Project Title:	Development of Neuroimaging Biomarkers for Predicting Neurological Disorders 開發神經影像生物標記物以預測神經系統疾病
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Research Objectives

1. Monitor AD progression using dynamic CEST MRI in mouse models
2. Investigate the sensitivity of dynamic CEST MRI to detect the factors that alter the glymphatic functions

Precise and early diagnosis of neurological disorders (Alzheimer's, Parkinson's, and glioma) is often preferred but clinically challenging. The conventional metallic or ionic contrast image settings and radioactive tracers possess associated risks and are unbefitting for repeated measurements. Though MRI enjoys an upper hand in non-invasive imaging, the standard MRI fails to bring about the needed signal-to-noise ratio, suffers spectral overlaps, and is ineffective in monitoring molecular level alterations. However, the early progression of neurological disorders is often associated with molecular-level alterations. Monitoring the early molecular-level alterations could lead to effective diagnosis and therapy. Therefore, a comprehensive approach is required to bring forward a precise diagnosis at molecular levels, a cornerstone of clinical neurological diagnosis. The chemical exchange saturation transfer (CEST) MRI sequence is gaining considerable attention clinically because of the distinctive molecular MR technique brought via interaction between bulk water and labile solute protons (amide, amine, and hydroxyl).[1] The CEST is sensitive and specific to the unique chemical shifts at molecular levels, even at the solute concentrations at clinical field strength MRI.[2]

Over the years, the team has demonstrated CEST MRI for diagnosing neurological disorders using exo and endogenous agents.[2] For example, liposomes and hydrogel-based exogenous CEST agents were employed for tumor imaging.[3] The liposomes are usually tethered with drug molecules to bring out CEST properties for image-guided tumor therapy. Recently, the team explored the CEST-enabled hydrogels (chitosan–dextran and alginate hydrogels) with liposomes and drug molecules for label-free image-guided tumor therapy and to monitor tumor pHe changes during treatment (Fig. 1).

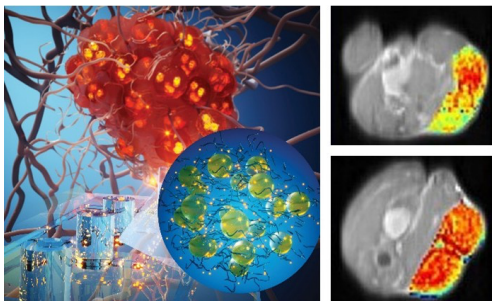

Fig. 1 CEST alginate microbeads (right panel) and CEST MRI of tumor (left panels)

Nevertheless, employing the exogenous agents questions the non-invasiveness of the CEST MRI. Since CEST MRI is sensitive to molecular alterations, employing endogenous molecules as CEST agents will put forward non-invasiveness and provide more detailed molecular-level alterations for early disease prediction. To advocate the non-invasiveness of CEST MRI, we focused on endogenous agents via various CEST parameters to monitor neurological changes. For example, Alzheimer's disease (AD) is recorded with the difference in cerebral glucose uptake, and such is distinctly detected in AD brain parenchyma and cerebrospinal fluid by dynamic glucose-enhanced CEST MRI.[4]

Recently, the team used a relayed nuclear overhauser effect (rNOE) CEST sequence to monitor neuropathological changes in myelin lipids/proteins.[5] The rNOE CEST MRI accentuates the myelin changes in the brain of multiple sclerosis patients. Besides, rNOE detected the molecular alteration of myelin lipid/protein after intracerebral hemorrhage (ICH). The rNOE enabled to monitor the myelin alteration during the treatment of hematoma in mice.

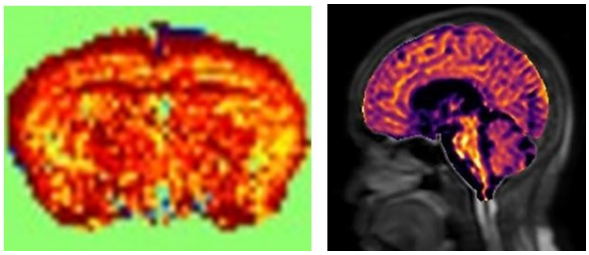

Fig. 2 DGE CEST of glucose uptake in AD mouse brain (right panel). rNOE CEST of myelin lipid/protein in multiple sclerosis patients (left panel)

As a foresight, the team will explore the non-invasiveness in monitoring the molecular level metabolic alterations during neurological dysfunction. Alongside, the age-related metabolic and pathological changes and the role of exosome vesicles in AD will be explored as diagnosing hallmarks. Nevertheless, obligatory initiatives will be laid to overcome the drawbacks of CEST MRI for clinical translation. Furthermore, considerable efforts will be put towards deep learning and artificial intelligence to skyrocket the clinical translation of CEST MRI. **(Potential treatment monitoring)**

Reference

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