<0.001$) was identified individually. The signals of these voxels were averaged to the signals of their 26 contiguous voxels defining isovolumetric regions of interest (ROIs) of 729 mm^3. Percentage of signal change (%SC) was calculated for each time point against a resting baseline. For each pair of homologous ROI, interhemispheric differences of %SC (Δ%SC=ipsilesional%SC−contralesional%SC) were calculated. Individual results are expressed in mean±SD and group results in mean±SEM. Statistics of clinical data and signal changes were conducted using statistical software (version 11.0; SPSS Inc). Comparisons between averaged group data were performed using *t* test, and between individual data using rank-order Wilcoxon, and Mann–Whitney tests when appropriate.

Results

Both controls and patients performed HV similarly. At rest, the respiratory rate and the $EtCO_2$ were 14.5±4.0/min and 34.6±4.0 mm Hg in controls, and 13.7±2.1/min and 35.2±3.3 mm Hg in patients. During HV, respiratory rate raised up to 58.9±9.5/min in controls and to 52.9±11.3/min in patients, and $EtCO_2$ decreased to 19.9±4.2 mm Hg in controls and to 20.5±2.5 mm Hg in patients (Figure 1). Illustrative HV statistical maps for controls and patients with right infarct are displayed in additional Figure II (available online only at http://www.strokeaha.org).

The results of each pair of ROIs are presented separately because of the different origins of their vascular supply, their nonlinear vascular dynamics,[2] and their different potential changes related to the brain infarct. In controls, the ROI side was noted left and right, whereas in patients ROIs were noted ipsilesional and contralesional. Furthermore, because of hemispheric specialization and to allow comparisons of activation for different ROIs in accordance to their functional role during unimanual tasks, the ROI side was additionally noted ipsilateral and contralateral to the moving hand.

During bimanual movements, all subjects had significant bilateral activation in SMC, SMA, and CRB. Anatomical coordinates in Talairach space of the maximum z values were in SMC: x=34.4±4.7, y20.7±6.0, z=53.6±4.8 in controls, and x=34.0±5.1, y=−26.1±4.5, z=51.1±3.7 in patients; for SMA: x=3.8±2.9, y=−11.3±4.7, z=49.9±4.0 in controls, and x=5.3±2.9, y=−10.1±5.3, z=54.4±5.2 in patients; for CRB: x=17.8±5.0, y=−55.4±3.6, z=−12.7±2.6 in controls, and x=17.4±4.6, y=−52.7±4.8, z=−17.4±3.6 in patients. These coordinates were similar in both groups.

Mean percentage of signal change (%SC) are displayed in Figures 2 and 3. In controls, comparisons based on averaged %SC showed no interhemispheric difference in all ROIs for HV and all motor tasks (Figure 2). In patients, interhemispheric comparisons showed that mean %SC were lower in ipsilesional SMC and SMA for all task. No difference was detected in CRB except decreased %SC in the contralesional CRB during contralateral movements (Figures 2 and 3).

Because of symmetrical %SC in controls, mean values of left and right ROIs were used for intergroup comparisons (Figure 3). Compared with controls, mean %SC were lower in ipsilesional SMC and SMA for all tasks, and in contralesional CRB during bimanual and contralateral movements. %SC were similar in contralesional SMC for all tasks, in contralesional SMA during bimanual and contralateral movements, and in ipsilesional CRB for all tasks. %SC were higher in contralesional SMA during HV and ipsilateral movements (Figure 3). Illustrative statistical maps for controls and patients with right infarct during HV and motor tasks are displayed in Figure 4.

For patients, linear regression analyses were conducted to evaluate the prediction of individual interhemispheric %SC difference during motor tasks ($\Delta\%SC_{MOT}$) from interhemispheric %SC difference during HV ($\Delta\%SC_{HV}$). No significant relationship was obtained from mean %SC calculated over

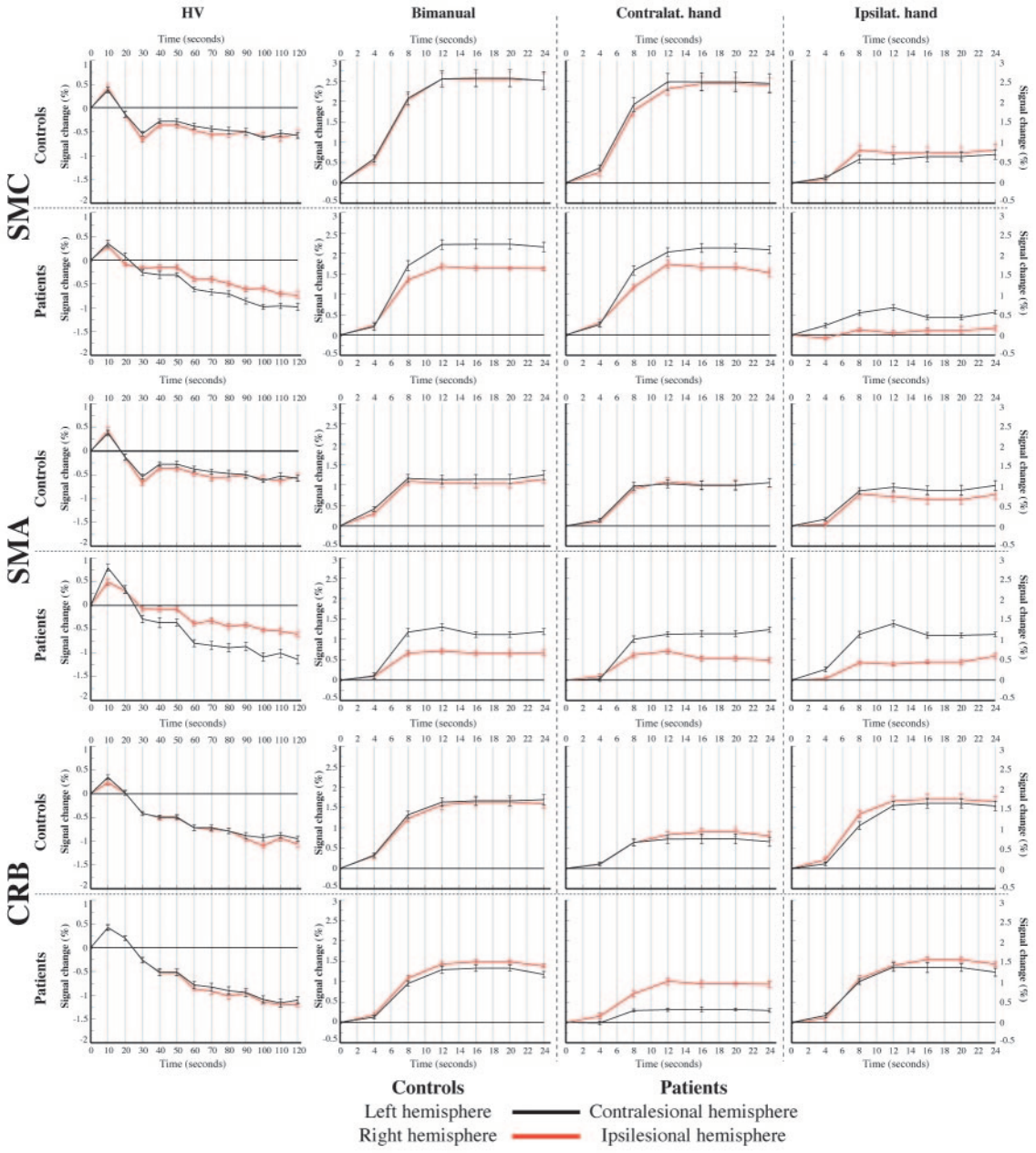

Figure 2. Mean temporal changes of BOLD signal during hyperventilation and motor tasks. In controls, time course of signal changes for stimulus block (%SC±SEM) were symmetrical in both hemispheres for all pairs of ROIs. In patients, decreased BOLD signal were noted in ipsilesional SMC and SMA for HV and all motor tasks. In CRB, decreased BOLD signal was only present in the contralesional hemisphere during contralateral movements.

the whole duration of tasks execution. Thus, mean difference signal change was evaluated over its steady state that was reached over the second half of the task execution. In SMC and for contralateral and bimanual movements, the scatterplot indicates that the 2 variables were linearly related such that as overall $\Delta\%SC_{HV}$ increased the overall $\Delta\%SC_{MOT}$ decreased. For ipsilateral movement, no significant correlation was detected (Figure 5). In SMA, linear regression analyses did not show any significant relationship between $\Delta\%SC_{HV}$ and $\Delta\%SC_{MOT}$ (data not shown). The lesion volume was not correlated to any interhemispheric %SC difference.

Discussion

In fully recovered patients after stroke, we have shown that the amplitude of BOLD signal detected within the ROIs was decreased during motor tasks in ipsilesional SMC and SMA despite their apparent anatomical integrity. Using HV to evaluate regional CVR, we have shown that CVR was heterogeneous across brain regions and asymmetrical in patients. Impaired CVR was a predictor of impaired motor-related BOLD response in the SMC during contralateral movements. Our preliminary results show that these CVR heterogeneities could be a methodological issue in functional

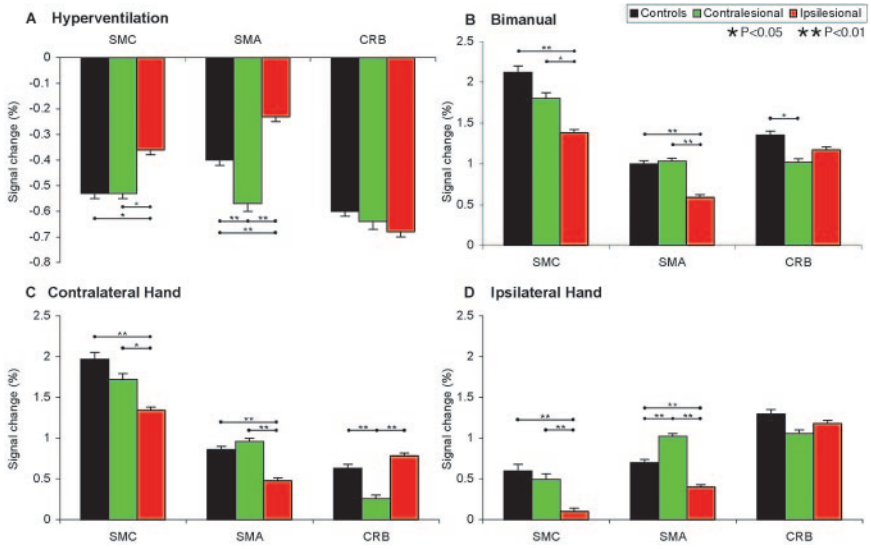

Figure 3. Mean amplitude of BOLD signal during hyperventilation and motor tasks. Comparisons across mean signal changes (%SC±SEM) in controls and contralesional and ipsilesional ROIs show significant decrease in ipsilesional SMC and SMA for both HV (A) and motor tasks (B to D). In CRB, similar signal changes were observed during ipsilateral movements and HV that suggest similar movements characteristics for each hand without CVR asymmetry.

imaging studies using task-related BOLD signal in poststroke patients.

After stroke, motor recovery is accompanied by changes in activation pattern over time and our results in patients with good motor performance are in line with previous studies, including a decrease of BOLD signal in ipsilesional SMC and SMA.[21] Although BOLD signal remains incompletely understood, impaired task-related BOLD signal might reflect local changes in microvascular dynamics, neural activity, and energy demand,[1] as previously suggested in patients[3] with significant cerebrovascular stenosis,[6,7] and focal brain lesions such as infarction[9,11] and neoplasm.[8,10]

Using fMRI BOLD signal during HV, CVR mapping showed intrahemispheric differences supported by regional CVR heterogeneities.[12,13] However, signal changes were symmetrical in controls and in CRB of patients remotely located from infarction. In contrast, asymmetrical responses were observed in SMC and SMA that were closer to the infarction. Such regional altered CVR has been already reported in patients after stroke without arterial occlusive disease.[22] It has also been described in patients with major cerebral arterial occlusive disease and correlated to impaired motor-related BOLD signal.[6] In patients with unilateral stroke but without cerebrovascular stenosis, bilateral impaired motor-related BOLD signal have been reported in SMC,[9] but no CVR evaluation was performed and most patients had arterial hypertension and lacunar infarct that might have decreased global CVR.[4] To better control neural activity, Rossini et al[11] used median nerve stimulation measured by magnetoencephalography and showed that impaired BOLD signal in primary sensory cortex was mainly related to impaired CVR evaluated by transcranial Doppler ultrasonography after CO_2 inhalation. However, no significant correlation was detected between altered CVR and BOLD responses. Such discrepancy could be caused by the method used to

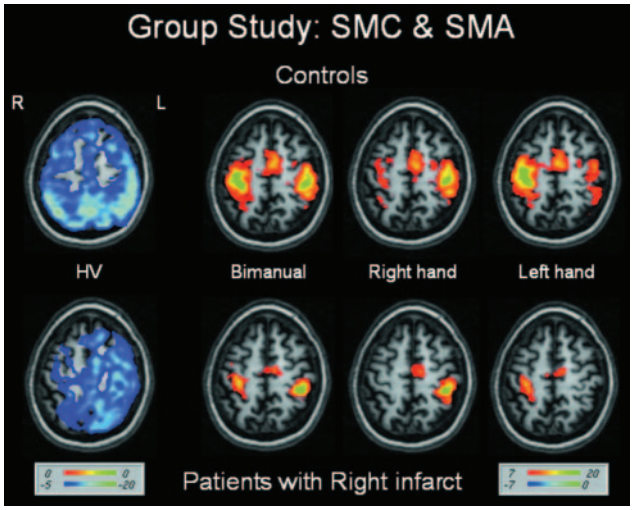

Figure 4. Hyperventilation and motor-related signal changes at the SMC and SMA level. The representation of group studies in controls and in patients with right infarct (n=6) show decreased z values in both ipsilesional ROIs for all tasks (color scales for HV on the left, and for motor tasks on the right).

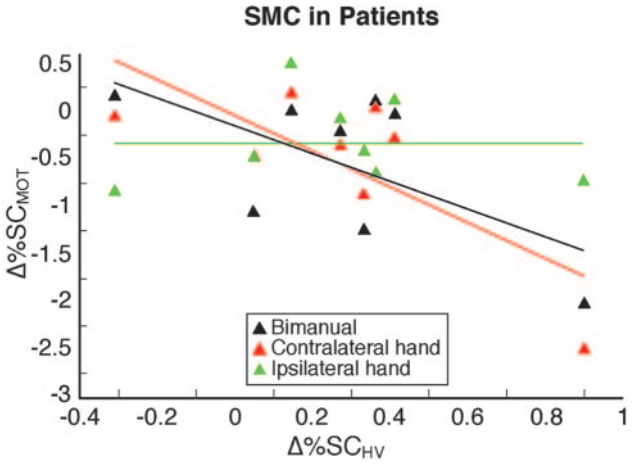

Figure 5. Relationships between altered cerebrovascular reactivity and motor-related BOLD signal in SMC of patients. Scatterplot with regression slopes in SMC shows that impaired steady-state motor-related BOLD signal estimated with $\Delta\%SC_{MOT}$ is dependent of impaired CVR estimated with $\Delta\%SC_{HV}$ during contralateral ($\Delta\%SC_{MOT}=-1.87\Delta\%SC_{HV}-0.04$; $R=-0.75$, $P<0.05$, 2-tailed) and bimanual movements ($\Delta\%SC_{MOT}=-1.45\Delta\%SC_{HV}-0.15$; $R=-0.62$; $P=0.05$, 1-tailed).

estimate CVR, which relies mainly on large-vessel dynamics rather than small-vessel reactivity involved in BOLD contrast. Furthermore, of 10 patients, 8 patients had an arterial hypertension and 3 had a significant carotid stenosis that might have accounted for interindividual variability.[11]

Here, we have shown that impaired CVR was a predictor of impaired motor-related BOLD signal in SMC during contralateral movements. A recent study in rats did not find a similar correlation although decreased CVR and stimulation-induced activation were reported in the affected hemisphere but were not significant.[23] This discrepancy may be caused by several methodological differences including examinations performed after incomplete and variable recovery across animals, ROI selection in the ipsilesional SMC by mirroring the contralesional ROI, possible extension of infarction within the ipsilesional ROI, and functional activation determined using the activation volume of statistical maps, whereas we used percentage of signal change to avoid threshold issues.

Several mechanisms like ultrastructural changes in cerebral vessels caused by atherosclerosis and changes in cerebrovascular reactivity have been advocated to explain impaired neurovascular coupling in elderly and in patients. After stroke, perilesional gliosis and disruption of aminergic and cholinergic fibers that innervate the vasculature may alter neurovascular coupling in macroscopically intact adjacent regions.[3]

Basal perfusion conditions may also influence BOLD response.[24] In healthy subjects using fMRI with CO_2 challenge, as expired CO_2 increased, basal CBF increased and task-related BOLD signal decreased.[24] Furthermore, CVR might be nonlinearly modulated by intra-arterial CO_2 pressure.[25] After stroke, changes in basal perfusion were reported in the surrounding zones of the infarct[26] but mean hemispheric CBF remained normal.[22,26] We cannot exclude limited regional changes in CBF that may account for the absence of relationship between impaired CVR and task-related BOLD signal in the SMA. It could be hypothesized that basal CBF in the territories of the anterior cerebral arteries is modulated by a persistent collateral perfusion of the infarcted territory of the middle cerebral artery with an increased CBF in the ipsilesional SMA and a decreased CBF in the contralesional SMA leading to a decrease and an increase of BOLD signal, respectively.[24] But such changes were observed during hyperventilation and ipsilateral movements only. Thus, further studies including a voxel-based evaluation of basal perfusion would be necessary to address this issue.

Influence of medication including antihypertensive treatment on BOLD signal and vasoreactivity is undergoing investigation.[27,28] In this study, 2 patients (patients 1 and 7) had current antihypertensive medication using β-blockers at the time of examination. We cannot exclude potential effects of medication on the results as reported for angiotensin-converting enzyme inhibitors in a transcranial Doppler study using acetazolamide.[27] However, a recent fMRI study showed no effect of β-blocker infusion on BOLD signal or vasoreactivity.[28] Despite methodological differences between these studies, these discrepancies suggest further investigation on medication effect on BOLD signal and vasoreactivity and careful interpretations of BOLD studies in patients administered medication.

Changes in neural activity could also be advocated because activation in SMC and SMA are correlated to movement characteristics such as frequency, amplitude, and strength.[29–31] This hypothesis seems unlikely, at least in contralateral SMC and SMA, because all patients had fully recovered at the time of examination, movement frequency was visually triggered and monitored, and signal changes in ipsilateral CRB, also dependent of movement parameters,[31] were similar. In ipsilateral SMC and SMA, and contralateral CRB, decreased neural activity remains possible in the affected hemisphere, suggesting that lesion-induced neural reorganization may give priority to eloquent regions.[32] However, based on BOLD fMRI data, evaluation of neural changes is deductive and largely speculative. Interpretation of the results must be performed cautiously, especially in patients by whom empirical evidence of BOLD signal impairment has been reported. Changes in energy demands are unlikely because increase in oxygen consumption could be excluded in patients after stroke.[33]

Because combined temporal changes in neural activity and cerebrovascular hemodynamics occur during recovery after brain lesion, appropriate evaluation of neural plastic changes remains challenging. In the present study, we have shown that CVR regional heterogeneities influence task-related BOLD signal in eloquent areas despite their apparent anatomical integrity but located close to an injured brain region. This relationship could partially explain empirical evidence of impaired activation in focal brain-lesioned patients.[3,6–11] Based on small individual samples, these preliminary results need to be confirmed on larger populations. The relationship between basal perfusion conditions and CVR remain to be determined at the voxel level. Although HV is a simple and reliable task to evaluate CVR, interindividual variability in task performance might have weakened the results and a standardized method independent of individual performance is suitable for further experiments. Further studies based on comparisons across populations must rely on selection criteria that control general and local conditions that may modify cerebrovascular hemodynamics such as comorbidities, medication, or smoking,[3] whereas methodological developments may improve modeling the neurovascular coupling at regional and individual levels.

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