Exploring the potential clinical application of CEST MRI in the diagnosis of Alzheimer's disease

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Synopsis

Motivation: CEST MRI has potential to image the molecular changes in the brain of Alzheimer's disease (AD).

Goal(s): Our objective was to evaluate the efficacy of CEST MRI in imaging AD and mild cognitive impairment (MCI) or non-AD dementia patients at 3T.

Approach: CEST MRI scans were conducted for 40 healthy volunteers and 22 MCI/AD/non-AD dementia patients. Other clinical assessments include PET scans to detect the amyloid plaques and Montreal Cognitive Assessment Hong Kong version (HK-MoCA) to evaluate the cognitive function.

Results: CEST revealed significant differences between HC and patient groups and exhibited strong correlations with the HK-MoCA score.

Impact: CEST revealed significant differences between HC and MCI/AD and exhibited strong correlations with the HK-MoCA score. CEST MRI has potential to detect molecular changes in brain, providing additional information for AD diagnosis in clinical MRI settings.

Introduction

Alzheimer's disease (AD) accounts for 60%-70% of all dementia cases and is widely recognized to be associated with the amyloid-beta (Aβ) peptide accumulated plaques and tau-containing neurofibrillary tangles[1,2]. An early and precise diagnosis of AD is essential for effective clinical intervention[3,4]. Positron Emission Tomography (PET) can detect the amyloid aggregation in AD[5], but its cost and reliance on radioactive tracers limit accessibility.

Chemical Exchange Saturation Transfer (CEST) MRI is an advanced molecular imaging modality which enables detecting in vivo proteins and metabolites through exchangeable protons[6-8]. Various CEST contrasts, including amide[9], relayed nuclear Overhauser effect (rNOE)[10], magnetization transfer (MT)[11], glucose[12], and guanidinium (Guan)[13], are believed to hold significant promise for investigating AD pathology and enhancing diagnostic capabilities.

This study aims to assess the effectiveness of CEST MRI in differentiating mild cognitive impairment (MCI) or non-AD dementia patients/AD from healthy controls (HCs), and investigate its correlation with amyloid burden and cognitive function.

Methods

The study was approved by the local institutional review board and consent form was obtained from all participants. Forty healthy volunteers and 22 patients diagnosed with MCI/Dementia were recruited for this study. CEST scans were conducted for all participants using a GE SIGNA Premier 3T MRI scanner. 18-F Flutemetamol amyloid PET scans were conducted for the patients within one week following the CEST MRI scans. Additionally, Montreal Cognitive Assessment Hong Kong version (HK-MoCA) tests[14], were administered to fifty-seven participants on the same day as the CEST scans.

The CEST sequence employed a continuous wave module with a saturation time of 2 seconds and a saturation power of 0.8 μT. M_0 images were acquired at a frequency offset of –300 ppm, along with 43 CEST images acquired at frequency offsets ranging from –20 to 20 ppm. Other parameters included: TR=3500 ms, TE=60 ms, slice thickness=6 mm, field of view (FOV)=220×220×72 mm^2, matrix size=256×256×12. The scanning time of CEST was about 8 minutes.

Three CEST post-processing methods were conducted using custom-written MATLAB codes, including multi-pool Lorentzian fitting (MPLF)[15] to extract signals of amide CEST at 3.5 ppm, rNOE at –3.5 ppm, and MT at –2.5 ppm; Lorentzian difference analysis (LDA)[16] to extract signals of amide, rNOE, and CEST at 2.0 ppm (CEST@2ppm); as well as magnetization transfer ratio asymmetry (MTR_{asym})[17] analysis to extract signals of amide and CEST@2ppm.

AD patients were classified into the amyloid-beta-positive (Aβ+) patient group, while patients with MCI or non-AD dementia were categorized into the amyloid-beta-negative (Aβ-) patient group. Cross-group analyses were conducted.

Current Results

The characteristics of the participants are summarized in Table 1. In CEST map comparison (Figure 1), the multiple CEST signals extracted using different methods in HCs exhibit more uniform patterns in brain tissues, while the signals in patients, especially Aβ+ patients, show a general reduction but with some patchy high-signal areas in certain brain regions.

In group comparison (Figure 2), the MT signal extracted from HCs using MPLF shows significantly higher values compared to both Aβ+ patients (P=0.0008) and Aβ- patients (P<0.0001). Similarly, the amide signal extracted from HCs using LDA is significantly higher compared to Aβ- patients (P=0.0001). Although this signal is also higher than that of Aβ+ patients, the difference does not reach statistical significance (P=0.6099). Furthermore, the rNOE signal obtained from HCs using LDA is significantly higher than that of both Aβ+ patients (P=0.0101) and Aβ- patients (P<0.0001). Additionally, the amide signal from HCs extracted using MTR_{asym} is significantly lower than that of both Aβ+ patients (P=0.0088) and Aβ- patients (P=0.0003). No significant differences are observed in CEST@2ppm among the three groups, and there are also no significant differences in CEST contrasts between Aβ+ and Aβ- individuals in the current small patient cohorts.

In the correlation analysis with the HK-MoCA score (Figure 3), all CEST signals extracted using three methods, apart from CEST@2ppm extracted by LDA, demonstrate a strong correlation with the HK-MoCA score. Specifically, CEST signals obtained through MPLF and LDA exhibit positive correlations with the HK-MoCA score, whereas CEST signals derived from MTR_{asym} display negative correlations.

Discussion and Conclusion

CEST contrasts extracted using three post-processing methods could differentiate MCI or non-AD dementia/AD patients from HCs. Moreover, the CEST signals exhibited strong correlations with the HK-MoCA score. These findings suggest that CEST MRI has the potential to assist in early AD

diagnosis. Current research efforts are directed towards regional analyses of common amyloid aggregation areas in AD patients, such as the frontal lobes, to further investigate CEST signals in the patients with and without amyloid burdens. Additionally, ongoing data collection from larger participant cohorts aims to validate the robustness of the current findings.

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References

1. Castellani, R. J., Rolston, R. K., & Smith, M. A. (2010). Alzheimer disease. Disease-a-month: DM, 56(9), 484.
2. Breijyeh, Z., & Karaman, R. (2020). Comprehensive review on Alzheimer's disease: causes and treatment. Molecules, 25(24), 5789.
3. Srivastava, S., Ahmad, R., & Khare, S. K. (2021). Alzheimer's disease and its treatment by different approaches: A review. European Journal of Medicinal Chemistry, 216, 113320.
4. Li, C., Zhou, J., Wang, D., Li, X., Jiang, S., Zhang, Y., ... & Chen, M. (2023). Amide proton transfer imaging of Alzheimer's disease and Parkinson's disease. Magnetic Resonance Letters, 3(1), 22-30.
5. Suppiah, S., Didier, M. A., & Vinjamuri, S. (2019). The who, when, why, and how of PET amyloid imaging in management of Alzheimer's disease—Review of literature and interesting images. Diagnostics, 9(2), 65.
6. Wolff, S. D., & Balaban, R. S. (1989). Magnetization transfer contrast (MTC) and tissue water proton relaxation in vivo. Magnetic resonance in medicine, 10(1), 135-144.
7. Guivel-Scharen, V., Sinnwell, T., Wolff, S. D., & Balaban, R. S. (1998). Detection of proton chemical exchange between metabolites and water in biological tissues. Journal of Magnetic Resonance, 133(1), 36-45.
8. Van Zijl, P. C., & Yadav, N. N. (2011). Chemical exchange saturation transfer (CEST): what is in a name and what isn't?. Magnetic resonance in medicine, 65(4), 927-948.
9. Wang, R., Li, S. Y., Chen, M., Zhou, J. Y., Peng, D. T., Zhang, C., & Dai, Y. M. (2015). Amide proton transfer magnetic resonance imaging of Alzheimer's disease at 3.0 Tesla: a preliminary study. Chinese medical journal, 128(5), 615-619.
10. Swain, A., Soni, N. D., Wilson, N., Juul, H., Benyard, B., Haris, M., ... & Reddy, R. (2023). Early-stage mapping of macromolecular content in APPNL-F mouse model of Alzheimer's disease using nuclear Overhauser effect MRI. Frontiers in Aging Neuroscience, 15, 1266859.
11. Huang, J., Lai, J. H., Tse, K. H., Cheng, G. W., Liu, Y., Chen, Z., ... & Chan, K. W. (2022). Deep neural network based CEST and AREX processing: Application in imaging a model of Alzheimer's disease at 3 T. Magnetic resonance in medicine, 87(3), 1529-1545.
12. Huang, J., van Zijl, P. C., Han, X., Dong, C. M., Cheng, G. W., Tse, K. H., ... & Chan, K. W. (2020). Altered d-glucose in brain parenchyma and cerebrospinal fluid of early Alzheimer's disease detected by dynamic glucose-enhanced MRI. Science advances, 6(20), eaba3884.
13. Wang, K., Sui, R., Chen, L., Li, Y., & Xu, J. (2022). The exchange rates of amide and arginine guanidinium CEST in the mouse brain. bioRxiv, 2022-02.
14. Yeung, P. Y., Wong, L. L., Chan, C. C., Leung, J. L., & Yung, C. Y. (2014). A validation study of the Hong Kong version of Montreal Cognitive Assessment (HK-MoCA) in Chinese older adults in Hong Kong. Hong Kong Medical Journal, 20(6), 504.
15. Zaiß, M., Schmitt, B., & Bachert, P. (2011). Quantitative separation of CEST effect from magnetization transfer and spillover effects by Lorentzian-line-fit analysis of z-spectra. Journal of magnetic resonance, 211(2), 149-155.
16. Jones, C. K., Polders, D., Hua, J., Zhu, H., Hoogduin, H. J., Zhou, J., ... & Van Zijl, P. C. (2012). In vivo three-dimensional whole-brain pulsed steady-state chemical exchange saturation transfer at 7 T. Magnetic resonance in medicine, 67(6), 1579-1589.
17. Zhou, J., Payen, J. F., Wilson, D. A., Traystman, R. J., & Van Zijl, P. C. (2003). Using the amide proton signals of intracellular proteins and peptides to detect pH effects in MRI. Nature medicine, 9(8), 1085-1090.

Figures

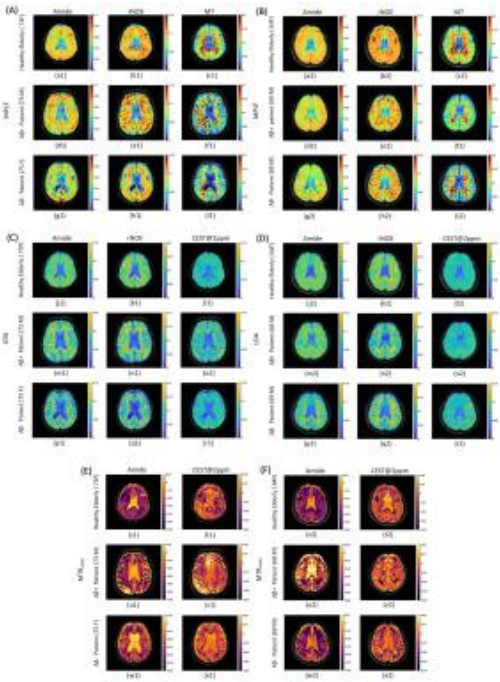

Figure 1. CEST maps for six representative subjects. (A)(C)(E) CEST maps for 73 years old female HC, 73 years old male Aβ+ patient and 75 years old female Aβ- patient generated by MPLF, LDA and MTR

methods respectively. (B)(D)(F) CEST maps for 64 years old female HC, 68 years old male Aβ+ patient and 69 years old female Aβ- patient generated by MPLF, LDA and MTR_{asym} methods respectively.

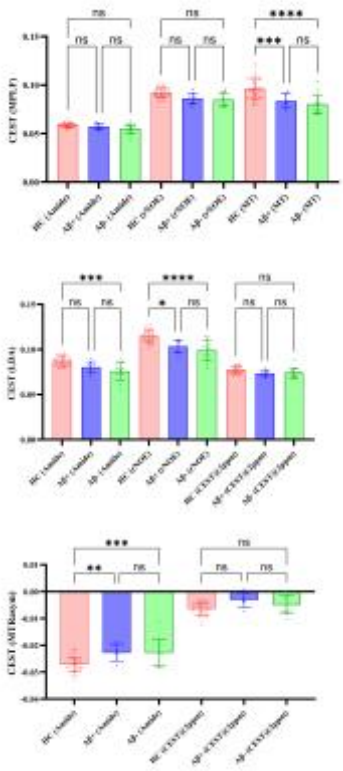

Figure 2. One-way ANOVA tests results of corresponding CEST contrast signals in whole brain generated from MPLF, LDA and MTR_{asym} methods (from top to bottom), with significance levels defined as follows: $p \leq 0.05$ indicated by *, $p \leq 0.01$ indicated by **, $p \leq 0.001$ indicated by ***, and $p \leq 0.0001$ indicated by ****.

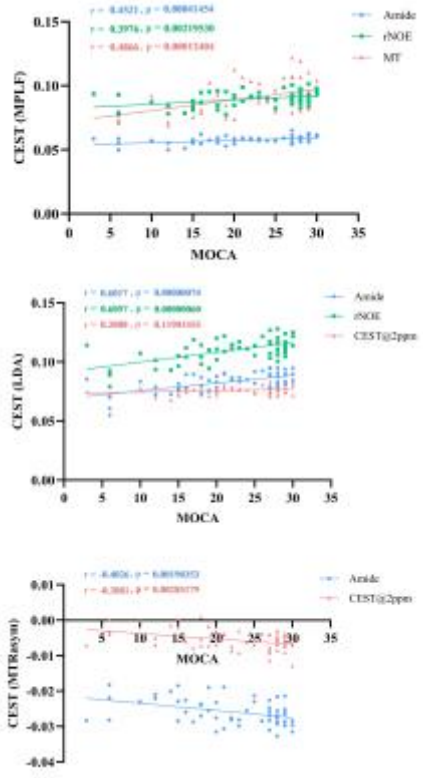

Figure 3. Correlation plots of HK-MoCA scores and CEST signals generated from MPLF, LDA and MTR_{asym} methods (from top to bottom).

	HC (n=40)	Aβ+ Patients(n=8)	Aβ- Patients(n=14)
Age (years)	67.08±5.89	72.75±4.37	77.07±8.59
Gender (F/M)	22/18	4/4	4/10
HK-MoCA Score	26.61±3.35 (n=36)	15.50±5.21(n=8)	12.73±5.82(n=13)
Education (years)	9.6±4.0	7.19±1.46	12.54±7.07

Table 1. Participant Demographics