Bayesian deep learning-based 1H-MRS of the brain: Metabolite quantification with uncertainty estimation using Monte Carlo dropout

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INTRODUCTION

The deep learning-based quantitative analysis of ^{1}H-MRS brain spectra(DL-MRS) has been reported as a potential alternative to the nonlinear-least-squares-fitting(NLSF) approach.[1-3] However, the previous studies used standard convolutional neural networks(CNNs) that do not provide uncertainty in the quantitative outcome,[4-5] which is an important prerequisite for the clinical application of DL-MRS. In the case of the NLSF approach, the Cramor-Rao-lower-bounds(CRLB) have long been used as a measure of fitting precision.[6]

Instead of a single set of optimized, deterministic weights in the standard CNNs, Bayesian convolutional neural networks(BCNNs) can be described in terms of the probability distribution of weights.[5,7,8] The distribution of weights results in the distribution of network outputs and thus provides information about the uncertainty in the outputs.

We investigated the BCNN with Monte Carlo dropout(MCDO) sampling[4,5,8] as a means of simultaneously estimating metabolite content and uncertainty therein at 3.0T. Using simulated spectra, a BCNN was trained to predict a metabolite-only spectrum from a typical human brain spectrum.[3] Both metabolite content and corresponding uncertainty are estimated from MCDO sampled spectra. The performance of the proposed method was tested first on the simulated spectra and further on the modified in vivo spectra.

METHODS

Simulated brain spectra: Spectra were simulated as previously described.[3] A total of 100,000 spectra were simulated and randomly assigned into a training(N=80,000), a validation(N=10,000), and a test(N=10,000) sets.

Modified in vivo spectra: The unmodified, original spectra were collected previously from the left frontal lobe($2\times2\times2cm^3$) of 5 healthy volunteers(30±3years) (PRESS[9], TR/TE=2000/30ms, SW=2kHz, NSA=64, and 2048 data points).[3] For each spectrum, the SNR was lowered and the linewidth was broadened simultaneously and gradually to generate 10 modified spectra with different SNR and linewidth combinations. Thus, 50 additional spectra were obtained from the 5 original data.

BCNN: A BCNN was designed based on a ResNet[10] and Bayesian-optimized[12] in Matlab. A dropout layer that was rendered to operate at test time as well was placed after every activation layer. The heteroscedastic noise variance(σ_t^2) of input data was learned also in the training phase.[8] The number of MCDO sampling(T) of 50 was determined that minimized the mean-absolute-percent-error(MAPE) in the quantification of 17 metabolites.

Prediction of metabolite content and corresponding uncertainty: Each individual metabolite content was estimated from the predictive mean spectrum by multiple regression using the metabolite basis set as previously described.[3] For the estimation of the corresponding uncertainty, first, a two-standard deviation (2×SD) spectrum(2σ) was obtained from the total uncertainty spectrum($\sigma^2 = \sigma_{alea}^2$ (aleatoric uncertainty) + σ_{epis}^2 (epistemic uncertainty) in Figure.1). Then, the uncertainty was estimated from the 2SD spectrum also by multiple regression, in which case the metabolite basis set was used in absolute mode in accordance with the 2SD spectrum. Finally, the uncertainty was converted into the percentage with respect to the metabolite content (%uncertainty) for each metabolite.

Evaluation of the proposed method: The BCNN was evaluated first on the simulated test set and then on the modified in vivo spectra, for which the metabolite content and uncertainty from the proposed method were compared with the metabolite content and CRLB from the LCModel.[11]

RESULTS

The MAPE of Cr, GSH, Gln, and Tau are < 10%, and the MAPE of Glu, NAA, and mI are < 5%. For the majority of the metabolites the mean %uncertainty are no less than MAPE (except for GPC and Gln) in the simulated test spectra set. For the majority of the metabolites, %uncertainty is comparable with MAPE (r ranges from 0.900 ($p < 0.001$; Gln) to 0.996 ($p < 0.001$; NAA) (0.963±0.034)).

For modified in vivo spectra, the variation in the estimated metabolite content tends to be increasing as the severity of degradation of the spectra increases both BCNN and LCModel analysis. However, the extent of variation in the metabolite content tends to be smaller with BCNN than with LCModel for all metabolites and both inside and outside the training ranges (or equivalently in the

normal brain spectra regime) except for mI, for which LCModel outperforms BCNN in the training range. For tCr and tNAA, the variation in metabolite content is more highly correlated with CRLB from LCModel than with %uncertainty from BCNN (r = 0.910 vs. 0.942 and 0.934 vs. 0.949, respectively). Overall, however, there is a trend towards higher r with BCNN than LCM (0.938±0.019 vs. 0.881±0.057 (p = 0.115)).

DISCUSSION

The finding that MAPE of Cr, GSH, Gln, Glu, NAA, mI, and Tau on the simulated test spectra were ≤ 10% is encouraging. However, the quantification of Ala, GPC, Lac, NAAG, and PC still requires far more technical improvement as found also in the previous study.[3] Overall, the high correlations between the GT errors and BCNN-predicted uncertainty support the potential application of the proposed method in DL-MRS with simultaneous uncertainty estimation.

CONCLUSION

The proposed method may be used for metabolite quantification with simultaneous uncertainty estimation in DL-MRS.

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