Proton MR spectroscopic imaging (MRSI) metabolite ratios in human brain: calculating repeatability when measurement error is proportional to the mean

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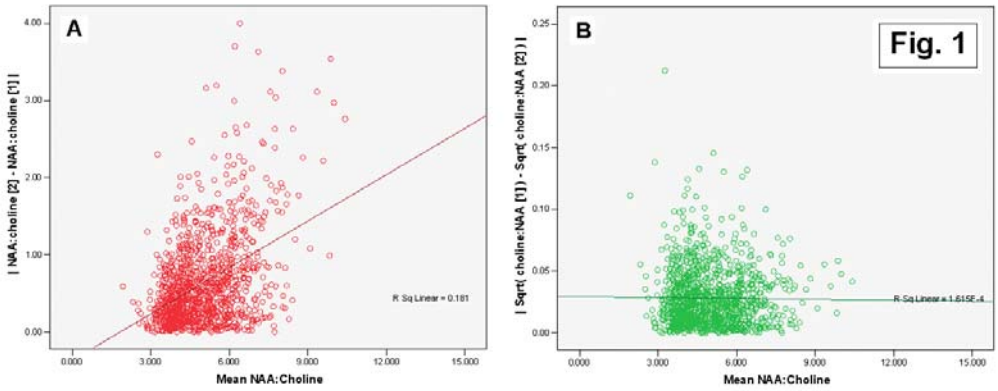
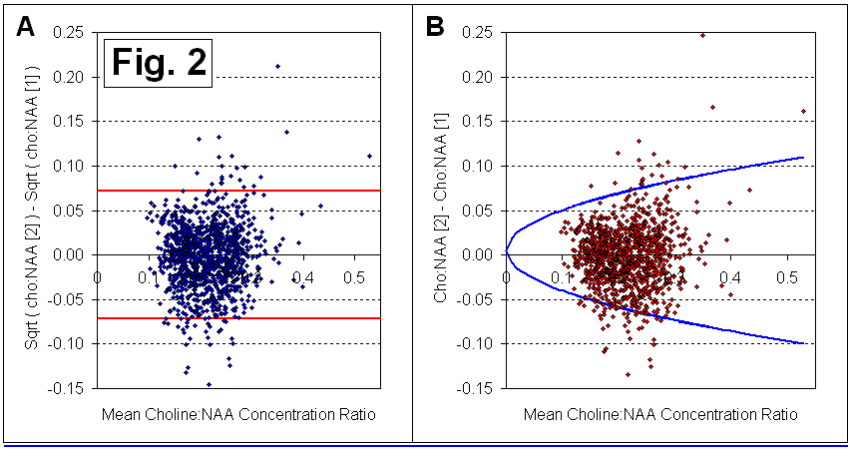
Introduction: *In vivo* proton magnetic resonance spectroscopic imaging (MRSI) has a proven track record as a research tool and shows clinical promise in a range of diseases including brain tumours [1, 2], stroke [3, 4], epilepsy [5, 6] and multiple sclerosis [7, 8]. To enable reliable clinical (diagnostic and longitudinal) use, the repeatability of the technique must be quantified. Whilst studies have quantified repeatability [9–16], it is imperative that the procedure is repeated for all scanners and institutions so as to account for differences in hardware, pulse sequences, etc. A study was, therefore, undertaken to quantify repeatability at our own institution.

Methods: MRSI was carried out using a 3.0 Tesla, whole-body Signa MRI Scanner (GE Healthcare, Milwaukee, WI, USA), a bird-cage head-coil and semi-automated higher-order shim optimisation. Eight healthy volunteers were scanned twice during the same examination, with shim settings and transmit/receive gains held constant. Informed consent was obtained in all cases. A 3D PRESS sequence was used with a 144 ms TE, a 1000 ms TR; a voxel over-sizing (OVERPRESS) factor of 1.3; a 12 × 12 × 8 cm FOV and 12 × 12 × 8 phase encode steps (1 ml nominal voxels). The region of interest ranged between 7 × 5 × 3 voxels and 7 × 7 × 5 voxels. Six outer-volume saturation (OVS) bands adjacent to voxel edges were employed along with four additional OVS bands to saturate artefactual signals arising from the frontal sinuses, the skull base and the mouth and naso-pharynx. Peak areas were quantified using the LCModel package (Stephen Provencher, Ph.D, Oakville, Ontario, Canada) with SAGE/IDL (GE Healthcare, Milwaukee, WI, USA) as an interface. The NAA:choline peak area ratio was taken as the "normality index" (where low values would indicate cancer, for example). SNR and Cramer-Rao (LCModel) thresholds of 2.0 and 20% were both employed to eliminate poor quality spectra.

Statistical Analysis was carried out using SPSS (SPSS Inc., Chicago, IL, USA) and Excel (Microsoft, Seattle, WA, USA). Kendall's tau was used to detect measurement error proportional to the mean and the following standard mathematical transformations were applied in order to correct for this [17–19]: 1. Natural logarithm, ln(NAA:choline); 2. Square root, √(NAA:choline); 3. Inverse, 1/(NAA:choline); 4. Natural logarithm of the inverse, ln(choline:NAA) and 5. Square root of the inverse, √(choline:NAA). Repeatability (equal to √2 × 1.96 × within subject standard deviation (SD) [20]= 1.96 × the SD of the observed differences [17]), was calculated on a suitable transformed scale (where measurement error was not proportional to the mean) then transformed back onto the non-transformed scale [18].

Results: Thresholding resulted in 152 (12% of) spectra being excluded leaving 1,108 voxels, all with varying proportions of grey and white matter, and cerebrospinal fluid. The measurement error (absolute difference between datum one and datum two) for NAA:choline was proportional to the mean; as shown by Figure 1a. Of all the transformations, only the square-root of the inverse removed this dependence; as shown by Figure 1b. Constant repeatability limits were calculated on the transformed scale, where measurement error was shown not to be proportional to the mean, as shown in Figure 2a, and these limits were then transformed back to the natural scale (giving non-constant repeatability limits), as shown in Figure 2b. The proportion of data lying between the repeatability limits in figures 2a and 2b are 95.1% and 94.4% respectively; thus proving that the calculated limits perform the desired function (acting as 95% confidence limits).





Conclusion: It has been shown that the measurement error for MRSI metabolite concentration ratios, as measured in the healthy human brain, can be proportional to the mean (for the common acquisition protocol used herein, at least). This means that simple repeatability limits (e.g. mean ± 1.96 standard deviation, the 95% confidence interval) may not be strictly applicable to the data, because the precision of the data changes with the mean. It has also been shown that an appropriate, well-known and trusted mathematical transformation of the data can ameliorate the problems associated with measurement error being proportional to the mean, thus permitting meaningful and robust estimates of (non-constant) repeatability limits to be calculated; limits which will be invaluable in permitting the robust clinical application of MRSI in the future.

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