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YNIMG-03105; No. of pages: 8; 4C:

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NeuroImage

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NeuroImage xx (2005) xxx–xxx

Rapid Communication

Sex differences in *N*-acetylaspartate correlates of general intelligence: An ^{1}H-MRS study of normal human brain

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Received 14 December 2004; revised 8 February 2005; accepted 25 February 2005

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Researchers have long attempted to determine brain correlates of intelligence using available neuroimaging technology including CT, MRI, PET, and fMRI. Although structural and functional imaging techniques are well suited to assess gross cortical regions associated with intelligence, the integrity and functioning of underlying white matter networks critical to coordinated cortical integration remain comparatively understudied. A relatively recent neuroimaging advance is magnetic resonance spectroscopy (MRS) which allows for interrogation of biochemical substrates of brain structure and function in vivo. In this study, we examined twenty-seven normal control subjects (17 male, 10 female) to determine whether *N*-acetylaspartate (NAA), a metabolite found primarily within neurons, is related to intelligence as assessed by the Wechsler Adult Intelligence Scale-III. Of the three white matter regions studied (i.e., left frontal, right frontal, left occipito-parietal), we found that a model including only left occipito-parietal white matter predicted intellectual performance [$F_{(1,25)} = 8.65$, $P = .007$; $r^2 = .26$], providing regional specificity to our previous findings of NAA–IQ relationships. Moreover, we found that a complex combination of left frontal and left occipito-parietal NAA strongly predicted performance in women, but not men [$F_{(2,7)} = 21.84$, $P < .001$; adjusted $r^2 = .82$]. Our results highlight a biochemical substrate of normal intellectual performance, mediated by sex, within white matter association fibers linking posterior to frontal brain regions.

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Keywords: Spectroscopy; Intelligence; *N*-acetylaspartate; Cognitive; Sex differences; White matter

Intelligence, both human and non-human, can be conceptualized as a global measure of brain function representing integration of specific cognitive skills important to adaptive behavior. Although initially defined operationally in the circular paradox as "that which intelligence tests measure" (Thorndike, 1921), the construct of intelligence has important social and health ramifications: for example, psychometric measures of the intelligence quotient (IQ) are correlated with school performance, years of education, income, job performance, and social outcomes (Gottfredson, 1997). Similarly, several biological variables may be associated with lower IQ including nutritional deficiency, lead poisoning, alcohol exposure, and perinatal complications (Neisser et al., 1996). Finally, IQ measures have been well associated with both health (Batty and Deary, 2004) and mental health outcomes (Walker et al., 2002).

Factor analysis has demonstrated that a wide range of cognitive tasks are positively correlated with one another, the commonality of which was termed *g* by Spearman (1904). Two richly articulated schools of thought have emerged regarding localization of higher cognitive function, one implicating discrete cortical regions (Broca, 1861; Gall, 1825; Kleist, 1934), the other assuming that the brain works in harmony as a single entity (Flourens, 1824; Jackson, 1932; Lashley, 1929). Pavlov (1949) synthesized these previously discordant viewpoints, summarizing brain function as comprised of distributed interactions between cortical regions united to perform a common cognitive task, a conceptualization that persists to the present day (Detterman, 2000).

Researchers have attempted to determine brain correlates of intelligence using technology available during their times. Earliest endeavors focused on brain size, crudely approximated by measures of head size (Galton, 1869), with meta-analysis

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Available online on ScienceDirect (www.sciencedirect.com).

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doi:10.1016/j.neuroimage.2005.02.039

suggesting an average correlation of +0.15 between head size and intelligence (Van Valen, 1974). Several studies have found positive correlations between magnetic resonance imaging (MRI) measures of brain volume and intelligence (Andreasen et al., 1993; Egan et al., 1994; Flashman et al., 1997; Gur et al., 1999; Haier et al., 1995; Harvey et al., 1994; Pennington et al., 2000; Raz et al., 1993; Reiss et al., 1996; Schoenemann et al., 2000; Wickett et al., 1994, 2000; Willerman et al., 1991), save for a single study showing no brain–IQ correlation in a group of monozygotic twins (Tramo et al., 1998). Thus, a consistent correlation of around +0.35 is generally found between measures of brain size and intelligence (Anderson, 2003). Moreover, white and gray matter appear to correlate to measures of intellectual functioning in roughly equal magnitudes (unweighted mean r = +0.31 and +0.27 respectively) (Gignac et al., 2003). Finally, an improvement in resolution upon gross volumetric correlates of IQ is voxel based morphometry (VBM) which has recently been used to identify discrete brain regions which are correlated with IQ, distributed throughout gray and white matter regions, and comprising only 6% of total brain volume in normal adults (Haier et al., 2004). Subsequent analysis of these data found that, compared to men, women showed more white matter and fewer gray matter regions related to intelligence (Haier et al., in press).

Although structural imaging techniques are very well suited to assess gross morphological regions associated with intelligence, the integrity and functioning of underlying white matter networks critical to coordinated cortical integration remain comparatively understudied. Proton magnetic resonance spectroscopy (^{1}H-MRS) is a powerful, non-invasive measure of brain biochemistry in vivo. Of particular interest to studies of cognition, *N*-acetylaspartate (NAA), produced within neuronal mitochondria, has been established as a marker of neuronal density and/or viability in numerous disease states (Barker, 2001) and has been associated with lower IQ in such disorders as mental retardation (Hashimoto et al., 1995), temporal lobe epilepsy (Gadian et al., 1996), and Williams syndrome (Rae et al., 1998). In cohorts of normal subjects, white matter NAA has been related to broad measures of cognition in relatively young (Jung et al., 1999a,b) and elderly subjects (Ferguson et al., 2002; Valenzuela et al., 2000), implicating NAA as a sensitive marker of brain–behavior relationships. More recently, researchers have found that frontal lobe NAA was related to a measure of verbal ability in women but not in men (Pfleiderer et al., 2004), suggestive of a potential biochemical sexual dimorphism in the normal brain, which may complement our recent findings of a structural sexual dimorphism underlying intelligence (Haier et al., in press).

In this study, we sought first to determine the regional specificity of the relationship between NAA levels and intellectual functioning in a cohort of normal subjects in three discrete regions including bilateral frontal and left parietal–occipital white matter fiber tracts. We also sought to determine whether NAA levels explain unique variance in intelligence when compared to gross gray and white matter brain parenchyma volumetric measures. Finally, we aimed to determine whether sex differences exist as a moderating variable between brain morphometry, biochemistry, and intelligence. These questions expand upon our earlier findings (Jung et al., 1999a,b, 2000) which utilized a single voxel of interest and did not include volumetric measures.

Methods

Sample

Twenty-seven normal control subjects (17 male, 10 female) were recruited from the local college population (mean age = 24.8, SD = 5.89, range = 18–37). All control subjects were interviewed and screened by an experienced clinical neuropsychologist (RJ) and were free of any neurological, psychiatric, or developmental learning disorders. Four of the twenty-seven experimental subjects were left handed (3 male, 1 female).

Cognitive measures

All subjects completed the Wechsler Adult Intelligence Scale-III (Wechsler, 1995) to assess intellectual functioning, administered by an experienced clinical neuropsychologist (RJ) under standardized procedures. Two subtests of the WAIS-III with the lowest reliability [Comprehension (r_{xx} = .84) and Picture Arrangement (r_{xx} = .74)] were not administered to reduce administration time: one each from the verbal and performance scales. The Verbal Intelligence Quotient (VIQ) and Performance Intelligence Quotient (PIQ) were prorated, and the sum of these prorated scores yielded a Full Scale Intelligence Quotient (FSIQ), as defined by the WAIS-III Administration and Scoring Manual (The Psychological Corporation, 1997, p. 59), and comprised of the following subtests: Picture Completion, Vocabulary, Digit Symbol-Coding, Similarities, Block Design, Arithmetic, Matrix Reasoning, Digit Span, and Information. Two additional subtests, Symbol Search and Letter–Number Sequencing, were obtained to complete the subtests comprising the Working Memory Index (WMI) and Processing Speed Index (PSI).

MR Imaging/volumetric segmentation

All experimental subjects were scanned on a separate occasion within 1–2 weeks of cognitive testing. All MR acquisitions were carried out on a 1.5 T GE clinical MR scanner using a birdcage quadrature head coil. A T1-weighted, fSPGR series (1.5 mm thick, 256 × 192 matrix, TE = 6.9 ms, TR = 17.7 ms, flip angle = 25°) was collected for the volumetric measurements. The skull was stripped using the Brain Extraction Tool (BET) (FMRIB Image Analysis Group, Oxford, UK). The Intracranial Volume was calculated from the mask produced from this program. Images were then segmented using an automated k-means clustering algorithm and the volumes of gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) were determined by the number of pixels in each of their respective clusters (Petropoulos et al., 1999). Pixels that could not be assigned exclusively to GM or CSF were considered partial volume (PV). Total brain parenchyma (TBP) values were calculated by adding GM, WM, and 1/2 PV values, as our segmentation of PV represents both gray matter–white matter interface and gray matter–cerebrospinal fluid interface.

MR spectroscopy

A single voxel Point Resolved Spectroscopy (PRESS) pulse sequence (TE = 40 ms, TR = 2000 ms, 128 averages), including water suppression, was prescribed within three brain

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regions: left frontal, right frontal, and left parietal–occipital (Fig. 1a). All spectroscopic voxels were 12 cm^3. All spectroscopic data were acquired with a separate non-water suppressed scan using the GE PROBE procedure (GE Medical Systems, Waukesha, WI, USA). Gradient order for the two frontal lobe voxels, which are particularly susceptible to artifacts arising from tissue/air/water interface, was optimized by applying the last slice selection pulse of the PRESS sequence in the axial direction as described previously (Ernst and Chang, 1996). Two of our experimental voxel regions (i.e., left frontal and left occipito-parietal) have previously been implicated in higher cognitive functioning utilizing MRS (Jung et al., 1999a; Valenzuela et al., 2000). Values for NAA were determined using LCModel (Provencher, 1993) and were corrected for percent tissue within each voxel with software developed within our laboratory (Petropoulos et al., 1999). Calibration phantoms were scanned separately for each metabolite for preparation of an LCModel basis set according to Provencher (1993). Thus, we report millimolar (mM) values of major metabolites (e.g., NAA, Cho, Cre) within the proton spectrum, as each metabolite was referenced to a separate water scan obtained within a given volume of interest. All data points for NAA measured with LCModel were valid (i.e., standard deviations <20%) for left-frontal, right-frontal, and occipito-parietal white matter voxel locations (a representative spectrum is shown in Fig. 1b).

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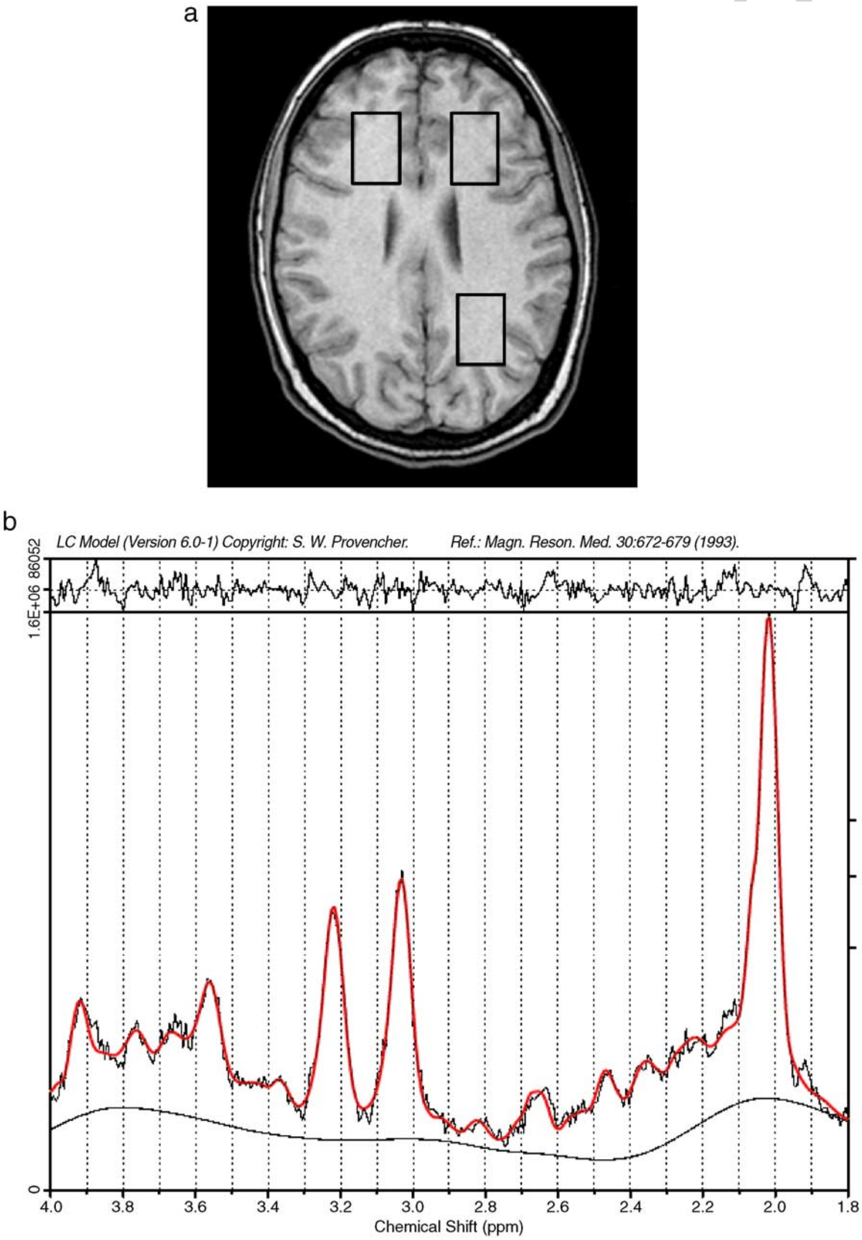

Fig. 1. (a) Representative T_1 axial MRI image with the three spectroscopic voxels located within bilateral frontal white matter and the left occipito-parietal white matter. All voxels are 12 cm^3. (b) Representative spectrum from one experimental subject, obtained from occipito-parietal white matter. The largest peak represents *N*-acetylaspartate.

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Statistics

Stepwise linear regression was computed in the combined group of men and women to determine regional specificity of NAA–IQ relationships for the major factors of intelligence as described previously (Jung et al., 1999a). In the first regression, NAA from the three voxel locations were regressed against FSIQ in the combined sample, and then individually by sex. Secondly, brain volumetric measures (i.e., GM, WM, PV) were regressed against FSIQ in the combined sample, and then individually by sex. Bonferroni correction of significance levels adjusted for multiple comparisons was .05/6 = .008. Regression equation r^2 values performed by sex were expressed as “adjusted” to account for shrinkage effects of small sample sizes. Post hoc Pearson correlation coefficients were calculated to characterize the relationships, by sex, between spectroscopic (i.e., NAA within three voxel locations), brain volumetric (i.e., WM, GM, PV), and specific cognitive subtests of the WAIS-III.

Results

Mean values for experimental variables stratified by sex are presented in Table 1. Males (N = 17) and females (N = 10) did not differ significantly in terms of age, handedness, or Full Scale IQ. Brain volume measures (all measures in cubic centimeters) differed significantly, with women having smaller volumes of pure WM [women = 523.19, men = 668.10, $t_{(25)}$ = −7.995, P < .001], pure GM [women = 560.29, men = 634.62, $t_{(25)}$ = −2.68, P = .013], and TBP [women = 1307.62, men = 1556.30, $t_{(25)}$ = −7.32, P < .001]. The ratio of pure GM to pure WM was slightly more for women (GM/WM = 1.07) than for males (GM/WM = .95), although not significantly. If PV values are all allocated to GM, the magnitude of the ratio differences is similar for women compared to men (1.46 versus 1.42) and is consistent with other reports using automated segmentation routines that create only GM and WM volumes (Goldstein et al., 2001; Haier et al., in press).

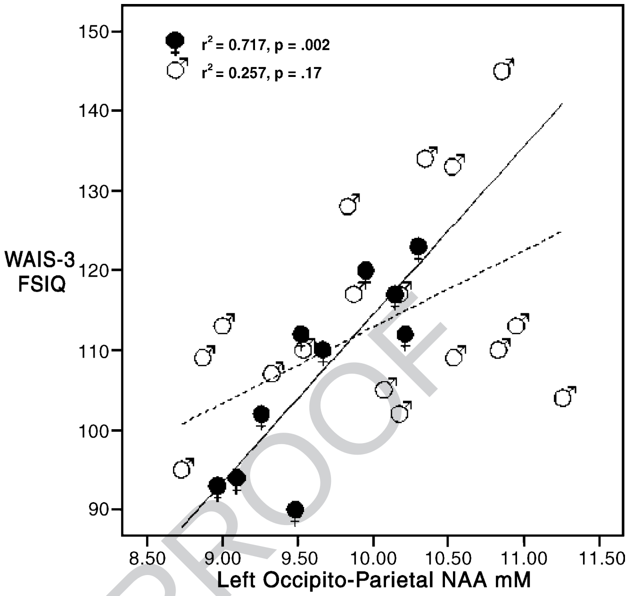

Fig. 2. Scatterplot of the relationship, by sex, between the Wechsler Adult Intelligence Scale-Revision 3, Full Scale Intelligence Quotient, and NAA within the occipito-parietal white matter. Female data points are represented by the symbol “♀”, male data points by the symbol “♂”.

Table 1

	Males (N = 17)	Females (N = 10)	t (P)
Age	24.9 (6.1)	24.6 (5.8)	.14 (.80)
Handedness (right/left)	14/3	9/1	ns
WAIS-FSIQ	114.8 (13.1)	107.3 (11.8)	1.48 (.15)
Left frontal NAA mM	9.6 (.72)	9.5 (.54)	.13 (.89)
Right frontal NAA mM	8.8 (.72)	8.3 (.49)	1.59 (.124)
Left occipito-parietal NAA mM	10.1 (.76)	9.7 (.48)	1.46 (.155)
White matter	668.1 (50.1)	523.2 (35.8)	8.00 (<.001)
Gray matter	634.6 (72.9)	560.3 (65.4)	2.68 (.01)
Partial volume	210.0 (30.5)	183.4 (38.3)	1.99 (.058)
Total brain parenchyma	1550.7 (66.5)	1303.6 (113.4)	7.18 (<.001)

WAIS FSIQ = Wechsler Adult Intelligence Scale-Full Scale Intelligence Quotient.
NAA = N-acetylaspartate.
mM = millimolar.

In the combined sample of men and women, we regressed NAA from the three voxel locations against FSIQ. We found that a model including only occipito-parietal white matter predicted FSIQ [$F_{(1,25)}$ = 8.65, P = .007; r^2 = .26], replicating and extending our previous findings (Fig. 2). Next, we performed linear regressions within each group, revealing a strong relationships for females, with a combination of higher occipito-parietal NAA and lower left-frontal NAA predicting FSIQ [$F_{(2,7)}$ = 21.84, P < .001; adjusted r^2 = .82]. Although positive relationships between neurometabolites and cognition were found in men, these did not reach statistical significance in any voxel location. In post hoc analyses undertaken in the total sample and separately by sex, neither Cho nor Cre were predictive of FSIQ in either regression or correlation analyses. Linear regression of volumetric measures (i.e., GM, WM, PV) showed that WM volumes alone predicted FSIQ in the combined sample, although this did not exceed significance thresholds given adjustments for multiple comparisons [$F_{(1,25)}$ = 5.38, P = .029; r^2 = .18]. Regression analysis revealed no significant relationships between volumetric and FSIQ measures when groups were stratified by sex. Table 2 shows post hoc correlations between each subtest and index of the WAIS-III and NAA in each voxel location stratified by sex. Table 3 shows post hoc correlations between brain volume measures (i.e., GM, WM, PV) and WAIS-III subtests stratified by sex. Of note, for women, NAA was positively related to FSIQ in the occipito-parietal WM (+0.85, P < .01) and inversely related to FSIQ within the left frontal WM voxel at trend levels (−.58, P = .08). This finding was generally consistent across WAIS subtests with positive correlations seen with NAA from the occipito-parietal WM (11/11 subtests in women; 10/11 subtests in men) and negative correlations seen with NAA in left frontal WM (10/11 subtests in women; 6/11 subtests in men). The only significant metabolic–volumetric

Table 2

WAIS-III	Males (N = 17)			Females (N = 10)		
	L-O NAA	LF NAA	RF NAA	L-O NAA	LF NAA	RF NAA
Picture completion	0.27	0.02	−0.07	0.77*	−0.56	0.01
Vocabulary	0.22	−0.40	−0.47	0.48	−0.39	0.58
Digit symbol	0.20	0.05	−0.02	0.53	0.25	0.07
Similarities	0.14	−0.35	−0.34	0.53	−0.69	0.52
Block design	0.05	0.18	−0.02	0.68	−0.75*	−0.18
Arithmetic	0.25	0.13	−0.09	0.85**	−0.64	0.09
Matrix reasoning	0.30	−0.26	−0.38	0.80*	−0.22	0.10
Digit span	0.31	−0.21	0.01	0.36	−0.31	0.00
Information	−0.09	−0.36	−0.25	0.63	−0.56	0.42
Symbol search	0.23	0.23	−0.07	0.79*	−0.52	0.24
Letter–number seq.	0.06	−0.41	−0.43	0.42	−0.39	0.37
WAIS-VIQ	0.29	−0.21	−0.21	0.68*	−0.60	0.19
WAIS-PIQ	0.41	0.03	−0.18	0.88**	−0.45	0.03
WAIS-WMI	0.26	−0.27	−0.25	0.59	−0.52	0.01
WAIS-PSI	0.19	0.15	−0.01	0.82**	−0.23	0.27
WAIS-FSIQ	0.35	−0.16	−0.22	0.85**	−0.58	0.13

WAIS-III = Wechsler Adult Intelligence Scale-Revision 3.
WAIS-VIQ = Wechsler Adult Intelligence Scale-Verbal Intelligence Quotient.
WAIS-PIQ = Wechsler Adult Intelligence Scale-Performance Intelligence Quotient.
WAIS-WMI = Wechsler Adult Intelligence Scale-Working Memory Index.
WAIS-PSI = Wechsler Adult Intelligence Scale-Processing Speed Index.
WAIS-FSIQ = Wechsler Adult Intelligence Scale-Full Scale Intelligence Quotient.
* $P < .05$.
** $P < .01$.

relationship observed for the total sample was between occipito-parietal NAA and pure WM volume [$r_{(27)} = .44$, $P = .02$].

Discussion

The current findings raise several important issues regarding the biological mechanisms underlying human intelligence. With respect to volumetric measures, we found relatively modest correlations with FSIQ, similar to previous findings, and volumetric measures were not generally related to our biochemical measures. With respect to brain biochemistry, in a combined sample of men and women, we found that broad measures of intellectual and neuropsychological performance were related to NAA measured in the occipito-parietal white matter, but not in the left or right frontal white matter, adding greater specificity to our

Table 3

WAIS-III	Males (N = 17)			Females (N = 10)		
	Partial volume	Gray volume	White volume	Partial volume	Gray volume	White volume
Picture completion	−0.14	−0.26	0.19	0.46	0.54	0.34
Vocabulary	0.31	0.22	0.41	0.48	0.51	0.67
Digit symbol	0.13	0.12	0.27	0.08	−0.31	0.16
Similarities	0.28	0.06	0.21	0.16	0.45	0.10
Block design	0.32	0.29	0.25	0.24	0.45	−0.08
Arithmetic	0.14	0.03	0.10	0.43	0.59	0.02
Matrix reasoning	0.05	0.01	0.03	0.11	0.25	−0.02
Digit span	−0.13	0.07	0.27	0.26	0.54	−0.09
Information	0.55*	0.53*	0.15	0.62	0.63*	0.64*
Symbol search	−0.21	−0.35	0.25	0.09	0.35	0.01
Letter–number seq.	−0.16	−0.25	0.39	0.73*	0.79**	0.64*
WAIS-VIQ	0.28	0.23	0.32	0.38	0.66*	0.26
WAIS-PIQ	0.26	0.18	0.42	0.40	0.40	0.22
WAIS-WMI	−0.06	−0.04	0.38	0.59	0.78**	0.23
WAIS-PSI	0.08	−0.05	0.39	0.15	0.07	0.21
WAIS-FSIQ	0.28	0.21	0.39	0.45	0.60	0.27

WAIS-III = Wechsler Adult Intelligence Scale-Revision 3.
WAIS-VIQ = Wechsler Adult Intelligence Scale-Verbal Intelligence Quotient.
WAIS-PIQ = Wechsler Adult Intelligence Scale-Performance Intelligence Quotient.
WAIS-WMI = Wechsler Adult Intelligence Scale-Working Memory Index.
WAIS-PSI = Wechsler Adult Intelligence Scale-Processing Speed Index.
WAIS-FSIQ = Wechsler Adult Intelligence Scale-Full Scale Intelligence Quotient.
* $P < .05$.
** $P < .01$.

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earlier findings (Jung et al., 1999a,b). We also found that, when subjects were stratified by sex, women exhibited much stronger associations between NAA and cognitive measures compared to men. Furthermore, within women, we found that a combined model of left occipito-parietal NAA (positive) and left frontal NAA (negative) accounted for 82% of the variance of FSIQ in women, representing a complex NAA–FSIQ interaction between posterior and frontal brain regions in women. Though preliminary, this last result is unique, as it implies a distinct biochemical signature underlying cognition that differs substantially between the sexes. As with many neuroimaging studies, these results are found within a relatively small sample, and replication with larger samples stratified by age would be highly desirable.

Our research would suggest that the WM volume–cognition relationships observed by others may be mediated by WM biochemistry, particularly levels of NAA within parietal regions underlying association cortices (e.g., angular gyrus). This relationship appears to be stronger in women than men, possibly related to the relative benefit of higher "neuronal efficiency" in which more intelligent individuals use less frontal brain capacity to solve a given task than less intelligent individuals (Haier et al., 1988, 1992; Neubauer et al., 2002). This may be an important factor in explaining why women and men score similarly on measures of intelligence, although women have smaller brains by roughly 8–10% (Filipek et al., 1994).

NAA has previously been conceptualized as a marker of intact neurons in numerous neurological and psychiatric disorders (Barker, 2001). This conceptualization is succinct in that more NAA could conceivably be linked to more neuronal mass (e.g., dendritic arbor, increased neuronal fraction), which in turn should underlie intelligent behavior; however, this conceptualization is contradicted by case reports of Canavan's disease (an NAA breakdown disorder) and an individual entirely lacking NAA within the proton spectrum (Martin et al., 2001). Thus, more recent conceptualizations of NAA are related to neuronal function and viability as opposed to neuronal mass (Barker, 2001). For example, NAA is observed to decline and recover in diseases including multiple sclerosis, stroke, and traumatic brain injury, likely related to metabolic depression as opposed to neuronal loss (Brooks et al., 2001; De Stefano et al., 1995; Narayanan et al., 2001). In light of these findings, we must reconsider the "more is better" concept that has informed brain–behavior research over the last century. Instead, the NAA resonance within white matter regions likely reflects both the metabolic function of the neuronal axons as well as the extent and efficiency of myelination of those axons.

Although the exact mechanism by which NAA is related to neuronal functioning, and hence broad measures of cognition, is unknown, it has been demonstrated that NAA is an important cellular osmolyte, is a storage vehicle for aspartate and glutamate, is a metabolic precursor of the excitatory dipeptide *N*-acetyl-aspartyl-glutamate, may be involved in neuronal–glial signaling, likely participate in myelin formation, and serves as a molecular water pump (Baslow, 2003a). NAA is turned over within neurons at a rate of roughly 1.4 times per day through a complex exchange between neurons and oligodendrocytes (Baslow, 2003b). The rate of synthesis of NAA has been demonstrated to be tightly coupled with the rate of glucose metabolism (Moreno et al., 2001). As the second most abundant metabolite within the brain (after glutamate), NAA must serve an important neuronal role to account for the energy consumed in its constant production and turnover. An anti-inflammatory role for NAA has also been elucidated (Rael et al., 2004), which would both explain its relative abundance in neurons and suggest a critical role for NAA in neuronal health, viability, and repair. The most compelling argument for the positive relationship between NAA and cognition performance is that NAA may serve a critical role in moving water across the hydrophobic myelin sheath during axonal firing (Baslow, 2003b), thus potentially allowing neurons to fire more rapidly and perhaps with more focused synchrony.

Research data support the notion that individuals differ in terms of the proportion of neuronal to glial cells present in various brain regions and that these differences underlie a unique metabolic signature detectable with MRS (Urenjak et al., 1993). Subsequent reports have revealed that brain metabolites are not distributed evenly throughout the brain, but rather vary systematically by region and tissue type. For example, supra-ventricular white matter has been demonstrated to have higher levels of NAA than corresponding gray matter regions (Hetherington et al., 1994; Soher et al., 1996), although others have found the reverse to be true in other regions (Noworolski et al., 1999). Similarly, posterior brain regions generally have higher levels of NAA than more anterior brain regions (Wiedermann et al., 2001), with highest white matter NAA within the centrum semiovale (Barker et al., 2000). These findings are consistent with reports that NAA is not found exclusively within neurons, but may be expressed in mature oligodendrocytes (Bhakoo and Pearce, 2000), and with reports of developmental brain maturation suggesting that myelination of the frontal lobes extends through the third decade (Bartzokis et al., 2003).

Functional studies generally find a combination of frontal and parietal–temporal regions to be related to IQ (Haier et al., 1988, 1999; Gray et al., 2003; Prabhakaran, 1997) depending upon the cognitive task, although one group has found only frontal regions to relate to more discrete aspects of cognitive performance (Duncan et al., 2000). In humans, "intelligence is what intelligence tests measure" because our measures rely so heavily upon language and verbal symbolism (numerical, spatial, relational). This would not be anticipated to hold true across species, as evolutionary selection pressures have not favored language development to the degree seen in man. However, certain brain designs will likely underlie intelligence in other species, including biochemical and structural integrity of white matter fibers, particularly within white matter regions connecting key cortical projections zones critical to adaptive function and thus evolutionary survival. Future cross-sectional studies with much larger cohorts, representing the range in age from young adulthood (i.e., 18) through healthy senescence, will be critical to further understand the biochemical underpinnings of intelligence within myelinated axons.

We predicted and found that cognitive function was related to biochemistry in predominantly occipito-parietal white matter in a complex interaction mediated by sex. While statistical significance was obtained in the combined sample, it appears that the NAA-cognitive links are much stronger in women than men. This finding has broad implications for the field of "cognitive spectroscopy" which endeavors to find biochemical links to cognitive status in health and across numerous neurologic and psychiatric disorders (Ross and Sachdev, 2004). Future studies with increased sample sizes may further elucidate whether NAA within white matter regions may play a moderating role in the differential susceptibility of the two sexes to various neurological diseases. Future research will address several questions raised by these findings: (1) are there regionally specific levels of NAA that underlie more discrete

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aspects of cognitive functioning (Grachev et al., 2001), (2) are these metabolites directly related to cognition or are they epiphenomena of other metabolic pathways, and (3) what are the underlying mechanisms of neurological disease that constrain the metabolic–cognitive functioning relationship?

Acknowledgments

We would like to thank Morris Baslow for his thoughtful insights and review of this manuscript. Portions of this research were presented at the 33rd annual meeting of the International Neuropsychological Society.

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