Hyperpolarized MRI, functional MRI, MR spectroscopy and CEST to provide metabolic information in vivo

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Abstract

Access to metabolic information *in vivo* using magnetic resonance (MR) technologies has generally been the niche of MR spectroscopy (MRS) and spectroscopic imaging (MRSI). Metabolic fluxes can be studied using infusion of substrates labeled with magnetic isotopes, with the use of hyperpolarization especially powerful. Unfortunately, these promising methods are not yet accepted clinically, where fast, simple, and reliable measurement and diagnosis are key. Recent advances in functional MRI and chemical exchange saturation transfer (CEST) MRI allow the use of water imaging to study oxygen metabolism and tissue metabolite levels. These, together with the use novel data analysis approaches such as machine learning, for all of these metabolic MR approaches, are increasing the likelihood of their clinical translation.

Introduction

Magnetic Resonance has a multitude of approaches for assessing molecular information *in vivo*. Until recently, the study of metabolism has been the niche of MRS or MRSI, both homonuclear and heteronuclear [1]. However, this has expanded to functional MRI and especially CEST MRI methods that indirectly assess molecular information through imaging of the water signal. In the following we briefly summarize recent advances in metabolic MR using MRS and MRI.

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1. Proton MRS and MRSI

While MRS is viewed by many as a mature technique, in fact over the last two years there have been substantial new developments, many of which have important implications for clinical application of this methodology. The main focus for clinical MRS is in the area of brain tumors, and in particular diagnosis of isocitrate dehydrogenase (IDH) mutation status using measurements of 2-hydroxyglutarate (2HG). Recently it has also been demonstrated that spectral editing could be used to measure cystathionine as well as 2HG, which gave information on 1p19q chromosome deletion as well as IDH status [2], opening up the possibility for accurate presurgical molecular tumor diagnosis. Brain tumors are known to often be very spatially inhomogeneous, from the viewpoint of both pathophysiology and metabolism, and it is therefore important to measure the distribution of metabolites within the tumor and surrounding brain. For mapping of multiple brain metabolites at relatively high spatial resolution, recent developments using MRSI at 7 T have also been demonstrated [3]. This technology could have multiple clinical applications, but a particularly promising one is the use of total choline (tCho) maps (or maps of the tCho/N-acetylaspartate ratio) to guide radiotherapy [4]. Preliminary results of this approach in high grade glioma with localized dose-escalation have given promising results (Dr H. Shim, Emory University, personal communication).

In the past, many MRS or MRSI studies have been hampered to some degree by variable technical quality or disparate technical approaches. Over the last 2 years there has been a substantial effort to reach consensus on optimal techniques that should be used for human MRS studies, both in terms of data acquisition and analysis. The result of this effort has been a series of technical consensus articles that have been published in the last year [5–9]. A second area of substantial and recent development is the application of deep learning (DL) to the analysis of MRS data. Given the particular strength of DL in extracting information from data with low signal-to-noise ratio (SNR), this is expected to remain a growth area. Applications of DL to MRS lag behind MRI somewhat, with the translation of DL-MRI approaches to the imaging domain of MRSI one immediately accessible area. For example, a densely connected U-Net that uses additional information from high-resolution T_1-weighted MR images was shown to be able to generate 'super-resolution' metabolic images [10]. In the spectral dimension, DL approaches have been used for post-processing steps including artifact identification and removal [11], accelerated spectral fitting [12], shot-to-shot frequency and phase correction [13], and replacement of Fourier transformation for truncated FIDs [14]. MRS quantification amounts to extracting the concentration of a small number of metabolites from a large number of spectral data points, a task that should be amenable to DL; significant recent progress has been made in this area, including the use of truncated MRS data (Fig. 1, [15]). An additional potential of DL lies in combining disparate information from different imaging modalities, for example, combining voxel-based morphometry analysis of structural MRI with MRS data to enhance the independent diagnostic power of each modality [16].

2. Heteronuclear MRS and MRSI

2.1: Hyperpolarized MR

While ^{1}H MRS is known to provide metabolite levels, the study of metabolic fluxes has relied on the infusion of substrates labeled with non-radioactive magnetic isotopes such as ^{13}C, but these have even less sensitivity to detection due to their lower gyromagnetic ratio. The advance to human imaging and possible clinical relevance has come from performing metabolic imaging with injected hyperpolarized ^{13}C-labelled substrates, where a more than 10,000 gain in sensitivity has enabled ^{13}C MRSI of these substrates and their downstream metabolites. After a decade of preclinical research with a variety of isotopically labelled and hyperpolarized cell substrates [17–20], [1-^{13}C]pyruvate has emerged as the most promising and widely used substrate. This is because it can be polarized to high levels (>60% at 7T), the ^{13}C nucleus has a relatively long T_1 (~30 s *in vivo*), and it undergoes rapid cell uptake and subsequent metabolism leading to substantial formation of downstream metabolites (lactate and CO_2/HCO_3^-) within the short lifetime of the polarization (2–3 minutes). Pyruvate, which is at the end of the glycolytic pathway, stands at a metabolic crossroads, where it can undergo reduction by NADH to produce lactate, in the reaction catalyzed by lactate dehydrogenase (LDH), or it can enter the mitochondria and be oxidized in the TCA cycle with the production of CO_2. The relative labeling of lactate and CO_2/HCO_3^- provides, therefore, an index of glycolytic versus TCA cycle activity. For example, in tumors, where there are often high levels of lactate and LDH activity, relatively high levels of lactate labelling are observed (Fig. 2), whereas in more aerobic tissues, such as heart and brain, there is increased CO_2/HCO_3^- labelling, which is decreased in ischemia.

The hyperpolarized [1-^{13}C]pyruvate technology was translated to the clinic in 2013 with a study of metabolism in prostate cancer [21]. This substrate now stands on the threshold of wider clinical application with the publication of initial studies in brain [22,23] and heart [24,25] plus further studies of prostate cancer [26–30], brain [31–34], breast [35,36], pancreas [37] and kidney [38]. The important question now is how metabolic imaging with hyperpolarized [1-^{13}C]pyruvate could change clinical practice? Early preclinical studies in cancer suggested that the technique could be used to provide early evidence of treatment response [39] and to determine tumor grade and disease progression [40] and some of the initial clinical studies support these ideas [26,27,29,31,36]. PET with 2-Deoxy-2-[^{18}F]fluoroglucose (FDG) is already established in the clinic as a method for detecting tumors and monitoring treatment response and therefore it is important to ask what advantage imaging with hyperpolarized [1-^{13}C]pyruvate might have. Several studies have directly compared the two techniques [33,41–45]. Importantly, FDG PET signal can detect a signal decrease after treatment with few false negative results (no response detected even though there was a treatment response), and therefore has good sensitivity for detecting response. However, FDG PET can give false positive results (decrease in signal not due to a treatment response), and thus has poor specificity. On the other hand, while hyperpolarized [1-^{13}C]pyruvate imaging currently is less likely to detect low volume disease and does not have whole body capability, its capacity to evaluate effectively more of the glycolytic pathway may make it more specific for detecting treatment response under some circumstances [42,44].

Even more than PET, hyperpolarized ^{13}C MRI is plagued by a lack of availability of specialized equipment (the need for a heteronuclear RF channel, not available on clinical scanners) and easy access to hyperpolarization (isotope lifetimes are shorter than PET). However, technical issues can always be addressed if the need is demonstrated and substrate availability could be addressed by centralized production of hyperpolarized contrast media. Removal of the stable radical, the source of the unpaired electron spins used in the dynamic nuclear polarization process, may allow storage and shipping of the hyperpolarized material at low temperature. Removal can be achieved by immobilizing the radical and physically separating it from the hyperpolarized ^{13}C spins [46] or by generating the radical using u.v. irradiation and removing it by transiently raising the temperature [47].

2.2. Deuterated substrates

Recently, the field of magnetic-isotope-labeled substrates for MR studies of metabolism has received a boost by the demonstration that deuterated substrates can also be used to study metabolic pathways with a spatial resolution comparable to hyperpolarized MR [48,49]. Deuterium has the advantage of unlimited lifetime, but similarly requires specialized equipment (RF hardware) not available on clinical scanners. This field is very young, but the first results are promising, for instance for monitoring tumor metabolism (lactate production) after administration of $[6,6\text{-}^2H_2]$glucose, in a manner similar to hyperpolarized $[1\text{-}^{13}C]$pyruvate [48,49]. Importantly, such metabolism can be detected indirectly through the proton spectrum [50,51], opening up the possibility to study metabolic pathways using deuterium-labelled substrates on standard human scanners [51], e.g. through isotopomer analysis. The promises and pitfalls of this approach were analyzed recently [52].

3. Chemical Exchange Saturation Transfer (CEST) MRI

CEST MRI is related to MRS but employs indirect detection of metabolites that contain groups with exchangeable protons such as hydroxyl, amide, amine, and guanidinium protons [53,54]. This is done by magnetically labeling these protons (using RF saturation or multi-pulse excitation [55]) and detecting a resulting saturation effect in the water signal. Using repetitive label-exchange events per acquisition, CEST MRI allows not only water detection, but also comes with a sensitivity enhancement of one or more orders of magnitude, allowing imaging of millimolar concentrations of metabolites. Importantly, mobile macromolecules such as proteins and glycogen can also be detected through labeling of aliphatic protons if these have a dipolar coupling with nearby exchangeable protons, through a process called exchange relayed nuclear Overhauser effect (rNOE). In principle any compound with exchangeable protons can be detected, but this unfortunately also comes with a detection specificity problem for individual metabolites *in vivo* due to overlap of these many broad resonances. There is also interference of background signals from direct water saturation (DS) and magnetization transfer contrast (MTC) from semi-solid tissue components, e.g. membranes, myelin sheets. In addition, the conventional CEST data analysis approach of asymmetry analysis with respect to the water resonance frequency further mixes signals and the use of different RF strengths (B_1) changes the proportions of these different signal contributions [54,56–59]. Signal interpretation in terms of concentration is also not straightforward because CEST signals are often pH dependent. In the physiological range,

exchange rates decrease with pH, which leads to a decrease in the detectability of amide and guanidinium protons, but an increase for OH and amine protons, because the signal intensities depend on the exchange regime at a particular field strength (B_0). This may lead to erroneous interpretation in terms of metabolite changes if the pH is changing, for instance during ischemia or exercise, or in tumor environments. A typical example is for the amine protons of glutamate (Glu), because Glu concentration increases during early ischemia and the reduced pH increases the visibility of amine protons and it is unclear what is being measured. Images of the endogenous *in vivo* CEST signals are therefore often called "weighted", to indicate contaminated signals. Specificity can be increased, for instance using difference experiments, e.g. from physical or physiological tasks or metabolite-specific drug treatment.

We focus here on recent literature for endogenous metabolites. The field has grown tremendously with many interesting applications in animal models, some having translated to humans. Multiple approaches are being developed to detect at least some species selectively, especially compounds with higher concentrations, such as glutamate (Glu) in the brain, creatine (Cr) and phosphocreatine (PCr) in muscle, and glycogen (Gly) in liver and muscle. For instance, there are many papers on glutamate CEST weighted (GluCESTw) MRI, confirming a major Glu signal contribution and also its reproducibility [60]. Recent data in humans [61], when not using asymmetry analysis and correcting for large background signals of DS and MTC, show a correct gray matter/white matter ratio for Glu, that corresponds with MRS measurements. GluCEST is showing potential for assessing neurodegenerative diseases such as Huntington's [62], Alzheimer's [63], Parkinson's Disease/dopamine-deficiency [64], Multiple Sclerosis [65], and the presence of epileptic foci [66]. Unfortunately, due to the high exchange rate of amines, it appears that GluCEST may be limited to high field scanners (7T and above). The second-most studied metabolic pathway using CEST MRI is the creatine kinase reaction, especially in muscle [67–69]. During exercise, the PCr concentration decreases and Cr increases, but the sensitivity for measuring increased Cr concentrations is compromised by a concomitant pH decrease. At the same time, PCr-CEST signal decreases will be amplified by such pH decreases. It is increasingly recognized that the use of asymmetry analysis is not that useful for Cr/PCr CEST MRI and that the full spectrum should be studied. At some B_0 and B_1 field strengths, the CEST signals of Cr and PCr can be measured simultaneously [70,71] and the data interpreted correctly. Importantly, at high B_0 the CrCEST signal dominates, while at low field (3T and below) the guanidinium protons of Cr are in the intermediate to fast exchange regime and disappear into the background. Interestingly, it was shown recently that for skeletal muscle in humans at 3T, B_1 can be tuned so that PCr is the only distinguishable CEST signal in the high frequency range relative to water [72]. Using a deep learning algorithm to assess the effects of B_0, exchange rate (pH dependent) and signal intensity, this allowed the effects of exercise to be monitored *in vivo* at high spatial and temporal resolution (Fig. 3). Another area of noteworthy progress has been the ability to study glycogen levels *in vivo* in liver using rNOE signals [73]. Overall, the relatively young CEST field is showing many interesting metabolic applications in animal models at higher field strengths and is increasingly being translated to humans at 7T and also 3T. We expect a continuous growth of the CEST field, especially judged from recent work using spectral

analysis with machine learning approaches [72,74–77] and fast acquisition approaches with reduced sampling and increased sensitivity, such as compressed sensing and fingerprinting [78–82].

4. Functional MRI

Functional MRI (fMRI) based on the Blood-Oxygenation-Level-Dependent (BOLD) signal can be used to assess metabolic activity. The BOLD signal reflects a hemoglobin-oxygenation-based magnetic susceptibility effect that affects the transverse relaxation times (T_2 or T_2*) of intravascular and extravascular water protons [83–85]. The venous oxygenation fraction (Y_v) of hemoglobin is determined by the tissue cerebral metabolic rate of oxygen ($CMRO_2$), cerebral blood flow (CBF), and the total hemoglobin concentration in blood ([Hb_{tot}], which is proportional to hematocrit (Hct). Importantly, focusing on the intravascular BOLD effect, $CMRO_2$ can be quantified without stimulation or contrast agent using the Fick Principle:

$$(Y_a - Y_v) = \frac{CMRO_2}{CBF \cdot [Hb_{tot}]} = OEF \cdot Y_a$$

where Y_a is the arterial oxygenation saturation fraction and OEF the oxygen extraction fraction. Using MRI, whole-brain Y_v can be measured either based on a calibrated relationship between blood T_2 and oxygenation fraction ([86–88] and references therein) or magnetic susceptibility quantification of blood ([89–92] and references therein). As one of several rapid MRI pulse sequences, T_2-Relaxation-Under-Spin-Tagging (TRUST) MRI [87] can measure global Y_v within approximately 1 minute and has been validated with ^{15}O-PET [93]. Recent advances in understanding the relationship between T_2 and Y allow calibration of Y at most field strengths [94], while T_1 can be used to noninvasively estimate Hct [95]. Knowing Y_a (typically from pulse oximetry) and whole-brain CBF (e.g. from phase-contrast MRI, which can be used to determine CBF in less than 1 minute, [96,97]), $CMRO_2$ can be calculated. Without CBF information, OEF can be calculated and used in clinical applications, as recently demonstrated for aging and neurodegenerative disease (Fig. 4, [98–100]).

Regional measurements of OEF and $CMRO_2$ are also receiving interest, for instance the ability to differentiate left versus right hemisphere, cortical versus subcortical regions, and major brain lobes. Given that CBF mapping techniques are available for MRI, the main efforts have been directed toward developing methods to measure regional Y_v. For instance, vessel-specific T_2-based methods are being developed that account for tissue partial volume effects [101,102]. With these newer techniques, Y_v in major intracerebral draining veins, the vein of Galen, and straight sinus have been determined in adults and neonates [101,102]. Smaller draining veins have lower signal and greater anatomic variability across individuals and their Y_v measurement is less established. An alternative approach to determine blood oxygenation with very high spatial resolution ($1\times1\times1$ mm^3 or better) is quantitative susceptibility mapping (QSM) [89–92]. Here the actual oxygen-sensitive physical quantity underlying intravascular T_2 changes, the tissue magnetic susceptibility χ, is calculated on a voxel-by-voxel basis from the local field in each voxel. The latter is generally determined

from the MR signal phase measured by gradient echo imaging. This local field in an MRI voxel is a parameter that depends on the brain orientation as well as on the susceptibility of surrounding voxels, and therefore is difficult to measure reproducibly between subjects. However, the magnetic susceptibility that is reconstructed through an inverse calculation is brain-orientation independent and voxel specific. Using referencing to a standard tissue (e.g. cerebral spinal fluid, CSF, assuming to have zero susceptibility) and a separate calibration of magnetic susceptibility differences as a function of blood oxygenation, the blood oxygenation can be calculated non-invasively *in vivo* [89–92].

Voxel-by-voxel mapping of $CMRO_2$ or OEF without the need for a physiological stimulation would be the holy grail of functional brain imaging, but when using the BOLD T_2^* effect these would require knowledge of the local venous cerebral blood volume (CBV_v) and advanced BOLD models [83,85]. However, the reliability and practicality of these methods remain to be further investigated, and represent an active area of research which is beyond the scope of this review.

5. A look to the Future of Metabolic MR

The field of metabolic MR is undergoing rapid progress. While often criticized for its lack of clinical applicability, MRS may finally cross this hurdle through the recent availability of deep learning approaches for SNR improvement and, importantly, fast and reliable data interpretation on the scanner. Similarly, CEST MRI may, either in combination with MRS or independently, provide high resolution metabolic information using water imaging. The use of hyperpolarized magnetic isotopes for the study of active metabolism has seen a decade of strong progress and is on the threshold of clinical application but its applicability is still hampered by a lack of common availability. Newer deuterium-based approaches have potential, especially when using proton detection. Combination of these methods with PET on PET-MR scanners, which are becoming more widely available, and the use of fast and higher SNR data acquisition and analysis approaches that exploit machine learning makes clinical translation of combinations of these advanced methods for voxel-based metabolic analysis increasingly likely. The capability for regional $CMRO_2$ determination may further enhance the clinical information content.

Acknowledgments

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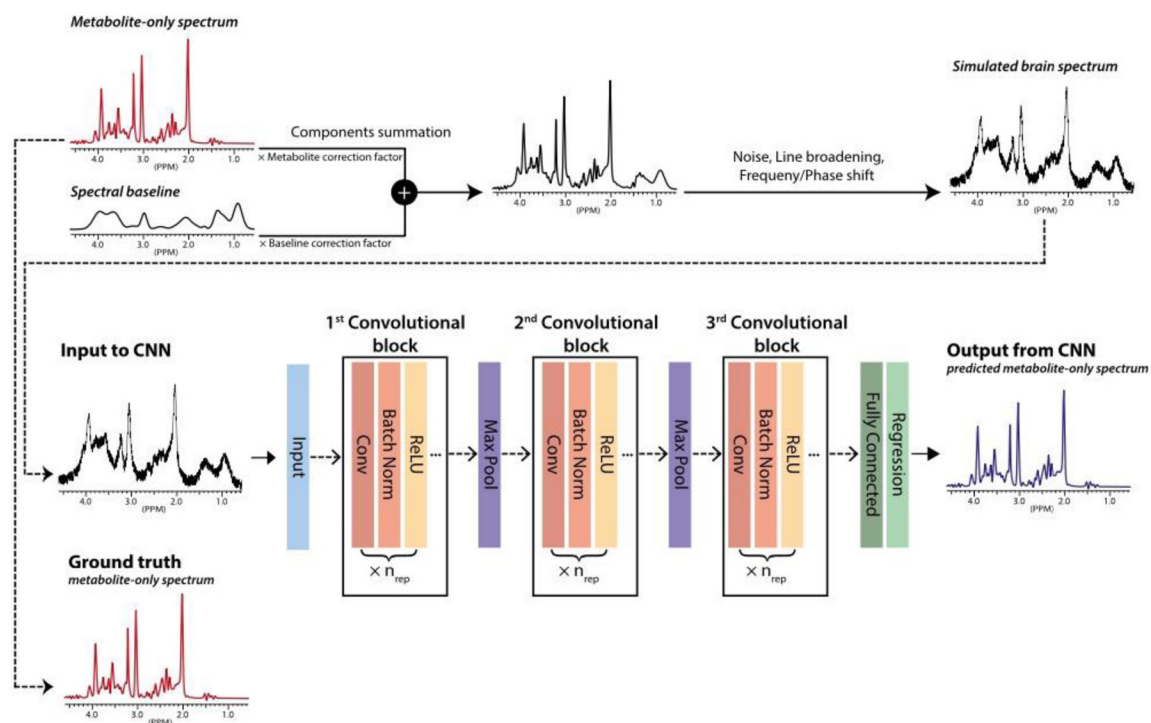
Fig. 1:
A schematic of the training of the convolutional neural network (CNN) to analyze brain proton MRS data. 'Metabolite-only' spectra, simulated by linearly combining phantom spectra of individual compounds according to randomly selected relative concentration ratios, are used as the ground truth in the training of the CNN. To mimic *in vivo* brain spectra, the metabolite-only spectra are combined with noise, line broadened, frequency and phase shifted, and a slowly varying baseline added. These simulated brain spectra are used as the input to the CNN in the training, whose goal is to determine the original metabolite-only spectra and the individual metabolite concentrations. Abbreviations: Conv, convolution; Batch Norm, batch normalization; Max Pool, max pooling; ReLU, rectified linear unit. Reproduced, with permission, from Lee H.H. and Kim H. [15].
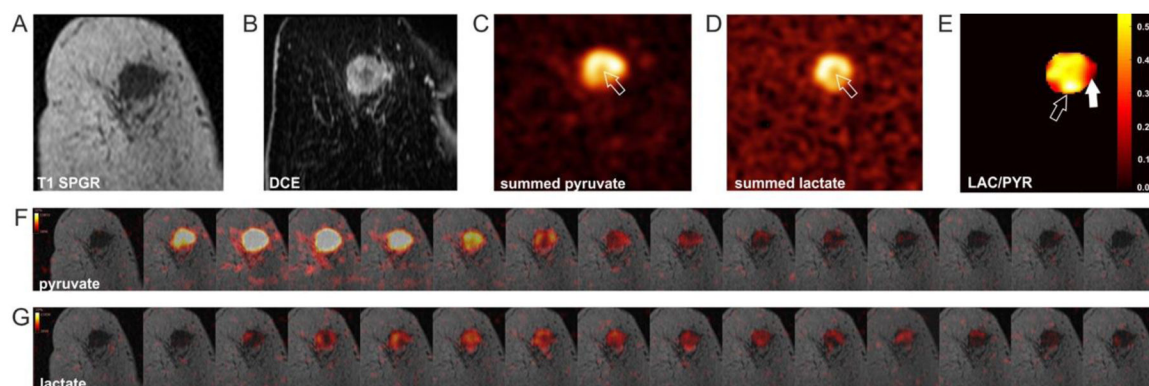
Fig. 2:

[1-^{13}C]pyruvate and [1-^{13}C]lactate images acquired following intravenous injection of hyperpolarized [1-^{13}C]pyruvate in a breast cancer patient. (A) Coronal image, where the tumor can be visualized as a region of hypointensity. (B) Dynamic contrast enhanced (DCE) image, where the tumor can be visualized as a region of hyperintensity. ^{13}C magnetic resonance spectroscopic images of (C) hyperpolarized [1-^{13}C]pyruvate and (D) hyperpolarized [1-^{13}C]lactate; arrows indicate a region with low signal intensity corresponding to a region of low enhancement on the contrast agent-enhanced image. (E) Map of the ratio of lactate and pyruvate signal intensities, showing intratumoral heterogeneity; open arrow indicates an area of low [1-^{13}C]pyruvate signal but high lactate labeling; closed arrow indicates a tumor area with high [1-^{13}C]pyruvate signal and intermediate lactate labelling. (F-G) Dynamic hyperpolarized [1-^{13}C]pyruvate and [1-^{13}C]lactate images acquired after intravenous injection of hyperpolarized [1-^{13}C]pyruvate (temporal resolution = 4 s). Reproduced from Gallagher, F.A. et al. [35], with permission (https://creativecommons.org/licenses/by-nc-nd/4.0/legalcode).
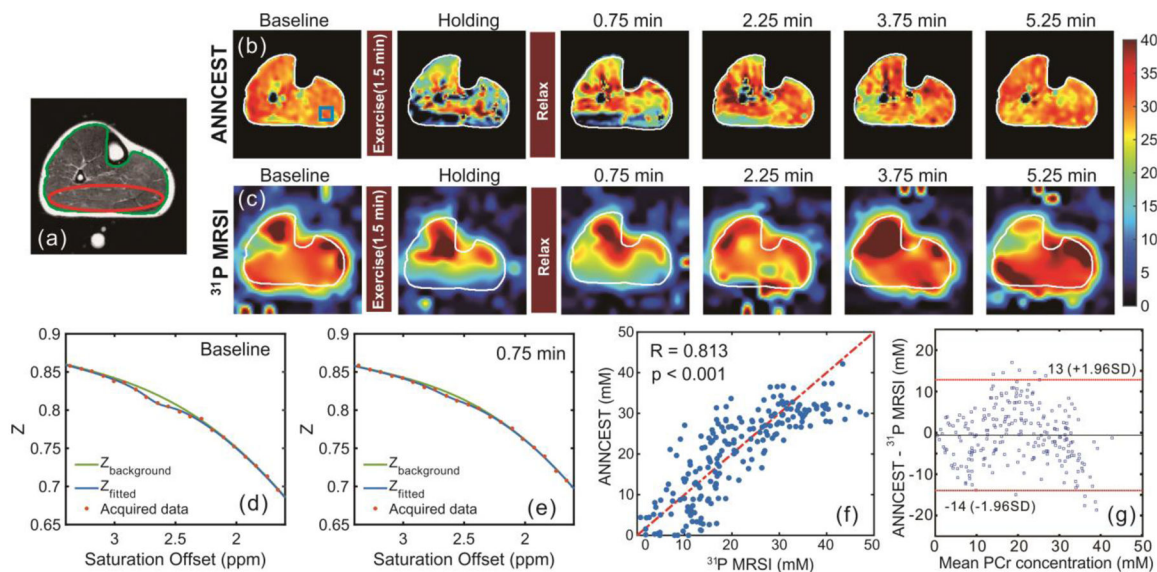
Fig. 3:

Maps of human skeletal muscle at 3 Tesla pre and post in-magnet plantar flexion exercise using PCr CEST analyzed with an artificial neural network (ANNCEST) compared with the same exercise observed using ^{31}P spectroscopic imaging. (a) T_2-weighted anatomical image. (b,c) PCr concentration maps (scale bar in mM) obtained by (b) ANNCEST and (c) ^{31}P MRSI during the exercise process. The water saturation spectrum (Z-spectrum, in which Z is the signal during radiofrequency saturation normalized by the signal without such saturation, $Z = S_{sat}/S_0$) at baseline (d) and post exercise (e) extracted from the blue rectangle region shown in (b). (f,g) Correlation and Bland-Altman analyses between concentrations obtained from ANNCEST and ^{31}P MRSI for all four subjects (n = 202 voxels) from the red ellipse region shown in (a). Reproduced, with permission, from Chen L. et al. [72]
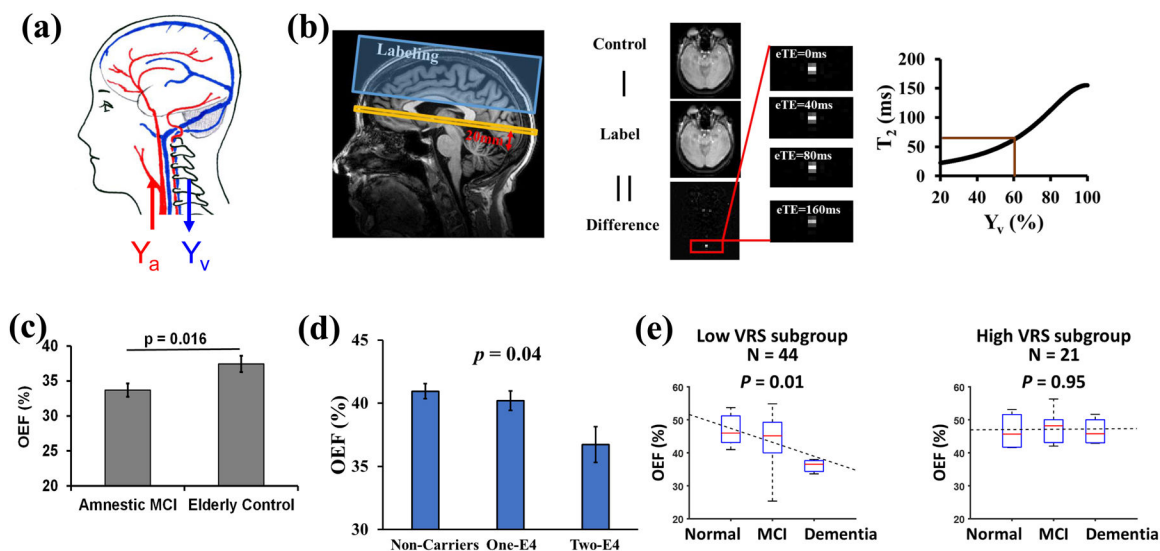
Fig. 4.

Example of OEF determination in neurodegenerative disease. (a) Illustration of arterial (Y_a) and venous (Y_v) oxygenation fraction in the brain. OEF = (Y_a-Y_v)/Y_a. (b) Measurement of Y_v with TRUST MRI. Left panel: Typical positions of imaging slice (yellow) and labeling slab (blue). The red arrow and label indicate that the imaging plane is placed to be parallel to the anterior commissure – posterior commissure (AC-PC) line and 20 mm above the sinus confluence point. Middle panel: Representative raw images of TRUST MRI. Right panel: Conversion from blood T2 to oxygenation fraction. (c) Diminished OEF in patients with mild cognitive impairment (MCI). Reproduced, with permission, from Thomas, B.P. et al. [100]. (d) OEF was decreased in cognitively normal older individuals who have a higher genetic risk (i.e. APOE4) to develop Alzheimer's disease. Reproduced, with permission, from Lin, Z. et al. [99]. (e) Vascular risk factors (VRS) have an additional effect on OEF. Reproduced, with permission, from Jiang, D. et al. [98].