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ORIGINAL ARTICLE

Body mass and cardiorespiratory fitness are associated with altered brain metabolism

Ryan J. Larsen[1] · Lauren B. Raine[2] · Charles H. Hillman[1,2,3] · Arthur F. Kramer[1,2] · Neal J. Cohen[1,4] · Aron K. Barbey[1,4,5]

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Abstract

Magnetic Resonance Spectroscopy provides measures of brain chemistry that are sensitive to cardiorespiratory fitness and body composition. The concentration of N-acetyl aspartic acid (NAA) is of interest because it is a marker of neuronal integrity. The ratio of NAA to creatine, a standard reference metabolite, has been shown to correlate with measures of both cardiorespiratory fitness and body composition. However, previous studies have explored these effects in isolation, making it impossible to know which of these highly correlated measures drive the correlations with NAA/Cr. As a result, the mechanisms underlying their association remain to be established. We therefore conducted a comprehensive study to investigate the relative contributions of cardiorespiratory fitness and percent body fat in predicting NAA/Cr. We demonstrate that NAA/Cr in white matter is correlated with percent body fat, and that this relationship largely subsumes the correlation of NAA/Cr with cardiorespiratory fitness. These results underscore the association of body composition with axonal integrity and suggests that this relationship drives the association of NAA/Cr with physical fitness in young adults.

Keywords Magnetic resonance spectroscopy · N-acetyl aspartic acid (NAA) · Body mass index · Cardiorespiratory fitness · Body composition

Introduction

Physical activity confers substantial cognitive benefits (Hillman et al. 2008), particularly for executive function (Colcombe and Kramer 2003; Kramer and Colcombe 2018) and memory (Hayes et al. 2015). Proposed mechanisms for these benefits include increased neurotropic factors, angiogenesis (Black et al. 1990), reduced inflammation, improved energy production and activity, and reduced atrophy, particularly in the hippocampus (Firth et al. 2018) and regions within prefrontal cortex (Williams et al. 2017). Physical activity also reduces the risk of overweight and obesity, which are associated with poorer cognitive performance (Fitzpatrick et al. 2013; Prickett et al. 2015; Smith et al. 2011) and are predictive of future cognitive declines (Gustafson et al. 2003). In recent years the mechanisms by which cardiorespiratory health and body composition impact brain structure and function have been elucidated by brain imaging techniques, such as structural imaging (Williams et al. 2017), functional MRI (Gonzales et al. 2014), cerebral blood flow measurements (Chapman et al. 2013; Pereira et al. 2007), and diffusion tensor imaging (DTI) (Voss et al. 2013).

A promising neural correlate of physical activity is the concentration of N-acetyl aspartic acid (NAA) in the brain, measured using Magnetic Resonance Spectroscopy (MRS). NAA is a marker of neuronal viability (Moffett et al. 2007) and has been shown to have favorable associations with memory, executive function, reasoning ability (Nikolaidis et al. 2017; Paul et al. 2016), and processing speed (Ross et al. 2005). Given its sensitivity to both neuronal health and

✉ Ryan J. Larsen
larsen@illinois.edu

Aron K. Barbey
barbey@illinois.edu

[1] Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana, Champaign, IL, USA

[2] Department of Psychology, Northeastern University, Boston, MA, USA

[3] Department of Physical Therapy, Movement, & Rehabilitation Sciences, Northeastern University, Boston, MA, USA

[4] Department of Psychology, University of Illinois at Urbana-Champaign, Urbana-Champaign, IL, USA

[5] Department of Bioengineering, University of Illinois at Urbana-Champaign, Champaign, IL, USA

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cognitive functions, NAA is a potential marker for the cognitive benefits bestowed by physical activity. Indeed, previous studies have observed correlations of NAA with both cardiorespiratory fitness and body composition; however, the relative contributions of these effects are poorly understood.

Cardiorespiratory fitness reflects the ability of the body to meet high energy demands; it is commonly measured by VO_2max, which is the maximum rate of oxygen consumption under maximal physical stress. In middle-aged adults, endurance-trained athletes exhibited higher levels of both VO_2max and grey matter NAA/creatine relative to healthy controls (Gonzales et al. 2013), where the total creatine (Cr) signal serves as a standard reference for metabolite quantification. In older adults, VO_2max was positively correlated with NAA/Cr, with NAA/Cr mediating the relationship between VO_2max and performance on a working memory task (Erickson et al. 2012). It is possible that the relationship between NAA/Cr and cardiorespiratory fitness is driven by energy production; NAA is synthesized in neuronal mitochondria and is directly related to ATP production by oxidative phosphorylation (Moffett et al. 2007). Elevated levels of NAA may therefore reflect greater energy availability or efficiency (Rae 2014).

Elevated levels of NAA are also associated with lower adiposity. In older adults NAA/Cr in grey matter has been shown to correlate with body mass index (BMI) (Gazdzinski et al. 2010), possibly reflecting dysfunctional glucose metabolism, insulin resistance, inflammation, or cardiorespiratory disease. Elevated BMI was found to be associated with reduced NAA in the hippocampus (Coplan et al. 2014), and visceral fat was found to be negatively correlated with NAA/Cr in occipital grey matter in middle-age adults (Kaur et al. 2017). However, this pattern of findings has not been universally observed, with two prior studies failing to detect NAA/Cr to BMI correlations in the occipital grey matter of middle-aged adults (Gonzales et al. 2012; Haley et al. 2013). In a study on middle-aged adults that included voxels in both white and grey matter, it appeared that the BMI to NAA/Cr correlation was weaker in grey matter than in white matter (Gazdzinski et al. 2008).

NAA concentration in white matter is a marker of axonal integrity (Charlton et al. 2006; Kantarci et al. 2013; Moffett et al. 2007; Narayana 2005; Rae 2014), with lowered values indicative of possible demyelination or axonal loss. White matter integrity, as quantified from fractional anisotropy (FA) measurements of DTI, is negatively associated with BMI (Kullmann et al. 2015; Stanek et al. 2011), suggesting that NAA-fitness associations in the white matter may be driven by adiposity.

Based on these observations, we propose two hypotheses to account for observed associations of NAA/Cr with physical fitness: 1) NAA/Cr serves as a marker of cardiorespiratory fitness, or 2) that NAA/Cr is a marker of the effects of body composition on the brain, possibly via white matter integrity. Unfortunately, it is impossible to compare these hypotheses in the current literature given that no prior MRS study reports measure of both cardiorespiratory fitness, such as VO_2max, and body composition in the same sample. Moreover, only one previous MRS study has provided a direct measurement of body composition using imaging tools rather than BMI (Kaur et al. 2017). Also, previous studies have employed single voxel MRS. Although this approach can be applied to examine predominately grey matter or white matter, it is impossible to measure one tissue type exclusively, thereby making it difficult to distinguish whether effects are driven by one tissue type.

The present study therefore aimed to address these methodological limitations, relating NAA concentration to both VO_2max and body composition, as measured using Dual-Energy X-ray Absorptiometry (DXA) (Kaur et al. 2017), and conducting one of the largest studies to date ($n = 290$). Rather than investigating single voxels, we probed metabolite concentrations in multiple voxels using Magnetic Resonance Spectroscopy Imaging (MRSI), which allows improved differentiation of grey and white matter. Additionally, most previous studies have focused on middle age to older adults. By contrast, the mean age of participants in our study is 24 years, and therefore the present study has the potential to elucidate brain changes associated with physical fitness earlier in life. Our study therefore offers the possibility of detecting the initial deficits in a cascade of effects associated with aging. Lastly, these data are derived from baseline measurements obtained from a large intervention trial aimed at improving reasoning ability through physical fitness training, cognitive training, and mindfulness meditation (Daugherty et al. 2018).

Method

Participants

This study was performed in accordance with the Institutional Review Board at the University of Illinois, and informed consent was obtained from all study participants. Participants were recruited from the University of Illinois at Urbana-Champaign and the surrounding community to participate in a multimodal intervention study (Daugherty et al. 2018). A subset of the participants received MRI at pre- and post-assessment ($n = 290$). The data reported here are from the pre-assessment phase of the study only. To be eligible for the study, participants were age 18–44 years; had at least a high school education; spoke English fluently; had normal or corrected-to-normal vision and hearing; no current or recent medications affecting the central nervous system or presenting a risk during aerobic exercise; no history of psychological, neurological, or endocrine disease, concussion within the past two years, or learning disorders; did not smoke >10 cigarettes

per day; body mass index <35; and did not respond negatively to all items on the physical activity readiness questionnaire revised (Thomas et al. 1992).

Cardiorespiratory fitness assessment (VO_2max)

A graded exercise test designed to measure maximal oxygen consumption (VO_2max) was used to assess aerobic fitness. VO_2max is considered the "gold standard" for measuring aerobic fitness (American College of Sports Medicine 2014) and was measured using a modified Balke protocol and a computerized indirect calorimetry system (ParvoMedics True Max 2400) (American College of Sports Medicine 2014). The test began with a warm-up period wherein participants walked on a motor-driven treadmill while the speed increased gradually. Following the warm-up period, the treadmill speed was increased to a run and remained constant for the remainder of the test, and the incline was increased 2–3% every 2 min. Throughout the test, heart rate was monitored using a Polar heart rate monitor (Polar WearLink +31, Polar Electro, Finland) and participants provided subjective ratings of perceived exertion every 2 min using the Borg scales of perceived exertion (American College of Sports Medicine 2014). Averages for oxygen uptake (VO_2) and respiratory exchange ratio (RER) were assessed every 15 s. The test ended at maximum effort, which was defined using two or more of the following criteria: (1) age-defined maximum heart rate norms (i.e., heart rate > 85% of predicted maximum heart rate), (2) respiratory exchange ratio (CO_2/O_2) greater than 1.1, (3) subjective rating of perceived exertion greater than 17, and (4) leveling of VO_2 despite increasing aerobic demand. Maximum oxygen consumption (VO_2max) is reported relative to body weight (VO_2max-relative) and was calculated as milliliters of oxygen per kilogram of body weight per minute (ml/kg/min). Results from the DXA scan were used to calculate fat free VO_2max (FF VO_2), which is absolute VO_2max, divided by lean body mass.

Body composition assessment (DXA)

Standing height and weight measurements were completed with participants wearing light weight clothing and no shoes. Height and weight were measured using a stadiometer (Seca; model 240) and a Tanita WB-300 Plus digital scale (Tanita, Tokyo, Japan), respectively. Body mass index (BMI) was calculated by dividing body mass (kg) by height (m) squared. Whole body soft tissue was measured by DXA using a Hologic Discovery bone densitometer (software version 12.7.3; Hologic, Bedford, MA). Whole body total percent fat (WBTPF) was calculated using manufacturer's software. DXA measured fat is typically within 1% of actual fat (Shepherd et al. 2017). DXA is a valid and accurate measure of body composition, with precision errors of approximately 1.4% (Fuller et al. 1992; Mazess et al. 1990) and correlates well (0.99) with CT measured fat (Kullberg et al. 2009).

MRS

Acquisition

Data were acquired on a Siemens TIM Trio 3 T system with a 32-channel head coil. A high resolution T_1-weighted scan was performed to aid with voxel placement (MPRAGE – Magnetization Prepared RApid Gradient Echo, TR/TE = 1900/2.32 ms, Inversion time 900 ms, Field of View (FOV): 230 × 230 mm, 0.9 mm isotropic resolution, GRAPPA – GeneRalized Autocalibrating Partial Parallel Acquisition, acceleration factor of 2). The structural scan was acquired in a sagital orientation and resliced into transverse and coronal parallel ranges to aid with positioning of the Magnetic Resonance Spectroscopy Imaging (MRSI) scan (TR/TE = 1600/30 ms, 90° flip angle, water suppression (50 Hz bandwidth), 2048 points, spectral bandwidth of 4000 Hz, 12 × 12 matrix size, elliptical phase encoding, slice thickness: 12 mm, 4 preparation scans, 1 average. To minimize chemical shift error associated with NAA signal, a frequency shift of −2.3 ppm was applied.

The MRSI scan was angled transverse to the subject's head, and placed immediately superior to the corpus callosum, as viewed in the center sagittal plane, taking care to avoid including the lateral ventricles within the MRSI scan, as shown in Fig. 1. The midline of the MRSI scan was aligned with the longitudinal fissure and the excitation volume, or Volume of Interest (VOI) was centered within the brain as viewed from the transverse view. To accommodate variations of head size, the technician performing each scan selected one of the rows of scan size-related parameters shown on Table 1. These dimensions were chosen to maintain an approximately constant aspect ratio for different head sizes, as shown in Fig. 1.

Because the MRSI protocol was included near the end of a large battery of MRI scans, additional pilot scans were obtained immediately before the MRSI acquisition to check positioning, and to readjust MRSI placement as necessary. These scans were performed in the transverse, coronal and sagittal orientations (FLASH –Fast Low Angle SHot, TR/TE = 250/2.46 ms, slice thickness 3 mm, 30% slice separation, 40 slices, 70° flip angle, interleaved 2D acquisition, FOV: 256 × 256 mm, 256 × 256 matrix size, GRAPPA acceleration factor of 2, bandwidth 330 Hz/Pixel).

Immediately after the acquisition of the MRSI scan, a second identical scan was performed with the same placement but without water suppression. After the MRSI acquisition, we performed a T2-weighted image with the same center position and slice orientation as the MRSI scans to aid with anatomy registration (TSE-Turbo Spin Echo, TR/TE = 5000/84 ms, slice thickness 2 mm, 36 slices, 120° flip angle, interleaved

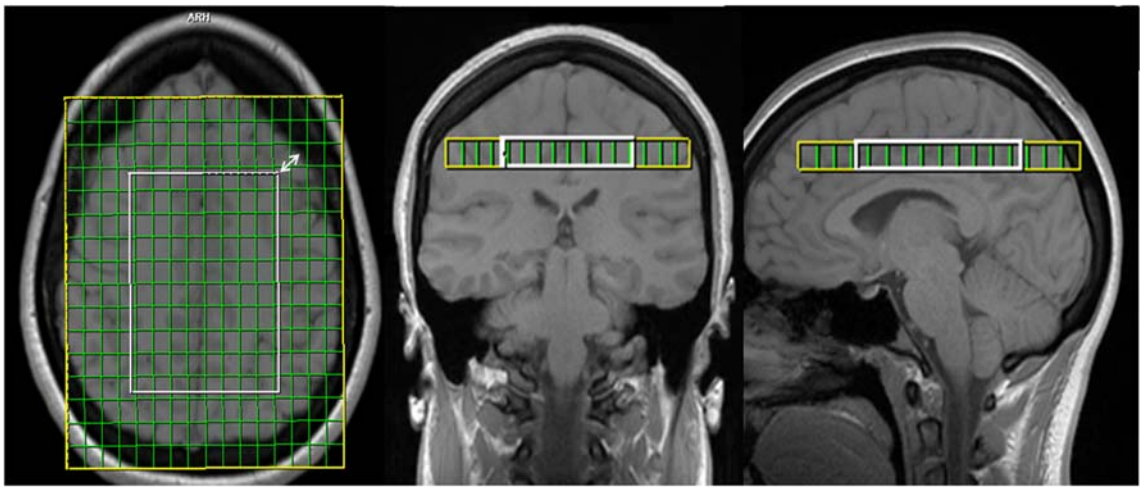

Fig. 1 Positioning of a MRSI scan with respect to the brain. The white box, excitation volume, or Volume of Interest (VOI), was centered in brain as viewed from the transverse plane. The size of the VOI was chosen from one of the rows of Table 1 so that the shortest distance from corners of the bounding box to the edge of the brain (shown by the white arrow) was approximately the size of an MRSI voxel

2D acquisition, FOV: 256 × 256 mm, 256 × 256 matrix size, GRAPPA acceleration factor of 2, bandwidth 222 Hz/Pixel).

Processing

Spectroscopy data from the scanner was processed using Matlab™ (Natick, MA) scripts. We applied a 50% Hamming filter along both spatial dimensions, Fourier transformed the data, and then combined data from all channels using a weighted combination technique adapted from the FID-A processing toolbox (Simpson et al. 2017). Phase and amplitude values from the non-water suppressed scan were used to phase the data from each channel and to determine the relative weighting coefficients of each coil. Spectra were analyzed using LCModel (Provencher 1993). Statistical analysis was performed using the total NAA signal obtained from both NAA and N-Acetylaspartylglutamic acid (NAAG). Spectral quality was excellent, as shown by a typical spectrum in Fig. 2. Spectra were analyzed from the central 6 × 6 voxels of the 12 × 12 voxels in the MRSI scan. Because the creatine signal in the most posterior row was attenuated due to the chemical shift effect, we did not include this row in our analysis, leaving a 5 × 6 grid.

Results from spectral analysis were used to calculate average concentration ratios within anatomical regions of interest using a SPM12-based processing stream that has been previously described (Larsen et al. 2016). Briefly, a normalization and tissue segmentation routine was used to define several anatomical regions based on the Automated Anatomical Labeling Atlas (Tzourio-Mazoyer et al. 2002), the Talairach Daemon Atlas (Lancaster et al. 2000), and the JHU White Matter Atlas (Hua et al. 2008). These maps were registered to the MRSI scan, and then region atlases and tissue probability maps were modified to match the point-spread distribution of the MRSI scan. The voxels of the structural scan were assigned to the region of maximum intensity or probability, with predominately white matter and grey matter voxels assigned to white or grey matter regions, respectively. Metabolite ratios were interpolated to the resolution of the structural images, and then averaged over all the voxels associated with each region (Larsen et al. 2016).

We performed statistical analysis on data obtained from the six anatomical regions, three from each hemisphere, which

Table 1 Scanning parameters were chosen from one of the rows above, based on the size of the subject's head

VOI R-L direction (mm)	VOI A-P direction (mm)	FOV R-L direction (mm)	FOV A-P direction (mm)
68	88	128	152
64	84	120	144
60	80	112	136
56	76	104	128
52	72	96	120

VOI refers to the volume of interest, or excitation volume. R-L is the right-left direction and A-P is the anterior-posterior direction

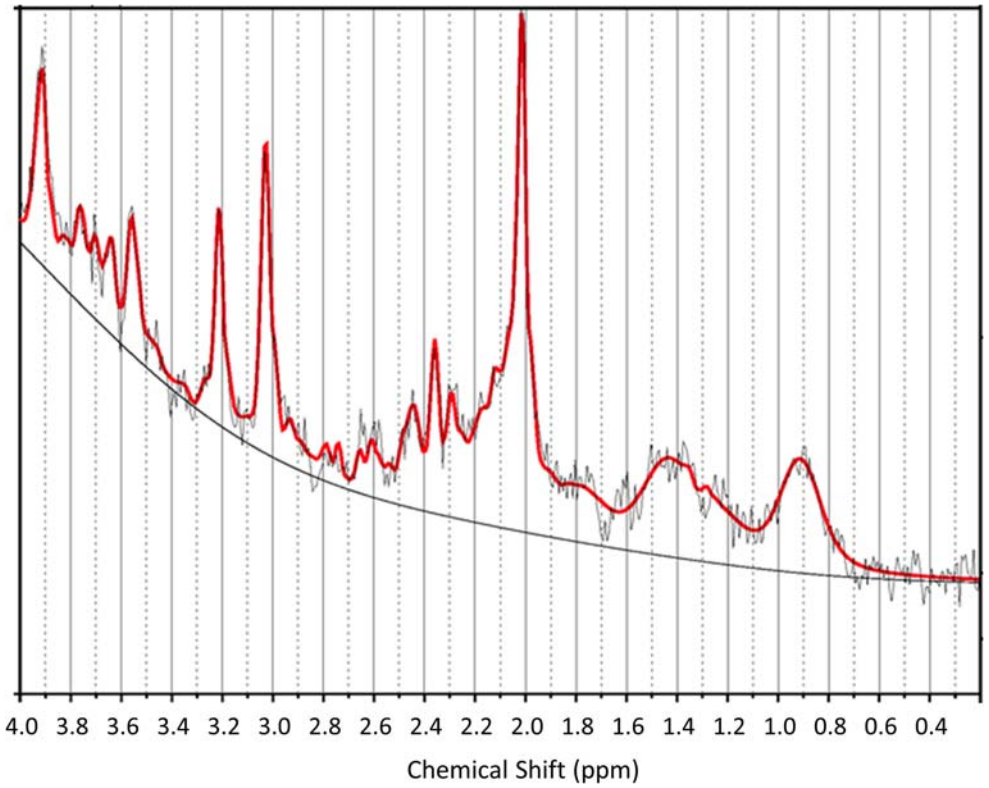

Fig. 2 A representative spectrum from an interior voxel of an MRSI scan

appeared in nearly all of the scans. The regions include the anterior medial cortex (Brodmanns areas 24, 32, and 33), the posterior medial cortex (Brodmanns areas 23 and 31), and a combined region from the corpus callosum and several white matter tracks, including the cingulum, superior corona radiata, superior longitudinal fasciculus.

Statistical analyses

Statistical analyses were performed on variables that were first corrected for control variables by creating a linear regression model and then computing the residual. The linear fit was performed without including outliers, defined as those points whose distance from the median exceeded 1.5 times the interquartile range, applied iteratively until no outliers remained. The variables VO_2max –relative, FF VO_2max, BMI, and WBTPF were corrected for age and sex.

Metabolite ratios from each of the six brain regions were corrected for age, sex, GM and CSF fraction in the region, the size of the excitation volume, the fraction of the brain region relative to the excitation volume, and the technician, out of four, who performed the scan. Corrected metabolite ratio values from the four GM regions and the two WM regions were then averaged to obtain total GM values and total WM values. In 27 of 290 scans, one or both of the posterior cortex regions were not included in the scan area due to variation in the placement of scan; in these cases, average values were obtained only from the anterior cortex.

We performed Pearson correlations on corrected variables. Because Pearson correlations can be sensitive to outliers, we report correlations with and without outliers included, where outliers of the corrected variables are those whose distance from the median exceeded 1.5 times the interquartile range. All statistical analyses and results were computed in Matlab®, version 2018b.

Results

Descriptive statistics

We obtained complete MRS data from 290 subjects. The sample was comprised of 144 males, 146 females, with ages ranging from 18 to 44 years (mean: 23.7, standard deviation: 4.9). Within our sample, 14 (5%) were underweight (BMI <18.5), 161 (57%) were healthy weight (BMI 18.5–25), 75 (27%) were overweight (BMI 25–30), and 32 (11%) were obese (BMI >30). BMI categories are typically applied to adults who are 20 years of age or older. However, because only 11% of subjects were less than 20 years of age, we applied these categories to assess the entire sample. Complete descriptive statistics from 290 subjects with MRS data are presented in Table 2.

Table 2 Descriptive statistics of primary variables, without correcting for control variables

		Mean	SD	N
Age (years)	Females	24.11	5.14	146
	Males	23.3	4.66	144
WM NAA/Cr	Females	1.69	0.1	146
	Males	1.68	0.11	144
GM NAA/Cr	Females	1.3	0.07	146
	Males	1.29	0.08	144
VO_2max–relative (mL/min/kg)	Females	36.03	6.05	141
	Males	46.07	7.34	139
BMI (kg/m^2)	Females	23.9	4.2	142
	Males	24.83	3.61	140
Fat Free VO_2max (mL/min/kg)	Females	53.61	6.85	141
	Males	59.09	7.25	138
Whole Body Total PercentFat (WBTPF)	Females	34.11	5.66	144
	Males	23.46	5.33	139

WM and GM NAA/Cr are calculated as the mean of 2 WM and 4 GM regions, respectively. Statistics are shown only from subjects for which MRS data were available

Baseline correlations

We found significant positive Pearson correlations of WM NAA/Cr with VO_2max –relative and FF VO_2max. We found significant negative Pearson correlations of WM NAA/Cr with WBTPF, and BMI (see Fig. 3). No significant correlations of NAA/Cr in grey matter were found with VO_2max - relative, FF VO_2max, WBTPF, and BMI.

Overall, we observed significant Pearson correlation coefficients, whether or not outliers are included. The exception to this is the correlation of FF VO_2max with WM NAA/Cr, where the p value increases from $p = 0.03$ to $p = 0.061$ when 5 outliers are included in the analysis. To avoid drawing conclusions that are driven by a small number of subjects, we exclude all outliers from further analysis.

Comparison of cardiorespiratory fitness vs. whole body percent fat

Our results show that the magnitude of the correlation of WM NAA/Cr with WBTPF is greater (R = -0.157) than the correlation with FF VO_2max (R = 0.131). This difference did not reach statistical significance ($p = 0.36$) (Meng et al. 1992).

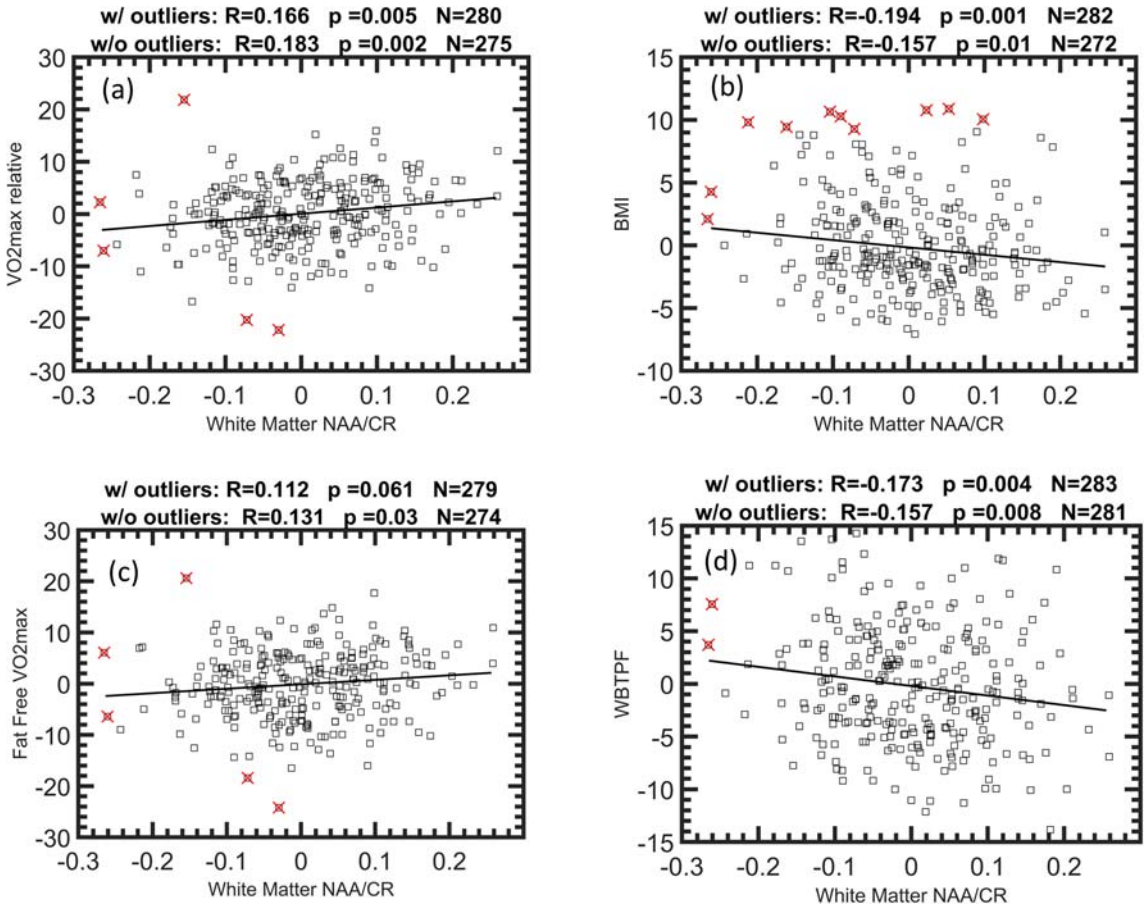

Fig. 3 Pearson correlation coefficients of WM NAA/Cr with (**a**) VO_2max – relative, (**b**) BMI, (**c**) FF VO_2max, (**d**) WBTPF. Outliers are indicated by 'x' symbols.

The difficulty of separating the relative contributions of WBTPF and FF VO_2max to predicting WM NAA/CR arises from the fact that WBTPF and FF VO_2max are correlated with each other (R = -0.258, $p < .0001$).

To separate the relative contributions of FF VO_2max and WBTPF for predicting WM NAA/Cr, we performed multilinear regression in which NAA/Cr in WM is predicted by both WBTPF and FF VO_2max. These results show that both factors combined predict 0.029 of the variance (R^2) in WM NAA/Cr (see Table 3). This is only slightly higher than the variance of 0.025 predicted by WBTPF alone, whereas FF VO_2max alone predicts only 0.017 of the variance in WM NAA/Cr (see Table 3). These results suggest that the relationship of WM NAA/CR with fitness is driven more by body composition than by cardiorespiratory fitness.

Discussion

Studying a sample size of 290 young adults, we have shown that NAA/Cr in white matter adjacent to medial grey matter is positively correlated with cardiorespiratory fitness (VO_2max-relative) and negatively associated with BMI. In contrast, no significant correlations of NAA/Cr in medial grey matter were observed with the cardiorespiratory fitness or body composition measures.

To elucidate the nature of the WM NAA/Cr- VO_2max-relative correlation, we separated contributions from cardiorespiratory fitness and fat content using FF VO_2max, and WBTPF derived from the DXA scan. We found that NAA/Cr in white matter is positively correlated with FF VO_2max and negatively correlated with WBTPF. Multilinear regression analysis shows that the WBTPF-WM NAA/Cr relationship dominates the FF VO_2max – WM NAA/Cr relationship. These results suggest that the relationship between fitness and WM NAA/Cr is driven primary by the association of WM NAA/Cr with adiposity.

Given that over a third of our participants were overweight or obese, it is possible that our results are driven by the negative consequences of adiposity. Our results are consistent with literature linking elevated body fat with reduced white matter integrity (Bettcher et al. 2013; Kullmann et al. 2015; Stanek et al. 2011). Obesity has been linked to lower fractional anisotropy (FA) values measured from DTI (Kullmann et al. 2015), and greater volumes of white matter hyper intensities or lesions (Kim et al. 2017; Lampe et al. 2019). These relationships may be driven by a variety of factors related to vascular health, such as inflammation (Bettcher et al. 2013; Lampe et al. 2019), insulin resistance (Sripetchwandee et al. 2018), hypertension (Lampe et al. 2019), oxidative stress (Miyamoto et al. 2013), or reduced blood profusion and oxygenation (Iadecola 2013). The lower values of NAA/Cr in subjects with greater adiposity may be indicative of demyelination that can occur in proinflammatory environments (Iadecola 2013).

Although we did not observe correlations of GM NAA/Cr with body composition, previous studies on older adults have observed such relationships. This suggests that in early adulthood, the effects of elevated fat content are limited to WM, with detriments to GM health or energy production accruing later in life. Lower levels of NAA/Cr in WM may indicate early stages of vascular deficiencies, to which WM is more vulnerable than GM (Iadecola 2013).

Prior studies have demonstrated that both NAA (Paul et al. 2016) and BMI (Cook et al. 2017) correlate with cognitive performance. Such findings suggest that NAA may be sensitive to mechanisms by which fat content affects cognition. Moreover, it is not clear whether changes in NAA concentration over time track changes of fat content, or whether the relationship is time-invariant, perhaps due to genetic effects. To the extent that changes to NAA are sensitive to changes in physical fitness and cognition, it is likely to be a marker of cognitive decline (Kantarci et al. 2013). Future work is required to link these correlations to cognitive performance, and to study longitudinal effects.

Table 3 Linear regression analysis predicting WM NAA/Cr as functions of combined WBTPF and FF VO_2max (first row), WBTPF (second row), and FF VO_2max

	B	*Se*	*p*	R^2
WBTPF +	−0.002	0.0011	0.072	0.029
FF VO_2max	0.0015	0.0009	0.101	
WBTPF	−0.0027	0.001	0.008	0.025
FF VO_2max	0.002	0.0009	0.03	0.017

B indicates the regression coefficients, *Se* indicates the standard error, and R^2 indicates the variance.

Conclusion

The present study provides a more comprehensive view of the relationship between brain metabolites and physical fitness using baseline measurements obtained from a large intervention trial (Daugherty et al. 2018). We characterize physical fitness using measurements of VO_2max and Whole Body Total Percent Fat (WBTPF), obtained with DXA. Measurements of brain metabolites using MRSI demonstrate that WM NAA is positively correlated with both VO_2max and WBTPF. The effect is driven primarily by WBTPF, demonstrating a close association of body fat with white matter integrity. Future work is needed to establish whether NAA/Cr is a marker for the effect of body fat and white matter on cognitive performance.

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Author's contribution **Ryan J. Larsen:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data Curation, Writing-Original Draft, Writing – Review & Editing, Visualization, Supervision. **Lauren B. Raine:** Writing – Review & Editing **Charles H. Hillman:** Conceptualization, Writing – Review & Editing, Project administration, Funding acquisition **Arthur F. Kramer:** Conceptualization, Writing – Review & Editing, Project administration, Funding acquisition **Neal J. Cohen**: Conceptualization, Writing – Review & Editing, Project administration, Funding acquisition **Aron K. Barbey**: Conceptualization, Writing – Review & Editing, Project administration, Funding acquisition.

Compliance with ethical standards

Conflict of interest The authors have no financial conflicts of interest to report.

Informed consent This study was performed in accordance with the Institutional Review Board at the University of Illinois, and informed consent was obtained from all study participants.

Data Sharing Study data are available at the Illinois Data Bank, https://doi.org/10.13012/B2IDB-9371397_V1.

References

American College of Sports Medicine (2014) ACSM s guidelines for exercise testing and prescription, 9th edn. Wolters Kluwer/ Lippincott, Williams, & Wilkins Health, Philadelphia

Bettcher BM et al (2013) Body mass and white matter integrity: the influence of vascular and inflammatory markers. PLoS One 8: UNSP e77741. https://doi.org/10.1371/journal.pone.0077741

Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT (1990) Learning causes synaptogenesis, whereas motor-activity causes angiogenesis, in cerebellar cortex of adult-rats. Proc Natl Acad Sci USA 87:5568–5572. https://doi.org/10.1073/pnas.87.14.5568

Chapman SB, Aslan S, Spence JS, Defina LF, Keebler MW, Didehbani N, Lu H (2013) Shorter term aerobic exercise improves brain, cognition, and cardiovascular fitness in aging. Front Aging Neurosci 5: 75. https://doi.org/10.3389/fnagi.2013.00075

Charlton RA et al (2006) White matter damage on diffusion tensor imaging correlates with age-related cognitive decline. Neurology 66: 217–222. https://doi.org/10.1212/01.wnl.0000194256.15247.83

Colcombe S, Kramer AF (2003) Fitness effects on the cognitive function of older adults: A meta-analytic study. Psychol Sci 14:125–130. https://doi.org/10.1111/1467-9280.t01-1-01430

Cook RL et al (2017) Relationship between obesity and cognitive function in young women: the food, mood and mind study, J Obes Artn 5923862. https://doi.org/10.1155/2017/5923862

Coplan JD et al (2014) Reduced hippocampal N-acetyl-aspartate (NAA) as a biomarker for overweight. Neuroimage-Clin 4:326–335. https://doi.org/10.1016/j.nicl.2013.12.014

Daugherty AM et al (2018) Multi-modal fitness and cognitive training to enhance fluid intelligence. Intelligence 66:32–43. https://doi.org/10.1016/j.intell.2017.11.001

Erickson KI et al (2012) Beyond vascularization: aerobic fitness is associated with N-acetylaspartate and working memory. Brain Behav 2: 32–41. https://doi.org/10.1002/brb3.30

Firth J, Stubbs B, Vancampfort D, Schuch F, Lagopoulos J, Rosenbaum S, Ward PB (2018) Effect of aerobic exercise on hippocampal volume in humans: A systematic review and meta-analysis. Neuroimage 166:230–238. https://doi.org/10.1016/j.neuroimage.2017.11.007

Fitzpatrick S, Gilbert S, Serpell L (2013) Systematic review: are overweight and obese individuals impaired on behavioural tasks of executive functioning? Neuropsychol Rev 23:138–156. https://doi.org/10.1007/s11065-013-9224-7

Fuller NJ, Laskey MA, Elia M (1992) Assessment of the composition of major body regions by dual-energy X-ray absorptiometry (Dexa), with special reference to limb muscle mass. Clin Physiol 12:253–266. https://doi.org/10.1111/j.1475-097X.1992.tb00831.x

Gazdzinski S, Kornak J, Weiner MW, Meyerhoff DJ, Nat R (2008) Body mass index and magnetic resonance markers of brain integrity in adults. Ann Neurol 63:652–657. https://doi.org/10.1002/ana.21377

Gazdzinski S, Millin R, Kaiser LG, Durazzo TC, Mueller SG, Weiner MW, Meyerhoff DJ (2010) BMI and neuronal integrity in healthy, cognitively normal elderly: a proton magnetic resonance spectroscopy study. Obesity 18:743–748. https://doi.org/10.1038/oby.2009.325

Gonzales MM, Tarumi T, Eagan DE, Tanaka H, Vaghasia M, Haley AP (2012) Indirect effects of elevated body mass index on memory performance through altered cerebral metabolite concentrations. Psychosom Med 74:691–698. https://doi.org/10.1097/PSY.0b013e31825fflde

Gonzales MM et al (2013) Aerobic fitness and the brain: increased N-acetyl-aspartate and choline concentrations in endurance-trained middle-aged adults. Brain Topogr 26:126–134. https://doi.org/10.1007/s10548-012-0248-8

Gonzales MM et al (2014) Central adiposity and the functional magnetic resonance imaging response to cognitive challenge. Int J Obes 38: 1193–1199. https://doi.org/10.1038/ijo.2014.5

Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I (2003) An 18-year follow-up of overweight and risk of Alzheimer disease. Arch Intern Med 163:1524–1528. https://doi.org/10.1001/archinte.163.13.1524

Haley AP, Gonzales MM, Tarumi T, Tanaka H (2013) Dyslipidemia links obesity to early cerebral neurochemical alterations. Obesity 21: 2007–2013. https://doi.org/10.1002/oby.20332

Hayes SM et al (2015) Physical activity is positively associated with episodic memory in aging. J Int Neuropsychol Soc 21:780–790. https://doi.org/10.1017/S1355617715000910

Hillman CH, Erickson KI, Kramer AF (2008) Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci 9: 58–65. https://doi.org/10.1038/nrn2298

Hua K et al (2008) Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. Neuroimage 39:336–347. https://doi.org/10.1016/j.neuroimage.2007.07.053

Iadecola C (2013) The pathobiology of vascular dementia. Neuron 80: 844–866. https://doi.org/10.1016/j.neuron.2013.10.008

Kantarci K et al (2013) MRI and MRS predictors of mild cognitive impairment in a population-based sample. Neurology 81:126–133. https://doi.org/10.1212/WNL.0b013e31829a3329

Kaur S, Birdsill AC, Steward K, Pasha E, Kruzliak P, Tanaka H, Haley AP (2017) Higher visceral fat is associated with lower cerebral N-acetyl-aspartate ratios in middle-aged adults. Metab Brain Dis 32: 727–733. https://doi.org/10.1007/s11011-017-9961-z

Kim KW, Seo H, Kwak MS, Kim D (2017) Visceral obesity is associated with white matter hyperintensity and lacunar infarct. Int J Obes 41: 683–688. https://doi.org/10.1038/ijo.2017.13

Kramer AF, Colcombe S (2018) Fitness effects on the cognitive function of older adults: a meta-analytic study-revisited. Perspect Psychol Sci 13:213–217. https://doi.org/10.1177/1745691617707316

Kullberg J et al (2009) Whole-body adipose tissue analysis: comparison of MRI, CT and dual energy X-ray absorptiometry. Br J Radiol 82: 123–130. https://doi.org/10.1259/bjr/80083156

Kullmann S, Schweizer F, Veit R, Fritsche A, Preissl H (2015) Compromised white matter integrity in obesity. Obes Rev 16:273–281. https://doi.org/10.1111/obr.12248

Lampe L et al (2019) Visceral obesity relates to deep white matter hyperintensities via inflammation. Ann Neurol 85:194–203. https://doi.org/10.1002/ana.25396

Lancaster JL et al (2000) Automated Talairach Atlas labels for functional brain mapping. Hum Brain Mapp 10:120–131. https://doi.org/10.1002/1097-0193(200007)10:3<120::Aid-Hbm30>3.0.Co;2-8

Larsen RJ, Newman M, Nikolaidis A (2016) Reduction of variance in measurements of average metabolite concentration in anatomically-defined brain regions. J Magn Reson 272:73–81. https://doi.org/10.1016/j.jmr.2016.09.005

Mazess RB, Barden HS, Bisek JP, Hanson J (1990) Dual-energy X-Ray absorptiometry for total-body and regional bone-mineral and soft-tissue composition. Am J Clin Nutr 51:1106–1112

Meng XL, Rosenthal R, Rubin DB (1992) Comparing correlated correlation-coefficients. Psychol Bull 111:172–175. https://doi.org/10.1037//0033-2909.111.1.172

Miyamoto N, Maki T, Pham LD, Hayakawa K, Seo JH, Mandeville ET, Mandeville JB, Kim KW, Lo EH, Arai K (2013) Oxidative stress interferes with white matter renewal after prolonged cerebral hypoperfusion in mice. Stroke 44:3516–3521. https://doi.org/10.1161/Strokeaha.113.002813

Moffett JR, Ross B, Arun P, Madhavarao CN, AMA N (2007) N-acetylaspartate in the CNS: From neurodiagnostics to neurobiology. Prog Neurobiol 81:89–131. https://doi.org/10.1016/j.pneurobio.2006.12.003

Narayana PA (2005) Magnetic resonance spectroscopy in the monitoring of multiple sclerosis. J Neuroimaging 15:46s–57s. https://doi.org/10.1177/1051228405284200

Nikolaidis A, Baniqued PL, Kranz MB, Scavuzzo CJ, Barbey AK, Kramer AF, Larsen RJ (2017) Multivariate associations of fluid intelligence and NAA. Cereb Cortex 27:2607–2616. https://doi.org/10.1093/cercor/bhw070

Paul EJ et al (2016) Dissociable brain biomarkers of fluid intelligence. Neuroimage 137:201–211. https://doi.org/10.1016/j.neuroimage.2016.05.037

Pereira AC et al (2007) An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci U S A 104:5638–5643. https://doi.org/10.1073/pnas.0611721104

Prickett C, Brennan L, Stolwyk R (2015) Examining the relationship between obesity and cognitive function: A systematic literature review. Obes Res Clin Pract 9:93–113. https://doi.org/10.1016/j.orcp.2014.05.001

Provencher SW (1993) Estimation of metabolite concentrations from localized in-vivo proton Nmr-spectra. Magn Reson Med 30:672–679. https://doi.org/10.1002/mrm.1910300604

Rae CD (2014) A guide to the metabolic pathways and function of metabolites observed in human brain H-1 magnetic resonance spectra. Neurochem Res 39:1–36. https://doi.org/10.1007/s11064-013-1199-5

Ross AJ, Sachdev PS, Wen W, Valenzuela MJ, Brodaty H (2005) Cognitive correlates of H-1 MRS measures in the healthy elderly brain. Brain Res Bull 66:9–16. https://doi.org/10.1016/j.brainresbull.2005.01.015

Shepherd JA, Ng BK, Sommer MJ, Heymsfield SB (2017) Body composition by DXA. Bone 104:101–105. https://doi.org/10.1016/j.bone.2017.06.010

Simpson R, Devenyi GA, Jezzard P, Hennessy TJ, Near J (2017) Advanced processing and simulation of MRS data using the FID appliance (FID-A)an open source, MATLAB-based toolkit. Magn Reson Med 77:23–33. https://doi.org/10.1002/mrm.26091

Smith E, Hay P, Campbell L, Trollor JN (2011) A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. Obes Rev 12:740–755. https://doi.org/10.1111/j.1467-789X.2011.00920.x

Sripetchwandee J, Chattipakorn N, Chattipakorn SC (2018) Links between obesity-induced brain insulin resistance, brain mitochondrial dysfunction, and dementia. Front Endocrinol 9:ARTN 496. https://doi.org/10.3389/fendo.2018.00496

Stanek KM, Grieve SM, Brickman AM, Korgaonkar MS, Paul RH, Cohen RA, Gunstad JJ (2011) Obesity is associated with reduced white matter integrity in otherwise healthy adults. Obesity 19:500–504. https://doi.org/10.1038/oby.2010.312

Thomas S, Reading J, Shephard R J (1992) Revision of the Physical Activity Readiness Questionnaire (PAR-Q). Canadian Journal of Sport Sciences 17(4), 338–345

Tzourio-Mazoyer N et al (2002) Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15:273–289. https://doi.org/10.1006/nimg.2001.0978

Voss MW et al (2013) The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: results of a one-year exercise intervention. Hum Brain Mapp 34:2972–2985. https://doi.org/10.1002/hbm.22119

Williams VJ, Hayes JP, Forman DE, Salat DH, Sperling RA, Verfaellie M, Hayes SM (2017) Cardiorespiratory fitness is differentially associated with cortical thickness in young and older adults. Neuroimage 146:1084–1092. https://doi.org/10.1016/j.neuroimage.2016.10.033