Frontal Lobe Function: Association between Neuropsychological Test Scores and N-Acetyl Aspartate.

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INTRODUCTION

Research linking neuroanatomical regions to brain function has provided a means for testing specific hypotheses regarding the structural or biochemical basis of the relationship between brain function and neuroanatomy. Compared to the adult brain, localization of brain function is less well understood at younger ages, due to continuing brain development and maturation. In order to appreciate variations caused by brain pathology or injury, it is essential to evaluate localization of brain function in healthy, typically developing brains. The goal of our study was to examine the relationship between performance on well-established neuropsychological measures of frontal lobe functioning (1,2), and frontal lobe levels of a putative neuronal marker (NAA; N-acetyl aspartate) in healthy, carefully screened children and adolescents.

MATERIAL AND METHODS

We examined 53 healthy children and adolescents (27 female, 5.5 to 18.3 years old, mean age 12.3 ± 3.7 years, 42 right-handed). All subjects were free of neurological disorder, mental retardation, learning disability or psychiatric disorder. All participants completed a neuropsychological assessment including measures of attention, executive function, memory, language, visual, and motor skills. The following tests were used in this study: Purdue Pegboard (right and left hands; RH, LH), a measure of manual dexterity and speed; Stanford-Binet-IV (SB-IV) Bead Memory, a visual working memory task; Woodcock Johnson Tests of Cognitive Abilities-III (WJ-III) Retrieval Fluency, a measure of rapid lexical retrieval, production, and efficient organization; and, WJ-III Auditory Working Memory, a test of auditory (verbal) working memory. Raw test scores were used in the statistical analyses.

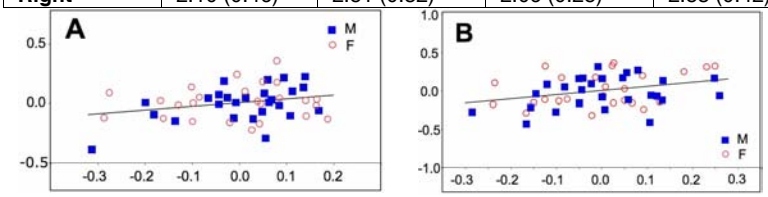
Routine brain MRI and ^{1}H MRSI were performed at 1.5 T. ^{1}H MRSI was performed using a multi-slice SE sequence with outer volume suppression (3), with four supratentorial oblique axial 15 mm thick slices (2.5 mm gap) with TR/TE=2000/140 ms and nominal voxel size 0.8 ml. Prior to MRSI, T_1-weighted localizer images were recorded at the same slice location and thickness as MRSI for ROI selection. Spectra were evaluated from the dorsolateral prefrontal cortex, frontal white matter (forceps minor), dorsal and inferior parietal cortex, and deep parietal white matter, in both hemispheres. Concentration of NAA was expressed as ratio to creatine (Cr), NAA/Cr, calculated from areas under the respective signals. Data collected from 2 to 4 voxels were averaged for each region.

Paired t-tests were used to evaluate differences in NAA/Cr between the hemispheres. Linear regression analysis was used to test for the effect of age on NAA/Cr and test scores. We hypothesized that the Purdue Pegboard-LH and SB-IV Bead Memory test scores would be associated with NAA/Cr ratio in the right frontal lobe and the Purdue Pegboard-RH, WJ-III Retrieval Fluency, and WJ-III Auditory Working Memory test scores with the NAA/Cr ratio in the left frontal lobe. To account for heteroscedasticity and for the effect of age (see below) on both dependent and independent variables, we log-transformed the variables and calculated the residuals after regressing on age. ANOVA was applied to evaluate the relationship between the test scores (residuals) and NAA/Cr ratio (residuals), controlling for gender. We also performed control analyses between test scores and NAA/Cr in a region where we did not expect any relationship (parietal lobe gray and white matter). In all tests, significance level was set to $p<0.05$.

RESULTS

Average lobar gray and white matter (GM, WM) NAA/Cr ratios (± standard deviations) are presented in the table. No differences between the hemispheres were detected. NAA/Cr tended to increase with age: significantly in right parietal white matter (slope 0.033 year^{-1}, $p=0.038$, $r^2=0.083$); and in left frontal white matter ($p=0.12$) and right parietal gray matter ($p=0.11$). No gender differences in NAA/Cr were detected.

NAA/Cr	Frontal GM	Frontal WM	Parietal GM	Parietal WM
Left	2.11 (0.35)	2.43 (0.29)	2.05 (0.27)	2.42 (0.28)
Right	2.10 (0.46)	2.51 (0.32)	2.06 (0.25)	2.53 (0.42)



Purdue Pegboard RH (A) and SB-IV Bead Memory scores (B) vs. left (A) and right (B) frontal WM NAA/Cr. Residuals (see Methods) are plotted in the graphs.

The raw scores of all tests improved with age (all $p<0.002$, $r^2=0.18$ to 0.57); girls had better scores on the WJIII-Retrieval Fluency ($p=0.007$) and tended to perform better on the Purdue Pegboard-LH ($p=0.06$). Of the tests hypothesized to be associated with the left frontal lobe, the Purdue Pegboard-RH showed a near significant relationship ($p=0.055$, $r^2=0.073$, Fig. A) with left frontal white matter NAA/Cr. Of the tests hypothesized to be associated with the right frontal lobe, SB-IV Bead Memory test scores showed a significant relationship with right frontal white matter NAA/Cr ($p=0.019$, $r^2=0.11$, Figure B). In both tests, higher scores were associated with higher NAA/Cr ratios. No significant relationship between the test scores and frontal gray matter was detected. The control analyses did not reveal any significant relationship between any of the tests associated with frontal lobe function and parietal NAA/Cr ratios.

DISCUSSION

Our findings are in agreement with our previous DTI study in frontal lobe (4) showing lower ADC values in the right frontal white matter with increasing SB-IV Bead Memory scores in 39 healthy children. We did not, however, detect any significant relationship between frontal cortical regions and working memory and executive function, as previously reported in studies using physiological neuroimaging (5,6). Although the relationship between the scores of two of the tests used in our study and NAA levels was significant or approaching statistical significance, the association was not strong, as evidenced by low r^2 values. The implication for future MR spectroscopic studies therefore is to minimize the "noise" in the data in order to detect a potentially significant association. This includes carefully screened subjects, reproducible data acquisition, and consistent selection of regions of interest, with minimal partial volume effects from sampling undesired tissue types. Our population included thoroughly screened subjects (detailed psychiatric interview, parents' ratings and a detailed neuropsychological test battery) and high-resolution MR spectroscopy technique. For the analyses, we included only voxels which appeared to be completely encompassed in the desired ROI on the localizer images and corrected for CSF presence by using the NAA/Cr ratio. In the future, collecting data in longitudinal studies may provide more power for statistical analyses (which pose a challenge due to the effect of age on both dependent and independent variables) (7).

Our data contribute to a growing body of literature on the association between neuropsychological test scores and neurometabolites (8). Since frontal lobe white matter is affected by a number of brain pathologies, (e.g. traumatic brain injury, brain tumors, ADHD), our data may provide a quantitative basis for assessment of frontal lobe impairments in disease states.

ACKNOWLEDGEMENT

Supported by NIH grants RO1 NS042851 and R 00052.

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