Review

In vivo magnetic resonance spectroscopy (MRS): A critical mini-review of MRS limitations and multiscale interpretation

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Abstract

Magnetic resonance spectroscopy (MRS) provides a non-invasive means of interrogating in vivo biochemical processes, extending magnetic resonance methodologies beyond structural and hemodynamic imaging into the domain of cellular metabolism. Unlike conventional magnetic resonance imaging (MRI), which primarily captures anatomical organization and indirect functional signals, MRS resolves metabolite-specific spectral features, enabling the quantification of neurochemical states within intact tissue. Advances over recent decades (including ultra-high-field systems, improvements in radiofrequency coil design, optimized pulse sequences, and increasingly sophisticated spectral modeling) have significantly enhanced signal fidelity and metabolite resolution. These developments have expanded the applicability of MRS across neurology, psychiatry, oncology, and metabolic research. However, such progress has also exposed fundamental interpretative challenges, particularly regarding spectral overlap, macromolecular contributions, and the limited specificity with which individual metabolites can be mapped onto discrete biological processes. Accordingly, the utility of MRS cannot be understood solely in terms of improved detection sensitivity or expanded clinical deployment. Rather, its interpretative power depends on how spectroscopic signals are situated within a broader multiscale framework linking molecular metabolism, cellular function, and systems-level dynamics. This mini-review, therefore, moves beyond purely technical accounts by critically examining the assumptions underlying metabolite attribution and emphasizing the necessity of multimodal integration. By synthesizing physical principles, methodological constraints, and neurobiological interpretation, this work advances a more constrained and context-sensitive framework for MRS analysis. Emerging developments (including multimodal imaging integration and machine-learning-assisted spectral decomposition) are evaluated in this light, with particular attention to their implications for multiscale neuroscience and multiscale brain imaging.

Keywords: Magnetic resonance spectroscopy, neurochemistry, metabolomics; multiscale brain imaging, multiscale neuroscience, spectral analysis.

1. Introduction

Magnetic resonance spectroscopy (MRS) represents a fundamental extension of magnetic resonance imaging (MRI), enabling the in vivo assessment of biochemical processes that are otherwise inaccessible through conventional imaging techniques (Bottomley, 1982; Hoult & Richards 1976). While MRI has revolutionized diagnostic medicine by providing high-resolution structural and functional information, it does not directly measure metabolic activity. MRS addresses this limitation by detecting signals from specific nuclei and translating them into spectra that reflect the concentration and environment of metabolites within tissues (Levitt, 2008; Ernst et al., 1987).

The development of in vivo MRS can be traced back to early nuclear magnetic resonance (NMR) studies, which demonstrated the feasibility of measuring metabolic signals from biological systems (Gruetter et al, 1994; Rothman et al., 2011). The transition from in vitro to in vivo applications marked a significant milestone, allowing researchers to study metabolism in real time within living organisms (Rothman et al., 2011). Among the various nuclei used in MRS, proton (1H) spectroscopy has become the most widely employed due to its high sensitivity and abundance, enabling the detection of a wide range of metabolites within clinically acceptable acquisition times (Hyder et al, 2006; Mason et al., 1992).

Complementary techniques, such as 31P-MRS and 13C-MRS, provide additional insights into bioenergetics and metabolic flux, respectively, further expanding the scope of MRS (Moffett et al., 2007; Baslow, 2002).

The increasing adoption of MRS in clinical and research settings has been driven by advances in hardware and methodology. Higher magnetic field strengths, particularly 3 Tesla and 7 Tesla systems, have significantly improved spectral resolution and signal-to-noise ratio, allowing for more accurate metabolite quantification and better separation of overlapping peaks (Merritt et al, 2016; Marsman et al., 2013). Improvements in radiofrequency coil design and magnetic field shimming have further enhanced signal quality, reducing artifacts and improving reproducibility (Petroff, 2002, Kantarci et al., 2003). In parallel, advances in computational analysis have enabled more robust spectral fitting and quantification, facilitating the translation of MRS into clinical practice (Schuff et al., 2005; De stefano et al., 1997).

Despite the extensive body of literature on MRS, several challenges remain in translating spectroscopic findings into routine clinical practice. While numerous studies report metabolite alterations across a wide range of neurological and psychiatric conditions, inconsistencies in acquisition protocols, analysis pipelines, and cohort characteristics often limit comparability and reproducibility. Moreover, many reported biomarkers lack sufficient specificity, raising concerns about overinterpretation. Therefore, a critical evaluation of both methodological constraints and biological variability is essential for advancing the field toward robust and clinically meaningful applications.

2. Physical principles and spectral formation

The physical basis of MRS lies in nuclear magnetic resonance (NMR), a quantum mechanical phenomenon in which nuclei with non-zero spin align with an external magnetic field and absorb radiofrequency energy at characteristic resonance frequencies (Davie et al., 1996; Petroff, 1994). These resonance frequencies are determined by the gyromagnetic ratio of the nucleus and are modulated by the local electronic environment, resulting in chemical shifts that serve as unique identifiers for different metabolites (Law et al. 2000; Howe et al., 2003)

Chemical shifts, typically expressed in parts per million (ppm), are central to the interpretation of MRS spectra, as they allow for the differentiation of molecular species based on subtle variations in electronic structure (Negendansk, 1992). In biological tissues, these shifts are influenced by factors such as molecular conformation, hydrogen bonding, and intermolecular interactions, leading to distinct spectral signatures for each metabolite (Yuksel & Ongur, 2010; Mullins et al., 2010). However, spectral interpretation is complicated by additional phenomena such as scalar (J) coupling, which causes peak splitting patterns that depend on molecular structure (Mullins et al., 2010).

Relaxation processes, including T1 and T2 relaxation, play a critical role in determining signal intensity and linewidth, influencing both sensitivity and spectral resolution (Mescher et al.,1994; Tkac et al., 2009). Magnetic field inhomogeneities and susceptibility effects can further broaden spectral lines, reducing the ability to resolve closely spaced peaks (Near et al., 2017). To address these challenges, advanced shimming techniques are employed to optimize magnetic field homogeneity within the region of interest (Wang et al., 2019; Zhou et al., 2020)

Signal localization in MRS is achieved using pulse sequences such as PRESS and STEAM, which utilize combinations of radiofrequency pulses and magnetic field gradients to isolate signals from specific volumes of tissue (Kreis, 2004; Pouwels & Frahm, 1998). The choice of acquisition parameters, including echo time (TE) and repetition time (TR), significantly influences spectral quality and metabolite visibility, necessitating careful optimization for each application (Barker, 1998) This is illustrated schematically in **Fig. 1**.

3. Neurochemical interpretation and metabolite profiling

A key strength of MRS lies in its ability to simultaneously detect multiple metabolites, each providing insight into specific aspects of cellular function and pathology. N-acetylaspartate (NAA) is widely considered a marker of neuronal integrity, with reductions in NAA levels reflecting neuronal loss or dysfunction in conditions such as Alzheimer's disease, multiple sclerosis, and traumatic brain injury (Govindaraju et al., 2000; Kreis 2013). Choline-containing compounds (Cho) are associated with membrane turnover and cellular proliferation, and elevated Cho levels are commonly observed in tumors and demyelinating diseases (Lin et al., 2005; Preul et al., 1996)

Creatine (Cr) plays a central role in cellular energy metabolism and is often used as an internal reference

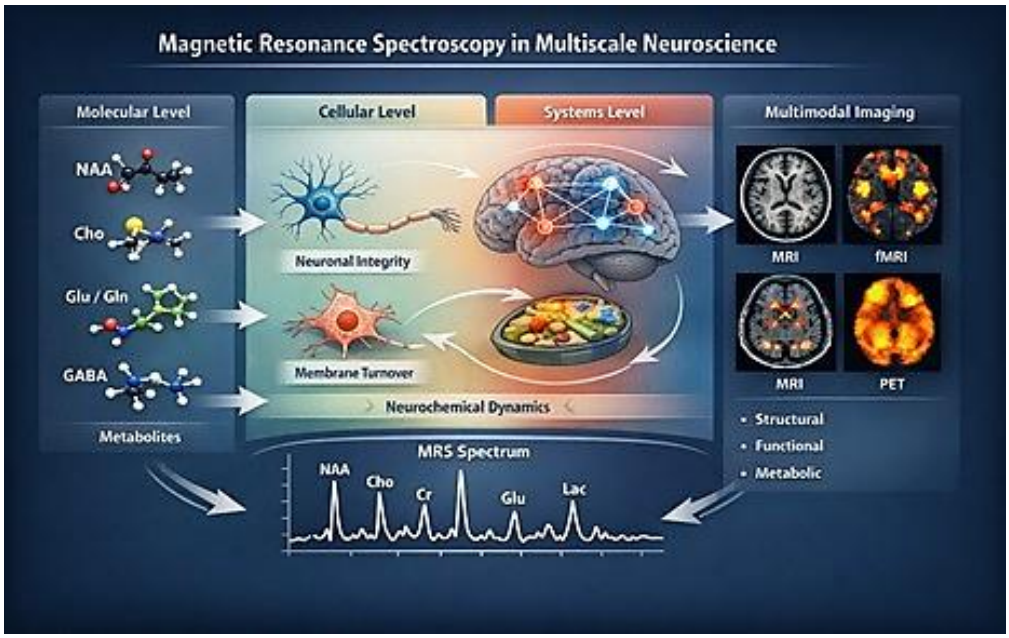

Figure 1. Multiscale framework of Magnetic Resonance Spectroscopy (MRS) depicting the hierarchical integration of molecular, cellular, and systems-level brain function. Spectroscopic observables serve as proxies for intrinsic metabolic states, constraining cellular interactions and enabling the emergence of coordinated dynamics across large-scale brain systems. This framework emphasizes cross-scale coupling between biochemical states and functional brain organization.

due to its relatively stable concentration across brain regions (Castillo, 1998) The glutamate–glutamine system is another critical component of the MRS spectrum, reflecting excitatory neurotransmission and astrocyte–neuron metabolic coupling. Alterations in glutamate and glutamine levels have been implicated in a range of psychiatric and neurological disorders, including schizophrenia, depression, and epilepsy (Alger, 1991; Duarte et al., 2012; Mullins et al., 2014).

Gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter, is present at low concentrations and is challenging to detect due to spectral overlap with other metabolites. Its reliable quantification typically requires spectral editing techniques such as MEGA-PRESS, which selectively suppress overlapping signals (Stagg, 2012; Sailasuta et al., 2010). Myo-inositol (mI), considered a marker of glial cells, is often elevated in conditions involving gliosis and neuroinflammation (Pan et al., 2004).

Lactate, a product of anaerobic metabolism, is typically low in healthy brain tissue but becomes elevated under pathological conditions such as hypoxia, ischemia, and tumors (Schubert et al., 2009: Mekle et al., 2009).

The interpretation of MRS spectra requires careful consideration of these metabolites in the context of their biochemical roles and interactions. Changes in metabolite concentrations often reflect complex underlying processes, including alterations in neuronal viability, membrane turnover, energy metabolism, and neurotransmitter cycling (Maudsley et al., 2006; Posse et al., 2001).

Importantly, while individual metabolite alterations provide valuable biomarkers, their interpretation remains non-specific in many clinical contexts. For instance, decreased NAA is often associated with neuronal loss, yet it may also reflect reversible metabolic dysfunction, highlighting the need for cautious interpretation. Similarly, elevated choline is commonly linked to increased membrane turnover, but cannot independently distinguish between tumor progression and inflammatory processes. These limitations emphasize that MRS findings should not be interpreted in isolation but rather integrated with complementary imaging and clinical data.

Taken together, these findings indicate that individual metabolite alterations, while are informative, lack

Table 1. Principal metabolites detected by ^{1}H-MRS: biological roles, clinical significance, and methodological limitations

Metabolite	Primary Biological Function	Clinical Significance	Key Limitations in Interpreta
N-acetylaspartate (NAA)	Marker of neuronal integrity and mitochondrial function	Decreased in neurodegenerative disorders (e.g., Alzheimer's disease, multiple sclerosis, traumatic brain injury)	Not disease-specific; may reflect reversible metabolic dysfunction
Choline-containing compounds (Cho)	Membrane phospholipid turnover and cellular proliferation	Elevated in brain tumors, demyelination, and inflammatory processes	Cannot differentiate neoplasia fror inflammatory processes
Creatine (Cr)	Cellular energy metabolism (ATP buffering system)	Common reference metabolite	May vary with pathological conditi
Glutamate / Glutamine (Glu/Gln)	Excitatory neurotransmission	Altered in psychiatric disorders (e.g., schizophrenia, bipolar disorder)	Spectral overlap between Glu and
GABA	Inhibitory neurotransmitter	Reduced in depression and epilepsy	Requires specialized spectral editi
Myo-inositol (mI)	Astroglial marker	Increased in gliosis and astrocytosis	Low specificity for glial pathology

sufficient specificity when considered in isolation, underscoring the necessity of systems-level and multimodal interpretation approaches (**see Table 1**).

4. Acquisition, processing, and quantification

The acquisition of MRS data involves the use of specialized pulse sequences designed to localize the spectroscopic signal within a defined volume of tissue. PRESS is the most used sequence in clinical applications due to its high signal-to-noise ratio, while STEAM offers advantages in detecting metabolites with short T2 relaxation times (Cendes et al., 1995; Hetherington et al., 1997). The selection of acquisition parameters, including voxel size, echo time, and repetition time, is critical for optimizing spectral quality and metabolite detection (Srinivasan et al., 2005).

Following acquisition, raw time-domain signals are converted into frequency-domain spectra through Fourier transformation. Subsequent processing steps include phase correction, baseline adjustment, frequency alignment, and removal of residual water signals, all of which are essential for accurate spectral interpretation (Arnold, 2003; Ende, 2010). Quantification is typically performed using model-based fitting algorithms, such as LC Model, which decompose the observed spectrum into contributions from individual metabolites based on predefined basis sets (Stanley, 2012).

Quantification can be performed using either relative or absolute methods. Relative quantification expresses metabolite concentrations as ratios, such as NAA/Cr or Cho/Cr, while absolute quantification requires calibration against a reference signal and correction for relaxation effects (Kreis, 2014; Emir et al., 2012). Each approach has its advantages and limitations, and the choice depends on the specific research or clinical context.

5. Clinical applications

MRS has been widely applied in the study of neurological disorders, providing valuable insights into disease mechanisms and progression. In Alzheimer's disease, decreased NAA and increased myo-inositol levels reflect neuronal loss and gliosis, respectively, and may serve as early biomarkers of disease (Choi et al., 2005; Edden et al., 2012). In multiple sclerosis, reduced NAA levels indicate axonal damage, while changes in choline reflect demyelination (Lin et al., 2005; Weybright et al., 2005) In epilepsy, MRS can identify metabolic abnormalities in seizure foci, aiding in surgical planning and treatment optimization (Rowland et al., 2009)

In neuro-oncology, MRS plays a critical role in tumor characterization, grading, and treatment monitoring. Elevated choline levels and reduced NAA are characteristic of high-grade tumors, while the presence of lactate may indicate hypoxia or necrosis. Importantly, MRS can differentiate tumor recurrence from radiation-induced necrosis, a distinction that is often difficult using conventional imaging techniques (Sanacora et al., 1999).

In psychiatric research, MRS has provided important insights into neurochemical dysregulation. Alterations in glutamate and GABA levels have been associated with schizophrenia, depression, and bipolar disorder, supporting models of excitatory–inhibitory imbalance (Bhagwagar et al., 2007; Butterworth, 2002; Kreis, 2004). Beyond the brain, MRS has been applied to systemic conditions such as hepatic encephalopathy and mitochondrial disorders, highlighting its versatility as a tool for investigating metabolic dysfunction (Ugurbil, 2012; Vaughan, 2006).

Collectively, the reviewed studies suggest that while MRS provides robust metabolic signatures across a range of neurological and psychiatric disorders, its greatest value lies not in single-metabolite biomarkers but in integrated, multivariate and multimodal interpretation frameworks.

6. **Advanced techniques and emerging trends**

Technological advancements have significantly expanded the capabilities of MRS. Ultra-high-field systems, operating at 7 Tesla and above, offer improved spectral resolution and sensitivity, enabling the detection of previously inaccessible metabolites (Henry, 2004; Bogner, 2012). Spectral editing techniques, such as MEGA-PRESS, have improved the detection of low-concentration metabolites such as GABA by suppressing overlapping signals (Maudsley, 2006).

Multivoxel spectroscopy (MRSI) enables spatial mapping of metabolite distributions across brain regions, providing a metabolic topography that complements anatomical imaging (Zhang, 2019; Liu, 2020). The integration of machine learning and artificial intelligence into MRS analysis has further enhanced its potential, enabling automated spectral classification, tumor grading, and biomarker discovery (Vieira, 2017; Logothetis, 2001; Phelps, 2000).

7. **Multiscale integration, limitations, and future perspectives**

The term “multiscale neuroscience” is adopted here to emphasize the integration of molecular, cellular, and systems-level processes, in contrast to traditional systems neuroscience approaches that primarily focus on network-level brain function without direct biochemical resolution.

MRS is increasingly positioned within the broader framework of multiscale neuroscience, where molecular, cellular, and systems-level processes are integrated to provide a comprehensive understanding of brain function. The combination of MRS with other imaging modalities, including structural MRI, functional MRI (fMRI), and positron emission tomography (PET), enables the simultaneous interrogation of anatomical, functional, and metabolic dimensions of neural systems (Fox, 1997; Raichle, 1988). This multimodal integration allows for a more holistic interpretation of neurological and psychiatric disorders, bridging the gap between biochemical alterations and systems-level dysfunction.

However, despite its significant potential, MRS remains subject to several methodological and practical limitations. Its inherently lower sensitivity compared to conventional MRI, along with spectral overlap between metabolites, poses challenges for accurate quantification (van der Graaf, 2010; Near et al., 2017). Additionally, relatively long acquisition times increase susceptibility to motion artifacts, while variability in acquisition protocols across institutions limits reproducibility and standardization (Deelchand et al., 2016; Nicholson, 2008).

Future developments in MRS are expected to address these limitations through advances in hardware, pulse sequence design, and computational analysis. The integration of artificial intelligence and machine learning approaches has already demonstrated potential in automated spectral interpretation and biomarker discovery (Zhou et al., 2020; Vieira et al., 2017). Furthermore, the incorporation of MRS into multi-omics frameworks and precision medicine strategies is anticipated to enhance its clinical relevance, enabling individualized diagnosis and treatment planning (Poldrack, 2014; Friston, 2010).

Overall, the evolution of MRS from a standalone spectroscopic technique to a core component of multiscale neuroscience underscores its growing importance in both research and clinical practice.

8. **Conclusions**

MRS represents a uniquely powerful tool for non-invasive metabolic investigation, offering insights that extend beyond conventional structural and functional imaging. However, its interpretation remains inherently complex, requiring careful consideration of methodological limitations and biological context. The integration of MRS within a multiscale neuroscience framework, combined with advances in artificial intelligence and multimodal imaging, is expected to

significantly enhance its clinical utility. Future research should prioritize standardization, reproducibility, and the development of more specific metabolic biomarkers to fully realize the translational potential of MRS.

Conflict of Interest Statement

The author declares no conflict of interest.

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