Serial Whole-Brain N-Acetylaspartate Concentration in Healthy Young Adults

SUMMARY: Although the concentration of N-acetylaspartate (NAA) is often used as a neuronal integrity marker, its normal temporal variations are not well documented. To assess them over the 1–2 year periods of typical clinical trials, the whole-brain NAA concentration was measured longitudinally, over 4 years, in a cohort of healthy young adults. No significant change (adjusted for both sex and age) was measured either interpersonally or intrapersonally over the entire duration of the study.

Proton MR spectroscopy (1H-MR spectroscopy) is often used to increase the specificity of MR imaging with the levels of several detectable brain metabolites. Key among them is N-acetylaspartate (NAA), which is second only to glutamate as the most abundant amino acid in the mammalian brain. Because it is almost exclusive to neuronal cells, it is regarded as a marker for their health and concentration, and 1H-MR spectroscopy studies to date used either single-voxel or 2D multivoxel matrix; 210 mm2 FOV) imaging using our MIDAS package, as described elsewhere. This research was supported by National Institutes of Health grants EB01015, NS050520, and NS29029.

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Restricted maximum likelihood was used to estimate within- and between-subject variance components within a mixed model analysis of variance framework that modeled WBNAA as a function of subject identification and time point, represented as random and fixed classification factors, respectively. A paired sample t test was used to compare time point pairs with respect to the mean WBNAA level.

The estimated between- and within-subject variance components and the observed correlation between longitudinal measures on a subject were used to compute the precision that can be expected when the yearly rate of WBNAA change is estimated using a linear mixed-model regression analysis with data from K equally spaced time points over 2 years for each of N subjects. This permitted us to determine the N needed to detect any specific annual rate of WBNAA change with either 80% or 90% statistical power at the 2-sided 5% significance level.

Results

Intrasubject $V_\beta$ changed by an annual average of $-0.25\%$, consistent with previous reports. Box plots of the WBNAA concentrations, shown in Fig 1, exhibit very similar median NAA levels between the time points with average $\pm$ SD of $12.5 \pm 1.4$, $12.8 \pm 1.4$, and $12.6 \pm 1.2$ mmol/L, at baseline, first, and second follow-ups, respectively.

The intrasubject distribution of WBNAA values at baseline was not different from the first or second follow-ups with respect to its mean ($P > .5$) or variation ($P > .3$). The mean intrasubject WBNAA level changes, $1.7\% \pm 9.0\%$ and $0.5\% \pm 12\%$ from baseline to first and second follow-up ($n = 14$ and 7, respectively) and $-0.3\% \pm 9.0\%$ between second and third time points ($N = 7$) were similar to previous reports for back-to-back and day-to-day changes. Based on this variability, estimates of the number of subjects needed to detect various annual percentages of WBNAA changes sampling K equally spaced time points over 2 years are compiled in the Table.

Discussion

This study quantifies, to the best of our knowledge, for the first time, the longitudinal course of the global brain NAA concentration in the healthy human brain over a 1- to 2-year period typical of most clinical trials of neurologic disorders. The results support the hypothesis that the concentration and health of neuronal cells are stable in this 20- to 50-year-old population to within the $\pm 6\%$–8% precision of the WBNAA method, regardless of exact age or sex. Because WBNAA is a ratio (see Eq 2) and its denominator, $V_\beta$, is stable to within $\pm 0.25\%$, the intersubject and intrasubject variability can be assigned entirely to the $Q_{WBA}$ quantification.

Knowledge of these variations can be used to aid the design of trials in which NAA is used as a surrogate marker. Specifically, how many measurements, on how many subjects, for how long, are needed to detect specific change? The Table shows, for example, that 3 measurements over 2 years on 11 patients suffices to establish 6% annual change with 90% power.

The WBNAA approach also has 3 main unavoidable limitations. First, it is inherently nonlocalization specific. Second, the age range, 18–50 years, studied here is most appropriate for neurologic disorders that afflict younger patients. Finally, because NAA decline has been associated with both neuronal loss and/or dysfunction, though its changes are specific to this cell type, they are not deterministic of the type of damage.

References


Table 1: Estimated sample sizes for 80% or 90% power at 2-sided 5% significance level to detect specific yearly rates of WBNAA change with $K$ equally spaced scans per subject over 2 years

<table>
<thead>
<tr>
<th>Yearly Rate of Change, mM (%)</th>
<th>Sample Size (80% Power)</th>
<th>Sample Size (90% Power)</th>
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<tbody>
<tr>
<td></td>
<td>K = 3 K = 4 K = 5 K = 6</td>
<td>K = 3 K = 4 K = 5 K = 6</td>
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<tr>
<td>0.25 (2%)*</td>
<td>57 52 46 42 76 68 61 55</td>
<td>57 52 46 42 76 68 61 55</td>
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<tr>
<td>0.51 (4%)*</td>
<td>15 15 13 12 21 19 17 16</td>
<td>15 15 13 12 21 19 17 16</td>
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<tr>
<td>0.77 (6%)*</td>
<td>8 8 7 7 11 10 9 8</td>
<td>8 8 7 7 11 10 9 8</td>
</tr>
<tr>
<td>1.03 (8%)*</td>
<td>6 6 5 5 7 7 6 6</td>
<td>6 6 5 5 7 7 6 6</td>
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* Yearly rate of millimoles in percentage assumes a mean baseline WBNAA concentration of 12.8 mmol/L.

Fig 1. Box plots showing the first, second (median), and third quartiles (box), ±95% (whiskers), of the WBNAA distributions at baseline, first, and second follow-up time points (the 7 subjects at the third time point are a subset of the original 14).