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Quantitative Mapping of Cerebral Metabolic Rate of Oxygen (CMRO₂) using Quantitative Susceptibility Mapping (QSM)

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Abstract

Purpose—To quantitatively map cerebral metabolic rate of oxygen (CMRO₂) and oxygen extraction fraction (OEF) in human brains using quantitative susceptibility mapping (QSM) and arterial spin labeling measured cerebral blood flow (CBF) before and after caffeine vasoconstriction.

Methods—Using the multiecho 3D gradient echo sequence and an oral bolus of 200 mg caffeine, whole brain CMRO₂ and OEF were mapped at 3mm isotropic resolution on 13 healthy subjects. The QSM based CMRO₂ was compared with an R_2^* based CMRO₂ to analyze the regional consistency within cortical gray matter (CGM) with the scaling in the R_2^* method set to provide same total CMRO₂ as the QSM method for each subject.

Results—Compared to pre-caffeine, susceptibility increased (5.1 ± 1.1 ppb, $p < 0.01$) and CBF decreased (-23.6 ± 6.7 ml/100g/min, $p < 0.01$) at 25min post-caffeine in CGM. This corresponded to a CMRO₂ of 153.0 ± 26.4 μmol/100g/min with an OEF of $33.9 \pm 9.6\%$ and $54.5 \pm 13.2\%$ ($p < 0.01$) pre- and post- caffeine respectively at CGM, and a CMRO₂ of 58.0 ± 26.6 μmol/100g/min at white matter. CMRO₂ from both QSM and R_2^* based methods showed good regional consistency ($p > 0.05$), but quantitation of R_2^* based CMRO₂ required an additional scaling factor.

Conclusion—QSM can be used with perfusion measurements pre- and post- caffeine vasoconstriction to map CMRO₂ and OEF.

Keywords

Quantitative; CMRO₂; OEF; QSM

INTRODUCTION

The cerebral metabolic rate of oxygen (CMRO₂) and the oxygen extraction fraction (OEF) are important markers for assessing neuronal viability in ischemic stroke when hypoperfusion leads to a compensatory OEF increase to maintain oxygen metabolism before the onset of brain tissue infarction (1–3). Positron emission tomography (PET) using ¹⁵O has been used to map CMRO₂, but its feasibility as a clinical tool is severely limited by the short half-life (123 sec) of ¹⁵O (4) and sparse availability compared to other imaging modalities like MRI.

When oxygen is released from arterial blood to brain tissue, the weakly diamagnetic oxyhemoglobin (oHb) turns into the strongly paramagnetic deoxyhemoglobin (dHb) in the draining veins (5). MRI is very sensitive to this change in magnetic susceptibility. Changes in R₂ (estimated from spin echo data) and R₂^{*} (estimated from gradient echo (GRE) data) by the magnetic field of dHb have been used to estimate dHb concentration ([dHb]) (6–11). As R₂^{*} is more sensitive than R₂ (12), R₂^{*} is more commonly used (13–15). However, R₂^{*} images are contaminated by blooming artifacts and are highly dependent on imaging parameters including field strength, echo time, voxel size, and object orientation (6,16), making it difficult to quantitatively map [dHb].

Because [dHb] is linearly related to blood magnetic susceptibility that is independent of imaging parameters (17,18), quantitative susceptibility mapping (QSM) derived from the magnitude and phase of the GRE signal (19–35) has the potential for quantitative [dHb] measurements. QSM may provide an advantage over the previous approaches by eliminating the blood vessel geometry dependence in estimating [dHb] in veins only (36–40). Here, we demonstrate the feasibility of CMRO₂ mapping using QSM and cerebral perfusion measurements.

THEORY

According to mass conservation, we have,

$$\text{CMRO}_2 = 4\text{CBF} \cdot ([\text{dHb}]_v - [\text{dHb}]_a) \quad [1]$$

Here CBF is the volumetric cerebral blood flow rate, and [dHb]_v and [dHb]_a are [dHb] in the draining veins and supplying arteries respectively. The factor 4 accounts for the four oxygen molecules in one oHb, each bound to one of four hemes. CBF can be measured using a quantitative perfusion technique such as arterial spin labeling (ASL) (41). The arterial dHb concentration can be written as [dHb]_a = (1 – SaO₂) [Hb] with arterial oxygen saturation SaO₂ = 0.97 and hemoglobin concentration [Hb] = 2.48 μmol/ml for healthy subjects (see Appendix). [dHb]_v can be derived using QSM in the following manner by carefully accounting for contributions from various components in blood and non-blood tissue weighted by the respective volume fractions, though the dominant contributions are from venous dHb and tissue ferritin.

The voxel susceptibility, χ , in QSM is linearly proportional to [dHb]_v,

$$\chi = \text{CBV}_v \cdot \Psi_{\text{Hb}} (X_{\text{dHb}} - X_{\text{oHb}}) \frac{[\text{dHb}]_v}{[\text{Hb}]} + \chi_o \quad [2]$$

Here $\text{CBV}_v = 0.5\text{CBV}$ is the venous blood volume fraction in a voxel assuming blood deoxygenates linearly (10). $\Psi_{\text{Hb}} = 0.12$ is the volume fraction of Hb within blood (see Appendix). $X_{\text{dHb}} = 10765\text{ppb}$ and $X_{\text{oHb}} = -813\text{ppb}$ are the volume susceptibilities of pure dHb and oHb respectively (see Appendix). The first term in the right hand side of Eq.2 reflects the susceptibility contribution from venous dHb relative to oxygenated blood. The second term χ_o in Eq.2 reflects susceptibility contributions from non-blood tissue sources (such as ferritin) χ_t , pure oxygenated blood X_{ba} , and arterial deoxyhemoglobin:

$$\chi_o = (1 - \text{CBV})\chi_t + \text{CBV} \cdot X_{\text{ba}} + \text{CBV}_a \cdot \Psi_{\text{Hb}} (X_{\text{dHb}} - X_{\text{oHb}}) \frac{[\text{dHb}]_a}{[\text{Hb}]}, \quad [3]$$

with $\text{CBV}_a = 1 - \text{CBV}_v = 0.5\text{CBV}$, and $X_{\text{ba}} = \Psi_{\text{Hb}} \cdot X_{\text{oHb}} + (1 - \Psi_{\text{Hb}})X_p = -131\text{ppb}$ is the volume susceptibility for pure oxygenated blood ($X_p = -37.7\text{ppb}$ is blood plasma volume susceptibility) (18,39,42).

With susceptibility (χ) and perfusion (CBV and CBF) measurements, Eqs.1&2 form an equation with two unknowns (CMRO_2 and χ_o):

$$\text{CMRO}_2 = 4\text{CBF} \cdot [\text{Hb}] \left(\frac{\chi - \chi_o}{\text{CBV}_v \cdot \Psi_{\text{Hb}} (x_{\text{dHb}} - x_{\text{oHb}})} - (1 - \text{SaO}_2) \right) \quad [4]$$

To determine CMRO_2 , it is necessary to correct for χ_t , which is independent of blood. This can be achieved using measurements at two different brain perfusion states that have the same CMRO_2 , such as before and after vasoconstriction in a caffeine challenge (43–45). It is reasonable to assume the non-blood contribution $(1 - \text{CBV})\chi_t$ to susceptibility in a voxel to be the same between the two states. Then Eq.4 leads to

$$\text{CMRO}_2 = \frac{4[\text{Hb}]}{\Delta(\text{CBV}_v/\text{CBF})} \left(\frac{\Delta\chi - \Delta\chi_o}{\Psi_{\text{Hb}} (X_{\text{dHb}} - X_{\text{oHb}})} - \Delta\text{CBV}_v(1 - \text{SaO}_2) \right) \quad [5]$$

where Δ denotes the difference between the two measurements (see Appendix for a detailed derivation of Eq.5 from Eq.4).

OEF is defined as the oxygen concentration difference between artery and vein scaled by the arterial oxygen concentration ($4 \cdot \text{SaO}_2 [\text{Hb}] = 4 \cdot 0.97[\text{Hb}]$) can then be determined as

$$\text{OEF} = \frac{\text{CMRO}_2}{4 \cdot \text{SaO}_2 \cdot [\text{Hb}] \cdot \text{CBF}} \quad [6]$$

METHODS

The study was approved by the local Institutional Review Board. Healthy volunteers were recruited (n=13, 13 males, mean age 35 ± 9.5 years) for brain MRI on a 3T scanner (HDxt,

GE Healthcare, Waukesha, WI, USA) using an 8-channel receive head coil. All subjects were instructed to avoid caffeine or alcohol intake 24 hours prior to MRI.

Data Acquisition

Given its well-described ability to safely cause measurable reductions in CBF within 30 minutes upon administration (45), a bolus of caffeine (~200 mg caffeine in black coffee) was administered orally through a flexible plastic tube to minimize head motion. MRI was performed before and 25 min after the oral administration of the caffeine challenge, using a protocol consisting of an anatomical T2 weighted 2D fast spin echo (FSE) sequence, a 3D FSE ASL sequence to measure CBF, and a 3D spoiled GRE sequence to measure magnitude and phase, from which QSM maps were calculated using dipole inversion algorithm (19,21). The total scan time was approximately 60 min (consisting of 15 min scan before caffeine administration to 45 min after).

The T2 weighted axial 2D FSE parameters were: 82 ms TE, 4250 ms TR, 22 cm FOV, $0.46 \times 0.46 \text{ mm}^2$ in-plane resolution, 3mm slice thickness, 46 slices, 23 echo train length (ETL), 2 signal averages, and 5 min scan time.

The 3D FSE ASL sequence parameters were: 1500 ms labeling period, 1525 ms post-label delay, spiral sampling of 8 interleaves with 512 readout points per leaf, 62.5 kHz readout bandwidth, 1 ETL, 3 mm isotropic resolution and identical volume coverage as the T2 weighted sequence, 10.5 ms TE, 4796 ms TR, 3 signal averages, and 6 min scan time. maps (ml/100g/min) were generated from the ASL data using the FuncTool software package (GE Healthcare, Waukesha, WI, USA).

The 3D spoiled GRE sequence parameters included: 11 equally spaced echoes, 4.4 ms first TE, 4.9 ms echo spacing, 58.5 ms TR, 0.46 mm in-plane resolution, 3 mm slice thickness, and identical volume coverage as the T2 weighted sequence, 62.5 kHz readout bandwidth, 15° flip angle, and 7 min scan time. The pulse sequence was flow-compensated in the readout (anterior-posterior) direction.

Image Processing

QSM maps were calculated from GRE magnitude and phase data. A Gauss-Newton nonlinear estimation of the field map was performed (33), followed by unwrapping (46) and background field removal using a projection onto dipole fields method (47) to obtain the local field map, from which tissue susceptibility was computed using the Morphology Enabled Dipole Inversion (MEDI) algorithm (20,33). R_2^* maps were generated from GRE magnitude data via voxel-by-voxel fitting using auto-regression on linear operations (ARLO) monoexponential fitting algorithm (48). Signal-to-noise ratio (SNR) of QSM and R_2^* maps were estimated as the ratio of mean over standard deviation of values measured in the caudate nucleus.

Grey matter (GM) and white matter (WM) masks were created using the FSL FAST algorithm on pre-caffeine CBF images covering the supratentorial brain parenchyma from the vertex to the superior aspect of the cerebellum (49). These masks were visually confirmed by a board-certified attending neuroradiologist (A.G.) for anatomical accuracy.

The cortical GM mask was further segmented by the same neuroradiologist into six vascular territories (VT, left and right anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA)) (Fig.1). For this feasibility study, pre-caffeine CBV was estimated from CBF based on the linear regression equations derived from ^{15}O steady-state inhalation PET (50): $\text{CBV} = (0.227\text{CBF} - 7.27)/100$ within the GM mask, and $\text{CBV} = (0.0316\text{CBF} + 1.9447)/100$ within the WM mask. Post-caffeine CBV was estimated from pre-caffeine CBV using Grubb's exponent of $\alpha = 0.38$ (51) for both masks. CMRO_2 maps of GM and WM were then calculated from pre- and post-caffeine QSM and CBF/CBV measurements by solving Eq.4 using a conjugate gradient method. The resulting maps were combined to obtain the final CMRO_2 maps of the whole brain. OEF maps were then calculated using Eq.8. Gaussian smoothing (2.1 mm kernel) was used to reduce noise in the CMRO_2 and OEF maps.

All images were co-registered and interpolated to the resolution of the maps using the FSL FLIRT algorithm (52,53). QSM values were referenced to the susceptibility of water (defined in this study as the mean susceptibility of cerebrospinal fluid (CSF) in the lateral ventricles).

CMRO_2 was also estimated using a calibrated fMRI approach based on R_2^* (13–15). The difference in R_2^* between pre- and post- caffeine challenge can be used to estimate the dHb component of R_2^* in a voxel during pre-caffeine state ($R_{2,\text{dHb,pre}}^*$) according to the following equation with Grubb's $\alpha = 0.38$ and an empirical $\beta = 1.5$ (54).

$$R_{2,\text{pre}}^* - R_{2,\text{post}}^* = R_{2,\text{dHb,pre}}^* \left(1 - \left(\frac{\text{CBF}_{\text{post}}}{\text{CBF}_{\text{pre}}} \right)^{\alpha - \beta} \right) \quad [7]$$

Then the relationship between $R_{2,\text{dHb,pre}}^*$ and pre-caffeine venous dHb concentration $[\text{dHb}]_{\text{v,pre}}$ is given as follow (7,8,11,54,55):

$$R_{2,\text{dHb,pre}}^* = A \cdot \text{CBV}_{\text{pre}} [\text{dHb}]_{\text{v,pre}}^\beta \quad [8]$$

Combining Eqs.7&8 with Eq.1 and using $[\text{dHb}]_{\text{a}} \approx 0$ and $\left(\frac{\text{CBF}_{\text{post}}}{\text{CBF}_{\text{pre}}} \right)^\alpha = \frac{\text{CBV}_{\text{post}}}{\text{CBV}_{\text{pre}}}$, we have

$$\text{CMRO}_2 = 4A^{-1/\beta} \cdot \text{CBF}_{\text{pre}} \text{CBF}_{\text{post}} \left(\frac{R_{2,\text{post}}^* - R_{2,\text{pre}}^*}{\text{CBV}_{\text{post}} \text{CBV}_{\text{pre}}^\beta - \text{CBV}_{\text{pre}} \text{CBV}_{\text{post}}^\beta} \right)^{1/\beta} \quad [9]$$

This R_2^* based CMRO_2 method requires the scaling factor A to be measured separately with an additional measurement at a different brain state (13–15). For this feasibility study, the regional consistency of CMRO_2 maps within cortical GM ROIs (Fig.1) derived from QSM and R_2^* based methods was compared under the assumption that their global averages or total CMRO_2 were the same for each subject, which allowed A to be determined from the QSM data without further experiment.

Statistical Analysis

For each ROI, the mean and standard deviation of QSM, CBF, OEF, and CMRO₂ values as well as the corresponding left/right (L/R) hemisphere ratio were measured for both the QSM based and R₂^{*} based method. Paired-sample t-tests were performed to assess the differences in QSM, R₂^{*}, CBF, and OEF in the GM ROIs before and after the caffeine challenge across the subjects. PET studies have shown that CMRO₂ and OEF maps are homogeneous in GM across the brain and exhibit left-right symmetry in healthy subjects (50,56). Paired-sample t-tests were performed to compare CMRO₂ in the VT ROIs between QSM based and R₂^{*} based method to analyze their consistency. To analyze the symmetry of the images, analysis of variance (ANOVA) was performed to assess the significance of differences in L/R hemisphere ratio of CMRO₂ and OEF among the VT ROIs. P values of less than 0.05 were considered to indicate statistical significance. All data were expressed as mean ± standard deviation.

RESULTS

All scans were completed successfully. The average GM volume for each vascular territory was 125.8 ± 17.7 mL (ACA, both left and right), 254.0 ± 25.4 mL (MCA), and 79.7 ± 14.2 mL (PCA) (n=13). Figure 2 shows an example of pre- and post-caffeine QSM and CBF maps and the calculated CMRO₂ and OEF maps. QSM and R₂^{*} maps have similar SNR (6.2 ± 1.9 vs. 7.2 ± 1.6, p>0.05). Figure 3 shows OEF and CMRO₂ maps across the brain volume, illustrating good GM and white matter contrast in reasonable agreement with T2 weighted images. Compared to the pre-caffeine values, a statistically significant increase in QSM (5.1 ± 1.1 ppb, p<0.01), R₂^{*} (1.5 ± 0.3 s⁻¹, p<0.01), and decrease in CBF (-23.6 ± 6.7 ml/100g/min, p<0.01) were measured in the global cortical GM ROI at 25 min post-caffeine. Consistent with the decrease in CBF after the caffeine challenge, OBF significantly increased from 33.9 ± 9.6% to 54.5 ± 13.2% (p<0.01) at 25 min post-caffeine. The mean CMRO₂ in the global cortical GM ROI calculated using QSM were 153.0 ± 26.4 μmol/100g/min. The mean CMRO₂, and pre- and post-caffeine OEF measured in the WM were 58.0 ± 26.6 μmol/100g/min, 26.3 ± 11.7% and 45.0 ± 18.7%, respectively.

Figure 4 compares CMRO₂ maps obtained from two other subjects using QSM-based and R₂^{*}-based methods. The mean R₂^{*}_{dHb,pre} in the global cortical GM ROI was 1.9 ± 0.8 s⁻¹. Table 1 shows the CMRO₂ measured within VT ROIs of QSM based and R₂^{*} based methods, demonstrating good agreement within all vascular territories (all differences were statistically non-significant). Table 2 shows the L/R hemisphere ratio of CMRO₂ and OEF measured within the VT ROIs. Both the QSM and R₂^{*} method show statistically comparable L/R hemisphere ratio values among vascular territories ranging from 0.92 to 1.07, indicating good hemispheric symmetry. (ANOVA, p > 0.05).

DISCUSSION

Our preliminary results demonstrate the in vivo feasibility of 3D CMRO₂ brain mapping using the recently developed QSM and quantitative perfusion. The QSM based CMRO₂ of 153.0 ± 26.4 μmol/100g/min in cortical GM agrees well with values reported in the MRI and

PET literature (13–15,50,56). The QSM based CMRO₂ is consistent with the R₂^{*} based CMRO₂ (our mean R₂^{*}_{|dHb,pre} of 1.9 ± 0.8 s⁻¹ is in agreement with values in calibrated fMRI literature (13,57–60)). Using measurements at two different brain states (pre- and post-caffeine challenge here), the QSM based CMRO₂ method can provide absolute quantitation while the R₂^{*} based CMRO₂ method relies on the additional measurement of a scaling factor.

The R₂^{*} model for blood oxygenation level-dependent (BOLD) signal (Eqs.7&8) have been used extensively to study neural function and oxygen metabolism in calibrated fMRI (13–15,55,61). For quantitation of venous dHb concentration [dHb]_v required for CMRO₂, the R₂^{*} model determines [dHb]_v up to a constant A (Eqs.7&8), which is a disadvantage compared to the absolute quantitation of [dHb]_v by the QSM based method (Eq.2). This may be explained by the underlying physics for R₂^{*} and QSM. QSM solves the field to susceptibility source inverse problem based on Maxwell's equation (21) using the phase of the gradient echo data. Magnetic susceptibility has a well-defined quantitative relationship with [dHb]_v (Eq.2). On the other hand, R₂^{*} is the decay rate of gradient echo magnitude signal and may be approximated as the variance of the field in a voxel (6,34,62). Its relationship with [dHb]_v is empirical and depends on a scaling factor that requires additional information to be determined (8,11,55). The calculation of the field variance requires input of detailed field pattern in a voxel that is not known, which is the fundamental cause of this indeterminacy of the R₂^{*} model. Measurements at a third brain state can estimate this scaling factor, which is why 3 brain states (normoxic, hyperoxic and hypercapnia) have been used in R₂^{*} based CMRO₂ mapping (13–15). Additionally, the empirical parameter β~1.5 may be spatially varying (63), as β~1 for voxels containing larger vessels (6) and β~2 for voxels containing capillaries (7,61). This may explain the greater difference between QSM and R₂^{*} based CMRO₂ measurements in regions with large vessels such as the posterior region near the large sagittal sinus (PCA in Table 1). Furthermore, Eqs.7&8 may not properly account for the ferritin (non-heme iron) contribution to R₂^{*}, possibly causing overestimation of CMRO₂ in the basal ganglia area with known high ferritin concentration (Fig.4c). Besides requiring fewer drug challenges, QSM based CMRO₂ offer other potential benefits such as reduced blooming artifacts near the air-tissue interface and improved robustness against changes in scanning parameters (64).

The voxel size used in this work was chosen mainly based on scan time and SNR considerations. In general, SNR is dictated by scan time, which in this study was kept comparable to that used in routine MRI (6 min for 3D ASL (65) and 7 min for QSM (66)) with the aim to prevent head motion and also to keep the total experiment time under 1 hour. As a result, the achievable spatial resolution for the ASL scan was 3 mm isotropic, which is lower than that of the QSM scan (0.5×0.5×3 mm³). The derived CMRO₂ and OEF maps therefore also have a 3 mm isotropic resolution, although due to the very small change in the observable MR signal between the two brain states we found that reliable quantitative analysis can be performed only with region-based (instead of voxel-based) measurements. This is a limitation of the current work and solutions for SNR improvement require further investigation.

In this work, several physiological parameters such as arterial oxygenation saturation level (SaO_2) and total hemoglobin concentration ($\psi_{\text{Hb}} = 0.12$) were assumed fixed for all subjects (see Appendix). In clinical practice, these parameters can be measured for each individual subject using highly automated devices: SaO_2 be obtained through pulse oximetry (67), and ψ_{Hb} can be measured directly using hemoximetry or estimated from hematocrit measurement. In healthy subjects, SaO_2 and ψ_{Hb} can range from 0.95 to 0.99 and 0.096 to 0.14 (68). Within these ranges, error propagation analysis showed a worst-case deviation of 11% from CMRO_2 obtained in GM with fixed SaO_2 and ψ_{Hb} values, which suggests that our method is fairly robust against changes in these physiological parameters.

While previous works have reported similar OEF over the whole brain (69,70), we found that OEFs were slightly lower in WM than in GM ($26.3 \pm 11.7\%$ vs. $33.9 \pm 9.6\%$ pre-caffeine, and $45.0 \pm 18.7\%$ vs. $54.5 \pm 13.2\%$ post-caffeine, $p < 0.05$). The observed discrepancy between WM and GM regions may be attributed to the challenges associated with accurately mapping the relationship between CBF and CBV in each region, which was derived empirically from normative PET data (50). A separate measurement of CBV may be performed using a dynamic susceptibility contrast, or a dynamic QSM method (71) and extracellular contrast agents that clear rapidly before the administration of caffeine, unless it is performed as the last scan.

In this work, CSF was used to provide the reference value for brain parenchymal susceptibility. To overcome the effect of CSF flow, our GRE pulse sequence was flow-compensated in the readout (anterior-posterior) direction. When compared to a fully compensated pulse sequence (72) in three of our subjects, we found that the difference in susceptibility of the CSF (measured in lateral ventricles) was relatively small (4.1 ± 3.7 ppb, $p > 0.05$). Further work is needed to study the effect of CSF flow on QSM and CMRO_2 accuracy.

Caffeine administration has been shown to have no significant change in CMRO_2 (45). Other CMRO_2 -invariant brain challenges may include hypercapnia and hyperoxia, which may have risks and discomforts associated with the prolonged ($>10\text{min}$) continuous inhalation of high concentration CO_2 and O_2 necessary for the data acquisition. In addition, this feasibility study lacks the second challenge for estimating coefficient in calibrated BOLD. Further work is warranted to compare the proposed QSM-based with the existing R_2^* based methods that include the additional hyperoxia or hypercapnia challenges.

CONCLUSION

Quantitative susceptibility mapping can be used in conjunction with cerebral perfusion measurements before and after a vasoconstricting caffeine challenge to map cerebral metabolic rate of oxygen consumption and oxygen extraction fraction.

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APPENDIX

Here we provide detailed derivation of Eq. 5 from Eq. 4 and estimation of parameters related to blood.

Derivation of Eq. 5 from Eq. 4

Eq. 4 is

$$\text{CMRO}_2 = 4\text{CBF} \cdot [\text{Hb}] \left(\frac{\chi - \chi_o}{\text{CBV}_v \cdot \Psi_{\text{Hb}} (X_{\text{dHb}} - X_{\text{oHb}})} - (1 - \text{SaO}_2) \right) \quad [4]$$

Moving $\chi - \chi_o$ to the left side, we have:

$$\chi - \chi_o = \Psi_{\text{Hb}} (X_{\text{dHb}} - X_{\text{oHb}}) \left(\frac{\text{CMRO}_2}{4[\text{Hb}]} \cdot \frac{\text{CBV}_v}{\text{CBF}} + \text{CBV}_v (1 - \text{SaO}_2) \right) \quad [4a]$$

Equation 4a applies to each of the two brain states (pre- and post-caffeine), the difference of which can be written as:

$$\Delta\chi - \Delta\chi_o = \Psi_{\text{Hb}} (X_{\text{dHb}} - X_{\text{oHb}}) \left(\frac{\text{CMRO}_2}{4[\text{Hb}]} \cdot \Delta \left(\frac{\text{CBV}_v}{\text{CBF}} \right) + \Delta\text{CBV}_v (1 - \text{SaO}_2) \right) \quad [4b]$$

By rearranging Eq.4b, we arrive at Eq.5:

$$\text{CMRO}_2 = \frac{4[\text{Hb}]}{\Delta(\text{CBV}_v/\text{CBF})} \left(\frac{\Delta\chi - \Delta\chi_o}{\Psi_{\text{Hb}} (X_{\text{dHb}} - X_{\text{oHb}})} - \Delta\text{CBV}_v (1 - \text{SaO}_2) \right) \quad [5]$$

Calculation of hemoglobin molar concentration in blood [Hb]

The hemoglobin molar concentration in blood $[\text{Hb}] = 2.48 \mu\text{mol/ml}$, is estimated from the Hematocrit $\text{Hct} = 0.47$ (68), Hb mass concentration in a RBC (0.34 g/ml), and the molar mass of dHb $M_{\text{Hb}} = 64450 \times 10^{-6} \text{ g}/\mu\text{mol}$ (73)

$$[\text{Hb}] = \frac{\text{Hct} \cdot 0.34 \text{ g/ml}}{M_{\text{Hb}}} = 2.48 \mu\text{mol/ml}$$

Calculation of hemoglobin volume fraction in blood Ψ_{Hb}

The hemoglobin volume fraction in blood $\Psi_{\text{Hb}} = 0.12$ is estimated from $[\text{Hb}]$, M_{Hb} , and Hb concentration in pure aggregate ($\rho_{\text{Hb}} = 1.335 \text{ g/ml}$) (74).

$$\Psi_{\text{Hb}} = \frac{[\text{Hb}] \cdot M_{\text{Hb}}}{\rho_{\text{Hb}}} = 0.12$$

Calculation of oxyhemoglobin X_{oHb} and deoxyHemoglobin X_{dHb} volume susceptibility

The volume susceptibility of oxyhemoglobins X_{oHb} relative to water is estimated from the reported mass susceptibility of globin relative to vacuum, $-4\pi (0.587 \times 10^{-6} \text{ mL/g})$ (4π for conversion from cgs to si) (74,75) as,

$$X_{\text{oHb}} = (-4\pi(0.587 \times 10^{-6} \text{ mL/g})\rho_{\text{Hb}}) - (-9035 \text{ ppb}) = -813 \text{ ppb}$$

where -9035 ppb is the volume susceptibility of water with respect to vacuum (76).

The volume susceptibility of oxyhemoglobins X_{dHb} relative to water is estimated by adding to X_{oHb} a paramagnetic term of $5.25 \mu_{\text{B}}$ (Bohr magneton $\mu_{\text{B}} = 9.274 \times 10^{-24} \text{ J/T}$) per heme (77,78) according to (18,34,79),

$$X_{\text{dHb}} = 4 \frac{N_{\text{A}} \rho_{\text{Hb}} \mu_0 (5.25 \mu_{\text{B}})^2}{3 M_{\text{Hb}} k_{\text{B}} T} + X_{\text{oHb}} = 10765 \text{ ppb}$$

where $N_{\text{A}} = 6.02 \times 10^{23} \text{ mol}^{-1}$ is the Avogadro number, $\mu_0 = 4\pi \times 10^{-7} \text{ Tm/A}$ is the magnetic permeability in vacuum, $k_{\text{B}} = 1.38 \times 10^{-23} \text{ J/K}$ is the Boltzman constant, and $T = 310 \text{ K}$ is the human body temperature.

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Figure 1.

Example of GM and WM masks on a mid-brain slice. The GM mask is segmented into six regions corresponding to different vascular territories as shown. The masks cover the supratentorial brain parenchyma from the vertex to the superior aspect of the cerebellum.

Figure 2.

An example of QSM and CBF maps acquired pre- and post-caffeine and the derived CMRO₂ and OEF maps in a healthy subject (subject 12).

Figure 3.

An example of volumetric pre- and post-caffeine OEF and CMRO₂ maps using the QSM-based method, and T₂ weighted images of a healthy subject (subject 7). The locations of the slices are marked on the scout images shown on the right.

Figure 4.

Examples of QSM- and R₂^{*}-based CMRO₂ maps of two representative subjects (subject 1 and 4). The locations of the slices are marked on the scout images.

Table 1

QSM and R_2^* based CMRO₂ measurements within cortical GM regions associated with different vascular territories ($\mu\text{mol}/100\text{g}/\text{min}$, mean $\pm$ std). All differences between the two methods were statistically non-significant ($p>0.05$).

	QSM based	R_2^* based
ACA_Left	175.5 $\pm$ 33.4	166.2 $\pm$ 29.9
ACA_Right	174.1 $\pm$ 33.6	160.6 $\pm$ 29.5
MCA_Left	149.3 $\pm$ 27.1	153.2 $\pm$ 42.1
MCA_Right	154.8 $\pm$ 37.7	144.8 $\pm$ 33.6
PCA_Left	143.9 $\pm$ 38.0	159.1 $\pm$ 39.8
PCA_Right	140.8 $\pm$ 32.8	157.0 $\pm$ 38.3

Table 2

L/R hemisphere ratio of QSM and R_2^* based $CMRO_2$ and OEF values measured within cortical GM regions.

No statistical significance has been found ($p>0.05$) among vascular territory within each method.

	OEF Pre-Caffeine		OEF Post-Caffeine		$CMRO_2$	
	QSM based	R_2^* based	QSM based	R_2^* based	QSM based	R_2^* based
ACA	0.99 ± 0.12	1.00 ± 0.13	0.99 ± 0.13	1.02 ± 0.15	1.03 ± 0.21	1.04 ± 0.15
MCA	0.99 ± 0.25	0.99 ± 0.23	0.97 ± 0.24	0.97 ± 0.26	1.00 ± 0.22	1.07 ± 0.23
PCA	0.94 ± 0.13	0.96 ± 0.19	0.92 ± 0.13	0.92 ± 0.15	1.03 ± 0.15	1.03 ± 0.23