Cost effective, high performance MRS screening of rodents

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Magnetic Resonance Spectroscopy (MRS), has become a powerful tool for screening changes in transgenic animals and to follow progressive pathology and treatment response. It has been shown already more than a decade that highly accurate and reproducible profiles of ≥18 brain metabolites can be obtained from the rat brain in high magnetic field strength (≥9.4T) when shimming, pulses sequence and hardware are carefully optimized (Pfeuffer et al. 1999). Practically equal spectral quality can be obtained also from mice when dedicated high performance high-order shimming is applied (Tkac et al 2004). When considering applications in pre-clinical drug research not only performance but also cost-effectiveness is an important factor. Typically relatively robust changes in MR spectra are used as markers for disease progression and possible treatment effects. Therefore some compromises to reduce cost can be made, while still maintaining high spectral quality and sensitivity to detect treatment effects.

The most fundamental factor affecting the costs and design of the MR system is the choice of the magnet. While horizontal large-bore (30 cm) high magnetic field (≥9.4T) magnets and dedicated gradient/shim coils have been used to obtain the best spectral quality, the price of these systems is many fold compared to standard 7T/16cm MRI systems that still can produce a good quality MRS if the setup is correctly optimized. With the current gradient technology, the 16 cm space inside the magnet is enough to provide the gradient strength required to avoid chemical shift displacement, eddy current compensation and sufficient shimming power. It should be noted that chemical shift displacement and magnetic field inhomogeneities scale with magnetic field strength, and therefore the requirements for gradient and shim hardware are somewhat more relaxed in 7T compared to 9.4T or higher.

The next hardware component to consider is RF-coil. The best spectral quality has been demonstrated using local quadrature transmit receive RF-coils. They provide excellent receive sensitivity, contributing to high S/N ratio, and also produce high B1+ fields making it possible to use high bandwidth pulses required to minimize chemical shift displacement in localization of the voxel. The drawback of these coils is that the B1+ is inhomogeneous, requiring extra calibration steps/factors, such as optimizing the outer volume suppression pulses that are placed around the voxel and therefore have different distances from the coil. B1 inhomogeneity is also one of the reasons (together with ultra short echo time) why the STEAM pulse sequence has been mostly used to obtain the ultra high quality spectra, as 180 degree pulse profiles are more influenced by flip angel inaccuracies than 90 degree pulses. One pulse sequence that avoids the aforementioned problems is LASER (Garwood and DelaBarre 2001), which is a modification of PRESS that uses pairs of adiabatic full passage RF-pulses to produce B1-insensitive refocusing with excellent pulse profiles, but has longer echo time. While the best spectral quality has been demonstrated using surface coils with high magnetic field strength in brain structures close to the coil, the surface coil approach is suboptimal for imaging experiments that require full brain coverage. Typical preclinical MR protocol contains both imaging and MRS components which are equally important and therefore a combination of actively decoupled volume transmit coil and local quadrature receive coil provides often a good compromise for both imaging and spectroscopy requirements. Modern MRI consoles are equipped typically with a high power RF amplifier (~1kW) that provides sufficiently high peak B1 and therefore large bandwidth to keep chemical displacement in the acceptable level at 7T, and also when a volume transmit coil is used. Homogenous B1 simplifies RF calibration and also makes PRESS, which theoretically provides 2 times more signal than STEAM with equal echo time, a feasible option.

The aforementioned selection of the hardware and software (pulse sequence) for MRS cannot be discussed as separate entities, but for an efficient and cost effective solution both components has to be taken into account. The fundamental step for high performance spectroscopy is always shimming. To obtain the good spectral quality automated shimming of at least first and second order shims must be performed. The most often used approach for high quality single voxel spectroscopy is FASTMAP (Gruetter 1993). As it is based on measurement of projections instead of full B_0 field map, excellent shimming results (water line widths of 9-12 Hz at 7T) can be obtained in less than a minute. Field map based approaches take typically a few minutes and can provide comparable shimming results and work even better in imaging applications.

Finally, spectra have to be analyzed in automatic and non-biased way. Keeping the echo time short in the acquisition helps to avoid contributions of relaxation and J-modulation to the quantification. There are several software packages available for fitting the spectra in either time or frequency domain. LCModel (Provencher, 1993) is one of the most commonly used approaches that fulfill the aforementioned requirements.

In the presentation, the aforementioned issues will be discussed using R6/2 mouse model of Huntington's disease in pre-clinical drug trials as an example. In Huntington's disease the most commonly used MRI and MRS markers for disease progression include time dependent volumetric changes in striatum and decrease in NAA accompanied by increase in Cre, Cho, Glu in striatal voxels. Spectral quality and reproducibility over several years and hundreds of animals will be demonstrated in the relatively low cost 7T MRI system using standard hardware components and minimally modified software components.

References:

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