Appendix E1: Technical Considerations for Clinical MR Spectroscopy

Data Acquisition

Choice of Pulse Sequence

When acquiring clinical MR spectroscopy data, the first decision is between single-voxel spectroscopy and MR spectroscopic imaging. Single-voxel spectroscopy enables robust metabolite quantification, with all acquisition parameters optimized for the volume of interest—in particular B_0 homogeneity and B_1 field strength. MR spectroscopic imaging, on the other hand, enables simultaneous assessment of large regions of interest in the brain. When choosing between single-voxel spectroscopy and MR spectroscopic imaging, the time needed to acquire a water reference image must be considered (if "absolute" concentrations are desired). Acquisition of a water reference substantially increases the imaging time in MR spectroscopic imaging unless acceleration techniques are used (178–182). The expected amount of motion is also important: A single-voxel spectroscopy acquisition can be aborted if the subject moves and the data used if the SNR is sufficient, whereas MR spectroscopic image acquisition cannot be interrupted without losing the entire data set. If the clinical question focuses on one metabolite, such as γ-aminobutyric acid, and if the volume of interest can be relatively large (at least 15 mL), one of several spectral editing techniques can be used to quantify the metabolite of interest without other overlapping signals (183).

Regarding the choice of specific pulse sequences, the basic PRESS (1,2) and STEAM (3) sequences are available as standard sequences on all clinical imaging units. In addition, optimized short TE STEAM (184), LASER (localization by adiabatic selective refocusing) (185), semi-LASER (67) (Fig 10), SPECIAL (spin-echo full-intensity acquired localized) (22), MEGA-PRESS (183), and PRESS+4 (186) sequences have been implemented by researchers on some clinical platforms. These offer advantages over the basic PRESS and STEAM sequences, such as sharper voxel and/or section profiles, more efficient water suppression, and smaller chemical shift displacement errors (the spatial displacement of the localized volume for metabolites at different chemical shifts). For MR spectroscopic imaging, various two- and three-dimensional techniques have been developed to suppress artifacts, increase volume coverage (182,187,188), and reduce the long imaging times (178–182). However, these state-of-the-art single-voxel spectroscopy and MR spectroscopic imaging sequences, which provide high-quality data and substantial time savings, are not currently commercially available. Some of these sequences can be obtained by means of the customer-to-customer sequence transfer route or as work-in-progress packages directly from vendors.

Last, physiologic and subject motion can lead to signal cancellation and line broadening and, therefore, may hamper acquisition of robust clinical MR spectroscopic data. Several procedures have been suggested to overcome motion artifacts, including prospective control or real-time update of the spectroscopy voxel position (189–191) and retrospective shot-per-shot frequency and phase correction before averaging (14,190,191). Issues related to subject motion are expected to be minimized, if not eliminated, with such techniques.

Choice of Hardware: Field Strength and Radiofrequency Coils

Theoretic considerations suggest that SNR should increase approximately linearly with increasing field, leading to a twofold higher SNR at 3.0 T compared with 1.5 T (18,192). However, some factors adversely affect SNR and resolution as field strength increases, in particular shorter in vivo T2 and T2* and longer T1 relaxation times (193). In fact, an almost linear increase in metabolite line widths occurs with increasing field strength (18,23). Therefore, although spectral quality at 3.0 T is superior to that at 1.5 T (given optimal spectral quality at each field), improvements in both SNR and spectral resolution are somewhat less than predicted by simple theoretic considerations in some studies (194,195). The greatest improvement is for the harder-to-detect metabolites with coupled spin systems; compounds such as Glu, Gln, and γ-aminobutyric acid are more accurately determined with increasing field strength (22,23,196). To achieve maximum benefit, optimal shimming methods to improve magnetic field homogeneity over the region of interest (197,198) are crucial at high field strengths owing to increased magnetic susceptibility effects. In addition, chemical shift displacement and excitation nonuniformity at 3.0 T are more severe than at 1.5 T, requiring high bandwidth refocusing pulses (67) and careful consideration for planning and analysis.

Note that the field strength alone does not determine the SNR: other aspects of the hardware, in particular the radiofrequency coils used for both transmission and reception, are critical for optimal sensitivity. Clinical MR imaging systems are typically provided with a body coil for transmit and an array of receiver elements to enable state-of-the-art MR imaging. The use of 32 (or more) channel receive-coil arrays can boost SNR, particularly for cortical regions close to the surface of the brain (199). For MR spectroscopy, the maximum achievable B_1 determines the localization accuracy and the minimum attainable TE. Local single or multichannel transceiver head coils (200) and pulse sequences designed to deal with limited B_1 (67) can be used to overcome transmit B_1 limitations at high field strengths.

Spectral Artifacts and Quality Assessment

Common artifacts (164) in MR spectra include signals with unusual phase appearance (eg, out-of-volume lipid signals or “ghost” signals from spurious echoes), lines that are too broad (owing to motion or shimming failures) or too narrow (ghosts, eddy current effects, external radiofrequency), or inappropriately large residual water signals.

The human expert is needed to control spectral quality in most applications of single-voxel spectroscopy, although automatic detection of compromised spectra has been proposed for specific settings (201). Artifacts can be identified by visual inspection of spectra that are analyzed with software provided with clinical MR units. In addition, more sophisticated research packages estimate errors for metabolite quantification, for example, Cramér-Rao lower bounds. Two times the Cramér-Rao lower bounds provides an estimate for the 95% confidence interval of the metabolite concentration. Therefore, metabolites quantified with Cramér-Rao lower bounds greater than 50% are considered unreliable, whereas quantification with Cramér-Rao lower bounds less than 20% is considered most reliable.

For quality assessment of MR spectroscopic imaging data, automated spectral analysis methods are important because visual evaluation of each and every spectrum (>2000 for volumetric studies) is impractical. Cramér-Rao lower bounds apply equally to MR spectroscopic imaging data, although additional considerations are required in studies that include regions with no metabolite signals, for example, from necrosis. A quality map, namely an image that indicates the relative weight that an observer (or automated analysis routine) can place on different

regions, is of particular value for such cases (180). Additional quality assessment methods that account for the presence of unsuppressed water or lipid resonances (202) can also be incorporated to generate a more comprehensive quality map.

Data Analysis, Display, and Interpretation

Data Processing and Metabolite Quantification

MR spectroscopy data require processing before quantification to remove line-shape distortions (203–205) and, if present, residual water and lipid signals (206,207). Additional processing should be minimized to avoid adding bias to the data. Most current fitting algorithms account for zero and first-order phase.

The peak area in the MR spectrum is proportional to the metabolite concentration (more precisely its proton equivalent) weighted by T1 saturation, T2 attenuation, and J-modulation for coupled spin systems. Most fitting algorithms are fully automated and, in commonly available research packages, quantify metabolites by fitting the measured in vivo spectrum to a linear combination of spectra of individual metabolites. This set of model spectra, the so-called "metabolite basis set," must be generated for the field strength, pulse sequence, and acquisition parameters used, either by acquiring spectra of individual metabolites in solution (208,209) or by simulating spectra based on known chemical shifts and coupling constants (210). Spectra can be fitted in the time domain (208,211,212), in the frequency domain, or in a hybrid of both domains (166,213–215). In addition, the baseline and macromolecule contributions in short TE spectra should be taken into account during the fitting procedure (21,208,209,216). The quality of a fit should be carefully assessed by examining the residual signal and the Cramér-Rao lower bounds.

Ratios, Absolute Tissue Concentrations, and Signal Normalization

To report the results of spectral quantification, the areas of metabolite peaks must be normalized by using a reference signal. "Absolute" (ie, molar) tissue concentrations can be obtained by taking ratios to the water signal acquired from the same volume of interest as long as relaxation effects are either minimized or taken into account and the water content of the volume of interest is known. The advantage of absolute metabolite concentrations is that such quantitative biochemical measures can be compared between patients, different brain regions, and across instruments. The drawbacks are *(a)* the need for a water reference, which adds to measurement time, and *(b)* the need to account for T1 saturation, T2 relaxation, and water content of the volume of interest. For single-voxel spectroscopy studies, T1 and T2 effects can be minimized by using long repetition times and short TEs, and a water reference image adds a single spectral acquisition (few seconds). For short repetition times and long TEs, if accurate measurements of T1 and T2 are not available and therefore prevent the correction of metabolite concentrations for these effects, care should be exercised when interpreting "absolute" concentrations. The water content within a volume of interest mainly depends on the relative contributions of white matter, gray matter, and cerebrospinal fluid with regional variations known for different brain regions (217,218), whereas cerebrospinal fluid contributions to the volume of interest can be quantified by using spectroscopy (219) or co-aligned image segmentation (220). It is therefore relatively straightforward to account for the water content of the volume of interest for absolute quantification; however, this level of specification is often not implemented in the MR

spectroscopy tools available on standard units and also more challenging for focal lesions (eg, regions of edema or necrosis).

Normalization based on taking metabolite ratios to tCr has been widely used because it is a relatively easy to obtain and robust measure that requires no additional assumptions once normative values are known for the volume of interest. However, tCr levels may change in neurologic diseases (116,132); therefore, changes in the ratio should not be assumed to reflect solely a change in the numerator. Notably, with Cr forming a key basis for the buffering of adenosine triphosphate, ratios to tCr can be informative for distortions in bioenergetic processes (221).

An alternative normalization method is to perform signal normalization, typically using the tissue water signal as a reference, but without correction for relaxation or water content measurement. The resultant measure is commonly referred to as being in "institutional units" (222) and is only valid for comparisons to data obtained with the identical measurement parameters and volumes of interest with similar tissue composition (or after correction for cerebrospinal fluid spaces and gray and white matter composition). For MR spectroscopic imaging, this represents a practical alternative to absolute quantification and enables calculation of images that represent differences from normative values (223) under the assumption of no changes in tissue water content or relaxation times.

Data Interpretation

For proper interpretation of MR spectroscopy data, reference data sets from the same brain region with the same degree of relaxation weighting in age-matched healthy subjects are needed for meaningful comparison to patients. If normative data from literature are used, local replication must be initially assured. In addition, correct interpretation of MR spectroscopy outcomes requires attention to the following potential pitfalls (11,164): *(a)* effects of differences in tissue composition (eg, gray and white matter) between subjects or volumes of interest in longitudinal studies, *(b)* effects of spectral artifacts and inappropriate data processing, *(c)* influence of incorrect quantification standards, *(d)* wrong interpretation of signals in MR spectroscopic imaging (eg, asymmetries due to chemical shift artifact, overestimation of the effective spatial resolution, underappreciation of the effects of the point spread function), *(e)* unusual spectral features (eg, peaks from medication), and *(f)* overinterpretation of results (neglecting measurement uncertainties, limits of reproducibility, and interindividual variability).

Translation to Routine Use in the Clinical Environment

Integration with Clinical Imaging

To facilitate translation of MR spectroscopy into routine use in the clinic, a seamless integration with the standard work flow is necessary. From an operator point of view, this starts with planning the actual volume or region of interest that might be done automatically on the basis of contour recognition or inheriting geometry information from previous images (224,225). Naming conventions and positions of all parameters should be as similar to imaging as possible. During patient examination, switching back and forth between MR spectroscopy and MR imaging sequences should be as smooth and flexible as it is between conventional imaging sequences. For an optimal work flow, all preparation phases should be automatic, with minimal operator interference and, where possible, based on previous (imaging) parameter settings to prevent any

redundancies in setup times. Finally, processing of the acquired information should be automated and easy to interpret by using standardized tabular forms (167) and, in the case of MR spectroscopic imaging, well-defined metabolic maps that can be compared and/or overlaid with other acquired MR imaging data.

Quality Management

In clinical MR spectroscopy studies, it is important that the quantitative metabolite measures are not confounded by variations in the MR imaging and spectroscopy hardware and software. These nonbiologic sources of data variation can be minimized with procedures for quality assurance, which prospectively aims to avoid production of poor quality data, and retrospective quality control to identify poor quality data (226–228). The selection of specific quality assurance and quality control procedures will depend on many factors, including the nature of the outcome measures (eg, ratios or absolute concentrations), the expected effect size and measurement precision, the duration of the study, and the diversity of systems, sites, and operators used to perform the MR spectroscopy measurements (228–230).

For the least complex studies, quality assurance procedures may be as simple as using the built-in quality testing of the MR imaging unit to verify system stability. Regularly performing MR spectroscopy–specific tests with a dedicated and stable phantom can help identify system and/or operational failures and provide a lower limit for the expected variation of in vivo measurements (231). For multisite studies (Fig 10), it is highly recommended that regular tests in phantoms and/or human subjects be performed at each site and that consistent performance metrics are met before subject accrual. Such prequalification procedures are even more crucial if the sites use imaging units from different manufacturers, with a range of field strengths and coils.

Regardless of study complexity, a consistent quality control should be applied uniformly to all data before inclusion in final analyses. The assessment should be based on quantitative quality metrics, such as SNR, line width, and Cramér-Rao lower bounds, as well as subjective identification of artifacts (164) by a reader with experience and training in MR spectroscopy. In studies with large data sets (eg, MR spectroscopic imaging), operator-independent automatic data processing including quality control (201) is recommended for greater efficiency and consistency. In multisite studies, centralized data analysis is recommended for consistency.

Reimbursement

Reimbursement of MR spectroscopy examinations is not an issue in many countries, for instance payment for MR spectroscopy is available in most European countries for numerous clinical indications. Although Medicare in the United States has determined MR spectroscopy to be investigational, other insurance carriers (232) reimburse MR spectroscopy for tumor diagnosis under CPT 76390, the current procedural terminology code (CPT-4) for MR spectroscopy. Some insurance carriers also reimburse for MR spectroscopy of inborn errors of metabolism and leukoencephalopathies. Strategies that encourage reimbursement include preauthorization, separating MR spectroscopy reports from MR imaging reports, and vigorously challenging denials of payment. The recommended reimbursement for MR spectroscopy (clinical read plus technical fees) set by the Centers for Medicare and Medicaid Services in 2011 is 10.78 relative value units, equivalent to $572.42 (233). With shorter imaging times, this rate of reimbursement for MR spectroscopy may compensate for those examinations deemed useful by ordering physicians, but that are not reimbursed.

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