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The Application of Human Spinal Cord Magnetic Resonance Spectroscopy to Clinical Studies: A Review

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This article reviews the current state of magnetic resonance spectroscopy applied in the human spinal cord with respect to its clinical applications and challenges in comparison to investigations in the human brain. Results from several disease processes affecting the spinal cord are presented, and potential advantages of applying clinical MRS in their investigation are emphasized.

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Motivation

Magnetic resonance spectroscopy (MRS) reveals metabolic changes related to a disease process at an early stage of the biochemical abnormality, before the perturbation of the tissue at the cellular or organ level. Thus, MRS can detect a specific pathology before the appearance of structural abnormalities in a routine clinical magnetic resonance imaging (MRI) examination. Pathological progresses in the spinal cord affect the clinical status of the patient at a relatively early stage of the disease and to a large extent. Therefore, clinically applied MRS in the spinal cord might deliver important additional information in the clinical routine. Potential application of complementary information at an earlier stage is crucial for planning of a successful pharmacological, surgical, or rehabilitative therapy.

Introduction of MRS

MRS is a noninvasive useful tool to obtain biochemical in vivo information of nervous tissue.[1,2] It can provide important information on early diagnosis of cell failure and aid in the differentiation of various disease processes and estimation of the efficacy of various treatments. Hence, MRS sometimes is called "virtual biopsy."[3] Different small molecules—so-called metabolites—give rise to different resonance signals owing to different electronic shielding of their outermost electrons. This information is provided in the form of a spectrum of different metabolite concentrations. Contrary to MRI where the acquired resonance signal is based on the relaxation property of water in different compounds, MRS allows insight into concentration and relaxation behavior of different metabolites. However, as the concentration of the metabolites in brain and spinal cord tissue is much lower than the concentration of water (concentration factor water/N-acetyl-aspartate [NAA] approximately 5000),[4] MRS suffers from an intrinsic lower sensitivity.

Metabolites

The most prominent metabolite peaks detected in the nervous tissue are NAA, phosphocreatine and creatine (Cr), choline-containing compounds (Cho), and myo-Inositol (mI). These components can be used as biomarkers reflecting the state of neuronal viability and function (NAA), tissue energy metabolism (Cr), cell membrane synthesis (Cho), or as a glial cell marker (mI).[2,4]

Additional metabolites, abundant at even lower concentration than the ones mentioned above, are also important for the well-functioning of the neural tissue and for maintaining homeostasis. These metabolites can also be detected with MRS by using advanced editing sequence[5] or by adjusting the echo

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times (TEs) T_{E1} and T_{E2} of the acquisition.[6] Among others, the neurotransmitters glutamate (Glu), glutamine (Gln), and γ-amino-butyric acid may serve for the investigation of neurodegenerative brain disorders and macromolecules (such as the recently detected 2-hydroxyglutarate with important applications in the genetic characterization of gliomas).[6] Presently, the detection of up to 18 metabolites is possible in the human brain by using 2-dimensional J-resolved spectroscopy,[7] evolving the coupling behavior of the spins in a second frequency dimension by increasing the TE sequentially. In the spinal cord, the detection of the glutamate-glutamine (Glu + Gln = Glx)[8-10] complex as well as scyllo-Inositol (sI)[11] has been successfully demonstrated in vivo. In addition, an age-dependent decrease in the metabolite concentrations in the healthy spinal cord has been shown for NAA and Glx.[12]

The spectral quality and the metabolite profile depend on the level of acquisition (Fig. 1)—the peak size of NAA, Cr, and Cho, as well as the amount of lipids and macromolecules contributing to the spectrum change dramatically in different areas including the pons, the medulla oblongata, the cervical, and the lumbar region of the spinal cord.[13]

Localization

Unlike MRI, single-voxel MRS focuses on a preselected area of the neural tissue (region of interest [ROI], volume of interest), hence, limiting the possibility to study the entire organ (ie, brain or spinal cord).[2,3] This area ranges from $2.5 \times 2 \times 2$ cm^3 for single-voxel spectroscopy in the brain to $0.6 \times 0.9 \times 3.5$ cm^3 in the spinal cord due to its elongated anatomy. Another MRS technique, so-called magnetic resonance spectroscopic imaging or chemical shift imaging (CSI), enables metabolic probing of multiple voxels at the same time. However, additional challenges (eg, increased scan time or additional artifacts) make the application of CSI difficult. Nevertheless, CSI is commonly used in clinical MRS of the brain and has also been applied to the medulla and the cervical spinal cord.[14]

MRS Acquisition Techniques

Excitation of the ROI is done mainly by using Point RESolved Spectroscopy (PRESS) technique.[15] Localization can also be achieved by applying STimulated Echo Acquisition Mode (STEAM)[16] or including adiabatic pulses as in Localization by Adiabatic SElective Refocusing (LASER)[17,18] or its modified version semi-LASER.[19-21] The resonance signal acquired using PRESS is twice as strong as the one using STEAM, where only the stimulated echo contains spectral information.[4] However, STEAM has the advantage that it can be run with smaller (minimal) TE allowing detection of metabolites with short T_2 relaxation times. Both STEAM and LASER have smaller chemical shift displacement artefacts.[2] Inner and outer volume saturation can be used to overcome chemical shift displacement and avoid signal contribution from outside the voxel.[22,23]

The signal from the metabolites is overpowered by the signal of the abundant water in the tissues; hence, water suppression techniques are usually applied to access the metabolic information. The most common ones are CHEmical Shift Selective (CHESS)[24] and VAriable pulse Power Optimized Relaxation delays (VAPOR).[25]

Processing

Commonly applied processing steps of the data include referencing the spectra, line shape, and eddy current correction as well as baseline correction. Also, line broadening and zero-filling might help to improve the spectrum and to control the noise level.[4]

Eventually, the acquired and processed data are fitted by prior knowledge basis sets providing the spectral profile of the detectable metabolites.

The most prevalent spectral fitting routine is Linear Combination MODELing (LCMODEL),[26] which is a commercial software to fit the signal to the basis sets in the frequency domain. It controls the coupling behavior of involved spins and can also be applied to nonproton spectroscopy (such as ^{13}C or ^{31}P). Freely available software tools for noncommercial use are java-based MR User Interface (jMRUI)[27] and Totally Automatic Robust Quantification in NMR (TARQUIN).[28] The first one fits the signal in the time domain, whereas the second does the fitting in the frequency domain. Basis sets for any fitting software can be generated using the GAMMA library.[29]

Challenges of MRS in the Human Spinal Cord

Although MRS has been extensively applied and gained acceptance among the clinicians as an important tool in the investigation of neurologic disease in the brain, applications in the spinal cord have been very limited. Unlike spectroscopy of the brain, the application of MRS in the spinal cord faces several methodological challenges regarding signal quality and resolution of the method.[30]

An important challenge originates from the anatomy of the spinal cord, including its small diameter (approximately 1 cm in the cervical enlargement) and its elongated shape in the craniocaudal direction, which limits the available tissue for obtaining enough signals for the spectroscopy. Moreover, its location deep inside the body limits the signal quality because a close application of coils is not possible. Furthermore, the presence of different types of surrounding tissues (meninges, cerebrospinal fluid [CSF], bone, and muscles) with differing magnetic properties induces strong susceptibility changes[30] and hampers a homogeneous static magnetic field B_0 leading to local B_0 inhomogeneities, which may significantly affect the quality of the spectra. Therefore, accurate shimming (ie, optimization of the magnetic field) in the spinal cord area is absolutely essential. The currently used shimming techniques are based on B_0 mapping or projections. Therefore, either a B_0 map is recorded in the voxel or projections toward certain shim directions are applied. The popular FASTERMAP shimming[31] is a derivative of the widely spread FASTMAP shimming.[32,33]

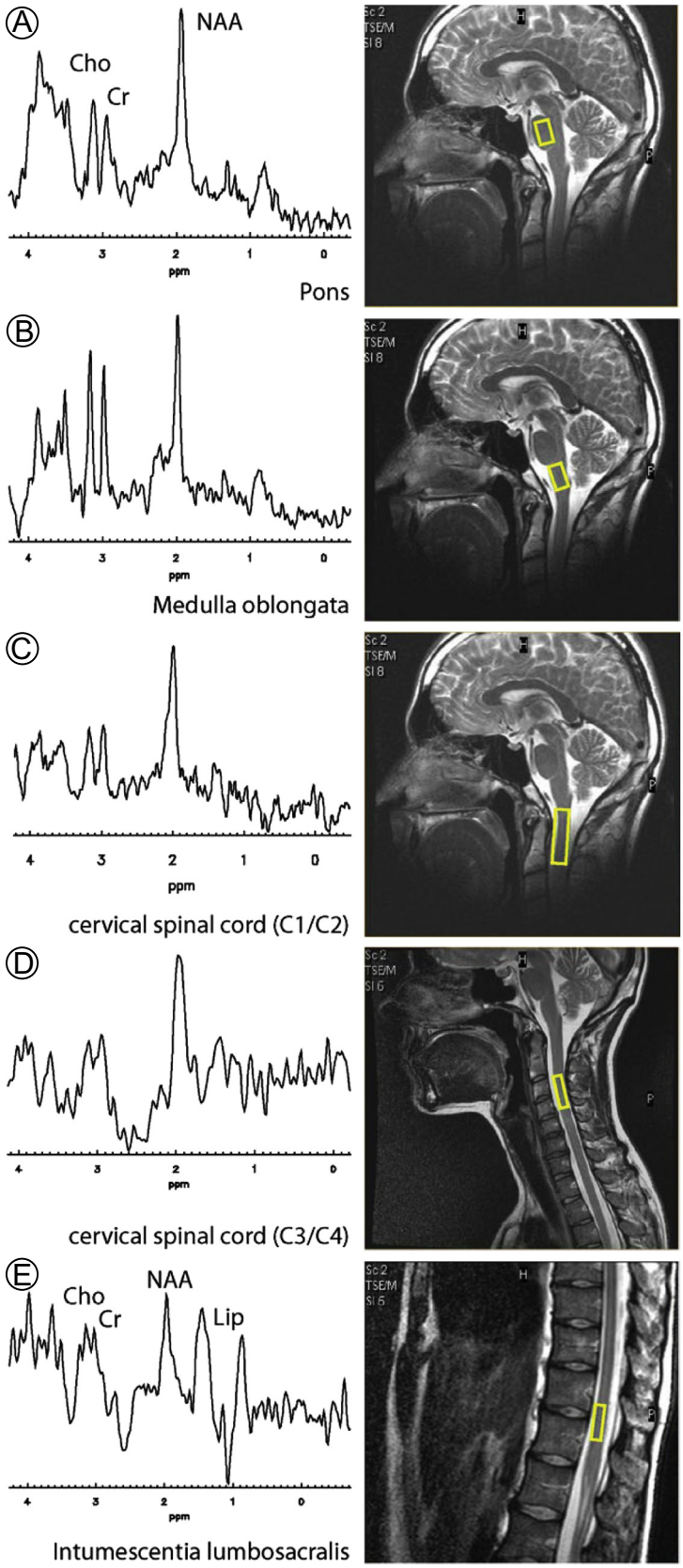

Figure 1 MR spectroscopy in different regions of the spinal cord. The spectrum of the metabolites depend on the level of acquisition—the peak size of NAA, Cr, and Cho as well as the amount of lipids and macromolecules contributing to the spectrum changes dramatically in different areas including the pons, the medulla oblongata, the cervical, and the lumbar region of the spinal cord. MR, magnetic resonance. (Reprinted with permission from Dydak et al.[13])

The spectral quality is also affected by artifacts related to involuntary motion (cardiac and CSF pulsations, breathing) and voluntary motion (swallowing, movements of the body during the examination). Pulsatile flow of the CSF can be controlled by applying (electrocardiogram [ECG])- triggered spectroscopy measurements,[30,34,35] and body motion can be detected by navigator-based measurement.[36] Because these limiting factors are more pronounced in the thoracic and lumbar regions, most publications of data in the spinal cord are done in the cervical region at the vertebrae level C3 or above.[14,34,37-44] Non–water-suppressed spectroscopy for the spinal cord[45] has been proposed to overcome the drawback of dynamic changes of the static magnetic field B_0 due to hardware instabilities or subject motion and to improve spectral quality. Instead of suppressing the water signal, an inversion pulse is applied with every other signal average measurement to invert the metabolites but not the water signal. Because the information of the water signal is still present in the data, the water signal can be used for frequency alignment, phase, and eddy current correction enabling MRS acquisitions with improved data quality.

Considerations on Spectral Data Quality

For an acquisition of spinal cord spectra with high data quality, important methodological progress[10,21,34,36,45-47] has been proposed that increases the chance of obtaining reliable biochemical information. However, the suggested methods require modifications of the scanner software and cannot be applied instantly with a conventional software package.

Figure 2 shows an example of spectra measured at a Philips Achieva 3 T (there might be significant manufacturer differences) and the corresponding LC-model[26] fittings of measurements in the human spinal cord of a 47-year-old female healthy volunteer. On the left, a spectrum and its metabolite fittings are shown acquired with a conventional available standard product sequence (PRESS, repetition time (TR)= 3000 ms, excitation water suppression, outer-volume suppression, cardiac triggering, 256 signal averages [approximately 12 minutes scan time]). For comparison, on the right, a spectrum and its metabolites are shown, acquired using an advanced research sequence (metabolite cycling[45] without water suppression, cardiac triggering, inner and outer-volume suppression, 256 signal averages [approximately 12 minutes scan time]). The following 3 challenges hamper the spectral quality of a conventional protocol: firstly, the water suppression is rarely perfect leading to baseline disturbances; secondly, the linewidth (full width at half maximum) of the metabolites is broader, as compared to the research sequence, because of the averaging of the signals and the drift of the static magnetic field. When using the non–water-suppressed research sequence, corrections can be made during postprocessing to account for static magnetic field drifts; thirdly, the saturation in the clinical protocol is of suboptimal quality compared to optimized outer-volume suppression in the research sequence, which enhances the spectral quality saturating signals from outside the ROI more effectively. Thus, commercially available clinical sequences are usually hampered in the detection of metabolites by low signal quality and larger linewidth, as illustrated at the bottom of Figure 2.

In conclusion, high data quality is necessary for a reliable quantification, and novel investigations help to improve data quality. However, commercially available sequences allow just a rough estimation of metabolic differences.

Clinical Application of MRS in the Brain and Spinal Cord

A consensus article on MRS of the central nervous system was published recently incorporating experience form a large number of previous publications, which emphasizes that MRS has evolved from a research tool into a clinical neuroimaging modality.[1] Its authors present a summary of brain disorders, including brain neoplasms, neonatal and pediatric disorders (hypoxia-ischemia, inherited metabolic diseases, and traumatic brain injury), demyelinating disorders, and infectious brain lesions, in which metabolic information provided by the method has an impact on clinical judgment and patient management. In addition, recent research shows that the list of central nervous system disorders may extend to neurodegenerative diseases, epilepsy, and stroke. The authors also emphasize the importance of guidelines for data acquisition and analysis, quality assessment, and interpretation to facilitate expanded clinical acceptance and standardization of the method. The number of MRS studies conducted in the spinal cord is far more limited in number and also in the volume of patients included and the spectrum of diseases where the method was applied. However, the potential of the method to detect metabolic alterations in the spinal cord makes it an attractive technique with potential clinical applications in a variety of disease processes, provided that the methodological challenges outlined in the previous sections are overcome. Figure 3 summarizes changes in metabolic profiles found in different diseases affecting the spinal cord. For direct comparison, the spectrum from a healthy human brain (occipital cortex; top row) and a spectrum from a healthy human spinal cord (cervical region; middle row) are provided. According to the brain spectrum, the range of detected metabolites is separated into multiple subsections. Several metabolites have multiple resonance lines resulting in a manifold appearance in the spectrum. The spectrum from the healthy spinal cord is divided in the same subsections as the brain spectrum. Note that the overlapping metabolites are hardly detectable in the spinal cord as the signal quality in spinal cord spectroscopy is lower than the signal quality in brain spectroscopy. In the lower part of the figure, various diseases and the corresponding changes in the metabolite concentrations are listed. In the following section, we describe experience from MRS findings in various diseases affecting the spinal cord. References to the brain are mentioned where applicable.

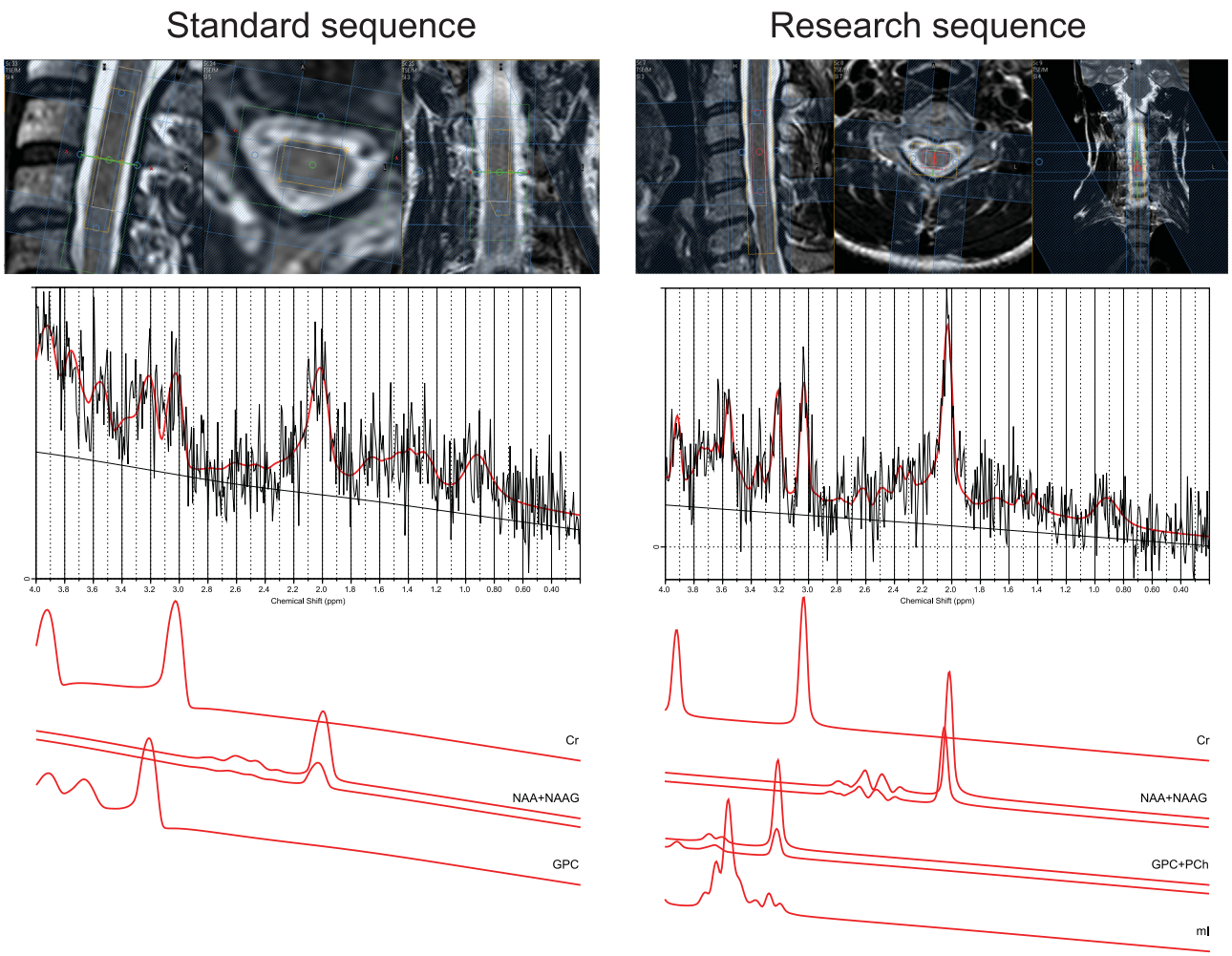

Figure 2 Comparison of available standard and research MRS sequences. LC-model[26] fittings of spectroscopic sequences in the human spinal cord from a 47-year-old female healthy volunteer. The structural planning image and the acquired spectrum with the LC-model fittings are shown for 2 cases—the standard sequence has been recorded with a clinically available standard sequence (PRESS, OVS, and ECG-triggering, 256 signal averages). The research sequence shows the spectrum (256 averages) acquired with metabolites cycling[45] including OVS and ECG-triggering where the water is not suppressed, and a metabolite inversion pulse is used in every second measurement. Below the spectrum the fittings of the detected metabolites is shown. The research sequence enables spinal cord acquisitions with higher SNR and lower linewidth enabling a more reliable quantification. OVS, outer-volume suppression.

Multiple Sclerosis

Multiple sclerosis is an immune-mediated, demyelinating, and neurodegenerative disease affecting the brain and the spinal cord.[48] Studies have been conducted in the brain examining metabolic profiles in both affected and normal-appearing white matter.[49] During active myelin breakdown, the elevation of membrane phospholipid levels causes an increase in the concentration of Cho, whereas the increase of lactate (Lac) levels might reflect inflammation.[50] Most publications on spectroscopic findings in the brain of patients with multiple sclerosis (MS) focus on changes in the NAA, which is considered a robust marker of neuronal integrity.[49] A change of NAA/Cr indicates a disturbance of "cerebral tissue integrity"[51] and correlates with the clinical status of the patient in isolated demyelinating lesions[50] and in established MS.[52-54]

Studies in the spinal cord of patients with MS showed decreased ratios of NAA/Cr,[39,40,42,43,55,56] NAA/Cho,[43] and increase of both Cho/Cr[43,56] and mI/Cr.[43,56] It has also been reported that an initial decrease of NAA/Cr in MS might be followed by a limited recovery.[4,40] Diffuse and focal cervical cord lesions were examined by quantitative MR imaging of the cervical cord area and T_2 relaxometry in a follow-up study and correlated with absolute quantification of the metabolite levels by MRS. Diffuse lesions showed more pronounced cord atrophy, longer T_2, increased levels of Cr, and reduced NAA/Cr compared with focal lesions.[47] These results suggest that MRS may be a reliable biomarker for measuring the degree of axonal degeneration and gliosis in MS.[47] In another study, biochemical information has been obtained in the corticospinal tracts using CSI, and differences in metabolite levels were reported in different clinical phenotypes of the disease. Patients with relapsing-remitting type of MS showed a greater mI concentration reflecting the stage of inflammation, whereas patients with the primary progressive type of disease showed lower Cho and Cr levels along the corticospinal tracts.[57] A more recent

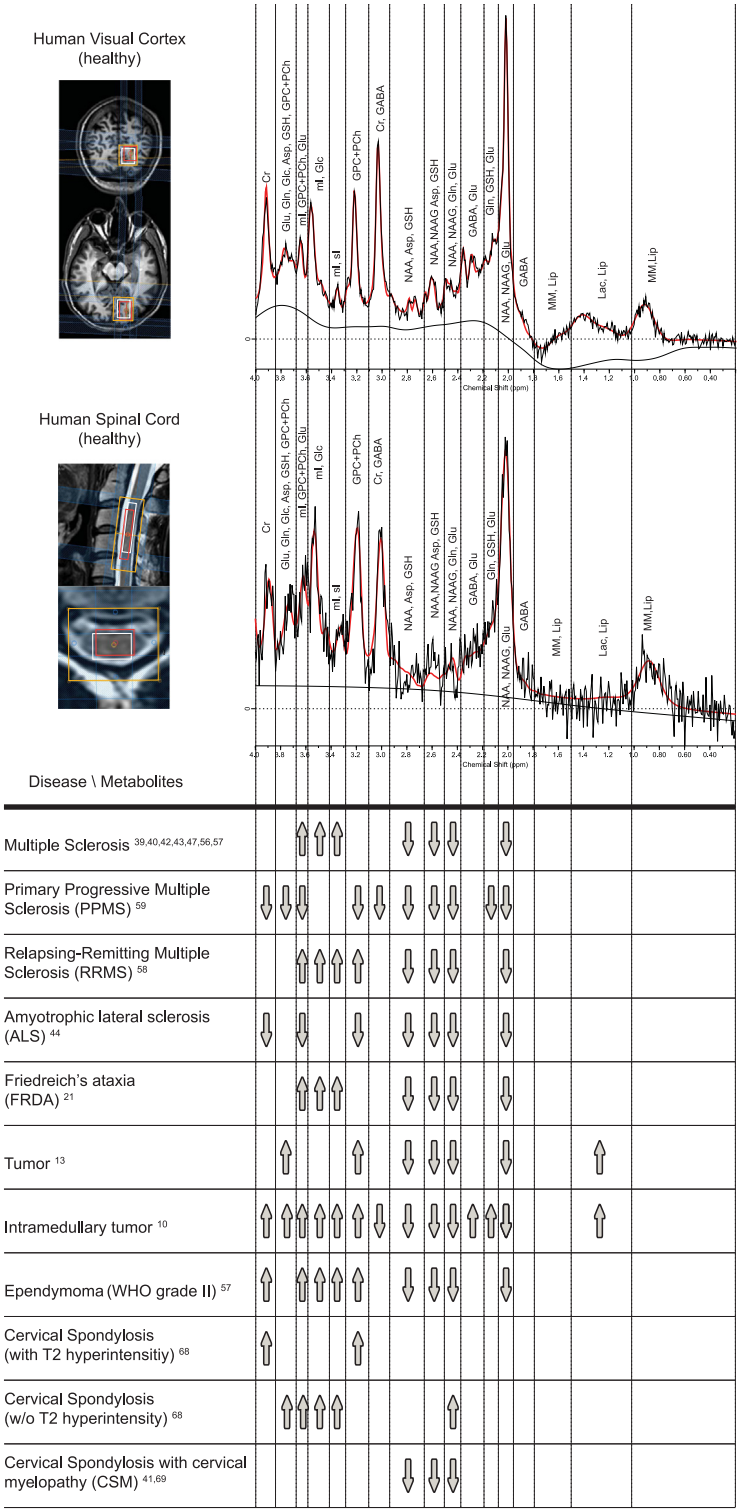

Figure 3 Overview of spinal cord metabolic profile changes in various diseases. Arrows indicate the changes in spinal cord metabolic profiles in different diseases compared with healthy controls—in the top row, the planning image and the spectrum with its fittings from the human visual cortex is shown. Based on the fitting of these metabolites, the spectrum is separated into multiple subsections assigning the corresponding metabolites. In the middle row, the planning image and the spectrum with its fittings from the human spinal cord are shown, and the metabolites are assigned accordingly. Owing to the methodological challenges of MRS in the spinal cord (see the section Challenges of MRS in the Human Spinal Cord), reduced SNR and increased linewidth is visible in spinal cord MRS. In the lower part, a table gives an overview of ongoing experience of the changes in metabolic profiles found in different diseases affecting the spinal cord (see the section Clinical Application of MRS in the Brain and Spinal Cord for more details).

study in patients with primary progressive disease showed evidence for early neurodegeneration in the cervical cord demonstrating significantly lower NAA than in healthy controls that correlated with higher disability.[58] Lower Glx indicated abnormalities in the glutamatergic pathways in the cervical spinal cord although the patients did not show spinal cord atrophy.[58]

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis is an idiopathic, neurodegenerative disease[59] involving motor neurons in the brain, brainstem, and the spinal cord. Studies have shown a decrease of NAA/Cr mainly in the motor cortex[60-64] and the brain stem,[61,62] but also in several other regions affected by amyotrophic lateral sclerosis including the caudate and the occipital lobe.[63] In the motor cortex, Cho and mI are increased and NAA and Glu are decreased.[64] These findings could be explained by progressive neuronal loss during the course of the disease. Similar findings have also been found in the cervical spinal cord where a reduction of NAA/Cr and NAA/mI of up to 40% and significantly reduced Cho/Cr were reported.[44]

Friedreich Ataxia

Friedreich ataxia is an autosomal recessive degenerative disorder affecting the nervous system and the heart.[65] Spectroscopic measurements in the brain showed decreased NAA in the vermis and the cerebellar hemispheres and increased mI in the vermis.[66] The total amount of Cr in the cerebellar hemispheres and Glu in the vermis was higher suggesting an alteration in the glutamatergic neurotransmission system.[66] Findings in the spinal cord were in accordance with those of the brain showing a reduction of NAA by 40% and an increase of mI by 46% reflecting neuronal damage and gliosis.[21]

Neoplasms

A few case studies in patients with spinal tumors have been reported. In a case of a primary spinal cord tumor at C3/C4, the MRS measurement revealed lower NAA and higher Cho and Lac levels.[13] Reduced NAA and Cr as well as increased mI, Cho, Lac, and Glx have been shown in high-grade intramedullary tumors at levels C4 and T9.[10] The NAA/Cr level of an ependymoma (WHO grade II) was strongly reduced, whereas Cho/Cr and mI/Cr were moderately increased.[56] Two tumor cases with high-grade tumor also showed reduced NAA/Cr and moderately increased Cho/Cr.[56] An extra-axial (extramedullary) tumor (schwannoma) did not show any metabolites.[56] A study in spinal mass lesions showed that although the resolution of the profiles of the metabolites were stable, no specific metabolic changes could be detected owing to signal broadening reflecting changes ongoing in the tissue.[38]

There are 3 points to state in the tumor cases: (1) The metabolic fingerprints of spinal cord tumors, according to our preliminary experience, seem to follow the same metabolic fingerprints of tumors in the brain, as it refers to malignant vs benign lesions. In malignant lesions, there is lower NAA, higher Cho, and the presence of lipids and lactate. (2) The presence of mI may be a promising marker to differentiate a singular demyelinating lesion (higher mI) from a low-grade intramedullary glioma (no significant changes in its concentration). (3) On the application side, owing to the mass effect associated with intramedullary tumors, artifacts related to spinal cord motion and CSF pulsations are reduced, which is favorable for further application of MRS in the investigation of intramedullary tumors.

Cervical Spondylosis

In cervical spondylosis, significantly elevated Cho/Cr was shown in patients with compressive myelopathy and T_2 signal abnormalities. In patients with missing T_2-hyperintensity, slightly elevated Glx and mI were detected. All patients showed increased Cho/NAA indicating destructive processes represented by ongoing axonal loss, metabolic dysfunction, and increased membrane turnover.[67] In cervical spondylosis with cervical myelopathy (CSM), reduced NAA/Cr but no differences in Cho/Cr have been observed.[41,68] More experience is needed to better understand the role of ischemia in the pathogenesis of CSM. In another study, the combination of diffusion MRI and MRS in the spinal cord has been suggested as a promising approach to predict neurologic impairment in patients with CSM.[69]

An overview of spectra in various diseases is illustrated in Figure 4. Different pathologies such as multiple sclerosis, neoplasms, and traumatic injury show specific metabolic fingerprints.[30]

Outlook

Further methodological developments are needed for the establishment of spinal cord MRS as a clinical tool in the evaluation of patients with myelopathies. Faster acquisition protocols to overcome patient motion during long acquisition measurements are required. More sophisticated coils to achieve higher signal-to-noise ratio (SNR) would increase spectral quality, enable the detection of small concentration metabolites, and reduce the scan duration.

Moreover, the ease of handling of the examination protocol as well as the processing pipeline should reach a certain level to become end-user friendly, and thus be applied in the daily clinical routine.

The ability to measure the absolute concentration values of the metabolites[47] is another challenging and fascinating aspect because the concentration levels of certain referencing metabolites such as Cr are not stable in many pathologies.[70] Besides, the segmentation of the spinal cord in white and gray matter parts with highly resolved imaging sequences (although limited by the small cross-sectional dimensions of the cord and the coarse spatial resolution of the method) might help to improve the absolute concentration values in different tissue types.

Furthermore, scientific (multicenter) studies enrolling a large amount of patients should be conducted to increase our experience regarding the specificity and sensitivity of the biochemical information provided by MRS in various disease processes primarily arising from or secondarily affecting the spinal cord.

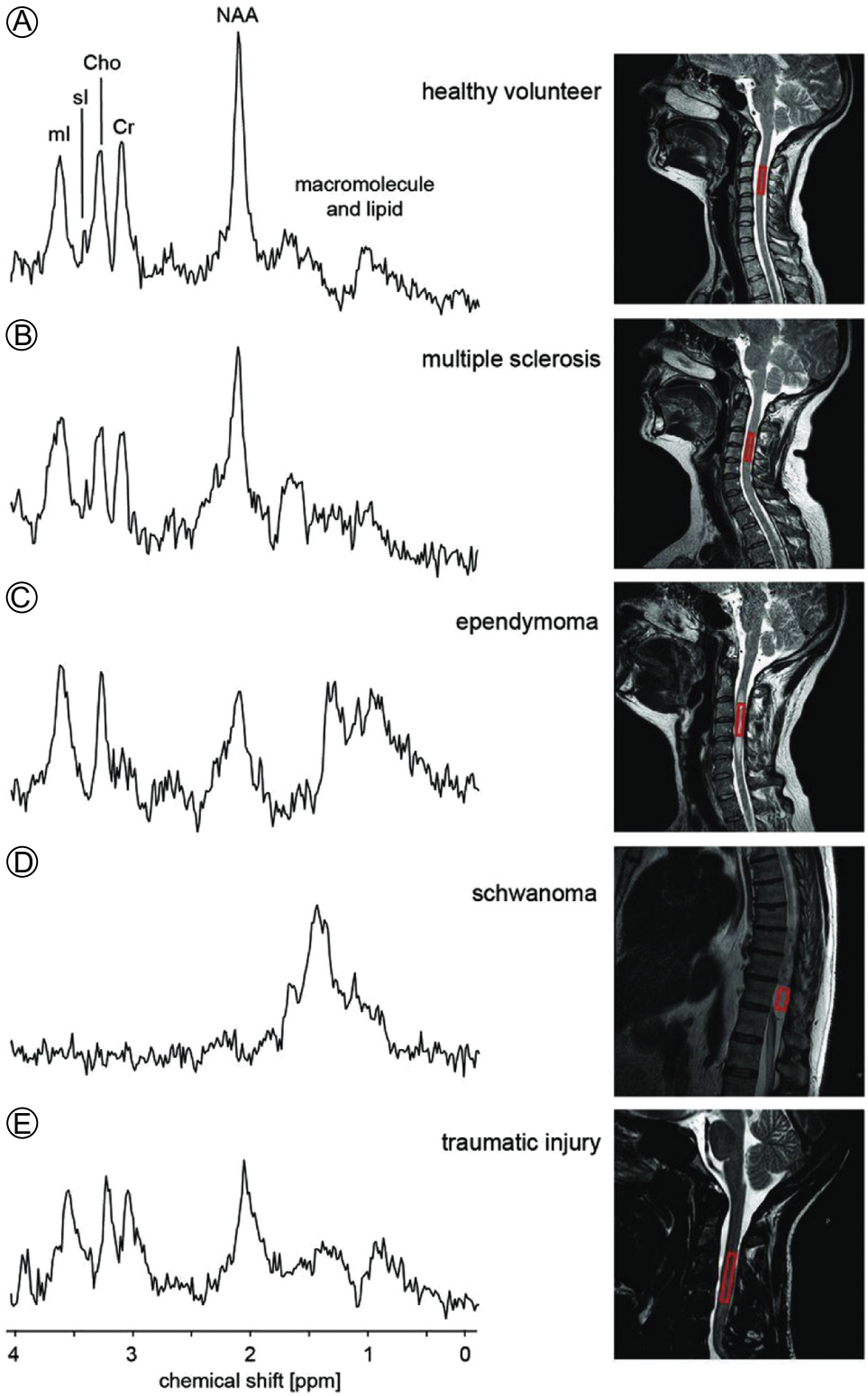

Figure 4 Metabolic fingerprint of different pathologies in the spinal cord. Different pathologies, such as multiple sclerosis (MS), neoplasms, and traumatic injury, show specific metabolic fingerprints. (Reprinted with permission from Hock et al.[30])

Conclusions

Early diagnosis and accessing supplementary vital information is important to provide accurate therapy decisions. In addition to the standardized structural and diffusion images of the spinal cord, MRS can provide chemical-pathological information of a disease. Therefore, MRS is a potentially useful tool for the exploration of pathophysiological mechanisms of various disease processes affecting the spinal cord and provides possible implications for early diagnosis and disease management.

Acknowledgments

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