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## ORAL PRESENTATIONS

# Emerging metabolic imaging and spectroscopic methods to study neurodegenerative diseases

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Proton magnetic resonance spectroscopy ($^1$H-MRS) allows non-invasive assessment of the metabolic landscape of biological tissue. Despite demonstrating promising findings in clinical practice, single-voxel or single-slice two-dimensional $^1$H-MRS methods present a few challenges mainly related to limited spatial coverage and low spatial and spectral resolutions. In the recent past, the advent of more sophisticated metabolic imaging and spectroscopic sequences, such as three-dimensional echo-planar spectroscopic imaging (3D-EPSI), two-dimensional correlation spectroscopy (2D-COSY), and chemical exchange saturation technique (CEST) has revolutionized the field of metabolomics.

For the metabolic characterization of diffuse neurodegenerative diseases, whole brain coverage is essential for a comprehensive overview of the topography and understanding of the underlying pathophysiological processes. The 3D-EPSI sequence allows the acquisition of whole brain (volumetric) metabolite maps with high spatial resolution.[1] These metabolite maps can be co-registered to anatomical images for facilitating the mapping of metabolite alterations from different brain regions in a single session, thus providing the true spatial extent of a global disease. The potential of 3D-EPSI in characterizing several neurological and neurodegenerative disorders has been reported.

On conventional one-dimensional $^1$H-MRS, spectral peaks due to methyl, methylene, and methine protons from N-acetyl aspartate, glutamate, glutamine, gamma-aminobutyric acid, and taurine extensively overlap in the spectral region of 2-4 ppm, often confounding the reliable detection and quantification of these metabolites. In contrast, 2D-COSY offers unambiguous identification of potentially overlapping resonances by dispersing the multiplet structure of scalar (J)-coupled spin systems into a second spectral dimension,[2] especially at higher field strength[3,4] and by exploiting the unlikely possibility that two metabolites would share identical chemical shifts in two-dimensions. Due to technical limitations and long acquisition time, 2D-COSY sequence has not been widely used to study neurodegenerative diseases. However, future modifications would benefit from implementing faster acquisition schemes and improved spectral fitting methods for data analysis. We believe that these new approaches could make the clinical applications of the 2D-COSY sequence faster, easier, and more versatile.

CEST is a relatively novel metabolic imaging modality that allows the detection of specific exogenous and endogenous metabolites/molecules present at millimolar concentrations. Exchangeable solute protons present in chemical functional groups such as amide (-CONH), amine (-NH2) or hydroxyl (-OH) resonate at a frequency different from bulk water protons. These labile protons are selectively saturated using radiofrequency irradiation, which is subsequently transferred to the bulk water pool, leading to a decrease in the water signal intensity proportional to the concentration of solute molecules, number of labile protons and proton exchange rate.[5] CEST offers more than two orders of magnitude higher sensitivity compared to $^1$H-MRS in detecting metabolites such as glutamate, creatine, myoinositol and mobile peptides.[5] While amide proton transfer (APT) imaging has been investigated in various neurological disorders, other CEST imaging techniques such as glutamate-CEST, creatine-CEST have been performed only in preclinical or pilot clinical studies related to neurodegenerative diseases.

We believe that these newer developments in metabolic imaging techniques will have a significant impact in reshaping our understanding of biochemical profiles of various neurodegenerative diseases. However, standardization and harmonization of acquisition parameters are required for fast-tracking the implementation of these metabolic techniques into routine clinical workflow.

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