**Abstract**

**Purpose:** To develop and validate a regularization approach of optimizing B1-insensitivity of the quantitative magnetization transfer (qMT) pool-size ratio (F).

**Theory and Methods:** An expression describing the impact of B1-inaccuracies on qMT fitting parameters was derived using a sensitivity analysis. To simultaneously optimize for robustness against noise and B1-inaccuracies, the optimization condition was defined as the Cramér-Rao lower bound (CRLB) regularized by the B1-sensitivity expression for the parameter-of-interest (F). qMT protocols were iteratively optimized from an initial search space, with and without B1-regularization. Three 10-point qMT protocols (Uniform, CRLB, CRLB+B1-regulatization) were compared using Monte Carlo simulations for a wide range of conditions (SNR, B1-inaccuracies, tissues).

**Results:** The B1-regularized CRLB optimization protocol resulted in the best robustness of F against B1-errors, for a wide range of SNR and for both white and grey matter tissues. For SNR = 100, this protocol resulted in errors of less than 1% in mean F values for B1-errors ranging between -10 to 20%, the range of B1 values typically observed in vivo in the human head at field strengths of 3 T and less. Both CRLB-optimized protocols resulted in the lowest σF values for all SNRs, and did not increase in the presence of B1-inaccuracies.

**Conclusion:** This work demonstrates a regularized optimization approach for improving the robustness of auxiliary measurements (e.g. B1) sensitivity of qMT parameters, particularly the pool-size ratio (F). Predicting substantially less B1-sensitivity using protocols optimized with this method, B1 mapping could even be omitted for qMT studies primarily interested in F.