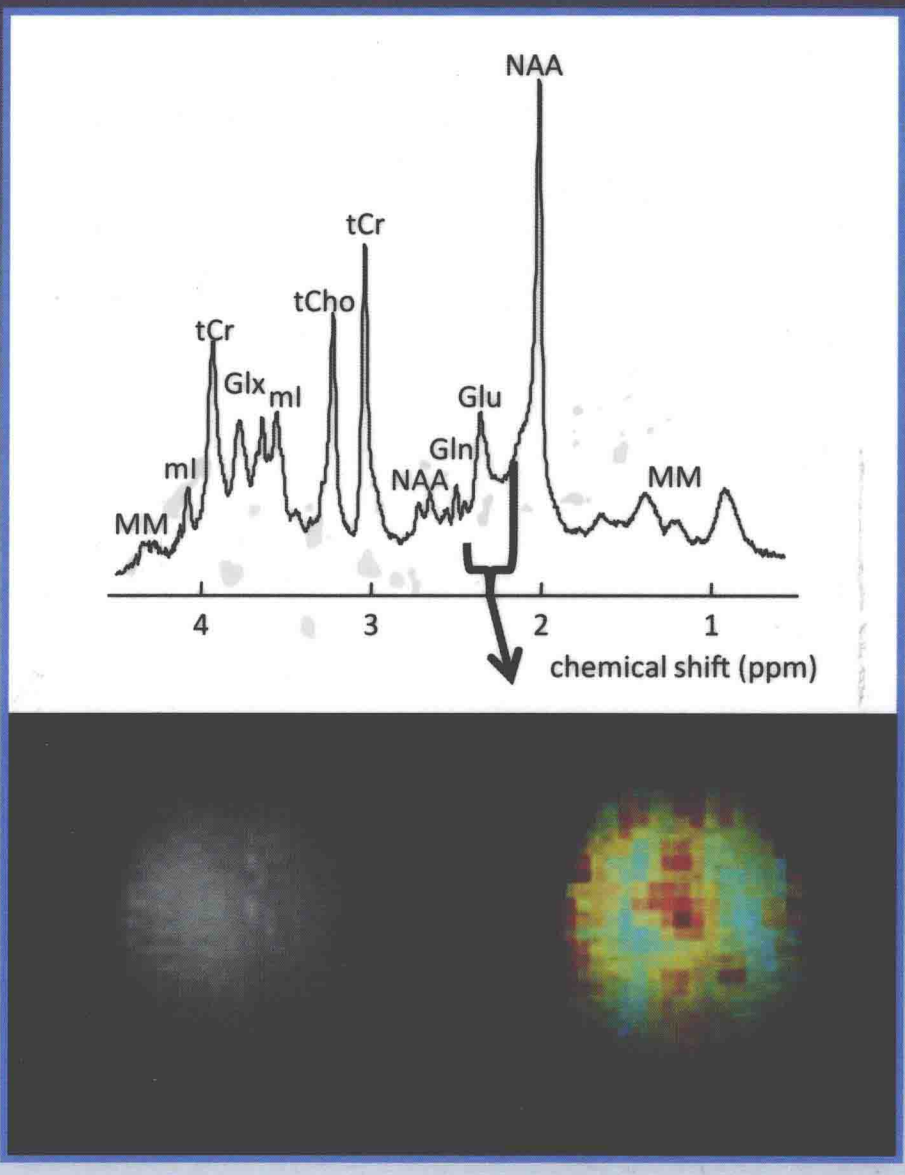
MAGNETIC RESONANCE SPECTROSCOPY

TOOLS FOR NEUROSCIENCE RESEARCH AND EMERGING CLINICAL APPLICATIONS

EDITED BY CHARLOTTE J. STAGG, DOUGLAS L. ROTHMAN



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Tools for Neuroscience Research and Emerging Clinical Applications

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Introduction

Magnetic resonance spectroscopy (MRS) is a noninvasive technique that uses the same physics principles and detection methods as magnetic resonance imaging (MRI) of H_2O, but adds an additional dimension of information by also detecting the resonance frequencies of metabolites. From the resonance frequencies (referred to as chemical shift) and other properties of these resonances the identity, concentration, and stable isotope enrichment of biochemicals can be determined. ^{1}H MRS, which is the most widely used, was first performed on the brain by Behar and coworkers in the lab of Professor Robert G Shulman in 1983 (Behar et al., 1983). In this pioneering study, performed on a rat in a vertical bore magnet, resonances of *N*-acetylaspartate (NAA), glutamate, glutamine, choline, creatine, and lactate were assigned. These remain the only major metabolites studied using *in vivo*[1] H MRS. Within several years after this study the first high-field (1.5 T and above) human magnets were built by Oxford Instruments and in 1985 Bottomley and coworkers at General Electric published the first localized human brain ^{1}H MRS spectra (Bottomley et al., 1985). The first applications to human disease were presented at the meeting of the Society of Magnetic Resonance in Medicine in 1986 by den Hollander and colleagues working at Philips, and these were soon followed by several groups who performed pioneering studies in stroke, tumors, and other clinical conditions.

Following these and other pioneering studies ^{1}H MRS has been used for many years in clinical neuroscience as a method for investigating brain neurochemistry, critical to understanding neurological and psychiatric disease. However, a relatively low signal-to-noise (SNR) ratio has limited its use on standard clinical scanners. Over recent years, with the increasing availability of high and ultrahigh field scanners, as well as a much increased understanding of how metabolism plays a critical role in neuroenergetics and neurotransmission, MRS has undergone something of a renaissance and gained traction within the MR community for translational and clinical neuroscience. Improved acquisition and analysis approaches have increased interest in its use both for traditional clinical applications and also for neuroscience research. However, although excellent books exist covering the technical aspects of MRS for physicists, there is currently no book targeted at clinicians and neuroscientists that covers all aspects of the technique. In this book we attempt to address this need. It is organized as a reference text that is aimed not at physicists but at experts in the *application* of MRS such as neurologists, psychiatrists, radiologists, and neuroscientists. However, we hope that the coverage of applications and basic methodologies is complete enough that physicists entering the field may benefit and even experienced MR physicists working in other areas could use it to determine the state-of-the-art methodology used in the field.

To achieve these goals we have divided the book into three sections, which we outline below.

SECTION 1: HOW MRS IS ACQUIRED

In this section we have enlisted experts in the field of MRS data acquisition and processing to provide an introduction to the field and an overview of state-of-the-art methodology in these areas. Even though the mathematics is kept at a minimum, enough technical detail is included to allow readers to understand the principles and relative strengths and weaknesses of the different methods. In Chapter 1.1 Drs. Christoph Juchem and Douglas Rothman describe the basis of Magnetic Resonance focusing on basic principles but also give an overview of some of the most common methods used in MRS and chemicals measured. In Chapter 1.2 Drs. Hongxia Lei, Lijing Xin, Rolf Gruetter, and Vladimír Mlynárik describe the state of the art of single-volume ^{1}H MRS as well as novel recent approaches such as ultra short TE MRS. This chapter describes the methods needed to meet the stringent requirements for volume localization with MRS due to large resonances from water and scalp lipids. The critical importance and optimal methods for improving field homogeneity and suppressing intravoxel water are also described in detail as well as artifacts that may occur if adequate criteria are not met. MRS can both be obtained as information from a single volume (or several) in the brain or as a metabolic image. In Chapter 1.3 Drs. Vincent Boer and Dennis Klomp provide an introduction to magnetic resonance spectroscopic imaging (MRSI) including its application at ultrahigh fields such as 7 T. This chapter demonstrates the great potential of MRSI but also reviews its limitations, many of which relate to the need to establish

adequate static and radiofrequency magnetic field homogeneity throughout the volume imaged (as compared to single-volume MRS where optimization is only required in a small region of the brain). With optimal B_0 homogeneity and higher B_0 fields more and more metabolites can be distinguished based on their resonance frequencies (chemical shift), but lower concentration metabolites such as γ-amino butyric acid (GABA) still cannot be resolved at clinical 3 T fields. To overcome these spectral overlap limitations MRS methods that separate resonances based not just upon resonance frequency but also upon quantum J-coupling between resonances within a single molecule have been developed. These methods are often referred to as "spectral editing" because they edit out resonances from specific chemicals from overlapping resonances from other chemicals. In Chapter 1.4 Dr. Robin de Graaf provides a guide to modern editing and related 2D MRS methods. While these methods have largely been limited to specialized research MR systems recent developments in clinical 3 T systems have greatly expanded their applicability. Even with the best data acquisition methodology the analysis and calibration methods used in MRS play a critical role in the accuracy and precision of the results obtained. In Chapter 1.5 Dr. Jamie Near covers in detail methods used to analyze and quantitate the *in vivo* MRS spectrum as well as the advantages and pitfalls of each.

SECTION 2: BIOCHEMISTRY—WHAT UNDERLIES THE SIGNAL?

This section covers the biochemistry of the major neurochemicals, and what we can infer from increased or decreased levels of these in the brain and what cannot be elucidated provide a description of modern strategies for interpreting MRS results. In Chapter 2.1 Drs. John Moffett, Prasanth Ariyannur, Peethambaran Arun, and Aryan Namboodiri cover *N*-acetylaspartate (NAA) and *N*-acetylaspartylglutamate (NAAG) in central nervous system (CNS) health and disease. NAA was identified in the very first *in vivo*[1] H MRS brain study performed and due to its high concentration and the presence of a singlet methyl group (which increases sensitivity by 3× due to proton multiplicity) has been the major biochemical studied in clinical MRS. Despite its wide use there is considerable uncertainty about the function of NAA in the CNS and how to interpret changes seen in the MRS spectrum. In this chapter evidence for our present understanding of the roles of NAA and NAG and their underlying biochemistry are covered in detail along with implications for clinical MRS studies. In Chapter 2.2 Drs. Clare Turner and Nicholas Gant cover creatine, another major metabolite measured in the MRS spectrum, again due to its high concentration and the presence of a methyl group. Creatine is often used as a concentration reference in the MRS spectrum (as described in Chapter 1.5) so that it is important to understand conditions where its concentration may change. Metabolites that have often been used in clinical MRS studies are the combined resonances of choline-containing compounds. In Chapter 2.3 Drs. Nicholas Gant and Joanne Lin cover in detail the biochemistry and functional roles of choline in the brain and how choline levels may reflect pathologies. Changes in choline, creatine, and NAA tend to be relatively slow, with the time for biosynthetic replacement of the pools (turnover time) on the order of days. However, MRS can also look at metabolites that are dynamically turning over through their involvement in energy metabolism and neurotransmission. In Chapter 2.4 Dr Jun Shen describes the role of glutamate in brain energy metabolism and neurotransmission and how these roles can be studied using ^{1}H MRS and ^{13}C MRS (which is followed up in more detail in Sections 3 and 4). This chapter also provides additional background on the MRS measurement of glutamate. In Chapter 2.5 Drs. Jonathan Best, Charlotte Stagg, and Andrea Dennis cover the biochemistry and functional roles of myo-inositol, GABA, glutamine, and lactate. GABA and glutamine provide, respectively, a measure of metabolism in GABAergic neurons and glial cells, which along with glutamatergic neurons (they contain the majority of the glutamate signal) account for the large majority of cells in the brain. The GABA signal measured by ^{1}H MRS is also related to tonic GABAergic inhibition, which opens up ^{1}H MRS to be applied to a variety of neuroscience-related applications as described in Section 3. Due to its production by nonoxidative glycolysis, lactate levels are highly sensitive to the oxygenation status of brain tissue and, as further described in Section 3, can be diagnostic for necrotic tumors and other conditions such as brain ischemia. Myo-inositol appears to be primarily localized to glial cells and the resonance is highly sensitive to the presence of neurodegenerative disease as well as alterations in brain osmotic levels like those found in ketoacidotic hyperglycemia and hyperammonemia.

SECTION 3: APPLICATIONS OF PROTON MRS

MRS is theoretically feasible on any nucleus that possesses a magnetic moment; however, by far the most common nucleus for study is the proton. Protons have the greatest gyromagnetic ration of any nuclei seen *in vivo* and are also by far the most abundant nucleus in

the brain. These two factors mean that ^{1}H MRS has a relatively high SNR and, because protons are found in all metabolically interesting compounds, there is great potential for the study of the brain. In addition, MRI is performed on H_2O, meaning that clinical MR scanners can be used for ^{1}H MRS without buying expensive additional hardware, theoretically opening up its use to a wide range of users.

This section discusses the undoubted potential of ^{1}H MRS for both clinical and neuroscientific applications, as well as raising the limitations of the technique in the context of the conditions in which they have been applied. In Chapter 3.1 Drs. Carles Majós, Margarida Julià-Sapé, and Carles Arús discuss the clinical applications of MRS in tumor detection and management—exploring the application of MRS most commonly seen in clinical practice. MRS can be used to distinguish between tumors and non-tumors, can help the clinician to determine the nature of a tumor before pathology can be acquired, and can monitor the sequelae of treatment by distinguishing between tumor regrowth and post-treatment changes. In Chapter 3.2 Drs. Nicola De Stefano and Antonio Giorgio discuss the potential of MRS to determine pathology and monitor progression in inflammatory conditions, particularly in multiple sclerosis. Although MRS has undoubted potential to provide informative biomarkers for the development of potential treatments for MS, these are currently limited by the difficulty of acquiring reproducible data between different scanners, and possible solutions to this problem are discussed.

Chapter 3.3 focuses on epilepsy, a common neurological condition and one in which, as Drs. Julie Pan and Hoby Hetherington discuss, the ability of MRS to quantify neuroenergetics means that ^{1}H MRS is invaluable in allowing underlying pathologies to be studied. They also describe complementary work using ^{31}P and ^{13}C MRS, nuclei covered in more detail in Section 4, to further assess altered energetics in epileptogenic tissue. In Chapter 3.4 Drs. Andrew Bivard, Peter Stanwell, and Mark Parsons review the potential of MRS to study the metabolic events in the hyperacute phases of stroke recovery and its developing use as a window into the changes underlying the recovery of function in the months that follow. As with all neurological conditions, however, there are significant challenges in acquiring and interpreting ^{1}H MRS data from these patients, particularly data acquired from within and surrounding the lesioned region where the tissue inhomogeneity leads to greatly broadened linewidths. Some potential solutions are discussed as well as the potential pitfalls associated with interpreting these data.

In Chapter 3.5 Dr. Kim Cecil discusses the unique potential of MRS in the study of pediatric conditions, where the acquisition of diagnostic information noninvasively (e.g., with no injected radioactive tracers) is perhaps of heightened importance. The study of inborn errors of metabolism such as the leukodystrophies and Canavan's disease in particular has shed considerable light on the pathology of these conditions. Chapter 3.6 highlights the potential of ^{1}H MRS to improve our understanding of psychiatric conditions. Dr. Matthew Taylor focuses particularly on psychotic conditions and mood disorders, where a range of abnormalities in neural metabolism and glutamatergic signaling have been identified. The final clinical MRS application to be considered is that of spinal MRS in Chapter 3.7, where Drs. Amber Hill and Olga Ciccarelli discuss the potential of this technologically challenging approach. Despite the difficulties of acquiring spectra of adequate quality from the cord, given its relatively small size and intrinsic movement, several preclinical and clinical studies have been performed, the results of which suggest that this may well become a much more widely used approach in the future.

Chapter 3.8 moves toward the application of ^{1}H MRS for neuroscientific questions. Drs. Velicia Bachtiar and Charlotte Stagg provide an overview of the potential of MRS studies focusing on GABA and glutamate in particular to increase our understanding of how differences in behavior between people may be driven by underlying physiology. In Chapter 3.9 Drs. Dallas Card, Margot Taylor, and John Sled discuss the use of MRS to study natural aging, where studies have been targeted in particular both at the rapid development occurring in the brains of infants during development *in utero* and in the elderly. The importance of these data, and the challenges of longitudinal studies, particularly in infants, are discussed.

In Chapter 3.10 Drs. Jennifer Brawn and Katy Vincent discuss the role of MRS in the study of hormonal influences in the brain. Until relatively recently the substantial effects of hormones on brain activity were not recognized, but there is now increasing evidence that hormones, their precursors, and their derivatives all have striking effects on neuronal metabolism and cell signaling. In particular, the role of the menstrual cycle is discussed in some detail, as this may be important to take into account when interpreting the results of MRS studies in other contexts. Finally, in Chapter 3.11, Drs. Nicola Sibson and Kevin Behar discuss the use of ^{13}C MRS to study brain biochemistry. Although not as widely available as ^{1}H MRS, ^{13}C MRS has a unique potential to study brain energetics and metabolism *in vivo*. ^{13}C MRS has already provided many insights into brain function in animal models and, with the ongoing improvements in the technique, its potential for the study of brain function in humans is beginning to be realized, a topic covered in more detail in Section 4.

SECTION 4: APPLICATIONS OF NON-PROTON MRS

Although the majority of *in vivo* MRS studies of the CNS have used the ^{1}H nucleus there is a large amount of complimentary information that can be obtained using other nuclei, including ^{13}C, sodium (^{23}Na), oxygen (^{17}O), phosphorus (^{31}P), and potassium (^{39}K). Considerable insights into brain energetics and function have been obtained in research studies using these nuclei, several of which are described in Sections 2 and 3. Because these nuclei gain in sensitivity with field to a greater degree than the ^{1}H nucleus they may become standard as ultrahigh field systems such as 7 T become more common. In this section we cover present and potential uses of these nuclei and how they can add information to both clinical diagnosis and basic understanding of brain metabolism and function. In Chapter 4.1 Drs. Keith Thulborn and Ian Atkinson provide an introduction to state-of-the-art sodium, oxygen, and phosphorous MRS, MRSI, and MRI and show how at ultrahigh fields even imaging of potassium is possible. MRI of sodium and potassium has great potential for detecting clinical imbalances that may profoundly impact brain function as well as even a more direct form of functional imaging. Further, the authors introduce the concept of bioscales in the clinical applications of these measurements making a strong argument for going beyond standard MRI and ^{1}H MRS. In Chapter 4.2 Drs. Henk De Feyter and Douglas Rothman cover the methodology and applications of ^{13}C MRS in combination with ^{13}C-labeled brain substrates such as glucose and acetate. While this is one of the most challenging areas of MRS due to the need for stable isotope infusion, metabolic modeling and modified MR hardware, it has already provided novel insight into brain function and disease and has shown high sensitivity to a variety of clinical conditions including Alzheimer's disease and healthy aging, cancer, developmental disorders, diabetes, depression, and stroke. It is also the only method that can be used to study cell type-specific metabolism and glutamate and GABA neurotransmission in humans.

An additional limitation of using ^{13}C MRS is its low sensitivity relative to ^{1}H MRS, which results in relatively course spatial resolution. While this can be recovered using inverse ^{1}H-[^{13}C] MRS, particularly at high fields, the overall achievable spatial resolution is still well below PET scanning and other metabolic imaging methods. However, this limitation has been overcome recently through the development of hyperpolarized ^{13}C MRS. The MRS signal is proportional to the difference in the number of nuclear spins pointing parallel versus antiparallel to the main magnetic field. Normally the excess is a small fraction of the total nuclei, but in hyperpolarized ^{13}C MRS the sensitivity of detection (and in principle spatial resolution) can be improved by over 10,000-fold due to prepolarization of the ^{13}C-labeled precursor prior to injection. In Chapter 4.3 Dr. Brian Ross describes the state of the art of the use of hyperpolarized ^{13}C MRS to study the brain. This application has been very challenging due to both the difficulties involved in performing conventional MRS and the additional challenges of delivering the hyperpolarized compound to the brain before it reverts through relaxation back to normal levels of polarization (losing the enhancement). However, recent breakthroughs described in this chapter make the prospects of performing these scans in patients much more promising.

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