MRS in Neurosciences: Recent advances in in-vivo spectroscopy methods and applications at the Stanford Center for Cognitive and Neurobiological Imaging (CNI)

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Introduction

Discoveries about the brain have implications for fields ranging from Business, Law, Psychology, and Education. The Stanford Center for Cognitive and Neurobiological Imaging (CNI) is a shared research and teaching facility providing resources for researchers and students in cognitive and neuroscientific studies. The core instrumentation is a research-dedicated 3T MRI scanner integrated with a range of experimental devices for neuroscience studies.

The interest of measuring metabolic changes via MRS techniques and combining that information with functional MRI measurements in neuroscience studies continues to grow. CNI continues to support the research of its user community by developing and incorporating for general use new data acquisition and data analysis capabilities as recommended by the at-large MRS community. Through collaborative efforts, the special interest spectroscopy group at CNI has enabled education and participated in experimental design, guided analyses, and interpretation of results.

Examples of studies at CNI using in-vivo spectroscopy techniques include characterization of biomarkers following transcranial magnetic stimulation, and metabolite characterization for conditions such as addiction, pain, depression, and various forms of dementia.

Collaborative studies performed at CNI include method applications¹, new methods developments², and participation in multi-site spectroscopy studies³.

Data Acquisition and Processing Tools

Spectroscopy Sequences

The Stanford CNI effort has become a best practice through a community effort with spectroscopy expertise from CNI staff, MRI scientists, and an expanding user community. Current spectroscopy sequences (Table 1) include methods both for edited GABA (gamma-aminobutyric acid) specific data acquisition (MEGA-PRESS⁴ and IM-SPECIAL⁵), and for multi-metabolite data acquisition (Optimized-PRESS⁶⁷ and semi-LASER)⁸. Further sequences, such as semi-LASER⁹¹⁰¹¹, have been evaluated and added as data acquisition methods available to the CNI user community.

Semi-LASER is the ISMRM current consensus recommended method for multi-site 3T MRS studies¹²¹³. As a result we have transitioned studies at CNI to the semi-LASER sequence for both single voxel and most recently to MRSI studies. We present both single voxel and MRSI results using the semi-LASER sequence in challenging and therefore less well studied but important areas of the human brain. The need to acquire the highest quality data in order to measure small metabolite differences in subregions of interest has led to the selection and optimization of MRSI data acquisition methods.

Data Management

CNI uses Flywheel as its data storage and curation system which allows for integrated data acquisition and data processing to enable open-source processing and visualization tools for integration into Flywheel for the semi-LASER sequence which are currently under evaluation.

Methods and Techniques

For all spectroscopy research projects CNI actively follows the recommended best practices from the ISMRM Spectroscopy Study Group (https://srg.ismrm.org) and recently published experts consensus recommendations¹⁴⁻¹⁵.

The work to date shown here has been focused on optimal data acquisition aspects for focal 2D MRSI (Figures 3 and 4) and single-voxel MRSI (see Figure 5 below), which includes 80 shimming, encoding and acceleration methods, slice selection, water suppression, extracellular lipid signal, and RF performance.¹⁶ The optimal data acquisition parameters for pilot participants for focal 2D MRSI were 14 x 14 FOV 140 mm, 10 mm slice, for a subcortical region and 16 x 16 FOV 160 mm, 10 mm slice, for a cortical region that worked well for both genders and took into consideration outer-bank fold back artifacts, location of subcortical VOI with respect to ventricles, the usefulness of saturation bands, and SNR: higher order shimming of each VOI region was included.

A comparison of spectral quality in the left hippocampus single voxel region showing improved data quality thought the use of high order shimming. A: Linear shims only (UW-21). B: HOB 28 cm x 28 cm x 21cm 60 map acquisition volume with a 94 X 64 matrix (UW-12). C: HOS 28 cm x 28 cm x 21cm 80 acquisition volume with a 128 X 128 matrix (UW-93) DE WIP.

Basic data reconstruction and visualization currently employ SAGE, a GE proprietary analysis and visualization tool with LCMed and (2) improvement of the accuracy of the LCMed model are set by the addition and validation of experimental lower concentration metabolites (glutathione and ascorbate, as examples) to an otherwise synthetic LCMed basis set.

Segmentation (Figure 7) - To identify and correct for potential influences on neuroimaging estimates from different tissue amounts in each subvoxel, using percentage of gray matter as a covariate.

The next phase in this research project will emphasize additional optimizations of data collection and processing for optimal quantification of metabolites including -

- Use of automated magnetic resonance voxel placement tools for longitudinal studies in using the central coordinate of an MRS voxel collected previously for placement in the same individual during follow-up scan sessions.
- Evaluation of improved coil combination methods.
- Improvement in data processing pipelines (1) mitigation of baseline and macromolecular contributions for data analysis with LCModel and (2) improvement of LCModel fitting accuracy by adding and validating of experimental lower concentration metabolites (glutathione and ascorbate, as examples) to an otherwise synthetic LCMed basis set.

References

11. IM
12. LASER sequence in challenging and therefore less well studied but important areas of the human brain. The need to acquire the highest quality data in order to measure small metabolite differences in subregions of interest has led to the selection and optimization of MRSI data acquisition methods.
13. Table 1

<table>
<thead>
<tr>
<th>Spectroscopy Sequences</th>
<th>Measured Metabolites</th>
<th>Analysis Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEGA-PRESS⁴</td>
<td>GABA+, Glx (Glutamate, Glutamine)</td>
<td>Garmet⁵</td>
</tr>
<tr>
<td>IM-SPECIAL⁵</td>
<td>GABA, Glu (Glutamate), Glx</td>
<td>Sequence specific Matlab code</td>
</tr>
<tr>
<td>Optimized-PRESS⁶</td>
<td>All metabolites</td>
<td>Sequence specific Matlab code, LCModel fitting⁵</td>
</tr>
<tr>
<td>semi-LASER⁷⁸</td>
<td>All metabolites</td>
<td>Sequence specific Matlab code, LCModel fitting⁵</td>
</tr>
</tbody>
</table>

Data fitting of caudate (A) and globus pallidus (B) subregions of the basal ganglia region shown in Figure 4 demonstrating different metabolite patterns in the 3.5-4.2 ppm region (Myo-inositol, Glx, Creatine) and the 3.0-3.5 ppm region (Creatine, Choline).

A 3T MRSI VOI mask overlaid on gray and white matter segmented masks from a T1 image using FreeSurfer. Red = total segmented gray matter voxels of the T1; white = total segmented white matter voxels of the T2; yellow box = MRSI VOI acquisition location; gray boxes = 90 subvoxels masks within the VOI. Tissue segmentation was performed utilizing FreeSurfer 7.3.2 (2017-11-30) and is in-house code. Gray matter, white matter, and cerebral spinal fluid within each of the subvoxels shown

The evaluation of open-source processing and analysis tools with potential integration into Flywheel as gears.

The potential of Bayesian analysis in MRS