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Brain Imaging Developments based on *In Vivo* MRS

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Abstract— **Magnetic resonance spectroscopy (MRS) known for its non-invasive and non-destructive nature, has been applied in biomedical and clinical research to assess the biochemical and metabolic information in a living brain. However, the applicability and detection sensitivity of *in vivo* MRS are, in general, limited by low concentrations of most cerebral metabolites of interest. The newly advanced high/ultrahigh MRI/MRS technology has substantially overcome this limitation and provided new and exciting opportunities for potential applications of *in vivo* MRS in brain research at high field. One particular interesting application is to measure and image the cerebral metabolic rates, ultimately, for investigating the neuroenergetics associated with brain function. Recently, significant progress has been made for developing *in vivo* MRS imaging (MRSI) methods for noninvasively measuring and imaging the cerebral metabolic rates of oxygen ($CMRO_2$) and ATP (CMR_{ATP}) noninvasively. These new methods have been successfully applied for investigating the neuroenergetics changes associated with brain activation.**

INTRODUCTION

The methodology of magnetic resonance applied in biomedical brain research can be divided into two categories: magnetic resonance imaging (MRI) and spectroscopy (MRS). MRI provides rich information of the tissue water with various image contrasts which are useful for assessing brain anatomy, physiology, function and disease. The major merit of *in vivo* MRS is its ability to noninvasively measure the neurochemical profiles of cerebral metabolites and neurotransmitters inside a brain, thus, provides an invaluable tool for measuring cerebral metabolites, metabolic rates and bioenergetics, neurotransmission cycling under physiological and pathological conditions. However, the applicability of *in vivo* MRS for biomedical application is, in general, limited by the extremely low concentrations of most cerebral metabolites of interest (in a range of few mM) compared to that of brain tissue water (> 50 M). This is particularly true for those *in vivo* heteronuclear MRS approaches commonly applied in biomedical research because of their low gyromagnetic ratio and relatively low detection sensitivity. This has become the major challenges for achieving high spatial/temporal resolutions and reliability of *in vivo* MRS measurement. The newly advanced high/ultrahigh MRI/MRS human scanner technology has significantly overcome this limitation through significant sensitivity gain and spectral resolution improvement. It opens new and exciting opportunities for potential applications of *in vivo* MRS in brain research at high fields. One particular interesting application is to measure and image the cerebral metabolites and metabolic rates, ultimately, for investigating the cerebral bioenergetics associated with brain function and dysfunction. This presentation will discuss recent research progresses for advancing *in vivo* ^{17}O MRS imaging (MRSI) for imaging $CMRO_2$ and *in vivo* ^{31}P MRSI for imaging CMR_{ATP} at high fields.

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In vivo ^{17}O MRSI for studying brain oxygen metabolism

The most valuable application of *in vivo* ^{17}O MRSI is to directly assess and image $CMRO_2$ [1-4]. The principle underlying this approach is to use *in vivo* ^{17}O MRSI for measuring the dynamic change of ^{17}O-isotope-labeled metabolic water incorporated from the inhalated $^{17}O_2$ gas through the oxygen metabolism in mitochondria. One great merit of this approach is that only the final product of ^{17}O-labeled metabolic $H_2{}^{17}O$ in the brain tissue is detectable by *in vivo* ^{17}O MRS. This simplifies both measurements and quantification of $CMRO_2$ substantially as compared to other established approaches such as PET [5]. During

the last decade, the high-field technology has significantly advanced the developments aiming to establish a robust, completely noninvasive ^{17}O MRSI approach for obtaining 3D $CMRO_2$ images within few minutes at high/ultrahigh fields [4-7]. This approach has been validated using animal models, and applied successfully to imaging $CMRO_2$ changes caused by mild hypothermia in the rat brain [7] and to functional metabolic mapping of $CMRO_2$ change in the cat brain during visual stimulation [8]. Figure 1 illustrates multiple-slice functional mapping results based on the stimulus-evoked $CMRO_2$ change and the blood oxygenation level dependence (BOLD) contrast using conventional fMRI. These results indicate that *in vivo* ^{17}O MRSI approach is reliable and sensitive to image $CMRO_2$ changes; and it should provide a useful neuroimaging modality for obtaining functional metabolic rate imaging of $CMRO_2$ during brain activation, ultimately, for investigating the potential roles of oxygen metabolism in supporting brain activation and function.

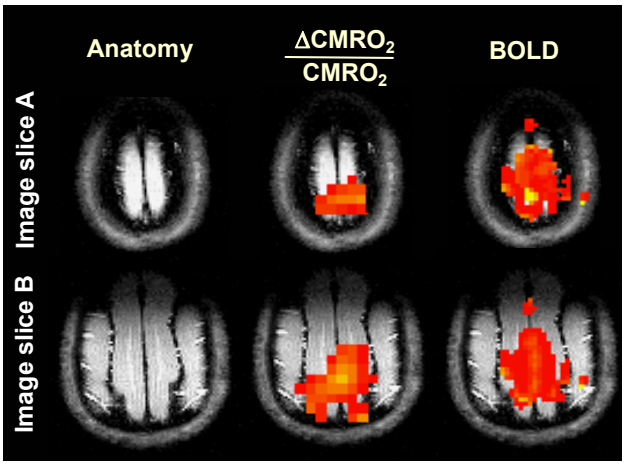

Fig. 1 Functional maps of $CMRO_2$ and BOLD changes during visual stimulation from a representative cat. Adapted from Reference 8.

In vivo ^{31}P MRSI for studying brain ATP metabolism

Another invaluable heteronuclear MRS approach is *in vivo* ^{31}P MRS, which allows noninvasive assessments of the fundamental biochemical, physiological and metabolic events occurring in a living brain. The prime information provided by *in vivo* ^{31}P MRS includes intracellular pH, high-energy phosphate (HEP) metabolites of ATP, ADP and PCr, and inorganic phosphate (Pi), uridine diphospho (UDP) sugar (an important precursor in glycogen metabolism), nicotinamide adenine dinucleotides (NAD) involving oxidative chains, and four resolved phospholipid compounds of glycerophosphoethanolamine (GPE), glycerophosphocholine (GPC), phosphoethanolamine (PE) and phosphocholine (PC), which actively involve in membrane phospholipid metabolism through phospholipid biosynthetic enzymes. All these resonance peaks can be reliably detected and resolved by a single *in vivo* ^{31}P spectrum at 7T with few minutes of sampling time [9]. They provide valuable information reflecting brain physiology.

One exciting research area is to further advance the methodology using *in vivo* ^{31}P MRS combined with the saturation magnetization transfer (MT) method [10-12] at high field for noninvasively measuring CMR_{ATP} in the human brain at 7T [13, 14]. Recent progress has provided evidence suggesting that *in vivo* ^{31}P MT is capable of noninvasively determining the metabolic rate of oxidative phosphorylation of ADP to produce ATP in brain mitochondria: one of the most fundamental biochemical rates for regulating brain bioenergetics associated with brain function. Recent studies have further demonstrated that the measured CMR_{ATP} is tightly correlated to the basal brain activity levels indicating a neuro-ATP-metabolic coupling (see Fig. 2 and [15]); and the ATP utilization rate was significantly increased in activated brain region. These results indicate a high likelihood to establish another MRS-based modality, for the first time, for direct assessment of the brain ATP metabolic rates *in vivo*.

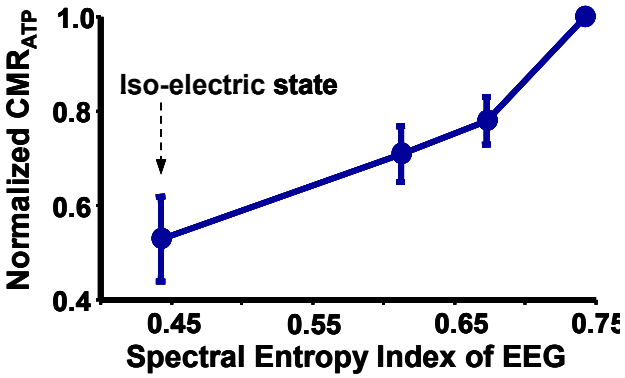

Fig. 2 Correlations of EEG signal quantified by Shannon spectral entropy index and the normalized cerebral ATP metabolic rate (CMR_{ATP}) in the rat brains with various anesthesia depth. Adapted from Reference 15.

In summary, *in vivo* heteronuclear MRS/MRSI approaches can provide unique information related to brain physiology and pathology at molecular and cellular levels, which is complementary to conventional MRI signals. They benefit substantially at high/ultrahigh fields, and have opened many exciting opportunities potentially for numerous biomedical applications, which are usually challenging at lower fields.

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