Metabolic brain imaging by magnetic resonance

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Novel magnetic resonance methods have been developed to noninvasively measure biochemical compounds in the human brain as guided by magnetic resonance imaging. Together, these methods are referred to as magnetic resonance spectroscopy (MRS) and can be divided into three major categories: single voxel MRS, magnetic resonance spectroscopic imaging and dynamic MRS, which is a novel adaption of the first method. The techniques and range of biochemical compounds that can be measured safely and serially are advancing rapidly, with many technical developments. MRS methods, when applied to the human brain, have an important diagnostic role, help monitor and guide therapeutic interventions and provide a tool to investigate the mechanisms of neuropsychiatric disease processes, normal brain development and neuropharmacology *in vivo*.

Keywords: biochemistry, brain imaging, magnetic resonance, magnetic resonance spectroscopy, metabolism, neuropharmacology

future medicine

Rapid advances in the application of magnetic resonance techniques to neurobiological investigations have occurred over the last 30 years. *In vivo* magnetic resonance spectroscopy (MRS) and magnetic resonance spectroscopic imaging (MRSI) have been used to interrogate the living brain for prognostic and diagnostic markers in neurological disorders, as well as define changes that occur during normal development. The safety and noninvasiveness of MR methods make them particularly well suited to investigations in children. Significant advances have been made in both the acquisition and interpretation of the data. Presently, magnetic resonance methods allow the investigation of neuroanatomy through magnetic resonance imaging (MRI), cerebral function in response to physiological stimuli (functional MRI [fMRI]), and cerebral metabolism through multinuclear MRS. Magnetic resonance provides the only methods whereby information on neuroanatomy, cerebral metabolism and brain function can be obtained noninvasively using a single instrumentation system. Early studies using anatomical MRI in infants and children have enabled characterization of many disorders of brain development and pathological conditions [1]. Application of quantitative, image analysis methods has identified anatomical changes in many cortical and subcortical regions that occur with normal development through early adulthood [2,3]. Several investigations using fMRI have been conducted to study changes that occur with visual [4], language, reading [5,6] and memory [7] function during development. fMRI has permitted the identification of anomalies in brain function that occur in many neurological and cognitive disorders, such as epilepsy [8] and dyslexia [5,9]. MRS has been particularly useful in both diagnosing and following the progression of many neurogenetic and neurodegenerative disorders, particularly those with onset in childhood. MRS is diagnostic in disorders such as Canavan's disease, glycine encephalopathy and creatine deficiency syndromes. MRS studies have demonstrated early metabolic changes in many neurological disorders prior to alterations in MRI. Several MRS investigations have identified characteristic changes in metabolites in neurological disorders such as stroke, tumors and multiple sclerosis. This review will discuss the methods for obtaining metabolic measurements *in vivo* by MRS that can be combined with any of these MR methods.

Obtaining a metabolic biopsy *in vivo* by single-voxel MRS

A number of nuclei that are present on biological molecules have physical properties which allow them to be observed *in vivo* using MR. When placed in an external magnetic field, the absorption and emission of electromagnetic radiation of nuclei that possess a magnetic moment can be observed. The electromagnetic radiation is typically in the radiofrequency range of 10–800 MHz. These nuclei can be divided into two broad classes: those that require the addition of exogenous label and those that do not. The most common nuclei used are phosphorus (^{31}P) and proton (^{1}H), which generate spectra that are dominated by resonances from endogenous metabolites. The proton signal from water is

used for MR imaging. Additionally, sodium is readily observed *in vivo*. By contrast, other nuclei, such as carbon (^{13}C), fluorine (^{19}F) and oxygen (^{17}O), have been used *in vivo*, but their use depends on the addition of exogenous label by intravenous infusion or inhalation. To perform MRS studies using these multiple nuclei, specifically designed hardware must be part of the MR system. The majority of MR systems used for clinical purposes are limited to studies of the ^{1}H and ^{31}P nucleus. However, the MR signal from the proton provides the greatest sensitivity compared with the other nuclei. Proton MRS is most widely used in both clinical and research studies.

MRS has become an important tool in quantitative analysis of brain metabolism in animals and humans. The technique can make serial noninvasive measurements of major metabolites in a safe fashion without exposure to ionizing radiation. MRS is a noninvasive method that permits measurement of the concentration of specific biochemical compounds in the brain and other organ systems in precisely defined regions guided by MRI. Over the past decade, several laboratories have developed specialized MRS methods to measure gamma amino butyric acid (GABA) and glutamate levels in experimental animals and, more recently, in humans [10,11]. Early studies in newborns and infants using phosphorus MRS identified changes in brain energetics by measurements of ATP, phosphocreatine and intracellular pH. Later MRS studies using proton MRS demonstrated changes in amino acids, choline-containing compounds, *myo*-inositol and lactate with development [12]. These studies demonstrate major changes in several biochemical compounds that occur with development and emphasize the importance of obtaining studies of brain metabolism on control subjects in order to distinguish normal from abnormal and follow metabolic changes that occur with treatment and recovery from injury. This can only be performed with MR techniques. With the increasing use of higher magnetic field strengths for both clinical and research studies, there is a great advantage for MRS methods such that over 20 biochemical compounds can now be measured in the human brain [13,14]. The higher magnetic field strength improves the spectral resolution with improved separation of signals in spectrum.

The MRS studies described above make use of predominantly single-voxel MRS measurements guided by the MRI. Single-voxel techniques can be integrated more easily with clinical MRI, are available on most clinical MR systems and add little additional time to the study. They are well suited to investigations of metabolic or toxic disorders that globally affect the brain [15]. Single-voxel MRS can give metabolic information and metabolic biopsy of discrete lesions seen on MRI, such as tumors, stroke or white matter lesions.

MRSI: a metabolic brain map

Multivoxel methods have recently been applied to investigations of neurological disorders and normal development of the human CNS. Spatial localization methods can be applied in addition to phase-encoding gradients used in imaging that enable the defined volumes to be subdivided. This technique yields signal acquisition from multiple voxels simultaneously. Since the metabolite distribution can be represented as maps, this process is known as MRSI. The relationship between signal–noise ratio, spatial resolution and acquisition time are defined by the physical properties of the MRS signals and electronics of the MR system. This creates a situation where there is a trade-off between spectral resolution and acquisition time. Nonetheless, there are ways to acquire data more efficiently. Single-voxel MRS spectra can be acquired rapidly with high spatial resolution. Even though MRSI acquisitions always take longer, they provide higher sensitivity because signals are averaged throughout the entire acquisition time. A disadvantage of MRSI is the poorer quality spectra compared with single-voxel methods. Another complexity observed with MRSI methods is determining optimum data processing and image presentation methods.

Many of these technical issues have been addressed by investigators and have demonstrated the utility of MRSI in many clinical neurological disorders, such as multiple sclerosis [16], CNS tumors [17] and epilepsy [18]. MRSI studies in multiple sclerosis have permitted a better understanding of the pathophysiology of the disorder, a differentiation of specific categories of the disorder and have been useful in following response to treatment protocols. MRSI studies, combined with other MR imaging methods in subjects with CNS tumors, have provided complementary data concerning the metabolic, physiological and structural properties of the tumors. Quantitative analysis of MRSI data in the context of other MR imaging

has begun to provide a basis for classifying tumors, predicting the response to specific treatment protocols in individual patients and an understanding of the pathophysiology and alterations in tumor biology with treatment successes and failures. MRSI studies in human epilepsy have identified alterations in neuronal function and neurotransmitter metabolism in several studies in humans [19,20]. Several investigators have demonstrated that MRSI is useful as part of the presurgical evaluation of medically-intractable epilepsy, as a marker of the extent of neuronal dysfunction in the epilepsy network and as a correlate to the cognitive dysfunction observed in these subjects. Investigators have also identified an alteration in neuronal function in generalized epilepsies [21].

MRSI is just beginning to be applied to a number of areas in neurology and psychiatry. As the methods of data acquisition and analysis improve and multivoxel imaging of specific neurotransmitters [22], and their turnover [23], become more widely available, great advances in the understanding and treatment of neuropsychiatric diseases will be made.

Dynamic MRS studies: studying biochemistry & kinetics *in vivo*

The safety of MRS permits serial measurements to be made in the same individual both during and after specific interventions or perturbations. Several investigators have performed single-voxel MRS studies before and after specific treatments known to alter neurotransmitters, such as GABA [24], or changes in brain glucose with physiological stimulation [14]. Using single-voxel MRS there is always a trade-off between time resolution and size of volume to be studied. Depending on the neurobiological compound of interest, measurements of endogenous MR signals can be performed within several seconds to a few minutes time resolutions. Using this approach, studies of glucose and amino acid transport across the blood–brain barrier have been performed [25,26].

Investigations of drug metabolism and transport in the human brain have been performed with dynamic MRS studies. Ethanol transport and kinetics in the human brain and its effect on brain structure, function and neurochemistry have been elucidated [27]. Many other drugs are of a concentration that is too low to be measured directly by MRS in the human brain, but their effects on neurotransmitter metabolism, neuronal function and energetics have been studied.

Several investigators have taken advantage of the use of stable isotopes that are MR visible and use specifically labeled compounds to study brain metabolism *in vivo*. These have included studies with ^{13}C and ^{19}F that have been studied in the human brain, and nitrogen, $^{17}0$ and other isotopes that have been used primarily in animal studies. The majority of ^{13}C studies in humans have utilized ^{13}C-labeled glucose or acetate to interrogate specific glial and neuronal pathways, and neurotransmitter fluxes. These studies have provided important information on the interpretation and basis of functional neuroimaging and allowed the measurement of both glutamate and GABA neurotransmission *in vivo* [28]. ^{19}F MRS has been used in studies of fluorinated agents used in oncology [29] and psychiatry [30].

These dynamic MRS studies are beginning to probe important questions in neurobiology and neuropharmacology. The cost of the stable isotopically-labeled compounds, specialized MR systems with multinuclear capabilities and the duration of time required in the MR system restrict these dynamic MRS primarily to research centers.

Conclusion

There have been tremendous advances in metabolic brain imaging using MR techniques. Single-voxel MRS has been used for decades and offers the opportunity to perform a metabolic biopsy on the brain *in vivo*. The high sensitivity and short duration of time to perform this MRS technique has made it more widely used for clinical purposes in neuropsychiatric disorders. Despite the limitations of the need for *a priori* knowledge of the optimum location for obtaining the MRS data, the extensive experience and numerous previous studies make this method a potential screening tool for specific neuropsychiatric disease processes, particularly neurometabolic and neurogenetic disorders observed in children. MRSI has the ability to provide a metabolic map of the brain that can provide information on the spatial extent, heterogeneity and an image of neuropsychiatric disease processes. MRSI studies will also elucidate normal biochemical and molecular changes that occur during development and with aging. Dynamic MRS studies permit probing and interrogation of specific biochemical and neurobiological processes, such as neurotransmission.

Future perspective

MRS methods will continue to evolve and have increasing application to clinical and research studies. Higher magnetic field strength, parallel imaging methods and automated shimming and data processing, combined with coregistration of anatomical and functional MRI, are a few of the technical advances that are now being used. MRS techniques will have a limited role for diagnostic purposes, but an increasing role in guiding and monitoring therapeutic interventions and providing information on the mechanisms of neuropsychiatric disease processes. MRS, when combined with other advanced MR methods, will have an important role in defining the phenocopy of neurogenetic and neurometabolic diseases. This role is critical when considering therapeutic interventions, such as gene therapy, at early periods in the disease process. MRS will be increasingly used as a biomarker of disease processes, which will aid in both choice and monitoring of therapy. MRS, particularly dynamic MRS studies, will also have an increasing role in neuropharmacology and neurotoxicology investigations and can be combined with metabolomics, which are also often nuclear magnetic resonance-based studies [31]. These advanced MRS studies will be performed at specialized centers on MR systems dedicated specifically to this type of combined MRS/MRI investigation.

Executive summary

Introduction

- Magnetic resonance spectroscopy (MRS) interrogates living brain for diagnostic and prognostic markers of neuropsychiatric disorders and their treatment.
- MRS is safe and serial tests are readily performed.
- MRS can be combined with other magnetic resonance (MR) methods, including advanced magnetic resonance imaging (MRI) and functional MRI.
- There are three categories of MRS studies: single voxel MRS, MRS imaging (MRSI) and dynamic MRS.

Obtaining a metabolic biopsy in vivo *by single-voxel MRS*

- Single-voxel MRS provides the greatest sensitivity and shortest examination time.
- Multiple nuclei can be studied by MRS, but proton MRS offers the greatest sensitivity and is most widely available on clinical systems.
- More than 20 biochemical compounds can presently be measured in the human brain by MRS.
- Single-voxel MRS is useful in metabolic and toxic disorders that affect the brain globally.
- Single-voxel MRS provides a metabolic biopsy of discrete anatomical lesions observed in MRI.

MRSI: a metabolic brain map

- Multivoxel MRS or MRSI acquires metabolic information from multiple regions simultaneously.
- MRSI has lower sensitivity and greater spatial resolution that permits determination of the spatial extent of diseases processes.
- MRSI requires a longer duration of examination time in the MR system.
- Data processing, combined with anatomical MRI data, provides a metabolic image of biochemical compounds in the brain.

Dynamic MRS studies: studying biochemistry & kinetics in vivo

- Both single-voxel MRS and MRSI can be compared before, after and during specific physiological, pharmacological or metabolic perturbations.
- Transport kinetics and metabolism of nutrients, drugs and other compounds can be studied *in vivo*.
- Addition of MR-visible stable isotopes permits 'magnetically tagging' compounds that can be used to probe neurotransmission and metabolism.

Conclusion

- Three categories of MRS techniques are used in clinical and research investigations of the human brain.
- Single-voxel MRS provides a metabolic biopsy with a short exam time.
- MRSI provides a metabolic map of biochemical processes with development, aging and diseases.
- Dynamic MRS probes specific neurobiological processes, such as neurotransmission and neuropharmacology.

Future perspective

- MRS will have an increasing role in guiding and monitoring therapies and will provide insights on the mechanisms of neuropsychiatric diseases.
- MRS will have an increasing role in defining the phenocopy of neurogenetic and neurometabolic disorders.
- MRS will provide biomarkers of many neuropsychiatric disorders.
- MRS, particularly dynamic MRS, will have an important role in future neuropharmacology and neurotoxicology studies.
- MRS can be combined with metabolomics.

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