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Lower Working Memory Performance in Overweight and Obese Adolescents Is Mediated by White Matter Microstructure

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Abstract

Objectives—Elevated body mass index (BMI) is associated with deficits in working memory, reduced gray matter volume in frontal and parietal lobes, as well as changes in white matter (WM) microstructure. The current study examined whether BMI was related to working memory performance and blood oxygen level dependent (BOLD) activity, as well as WM microstructure during adolescence.

Methods—Linear regressions with BMI and (1) verbal working memory BOLD signal, (2) spatial working memory BOLD signal, and (3) fractional anisotropy (FA), a measure of WM microstructure, were conducted in a sample of 152 healthy adolescents ranging in BMI.

Results—BMI was inversely related to IQ and verbal and spatial working memory accuracy; however, there was no significant relationship between BMI and BOLD response for either verbal or spatial working memory. Furthermore, BMI was negatively correlated with FA in the left superior longitudinal fasciculus (SLF) and left inferior longitudinal fasciculus (ILF). ILF FA and IQ significantly mediated the relationship between BMI and verbal working memory performance, whereas SLF FA, but not IQ, significantly mediated the relationship between BMI and accuracy of both verbal and spatial working memory.

Conclusions—These findings indicate that higher BMI is associated with decreased FA in WM fibers connecting brain regions that support working memory, and that WM microstructural deficits may underlie inferior working memory performance in youth with higher BMI. Of interest, BMI did not show the same relationship with working memory BOLD activity, which may indicate that changes in brain structure precede changes in function.

Keywords

Body mass index; Diffusion tensor imaging; Magnetic resonance imaging; Multimodal imaging; Executive function; Adolescent development

Introduction

Rates of adolescent obesity in the United States have increased at a staggering rate, with four times as many adolescents reaching obese states today compared to 30 years ago (Ogden, Carroll, Kit, & Flegal, 2014). Overweight youth are more likely to remain overweight as adults (Whitaker, Wright, Pepe, Seidel, & Dietz, 1997), which puts them at an even greater risk for developing health problems, including heart disease, type 2 diabetes and depression. Adolescence is a critical period in development for establishing healthy behaviors and implementing interventions, given the tremendous physiological and social changes occurring during this time that make the brain particularly receptive to adaptation (Lee et al., 2014).

Obesity is defined through several factors including body mass index (BMI) and excess peripheral fat accumulation, which lead to changes in blood pressure, inflammation, dyslipidemia and insulin resistance (Bastard et al., 2006). At the level of the brain, elevated BMI is linked to reductions in gray matter volume in temporal, frontal and occipital cortices, as well as hippocampus, thalamus, and midbrain across the lifespan (Shefer, Marcus, & Stern, 2013). Alterations in WM volume and microstructure, the latter determined with diffusion tensor imaging (DTI), are more complex, with studies often reporting both positive and negative associations between these measures and obesity or BMI (Shefer et al., 2013). Some studies using DTI have shown that elevated BMI is linked to reduced WM microstructure, more broadly (Yau, Castro, Tagani, Tsui, & Convit, 2012; Yau, Kang, Javier, & Convit, 2014), although one study found no association between BMI and WM microstructure in adolescents (Alosco et al., 2014). Moreover, studies in obese mice showing reduced myelin and compromised fatty acid metabolism (Sena, Sarlieve, & Rebel, 1985) and magnetic resonance spectroscopy research showing reduced N-acetylaspartate in the brains of overweight adults (Gazdzinski, Kornak, Weiner, & Meyerhoff, 2008) suggest that obesity is associated with myelin and axonal abnormalities, which makes the continued study of WM microstructure in human obesity particularly relevant.

Accompanying the structural deficits observed in adolescent obesity, previous literature has shown an inverse relationship between BMI and executive functioning, including working memory (for review, see Reinert, Po'e, & Barkin, 2013). Working memory is primarily supported by frontal and parietal cortical networks across development (Kwon, Reiss, & Menon, 2002), which largely coincides with cortical maturation of these regions, such that frontal and parietal lobes undergo the most protracted rates of development (Gogtay et al., 2004). In addition, WM tracts connecting frontal and parietal brain regions, namely the superior longitudinal fasciculi (SLF), have been linked with working memory performance across development, such that higher fractional anisotropy (FA), an index of WM microstructure, relates to superior performance (Darki & Klingberg, 2015). To our knowledge, the relationship between BMI and blood oxygen-level dependent (BOLD) activity during working memory has not been investigated in healthy adolescents; however, one study in adults found that obese individuals had significantly decreased activation of the superior parietal lobule compared to overweight and healthy weight individuals, and that working memory accuracy was positively related to activation in this brain region (Gonzales et al., 2010). Of interest, research in healthy adolescents has also observed that working

memory capacity is positively related to BOLD activation in frontal and parietal cortices (Klingberg, Forssberg, & Westerberg, 2002). Furthermore, a study measuring metabolic activity with positron emission tomography found an inverse association between BMI and prefrontal cortical glucose metabolism in adults, which was also positively correlated with performance in tasks of executive function (Volkow et al., 2009). Taken together, these studies implicate working memory and its underlying physiologic and anatomical substrates to BMI and obesity, particularly during adulthood.

Given the above, more research examining the underlying neural substrates that link working memory and obesity in adolescence is needed. The present study attempted to address this gap by relating BMI to working memory accuracy and BOLD activation, as well as WM micro-structure in a sample of healthy adolescents ranging from healthy weight to obese. Due to the importance of frontal and parietal cortices in working memory ability (Gonzales et al., 2010; Klingberg et al., 2002), the negative impact of obesity on working memory (Reinert et al., 2013), and reduced BOLD activation (Gonzales et al., 2010) and glucose metabolism (Volkow et al., 2009) in working memory-relevant brain regions of adults, we predicted that higher BMI would be negatively related to working memory accuracy and BOLD activation in frontal and parietal cortices during a working memory task. Furthermore, we predicted that the WM tracts connecting frontal and parietal cortices, namely the SLF, would show lower FA in youth with higher BMI. FA, a measure of anisotropic diffusion that reflects the degree of directionality of water diffusion, is highest in brain regions with parallel-oriented fibers and is thought to indicate superior WM integrity; therefore, more specifically, we predicted youth with elevated BMI would have lower FA in SLF, reflecting less coherent or myelinated WM.

Method

Participants

Adolescent data were obtained from an ongoing developmental neuroimaging study. Participants that met the following criteria were considered for analyses: (1) height and weight data were available, (2) working memory functional magnetic resonance imaging (fMRI) task completed with minimal head movement (see *Task fMRI processing and analysis*) and (3) DTI data collected with minimal head movement (see *DTI processing and analysis*). Exclusionary criteria included current (past 12 month) diagnosis of DSM-IV psychiatric disorders, significant substance use (>10 lifetime alcoholic drinks or >2 drinks/occasion, >5 uses of marijuana, any other drug use, or > 4 cigarettes per day), significant head trauma, neurological illness, chronic medical problems affecting the central nervous system (e.g., diabetes, hypo/hyperthyroidism), prenatal exposure to drugs or alcohol, reported history of psychotic disorders in biological parents, current pharmacological treatment that may affect neural function (e.g., psychoactive medication), the inability of a parent to provide family history information, left-handedness, pregnancy, and MRI contraindications. The final sample was comprised of 152 youth (girls = 67) between the ages of 12 and 17 years. Written assent and consent from all children and their parents, respectively, were obtained in accordance with the Oregon Health & Science University (OHSU) Institutional Review Board and the Helsinki Declaration.

Within 1 week of the scan session, youth completed the 2-subtest version of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) to estimate intellectual functioning and the Pubertal Development Scale (PDS) (Petersen, Crockett, Richards, & Boxer, 1988) to provide an estimate of pubertal maturation *via* self-report. Youths' parents completed the Hollingshead Index of Social Position to determine socioeconomic status (SES) (Hollingshead, 1975). Weight and height were also obtained on-site within 1 week of the scan session. Age-adjusted BMI percentile was calculated with the Centers for Disease Control and Prevention's BMI Percentile Calculator for Child and Teen English Version (<http://nccd.cdc.gov/dnpabmi/Calculator.aspx>) by providing participant birth date, date of measurement, sex, height (to nearest 0.1 cm) and weight (to nearest 0.1 kg). Percentiles are distributed such that youth were classified as underweight (<5th percentile), healthy weight (5-85th percentile), overweight (85-95th percentile), or obese (>95th percentile). Underweight youth were not included in the current study due to potential distinct mechanisms supporting their neurodevelopment (Van den Eynde & Treasure, 2009).

Image Acquisition

Participant scanning occurred on a Siemens Tim Trio 3.0 Tesla MRI scanner (Siemens Medical Solutions, Erlangen, Germany) at the Advanced Imaging Research Center at OHSU. Task stimuli were presented from a laptop computer through a data projector to a screen at the rear of the MRI bore. Participants viewed stimuli through a mirror mounted on a 12-channel head coil and made responses with their right hands using a four-button opto-isolated button box.

fMRI

Functional images were collected in the axial plane oblique to anterior commissure–posterior commissure (AC-PC), using a high-angular resolution T2*-weighted echo-planar imaging (EPI) sequence [repetition time (TR) = 2000 ms, echo time (TE) = 30ms, field of view (FOV) = 240 mm², flip angle = 90°, slices = 33 contiguous, slice thickness = 3.8 mm, repetitions = 166, scan time = 7:22]. During fMRI data acquisition, the subjects performed a blocked design spatial and verbal working memory task, which has been previously published (Alarcon, Cservinka, Fair, & Nagel, 2014; Nagel, Herting, Maxwell, Bruno, & Fair, 2013). The task included 12 blocks alternating between spatial working memory (4 blocks), verbal working memory (4 blocks), and control vigilance (4 blocks) conditions. Task conditions were differentiated by way of task instructions presented for 4000–6000 ms. Spatial and verbal working memory blocks contained 16 trials per block, while vigilance blocks contained 8 trials per block for a total of 160 trials.

Stimuli were presented on the screen for 500ms with an inter-trial interval of 1500 ms. Task duration was 7 min and 22s. The stimuli consisted of capitalized, white, phonemically similar letters (e.g., D, G, P, etc.) that were presented one at a time in various spatial locations. During spatial working memory trials, participants were instructed to make a button press each time a stimulus appeared in a repeat location two stimuli prior, regardless of the stimulus content. During verbal working memory trials, the participant pressed a button each time the same letter was repeated two stimuli prior, regardless of spatial location. A vigilance condition was included to act as a control for motor response and

visual and attentional processing of stimuli. During vigilance, white and gray dots were presented in the same spatial locations as letter stimuli, and youth were asked to make a response when a gray dot was presented. The task was displayed with Presentation software (Version 0.70, www.neurobs.com). Accuracy (as a proportion of all trials) and reaction time; (RT; for correct trials) were collected for all blocks (Figure 1).

Anatomical MRI

Diffusion-weighted images (DWI) were acquired oblique to AC-PC, using a high-angular resolution EPI sequence (TR = 9100 ms, TE = 88ms, FOV = 256 mm², slices = 72, slice thickness = 2 mm, scan time = 16:52). Gradient encoding pulses were applied in 30 directions with b-values of 0 s/mm² and 1000 s/mm², three DWI runs were collected with five b0 (nondiffusion-weighted) images per run. In some cases ($n = 26$), only two DWI runs were collected due to time constraints, reducing scan time to 11:24. A diffusion field map was also acquired (TR = 790 ms; TE 1 = 5.19 ms; TE 2 = 7.65 ms; flip angle = 6°; FOV = 240 mm²; slices = 72; slice thickness = 2 mm; scan time = 3:13) to correct DWIs for eddy current-induced field distortions.

A high-resolution T1-weighted MPRAGE sequence was acquired along the sagittal plane (TR = 2300 ms; TE = 3.58 ms; FOV = 256 mm²; flip angle = 10°; slice thickness = 1.10 mm; scan time = 9:14) for co-registration of fMRI and DWI data.

Data Analysis

Demographic and task performance—Demographic and task performance data were examined for normality and occurrence of outliers using IBM SPSS Statistics 20 (IBM Corp.; Armonk, NY). Correlations between BMI percentile and continuous variables, including working memory accuracy, were conducted with Pearson's correlations. PDS, an ordinal variable, was correlated with BMI percentiles using a Spearman correlation, while the distribution of BMI percentile across the sexes was tested with a chi-square test.

Task fMRI processing and analysis—Task fMRI data were processed and analyzed using Analysis of Functional NeuroImages (AFNI) (Cox, 1996). Previously published standard image processing steps (Alarcon et al., 2014; Cservenka, Herting, & Nagel, 2012; Mackiewicz Seghete, Cservenka, Herting, & Nagel, 2013; Nagel et al., 2013) were used in the present study. Briefly, those steps included slice timing correction, motion correction, co-registration, and spatial smoothing. Motion correction included a rigid body transformation (participants >2.5 mm or 2.5° were excluded); runs with mean absolute root mean square (RMS) values exceeding 1.5 mm were also excluded. Data were modeled with a block design, accounting for the delay of the hemodynamic response, while covarying for motion and linear trends (Cohen, 1997). Contrasts of interest included verbal working memory-vigilance and spatial working memory-vigilance.

The relationship between BMI percentile and working memory BOLD activation was probed using linear regressions. Group analyses were constrained to regions relevant to working memory task activation, as defined with a one-sample *t*-test and binarized to create a mask. Therefore, linear regressions with BMI and BOLD response were restricted to

voxels within the task activation mask. In the first regression, the verbal working memory-vigilance contrast was used as the dependent measure and BMI percentile was the independent measure. Clusters were considered significant if they met a voxel-wise threshold of $p < .05$, a cluster-level threshold of $\alpha < .05$ and a minimum cluster size (37 voxels) determined with a Monte Carlo simulation implemented with AFNI's AlphaSim (Cox, 1996; Forman et al., 1995; Xiong, Gao, Lancaster, & Fox, 1995). A similar regression was conducted with the spatial working memory-vigilance contrast used as the dependent measure. A slightly different minimum cluster size (40 voxels) was determined with AlphaSim using a voxel-level threshold of $p < .05$ and cluster-level threshold of $\alpha < .05$ (Cox, 1996).

DTI processing and analysis: Raw DWI data underwent motion quality assessment with an in-house algorithm, such that RMS values were calculated for each frame ($n = 36$), and if any frame in a given dataset met the following criteria: (1) the difference in amplitude (A) and mean of amplitudes exceeded 0.8 and (2) the difference in amplitude (A) and the maximum of amplitudes exceeded 1.5, the frame was determined to have excessive motion. If a given run had more than 75% of frames with excessive motion, it was excluded altogether. Thresholds for determining sub-optimal data were empirically determined through multiple simulations.

DWI data were processed using a protocol previously published (Herting, Maxwell, Irvine, & Nagel, 2012). Briefly, processing included correction of eddy currents, magnetic field inhomogeneities and head motion, co-registration of runs, averaging, and brain extraction (Jenkinson, 2003; Jenkinson, Bannister, Brady, & Smith, 2002; Smith, 2002). AFNI was then used to calculate the diffusion tensor and identify the eigenvalues of the tensor (λ_1 , λ_2 , λ_3) for each voxel. Axial diffusion (AD) corresponded to λ_1 and radial diffusion (RD) was calculated by computing $(\lambda_2 + \lambda_3)/2$. FA and mean diffusivity (MD) values were determined for each voxel using a nonlinear computational algorithm (Cox, 1996).

Voxel-wise statistical analyses were performed using Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006), also detailed previously (Herting et al., 2012; Herting, Schwartz, Mitchell, & Nagel, 2010; Seghete, Herting, & Nagel, 2013). A group FA map was created by averaging individual FA maps thresholded at 0.2, resulting in a WM skeleton representing only the common tracts across all participants (Smith et al., 2006). MD images were averaged and projected onto the WM skeleton.

A voxel-wise linear regression was performed on FA maps with BMI percentile as the independent variable. To correct for multiple comparisons, a minimum cluster size was calculated with AlphaSim (Cox, 1996). Using a voxel-level threshold of $p < .01$ and cluster-level threshold of $\alpha < 0.05$, 71 contiguous voxels were necessary to reach significance. A similar voxel-wise linear regression with MD maps as the dependent variable was also conducted. WM tracts were identified using a MRI WM atlas (Oishi, Faria, van Zijl, & Mori, 2011).

Mediation analyses: Mean FA values were extracted from clusters that were significantly related to BMI percentile and found to correlate with verbal and spatial working memory

accuracy. In addition, BMI percentile was correlated with verbal and spatial working memory (see *Behavior*), warranting mediation analyses. Previous research has shown that IQ is related to FA across the lifespan (Chiang et al., 2009), as well as to working memory performance (Nagel et al., 2013). Although IQ did not correlate with FA values in the present sample, it was related to verbal and spatial working memory accuracy and BMI percentile (see *Behavior* and *BMI percentile is negatively related to FA*). Therefore, a serial two-mediator analysis was implemented in SPSS using the PROCESS macro (Hayes, 2013), such that BMI percentile was the independent variable, verbal or spatial working memory accuracy was the dependent variable, FA was the first mediator, and IQ was the second mediator. Serial mediation models should be implemented when the first mediator (e.g., FA) may causally influence the second mediator (e.g., IQ), as suggested previously (Chiang et al., 2009). Therefore, three indirect paths were tested with this model: (1) BMI → FA → working memory accuracy, (2) BMI → FA → IQ → working memory accuracy, and (3) BMI → IQ → working memory accuracy. This mediation was repeated for FA values from each significant cluster related to BMI percentile. Bias corrected bootstrapped 95% confidence intervals were determined with 1000 bootstrap samples.

Results

Behavior

Participant BMI ranged across healthy weight (25–84th percentile), overweight (85–95th percentile), and obese (95th percentile) categories. BMI percentile was negatively correlated with IQ ($r^2 = -0.17$; $p < .05$) and verbal ($r^2 = -0.21$; $p < .05$) and spatial ($r^2 = -0.18$; $p < .05$) working memory accuracy, but not accuracy on vigilance trials ($r^2 = -0.07$; $p > .05$). IQ was positively correlated with verbal working memory accuracy ($r^2 = 0.32$; $p < .001$), spatial working memory accuracy ($r^2 = 0.31$; $p < .001$), but not correlated with vigilance accuracy ($r^2 = 0.11$; $p > .05$). BMI percentile was not correlated with age ($r^2 = 0.03$; $p > .05$), SES ($r^2 = 0.13$; $p > .05$), PDS ($p = 0.02$; $p > .05$) or RT on verbal working memory ($r^2 = -0.05$; $p > .05$), spatial working memory ($r^2 = 0.02$; $p > .05$) or vigilance ($r^2 = -0.0$; $p > .05$) trials. Using BMI categories, rather than percentile, sex was distributed equally across the range of BMI ($\chi^2 = 0.96$; $p > .05$), as was the proportion of scans where two, rather than three, runs of DWI data were acquired ($\chi^2 = 1.69$; $p > .05$). See Table 1 for participant characteristics.

BMI Percentile does not Relate to Working Memory BOLD Activation

A voxel-wise linear regression of BMI percentile on verbal working memory-vigilance task activation yielded no significant results. Spatial working memory-vigilance task activation was also not significantly related to BMI percentile.

To account for potentially confounding effects of age and sex, previously shown to relate to working memory BOLD response (Alarcon et al., 2014; Klingberg et al., 2002; Kwon et al., 2002), linear regressions for spatial and verbal working memory, covarying for age and sex, were repeated. BMI percentile was not significantly related to verbal or spatial working memory-related BOLD activity.

BMI Percentile Is Negatively Related to FA

BMI percentile was negatively associated with FA in the left SLF and left inferior longitudinal fasciculus (ILF) (Figure 2). BMI percentile was not significantly related to MD in any WM region. Within the clusters defined by the BMI-FA regression, SLF AD was negatively correlated with BMI percentile ($r^2 = -0.13$; $p < .05$), while SLF RD and ILF RD were both positively correlated with BMI percentile ($r^2 = 0.27$; $p < .01$ and $r^2 = 0.37$; $p < .001$, respectively) (Table 2). Importantly, neither SLF FA nor ILF FA were significantly related to IQ ($r^2 = 0.12$; $p > .05$ and $r^2 = -0.004$; $p > .05$, respectively).

FA Mediates the Relationship between BMI and Working Memory Accuracy

The outcomes of the mediation analyses were the same when the dependent measure was either verbal or spatial working memory accuracy. The ILF FA indirect path and IQ indirect path both significantly mediated the direct relationship between BMI and working memory accuracy. When comparing these indirect effects, neither factor mediated the direct effect of BMI on working memory accuracy to a larger extent. Additionally, the IQ *via* ILF FA indirect path did not mediate this relationship. In the SLF model, the FA indirect path significantly mediated the relationship between BMI and working memory accuracy. Neither IQ nor IQ *via* SLF FA indirect paths significantly mediated the direct effect of BMI on working memory accuracy (Figures 3, 4; Tables 3, 4).

Discussion

This is the first study of its kind to examine relationships between BMI, working memory BOLD response and task performance, and WM microstructure in healthy adolescents. The results of the study show that neither verbal nor spatial working memory BOLD response was significantly related to BMI percentile in our sample of adolescents; however, BMI was inversely related to both verbal and spatial working memory accuracy and to WM microstructure of association fibers, ILF and SLF, that connect brain regions linked to working memory ability. Mediation of the relationship between BMI and working memory accuracy by both ILF and SLF indicates that these alterations in WM micro-structural have consequences on executive functioning of youth with elevated BMI, and that the effect of BMI on working memory is task-general, rather than domain (e.g., verbal or spatial) specific.

WM Microstructure of Association Fibers Is Inversely Related to BMI

Decreased FA in youth with higher BMI was further characterized by increased RD in both ILF and SLF and decreased AD in ILF. RD is typically negatively correlated with FA and reflects myelin integrity, such that decreased RD is interpreted as increased integrity of myelin or increased myelination (Sun et al., 2006). Conversely, AD is typically positively correlated with FD; increases in AD can result from heightened fiber coherence or decreased axonal branching, while decreases in AD can result from damage to the axon (Sun et al., 2006). Concurrent higher RD and lower AD in SLF may indicate that overweight and obese states are linked with disruptions to both myelin and axon integrity, whereas WM microstructural damage in ILF may be more specific to myelin or the myelination process. Research in genetically obese mice provides evidence that the fatty acid composition of

myelin primarily explains WM deficits observed in obesity (Sena et al., 1985), which may, in turn, be mediated by neuroinflammatory processes (Miller & Spencer, 2014).

An alternative and not mutually exclusive interpretation is that impaired vascular function in individuals with elevated BMI leads to damage of WM. Using retinal arterial diameter as a proxy for cerebral microvessel integrity, a robust indicator of cerebrovascular health, Yau and colleagues reported that retinal arteriolar integrity was significantly related to DTI-based WM microstructure measures in obese adolescents (Yau, Kim, Tirsi, & Convit, 2014), which supports the interpretation that cerebral WM damage may be vascular in nature. In fact, increased inflammation in obesity may contribute to endothelial dysfunction, which leads to reduced vascular function and blood supply that is necessary for maintenance of WM microstructure (Yau, Kang, et al., 2014). It is notable that the microstructural integrity of WM fibers inversely related to BMI were association fibers, rather than commissural or projection fibers, in the present study. Association fibers, specifically ILF and SLF, display the most protracted rate of development over the course of adolescence and young adulthood (Lebel & Beaulieu, 2011), which could make them particularly vulnerable to inflammatory insults.

Few studies have examined the relationship between body weight and WM microstructure in otherwise healthy adolescents (Alosco et al., 2014; Schaeffer et al., 2014; Yau, Kang, et al., 2014). Although one of such studies reported no significant relationship between BMI and WM FA (Alosco et al., 2014), other studies have reported reductions in FA in WM connecting the limbic cortex to temporal (Yau, Kang, et al., 2014) and frontal cortices (Schaeffer et al., 2014; Yau, Kang, et al., 2014). The lack of agreement between studies may be due to differences in sample size and age, as well as magnet strength and analytic strategy. For instance, previous studies have not used voxel-wise statistics to assess the relationship between body weight and WM FA (Alosco et al., 2014; Schaeffer et al., 2014; Yau, Kang, et al., 2014); rather, FA values were extracted from WM regions of interest and mean FA was compared in two dimensional space. Such an approach reduces the richness of the data and cannot detect regional differences or associations within a WM tract.

The current study used voxel-wise statistics in a sample larger than previously published and restricted analyses to the adolescent period, effectively maximizing the likelihood of detecting the relationship between BMI and WM microstructure during this stage of development. Indeed, reductions in ILF and SLF FA, which connect occipital-temporal and frontal-parietal cortices, respectively, as a function of BMI in adolescents were observed in the present study. The ILF is part of the visual-limbic pathway and plays an important role in focusing attention, as well as scanning, discriminating between, and sequentially ordering visual stimuli (Choi, Jeong, Polcari, Rohan, & Teicher, 2012). The working memory task used in the current study placed a large demand on visual attention processes, and the WM deficits observed in ILF may have contributed to worsened performance in youth with heightened BMI. Moreover, FA of bilateral SLF has been positively linked with working memory performance, partly mediated by verbal fluency, in a recent meta-analysis of adolescents and young adults (Peters et al., 2012); therefore, there is an additional potential mechanism through which verbal working memory performance in particular may be negatively impacted in overweight or obese states.

Working Memory BOLD Activation Is not Related to BMI

Our hypothesis predicting an inverse relationship between BMI and BOLD response in frontal and parietal cortices during working memory was not substantiated. Research conducted with adults has shown that obesity is linked with reduced BOLD activity in parietal cortex during working memory (Gonzales et al., 2010). However, this relationship was mediated by insulin, which has been shown to alter cerebral glucose metabolism (Doyle, Cusin, Rohner-Jeanrenaud, & Jeanrenaud, 1995) *via* endothelial dysfunction (Muniyappa, Iantorno, & Quon, 2008). Insulin levels were not measured in the present sample and we cannot confirm an association between insulin and working memory-related BOLD response. However, BMI is positively correlated with insulin (Kullmann, Schweizer, Veit, Fritsche, & Preissl, 2015), suggesting that elevated levels of insulin typically present in overweight and obese adolescents may be precipitating endothelial dysfunction, even if it is not reflected in the BOLD signal *per se*. Importantly, the BOLD signal is affected by cerebral blood flow (CBF), as well as oxygen and glucose metabolism (Ogawa, Lee, Kay, & Tank, 1990; Ogawa et al., 1992), and although baseline CBF is higher in adolescents, they also have higher rates of oxygen and glucose metabolism that equilibrates relative BOLD signal to that of adults (Moses, DiNino, Hernandez, & Liu, 2014; Moses, Hernandez, & Orient, 2014).

It is possible that obesity impacts components of the BOLD signal differentially in adolescents compared to adults, such that a decrease in BOLD signal during working memory is observed in adults with elevated BMI (Gonzales et al., 2010), but not in adolescents. There is some evidence in adults that elevated BMI is associated with decreased blood flow (Willeumier, Taylor, & Amen, 2011) and metabolic function (Volkow et al., 2009) in the brain; however, research is needed to confirm that these effects are also present in adolescents. Alternatively, it possible that the negative metabolic effects of obesity, insulin insensitivity or otherwise, are cumulative and only impact BOLD signal in chronic states of obesity.

Limitations and Future Directions

Despite the large sample size and multimodal approach, there are some limitations in the study that should be addressed. For instance, obesity was categorized using age-adjusted BMI percentile, which is based on weight, height, and age only. Additional measures that characterize overweight and obese states, such as abdominal adiposity, insulin, cholesterol, blood pressure, and glucose were not collected in the current study, though such measures are assumed to correlate with BMI (Bastard et al., 2006). Although BMI is the most common metric used by studies to operationalize obesity, other measures have been used to examine the neural correlates of elevated weight (Kullmann et al., 2015). Accounting for the complex effects of these factors will be important in future studies investigating neural correlates of not only obesity, but also overweight states, given that the correlations with BMI and associated factors (e.g., dyslipidemia, blood glucose) have been present in individuals who have not reached obesity (Kullmann et al., 2015).

The cross-sectional design of this study limits our conclusions regarding causality; however, there is evidence that overweight and obese states lead to changes in WM microstructure. No

studies have examined the relationship between BMI and WM microstructure longitudinally (Kullmann et al., 2015); however, recent exercise intervention studies have shown positive effects of physical exercise on WM microstructure of obese children, despite a lack of change in BMI (Krafft et al., 2014; Schaeffer et al., 2014). In one study of overweight children, an 8-month exercise intervention improved WM microstructure in the uncinate fasciculus, accompanied by a reduction in body fat (Schaeffer et al., 2014). These studies suggest a causal relationship between body weight and WM FA, such that changes in body fat lead to alterations in WM microstructure. Additionally, research in rodents supports this causal link between body weight and subsequent peripheral (Jayaraman, Lent-Schochet, & Pike, 2014) and central nervous system demyelination (Sena et al., 1985).

However, an alternative interpretation is that preexisting WM deficits may lead to elevated BMI. Although there are no studies reporting a causal effect of WM on BMI, there are rare cases of hypothalamic (Bray & Gallagher, 1975; Purnell, Lahna, Samuels, Rooney, & Hoffman, 2014) and amygdalar (King, 2006) lesions precipitating obesity in adults. However, in the present study subcortical WM micro-structure was not related to BMI. Additional longitudinal work must be conducted to confirm whether initial onset of overweight and obese states negatively impacts WM microstructure, or vice versa.

Conclusions

The current study revealed an inverse relationship between BMI and WM microstructure of left ILF and SLF in a large sample of healthy adolescents. These association fibers connect regions of the cortex that are relevant for visual attention and working memory, respectively. Furthermore, BMI shared an inverse relationship with verbal and spatial working memory accuracy that was mediated by FA in both ILF and SLF, suggesting a meaningful effect of BMI on working memory performance that is explained, in part, by the integrity of WM fibers connecting cortical regions important for cognitive and executive functions. In contrast to research conducted in adults (Gonzales et al., 2010), regional BOLD activation during working memory was not significantly related to BMI, which could indicate that the detrimental effects of elevated BMI on WM microstructure are cumulative or operate through distinct mechanisms. A lack of neurofunctional deficits during working memory may also indicate a level of resilience during the adolescent period (Lee et al., 2014) that is conducive to obesity intervention treatments (Martin, Saunders, Shenkin, & Sproule, 2014).

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Fig. 1.

Working memory task paradigm includes spatial and verbal working memory trials. In spatial working memory trials, participants are instructed to press a button when the current stimulus is in the same location as the stimulus presented two trials back, regardless of actual stimulus. In verbal working memory trials, participants press a button when the current stimulus is the same one presented two trials back, regardless of spatial location.

Fig. 2.

Age-adjusted body mass index percentile is inversely related to fractional anisotropy in left superior and inferior longitudinal fasciculi (SLF and ILF, respectively). Results (blue) are overlaid on a white matter skeleton (green), which represents common white matter tracts across all participants ($n = 152$) and a standard Montreal Neurological Institute (MNI) template. For display purposes, ILF and SLF regions were dilated with `tbss_fill` implemented in FSL.

Fig. 3.

Fractional anisotropy (FA) in left inferior (top) and superior (bottom) longitudinal fasciculi significantly mediated the relationship between age-adjusted body mass index (BMI) percentile and verbal working memory accuracy (red arrows). In addition, IQ significantly mediated the relationship between age-adjusted BMI percentile and verbal working memory accuracy (orange arrows).

Fig. 4.

Fractional anisotropy (FA) in left inferior (top) and superior (bottom) longitudinal fasciculi significantly mediated the relationship between age-adjusted body mass index (BMI) percentile and spatial working memory accuracy (red arrows). In addition, IQ significantly mediated the relationship between age-adjusted BMI percentile and spatial working memory accuracy (orange arrows).

Table 1
Participant characteristics

	Total sample (<i>n</i> = 152)	Healthy weight (<i>n</i> = 88)	Overweight (<i>n</i> = 46)	Obese (<i>n</i> = 18)
Age (years)	14.1 (1.3)	14.2 (0.1)	13.8 (0.2)	14.4 (0.4)
Sex (M/F)	85/67	48/40	25/21	12/6
^a Puberty	3.5 (0.9)	3.5 (0.1)	3.5 (0.1)	3.4 (0.2)
^b Body mass index	22.7 (4.3)	20.3 (1.9)	24.2 (1.6)	30.9 (5.4)
Percentile	72.8 (21.1)	58.9 (1.8)	90.0 (0.4)	96.9 (0.3)
^c IQ	110.6 (11.9)	111.5 (1.3)	110.2 (1.6)	106.7 (3.1)
^d Socioeconomic status	30.1 (14.1)	28.2 (1.5)	32.8 (2.2)	33.1 (3.0)
Verbal working memory accuracy (%)	94.6 (6.0)	95.3 (4.7)	93.9 (6.5)	93.2 (9.5)
Verbal working memory reaction time (ms)	598.5 (118.7)	607.5 (113.8)	590.3 (132.5)	576.1 (105.8)
Spatial working memory accuracy (%)	90.2 (9.1)	91.3 (7.5)	88.4 (10.8)	89.2 (10.8)
Spatial working memory reaction time (ms)	554.9 (134.4)	556.0 (132.5)	548.6 (143.1)	565.7 (149.9)
Vigilance accuracy (%)	96.9 (4.7)	97.2 (5.0)	96.8 (4.2)	95.8 (4.8)
Vigilance reaction time (ms)	504.2 (82.9)	507.3 (92.8)	500.4 (71.0)	498.7 (59.2)

^a Crockett Pubertal Development Scale. Values range from 1 to 5, with larger values referring to more advanced pubertal development.

^b Age-adjusted body mass index; 5–85th percentile corresponds to a healthy weight, 85–95th percentile is overweight, and greater than 95th percentile is obese.

^c The 2-subtest version of the Wechsler Abbreviated Scale of Intelligence.

^d Hollingshead Index of Social Position; larger values indicate lower socioeconomic status (middle class corresponds to 32–47 range).

Table 2
BMI percentile is negatively related to fractional anisotropy in association fibers

White matter tracts	No. of voxels	MNI coordinates (x, y, z)	Mean FA value (SD)	Effect size (f^2) ^a	Mean axial diffusion ($\mu\text{m}^2/\text{ms}$) (λ_1)		Mean radial diffusion ($\mu\text{m}^2/\text{ms}$) ($(\lambda_2 + \lambda_3)/2$)	
					β	p- value	β	p- value
Left inferior longitudinal fasciculus	131	-42, -41, -4	0.60 (0.04)	0.15	-0.13	.11	-0.37	<.001
Left superior longitudinal fasciculus	82	-23, -46, 36	0.43 (0.05)	0.12	-0.20	.02	-0.27	.001

^aCohen's f^2 of 0.15 corresponds to medium effect size.

MNI = Montreal Neurological Institute; FA = fractional anisotropy (range 0–1); SD = standard deviation.

Table 3
Fractional anisotropy mediates the effect of BMI on verbal working memory accuracy

	Effect	BootSE ^a	BootLLCI ^b	BootULCI ^c
Left inferior longitudinal fasciculus				
Total effect	– 0.0345	0.0160	– 0.0704	– 0.0079
<i>d</i> _{Ind1}	– 0.0194	0.0107	– 0.0456	– 0.0018
<i>e</i> _{Ind2}	0.0025	0.0033	– 0.0030	0.0106
<i>f</i> _{Ind3}	– 0.0176	0.0094	– 0.0436	– 0.0045
Ind1 – Ind2	– 0.0220	0.0107	– 0.0471	– 0.0048
Ind1 – Ind3	– 0.0018	0.0127	– 0.0317	0.0198
Ind2 – Ind3	0.0201	0.0105	0.0049	0.0490
Left superior longitudinal fasciculus				
Total effect	– 0.0353	0.0125	– 0.0635	– 0.0147
Ind1	– 0.0216	0.0095	– 0.0462	– 0.0070
Ind2	– 0.0019	0.0028	– 0.0102	0.0016
Ind3	– 0.0118	0.0087	– 0.0376	0.0001
Ind1 – Ind2	– 0.0197	0.0097	– 0.0459	– 0.0049
Ind1 – Ind3	– 0.0098	0.0135	– 0.0376	0.0168
Ind2 – Ind3	0.0099	0.0094	– 0.0040	0.0355

Note. Significant effects are indicated in bold

^aBootSE = Bootstrapped standard error.

^bBootLLCI = Bootstrapped lower limit confidence interval.

^cBootULCI = Bootstrapped upper limit confidence interval.

^dIndirect Effect 1 = Body mass index → Fractional anisotropy → Verbal working memory.

^eIndirect Effect 2 = Body mass index → Fractional anisotropy → IQ → Verbal working memory.

^fIndirect Effect 3 = Body mass index → IQ → Verbal working memory.

Table 4
Fractional anisotropy mediates the effect of BMI on spatial working memory accuracy

	Effect	BootSE ^a	BootLLCI ^b	BootULCI ^c
Left inferior longitudinal fasciculus				
Total effect	– 0.0003	0.0001	– 0.0006	– 0.0001
<i>d</i> _{Ind1}	– 0.0002	0.0001	– 0.0004	– 0.00001
<i>e</i> _{Ind2}	0.0000	0.0000	0.0000	0.0001
<i>f</i> _{Ind3}	– 0.0001	0.0001	– 0.0003	– 0.00003
Ind1 – Ind2	– 0.0002	0.0001	– 0.0004	– 0.00003
Ind1 – Ind3	0.0000	0.0001	– 0.0003	0.0002
Ind2 – Ind3	0.0002	0.0001	0.00005	0.0004
Left superior longitudinal fasciculus				
Total effect	– 0.0003	0.0001	– 0.0005	– 0.0001
Ind1	– 0.0002	0.0001	– 0.0004	– 0.0001
Ind2	0.0000	0.0000	– 0.0001	0.0000
Ind3	– 0.0001	0.0001	– 0.0003	0.0000
Ind1 – Ind2	– 0.0002	0.0001	– 0.0004	– 0.0001
Ind1 – Ind3	– 0.0001	0.0001	– 0.0004	0.0001
Ind2 – Ind3	0.0001	0.0001	0.0000	0.0003

Note. Significant effects are indicated in bold.

^aBootSE = Bootstrapped standard error.

^bBootLLCI = Bootstrapped lower limit confidence interval.

^cBootULCI = Bootstrapped upper limit confidence interval.

^dIndirect Effect 1 = Body mass index → Fractional anisotropy → Spatial working memory.

^eIndirect Effect 2 = Body mass index → Fractional anisotropy → IQ → Spatial working memory.

^fIndirect Effect 3 = Body mass index → IQ → Spatial working memory.