The Variance of Whole-Brain N-acetylaspartate Concentration Amongst Different Sites and MR Scanners is Statistically Insignificant

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Objective:

To estimate how robust the whole-brain *N*-acetylaspartate (WBNAA) concentration quantification method is to site, MR hardware type and magnetic field strength differences, *i.e.*, its suitability for clinical trials.

Background:

The efficacy of new drugs for neurological disorders is typically monitored in phase II clinical trials with surrogate markers, which provide outcome feedback in a much shorter timeframes and fewer patients than clinical assessment. The amino acid derivative *N*-acetylaspartate (NAA), which is exclusive to neuronal cells (1) is considered a marker for their health and density (2). Since it can be quantified non-invasively with proton MR spectroscopy (^{1}H-MRS), NAA could be a specific surrogate marker. Unfortunately, most ^{1}H-MRS studies to date have focused on metabolite changes in single or multi-voxel volumes-of-interest which typically comprise ‹100 ml, thereby, missing 80-99% of the brain, including most of the gray matter close to the skull (to avoid lipid contamination). This limitation has been overcome with an non-localized sequence which quantifies the whole-brain NAA (WBNAA) concentration (3). This method, however, has not been validated with respect to measurement sites and MR scanner differences, since these often confound data consolidation and the final analysis of multi-site clinical trials (4,5). This study addresses this issue by comparing the variability of WBNAA concentrations across four sites.

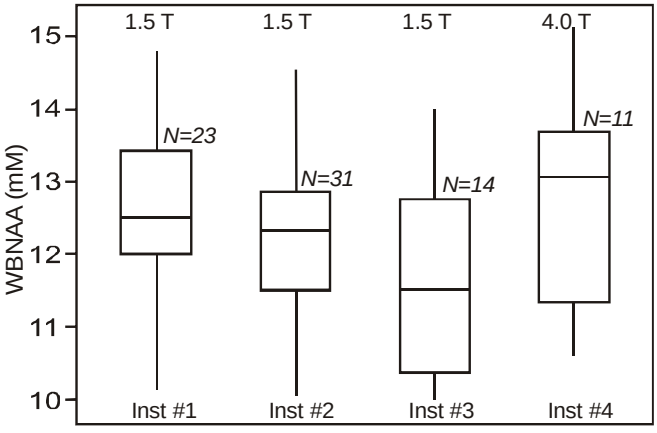

Fig. 1. Box plot showing 25, 50 (median and 75% quartiles (box) and ±95% (whiskers) demonstrating the (insignificant) variability of WBNAA measurements in the 4 different sites.

Methods:

To estimate how robust the WBNAA method is, we calculated the variance of WBNAA quantification amongst four clinical research sites, using three different MRI scanners from two manufacturers, operating at two different magnetic field strengths. Seventy nine healthy subjects (45 female, 34 male) ranging in age from 16 to 59 (mean 34.2) years, were studied. Twenty-three were from Institute #1 using a 1.5 T Siemens Vision, 31 were from Institute #2 using a 1.5 T Siemens SP63, 14 were from Institute #3 using a 1.5 T Siemens Vision, and 11 were from Institute #4 using a 4.0 T GE Signa, as shown in Fig. 1. Each subject underwent a WBNAA, non-localizing, ^{1}H-MRS acquisition, as well as anatomical T1-weighted MRI for brain segmentation. The absolute amount of NAA in each subject's brain, quantified with phantom-replacement, was divided by their brain volume, segmented from the MRI, to yield the WBNAA concentration, a metric comparable amongst all individuals regardless of brain size.

Results:

The subjects' WBNAA distributions did not differ significantly amongst the institutions, instruments or field strength, as shown in Fig. 1. Specifically, neither the four average WBNAA concentrations, 12.3±1.2 millimolar, nor their individual standard deviations differed statistically.

Conclusions:

Absolute quantification against a phantom makes comparisons of the WBNAA concentrations a robust metric, regardless of scanner, manufacturer, model, or magnetic field strength. Consequently, WBNAA is a hardware-insensitive surrogate suitable for multi-center neurological drug or treatment trials.

References:

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