Acquisition and Processing of Meaningful MRS Data

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1. Introduction

The acquisition of 'meaningful' MRS data is, for the majority of applications *in vivo*, synonymous with the acquisition of quantitative MRS data. Expression of the information content of MR spectra in molar (mmol/L) or molal (mmol/kg) units is crucial to exclude the contributions from NMR parameters like T_1 and T_2 relaxation and RF coil sensitivity thereby allowing a direct comparison of the tissue metabolic profile between different populations, studies and laboratories. MRS data must adhere to a number of criteria to be fully quantitative. These criteria include a high spectral resolution, a high spectral sensitivity, the minimization or correction of relaxation effects, the absence of random or systematic artifacts and accurate knowledge of the spatial origins. This syllabus will summarize the MRS acquisition steps required to obtain ^{1}H MRS data from brain that can be quantified by subsequent processing algorithms.

2. Acquisition strategies

2.1. Spatial localization

Accurate and high-quality spatial localization is arguably the most important step in obtaining quantitative, artifact-free ^{1}H MRS data. Despite the fact that ^{1}H MRS of the entire human brain can, in principle, be quantitative, it is typically not performed because (1) the spectrum would be dominated by intense, unwanted signals from lipids in the skull, (2) the B_0 magnetic field homogeneity across the entire brain is typically poor, leading to broad MRS signals, (3) the B_1 magnetic field homogeneity is equally poor, leading to artifacts due to imperfectly-calibrated RF pulses and (4) the MRS signal is not specific and holds contributions from many different cerebral areas and tissue types. The primary function of spatial localization is to limit the acquired signal to a well-defined spatial position (e.g. hippocampus), thereby simultaneously excluding all unwanted signals (e.g. lipids). However, the secondary effects, namely the improvement in B_0 and B_1 magnetic field homogeneity over the smaller volume, are equally important. Spatial localization does not affect the intrinsic quantitative nature of MRS; it simply creates more optimal conditions under which quantification becomes more accurate and robust. For single-volume MRS there are several spatial localization methods that are equally suitable, most noticeably being STEAM (1), PRESS (2) and LASER (3,4). While each technique has specific considerations, they can all be set up in such a way that the resulting MRS data is quantitative in nature (i.e. the spectral intensity is directly proportional to the number of spins and thus the concentration). Special care should be taken to ensure that signal from outside the volume is completely destroyed/crushed, as any remaining signal is typically variable in nature, leading to random, non-reproducible artifacts.

2.2. Water suppression

A problem specific to ^{1}H MRS is the presence of a large, dominant water resonance. Given that water is present in the 40-50 M range, whereas metabolites occur in the mM range, the water resonance is typically 5 to 6 orders of magnitude larger than the metabolite resonances. This can lead to several undesirable effects, including (1) a limitation of the receiver dynamic range for metabolites, (2) the presence of a strong baseline and (3) the presence of sidebands originating from gradient vibrations and other temporal B_0 variations. All of these effects can make the quantification of metabolite signals difficult, if not impossible. As a result, water suppression is normally a standard pulse sequence element for ^{1}H MRS. While water suppression does not have to be perfect, as small residuals can be removed post-acquisition, it must be good enough to not significantly affect the receiver gain setting or spectral baseline and should not introduce spurious spectral sidebands. Typical water suppression methods are based on frequency-selective excitation or refocusing in combination with magnetic field gradient signal spoiling (5-7).

2.3. Magnetic field homogeneity

Besides spatial localization and water suppression the optimization of magnetic field homogeneity is crucial for reproducible and quantitative ^{1}H MRS. Since the majority of ^{1}H NMR resonances fall inside a very narrow chemical shift range (1-4 ppm), spectral overlap of resonances is the rule, even at high magnetic fields. Any additional broadening of the resonances by magnetic field inhomogeneity thus leads to increased spectral overlap which ultimately translates into a decreased accuracy of the obtained concentrations. For ^{1}H MRS of small, single volumes, the use of first-and second-order spherical harmonic shims is perfectly adequate, which can be determined and set in a matter of seconds with the FASTMAP algorithm (8). For ^{1}H MRS of larger volumes or for ^{1}H MR spectroscopic imaging, higher-order shim fields or alternative shimming strategies, like dynamic (9), passive (10) or local active (11) shimming may be needed to achieve an adequate magnetic field homogeneity.

2.4. Other considerations

While accurate and reproducible spatial localization, water suppression and high magnetic field homogeneity are the most crucial factors to obtain high-quality ^{1}H MRS data, there are additional considerations can come into play under specific conditions. For example, when MRS signal is acquired and averaged over time in the presence of a drifting main magnetic field or in the presence of macroscopic motion, the resonances are broadened. This can be prevented by acquiring the signal from each excitation separately and then performing a post-acquisition frequency alignment before adding the signals.

3. Processing strategies

Once the MRS data has been acquired, it will need to be processed further in order to obtain the absolute metabolite concentrations. The concentration is proportional to the area underneath the metabolite resonances. Unfortunately, integration or simple line fitting are not suitable since many ^{1}H NMR resonances are partially overlapping and have highly complex splitting patterns.

Over the last decade, the LCmodel algorithm (12) has been shown to be highly effective in quantifying the resonance areas in ^{1}H MR spectra. LCmodel approximates the measured ^{1}H MR spectrum with a *L*inear *C*ombination of *model* solution spectra of the pure compounds. Since the model solution spectra are measured with the same pulse sequence as used *in vivo*, many of the spectral features like J-coupling, chemical shifts, spectral distortions and localization errors will be identical. Allowing for small frequency shifts and line broadening allows the *in vivo* ^{1}H MR spectrum to be well approximated by the sum of the included model spectra. It is important that all metabolites that are present *in vivo* are included in the algorithm, since exclusions will lead to systematic bias. A significant fraction, namely the macromolecular baseline, of the *in vivo* ^{1}H MR spectrum cannot be approximated by *in vitro* model solutions. This baseline needs to be measured in a separate experiment in which the large difference in T_1 relaxation between macromolecules and metabolites can be utilized to 'null' the metabolites.

Once the metabolite areas have been established, they have to be compared to an internal or external reference of known concentration. Due to significant B_1 field variations the use of external concentration references is not recommended for ^{1}H MRS. Suitable internal concentration references include water and the sum of creatine and phosphocreatine.

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