Session Title: **Quantitative Physiology**
Talk Title: **Imaging of Oxygenation**

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Highlights

- Cerebral oxygenation is a general term that covers several specific parameters including blood oxygen saturation (SO_2), blood and tissue oxygen partial pressure (PO_2), oxygen extraction fraction (OEF) and the cerebral metabolic rate of oxygen ($CMRO_2$). These parameters are fundamental indicators of brain tissue health and function, and are perturbed during both functional neuronal activation and in disease states such as stroke and brain tumor. As such, quantification of these parameters will facilitate understanding of normal brain operation and enable detailed investigation of neuropathology.
- MR and optical imaging approaches have been recently developed to image cerebral oxygenation, and provide complementary information spanning several spatial orders of magnitude.
- Optical approaches are based on two-photon microscopy method that maps PO_2 and SO_2 with sub-capillary resolution (1-4). Measurement of PO_2 and SO_2 along cortical microvasculature and surrounding tissues in animal models has provided a deeper understanding about cortical microvascular oxygen distribution (5,6).
- MR-based techniques have been developed to quantify SO_2, OEF, and $CMRO_2$ in humans and are the focus of this presentation. These methods involve first determining SO_2 and OEF and then use a separate cerebral blood flow (CBF) measurement to estimate $CMRO_2$. Three general classes of MR methods exist for OEF quantification:
    - Intravascular T_2-based methods target the relationship between blood oxygenation and the transverse (T_2) MR relaxation of intravascular blood. TRUST MRI uses spatial-based spin labeling to measure whole brain SO_2 and OEF, whereas QUIXOTIC-based MRI uses velocity selective spin labeling to map SO_2 and OEF on a voxel-by-voxel basis.
    - Phase-based MR methods assess oxygenation in individual veins by quantifying susceptibility shift between vessels and tissue. Susceptibility shift is directly related to blood oxygenation; extrapolating shift from MR phase images allows for regional SO_2 and OEF measurement.
    - Quantitative BOLD techniques quantify the effects of inhomogeneous magnetic fields in the extravascular space, as created by deoxygenated intravascular blood. The magnitude of these effects on the MR signal depends on level of intravascular blood oxygenation; careful modeling of the MR signal allows voxel-wise SO_2 and OEF mapping.

Target Audience: MR physicists & developers, neuroscientists, neuroradiologists, neurologists

Outcome/Objectives:

- Summarize key two-photon optical results of PO_2/SO_2 in and around microvasculature
- Understand cerebral SO_2, OEF, and $CMRO_2$ from a physiologic perspective
- Learn state-of-the-art MR approaches for imaging SO_2, OEF, and $CMRO_2$
- Identify clinical and basic science applications of SO_2, OEF, and $CMRO_2$ imaging

Problem Summary

Continuous oxygen delivery to neural tissue is necessary to maintain normal brain function and viability. The brain consumes 20% of total body energy through aerobic metabolism under healthy conditions (7). The ability to easily map human brain oxygenation would provide new information about normal cerebral physiology at rest and during functional activity (8), and improve understanding about disorders in which oxygen supply to the brain is disturbed, such as stroke (9), tumor (10), and multiple sclerosis (11). In acute stroke, for instance, metabolic indicators such as local oxygen extraction can identify tissue at risk of infarction and potentially guide therapy (12).

Assessing blood oxygenation *in vivo,* however, is technically challenging. Until recently, established *in vivo* human methods to measure brain oxygen utilization have relied on positron emission tomography (PET) imaging with ^{15}O radiotracers (13,14). However, ^{15}O PET is not used clinically as it requires injection of short-lifetime radiotracers, veno/arterial puncture and blood monitoring, and a large staff for a single experiment. Aforementioned optical techniques have provided valuable insights into the cerebral oxygenation, but are invasive and currently limited to animal models. Consequently, clinically feasible MR-based assessment of brain oxygenation is highly desirable. Since MRI is sensitive to oxygenation-dependent modulations in the blood signal, primarily through magnetic properties of deoxygenated hemoglobin (dHb), measuring SO_2, OEF, and $CMRO_2$ has become possible, with quantitative MR methods showing great promise in recent years.

Oxygenation Parameter Definitions

Because oxygen is not produced endogenously in the brain, it must be delivered by inflowing blood and extracted into the surrounding tissue, in order to meet metabolic demands. The following schematic based on recent two-photon optical work (5) provides a simplified representation of SO_2 along the microvascular tree, from arterioles to capillaries to venules, with SO_2 decreasing as oxygen extracts into surrounding tissue territories.

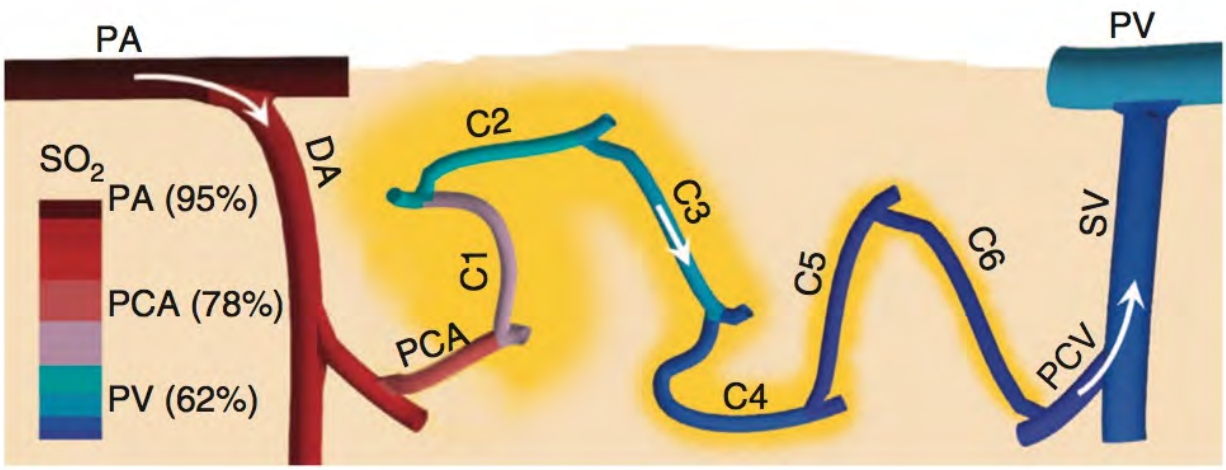

Figure **1.** Simplified representation of cortical microvascular path, intravascular oxygen, and supplied territories. Pial arterioles (PA), diving arterioles (DA), precapillary arterioles (PCA), capillaries (C1-C6), postcapillary venules (PCV), surfacing venule (SV), and pial venlues (PV) are depicted, with colors representing approximate average segment SO_2. Presumably, decreasing SO_2 along the microvascular path of flow is secondary to oxygen extracting into surrounding tissue. Tissue territories supplied are outlined in yellow. From **Sakadžić** et. al (5).

The percent of oxygen extracted by tissue from the vasculature is commonly expressed as the oxygen extraction fraction (OEF):

$$OEF = \frac{SaO_2 - SvO_2}{SaO_2} \quad [1]$$

where SaO_2 is the blood oxygen saturation level in arteries and SvO_2 is the oxygen saturation in veins after extraction (where are SaO_2 and SvO_2 are specialized instances of SO_2). Often, SaO_2 is close to one since arterial blood is typically fully oxygenated.

If OEF and cerebral blood flow (CBF) are known, the absolute rate of oxygen consumption by brain tissue ($CMRO_2$), can be determined in micromol O_2/100g·min using Fick's principle (15):

$$CMRO_2 = OEF \cdot CBF \cdot C_a \quad [2]$$

where C_a is the oxygen carrying capacity of hemoglobin molecules per volume of blood.

MR method classes to quantify OEF and $CMRO_2$

Intravascular T_2-based MRI (16)

One class of approach to measure OEF involves quantifying dHb-induced signal loss in intravascular blood. These techniques invoke an MR signal model that establishes an analytic relationship between the T_2 relaxation of blood, SO_2, and hematocrit, and exclude signal contributions from extravascular constituents. The model has been extensively described (17-20) and recently applied in humans at 3T (21). Using this model, T_2 versus SO_2 calibration curves can be generated (figure 1a) and used to convert venous blood T_2 to absolute S_vO_2 and OEF.

The major challenge in using intravascular T_2 to measure S_vO_2 is isolating pure venous blood signal, free from extravascular and non-venous blood components. This is a nontrivial task due to partial voxel voluming with tissue, CSF, and non-venous blood. To circumvent this issue, initial intravascular T_2 studies targeted blood in large veins only, as it was easier to find blood-containing voxels within large-caliber vessels (18,20). These studies used BOLD contrast to first locate draining veins from active sites and then measured T_2 and S_vO_2 within voxels within these vessels. Despite careful voxel selection, however, limits on spatial resolution made partial volume effects difficult to avoid.

More recently, spin-labeling based approaches have been creatively employed to isolate venous blood signal. Lu and colleagues proposed T_2-Relaxation Under Spin Tagging (TRUST) MRI and measure S_vO_2 in the sagittal sinus (22). TRUST uses pulsed arterial spin labeling (ASL) MRI theory (23), but instead labels blood on the venous side of circulation. Paired subtraction (as in typical ASL data processing) results in an image containing blood signal from large veins only, with tissue and CSF completely subtracted. By acquiring these images at multiple echo times and measuring T_2 in a large vein, an estimate of global S_vO_2 becomes possible. Figure 1b (top row) shows representative multi-echo TRUST images; T_2 signal decay within the sagittal sinus is demonstrated. TRUST MRI has been recently applied and validated in humans for both global OEF and $CMRO_2$ measurements. Despite being a spin-labeling technique, TRUST has high SNR due to the large blood volume within draining vein voxels and can thus be accurately performed in minutes. A limitation of TRUST is that measurements are restricted to terminal veins, making regional S_vO_2 estimation difficult.

A second approach dubbed QUantitative Imaging of eXtraction of Oxygen and TIssue Consumption (QUIXOTIC) extends the utility of spin labeling and isolates venous blood on a voxel-by-voxel basis, thus allowing localized S_vO_2 measurements (24). QUIXOTIC uses a novel velocity-selective excitation scheme and is related to velocity-selective arterial spin labeling (VS-ASL) (25). In principle, QUIXOTIC applies velocity-sensitive pulses to eliminate signal from blood flowing above preset cutoff velocities. By carefully timing these pulses, it is possible to exploit the physiological blood velocity distribution and create a venular-blood bolus that persists after subtraction (24). Signal from static tissue, CSF, and non-venular blood compartments are eliminated, resulting in a pure venular-blood signal map. As in TRUST, QUIXOTIC blood-weighted images are acquired at multiple echo times (Figure 1b). Voxel-wise exponential fitting generates T_2 maps from which S_vO_2, OEF, and $CMRO_2$ images are subsequently computed (Figure 1c). Notably, QUIXOTIC reports parenchymal S_vO_2 values higher than those reported by quantitative BOLD and other methods. The source of this discrepancy is currently under investigation; an in-depth discussion can be found in reference (24). The main limitation of QUIXOTIC is low SNR, due to low CBV in a typical parenchymal voxel. This is expected to become less of an issue at higher field strengths and with many-element imaging coils. Notably, like ASL, QUIXOTIC can be used in functional imaging to create quantitative S_vO_2 and OEF activation maps.

Several novel approaches have been introduced since QUIXOTIC, which offer improvements and address existing issues. VSEAN (Venous Oxygenation Mapping Using Velocity-Selective Excitation and Arterial Nulling) was recently introduced by Guo and colleagues (26), similarly uses velocity-selective excitation (but in a different manner than QUIXOTIC), and adds arterial nulling capabilities. VSEAN reduces contamination from unwanted diffusion-weighting and also offers improved SNR. Schmid and colleagues introduced inflow QUIXOTIC OEF (IQ-OEF) in 2012 (27), which uses a combination of velocity selective labeling and pulsed arterial spin labeling to label the local venous blood pool and eliminates the need for the TO_1 inversion pulse. Consequently, a substantial increase in SNR is achieved.

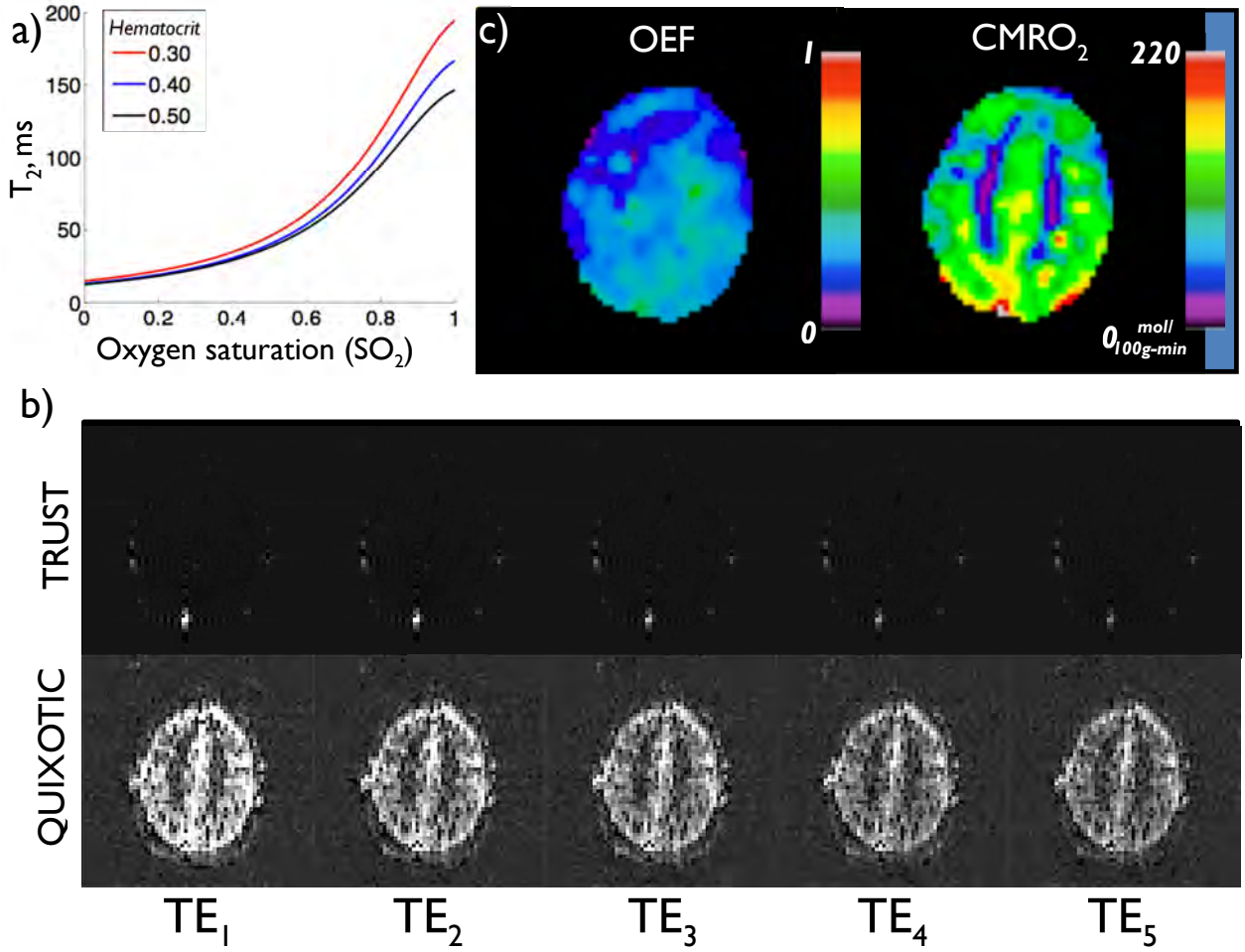

Figure 2. Results from intravascular T2-based approaches. A) sample T2 versus SO_2 calibration curve. B) Representative venous-blood weighted images at multiple TEs for TRUST (top row) and QUIXOTIC (bottom row). C) QUIXOTIC-generated OEF and $CMRO_2$ maps. Adapted from Bolar et. al. (24).

Phase-based Oxygenation Measurements

MR Susceptometry. An alternate MR contrast mechanism for oxygenation derives from deoxyhemoglobin (dHb)-induced increases in magnetic susceptibility within veins compared to the surrounding brain tissue. This susceptibility shift creates local magnetic field perturbations ($\Delta B_{vein-tissue}$) that manifest in MR phase images as $\Delta\varphi = \gamma \cdot \Delta B \cdot TE$, where γ is the gyromagnetic ratio and TE is the echo time. In this way, MR phase images provide information about susceptibility changes that enable quantification of the underlying SvO_2 in individual vessels.

This approach, termed *MR susceptometry*, has been used to study oxygenation in large draining veins such as the femoral vein of the leg (28) and the internal jugular vein (29) and sagittal sinus of the brain (30). Combining MR susceptometry in the sagittal sinus with whole-brain flow measurements, Jain et al. also recently demonstrated reproducible global $CMRO_2$ estimates in healthy subjects at rest, and during functional changes induced by CO_2 gas inhalation (31).

Phase-based regional oxygen metabolism (PROM). With sufficient resolution, phase-based oxygenation can be assessed in smaller veins, which is expected to be more reflective of local brain physiology. A recently proposed method called PROM combines susceptometry in parallel pial veins with regional estimates of CBF from arterial spin labeling MRI to estimate local cortical $CMRO_2$ (32). PROM at 3 Tesla and achieved gradient echo phase imaging with 0.5mm in-plane resolution. In this initial study on 12 healthy volunteers, mean gray matter $CMRO_2$ was measured as 151 □mol/100g·min, which is in line with ^{15}O PET values in the literature. Greater $CMRO_2$ was observed in the occipital cortex compared to frontal and temporal areas, suggesting that PROM is sensitive to regional variations in metabolism across the brain.

Quantitative Susceptibility Mapping. One limitation of PROM its assumption of a long, parallel cylinder model for veins of interest, which restricts the set of vessels amenable to phase-based analysis. It is possible to extend SvO_2 estimates to veins of arbitrary curvature and orientation using quantitative susceptibility mapping (QSM) techniques to directly reconstruct 3D susceptibility distributions from measured field maps (33). In general, recovery of the underlying susceptibility map is challenging due to the complex and nonlocal relationship between susceptibility and magnetic field. Current research aims to utilize new 3D QSM methods to directly assess susceptibility differences between veins and tissue (34). This work potentially can provide whole-brain coverage of SvO_2 in a larger set of veins, and improve applicability of PROM.

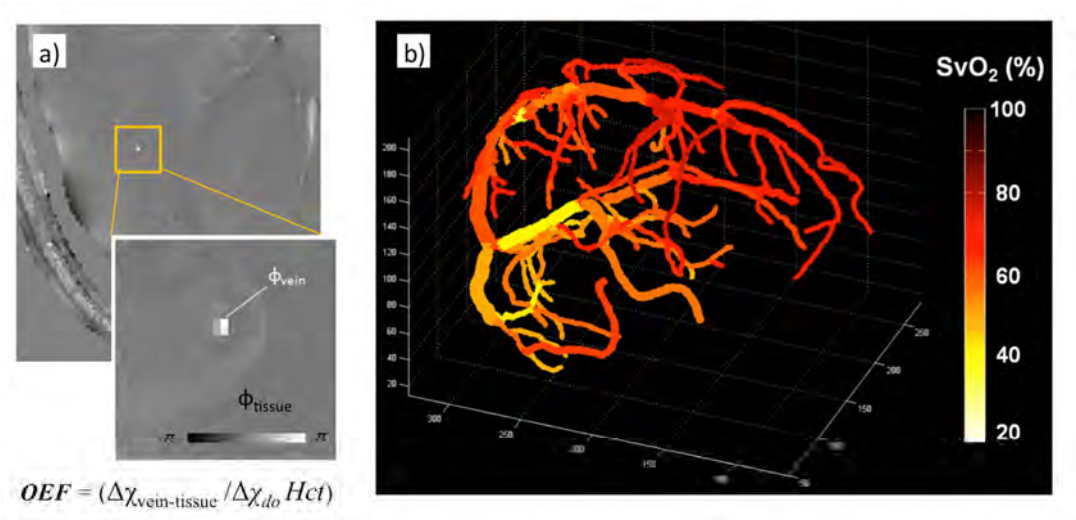

Figure 3. A) PROM-based calculation of OEF. B) Quantitative susceptibility mapping to generate SvO_2 projections along draining veins. Adapted from Fan et. al. (32) and (34).

Extravascular-based OEF measurements:

A third class of methods invokes an MRI signal model that quantifies OEF primarily based on dHb-induced signal loss in the extravascular tissue; in other words, tissue surrounding blood vessels.

This model utilizes the so-called "static-dephasing regime", a regime where the MRI signal is influenced by static magnetic field inhomogeneities. In the static dephasing regime, the phase distribution at a given TE is identical to local magnetic field distribution around vessels containing paramagnetic dHb particles. This allows the derivation of a relationship between the dHb-induced frequency shift and the SvO_2 within the vessels (assuming a random orientation of vessels in the voxel space). It follows that the relaxivity due to these static field inhomogeneities (characterized by a R_2', which is inversely related to the time constant T_2'; i.e. $R_2'=1/T_2'$) is the product of blood volume and this frequency shift.

R_2' is the difference between R_2^* ($1/T_2^*$) and R_2 ($1/T_2$) and can thus be estimated by measuring T_2 and T_2^* using gradient echo and spin echo MRI sequences, respectively. Extravascular-based methods typically use a hybrid spin-echo and gradient multi-echo sequence where R_2' is estimated by removing the R_2 effect from the net signal collected ($R_2' = R_2^* - R_2$). Development of these hybrid sequences was a key innovation allowing these measurements.

Early approaches by An and colleagues used a single compartment model that assumed that MR signal originates from a single extravascular tissue constituent and ignores blood and CSF signal. Using this model, they produced OEF (35) and $CMRO_2$ (36) maps based on the aforementioned T_2' methodology. He and Yabolinskiy took this approach a further by considering a multiple-compartment model, which factors the effects of blood and CSF on the MR signal (37). This technique is called quantitative BOLD (qBOLD), and has been fine-tuned and recently validated in animal and human models, producing OEF and $CMRO_2$ maps (38,39). Even more recently, novel MRI-fingerprinting approaches have been used with qBOLD to further refine the parameter mapping process (40).

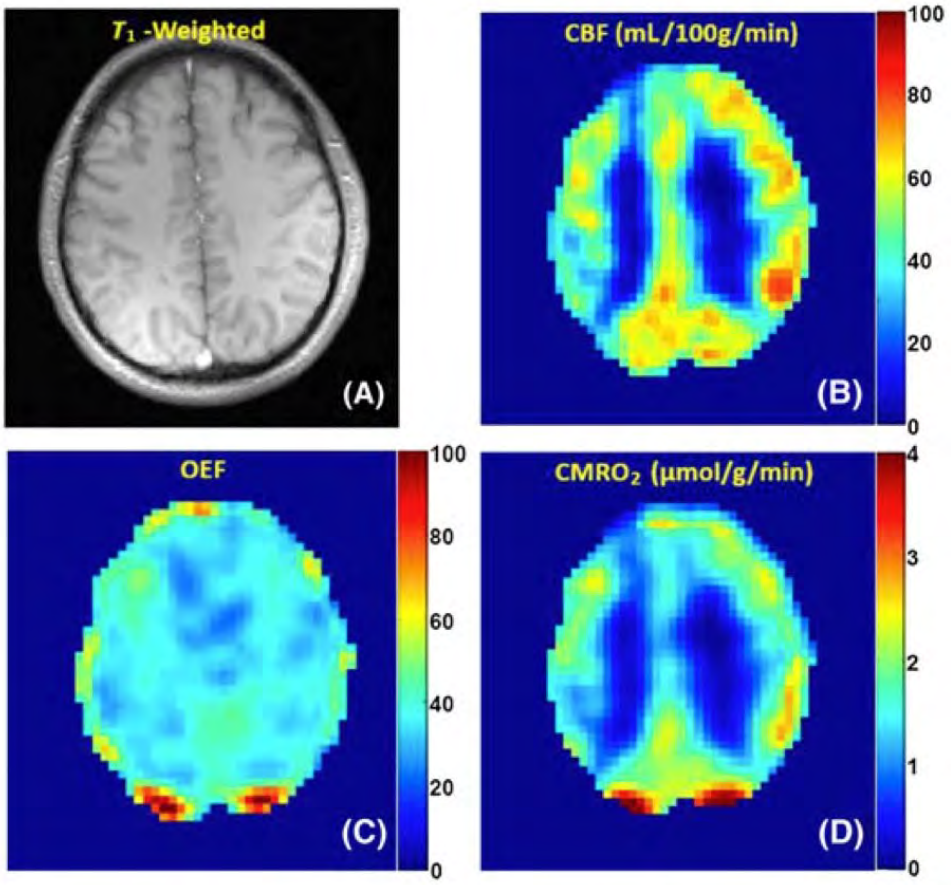

Figure 4. Quantification of OEF and $CMRO_2$ using quantitative BOLD methodology. A) T1-weighted anatomical image; (B) cerebral blood flow (CBF) map (in mL/100 g/min), (C) OEF map. D) map of CMRO2 (in mmol/g/min). Adapted from He et. al, (38).

Summary

- Quantitative BOLD, intravascular T2-based spin labeling approaches like QUIXOTIC, and phase-based oxygenation methods like PROM are promising for their ability to quantitatively measure OEF and $CMRO_2$.
- These MR-based tools to measure oxygenation (previously only accessible by PET) will further our understanding of neuropathology like stroke, brain tumor, and multiple sclerosis, and of normal brain function, for example, through functional MRI.

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