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Heterogeneous motor BOLD-fMRI responses in brain areas exhibiting negative BOLD cerebrovascular reactivity indicate that steal phenomenon does not always result from exhausted cerebrovascular reserve capacity

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Heterogeneous motor BOLD-fMRI responses in brain areas exhibiting negative BOLD cerebrovascular reactivity indicate that steal phenomenon does not always result from exhausted cerebrovascular reserve capacity

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ABSTRACT

Introduction: Brain areas exhibiting negative blood oxygenation-level dependent cerebrovascular reactivity (BOLD-CVR) responses to carbon dioxide (CO_2) are thought to suffer from a completely exhausted autoregulatory cerebrovascular reserve capacity and exhibit vascular steal phenomenon. If this assumption is correct, the presence of vascular steal phenomenon should subsequently result in an equal negative fMRI signal response during a motor-task based BOLD-fMRI study (increase in metabolism without an increase in cerebral blood flow due to exhausted reserve capacity) in otherwise functional brain tissue. To investigate this premise, the aim of this study was to further investigate motor-task based BOLD-fMRI signal responses in brain areas exhibiting negative BOLD-CVR.

Material and methods: Seventy-one datasets of patients with cerebrovascular steno-occlusive disease without motor defects, who underwent a CO_2-calibrated motor task-based BOLD-fMRI study with a fingertapping paradigm and a subsequent BOLD-CVR study with a precisely controlled CO_2-challenge during the same MRI examination, were included. We compared BOLD-fMRI signal responses in the bilateral pre- and postcentral gyri – i.e. Region of Interest (ROI) with the corresponding BOLD-CVR in this ROI. The ROI was determined using a second level group analysis of the BOLD-fMRI task study of 42 healthy individuals undergoing the same study protocol.

Results: An overall decrease in BOLD-CVR was associated with a decrease in BOLD-fMRI signal response within the ROI. For patients exhibiting negative BOLD-CVR, we found both positive and negative motor-task based BOLD-fMRI signal responses.

Conclusion: We show that the presence of negative BOLD-CVR responses to CO_2 is associated with heterogeneous motor task-based BOLD-fMRI signal responses, where some patients show -more presumed- negative BOLD-fMRI signal responses, while other patient showed positive BOLD-fMRI signal responses. This finding may indicate that

Abbreviations: BOLD, Blood oxygenation-level dependent; CBF, Cerebral blood Flow; CO_2, Carbon dioxide; $CRMO_2$, Cerebral metabolic rate of oxygen; CVR, Cerebrovascular reactivity; fMRI, Functional magnetic resonance imaging; O_2, Oxygen; $PetCO_2$, End-tidal pressure of CO_2; $PetO_2$, End-tidal pressure of O_2; ROI, Region of Interest; SPM, Statistical parameter mapping (software Program).

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the autoregulatory vasodilatory reserve capacity does not always need to be completely exhausted for vascular steal phenomenon to occur.

1. Introduction

For blood oxygenation-level dependent cerebrovascular reactivity (BOLD-CVR), the theorem of vascular steal phenomenonin patients with cerebrovascular steno-occlusive disease is the observation of a negative -paradoxical- BOLD-functional magnetic resonance imaging (fMRI) signal response to hypercapnia (carbon dioxide -CO_2-). [1] This paradoxical BOLD-fMRI signal response is thought to be associated with maximal vasodilatation of the affected vascular bed, indicating an exhausted autoregulatory vasodilatory reserve capacity. [2]

The BOLD contrast depends on changes in deoxyhemoglobin content as well as blood volume, and therefore no cerebral blood flow (CBF) changes per sé, but it has been shown to have a good correlation with CBF-based CVR in patients with cerebrovascular steno-occlusive disease. [3,4] In healthy brain tissue with normal autoregulatory vasodilatory reserve capacity, a positive BOLD-fMRI signal response after hypercapnia arises from the outwash of deoxyhemoglobin due to an increase in CBF. [5] In regions with vascular steal phenomenon, the paradoxical blood flow decrease results in a relative increase in deoxyhemoglobin and consequently a negative BOLD-CVR. [2]

Traditionally, the BOLD-fMRI signal response is used not as a CBF surrogate, but as a surrogate marker for underlying neuronal activity, by combining a task-based paradigm with a BOLD-fMRI study. [6] Based on the premise that neuronal activity causes a functional hyperemia (i.e. increased cerebral blood flow and therefore increased oxygen delivery that is greater than the increase in oxygen consumption), this results in a decrease in deoxyhemoglobin, which consequently produces a positive BOLD-fMRI signal response. [5] This means that obtaining a positive task-based BOLD-fMRI signal response is dependent on the available autoregulatory vasodilatory reserve capacity and accordingly it has been shown that lower autoregulatory vasodilatory reserve capacity inevitably leads to a dampened BOLD-fMRI signal response. [7–9]

This relationship between task-based BOLD-fMRI and BOLD-CVR would even be more skewed when taking the classical vascular steal phenomenon theorem into account.

Here, in brain regions exhibiting vascular steal phenomenon, neuronal activity would cause a local increase in cerebral metabolism (i.e., increase in deoxyhemoglobin) without the expected functional hyperemia, necessary for a positive BOLD-fMRI signal response. This would consequently increase the deoxyhemoglobin concentration and result in a negative BOLD-fMRI signal response. Although this pathophysiological mechanism seems plausible, this theorem needs further investigation.

Therefore, to study the premise that vascular steal phenomenon, seen in patients with cerebrovascular steno-occlusive disease, comes with a completely depleted autoregulatory vasodilatory reserve capacity, we investigated motor-task based BOLD-fMRI signal responses in the presence of negative BOLD-CVR.

2. Material and methods

2.1. Patient enrollment and MRI protocol

From an ongoing prospective database of BOLD-CVR measurements, approved by the local research ethics board (KEK-ZH-Nr. 2012–0427 & KEK 2020–02314), we analyzed patients with cerebrovascular steno-occlusive disease who had undergone both BOLD-CVR and task-based BOLD-fMRI studies on the same day. Informed consent was signed by all the included patients prior to inclusion in the BOLD-CVR database.

Only patients without sensory-motor deficits at the time of scanning were considered for this study. All additional clinical information (e.g. age, dominant hemisphere, side of cerebrovascular steno-occlusive disease)were gathered from review of the medical record.

Exclusion criteria were as follows: Head motion of >2 mm during either the BOLD-CVR or the task based BOLD fMRI study, failure of completing the whole task-based BOLD fMRI sequence.

Additionally, BOLD-CVR and task-based BOLD-fMRI data from 42 healthy subjects were extracted, which were used to quantitatively define our bilateral Regions of Interest (ROI).

MRI-data were obtained on a 3 Tesla Skyra VD13 MRI (Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil. BOLD-fMRI parameters used for both BOLD-CVR as well as the task-evoked BOLD-fMRI measurements consisted of axial two-dimensional (2D) single-shot EPI sequence planned on the ACPC line plus 20° (on a sagittal image) voxel size 3 × 3 × 3 mm3, acquisition matrix 64x64x35 ascending interleaved slice acquisition, slice gap 0.3 mm, GRAPPA factor 2 with 32 ref. lines, repetition time/ echo time 2000/30 ms, flip angle 85°, bandwidth 2368 Hz/Px, Field of View 192 × 192 mm. For every subject, we obtained 200 BOLD-fMRI volumes during the BOLD-CVR study and 135 volumes during the task-based BOLD-fMRI study. A three-dimensional (3D) T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo volume was obtained with the same orientation as the fMRI scans for overlay purposes. Acquisition parameters of the T1-weighted image were voxel size 0.8 × 0.8 × 1.0 mm3 with a field of view 230x230x176 mm3 and scan matrix of 288x288x176, TR/TE/TI 2200/5.14/900 ms, flip angle 8°.

2.1.1. CO_2 stimulus

We used an automated gas delivery system (RespirAct™, Thornhill Research Institute, Toronto, Canada) with computer-controlled CO_2 and oxygen (O_2) application measuring end-tidal partial pressure of CO_2 and O_2 ($PetCO_2$ resp. $PetO_2$) that are equivalent to P_aCO_2 resp. P_aO_2. [10]

2.1.2. BOLD cerebrovascular reactivity study protocol

Each study protocol started with a preparation phase in the MRI for measurement of resting state $PetCO_2$ during normal breathing. During the BOLD-CVR scan, the subject's $PetCO_2$ derived from the preparation phase was clamped at their individual $PetCO_2$ resting level for 100 s, the $PetCO_2$ was then increased to ~10 mmHg above the resting $PetCO_2$ level for 80 s. The $PetCO_2$ was then decreased to the resting level again for the remaining time. During this whole protocol, $PetO_2$ was clamped at the individual resting state level.

2.1.3. Task-based BOLD-fMRI study protocol

Following the BOLD-CVR scan, every patient underwent a task-based BOLD-fMRI scan. The task-based BOLD-fMRI study consisted of a bilateral thumb-to-finger (finger-tapping) paradigm, using all digits - with arms and hands placed on the MRI table along the body - which lasted 30 s each time and was repeated 4 times with a resting period of 30 s in between. This protocol was used in 2 previous studies. [7,8] All patients received an instruction beforehand and the correct execution of the task was checked by one of the investigators each time. In case of suboptimal execution, the task-based BOLD-fMRI study was repeated. The $PetCO_2$ and $PetO_2$ was clamped at the subjects own resting $PetCO_2$ during the whole protocol. [8]

2.2. Image analysis

2.2.1. Pre-processing

Temporal and spatial pre-processing of the anatomical (T1-weighted image) and functional (BOLD-CVR and task-based BOLD fMRI) images were done using Statistical Parametric Mapping (SPM) 12 (Wellcome

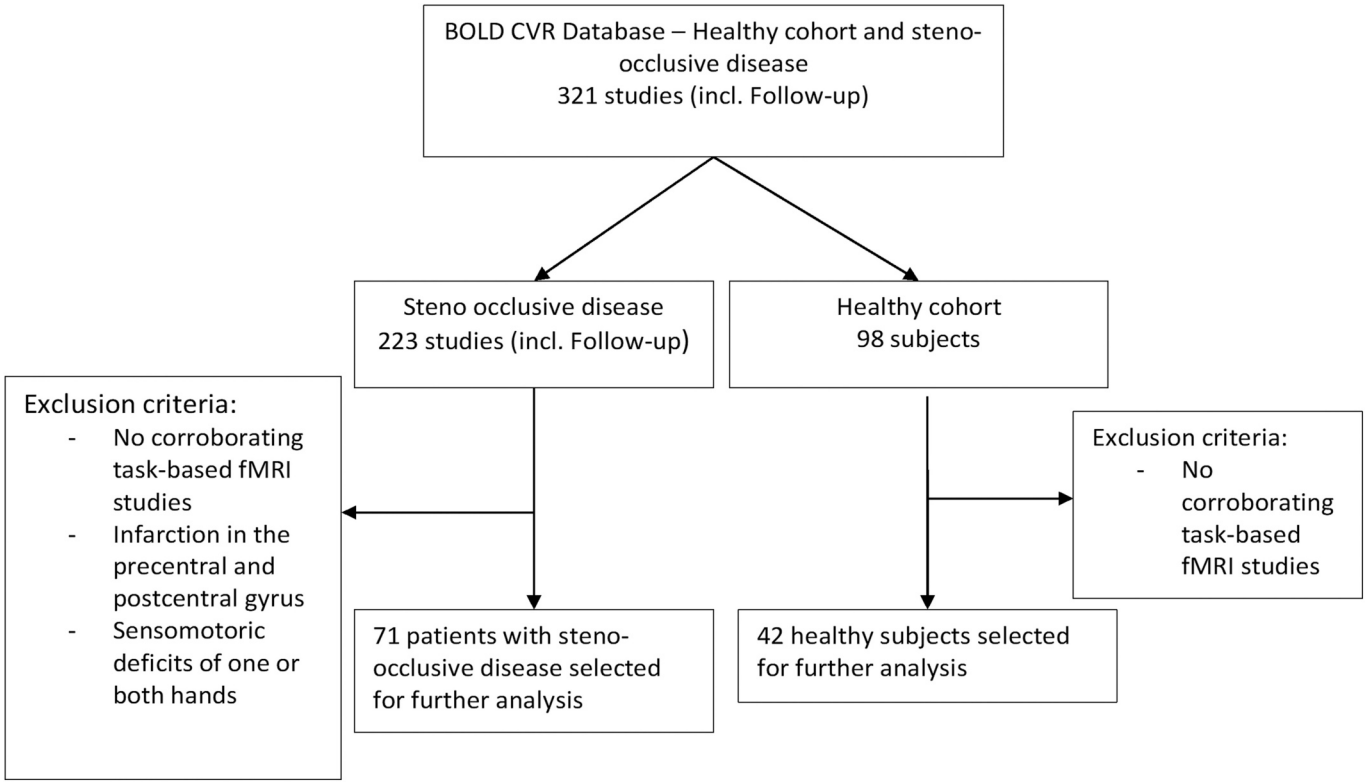

Fig. 1. Flow chart depicting patient inclusion.
Abbreviation: BOLD: Blood-oxygenation-level-dependent; CVR: cerebrovascular reactivity (%BOLD signal change/mmHg CO2); fMRI: functional magnetic resonance imaging (in t-values).

Trust Centre for Neuroimaging, Institute of Neurology, University College London, UK). For both BOLD-fMRI sequences, slice-timing and motion-correction was used. Then, the T1-weighted imaging was segmented into grey and white matter probability maps. The T1-weighted image and the BOLD-fMRI images derived from both protocols were normalized into Montreal Neurological Institute Space using predefined algorithms within SPM. Last, all BOLD-fMRI images were smoothed using a Gaussian Kernel of 6 mm full-width-at-half-maximum.

2.2.2. BOLD-CVR calculations

Time delay corrections were done between the CO_2 and BOLD-fMRI time courses on a voxel-by voxel basis. [11] After these time delay corrections were executed, BOLD-CVR, defined as the percentage BOLD-fMRI signal change/mmHg CO_2 was calculated from the slope of a linear least square fit of the BOLD-fMRI signal time course and the CO_2 time series on a voxel-by-voxel basis. [11] This method has been described and applied in previous work by our group. [4,12,13]

2.2.3. Task-based BOLD-fMRI signal response

Task-based BOLD-fMRI signal responses were derived as followed: BOLD-fMRI signal response maps in the Montreal Neurological Institute space containing t-values for patients and controls were created through first level analysis using SPM12. This analysis paradigm uses a mass-univariate approach based on General Linear Models (i.e. voxel-wise *t*-test). Motion correction, as well as correction for small CO_2 changes during the whole paradigm were applied to optimize the signal.

2.3. Defining the ROI

2.3.1. Second level analysis

BOLD-fMRI signal response maps of all healthy subjects created from the first-level (or subject-level) analysis were used as inputs for the second-level (group-level) analysis. The BOLD-fMRI signal response maps of the included healthy subjects ($n = 42$) contained results from the whole-brain test during the fingertapping paradigm. In the case of this study, each voxel in the BOLD-fMRI signal response image represented the relative BOLD-fMRI signal difference between the fingertapping and rest period for that specific voxel.

The resulting group-analysis BOLD-fMRI signal response image was further processed using in-house scripts made using Matlab 2020. We determined the region in which a significant BOLD-fMRI signal response was present in 99% of the included healthy control group (+2.5 standard deviation). This segmentation resulted preservation of activated regions within the bilateral pre- and postcentral gyrus, activation within the supplementary motor area and the cerebellum. The pre-and postcentral gyri are anatomically well defined and have a strong inter-subject spatial agreement on structural imaging. As such, the supplementary motor area shows more anatomical variation and is therefore is less well suited for BOLD-fMRI group analyses. Moreover, BOLD-CVR in the cerebellum is potentially affected by crossed cerebellar diaschisis in this particular cerebrovascular patient cohort, and is therefore also not suitable for a BOLD-CVR and BOLD-fMRI signal response analysis. Thus, we decided to only study the BOLD-fMRI signal responses in the pre- and post-central gyri. [12,14]

To maintain only the significant BOLD-fMRI signal responses within the pre- and postcentral gyrus all other regions were manually masked out.

2.4. Determination of the BOLD-fMRI and BOLD-CVR signal patterns

The subsequent ROI was then placed on both the BOLD-CVR and task-based BOLD-fMRI signal response maps. The following values were extracted from each ROI

1. Average BOLD-CVR for each ROI
2. Average task-based BOLD-fMRI signal response in t-values

Table 1
Baseline characteristics.

Baseline characteristics and BOLD evaluations ($n = 71$)	
Sex (n/%)	
Female	23 (32%)
Male	48 (68%)
Age (mean ± SD)	62
Dominant hemisphere (right)	70 (99%)
Location of primary/most affected artery: (n/%)	
Right	28 (39%)
Left	36 (51%)
Bilateral (affected = left in results)	7 (1%)
TIA	9 (13%)
Ischemic event	44 (62%)
Amaurosis fugax	8 (11%)
NO symptoms	10 (14%)
Vascular Risk factors: (n/%)	
Hypertension:	49 (69%)
Dyslipidemia:	31 (44%)
Smoking:	35 (49%)
Diabetes:	10 (14%)
Obesity	14 (20%)
Positive family history:	13 (18%)
CO_2 during baseline (mean ± SD)	36.3 ± 2.1
CO_2 during hypercapnia (mean ± SD)	45.4 ± 3.2
CO_2 during fingertapping (mean ± SD)	35.8 ± 2.8
Mean BOLD-CVR within the ROI of the:	
The affected hemisphere (mean ± SD)	0.07 ± 0.08
The unaffected hemisphere (mean ± SD)	0.13 ± 0.06
Both hemispheres (mean ± SD)	0.10 ± 0.07
Mean BOLD fMRI signal activation within the ROI of the:	
The affected hemisphere (mean ± SD)	3.5 ± 2.7
The unaffected hemisphere (mean ± SD)	4.0 ± 2.4
Both hemispheres (mean ± SD)	3.7 ± 2.6

Abbreviations: BOLD: blood oxygenation level dependent, CO_2: carbon dioxide, CVR: cerebrovascular reactivity (% BOLD signal change/mmHg CO_2), fMRI: functional magnetic resonance imaging (here applied using a bilateral finger-tapping protocol, SD: standard deviation, TIA: transient ischemic attack.

3. Number of voxels with negative BOLD-CVR within the ROI
4. Number of voxels with negative BOLD-fMRI signal response t-values.

2.5. Statistical analysis

Statistical analyses were done using the statistical program Statistical Package for Social Sciences (version 29.0). Each variable was tested for normal distribution using the Shapiro Wilks test. Correlation analysis of normal distributed variables was done by determining the Pearson correlation coefficient (R) and deemed significant if $p < 0.05$.

3. Results

A total of 71 studies with respectively 142 ROI's (affected/unaffected hemispheres) were included for further analysis. A flow chart showing subject inclusion can be found in Fig. 1. Baseline characteristics, mean BOLD-CVR and BOLD-fMRI signal response can be found in Table 1.

Images of the fingertapping region of the healthy cohort and 2 examplary patients can be found in Fig. 2. Within our ROI, the mean BOLD-CVR and BOLD-fMRI t-values did correlate ($R = 0.40$, $p < 0.001$, Fig. 3). Regions with strong positive BOLD-CVR showed a strong positive t-values in the BOLD-fMRI signal response maps. However, the patients with impaired BOLD-CVR showed a mixed result. On average the BOLD-fMRI signal response t-values were attenuated, however even in patients with BOLD-CVR around or even below zero, the corroborating BOLD-fMRI signal response t-values differed between patients with high amounts of voxels with negative BOLD-fMRI signal response t-values and patients with no voxels with negative BOLD-fMRI signal response t-values (Fig. 4). This is more seen in Fig. 5, where we displayed the number of negative voxels of BOLD-fMRI signal response in function of the number of negative voxels with BOLD-CVR. Here some voxels

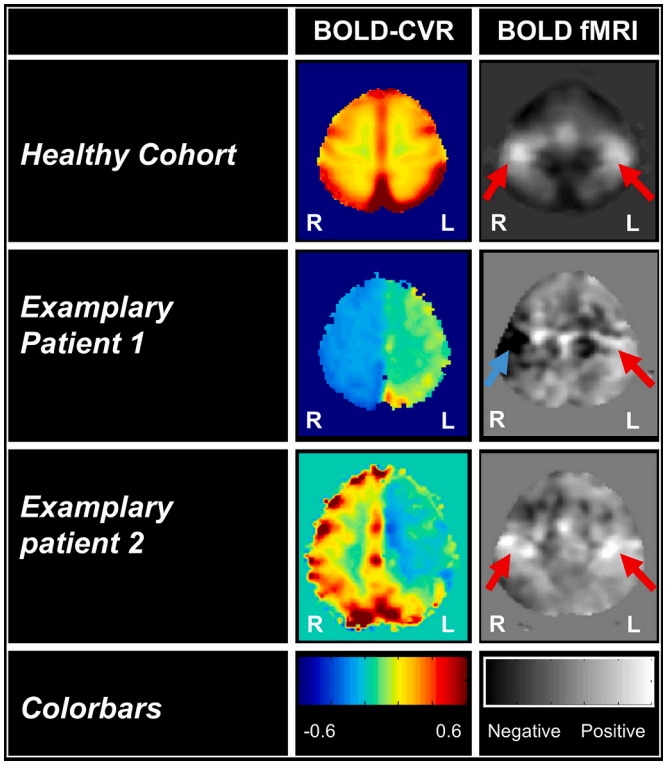

Fig. 2. Images of the healthy cohort and 2 exemplary patients. Patient 1 (male – 68 years old - right sided ICA occlusion) shows steal phenomenon (blue) on the CVR map (left) with a concurring negative (black) response in the motor-task BOLD fMRI map (right). The blue arrow points to the region with a negative BOLD fMRI response. The other side with intact CVR shows preserved (white) activation. The red arrows in the image point to the regions with positive BOLD fMRI response.
The top image represents the map derived from the second level analysis of the combined healthy database with the red arrows pointing to the bilateral regions of interest.
Exemplary patient 2 (male – 58 years old – left sided ICA occlusion) shows steal phenomenon on the left side with both positive responses (red and blue arrow) in the motor-task BOLD fMRI maps.
Abbreviation: BOLD: Blood-oxygenation-level-dependent; CVR: cerebrovascular reactivity (%BOLD signal change/mmHg CO2); fMRI: functional magnetic resonance imaging (in t-values); ICA: internal carotid artery; (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

increase linearly meaning a negative voxels with BOLD-CVR results in a voxel with negative BOLD-fMRI signal response, however most patients show no or limited number of voxels with negative BOLD-fMRI signal response.

4. Discussion

With our study, we demonstrate that the presence of negative –paradoxical- BOLD-CVR results in heterogeneous BOLD-fMRI signal responses. It does result in negative motor task-based BOLD-fMRI signal responses in some patients, following the classical vascular steal phenomenon theorem, however in most patients positive BOLD-fMRI responses are still seen in regions with negative BOLD-CVR. This finding may indicate that the autoregulatory vasodilatory reserve capacity does not necessarily need to be completely exhausted for a vascular steal phenomenon to occur. We aimed to investigate the theorem that vascular steal phenomenon requires a completely depleted autoregulatory cerebrovascular reserve capacity. Here, vascular steal phenomenon is referred from the presence of negative – paradoxical - hypercapnia-induced BOLD-CVR. We investigated this premise by

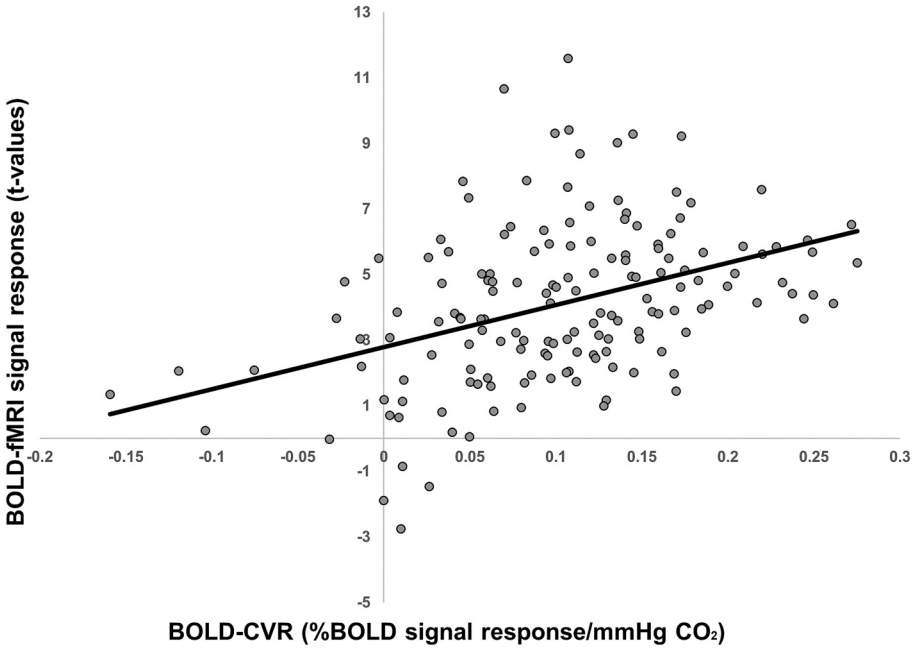

Fig. 3. Average BOLD-CVR versus average task-based BOLD-fMRI signal response.
Display of the mean BOLD-CVR values against the mean BOLD fMRI t-values in our patient cohort with steno-occlusive disease ($R = 0.40$, $p < 0.001$, Fig. 2). On average a decrease of BOLD fMRI t-values can be seen with a decrease in BOLD-CVR.
Abbreviation: BOLD: Blood-oxygenation-level-dependent; CVR: cerebrovascular reactivity (%BOLD signal change/mmHg CO2); fMRI: functional magnetic resonance imaging (in t-values).

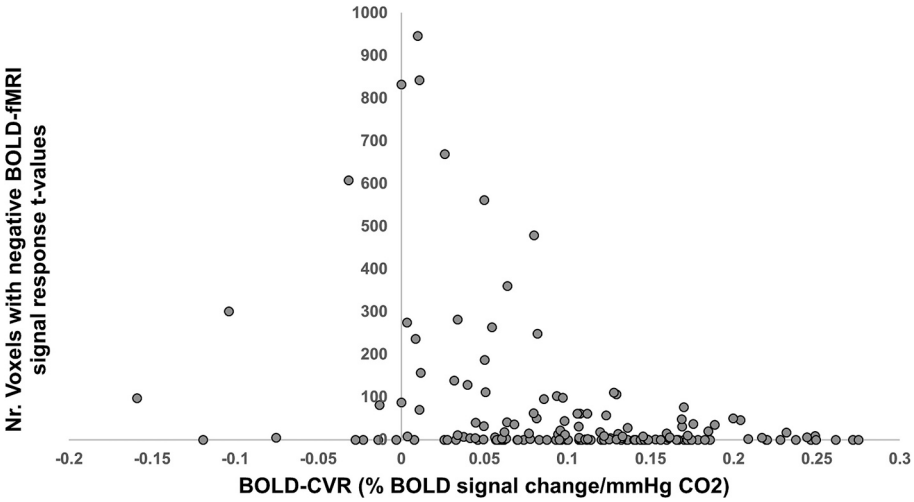

Fig. 4. Overview of negative BOLD-fMRI signal responses in relationship to average BOLD-CVR within the ROI.
Although most patients had zero voxels with negative BOLD fMRI t-values, some experienced a lot. Below or around an average BOLD-CVR of zero within the ROI, a few patients had zero voxels with negative BOLD-fMRI signal response meaning a positive reaction allover, while others did show significant number of voxels with negative voxels, showing the diversity of responses in regions with low BOLD-CVR.
Abbreviation: BOLD: Blood-oxygenation-level-dependent; CVR: cerebrovascular reactivity (%BOLD signal change/mmHg CO2); fMRI: functional magnetic resonance imaging (in t-values); ROI: Region of interest (here: the bilateral pre- and postcentral gyrus).

conducting a concurring CO_2-controlled task-based (bilateral finger-tapping) BOLD-fMRI study. In case a depleted cerebrovascular reserve capacity is present, neuronal activity will only result in an increase in metabolism without the functional hyperemia to wash out the surplus of deoxyhemoglobin. [5] The increase in deoxyhemoglobin leads to a negative BOLD-fMRI signal response.

4.1. BOLD-fMRI and BOLD-CVR

BOLD-CVR as an imaging marker to determine the hemodynamic status in patients with cerebrovascular steno-occlusive disease has been around for almost 20 years. Usually in combination with CO2 as a vasoactive stimulus, either through breathholding or direct inhalation or in combination with acetazolamide, positive BOLD-CVR response is associated with a preserved cerebrovascular reactivity, whereas negative BOLD-CVR is associated with hemodynamic failure stage 2 and steal phenomenon [2,4,15–17]. (For more information see the extensive review on this topic by J. Fisher, L. Venkatraghavan and D. Mikulis [18]).

Moreover, it is known that there is a strong relationship between BOLD-fMRI response to neuronal activity and BOLD-CVR. In brain tumor patients, in which task-based BOLD-fMRI is already a conventional imaging tool, BOLD-fMRI is used to detect eloquent regions in the brain, based on the premise that alterations in neuronal activity cause a so-called uncoupling between $CMRO_2$ and CBF. Consequently, in response to a neuronal stimulus, the CBF increases disproportionally to the increase of $CMRO_2$, leading to a hyper-oxygenated state and a lower concentration of dHb. [5,19]. Subsequently, the BOLD-fMRI signal in those regions will increase, making it possible to indirectly detect and map neuronal activity and thereby localize important eloquent brain regions. [6,20] Such investigations can be very useful in pre-operative surgical planning for brain tumors located in the vicinity of eloquent areas. [21,22] The normal ratio of uncoupling of CBF and $CMRO_2$ after a neuronal stimulus is between 2 and 4 (i.e. increase in CBF is on average 2 to 4 times higher than the increase in $CMRO_2$). [23] A decrease in this ratio, for instance due to an underlying pathology, can potentially lead to catastrophic resection of apparently “silent” eloquent cortex, which is incapable of producing a BOLD-fMRI signal response. A renowned factor causing such a decrease in ratio is a reduction in CVR. If the CBF

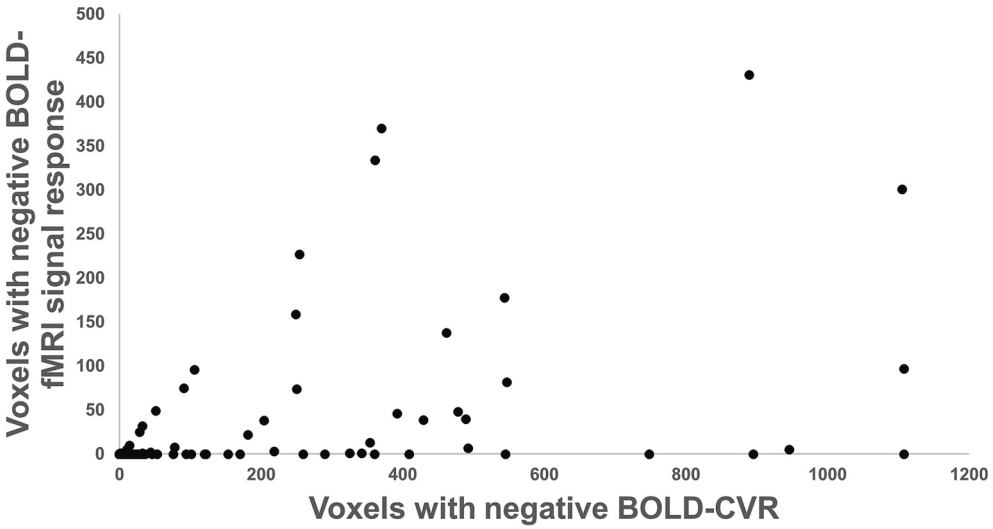

Fig. 5. Relation between voxels with negative BOLD-CVR and the corresponding BOLD-fMRI values.
This figure depicts the relationship between voxels with negative BOLD-CVR and the corresponding BOLD-fMRI signal response. As can be seen, some patients show a linear increase meaning that for all negative BOLD-CRV voxels, a corresponding negative BOLD-fMRI signal response is seen. Most patients show no corresponding negative BOLD-fMRI response (i.e. only voxels with positive BOLD-fMRI signal response to voxels with negative BOLD-CVR.
Abbreviation: BOLD: Blood-oxygenation-level-dependent; CVR: cerebrovascular reactivity (%BOLD signal change/mmHg CO2); fMRI: functional magnetic resonance imaging (in t-values);

overshoot due to limited vasodilatory capacity cannot occur, the uncoupling ratio will decrease to a point without a hyper-oxygenated state and no or even negative BOLD-fMRI signal response. Therefore, the use of BOLD-CVR values to detect false-negative BOLD-fMRI signal responses, i.e. detection of a BOLD-fMRI signal response too low to cross the threshold set by the investigator is currently advocated. [7,8]

We have recently shown that in regions with reduced BOLD-CVR the BOLD-fMRI signal response is also diminished. [7,9,24,25] We could even provoke such a decrease in BOLD-fMRI signal response when artificially reducing BOLD-CVR in healthy patients by applying an increase in baseline CO_2 (i.e. causing pre-emptive vasodilatation). [8] Interestingly, in this paper we have found a similar linear correlation coefficient ($r = 0.4$) as in those papers in healthy cohorts.

In our cohort, on average we have seen a reduced BOLD-fMRI signal response with decreasing BOLD-CVR in our ROI. This observation is in accordance with the findings by Para et al. and others. [7–9]

However, when focusing on negative BOLD-CVR, we have observed contradictory results. In some patients, as expected when the theory of maximal vasodilatation is correct, clear negative BOLD-fMRI signal responses were found (Fig. 4). However, in other patients with similar negative BOLD-CVR values, positive task-based BOLD-fMRI responses are seen (Fig. 5). This finding leads to our assumption that BOLD-CVR derived vascular steal phenomenon does not by definition require a maximally – exhausted - vasodilated vascular bed. Specially, a global vasodilatory stimulus like CO_2 can cause regions with diminished but presumptuously preserved vasodilatory capacity to show negative BOLD-CVR if other regions can produce a markedly stronger vasodilatory response resulting in redirection of cerebral blood flow. This conclusion presents a very interesting premise. Current hemodynamic staging is rigid in its subdivision of patients according to different criteria, although Derdeyn et al. has shown that within these stages there is a lot of variability of other parameters. [26] However, within this variability, CVR should only become negative once maximal vasodilatation is reached.

For the latter finding there is only limited corroborating literature. These findings correspond with earlier findings by Akiyama and colleagues using functional near-infrared spectroscopy in patients with ischemic stroke. [27] Pre-operatively, CVR was measured using Positron Emission Tomography or Single-Photon-Emission-Computed-Tomography and 3 patients presented with clear signs of vascular steal phenomenon and 5 patients showed impaired CVR. Interestingly, the amount of deoxyhemoglobin measured during the task decreased in 1 patient with vascular steal phenomenon and in 1 patient with impaired CVR, which is a response also seen in healthy subjects and in accord with a preserved vasodilatory response. By contrast 3 patients (1 with steal phenomenon) showed a clear increase in deoxyhemoglobin, which is in accordance with a depleted vasodilatory capacity. Moreover, another study by Mazerolle et al. investigating both BOLD-CVR and task based BOLD fMRI using the same methodology as we have used, observed positive BOLD fMRI signal and negative BOLD-CVR within the precentral gyrus in two Moyamoya patients. [28]

On the other hand, we must consider reasons for the finding of negative BOLD-CVR other than vascular steal. Arteaga et al. previously reported contradictory CBF findings (decrease, increase, no change) in patients with negative BOLD-CVR, which means, that the vascular steal phenomenon cannot be the only explanation for a negative BOLD-CVR, but may also imply autoregulation involving the upregulation of $CMRO_2$. [29] Although limitations regarding methodology exist, the authors pose an interesting and heavily debated hypothesis, that a CO_2 increase is not necessarily isometabolic. However, if the premise of these authors is correct, we would likely have found many more patients with primarily negative BOLD-fMRI signal responses. If an upregulation of metabolism in response to hypercapnia had resulted in a relative higher metabolism increase then a possible increase in cerebral blood flow, the increase of metabolism due to neuronal activity would surely suffice to results in a negative BOLD-fMRI signal response.

4.2. Limitations

We have included a heterogeneous cohort of patients with cerebrovascular steno-occlusive disease, including patients with either unilateral or bilateral disease and in different stages after stroke occurrence (i.e., acute subacute and chronic patients were included). Whether this choice has influenced our results is unknown, however, we would not expect so since the presence of the BOLD-CVR vascular steal phenomenon is a consequence of hemodynamic failure at the brain tissue level irrespective of any underlying vascular steno-occlusion or stroke stage. [4,30] Another study with only patients with Moyamoya disease did show a more attenuated BOLD-fMRI signal activation with negative BOLD-CVR but there were some strong positive responses and on average no negative responses were seen. [9]

In addition, the vascular steal phenomenon is a primarily cerebral blood flow measurement. BOLD-CVR measures the relevant difference between deoxyhemoglobin and the cerebral blood flow changes are dependent on multiple factors such as cerebral blood volume and hematocrit. Indeed, many recent studies have demonstrated a strong correlation between primary cerebral blood flow based CVR measurements with H_2O-PET and BOLD-CVR. [4]

5. Conclusions

We show that the presence of negative BOLD-CVR responses to CO_2 is associated with dichotomous motor task-based BOLD-fMRI signal responses, whereas some patients show -more presumed- negative BOLD-fMRI signal responses, while other patient showed positive BOLD-fMRI signal responses. This finding may indicate that the autoregulatory vasodilatory reserve capacity does not always need to be completely exhausted for vascular steal phenomenon to occur.

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Author statement

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Provision of study materials or patients: CHBvN, AH, MS, MH, JD, LR, DM and JF.
Collection and assembly of data: CHBvN, AH, MS, MH, MP& JF.
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Manuscript writing: All authors.
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Declaration of Competing Interest

Dr. Fisher and Dr. Mikulis report that they contributed to the development of an automated end-tidal targeting device, RespirAct™ which is designed, assembled, and made available as a research tool by Thornhill Medical Inc. Thornhill Medical Inc. is a for profit spin-off company from the University Health Network/University of Toronto. Drs. Fisher and Mikulis have equity in Thornhill Medical Inc. The other authors have no conflicts of interest to declare.

References

[1] Poublanc J, Han JS, Mandell DM, Conklin J, Stainsby JA, Fisher JA, et al. Vascular steal explains early paradoxical blood oxygen level-dependent cerebrovascular response in brain regions with delayed arterial transit times. Cerebrovasc Dis Extra 2013;3(1):55–64.
[2] Sobczyk O, Battisti-Charbonney A, Fierstra J, Mandell DM, Poublanc J, Crawley AP, et al. A conceptual model for CO(2)-induced redistribution of cerebral blood flow with experimental confirmation using BOLD MRI. Neuroimage 2014;92:56–68.
[3] Mandell DM, Han JS, Poublanc J, Crawley AP, Stainsby JA, Fisher JA, et al. Mapping cerebrovascular reactivity using blood oxygen level-dependent MRI in patients with arterial steno-occlusive disease: comparison with arterial spin labeling MRI. Stroke 2008;39(7):2021–8.
[4] Fierstra J, van Niftrik C, Warnock G, Wegener S, Piccirelli M, Pangalu A, et al. Staging hemodynamic failure with blood oxygen-level–dependent functional magnetic resonance imaging cerebrovascular reactivity. Stroke 2018 Mar;49(3):621–9.
[5] Davis TL, Kwong KK, Weisskoff RM, Rosen BR. Calibrated functional MRI: mapping the dynamics of oxidative metabolism. Proc Natl Acad Sci U S A 1998;95(4):1834–9.
[6] Ogawa A, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, et al. Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping with magnetic resonance imaging89; 1992. p. 5951–5.
[7] van Niftrik CHB, Piccirelli M, Muscas G, Sebok M, Fisher JA, Bozinov O, et al. The voxel-wise analysis of false negative fMRI activation in regions of provoked impaired cerebrovascular reactivity. PloS One 2019;14(5):e0215294.
[8] van Niftrik CHB, Piccirelli M, Bozinov O, Maldaner N, Strittmatter C, Pangalu A, et al. Impact of baseline CO2 on blood-oxygenation-level-dependent MRI measurements of cerebrovascular reactivity and task-evoked signal activation. Magn Reson Imaging 2018 Jun;49:123–30.
[9] Para AE, Sam K, Poublanc J, Fisher JA, Crawley AP, Mikulis DJ. Invalidation of fMRI experiments secondary to neurovascular uncoupling in patients with cerebrovascular disease. J Magn Reson Imaging 2017. Nov;46(5):1448–55. https://doi.org/10.1002/jmri.25639.
[10] Slessarev M, Han J, Mardimae A, Prisman E, Preiss D, Volgyesi G, et al. Prospective targeting and control of end-tidal CO2 and O2 concentrations. J Physiol 2007;581(Pt 3):1207–19.
[11] van Niftrik CHB, Piccirelli M, Bozinov O, Pangalu A, Fisher JA, Valavanis A, et al. Iterative analysis of cerebrovascular reactivity dynamic response by temporal decomposition. Brain Behav 2017 Jul 26;7(9):e00705.
[12] Sebok M, van Niftrik CHB, Piccirelli M, Bozinov O, Wegener S, Esposito G, et al. BOLD cerebrovascular reactivity as a novel marker for crossed cerebellar diaschisis. Neurology 2018 Oct 2;91(14):e1328–37.
[13] van Niftrik CHB, Sebok M, Muscas G, Piccirelli M, Serra C, Krayenbuhl N, et al. Characterizing ipsilateral thalamic diaschisis in symptomatic cerebrovascular steno-occlusive patients. J Cereb Blood Flow Metab 2019. Jun 24;12:645157.
[14] Sebök M, van Niftrik CHB, Piccirelli M, Muscas G, Pangalu A, Wegener S, et al. Crossed cerebellar Diaschisis in patients with symptomatic unilateral anterior circulation stroke is associated with hemodynamic impairment in the ipsilateral MCA territory. J Magn Reson Imaging 2020. Apr;53(4):1190–7.
[15] Sebök M, van Niftrik CHB, Winklhofer S, Wegener S, Esposito G, Stippich C, et al. Mapping cerebrovascular reactivity impairment in patients with symptomatic unilateral carotid artery disease. J Am Heart Assoc 2021 Jun 15;10(12):e020792.
[16] Venkatraghavan L, Poublanc J, Han JS, Sobczyk O, Rozen C, Sam K, et al. Measurement of cerebrovascular reactivity as blood oxygen level-dependent magnetic resonance imaging signal response to a Hypercapnic stimulus in mechanically ventilated patients. J Stroke Cerebrovasc Dis 2018;27(2):301–8.
[17] Fierstra J, Sobczyk O, Battisti-Charbonney A, Mandell DM, Poublanc J, Crawley AP, et al. Measuring cerebrovascular reactivity: what stimulus to use? J Physiol 2013;591(Pt 23):5809–21.
[18] Fisher JA, Venkatraghavan L, Mikulis DJ. Magnetic resonance imaging-based cerebrovascular reactivity and hemodynamic reserve. Stroke 2018;49(8):2011–8.
[19] Fox PT, Raichle ME. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. Proc Natl Acad Sci U S A 1986;83(4):1140–4.
[20] Ugurbil K. Development of functional imaging in the human brain (fMRI); the University of Minnesota experience. NeuroImage 2012;62(2):613–9.
[21] Pillai JJ, Zaca D. Clinical utility of cerebrovascular reactivity mapping in patients with low grade gliomas. World J Clin Oncol 2011;2(12):397–403.
[22] Zaca D, Jovicich J, Nadar SR, Voyvodic JT, Pillai JJ. Cerebrovascular reactivity mapping in patients with low grade gliomas undergoing presurgical sensorimotor mapping with BOLD fMRI. J Magn Reson Imaging 2014;40(2):383–90.
[23] Cohen ER, Ugurbil K, Kim SG. Effect of basal conditions on the magnitude and dynamics of the blood oxygenation level-dependent fMRI response. J Cereb Blood Flow Metab 2002;22(9):1042–53.
[24] Hamzei F, Knab R, Weiller C, Röther J. The influence of extra- and intracranial artery disease on the BOLD signal in FMRI. Neuroimage 2003;20(2):1393–9.
[25] Röther J, Knab R, Hamzei F, Fiehler J, Reichenbach JR, Büchel C, et al. Negative dip in BOLD fMRI is caused by blood flow - oxygen consumption uncoupling in humans. Neuroimage 2002;15(1):98–102.
[26] Derdeyn CP, Videen TO, Yundt KD, Fritsch SM, Carpenter DA, Grubb RL, et al. Variability of cerebral blood volume and oxygen extraction: stages of cerebral haemodynamic impairment revisited. Brain 2002;125(Pt 3):595–607.
[27] Akiyama T, Ohira T, Kato T, Toda Y, Orii M, Hiraga K, et al. Motor-related intracortical steal phenomenon detected by multichannel functional near-infrared spectroscopy imaging. Cerebrovasc Dis 2005;20(5):337–46.
[28] Mazerolle EL, Ma Y, Sinclair D, Pike GB. Impact of abnormal cerebrovascular reactivity on BOLD fMRI: a preliminary investigation of moyamoya disease. Clin Physiol Funct Imaging 2018;38(1):87–92.
[29] Arteaga DF, Strother MK, Faraco CC, Jordan LC, Ladner TR, Dethrage LM, et al. The vascular steal phenomenon is an incomplete contributor to negative cerebrovascular reactivity in patients with symptomatic intracranial stenosis. J Cereb Blood Flow Metab 2014;34(9):1453–62.
[30] Sebök M, van Niftrik CHB, Winklhofer S, Wegener S, Esposito G, Stippich C, et al. Mapping cerebrovascular reactivity impairment in patients with symptomatic unilateral carotid artery disease. J Am Heart Assoc 2021;10(12):e020792.

# Begleittext zur Publikation (equal contribution)

Von Aimée Hiller

Hintergrund/Fragestellung:
Für das Auftreten von einem sogenannten «vascular steal phenomenon» wird in der Literatur beschrieben, dass das nachgeschaltete Gefässsystem maximal dilatiert, also erschöpft sein muss. Im Falle eines erschöpften Gefässsystems, respektive maximaler Vasodilatation erwarten wir aufgrund eines reduzierten Blutflusses und damit erhöhter Deoxyhämoglobin-Konzentration ein negatives/paradoxes «blood oxygenation-level dependent functional magnetic resonance imaging» (BOLD-fMRI) Signal. [1, 2] Das ist erklärt wiederum durch das Prinzip des «blood oxygenation-level dependent» (BOLD) Kontrastes, welches auf der Veränderung der Deoxyhämoglobin-Konzentration im Blut und des Blutvolumens beruht – d.h. es detektiert das vorhandene Deoxyhämoglobin. [3, 4] Durch das Einatmen von Kohlenstoffdioxid (CO_2) respektive Erhöhen des P_aCO_2 im Blut, erreichen wir eine Vasodilatation der zerebralen Gefässe, was wiederum ein erschöpftes Gefässsystem widerspiegelt, wobei wir dann einen negativen «blood oxygenation-level dependent cerebrovascular reactivity» (BOLD-CVR) erwarten. Bei neuronaler Aktivierung erhöht sich normalerweise die Oxyhämoglobin-Konzentration bei gleichzeitiger Reduktion der Deoxyhämoglobin-Konzentration. Dies aufgrund eines erhöhten Blutflusses während neuronaler Aktivität, was im Vergleich zum erhöhten Sauerstoffverbrauch die Oxyhämoglobin-Konzentration stärker beeinflusst. Somit löst dies durch die reduzierte Deoxyhämoglobin-Konzentration ein positives BOLD-fMRI Signal aus. [2] Dies bedeutet, dass wir bei einem erschöpften Gefässsystem ein gedämpftes / negatives BOLD-fMRI Signal erwarten müssen, was in früheren Studien auch schon gezeigt wurde. [5-7] Wenn wir also in einem Hirnareal mit «vascular steal phenomenon» und demnach, nach den oben genannten Erläuterungen zu erwartendem negativem BOLD-CVR, die neuronale Aktivität mit Hilfe von BOLD-fMRI messen wollen, ist dies gemäss der «vascular steal phenomenon» Theorie nicht möglich, da wir keine Hyperämie erzeugen können und somit der zerebrale Metabolismus den Blutfluss übersteigt und dadurch die Deoxyhämoglobin-Konzentration erhöht bleibt. Mit dieser Studie wollten wir anhand einer motorischen Aufgabe - und damit erzeugten neuronalen Aktivität - bei Patienten/Patientinnen mit negativem BOLD-CVR analysieren, ob diese wie erwartet, ein negatives BOLD-fMRI Signal zeigen im Sinne einer erschöpften autoregulatorischen Kapazität des Gefässsystems als Voraussetzung für das Auftreten von dem «vascular steal phenomenon».

Material und Methoden:
Wir analysierten Patienten/Patientinnen mit steno-okklusiver Pathologie der zerebralen Gefässe aus unserer bereits bestehenden prospektiven BOLD-CVR Datenbank, die eine vorhandene Studieneinwilligung vorwiesen vor Durchführung der Untersuchung. Als Voraussetzung hatten alle Studienteilnehmer/-innen gleichentags eine BOLD-CVR und eine «task-based» BOLD-fMRI Studie durchlaufen (genehmigt durch die lokale Ethikkomission KEK-ZH-Nr. 2012-0427 & KEK 2020-02314.). Bei Patienten/Patientinnen mit steno-okklusiver Erkrankung der zerebralen Gefässe ist das sogenannte «vascular steal phenomenon» gut zu beobachten, weswegen wir uns für diese Patientengruppe entschieden haben. Zu den Exklusionskriterien gehörten unter anderem

Patienten/Patientinnen mit senso-motorischem Defizit zum Zeitpunkt der Studiendurchführung, sowie Kopfbewegung über 2mm und frühzeitig beendete «task-based» BOLD-fMRI Studien. Die für diese Studie benötigten Patientencharakteristika wurden nachträglich aus dem Krankenaktensystem gesammelt.
Unsere bilaterale «region of interest» ROI definierten wir anhand von 42 gesunden Personen, welche ebenfalls die Studie unterliefen. In der definierten Region zeigten die gesunden Kontrollpersonen in 99% der Fälle ein signifikantes BOLD-fMRI Signal. Es wurden aufgrund der anatomisch gut definierten und dem kleinen interpersonellen Unterschied ausschliesslich BOLD-fMRI Signale im Bereich des prä- und postzentralen Gyrus berücksichtigt. Die Aktivierung im Bereich des supplementären Motorik-Areals und im Zerebellum wurden für die Analyse nicht verwendet.
Alle Sequenzen wurden mittels eines 3 Tesla Skyra VD13 MRI akquiriert.
Für den CO_2-Stimulus zur Durchführung der BOLD-CVR Studie wurde uns vom «Thornhill Research Institute» in Toronto ein automatisiertes Gas-Applikationssystem zur Verfügung gestellt. Zur Messung der Ruhedrücke wurde jedes Studienprotokoll mit einer Anfangsphase im MRI begonnen. Für die BOLD-CVR Aufnahme wurde der «end-tidal partial pressure of CO_2» ($PetCO_2$) für 80 Sekunden um ca. 10mmHg erhöht, nachdem der Druck die ersten 100 Sekunden auf dem Ruhe-$PetCO_2$ belassen wurde. Für die verbleibende Zeit wurde der Druck am Ende der 80 Sekunden wieder auf den Ruhedruck reduziert. Für die «task-based» BOLD-fMRI Studie wurde den Studienteilnehmer/-innen eine Hand-/ Finger-motorische Aufgabe, respektive eine sogenannte «finger-tapping» Aufgabe vor dem Beginn der Untersuchung erklärt. Diese musste im MRI vier Mal für jeweils 30 Sekunden mit 30 Sekunden Pause dazwischen durchgeführt werden. Die genaue Aufgabe wurde bereits in früheren Studien beschrieben und erklärt. [5, 6]
Die anatomischen Bilder wurden mittels «Statistical Parametric Mapping» (SPM) prozessiert. Der BOLD-CVR (Prozent BOLD-fMRI Signaländerung pro mmHg CO_2) wurde berechnet, wie in früheren Studien unserer Gruppe publiziert. [4, 8, 9]
Das Programm «Statistical Package for Social Science» wurde zur statistischen Analyse benutzt.

Resultate:
Analysiert haben wir schlussendlich 142 ROI's, das heisst 71 Studien mit jeweils den beiden Hemisphären. Ein positives BOLD-fMRI Signal konnte bei Patienten/Patientinnen respektive Arealen mit stark positivem BOLD-CVR aufgezeichnet werden. Von den Patienten/Patientinnen respektive Arealen mit negativem BOLD-CVR zeigten einen Teil wie erwartet ein negatives BOLD-fMRI Signal, wobei es andere gab mit dennoch unerwartet positivem BOLD-fMRI Signal.

Konklusion:
Wir schliessen aus unseren Resultaten, dass diese - mit den gezeigten widersprüchlichen BOLD-fMRI Signalen beim Vorliegen von negativem BOLD-CVR - darauf hinweisen, dass das sogenannte "vascular steal phenomenon" bereits auftreten kann, wenn die vasodilatatorische Reservekapazität des Gefässsystems noch nicht komplett ausgeschöpft ist. Weitere Studien zur Prüfung dessen sind notwendig.

Eigener Beitrag zur Forschungsarbeit:

Ich habe zur Durchführung der Studie mitgeholfen bei der Rekrutierung eines Teils der Patienten/Patientinnen für dieses und weitere Projekte mit demselben Projektteam. Weiter habe ich Patienten/Patientinnen über den Ablauf der Studie und spezifisch über die Untersuchung informiert und aufgeklärt. Auch habe ich mitgeholfen beim Aufbau und der Vorbereitung für den Untersuch, im Sinne der Bereitstellung unseres Gas-Applikations-Systems und dessen Kalibrierung am Anfang.
Ich habe die jeweiligen Utensilien, wie zum Beispiel die zur Untersuchung notwendige Maske für die Applikation der Gasmischung an den Studienteilnehmer/-innen angebracht und die Dichtigkeit und korrekte Funktion überprüft. Anschliessend habe ich teilweise die Ausführung bei den verschiedenen akquirierten MRI-Sequenzen kontrolliert, speziell bei der Ausführung unserer «finger-tapping» Aufgabe. Andererseits habe ich teilweise selbständig die MRI-Sequenzen akquiriert mit fortlaufender Instruktion der Patienten/Patientinnen. Des Weiteren, habe ich mitgeholfen beim Bestimmen der Partial- und Ruhedrücke mit unserem Gas-Applikations-System.
Schliesslich habe ich die Auswertung der Untersuchung und Prozessierung der Bilder mit Hilfe des «Statistical Parametric Mapping 12» (SPM 12) Programms selbständig unter vorheriger Anleitung meines Betreuers durchgeführt.
Zudem habe ich die Excel Tabellen erstellt nach Sammeln der Basischarakteristika, respektive der benötigten Patientendaten im Krankenaktensystem (KISIM) des Universitätsspitals Zürich. Daraufhin habe ich einen Teil der Diagramme und Tabellen für das Manuskript erstellt und eine ausführliche Literaturrecherche für das Schreiben des ersten Entwurfes des Manuskripts betrieben. Ich habe sodann mitgeholfen bei der Überarbeitung des Manuskripts nach Korrektur und Verbesserungsvorschlägen meines Betreuers und nochmals nach dem Einreichen im Journal.

Referenzen

[1] Sobczyk O, Battisti-Charbonney A, Fierstra J, Mandell DM, Poublanc J, Crawley AP, et al. A conceptual model for CO_2-induced redistribution of cerebral blood flow with experimental confirmation using BOLD MRI. Neuroimage 2014;92:56-68.

[2] Davis TL, Kwong KK, Weisskoff RM, Rosen BR. Calibrated functional MRI: mapping the dynamics of oxidative metabolism. Proc Natl Acad Sci U S A 1998;95(4):1834-9.

[3] Mandell DM, Han JS, Poublanc J, Crawley AP, Stainsby JA, Fisher JA, et al. Mapping cerebrovascular reactivity using blood oxygen level-dependent MRI in Patients with arterial steno-occlusive disease: comparison with arterial spin labeling MRI. Stroke 2008;39(7):2021-8.

[4] Fierstra J, van Niftrik C, Warnock G, Wegener S, Piccirelli M, Pangalu A, et al. Staging Hemodynamic Failure With Blood Oxygen-Level-Dependent Functional Magnetic Resonance Imaging Cerebrovascular Reactivity: A Comparison Versus Gold Standard (Stroke 2018;49(3):621-9.

[5] van Niftrik CHB, Piccirelli M, Muscas G, Sebök M, Fisher JA, Bozinov O, et al. The voxel-wise analysis of false negative fMRI activation in regions of provoked impaired cerebrovascular reactivity. PLoS One 2019;14(5):e0215294.

[6] van Niftrik CHB, Piccirelli M, Bozinov O, Maldaner N, Strittmatter C, Pangalu A, et al. Impact of baseline CO. Magn Reson Imaging 2018;49:123-30.

[7] Para AE, Sam K, Poublanc J, Fisher JA, Crawley AP, Mikulis DJ. Invalidation of fMRI experiments secondary to neurovascular uncoupling in patients with cerebrovascular disease. J Magn Reson Imaging 2017;46(5):1448-55.

[8] Hendrik Bas van Niftrik C, Sebök M, Muscas G, Piccirelli M, Serra C, Krayenbühl N, et al. Characterizing ipsilateral thalamic diaschisis in symptomatic cerebrovascular steno-occlusive patients. J Cereb Blood Flow Metab 2020;40(3):563-73.

[9] Sebök M, van Niftrik CHB, Piccirelli M, Bozinov O, Wegener S, Esposito G, et al. BOLD cerebrovascular reactivity as a novel marker for crossed cerebellar diaschisis. Neurology 2018;91(14):e1328-e37.

Curriculum Vitae

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