Optimization of the MR acquisition parameters for quantitative measurement of brain iron in Alzheimer’s disease
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Introduction: Alzheimer’s disease (AD) is estimated to affect approximately 22 million people globally and accounts for more than 60% of all dementia cases [1]. AD is typically identified after the onset of neuropathological symptoms. Biomarkers whose manifestation precedes the symptoms can enable preemptive intervention. Neuroscience research points towards the role of iron in the pathogenesis of AD, and accurate quantification of brain iron would be useful in early diagnosis [2, 3]. Iron accumulation alters the MR characteristics of the brain tissue which is assessed through the quantitative measurement of surrogate biomarkers such as $T_1$, $T_2$, and $T_2^*$. The purpose of this work is to optimize the MR acquisition parameters for quantitative measurement of brain $T_2$ values through the use of Cramér-Rao bound (CRB) analysis [6]. CRB theory allows the determination of the smallest possible variance on the parameter estimates from any unbiased estimator [6, 7]. The noise performance (minimum standard-deviation on $T_2$ estimates) at different acquisition parameters was analyzed at different signal-to-noise ratios (SNR) and at different $T_2$ values to determine the optimal echo-times for measuring brain iron.

Theory and Methods: The signal model, $s(t)$, considered for the CRB analysis is shown in Equation 1, where $M$ is the bulk magnetization vector, $T_2$ is the transverse relaxation time and $\eta$ is additive noise. The analysis shown in the reminder of this work is independent of magnet field strength and is applicable for both spin-echo and gradient-echo imaging, with the replacement of $T_2$ with $T_2^*$ for gradient-echo. The distribution of noise in an MR magnitude image is Rician (square root of sum-of-squares of the Gaussian noise on the real and imaginary channels) in nature. However, for a SNR greater than 10, Rician noise can be approximated to have a Gaussian distribution. In this work noise performance was analyzed for SNR greater than 10; hence, for the CRB computations a Gaussian noise model was assumed.

$$s(t) = M \exp(-t/T_2) + \eta$$ [1]; $S = A \Gamma + \eta$ [2]; $S\Gamma = \{s(TE_1) \ s(TE_2)\}'$ [3]; $\Gamma = [M \ M]^T$ [4]; $\eta = [\eta_1 \ \eta_2]^T$ [5];

$$A = \begin{bmatrix} e^{-TE_1/T_2} & 0 \\ 0 & e^{-TE_2/T_2} \end{bmatrix}$$ [6]; $FIM_{11} = \frac{1}{\sigma^2} (A^T A)_{11}$ [7]; $FIM_{12} = FIM_{21} = \frac{1}{\sigma^2} (A^T \partial \partial \Gamma)_{11}$ [8]; $FIM_{22} = \frac{1}{\sigma^2} A^T \partial \partial \Gamma$ [9];

Equations 2-6 show the matrix representation of signal model for two measurements at first-echo time ($TE_1$) and second echo-time ($TE_2$). The equations for the four elements (indexed 11, 12, 21, 22) of the Fisher information matrix (FIM) used for CRB computations are shown in Equations 7-9. The Cramér-Rao lower bound (CRLB) of $T_2$ was obtained by calculating the inverse of FIM. The CRLB for $T_2$ was computed with varying inputs of $TE_1$, $TE_2$, SNR and $T_2$ values. In this work, SNR of $X$ means an M value of $X$ and noise with unity standard-deviation (SD) on the signal acquired at the first and second echoes.

Results and Conclusions: Figure 1 shows the CRLB in the estimation of $T_2$ for different $TE_1$ and echo-spacing ($\Delta T E = TE_2 - TE_1$) conducted at four different combinations of SNR and the $T_2$ values. The line of symmetry is shown as a dark line on the images. For a typical $TE_1$ and $TE_2$ of 18ms and 80ms used in earlier works [4] there would be a minimum SD of 3.85ms in the estimation of $T_2$ of 25ms at a SNR of 50. Symmetry of the CRB values around the line with $\Delta T E = TE_1$ on images A-D of Figure 1, and plots shown in Figure 2 demonstrate that $T_2^*$ is the determining factor for the noise performance in the estimation of $T_2$. The CRLB is independent of the variation of the $T_2$ values except for the limiting cases ($ATE$ needs to be finite positive value). Computations were conducted over different sets of values for SNR and $T_2$ other than shown in Figure 2, and the pattern of results were similar to those in Figure 2. Figure 3 shows the CRLB computed at different $TE_1$ values, choosing $TE_1$ $= TE_2/2$, over a range of $T_2$. These results show that the $T_2$ which provides optimal noise performance differs with changing $T_2$ values. However, there exists a line of optimality around which the optimal $T_2$ values are clustered. Hence, the $T_2$ needs to be chosen according to the brain region for which optimal noise performance is desired. For example, for regions such as hippocampus with $T_2$ values between 55 to 65ms at 3T [4], a $TE_2$ of 25 to 30ms would be optimal.