Ultra-small voxel spectroscopy

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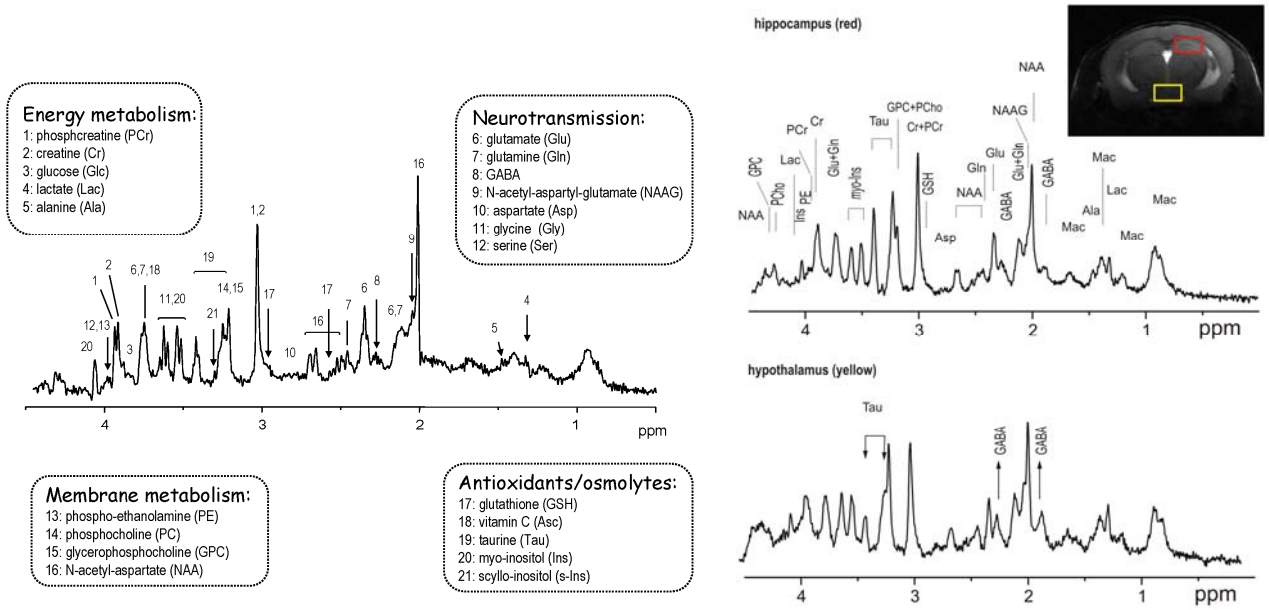
Spectroscopy of the mouse presents several challenges: The small size of the animal implies that the measurement location is typically close to the susceptibility interface between the diamagnetic mouse and paramagnetic oxygen in air and it implies small VOI on the order of µl to localize to functionally distinct regions, which represents a challenge for sensitivity.

For most localized spectroscopy applications contemporary shim coil designs permit elimination of much of the macroscopic susceptibtility effects in mouse brain. These advances are likely to be of benefit to mouse imaging in general: For example, ***higher-order shimming*** has been shown beneficial for imaging sequences that are prone to such susceptibility effects, such as single-shot gradient echo EPI.

Sensitivity can be optimized: Using e.g. ***quadrature surface coils*** at least for reception allow to greatly improve sensitivity and thus reduce acquisition time compared to using volume coils as transceivers which incurs sensitivity losses, due to the small filling factor of the mouse brain.

Sensitivity has been shown to improve substantially when using ***high magnetic fields***, combined with short echo times, allowing the measurement of the neurochemical profile in functionally distinct brain regions, as illustrated for mouse hypothalamus, shown in the Figure below:



Left: Neurochemical profile and its over 20 biomarkers accessible in rodent brain. **Right:** ^{1}H NMR spectroscopy of 4µl volume of the hypothalamus at 14.1 Tesla compared to 3µl volume measured in the hippocampus using SPECIAL localization (TE=2.8ms). In both locations, more than 20 constituents of the neurochemical profile were quantified with a precision better than 30%. Note the comparatively low taurine and the high GABA content in the hypothalamus (arrows), both hallmarks of the neurochemical profile in rodent hypothalamus. Data was acquired using a 10mm quadrature surface coil as transceiver.

Clearly, a spatial resolution allowing the measurement of a comprehensive ***neurochemical profile*** is feasible in functional regions of the mouse brain: Examples to-date include, but are not limited to stroke, cancer models, and a plethora of transgenic models.

These approaches can be extended to µl spatial resolution using ***chemical shift imaging***, which is a spatial resolution comparable to what is achievable with animal PET imaging.

Summary: The measurement of the neurochemical profile with microliter spatial resolution is routinely achieved in murine brain, allowing for a quantitative measurement of more than 20 biomarkers, covering membrane metabolism, energy metabolism, neurotransmitters, antioxidants and osmolytes (Figure 2).
Such a highly quantitative, sensitive approach is likely to yield important insights into the function of many genes and mouse models of disease.

Suggested reading:

Review articles

1. Choi IY, Lee SP, Guilfoyle DN, Helpern JA (2003) In vivo NMR studies of neurodegenerative diseases in transgenic and rodent models. *Neurochem Res* **28**, 987-1001
2. Choi JK, Dedeoglu A, Jenkins BG (2007) Application of MRS to mouse models of neurodegenerative illness. *NMR Biomed* **20**, 216-37

Advances in methodology

3. Tkac I, Henry PG, Andersen P, Keene CD, Low WC, Gruetter R (2004) Highly resolved in vivo 1H NMR spectroscopy of the mouse brain at 9.4 T. *Magn Reson Med* **52**, 478-84
4. Mlynarik V, Gambarota G, Frenkel H, Gruetter R (2006) Localized short-echo-time proton MR spectroscopy with full signal-intensity acquisition. *Magn Reson Med* **56**, 965-70
5. Miyasaka N, Takahashi K, Hetherington HP (2006) 1H NMR spectroscopic imaging of the mouse brain at 9.4 T. *J Magn Reson Imaging* **24**, 908-13
6. Koch KM, Brown PB, Rothman DL, de Graaf RA (2006) Sample-specific diamagnetic and paramagnetic passive shimming. *J Magn Reson* **182**, 66-74
7. Mlynarik V, Kohler I, Gambarota G, Vaslin A, Clarke PG, Gruetter R (2008) Quantitative proton spectroscopic imaging of the neurochemical profile in rat brain with microliter resolution at ultra-short echo times. *Magn Reson Med* **59**, 52-8
8. Mlynarik V, Cudalbu C, Xin L, Gruetter R (2008) 1H NMR spectroscopy of rat brain in vivo at 14.1Tesla: improvements in quantification of the neurochemical profile. *J Magn Reson* **194**, 163-8

Application examples

9. Larvaron P, Bielicki G, Boespflug-Tanguy O, Renou JP (2006) Proton MRS of early post-natal mouse brain modifications in vivo. *NMR Biomed* **19**, 180-7
10. Tkac I, Dubinsky JM, Keene CD, Gruetter R, Low WC (2007) Neurochemical changes in Huntington R6/2 mouse striatum detected by in vivo 1H NMR spectroscopy. *J Neurochem* **100**, 1397-406
11. Broom KA, Anthony DC, Lowe JP, Griffin JL, Scott H, Blamire AM, Styles P, Perry VH, Sibson NR (2007) MRI and MRS alterations in the preclinical phase of murine prion disease: association with neuropathological and behavioural changes. *Neurobiol Dis* **26**, 707-17
12. Heerschap A, Kan HE, Nabuurs CI, Renema WK, Isbrandt D, Wieringa B (2007) In vivo magnetic resonance spectroscopy of transgenic mice with altered expression of guanidinoacetate methyltransferase and creatine kinase isoenzymes. *Subcell Biochem* **46**, 119-48
13. Simoes RV, Garcia-Martin ML, Cerdan S, Arus C (2008) Perturbation of mouse glioma MRS pattern by induced acute hyperglycemia. *NMR Biomed* **21**, 251-64