Impact of Metabolic Syndrome on Cognition and Brain
A Selected Review of the Literature

Kathy F. Yates, Victoria Sweat, Po Lai Yau, Michael M. Turchiano, Antonio Convit

Abstract—Metabolic syndrome (MetS), a clustering of risk factors for type 2 diabetes mellitus and cardiovascular disease, has been associated with cognitive dysfunction and brain abnormalities. This review describes the literature on the impact of MetS on brain and cognition and suggests directions for future research. A literature search for reports of MetS and cognition and brain imaging was conducted for both nonelderly adults and adolescents. No studies were found describing MetS and brain or cognition among adolescents; therefore, we also included studies investigating individual components of MetS in this age group. Most studies found associations between MetS and cognitive dysfunction. Multiple cognitive domains were affected by MetS in adults. In adolescents, the majority of findings were in executive functioning. Brain imaging literature in adults implicated MetS in ischemic stroke, white matter alterations, and altered brain metabolism. For adolescents, individual MetS factors were linked to volume losses in the hippocampus and frontal lobes. MetS negatively impacts cognitive performance and brain structure. Potential explanatory models include impaired vascular reactivity, neuroinflammation, oxidative stress, and abnormal brain lipid metabolism. We posit that insulin resistance-associated impairment in cerebrovascular reactivity is an important mechanism underlying brain deficits seen in MetS.

Key Words: metabolic syndrome ■ cognitive performance ■ adults ■ adolescents ■ brain imaging

The Metabolic Syndrome (MetS) has been called a global epidemic by the World Health Organization and is considered a major public health problem, with 34% of Americans over the age of 20 estimated to be affected. Among adolescents, 9.4% are estimated to have MetS, and the prevalence rises to 44.2% among those who are obese. Therefore, the MetS is one of the few clinical syndromes that affects a large portion of the general population that is potentially reversible by established interventions.

MetS is known to affect cognition and raise the risk for dementia. Interest in understanding the pathophysiological mechanisms underlying MetS and its impact on brain function will inform possible interventions. Positive cognitive changes have been seen with some interventions targeting MetS components.

MetS, first described as Syndrome X, was proposed by Reaven in 1988 in an attempt to provide a unifying pathophysiological explanation for the tendency of impaired fasting glucose, dyslipidemia, and hypertension to cluster in some individuals, who were at increased risk for cardiovascular disease and type 2 diabetes mellitus (T2DM). Because insulin resistance (IR) is thought to be the key underlying condition in Syndrome X, others then coined the term IR syndrome. This focus on the associations between IR and other cardiovascular risk factors led to the creation of clinical MetS definitions by the World Heart Organization, the International Diabetes Federation (IDF), and the National Cholesterol Education Program Third Adult Treatment Panel (NCEP ATP III), in an attempt to identify patients at increased risk for cardiovascular disease and T2DM.

The most commonly used definition for MetS in the United States is the one described by the NCEP ATP III, which is the presence of 3 or more of the following criteria: (1) abdominal obesity: waist >102 cm (>40 inches) for men or >88 cm (>35 inches) for women; (2) triglycerides ≥150 mg/dL; (3) high-density lipoprotein <40 mg/dL for men or <50 mg/dL for women; (4) blood pressure ≥130/85 mm Hg or current use of antihypertensive medications; and (5) fasting glucose level ≥110 mg/dL. The IDF uses a slightly modified definition where 1 of the 3 criteria must be abdominal obesity in addition to 2 of the other 4 criteria, and the abnormal threshold for fasting glucose is set at ≥100 mg/dL or previously diagnosed T2DM.

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Goals of the Review

Three reviews have been published recently regarding MetS and cognitive decline in older adults with a focus on individuals at high risk for dementia or with dementia.16–18 This review concentrates on the impact of MetS on cognitive functioning and brain integrity in functionally normal nonelderly adults and adolescents. Although our focus is predominantly in brain associations to MetS proper, our review for young populations also highlights associations of the individual MetS factors with cognition and brain because of the paucity of research for this population. We focus particular attention to IR, as in our opinion it is central to the impact of the syndrome on brain. At the end of the review, we provide a brief overview of one potential explanatory model for the impact of MetS on brain.

Literature Selection

Cognition

Only articles that examined cognitive functioning as an outcome associated with a diagnosis of MetS were selected for the adult review. Use of multiple neuropsychological tests for at least one cognitive domain was required. Reports that relied on self-report or that used only global/screening measures of functioning, such as the Mini-Mental State Examination, were excluded. Electronic databases were searched using the terms: metabolic syndrome paired with cognition, cognitive function, cognitive performance, or neuropsychological function.

For the children and adolescent search, inclusion criteria and search terms mirrored that of the adult studies with the exception that papers addressing Prader-Willi syndrome or focusing on children younger than 10 years of age were excluded. An expanded search was conducted, including terms such as obesity, overweight, body mass index, hypertension, lipids, high-density lipoprotein, triglycerides, blood pressure, IR, and hyperglycemia. A total of 20 studies were included, 10 for adults and 10 for adolescents.

Brain Imaging

For the brain imaging literature, MEDLINE searches were performed for keywords and terms, such as metabolic syndrome, brain, cerebral, infarct, lesion, MRI, diffusion tensor imaging, and spectroscopy. The literature reporting the brain involvement in MetS in adults was quite limited, and we found no publications among children or adolescents describing the associations between MetS and brain. Therefore, among children or adolescents, we expanded our search to also include the terms IR, prediabetes, and T2DM (the extreme of the MetS spectrum).

Neuropsychological Assessment of Cognition

Neuropsychological tests assess functioning in cognitive domains, such as intelligence, memory and learning, language, executive functioning, processing speed, and sensory-perceptual abilities. However, the literature offers little consistency in individual tests used to measure particular cognitive domains.

Impact of MetS on Cognition in Adults

A summary of the studies included in this review can be found in Table 1. Most studies report that MetS and its components have a negative impact on cognition.19–25 However, findings may vary by sex, with men being more affected in some reports,22,26 women in others,25 and some reporting no sex differences.23 Multiple cognitive domains are affected, even after controlling for medical factors, such as cardiovascular disease and T2DM,27 silent brain lesions,21 education and socioeconomic status,21,22 depressive mood, coronary heart disease, and magnetic resonance imaging findings.22 MetS has been linked to deficits in memory, visuospatial abilities, executive functioning, processing speed, and overall intellectual functioning.21–25,27,28

A few studies report no significant associations between MetS and cognition.29,30 Lack of significant findings could be a result of the low sensitivity of the test battery chosen, as well as the health status of the control group, which often includes subjects with 1 or 2 risk factors for MetS. For example, Gatto et al31 showed no group differences; however, regression analysis of their whole population using the actual number of MetS criteria met (0–5) showed significant reductions in cognitive performance with each additional MetS criterion met.

Impact of MetS on Cognition in Children and Adolescents

There is currently no literature on MetS and cognition in children and adolescents, but there is some on individual MetS components (Table 2). In 2011, Smith et al32 published a review exploring the links between obesity and cognition across the life span. In children, the majority of findings on cognition in obesity have been predominantly in executive functioning33–36 a cognitive domain known to depend on an intact frontal lobe. Frontal lobes are still developing during adolescence,37 which may render this brain region more vulnerable to metabolic dysregulation. Impaired executive function may also play a role in the development of obesity, particularly if it leads to impaired response inhibition and overeating.38 Reductions in attention and global functioning or IQ have also been reported in childhood obesity.33,36,39,40 Impairments in attention can contribute to poor performance in other cognitive domains and may help explain the deficits reported in executive functioning and IQ.

Lande et al41 found that 50% of the children with elevated blood pressure were overweight or obese and that those with systolic blood pressure ≥90th percentile for age, sex, and height scored significantly worse on attention/concentration, visual-spatial, and math tasks.

Impaired fasting glucose, an important MetS component, is often a precursor for T2DM, which has been strongly linked to cognitive dysfunction in adults.42 Our lab reported that obese adolescents with T2DM perform consistently worse than well-matched, also obese, peers on global functioning, executive function, memory, and attention.43 Given that it is rare to find a young individual with T2DM who does not also fulfill criteria for MetS, it is likely that similar findings will be present among obese adolescents with MetS.

There is only one report failing to find statistically significant cognitive impairments associated with obesity and excess weight.44 However, in this report the heaviest group of children consistently scored lower on all but one of the cognitive measures assessed.
### Table 1. Ten Studies of the Association Between Cognition and Metabolic Syndrome in Nonelderly Adults (Mean Age <65 Years)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population (MetS)</th>
<th>Control Group (No MetS)</th>
<th>Cognitive Tests</th>
<th>Covariates/Exclusions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bokura et al (2010)*</td>
<td>186 Japanese, mean age 61.2</td>
<td>1357, mean age 62.2</td>
<td>Kohs test, FAB, (sig); Okabe test (nonsig)</td>
<td>Age, sex, education, smoking, alcohol use, subclinical ischemic brain lesions; Exclusions: Neurological and psychiatric diseases</td>
<td>MetS associated with impaired executive function independent of silent brain lesions</td>
</tr>
<tr>
<td>Cavalieri et al (2010)*</td>
<td>232, mean age 65.1</td>
<td>587 (W: 149±25.3, mean age 64.8)</td>
<td>BLG, WCST, TMT-B, DSB (sig); PPT (nonsig)</td>
<td>Model 1: Age, education, sex, depressive mood, coronary heart disease, physical activityModel 2: Model 1 plus WML volume, presence of lacunes, silent infarcts, brain parenchymal factor</td>
<td>MetS related to memory and executive function in men but not women; further compromise with high hs-CRP and increasing MetS components</td>
</tr>
<tr>
<td>Gatto et al (2008)</td>
<td>112, mean age 61.8</td>
<td>741 (BMI: 26.7±4.7), mean age 60.8</td>
<td>SDMT, TMT-B, JLO, WASI-III block design, Category Fluency, BNT, Shipley, CVLT-II (nonsig)</td>
<td>Age, sex, race, education, income, smoking, CVD risk factors, statins, antihypertensives, depression</td>
<td>Correlation between hypertension and lower cognition; significant cognitive impairment with increasing MetS factors</td>
</tr>
<tr>
<td>Haley et al (2010)†</td>
<td>13, mean age 47.6</td>
<td>25 (BMI: 26.8±4.8), mean age 51.3</td>
<td>MMSE, WASI, Animal Fluency, CVLT-II, RCF, DSS, COWAT, TMT, and GPT (nonsig)</td>
<td>Age, sex, education, depression</td>
<td>No significant cognitive differences</td>
</tr>
<tr>
<td>Hassenstab et al (2010)*</td>
<td>73, mean age 60.4</td>
<td>70 (BMI: 25.0±3.4), mean age 60.1</td>
<td>Shipley, Phonemic and Category Fluency, WMS-R and WAIS-R (selected subtests), CVLT, and Stroop (mixed findings)</td>
<td>Age, sex, education, T2DM</td>
<td>Significant reductions in recall, lower overall IQ; increasing MetS factors associated with lower performance</td>
</tr>
<tr>
<td>Komulainen et al (2007)*</td>
<td>13 Women, mean age 63.6</td>
<td>88 (BMI: 26.9±3.9), mean age 63.8</td>
<td>WRT (sig); Stroop, LDST, and MMSE (nonsig)</td>
<td>Age, education, depression, HRT, BMI, prevalent CVD</td>
<td>MetS at baseline = greater risk of memory impairment at follow-up; memory declines with increasing MetS factors</td>
</tr>
<tr>
<td>Muller et al (2009)*</td>
<td>295, mean age 59</td>
<td>528 (BMI: 26±3), mean age 58</td>
<td>15LWT, RCF, VET, BSAT, Letter Fluency, and DART (sig)</td>
<td>Model 1: Age, sex, education, intellectual functioning, smoking, alcohol useModel 2: Model 1 plus extent of vascular disease, atherosclerosis, inflammation</td>
<td>MetS related to memory and visuospatial dysfunction but not executive dysfunction</td>
</tr>
<tr>
<td>Schuur et al (2010)*</td>
<td>434, mean age 61.4</td>
<td>1464, mean age 46.2</td>
<td>Stroop (sig); DART, AVL, TMT, Verbal Fluency, and WASI-III block design (nan sig)</td>
<td>Age, sex, smoking, alcohol use, education, depression, APOE</td>
<td>MetS and high HOMA-IR associated with executive dysfunction in women but not men</td>
</tr>
<tr>
<td>Segura et al (2010)*</td>
<td>19 Spanish, mean age 61.26</td>
<td>19 Spanish, mean age 59.63</td>
<td>SDMT, WASI-III vocabulary, GPT, and CPT-II (nonsig)</td>
<td>Age, education, IQ, sex</td>
<td>No significant cognitive differences between groups; FA significantly correlated with SDMT and CPT-II</td>
</tr>
<tr>
<td>Tournoy et al (2010)*</td>
<td>1007 European, mean age 61.0</td>
<td>2145 (BMI: 26.3±3.3), mean age 59.3</td>
<td>RCF, CTRM, DSST (sig when applied to individual MetS components)</td>
<td>Age, age leaving education, smoking, alcohol consumption, physical activity, depression, hs-CRP, center location</td>
<td>MetS not associated with cognitive impairment; T2DM linked to poorer memory, executive functions, and processing speed</td>
</tr>
</tbody>
</table>

Cognitive Tests: AVL indicates Auditory Verbal Learning Test; BLG, Baumler’s Lern und Gedachtnistest; BNT, Boston Naming Test; BSAT, Brixton Spatial Anticipation Test; COWAT, Controlled Oral Word Association Test; CPT, Continuous Performance Test; DART, National Adult Reading Test - Dutch version; DSS, Digit Span Backwards; DSS, Digit Span Subtest; DSST, Digit Symbol Substitution Test; FAB, Frontal Assessment Battery; GPT, Grooved Pegboard Test; JLO, Judgment of Line Orientation; LDST, Letter-Digit Substitution Test; MMSE, Mini-Mental State Examination; PPT, Purdue Pegboard Test; RCF, Rey Complex Figure; SDMT, Symbol Digit Modalities Test; TMT, Trail Making Test; TMT, Trail Making Test (B); TSB; VET, Visual Elevator Test; WAS, Wechsler Adult Intelligence Scale (R, Revised; III, 3rd edition); WAS, Wechsler Abbreviated Scale of Intelligence; WCST, Wisconsin Card Sorting Test; WMS, Wechsler Memory Scale (R, Revised; III, 3rd edition); WRT, Word Recall Test; Terms: APOE, apoE; BMI, body mass index; CVD, cardiovascular disease; FA, fractional anisotropy; HOMA-IR, homeostasis model assessment; HRT, hormone replacement therapy; hs-CRP, high sensitivity C-reactive protein; Hx, history; IQ, intelligence quotient; MetS, metabolic syndrome; MRI, magnetic resonance imaging; NCEP-APT III, National Cholesterol Education Program Third Adult Treatment Panel III; nonsig, nonsignificant; sig, significant; T2DM, type 2 diabetic mellitus; WML, white matter lesion.

*Used NCEP-APT III MetS criteria.
†Used a modified NCEP-APT III MetS criteria.
‡Used International Diabetes Federation MetS criteria.
<table>
<thead>
<tr>
<th>Reference</th>
<th>MetS Factor</th>
<th>Clinical Population</th>
<th>Control Group</th>
<th>Cognitive Tests</th>
<th>Covariates</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cserjesi et al (2007)</td>
<td>Elevated waist circumference</td>
<td>12 Obese boys, mean age 12.1</td>
<td>12 Age–matched nonobese boys</td>
<td>D2 Attention Endurance Test, WCST (sig); DSMT, Raven Matrices, and Semantic Verbal Fluency (nonsig)</td>
<td>None</td>
<td>Obese performed worse on WCST and D2 Attention Endurance Task despite similar memory and intelligence</td>
</tr>
<tr>
<td>Gunstad et al (2008)</td>
<td>Elevated waist circumference</td>
<td>45 BMI ≥95% 6–19 y; mean age of entire sample =12.45</td>
<td>433 BMI &lt;95% divided into 3 weight groups</td>
<td>DSB, TMT-B, Verbal Recall, Animal Fluency, and Finger Tapping (nonsig)</td>
<td>Age, estimated IQ</td>
<td>No associations between BMI and cognition</td>
</tr>
<tr>
<td>Lande et al (2003)</td>
<td>Elevated waist circumference, hypertension</td>
<td>5077 6–16 y (NHANES)</td>
<td>None</td>
<td>WISC-R block design and digit span, WRAT arithmetic (sig); and WRAT reading (nonsig)</td>
<td>Race, sex, parent’s education, poverty, medicines/antihistamines, general health, lead level, BMI, and heart rate</td>
<td>Those with systolic BP &gt;90% performed worse on block design, digit span and math; 55.6% of these were overweight or obese</td>
</tr>
<tr>
<td>Li et al (2008)</td>
<td>Elevated waist circumference</td>
<td>360 BMI ≥95% 8–16 y, mean age 12.03</td>
<td>2159 BMI &lt;95% divided into 2 weight groups</td>
<td>WISC-R block design and digit span (sig); WRAT reading, and arithmetic (nonsig)</td>
<td>Age, sex, ethnicity, education, marital status of family head, family income, dwelling, hours watching TV, exercise, health status, blood pressure, heart rate, iron deficiency, psychological and social variables</td>
<td>Those with BMI ≥95% performed significantly worse on digit span, block design, and global functioning</td>
</tr>
<tr>
<td>Lokken et al (2009)</td>
<td>Elevated waist circumference</td>
<td>25 12–19 y, mean age 16.2, mean BMI =54</td>
<td>Compared performance across existing normative test data</td>
<td>WRAT-IV reading, WASI, CCTB (digit span, verbal inference, switching attention, and maze task) (sig); CCTB go-no-go (nonsig); CCTB CPT (varying results)</td>
<td>None</td>
<td>Obesity associated with worse performance, especially attention and executive functioning</td>
</tr>
<tr>
<td>Maayan et al (2011)</td>
<td>Elevated waist circumference</td>
<td>54 Obese 14–21 y, mean age 17.32</td>
<td>37 lean 14–21 y, mean age 17.50</td>
<td>COWAT, TMT, Stroop, and WRAML-2 attention/concentration and memory indices from WRAML-2 (sig)</td>
<td>IQ</td>
<td>Obese performed worse on all cognitive measures</td>
</tr>
<tr>
<td>Parisi et al (2010)</td>
<td>Elevated waist circumference</td>
<td>71 Overweight and 51 obese 6–13 y</td>
<td>188, 6–13 y</td>
<td>WISC-R and SDAG (parents) (varying results)</td>
<td>None</td>
<td>Sig weight group differences on PIQ; BMI group predicts PIQ; Sex and parental education predicts VIQ; Parent education predicts TIQ</td>
</tr>
<tr>
<td>Pauli-Pott et al (2012)</td>
<td>Elevated waist circumference</td>
<td>177 Overweight and obese 8-15 y</td>
<td>None</td>
<td>AAB go-no-go and incompatibility tasks (sig)</td>
<td>Age, sex, education, SES, and general mental ability</td>
<td>Obese showed more inattention; at younger ages, high impulsivity is associated with higher body weight</td>
</tr>
<tr>
<td>Yau et al (2010)</td>
<td>Elevated waist circumference, hyperglycemia</td>
<td>18 Obese T2DM, mean age 16.46 y</td>
<td>18 Obese non-T2DM, mean age 17.16 y</td>
<td>DUST, WASI, WRAML verbal (sig); WRAT, WRAML visual and working memory, DVT, WCST, ToL, and COWAT (nonsig)</td>
<td>Age, sex, grade, SES, BMI, waist circumference, WHR, and sleep apnea</td>
<td>T2DM performed significantly worse performance on all cognitive domains</td>
</tr>
</tbody>
</table>

Cognitive Tests: AAB indicates Attention Assessment Battery; CCTB, Computerized Cognitive Test Battery; CPT, Continuous Performance Test (original; II, 2nd edition); DSB, Digit Span Backward; DSMT, Digit Span Memory Task; DVT, Digit Vigilance; IGT, Iowa Gambling Task; IQ, Intelligence Quotient; K-BIT, Kaufman Brief Intelligence Test; SDAG, Parent Attention Deficit Scale; ToL, Tower of London; TMT, Trail Making Test (B, Trial B); WASI, Wechsler Abbreviated Scale of Intelligence; WCST, Wisconsin Card Sorting Test; WISC, Wechsler Intelligence Scale for Children (R, Revised; IV, 4th edition); WRAT, Wide Range Achievement Test (original; IV, 4th edition); WRAML, Wide Range Assessment of Memory and Learning (original; 2, 2nd edition); WRAT-IV; Terms: BP, blood pressure; IQ, intelligence quotient; nonsig, nonsignificant; PIQ, performance intelligence quotient; SES, socio-economic status; sig, significant; TIQ, total intelligence quotient; TV, television; VIQ, verbal intelligence quotient; WHR, waist-hip ratio.
Impact of MetS on the Brain in Adult Imaging

Individual MetS components are known to have independent negative brain consequences,\textsuperscript{45-48} but evidence of brain involvement in MetS as a whole remains rather limited. MetS is a known risk factor for ischemic stroke.\textsuperscript{49} There have been a handful of reports of subclinical ischemic brain damage in adults with MetS. Increased silent brain infarction has been observed in both elderly\textsuperscript{50} and middle-aged individuals with MetS.\textsuperscript{21,51} Others have reported increased prevalence of intracranial arteriosclerosis,\textsuperscript{52} periventricular white matter (WM) hyperintensities, and subcortical WM lesions.\textsuperscript{53} Using diffusion tensor imaging, Segura et al\textsuperscript{54} characterized reductions of WM microstructural integrity involving primarily the frontal and temporal lobes. More WM abnormalities have been associated with increasing number of MetS components present,\textsuperscript{50,53} and these associations may also be driven by individual vascular risk factors.\textsuperscript{50,51,53}

Haley et al\textsuperscript{50} demonstrated changes in brain metabolism characterized by increased myoinositol/creatine and glutamate/creatine ratios in occipitoparietal gray matter in cognitively intact middle-aged adults with MetS. Increased myoinositol/creatine ratios, suggestive of increased microglia or neuroinflammation, have been reported in T2DM.\textsuperscript{55} Using functional magnetic resonance imaging, Hoth et al\textsuperscript{56} observed blunted brain activation in the absence of cognitive compromise. Taken together, these subclinical alterations in cerebral metabolism and cerebrovascular reactivity may represent early brain compromise associated with peripheral metabolic disturbances.

Impact of MetS on the Brain in Children and in Adolescent Imaging

No data currently exist on the impact of MetS on the pediatric brain. Most individuals with MetS have IR,\textsuperscript{71} which is likely the driving force behind the brain complications reported in MetS.\textsuperscript{10,58} Bruehl et al\textsuperscript{59} reported that relative to those without IR, obese adolescents with T2DM had smaller hippocampal volumes and more frontal lobe atrophy. In addition, we have described among adolescents with IR a blunted cortisol awakening response (CAR), a good indicator of the hypothalamic-pituitary-adrenal (HPA) axis integrity.\textsuperscript{60} More importantly, the finding of an inverse relationship between CAR and fasting insulin levels and between CAR and hippocampal volumes supports the role of metabolic disturbances in the brain structural abnormalities, which lead to the HPA axis dysregulation.\textsuperscript{81} Further, we have described specific gray matter volume reductions in the orbitofrontal cortex, associated with disinhibition of feeding behavior among obese adolescents (with and without IR).\textsuperscript{96}

Discussion

There is a lack of consensus on the relationships between MetS and its components and cognitive health, which is partly explained by a lack of consistency in the cognitive domains selected for assessment, differences in quality of tests selected, demographics of populations studied (ie, differences in age, race, sex, and educational level), lack of a standard definition of MetS, cross-sectional versus longitudinal study designs, and difficulty in uncoupling the impact of individual or combinations of MetS factors from that of the syndrome itself. Cognitive and brain abnormalities associated with MetS may result from synergy of the different component risk factors. In addition, few studies used a control group free of any MetS risk factor. Furthermore, sex differences have not been extensively addressed and findings to date have been inconsistent. MetS has been associated with poorer executive performance in women but not in men.\textsuperscript{25} Moreover, impairments have been found in varying cognitive domains across the lifespan with memory preserved until the 6th decade when impairments are found,\textsuperscript{24} indicating that MetS may be an important contributory factor in worsening memory for women. Although some of the studies that we cited exclude individuals with major psychiatric or neurological illness, studies either do not specify other medications or if they do, they do not account for them. Given that we excluded studies with subjects with a mean age >65 years, it is less likely that the reported studies will have the confounding effects of the polypharmacy that often occurs in the elderly. However, we have no way of identifying whether some cognitive findings reported in the literature are a result of pharmacological side effects.

Potential Explanatory Model for Brain Deficits Associated With MetS

A number of potential explanatory models have been proposed for the ill effect of MetS on brain and cognition, including neuroinflammation, oxidative stress, abnormal brain lipid metabolism, and impaired vascular reactivity among others. Although a discussion of all of these models would be beyond the scope of this brief review, we will use an explanatory model based on IR-associated vascular reactivity problems as an example.

Impaired cerebrovascular reactivity,\textsuperscript{62} increased carotid stiffness, and intima-media thickness\textsuperscript{63,64} have been reported in adults with MetS. Given that the carotid artery is the main blood supply to the central nervous system and that carotid atherosclerosis has been linked to cognitive impairment\textsuperscript{65} and increased brain atrophy,\textsuperscript{66} such findings suggest that the WM damage seen in adults with MetS is likely vascular in nature.

Similarly, endothelial dysfunction, carotid stiffness, and intima-media thickness also have been reported in children with MetS,\textsuperscript{67-69} obesity,\textsuperscript{70-73} hypertension,\textsuperscript{74-76} and T2DM.\textsuperscript{77,78} Those with uncontrolled T2DM have more severe carotid alterations.\textsuperscript{77} Vascular involvement likely plays a role in cognitive and brain impairment in adults.\textsuperscript{79,80} Given the increasing vascular abnormalities with increasing metabolic alterations along the MetS spectrum in children, MetS also likely adversely impacts brain structure and function in adolescents.

We propose the damaging effects of MetS and IR on brain integrity are partly dependent on the vascular reactivity abnormalities associated with those conditions.\textsuperscript{81} We suggest a conceptual model that posits that when a region of the brain is activated (as when performing a cognitive task), there is increased synaptic activity in that region, which normally results in regional vasodilatation.\textsuperscript{82} Vascular reactivity is key
to maintaining energy-dependent processes, such as regional brain activation by clearing the metabolic waste produced by neuronal activity (carbon dioxide, excess lactate, other metabolites, heat, etc).\textsuperscript{82} We know that in T2DM and MetS there are impairments in endothelial-dependent vasodilatation.\textsuperscript{83,84} Consequently, individuals with MetS may not be able to maintain an optimal neuronal environment, particularly during periods of high demand. We propose that among individuals with IR and MetS, vascular reactivity (capillary recruitment, no. 1 in the Figure), a mechanism that maintains an optimal neuronal environment during brain activation, is dysfunctional. We propose that these reductions in vascular reactivity are a result of the direct or indirect deleterious effects of IR (no. 2) and obesity-associated inflammation (no. 3) on the microvasculature. There is new evidence to support that IR leads to inflammation and that inflammation leads to IR (no. 4). The resultant effect of both IR and inflammation is to reduce cerebral vascular reactivity. The impaired vascular reactivity may, in turn, lead to an inability to maintain energy-dependent processes and clear metabolic waste under conditions of increased demand. We propose that this endothelial dysfunction, when coupled with other potentially damaging influences, such as inflammation, HPA axis dysregulation, or increased oxidative stress, may damage the brain, particularly those regions more vulnerable to damage. The model does not address possible problems that may occur after vascular reactivity (no. 5 in diagram above).

Future studies should also explore other explanatory models, including the impact of inflammation as a potential mediator for the damaging effects of MetS on brain structure and function. Assessment of inflammation and oxidative stress directly in the brain by using magnetic resonance imaging–based spectroscopy could be a logical next direction to understand the associations between MetS and cognitive impairments. Furthermore, future studies should use prospective longitudinal designs, which will allow stronger conclusions about possible mechanisms and better inform follow-up animal models. Intervention studies and those that incorporate protective factors, such as a well-balanced, healthy diet and exercise, will also assist in better elucidating candidate mechanisms and iteratively improve interventions intending to protect the brain.

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None.

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