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REVIEW ARTICLE

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Paediatric obesity and metabolic syndrome associations with cognition and the brain in youth: Current evidence and future directions

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Summary

Obesity and components of the metabolic syndrome (MetS) are associated with differences in brain structure and function and in general and food-related cognition in adults. Here, we review evidence for similar phenomena in children and adolescents, with a focus on the implications of extant research for possible underlying mechanisms and potential interventions for obesity and MetS in youth. Current evidence is limited by a relative reliance on small cross-sectional studies. However, we find that youth with obesity and MetS or MetS components show differences in brain structure, including alterations in grey matter volume and cortical thickness across brain regions subserving reward, cognitive control and other functions, as well as in white matter integrity and volume. Children with obesity and MetS components also show some evidence for hyperresponsivity of food reward regions and hyporesponsivity of cognitive control circuits during food-related tasks, altered brain responses to food tastes, and altered resting-state connectivity including between cognitive control and reward processing networks. Potential mechanisms for these findings include neuroinflammation, impaired vascular reactivity, and effects of diet and obesity on myelination and dopamine function. Future observational research using longitudinal measures, improved sampling strategies and study designs, and rigorous statistical methods, promises to further illuminate dynamic relationships and causal mechanisms. Intervention studies targeted at modifiable biological and behavioural factors associated with paediatric obesity and MetS can further inform mechanisms, as well as test whether brain and behaviour can be altered for beneficial outcomes.

Jennifer R. Sadler and Gita Thapaliya are joint first author.

KEYWORDS
brain function, brain structure, Diffusion Tensor Imaging (DTI), food motivation, food reward, functional MRI (fMRI), glucose, inhibitory control, insulin, Magnetic Resonance Imaging (MRI), neuroimaging, type 2 diabetes

1 | INTRODUCTION

Obesity, defined as having a BMI at the 95th percentile or greater for age and sex based on population reference data, is present in 17% of US children and adolescents, with prevalence increasing as children age.[1] Obesity is associated with type 2 diabetes mellitus (T2DM) and other comorbidities throughout the life course,[2] and central obesity is a key component of the metabolic syndrome (MetS), a cluster of factors including large waist circumference, hypertension, elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, and dysregulation of glucose metabolism as indicated by impaired fasting glucose (IFG) or marked insulin resistance (IR).[3] Growing evidence suggests that obesity, T2DM and IR in adulthood are associated with impairments in cognition and differences in measures assessing cognition in relation to food.[4–6] However, although a substantial body of work suggests that paediatric obesity (i.e., obesity in children or adolescents ages 2–20 years) is also associated with differences in general cognitive function[7–9] and food-related cognition,[10–12] and obesity based on body mass index (BMI) values in childhood is highly associated with central obesity and other components of the metabolic syndrome,[13] fewer studies have examined the relationship of MetS and other MetS components with general or food-related cognition in youth.

While the specific cutoffs used to define the components of MetS are not yet widely agreed upon for paediatric populations, the components of MetS in children and adolescents are the same as in adults[14] (Table 1). Yates et al. previously reviewed research on the impact of MetS on cognition and brain structure and function in children and adolescents, and found that youth with components of MetS showed decreased cognitive function in domains such as executive function, memory, and attention.[15] They also described several studies showing that components of MetS were associated with decreased grey matter volume (GMV) in the hippocampus and frontal lobes[16] and GMV reductions in the orbitofrontal cortex (OFC).[17] Since 2012, more research has examined the impact of MetS and its components on cognition and brain structure and function in youth. The goal of the current narrative review was to summarize recent research, as well as to outline potential future research directions to further investigate causal relationships and biological mechanisms.

TABLE 1 Components of Metabolic Syndrome in children and adolescents.

Component	Measure
Abdominal obesity	Waist circumference, waist to hip ratio
Insulin resistance (IR)	Homa-IR, fasting blood glucose
Hypertension	Systolic and/or diastolic blood pressure
Elevated triglycerides	Triglycerides level
Decreased high-density lipoproteins (HDL)	High-density lipoprotein level

Note: Listed are the components of metabolic syndrome and measures commonly used to assess each component in paediatric samples. No standard cut-offs for measures of each component are currently available for children or adolescents.

2 | LITERATURE SEARCH AND SELECTION

We selected extant literature on the impact of paediatric obesity and other components of MetS on (1) cognition (general cognition, food-related cognition), (2) brain structure (grey matter volume, cortical thickness, white matter integrity), and brain function (neural responses to food stimuli, resting state functional connectivity). Since the extant literature on effects of paediatric obesity on general and food-related cognition is substantial, we draw on review papers and meta-analyses to briefly summarize this literature. Studies comparing cognitive outcomes in children with diagnosed T2DM with healthy controls were recently reviewed elsewhere (see Reference 18), and are also excluded from detailed discussion here. Consistent with our mechanistic focus, research examining the effect of paediatric obesity and T2DM on brain structure and function is included in the discussion, along with a small number of studies relating specific components of MetS to brain outcomes.

PubMed searches using keywords including: a) adolescent, child, b) MetS, obesity, insulin resistance, hypertension, abdominal obesity, c) cognition, executive function, reinforcing value food, food delay discounting, food attention, food inhibitory control and d) Magnetic Resonance Imaging (MRI), Diffusion Tensor Imaging (DTI), functional MRI (fMRI), were conducted. Articles reporting the impact of obesity, MetS, and MetS components on neurocognitive outcomes in otherwise healthy children or adolescents ages 2–20 years were included for consideration as outlined above. Titles and abstracts were then screened to ensure eligibility. Emphasis was placed on papers published in 2012 or later. We excluded papers addressing other physical and mental health conditions (e.g., Prader-Willi syndrome).

3 | GENERAL AND FOOD-RELATED COGNITION DIFFERENCES IN PAEDIATRIC OBESITY AND METS

3.1 | General cognition

Paediatric obesity has been associated with small to moderate negative effects on functioning across multiple cognitive domains including

TABLE 2 Associations of MetS and MetS components with cognitive outcomes in children and adolescents (2–20 years).

Reference	Sample	MetS Definition/Components	Cognitive outcomes	Covariates/Exclusions	Results
(A) MetS diagnosis					
Mangone et al. 2017, USA	288 adolescents (14–19 years) • 84 MetS, mean age 16.4 years • 204 no MetS, mean age 16.8 years	3 of 5 components (a) Abdominal obesity (b) Reduced HDL (c) Hypertriglyceridemia (d) Hypertension (e) Insulin resistance	(1) Memory (2) Processing speed (3) Reaction time (4) Executive function (5) Complex attention (6) Cognitive flexibility	Sample was predominantly adolescents with low-income backgrounds.	• Adolescents with MetS showed lower scores on executive function and cognitive flexibility.
Rubens et al. 2016, USA	1170 adolescents (12–16 years) • 106 MetS, mean age 14.0 years • 1064 no MetS, mean age 14.1 years	3 of 5 components (a) Abdominal obesity (b) Reduced HDL (c) Hypertriglyceridemia (d) Hypertension (e) Insulin resistance	(1) Academic achievement (2) Executive function (3) Visual–spatial processing	Covariates controlled in the analyses included age, sex, race/ethnicity, education level of family reference person, poverty-income ratio, BMI, C-reactive protein (CRP), and environmental tobacco smoke exposure.	• Adolescents with MetS showed lower scores on reading, and visual • Spatial processing.
Yau et al., 2012, USA	111 adolescents (12–16 years) • 49 MetS, mean age 17.8 years • 62 no MetS, mean age 17.5 years	3 of 5 components (a) Abdominal obesity (b) Reduced HDL (c) Hypertriglyceridemia (d) Hypertension (e) Insulin resistance	(1) Intelligence (2) Academic achievement (3) Verbal, visual, and working memory (4) Attention (5) Executive function (6) Psychomotor efficiency	Samples matched on age, socioeconomic status, school grade, gender, and ethnicity. Analysis adjusted for number of MetS components exhibited.	• Adolescents with MetS showed lower scores on arithmetic and spelling, attention and cognitive flexibility.
(B) Components of MetS					
Akin et al., 2017, Turkey	115 children/adolescents (6–16 years) • 73 obesity, mean age 11.8 years • 42 healthy weight, mean age 11.5 years	(a) HOMA-IR >4 (90th percentile or higher)	Wechsler intelligence scale for children (WISC) test (1) Verbal ability (general, similarities, information, judgement, vocabulary, arithmetic and digit span) (2) Performance (picture completion, object assembly, block design, picture arrangement, labyrinths and digit symbol)	Excluded prepubertal children (according to Tanner stages) and those with neurological, psychiatric, or systemic disorders, or obstructive sleep apnea.	• Verbal scores were negatively correlated with obesity duration and HOMA-IR.
Bugge et al., 2018, Denmark	558 children, mean age 14.2	(a) Waist circumference (b) MetS score: HDL; Triglycerides; Blood pressure; Insulin resistance	(1) Cognitive control (Flanker Task)	Covariates included sex, pubertal status, socioeconomic status, and age.	• Waist circumference and MetS composite score were not associated with cognitive control. • HDL was associated with slower reaction times.

(Continues)

TABLE 2 (Continued)

Reference	Sample	MetS Definition/Components	Cognitive outcomes	Covariates/Exclusions	Results
Da Costa et al., 2019, Brazil	48 children (9–11 years), mean age 10.7	(a) Fat mass (b) Waist-Hip Ratio (c) Blood pressure	(1) Food-related inhibitory control (food go/no task)	Excluded children taking medications and with cardiovascular/physical limitations.	• Fat mass was associated with poorer food-specific inhibitory control. • No association with waist- hip ratio or blood pressure.
Lande et al., 2017, USA	150 adolescents (10–18 years) • 75 hypertension, mean age 15.1 years • 75 without hypertension, mean age 15.4 years	(a) Hypertension (BP≥95th percenttile)	(1) General intelligence (2) Attention (3) Memory (4) Executive function (5) Processing speed	Samples matched on maternal education, sex, and proportion of group with obesity.	• Children with hypertension showed poorer performance on attention, learning, and memory tasks.
Scudder et al., 2015, USA	139 adolescents (14–20 years) • 70 children no MetS risk factors, mean age 7.6 years • 69 at least one MetS risk factor, mean age 7.5 years	One or more risk factors: (a) HDL (<50 mg/d) (b) Waist circumference (>75th percentile) (c) systolic and/or diastolic BP (>90th %tile) (d) TG (≥100 mg/dL) (e) FBG (≥110 mg/dL)	(1) Cognitive control (Flanker Task)	Covariates included demographic variables and aerobic fitness.	• Children with no risk factors showed faster reaction time. • At-risk children performed worse on difficult task conditions. • HDL cholesterol was negatively associated with reaction time.
Shapiro et al., 2019, USA	137 children (4–6 years), mean age 4.6	(a) Fasting blood glucose (b) Fasting insulin (c) Insulin resistance	(1) Inhibitory control (2) Cognitive flexibility (3) Receptive language	Covariates included ethnicity, Apgar-5 score at birth, birth weight z score, maternal education and smoking in pregnancy.	• Fasting blood glucose, insulin, and insulin resistance were negatively associated with inhibitory control. • Fasting glucose was negatively associated with cognitive flexibility.
Sweat et al., 2017, USA	162 adolescents (12–19 years) • 108 obesity, mean age 19.3 years • 54 healthy weight, mean age 19.6 years	Criteria: (a) Waist circumference (90th percentile or higher) (b) TG (>100 mg/dL) (c) Low HDL (<40 mg/dL) (d) Elevated BP (e) HOMA-IR (>3.99)	(1) Verbal fluency (2) Attention (3) Psychomotor (4) Executive function (5) Processing speed	Covariates included sex. Exclusion criteria included T2D, neurological disorder, head trauma, psychiatric illness (including substance abuse), or history of significant medical conditions not associated with obesity.	• Adolescents with obesity showed slower cognitive processing.

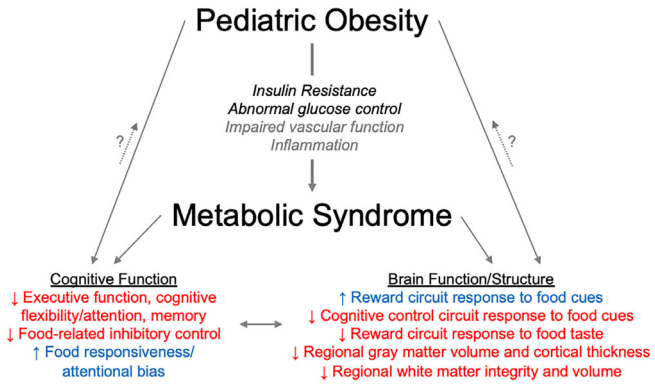

FIGURE 1 Schematic showing relationships of paediatric obesity and metabolic syndrome with cognitive function and brain structure and function. Grey font/lines represent potential mechanisms. Relationships depicted are not universal but have been reported across multiple studies.

attention, switching, inhibition, interference, working memory, reward, and delay of gratification, as described in a recent meta-analysis including 70 studies.[7] However, fewer studies have examined the effects of MetS or specific MetS components.

A summary of the results of extant studies investigating relationships between MetS and general cognition in youth can be found in Table 2, Section A and Figure 1. In two of the three studies examining adolescents diagnosed with MetS, those with MetS demonstrated evidence for lower cognitive flexibility (the ability to adapt behaviours in response to changes in the environment), which is considered a dimension of executive function.[16,19] One of these studies additionally demonstrated poorer executive function scores based on several sub-tests from a computerized neurocognitive battery and the other decreased scores on arithmetic and spelling.[16] A third study found no association between MetS and indices of executive function, but reported lower reading scores and poorer visual–spatial processing in children with MetS.[20] Notably effect sizes reported across these studies were small (Cohen's $d = 0.15–0.21$), with the exception of the observed effect on arithmetic ($d = 0.69$).

Components of MetS have been similarly associated with cognitive deficits (Table 2, Section B), including decreased inhibitory control as measured via the Flanker task in children who demonstrated some MetS components.[21,22] Additionally, one study found that insulin resistance was related to poorer Flanker task performance during early childhood.[23] However, another study of adolescents found no evidence for an association between waist circumference and Flanker performance.[22] One further paediatric study reported hypertension to be associated with lower attention, learning, and memory scores,[24] while others have reported no relationship between hypertension and inhibitory control task performance.[22,25]

Taken together these studies suggest that MetS and its components are associated with impairments across a range of cognitive domains, with the most evidence of negative effects for obesity and insulin resistance. However, few studies have assessed other key components of MetS (e.g., waist circumference, hypertension, HDL cholesterol, triglycerides). Possible sources of inconsistencies among existing findings may be between-study differences in the cognitive function domain assessed, developmental stage, disease duration, or interactions between these factors.

TABLE 3 Common food-related cognition tasks and main outcomes.

Task type	Main outcomes
Reinforcing value of food	Work exerted to obtain a food reward before switching to a less-demanding non-food reward
Food-related delay discounting	Selection of smaller food reward in the present over a larger food reward in the future
Attentional bias for food	Attention paid to food stimuli over alternative stimuli
Food-related inhibition	Ability to inhibit a food-related response

3.2 | Food-related cognition

Several types of behavioural task are commonly used to examine food-related cognitive processes[26] (see Table 3).

In general, studies support that adolescents and children with obesity show greater reinforcing value of food,[12] greater discounting of future food rewards,[12] increased attentional biases toward food,[10] and decreased food-related inhibitory control,[7] all of which may contribute to (or be impacted by) overeating, weight gain and development of MetS.

To date, few studies have directly addressed relationships between components of MetS and measures of food-related cognition in school-aged children (Table 2, Section B). Using a go/no go task adapted to include food and non-food (toy) stimuli, Da Costa et al[25] found that higher fat mass, but not blood pressure or waist to hip ratio, or BMI, was associated with lesser ability to inhibit a prepotent response to food but not toy stimuli, supporting a direct relationship between adiposity and food-specific alteration in inhibitory control. Given the confines of extant research to effects of obesity and whole body (vs. central) fat mass, more data are needed to understand the impact of other components of MetS on food-related cognition.

4 | STRUCTURAL AND FUNCTIONAL BRAIN DIFFERENCES IN PAEDIATRIC OBESITY AND METS

4.1 | Structural brain differences

4.1.1 | Grey matter differences

Grey matter is primarily composed of neuronal and non-neuronal cells such as glial cells, while white matter is primarily composed of axons.

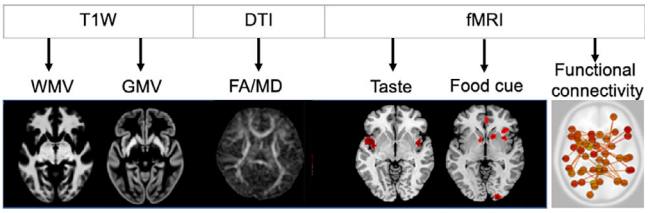

FIGURE 2 Brain imaging methods commonly used to investigate effects of paediatric obesity and metabolic syndrome. Grey matter volume (GMV) and white matter volume (WMV) can be measured using T1 weighted (T1W) structural MRI; white matter integrity can be estimated by fractional anisotropy (FA) and mean diffusivity (MD) derived from Diffusion Tensor Imaging (DTI); neural activation to food cues and food tastes can be assessed using Blood Oxygen Level Dependent (BOLD) responses assessed via functional MRI (fMRI); functional connectivity of brain regions can be assessed using resting state fMRI.

GMV can be estimated using structural MRI (Figure 2),[27] and estimates can additionally be decomposed into measures of cortical surface area (CSA) and cortical thickness (CT), which are phenotypically and genetically distinct and may relate differentially to cognitive outcomes, with GMV estimates being more closely related to CSA than CT.[28] GMV demonstrates a rapid increase in early life[29] followed by reductions in both GMV and CT from childhood to adulthood,[30] a pattern which is thought to partly reflect a process of initial neuronal proliferation followed by synaptic pruning as development advances. Against this background, global or regional decreases in GMV and CT may also result from a range of pathological processes.[31]

Table 4 summarizes studies reporting differences in grey matter metrics in youth with obesity and MetS or its components and Figure 3 illustrates key brain regions that have demonstrated such differences. Several studies have reported regional reductions in grey matter metrics. For example, two small studies found that children with overweight/obesity ($n = 15$) showed lower GMV in the hippocampus relative to a healthy weight group ($n = 15$ vs. $n = 18$,[32] $n = 12$ vs. $n = 10$[33]), while another found that children with obesity ($n = 12$) versus healthy weight ($n = 12$) showed lower GMV in the right middle temporal gyrus, left and right thalami, left superior parietal gyrus, left pre/postcentral gyri, and left cerebellum.[34] In our own study of adolescents ($n = 36$), an obesity/overweight group versus a healthy weight group with low familial risk for obesity based on current maternal weight status showed lower GMV and lower CT in the anterior cingulate cortex (ACC),[35] while two larger studies of adolescents respectively found that higher BMI z-score was associated with lower GMV in frontal and limbic regions ($n = 120$[36]), and in the caudate, medial prefrontal cortex (PFC), ACC, frontal pole and uncus ($n = 137$[37]). Studies of much larger cohorts have similarly reported reductions. For example the Generation R study found that children with overweight and obesity ($n = 536$) versus healthy weight ($n = 2355$) had lower GMV in the frontal lobe, and that a one standard deviation score (SDS) in fat mass percentage was associated with significantly lower frontotemporal GMV.[38] Further, two large, cross-sectional analyses of children from the ABCD study ($n = 3190$[39,40]) showed that greater BMI was associated with lower CT in the prefrontal cortex, with one larger analysis ($n = 11\,875$) further demonstrating that BMI z-score showed a quadratic relationship with total GMV and right hippocampus volume.[41]

Several studies have also examined structural brain metrics in youth with T2DM. For example, one study of adolescents found that a group with obesity and T2DM ($n = 18$) showed reduced GMV in the hippocampus and prefrontal lobe relative to a group with obesity but without T2DM ($n = 18$), and that lower prefrontal GMV was associated with greater HbA1C.[42] A further study found that obesity without T2DM ($n = 21$) and obesity with T2DM ($n = 15$) groups had lower GMV in the caudate, putamen, hippocampus, amygdala and thalamus, relative to a healthy weight group ($n = 22$).[43] Similarly, Rofey et al. reported that a group with obesity ($n = 5$) and T2DM ($n = 5$) had lower caudate and thalamus GMV than a healthy weight group ($n = 5$).[44] Further, Redel et al. showed that youth with obesity and T2DM ($n = 20$) had lower global GMV than a healthy weight group ($n = 20$), as well as reduced regional volumes in the temporal and occipital lobes.[45] Comparatively few studies have reported GMV differences in relation to MetS and its components. Yau et al. found that adolescents with MetS ($n = 49$) showed reduced hippocampal GMV compared to adolescents without MetS ($n = 62$).[16] Further, Yau et al. found that adolescents with uncomplicated obesity (no insulin resistance) ($n = 30$) versus healthy weight ($n = 30$) had lower CT of the OFC and ACC, consistent with a potential dose effect of metabolic dysregulation.[46]

Notably, *increases* in the structural metrics of the brain have also been reported in certain regions. For example, in one of our own studies we observed greater GMV in the precentral gyrus and frontal pole in adolescents with overweight/obesity ($n = 36$) versus a healthy weight group with low familial risk of obesity based on maternal weight status ($n = 22$).[35] Higher BMI was also associated with greater GMV in the globus pallidus in a small study of 6–8 years old children ($n = 33$),[32] while higher BMI z-score was associated with greater GMV in the nucleus accumbens (NAcc) and amygdala in a study of 10–16.5 years old children ($n = 51$).[47] In the large Generation R study, 10 years olds with overweight/obesity ($n = 536$) versus healthy weight ($n = 2355$) had larger amygdala and hippocampal GMV, with a one SDS increase in fat mass index being associated with greater GMV in the thalamus, amygdala, hippocampus and putamen.[38] A further analysis using the same cohort ($n = 3160$) found that greater BMI standard deviation score (SDS) was associated with greater CT in superior parietal, superior temporal, inferior temporal, pericalcarine, occipital, postcentral, lingual and superior parietal gyri.[48] A small study of youth with obesity and T2DM ($n = 20$) versus healthy controls ($n = 20$) also reported higher GMV in the putamen, thalamus, inferior temporal lobe and paracentral lobule,[45] while another study found that increased visceral fat (ratio of abdominal fat volume to overall abdomen volume) as assessed by an MRI and hepatorenal gradient measured with an ultrasound, but not BMI, was associated with increased CT across multiple brain regions ($n = 44$).[49]

Methodological variation between studies including developmental stage and also treatment of potential covariates such as total

TABLE 4 Associations of paediatric obesity and MetS components with brain structure in children and adolescents (2–20 years).

Reference	Sample	MetS definition/ Components	Brain Structure Outcomes	Analytic approach/Matching criteria	Results
(A) Paediatric obesity					
Alarcon et al., 2016, USA	176 adolescents (12–17 years) • 88 overweight, 18 obesity; mean age 14.4 years • 88 healthy weight, mean age 14.2 years	BMI	WM integrity	• Whole brain approach • Adjusted for age, sex • To correct for multiple comparisons, a minimum cluster size was calculated using AlphaSim. Using voxel-level threshold of $p < 0.01$ and cluster-level threshold of alpha<0.05, k (number of continguous voxels) = 71 required for significance.	• BMI was negatively correlated with FA in left superior longitudinal fasciculus and left inferior longitudinal fasciculus.
Alosco et al., 2014, Australia	120 children and adolescents (6–18 years), mean age 13.5 years	BMI z-score	GMV, WM integrity	• ROI approach • Adjusted for age, gender, education, global GMV • Bonferroni correction to correct for type 1 error across analyses (0.05/29 MRI and DTI indices; two-tailed α level of $p < 0.0017$)	• BMI z-score was negatively associated with GMV of frontal lobe and limbic regions. • No association between BMI z-score and WM integrity.
Bauer et al., 2015, Mexico	33 children (6–8 years) • 15 overweight/obesity, mean age 7.6 years • 18 healthy weight, mean age 7.6 years	Overweight/obesity, BMI	GMV	• Whole brain approach • All cortical and subcortical region volumes for each subject normalized to subject's total brain volume • Group comparisons and regressions with BMI considered significant at $p < 0.05$ uncorrected	• Overweight/obesity group showed reduced GMV in hippocampus. • Overweight/obesity group showed larger WM volume in cerebellum and mid-posterior corpus callosum. • Positive correlation between BMI and GMV in globus pallidus.
Bohon & Welch 2021 (ABCD study), USA	11 875 children (9–11 years), mean age 9.9 years	BMI z-score	GMV	• Whole brain approach • Per ABCD recommendations due to the large n the authors focused on effect sizes rather than *p*-values. Effects of $p < 0.001$ uncorrected are reported. • Adjusted for TIV, age, sex, race, site, family	• BMI z-scores showed quadratic relationship with total GMV as well as right hippocampus GMV.
Carbine et al., 2020, USA	87 adolescents (12–20 years) • 40 overweight/obesity, mean age 16.13 years • 47 healthy weight, mean age 16.70 years	Obesity	WM integrity	• ROI approach • Adjusted for age, sex • Bonferroni correction applied (0.05/64 analyses using 4 models across 16 tracts of interest)	• Overweight/obesity group showed *decreased* WM integrity in superior frontal corpus callosum, left and right uncinate fasciculi, left inferior fronto-occipital fasciculus, and left corticospinal tract. • Overweight/obesity group showed *increased* white matter integrity in orbital and anterior frontal corpus callosum, right inferior fronto-occipital fasciculus, left cingulum, left corticospinal tract.

(Continues)

TABLE 4 (Continued)

Reference	Sample	MetS definition/ Components	Brain Structure Outcomes	Analytic approach/Matching criteria	Results
Kennedy et al., 2016, USA	137 children and adolescents (9–20 years), mean age 14.9 years	BMI percentile	GMV, WMV	• Whole brain approach • Adjusted for age, sex • Results surviving familywise error (FWE) correction of $p < 0.05$ using Threshold Free Cluster Enhancement (TFCE) reported	• BMI% was negatively correlated with GMV in the caudate, medial PFC, ACC, frontal pole, uncus. BMI% was negatively correlated with WMV in anterior limb of the internal capsule, extending to left middle frontal subgyral WM.
Laurent et al., 2020, USA	3190 children (9–10 years), mean age 10.0 years	BMI	CT	• Whole brain approach • Adjusted for ICV, age, sex, handedness, MRI scanner serial number, puberty, race • Bonferroni correction applied	• BMI was negatively associated with global CT, with the strongest negative association in the PFC. • The association between BMI and working memory was partially mediated by PFC thickness.
Mestre et al., 2017, USA	25 children (8–12 year) • 12 obesity, mean age 10.08 years • 13 healthy weight, mean age 10.38 years	Obesity	GMV	• ROI approach (bilateral hippocampus) • Adjusted for TIV	• Obesity group showed lower hippocampal volume.
Ou et al., 2015, USA	24 children (8–10 years) • 12 obesity, mean age 9.1 years • 12 healthy weight, mean age 9.8 years	Obesity	GMV, WM integrity	• Whole brain and ROI approach • For GMV: Adjusted for TIV, age, gender. Group differences are reported at $p < 0.001$ uncorrected in two sample t-test with cluster size threshold of 100 voxels, differences surviving $p < 0.05$ FWE corrected at cluster level considered significant. • For WM integrity: Adjusted for age, gender. Results surviving $p < 0.05$, FWE corrected, using Threshold Free Cluster Enhancement (TFCE), are reported	• Obesity group showed reduced GMV in right middle temporal gyrus, left and right thalami, left superior parietal gyrus, left pre/postcentral gyri, left cerebellum. • Obesity group showed higher FA in multiple regions in left hemisphere, mostly involving association fibres for example, posterior part of inferior/superior fronto-occipital fasciculus, projection fibres for example, superior corona radiata.
Perlaki et al., 2018, Hungary	51 adolescents (10–17 years) • At timepoint 1, 9 overweight/obesity; at timepoint 2, 13 overweight/obesity, mean age 13.8 years • At timepoint 1, 38 healthy weight; at timepoint 2, 35 healthy weight; mean age 13.8 years	BMI z-score	GMV	• Whole brain and ROI approach • Adjusted for TIV, age, sex • For ROI analysis, results reported at two-tailed $p < 0.05$, and considered significant with Benjamin-Hochberg correction across 10 regions $\times$ 2 timepoints • For whole brain analysis, results surviving $p < 0.05$ corrected using Threshold Free Cluster Enhancement (TFCE) are reported	• BMI z-score was positively associated with GMV in right NAcc and right amygdala. at both timepoints.

TABLE 4 (Continued)

Reference	Sample	MetS definition/ Components	Brain Structure Outcomes	Analytic approach/Matching criteria	Results
Ronan et al., 2020, USA	2700 children (9–11 years), mean age 10.0 years	BMI z-score	CT	• Whole brain approach • Adjusted for age, sex, race, birth weight, in-scanner motion, parental education, household income • FDR correction applied	• Higher BMIz was associated with lower mean CT. • Higher BMIz was associated with lower CT in prefrontal cortical regions. • CT of 11 cortical regions including multiple frontal regions and fusiform gyrus mediated the relationship between BMIz and composite executive function measure.
Silva et al., 2021 (Generation R study) NETHERLANDS	2891 children (9–11 years) • 536 overweight/ obesity, mean age 9.8 years • 2355 healthy weight, mean age 9.8 years	Obesity, BMI, fat mass index, android fat mass percentage assessed by Dual- energy x-ray absorptiometry	GMV, WMV, WM microstructure (fractional anisotropy, mean diffusivity)	• Whole brain approach • Models adjusted for intracranial volume (ICV), maternal age, educational level, pre-pregnancy BMI, prenatal psychological distress, prenatal smoking and prenatal alcohol consumption and child sex, age, ethnicity, birth weight • To correct for multiple comparisons, each p value was compared with a p value divided by the effective number of independent tests estimated based on the correlation between the exposures to minimize false positive findings due to multiple testing ($p = 0.0077$).	• Overweight/obesity versus healthy weight group showed lower frontal lobe GMV, higher amygdala and hippocampal GMV. • One SDS (Standard Deviation Score) increase in fat mass index was associated with lower frontal and temporal lobe GMV, and higher thalamus, amygdala, hippocampal and putamen GMV. • One SDS increase in android fat mass percentage was associated with lower WM diffusivity.
Steegers et al., 2021 (Generation R study), Netherlands	3160 children (9–11 years), mean age 9.8 years	BMI-SDS	CT and cortical gyrification	• Whole brain approach • Adjusted for sex, age, handedness; for second model maternal education, ethnicity, smoking and drinking during pregnancy and child IQ were added. • For global (mean) gyrification and CT, FDR correction applied; for surface-based analyses, cluster-forming threshold of $p < 0.001$ and Bonferroni correction accounting for two hemispheres ($p < 0.025$).	• Inverted-U relationship between BMI-SDS and gyrification such that children with both lower and higher BMI-SDS showed lower gyrification throughout brain. • BMI-SDS showed positive linear association with CT in right superior parietal, bilateral superior temporal, right inferior temporal, right pericalcarine, bilateral occipital, right postcentral, bilateral lingual and left superior parietal gyri.
Thapaliya et al., 2021, USA	58 adolescents (14–20 years) • 36 obesity/overweight, mean age 16.0 years • 22 healthy weight with low familial obesity risk based on maternal overweight/obesity, mean age 16.5 years	Overweight	GMV, WMV, CT	• Whole brain approach • GMV analyses adjusted for TIV, age, sex; CT analyses adjusted for age, sex • Group differences are reported at $p < 0.001$ uncorrected, differences surviving FWE $p < 0.05$ using TFCE considered significant	• Obesity/overweight group versus healthy weight low familial obesity risk group showed: • Lower GMV in middle temporal gyrus and ACC, higher GMV in the frontal pole and precentral gyrus. • Lower WMV in middle temporal gyrus and higher WMV in frontal pole and precentral gyrus.

(Continues)

TABLE 4 (Continued)

Reference	Sample	MetS definition/ Components	Brain Structure Outcomes	Analytic approach/Matching criteria	Results
					• Lower CT in middle temporal gyrus and ACC.
(B) MetS components					
Bruehl et al., 2011, USA	36 adolescents (16–17 years) • 18 obesity+T2DM, mean age 16.5 years • 18 obesity w/o T2DM, mean age 17.1 years	T2DM	GMV	• ROI approach • Groups matched on age, sex, school grade, ethnicity, socioeconomic status, BMI, waist circumference • Adjusted for ICV • Group differences and correlations considered significant at $p < 0.05$ uncorrected	• Obesity+T2DM group showed lower GMV in hippocampus and prefrontal lobe. • HbA1c was negatively associated with prefrontal lobe GMV.
Nouwen et al., 2017, UK	58 adolescents (12–18 years) • 15 obesity+T2DM, mean age 18 years • 21 obesity w/o T2DM, mean age 15.4 years • 22 healthy weight, mean age 14.5 years	Obesity+T2DM, and obesity w/o T2DM	GMV, WM integrity	• Whole brain approach • Adjusted for age, BMIz • For GMV: Group differences considered significant at $p < 0.001$ with $k \geq 200$ • For WMV: FA maps used TFCE then Bonferroni correction applied to group comparisons	• Obesity+T2DM versus healthy weight group showed reduced GMV in the caudate, amygdala and putamen. • Obesity+T2DM versus healthy weight group showed reduced FA in L corticospinal tract, corpus callosum, L fornix, L thalamic radiation, L retrolenticular internal capsule, inferior fronto-occipital fasciculus, R anterior corona radiata, L uncinate, L callosal body, cingulum, and L anterior external capsule.
Redel et al., 2017, USA	40 adolescents (10–22 years) • 20 obesity+T2DM, mean age 16.7 years • 20 healthy weight matched on age, race and sex, mean age 16.7 years	Obesity+T2DM	GMV	• Whole brain approach • Adjusted for ICV • Group differences surviving FWE $p < 0.05$ considered significant	• Obesity+T2DM group showed lower global GMV. • Obesity+T2DM group showed lower GMV in regions in the temporal and occipital lobes, and greater GMV in subcortical and frontal regions including bilateral putamen and frontal lobe.
Rofey et al., 2015, USA	15 adolescents (11–19 years) • 5 obesity+T2DM • 5 obesity w/o T2DM, mean age 15.4 years • 5 healthy weight, mean age 14.5 years	Obesity+T2DM, and obesity w/o T2DM	GMV, WM integrity	• Whole brain and ROI approach • Adjusted for BMI • Adolescents with T2DM and obesity matched on race, sex, BMI ≥95th percentile, Tanner stage IV–V; Healthy weight group matched to T2DM and obesity groups on • Age, race, and sex. • Exploratory analyses, uncorrected	• Obesity+T2DM versus obesity w/o T2DM group showed lower GMV in caudate and thalamus. • Obesity+T2DM and obesity w/o T2DM versus healthy weight group showed lower GMV in the caudate, and lower WM integrity in thalamic pathways in analyses without controlling for BMI.

TABLE 4 (Continued)

Reference	Sample	MetS definition/ Components	Brain Structure Outcomes	Analytic approach/Matching criteria	Results
Saute et al., 2018, Brazil	44 adolescents (15–18 years) • 18 obesity; mean age 16.22 years • 26 healthy weight, mean age 16.81 years	Visceral body fat (assessed by abdominal MRI and ultrasound) and BMI	CT	• Whole brain approach • Adjusted for ICV, age, gender • Correlations using cluster extent threshold determined by Monte Carlo simulation to meet $p < 0.05$, with additional Bonferroni correction, are reported.	• Visceral fat, not BMI, was associated with greater CT across cortex.
Yau et al., 2012, USA	111 adolescents (14–10 years) • 49 obesity with MetS, mean age 17.8 years • 62 obesity with no MetS, mean age 17.5 years	3 of 5 components (a) Abdominal obesity, assessed by waist circumference values ≥90th percentile for age and gender. (b) Reduced HDL. (c) Hyper-triglyceridemia. (d) Hypertension (e) Insulin resistance.	GMV, WM integrity	• Whole brain and ROI approach • Groups matched on age, socioeconomic status, school grade, gender, ethnicity • Adjusted for ICV, age, gender • Results meeting $p < 0.05$ uncorrected are reported	• Obesity with MetS group showed lower hippocampal GMV, increased brain cerebrospinal fluid, and reductions of microstructural integrity in major WM tracts.
Yau et al., 2014, USA	60 adolescents (14–20 years) • 30 obesity, mean age 17.6 years • 30 healthy weight, mean age 17.2 years	Obesity	GMV, CT, WM integrity	• Whole brain and ROI approach • Adjusted for ICV, age • Results meeting $p < 0.05$ uncorrected are reported	• Obesity group showed lower CT in OFC and ACC. • Obesity group showed lower microstructural integrity in major WM tracts.

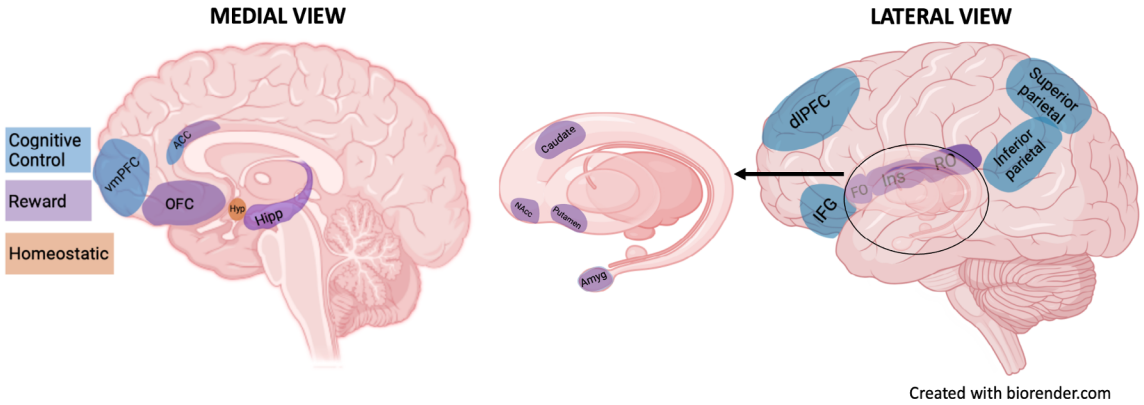

FIGURE 3 Brain regions implicated in food reward, cognitive control and homeostatic regulation demonstrating functional and structural differences in paediatric obesity and metabolic syndrome. ACC, anterior cingulate cortex; Amyg, amygdala; dlPFC, dorsolateral prefrontal cortex; FO, frontal operculum; Hipp, hippocampus; Hyp, hypothalamus; Ins, insula; IFG, inferior frontal gyrus; NAcc, nucleus accumbens; OFC, orbitofrontal cortex; RO, rolandic operculum; vmPFC, ventromedial prefrontal cortex. Regions showing functional as well as structural differences are preferentially represented. [Correction added on 9 June 2023, after first online publication: Figure 3 has been corrected in this version.]

intracranial volume and socioeconomic status (relevant to all studies), and of BMI or other measures of adiposity in studies of T2DM or MetS and its components (see Table 4), precludes direct comparison across studies. Variation in sociodemographic characteristics including race could also contribute to differences in results[50] – the majority of studies have been of youth with white European ancestries, with only a handful of studies focusing on youth with minority backgrounds,[32,49] or including significant representation of minorities.[50,51] When considered together extant results support that paediatric obesity and MetS are likely associated with alterations – most often reductions – in grey matter metrics within areas implicated in a wide range of functions including cognitive control, reward, emotion, memory and sensory processing. However, further research is required to establish robust phenomena and to identify the sources of variability among findings.

4.1.2 | White matter differences

Structural MRI techniques can also be used to estimate white matter volume (WMV), and white matter microstructure via Diffusion Tensor Imaging (DTI). DTI assesses diffusion of water molecules in white matter tracts (Figure 2), and can be used to derive measures of fractional anisotropy (FA), that is, the preference of water to diffuse in one direction. Since diffusion along white matter tracts is anisotropic, higher FA values reflect greater integrity and directionality of white matter fibre tracts, assumed to support more efficient communication between brain regions.[52]

Table 4 includes summaries of studies reporting WMV and WM integrity differences in youth with obesity and MetS or its components. Several studies have demonstrated reductions in both metrics among youth with higher body weight. For example, we ourselves found that a group of adolescents with overweight/obesity showed lower WMV compared with healthy weight adolescents with both low and high familial obesity risk in the middle temporal gyrus ($n = 36$).[35] BMI percentile additionally showed a negative correlation with WMV in the anterior limb of the internal capsule, extending to the middle frontal subgyral WM in a larger study of adolescents ($n = 137$).[37] Other studies using DTI methods have found that adolescents with overweight/obesity ($n = 40$) versus healthy weight ($n = 47$) demonstrated lower WM integrity in the superior frontal corpus callosum, uncinate fasciculi, inferior fronto-occipital fasciculus and corticospinal tract,[53] and that higher BMI was associated with decreased FA in WM fibres connecting the left superior longitudinal fasciculus and left inferior longitudinal fasciculus regions that support working memory ($n = 52$[54]).

Other studies have demonstrated reductions in WMV and WM integrity in youth with T2DM or with MetS or its components. One study found that adolescents with T2DM ($n = 15$) showed reduced FA within many key white matter tracts, including the corpus callosum, fornix, inferior fronto-occipital fasciculus, uncinate, and internal and external capsule, compared to adolescents with obesity ($n = 21$) and adolescents with healthy-weight ($n = 22$),[43] with a further smaller study finding that groups with obesity and T2DM ($n = 5$) and obesity without T2DM ($n = 5$) versus healthy weight ($n = 5$) showed lower WM integrity in thalamic pathways but only in analyses that did not adjust for BMI.[44] Yau et al. further found that adolescents with MetS and obesity ($n = 49$) versus adolescents who were overweight without MetS ($n = 62$), showed reduced FA in a number of major fibre tracts (including corpus collosum, optic radiations, medial longitudinal fasciculi), suggesting impaired interhemispheric and cortico-subcortical communications.[16] Complementarily, Yau et al. found that adolescents with uncomplicated obesity (no insulin resistance) ($n = 30$) versus healthy weight ($n = 30$) had reduced FA in major white matter tracts (including temporal stem, optic radiations, internal capsule, splenium, external capsule), potentially reflecting a dose effect of metabolic dysregulation.[46] Another study of Generation R found that a one standard deviation score (SDS) increase in android

fat mass percentage as assessed by Dual x-ray Absorpiometry (DEXA)—a high-quality indicator of abdominal obesity—was associated with globally lower white matter diffusivity.[38]

Reductions of WMV and WM integrity are not universally observed. In one of our own studies, we found *higher WMV* in the frontal pole and precentral gyrus among adolescents with overweight/obesity ($n = 36$) compared to a group of healthy weight adolescents with low familial risk for obesity ($n = 22$).[35] Higher WMV in the cerebellum and mid-posterior corpus callosum has additionally been reported in children with overweight and obesity versus healthy weight.[32] One study using DTI further found that adolescents with overweight/obesity ($n = 40$) versus healthy-weight ($n = 47$) demonstrated *increased WM integrity* in the orbital and anterior frontal corpus callosum, inferior fronto-occipital fasciculus, cingulum, and corticospinal tract.[53] However, a larger study ($n = 120$) of 6–18 years old children found no relationship between BMI and FA.[36]

As for the GM findings described above, comparison across WM results is challenging due to sample and method variance and a relatively small number of studies assessing WM as opposed to GM metrics. Extant evidence supports further examination of potential differences in WM in children according to body weight and MetS.

4.2 | Functional brain differences

A substantive body of literature has examined the association of obesity in youth with brain activation in response to food stimuli and at rest. Brain activation in response to acute administration of food cues or food tastes is typically measured using functional Magnetic Resonance Imaging (fMRI) methods which assess changes in the flow of oxygenated blood (the Blood Oxygen Level Dependent (BOLD) response) as a proxy for neural activity (see here for a critique[55]). In adults, obesity and MetS are associated with alterations in brain response to food cues and taste stimuli[56,57] and resting state functional connectivity[58] that may perpetuate overeating. Here, we discuss evidence for functional brain differences in adolescents and children with obesity and components of MetS.

4.2.1 | Brain response to food cues

Mounting evidence from a considerable number of small studies suggests that children and adolescents with obesity show increased response to food cues (e.g., food images, food commercials, food brand logos, food words) in brain regions associated with motivation and reward and decreased response in regions associated with cognitive control[59] (Table 5, Section A, Figure 3).

For example, adolescents with obesity ($n = 25$) showed increased brain response to high calorie food images in striatal-limbic regions (putamen/caudate, insula, amygdala) compared to adolescents with healthy weight ($n = 15$).[60] Similarly, in response to food commercials, percent body fat in adolescents was correlated with increased response in the insula and OFC as well as sensorimotor cortex ($n = 37$[61]). In a study testing responses to food images following exposure to food commercials, children with overweight and obesity showed increased response in the OFC as well as the fusiform gyrus and supramarginal gyrus, to high-calorie food images as compared to children with healthy weight.[62]

Other studies have primarily found evidence of reduced activation in regions of the frontal cortex associated with obesity. In response to food brand logos presented when fasted, children with obesity ($n = 10$) showed reduced activation of bilateral middle and inferior PFC, compared to children with healthy weight ($n = 10$).[63] In another child sample ($n = 53$), percent body fat was negatively associated with response in the medial PFC and lateral OFC to palatable food images in a fasted state.[64] A separate paediatric study found that higher BMI was associated with lower dorsolateral PFC activation in response to unhealthy versus healthy food images,[65] while a different study reported that children with obesity ($n = 11$) compared to children with healthy weight ($n = 11$), showed a weaker response in the dorsomedial PFC to high-calorie food images following a meal.[66] In a study of adolescents, we found that those with overweight and obesity ($n = 10$) showed weaker responses in an attentional/regulatory system including dorsolateral PFC and dorsal ACC as well as basal ganglia nuclei, to high energy-density food words as compared with healthy weight adolescents ($n = 10$).[67]

Few studies have examined associations between other components of MetS and brain response to food cues. However, one small study of Hispanic girls with overweight ($n = 10$) found that fasting blood glucose was positively associated with responses in the insula and caudate to high calorie food images in a fasted state,[68] suggesting that certain components of MetS may be associated with increased food cue responsiveness in regions implicated in food motivation.

Taken together, extant results on the whole support a model in which paediatric obesity is associated with hyperactivation of regions involved in food reward and with altered, usually weakened, responses in circuits involved in cognitive control in response to visual stimuli relating to food. However we note that differences in activation are also seen in regions implicated in emotion, memory and sensory and motor processing when using whole brain analysis approaches that test for differences across the brain rather than confining testing to specified ROIs. This supports a distributed model of appetitive processing and advocates for interpreting activation at a circuit versus individual region level.[69] We also note significant variation between studies in terms of study design (e.g., fasting status) and task features (e.g., task stimuli and response requirement (passive viewing, appetitive response made for each stimulus)), as well as in statistical approach (see Table 5, Section A for details); these differences may contribute to between-study variability in results.

4.2.2 | Brain response to taste administration and cues predicting delivery of taste

Delivery of taste stimuli in the scanner via a gustometer (a mouthpiece designed to drop liquid on the participant's tongue

TABLE 5 Associations between MetS components and brain function in children and adolescents (2–20 years).

Reference	Sample	MetS definition/ Components	Task and outcomes	Hunger state/Analytic approach	Results
(A) Food cues					
Adam et al., 2015, USA	10 girls with overweight (8–11 years), Hispanic, mean age 9.9	Overweight	• Block design • Response to high-calorie food (>non-food) images • Passive viewing with intention to recall after scanning	• Adjusted for BMI • ROI approach • Contrast maps thresholded at $p < 0.05$ corrected for multiple comparisons • Regressions considered significant at $p < 0.05$	• Insulin sensitivity was negatively associated with response in ACC, insula, OFC, and frontal and rolandic operculum.
Allen et al., 2016, UK	36 adolescents (12–18 years), mean age 16 years • 15 obesity with T2DM • 21 obesity w/o T2DM • 21 healthy weight	T2DM and obesity	• Event-related design • Response to food (>non-food) and high-fat food (>non-food) images • Participants instructed to look carefully at each picture and imagine eating the food item	• Served breakfast or asked to eat breakfast at home 2.5 h prior to scanning • Whole brain approach • Contrast maps thresholded using clusters determined by Z > 2.3 and cluster-level threshold of $p = 0.05$ corrected	• Obesity+T2DM versus obesity w/o T2DM group showed greater response to high-fat food images in visual and attention areas including calcarine sulcus, temporal gyrus, angular gyrus and inferior parietal regions. • Obesity w/o T2DM versus healthy weight group showed greater response to high fat food images in regions including L and R insula, L and R operculum and around R supramarginal gyrus and L inferior frontal gyrus.
Bruce et al., 2013, USA	20 adolescents (9–16 years) • 10 obesity, mean age 11.9 • 10 healthy weight, mean age 11.9	Obesity	• Block design • Response to food (>baseline or >non-food) logos • Passive viewing of stimuli	• Fasted for >4 h • Whole brain approach • Voxels considered activated if survived cluster-level threshold of $p < 0.01$ corrected • Multiple comparison correction using familywise approach ($\alpha < 0.05$; $p < 0.01$; $k = 9$), determined by Monte Carlo simulation	• Obesity group showed greater response to food logos > baseline in postcentral gyrus and midbrain. • Obesity group showed lesser response to food > non-food logos in middle and inferior frontal gyrus, superior temporal gyrus, parahippocampal gyrus and insula.
Carnell et al., 2017, USA	20 adolescents (14–19 years) • 10 overweight/obesity, mean age 15.8 years • 10 healthy weight with low familial obesity risk based on maternal healthy-weight, mean age 16.0 years	Overweight/ Obesity	• Event-related design • Response to high energy-density food (>low energy-density food & non-food) words • For each food word, participant instructed to focus on food word and think about how food looks, smells, and tastes, and how it would feel to eat it at that moment, and to rate how much they wanted	• Consumed standardized lunch, scanned >5 h after meal • Whole brain approach • Voxels identified as having posterior probability of 98.75% using $p < 0.0125$ and $k \leq 8$ were reported. Based on an approximation formula this conjoint requirement yields	• Overweight group showed lesser response to food > non-food cues in dorsal ACC, caudate, thalamus, middle temporal cortex, cerebellum, dlPFC, sensory motor cortex; greater activation to food > non-food cues in inferior parietal cortex. • Overweight group showed lesser response to high>low energy-

TABLE 5 (Continued)

Reference	Sample	MetS definition/ Components	Task and outcomes	Hunger state/Analytic approach	Results
			to eat it, and how much they felt they should not eat it • For non-food words, participants instructed to think about how object looks and how it would feel to use it at that moment, and to rate how much they wanted to use the object, and how much they felt they should not use it	conservative effective $p < 0.000005$.	density foods in hippocampus, ACC, posterior cingulate cortex (PCC), middle cingulate cortex (MCC), superior PFC, inferior parietal cortex, motor cortex.
Jastreboff et al., 2014, USA	40 adolescents (12–17 years) • 25 obesity, mean age 15.7 years • 15 healthy weight, mean age 15.5 years	Obesity	• Event related design • Response to high-calorie food (>non-food) images • Participants instructed to view each picture and rate liking and wanting of each item	• Served 500 kcal meal 2 h prior to scan • Whole brain approach • Whole brain analyses used cluster extent threshold determined by Monte Carlo simulation to meet $p < 0.05$	• Obesity group showed greater response in putamen/caudate, insula, amygdala.
Luo et al., 2019, USA	53 children (7–11 years)	Percent body fat	• Block design • Response to food (>non-food) images • Participants instructed to view pictures attentively (passive viewing)	• Fasted overnight, adjusted for age, sex • Whole brain approach • Whole brain analysis used cluster forming threshold of $Z > 2.3$ (equivalent to $p < 0.01$), and minimum cluster size for a FWE correction of $p < 0.05$ determined by FLAME1 modelling procedure	• Percent body fat was negatively associated with response in medial PFC and lateral OFC.
Masterson et al., 2019, USA	41 children (7–9 years) • 16 overweight/obesity, mean age 8.0 • 25 healthy weight, mean age 7.8	Overweight	• Block design • Response to high-calorie food (>non-food) images, following exposure to food commercials • To improve engagement in the task, children responded to the question, "Would you eat this in the morning or the evening?" while viewing each picture.	• Fasted for >3 h • Whole brain approach • Whole brain analyses used threshold of $p < 0.005$ and $k = 5$, then 10 000 Monte Carlo simulations for estimations for overall $p < 0.05$	• Overweight/obesity group showed greater response in OFC, fusiform gyrus, and supramarginal gyrus.
Rapuano et al., 2016, USA	37 adolescents (12–17 years), mean age 14.4	Percent body fat	• Event related design • Response to food (>non-food commercials) • Passive viewing	• Fasted for >2 h • Adjusted for age, sex • Whole brain and ROI approach • For ROI analyses, $p < 0.005$ with cluster threshold of $k = 913$ based on 5000 Monte Carlo simulations for $p < 0.05$	• Percent body fat was positively associated with response in OFC and insula ROIs. • Whole brain analysis found percent body fat was positively associated with response in insula, cerebellum and sensorimotor cortex.

(Continues)

TABLE 5 (Continued)

Reference	Sample	MetS definition/ Components	Task and outcomes	Hunger state/Analytic approach	Results
				• For whole-brain analyses, $p < 0.001$ with cluster threshold of k = 74 based on 5000 Monte Carlo simulations for $p < 0.05$ corrected	
Samara et al., 2018, USA	22 children (8–10 years) • 11 obesity, mean age 9.1 • 11 healthy weight, mean age 9.8 years	Obesity	• Block design • Response to high-calorie food (>non-food) images • Passive viewing	• Consumed breakfast before scans • Whole brain and ROI approach • Contrast maps thresholded at Z > 2.3 and cluster-level threshold of $p < 0.05$ corrected • Group comparisons of activation in anatomical ROIs that showed differences in averaged activation maps were considered significant at $p < 0.05$	• Obesity group showed lesser response in posterior parahippocampal gyri and dorsomedial PFC.
(B) Taste and cue predicting taste					
Bohon et al., 2017, USA	18 children (6–8 years) • 8 overweight • 10 healthy weight	Overweight	• Event-related design • Response to cues predicting taste, and taste administration (milkshake > tasteless)	• Fasted for 4–6 h • Whole brain approach • Contrast maps thresholded at Z > 1.7 and cluster-level threshold of $p < 0.05$ uncorrected (pilot study)	• Overweight group showed greater response in insula, precentral gyrus, precuneus, and posterior cingulate cortex to milkshake taste. • No group difference in response to cues predicting milkshake.
Bohon et al., 2014, USA	• 162 adolescents, mean age 15.3 years	BMI, Body fat percentage	• Event-related design • Response to cues predicting taste and taste administration (milkshake>tasteless)	• Fasted for 5 h preceding scan • ROI approach • Contrast maps thresholded at Z > 2.3 and cluster-level threshold of $p < 0.05$ corrected	• No significant relation between neural response to milkshake taste and BMI or body fat percentage when controlled for emotional eating.
Boutelle et al., 2015, USA	23 children (8–12 years) • 10 obesity, mean age 9.9 • 13 healthy weight, mean age 10.4	Obesity	• Block design • Response to cues predicting taste, and taste administration (sucrose solution, water)	• Scanned after a standardized breakfast • Whole brain and ROI approach • ROI and whole brain analyses used cluster extent threshold determined by Monte Carlo simulation to meet $p < 0.05$	• Obesity group showed greater response to taste (sucrose+water) in insula and amygdala ROIs. • Obesity versus healthy weight group showed greater response to sucrose versus water in paracingulate, medial frontal, middle frontal gyri, and right amygdala.
Mestre et al., 2017, USA	25 children (8–12 years) • 12 obesity, mean age 10.1 years • 13 healthy weight, mean age 10.4 years	Obesity	• Block design • Response to cues predicting taste and taste administration (sucrose solution>water)	• Scanned after a standardized breakfast • ROI approach • ROI analysis in bilateral hippocampus used cluster extent	• Obesity group showed greater response to sucrose solution in three clusters within left hippocampus.

TABLE 5 (Continued)

Reference	Sample	MetS definition/ Components	Task and outcomes	Hunger state/Analytic approach	Results
				threshold determined by Monte Carlo simulation to meet $p > 0.05$ in left and right hippocampus respectively.	
Stice et al., 2008, USA	18 adolescents • 7 girls with obesity, mean age 15.7 • 11 girls with healthy weight, 15 girls with overweight, mean age 15.7	Obesity	• Event-related design • Response to cues predicting taste, and taste administration (milkshake>tasteless)	• Fasted for 4–6 h • Whole brain approach • Whole brain analyses used voxel-wise $p < 0.001$ and cluster-level threshold of $p < 0.05$ corrected	• Obesity versus healthy weight group showed greater response in insula and Rolandic operculum to cues predicting milkshake. • BMI was negatively associated with response in the caudate to milkshake administration.
(C) Resting state functional connectivity					
Black et al., 2014, USA	18 adolescents • 9 obesity, mean age 11.7 • 9 healthy weight, mean age 12.3	Obesity	• Seed-to-voxel connectivity	• Within ROIs voxel-wise $p < 0.05$ and small volume correction using Monte Carlo simulations. • Outside of ROIs, voxel-wise threshold of $p < 0.001$, combined with Monte Carlo simulations of cluster size for the whole brain	• Obesity group showed greater connectivity of middle frontal gyrus seed with ventromedial PFC and lateral OFC.
Borowitz et al., 2020, USA	124 adolescents (13–16 years) • 36 obesity, mean age 14.6 years • 88 healthy weight, mean age 14.1, 40 overweight, mean age 14.4 years	Obesity/ overweight	• ROI-to-ROI connectivity	• Controlled for age, sex, hunger, handedness • Effects considered significant after thresholding at $p < 0.001$ and FDR correction at $p < 0.05$ for analysis	• Obesity group showed greater within-network connectivity of salience network ROIs. • Obesity group showed lesser connectivity of salience network with default mode network, and of salience network with executive function network.
Chodkowski et al., 2016, USA	38 children (8–13 years)	BMI z	• Seed-to-voxel connectivity	• Functional connectivity considered significant with $p \leq 0.05$. • Regressions of connectivity parameters with BMIz considered significant at $p < 0.05$	• Higher BMIz was associated with relatively greater frontal pole: NAcc connectivity (interpreted as impulsivity-associated) compared to IPL:NAcc connectivity (interpreted as inhibition-associated).
Martin-Perez et al., 2019	104 adolescents (10–19 years) • 53 overweight/obesity; mean age 14.64 years • 51 healthy weight, mean age 15 years	Overweight/ obesity	• Seed-to-voxel connectivity	• Controlled for age, sex and pre-scan hunger rating • Effects considered significant at $p < 0.05$, FWE corrected for multiple comparisons across all in-mask voxels (i.e., small-volume correction)	Overweight/obesity group showed: • Greater functional connectivity of lateral hypothalamus (LH) with OFC and anterior insula, ventral striatum • Lesser connectivity of LH with cerebellum

(Continues)

TABLE 5 (Continued)

Reference	Sample	MetS definition/ Components	Task and outcomes	Hunger state/Analytic approach	Results
					• Greater connectivity of medial hypothalamus (MH) with middle temporal cortex networks. • Lesser connectivity of MH with middle prefrontal, pre-, and postcentral gyri networks
Moreno-Lopez et al., 2016, Spain	115 adolescents (12–17 years) • 60 overweight/obesity, mean age 14.7 • 55 healthy weight, mean age 15.1	Overweight	• Voxel-to-voxel and seed-to-voxel connectivity	• Scanned 1–4 h after main meal • Minimum cluster sizes were 3 voxels for the global connectivity degree (voxel-to-voxel) analysis and 125 voxels for seed-based functional connectivity analysis to satisfy whole-brain FWE correction of $p < 0.05$.	• Overweight/obesity group showed lower global connectivity of regions in insula/operculum, middle temporal cortex, and dorsolateral PFC regions with voxels across the whole brain. • Overweight/obesity group showed lower connectivity of the functionally-derived insula/ operculum seed with dorsal ACC and supplementary motor area, and increased connectivity of the dlPFC seed with primary visual cortex.
Singh et al., 2019	42 adolescents with overweight and depression (9–17 years)	Insulin Resistance, overweight	• Seed-to-voxel connectivity	• Controlled for age and sex • Effects considered significant with cluster threshold of $z > 2.3$ and $p < 0.025$ (for 2 seed regions).	• Greater insulin resistance was associated with decreased connectivity between ACC and hippocampus seeds to fronto-limbic reward networks.
Synder et al., 2022	21 adolescents (12–17 years) • 5 adolescents with T2DM with obesity • 6 nondiabetic controls • 10 lean controls	T2DM, overweight	• Independent component analysis (ICA)	• Pilot study, adjustment for covariates and multiple comparisons not performed.	• No group differences in connectivity within the DMN.

Abbreviations: ACC, anterior cingulate cortex; DMN, default mode network; MetS, metabolic syndrome; OFC, orbitofrontal cortex; PFC, prefrontal cortex; ROI, region of interest.

during MRI scanning) enables assessment of regional brain responses to small amounts (3–5 mL) of liquid (also referred to as "tastes") and cues predicting the delivery of those tastes (Table 5, Section B, Figure 3). A large body of work has investigated brain responses to tastes among healthy weight adolescent girls,[70] but only a few studies have examined effects of obesity in youth. In adolescents ($n = 33$), girls with obesity ($n = 7$) showed *increased* activation of sensory processing regions including the insula and rolandic operculum during *anticipation* of delivery of a high fat and high sugar milkshake, but BMI was negatively associated with response in the caudate, a region implicated in motivation, during *receipt* of milkshake taste.[71] In contrast, in young children with overweight ($n = 8$) versus healthy-weight ($n = 10$) there was no difference in response to cues predicting taste.[72] In response to a high-fat/high sugar taste, children with overweight showed a *greater* response in regions involved in gustatory processing, including the insula, precentral gyrus, precuneus, and posterior cingulate cortex.[72] Similarly, in a sample of slightly older children, those with obesity ($n = 10$) versus healthy-weight ($n = 13$) showed *greater* response in the insula and amygdala in response to taste administration (sucrose or water) and greater responses to sucrose versus water relative to the healthy-weight group in the paracingulate, medial frontal and middle frontal gyri, and right amygdala following a standardized meal.[73] Further, taking a region of interest [ROI] analytic approach (which examines signal within pre-defined, specified regions of the brain) focused on the hippocampus, another study found that children with obesity ($n = 12$) versus children with healthy-weight ($n = 13$) showed increased response in the hippocampus to a sucrose solution.[33] However, in a sample of 162 adolescents, no significant relationship was found between neural response to taste and BMI or body fat percentage while controlling for emotional eating.[74] As far as we aware, no study to date has tested the effect of other components of MetS on neural response to palatable tastes.

The samples used in the literature described above are small and thus findings should be interpreted with caution.[75] However, we note that, if confirmed, the observed phenomenon of increased neural responses to *taste* in heavier children, and increased neural responses to *cues* signalling taste delivery in older youth would be consistent with a dynamic vulnerability model similar to that seen in addiction[76] such that individuals at raised obesity risk initially demonstrate a hyper-responsivity of the reward system to palatable foods which decreases over time, while responsivity to cues signalling such foods increases over time (see Reference 77 for a fuller discussion of the dynamic vulnerability model of obesity).

4.2.3 | Resting state functional connectivity

Resting state functional connectivity assessed via fMRI (rsfMRI) is a measure of the temporal correlations of spatially distinct brain regions, and can be considered a proxy for functional organization of brain networks, with increased resting state connectivity thought to reflect increased functional communication between regions.[78] Although there are now several large studies in adults demonstrating altered resting state connectivity of the default mode network and salience networks associated with obesity,[79–81] studies of comparing resting state functional connectivity in youth with obesity to youth with healthy weight are less common (Table 3, Section C, Figure 3).

In one study using a whole brain connectivity analysis that evaluated connectivity between every voxel (i.e., small volume element in brain image on the order of 1–3 mm^3) (rather than examining ROI-to-ROI connectivity or connectivity between a seed ROI and every voxel in the brain), adolescents with obesity ($n = 60$) versus healthy-weight ($n = 55$) showed reduced global connectivity of the insula/operculum, middle temporal cortex, and dorsolateral PFC.[82] Subsequent seed-based analyses revealed reduced connectivity of the insula/operculum seed with the dorsal ACC and supplementary motor area among adolescents with obesity, as well as increased connectivity of the dorsolateral PFC seed with the primary visual cortex.[82] A separate study taking a seed-to-voxel approach (calculated as the connectivity of a ROI, or seed, to all other voxels in the brain) found that adolescents with obesity ($n = 60$) versus healthy-weight ($n = 55$) demonstrated increased functional connectivity between middle frontal gyrus and ventromedial PFC, and between middle frontal gyrus and lateral OFC.[83] A study using an ROI-to-ROI approach found that adolescents with obesity ($n = 36$) versus healthy-weight ($n = 88$) showed increased connectivity of ROIs within the salience network (e.g., between the medial orbitofrontal cortex, olfactory tubercle, and pallidum) but lower connectivity of salience network regions to regions in other networks, such as the default mode network and executive function network.[84] Another study in children ($n = 38$), showed that higher BMIz was associated with relatively greater connectivity between the NAcc and frontal pole (interpreted as impulsivity-associated) and relatively lesser connectivity between NAcc and inferior parietal lobule (interpreted as reward-associated).[85] Finally, a study in adolescents showed that those with excess weight ($n = 53$) versus healthy weight ($n = 51$), showed greater connectivity of the lateral hypothalamus (LH) with OFC, ventral striatum and anterior insula, and of the medial hypothalamus (MH) with the middle temporal cortex but lower connectivity of the LH with the cerebellum, and of the MH with middle prefrontal, pre-, and postcentral gyri.[86]

We are aware of only one study reporting an association between an MetS component, insulin resistance (IR), with resting state functional connectivity. This study of adolescents with overweight and depression ($n = 42$) found that IR was associated with decreased resting state functional connectivity of the two seed regions, ACC and hippocampus with fronto-limbic reward networks.[87]

The methodological and analytic variation among existing rsfMRI studies of obesity in youth prevents generalization of findings but together these results suggest that excess weight may be associated with altered patterns of functional connectivity,[82] with some results consistent with a pattern of reduced connectivity of brain regions executing cognitive control with regions implicated in food reward in youth with obesity[82,84,85] or insulin resistance.[87]

5 | MECHANISMS UNDERLYING COGNITION AND BRAIN DIFFERENCES IN PAEDIATRIC OBESITY AND METS

5.1 | Causal and temporal relationships

Most research into alterations in cognition, brain structure, and function in youth with obesity and MetS is cross-sectional, thus leaving unanswered whether cognitive and brain differences play a causal role in influencing weight trajectories or vice versa. The strongest evidence for causal mechanisms comes from animal model studies. For example, rodents fed a diet composed of high-fat and high-sugar ultra-processed foods (a.k.a. 'cafeteria' or 'Western' diet) to induce obesity and MetS show an elevated neuroinflammatory response in the hippocampus[88,89] and cognitive impairments in learning and memory[90] relative to lean animals fed a control diet. Evidence further suggests that exposure to a high-fat/high-sugar diet during early development can cause long-term behavioural impairments across multiple cognitive domains in animal models.[91] However, switching rodents initially fed a high-fat/high-sugar diet to a control diet results in significant weight loss and amelioration of cognitive deficits.[92,93] The effects of high-fat diet are often confounded with those of diet-induced obesity in these studies, although other research in rodents has observed effects on the brain of high fat diet prior to weight gain.[94] Translation of findings in rodents to humans is not straightforward and results should not be over-interpreted.[95] However, these findings provide some support for a causal impact of diet-induced obesity on cognition and brain structure.

Other evidence comes from human studies showing that weight loss resulting from bariatric surgery is accompanied not only by improvements in metabolic function, but also by neurocognitive changes. Studies of adolescents undergoing bariatric surgery have reported improvements in executive function and changes in reward-related decision-making 3–4 months following surgery as compared with wait-listed controls,[96] and reduced striatal responses to monetary reward, suggesting weight loss may recalibrate brain mechanisms underlying general reward processing.[96] These findings are consistent with the larger body of research in adults which has demonstrated post-surgical improvements in general cognition,[97] reduced responses to food cues in reward processing regions,[98–100] decreased responses in prefrontal areas implicated in executive function,[101,102] increases in GMV within frontotemporal brain regions,[103–105] and associations between weight loss from Roux-en-Y Gastric Bypass with increases in post-surgical ventral tegmental area (VTA) responses to taste stimuli.[106] Collectively, these results suggest that effects of obesity on brain function and function may be partly reversible with weight loss. However, engagement of cognitive control circuitry during food tasks may decrease, rather than increase, perhaps due to a lesser need for conscious self-regulation of the drive to eat.

Longitudinal observational studies also support a model in which general and food-related cognition and food-associated brain function *may predict* weight change. For example, childhood intelligence has demonstrated associations with adult BMI (for review see[107]) although studies showing this association often do not adjust for BMI at the time of the baseline IQ assessment, so effects could also be driven by an effect of excess BMI on intelligence,[107] and failure to delay gratification at preschool age has been associated with a greater likelihood of being overweight at 11 years old ($n = 805$).[108] Further, prospective data have demonstrated that heightened reinforcing value of food was associated with BMI increases in children after 1 years ($n = 316$),[109] while elevated brain response during taste anticipation in regions involved in reward processing was associated with future body fat gain ($n = 153$).[110]

Consistent with these findings, children and adolescents who show certain patterns of food-related cognition may respond differently to weight loss interventions, supporting an influence of food-related cognition on weight. For example, heightened attentional food bias as assessed by a visual probe task was associated with reduced weight loss in children with obesity,[111] and school-aged children with greater food-related delay discounting and higher reinforcing value of food showed less success in a 16-week behavioural obesity treatment relative to school-aged children.[112] Conversely, interventions that target food-related cognition in children and adolescents show potential impact on eating behaviours and downstream weight gain prevention or weight loss outcomes. For example, a one-session training program designed to train attention away from food cues in children with overweight/obesity prevented increases in attentional bias and eating in the absence of hunger,[113] while a study in children with obesity found that episodic future thinking both improved performance on a delay discounting task and lowered subsequent ad lib intake of sweet, energy-dense foods (~1300 kcal).[114] These interventions provide early evidence that food-related cognition can be targeted to improve eating behaviour in youth.

To summarize, available data do not conclusively support one causal direction over another. Notably, the fact that obesity-associated brain alterations are reversed with weight loss interventions may not negate the primacy of brain alterations. Such alterations, coupled with an obesogenic environment, can lead to weight gain and additional brain alterations, creating a positive feedback cycle. A bidirectional causal relationship is more plausible than a unidirectional one.

5.2 | Biological mechanisms

The biological mechanisms underlying the neural and behavioural correlates of obesity and MetS are not fully understood, but cellular and cerebrovascular mechanisms have been proposed.[115,116] Low grade systemic inflammation contributing to IR is hypothesized to mediate the association of obesity and MetS with neurocognitive deficits.[117–119] Obesity is associated with increased visceral adipose tissue, which is generally associated with chronic low grade systemic inflammation.[120,121] Inflammation has also been associated with IR and compromised endothelial function in animal models.[122] While the mechanisms are not clear, it is possible that the inflammatory state leads to the disruption of the tight junctions between endothelial

cells,[123] which may result in infiltration of immune cells into the brain and increased production of local inflammatory cytokines.[124] Several groups have reported an association between low grade systemic inflammation and structural brain abnormalities in the hypothalamus in obesity[125] and MetS[126] in adults. This effect is also observed in paediatric samples and shows an interaction with sex such that adolescent girls with obesity who have significant insulin resistance have smaller hypothalamic volumes than adolescent boys with obesity.[127] Further, evidence in adults suggests that weight loss following bariatric surgery may reverse hypothalamic inflammation and lower systemic inflammation.[128] However, other research in adolescents has demonstrated that low-grade systemic inflammation is not consistently associated with IR,[129] suggesting that in youth, the relationship between adiposity, inflammation, and IR may not be as clear as in adults. Further research in children is needed to elucidate the relationship between obesity, insulin resistance and inflammation.

Another potential mechanism for MetS and obesity-related differences in cognition and brain structure and function is alterations to vascular reactivity. Vascular reactivity is key to energy-dependent processes, such as providing increased perfusion to activated brain regions and clearing the metabolic "waste" produced by neuronal activity.[130] We have proposed a conceptual model suggesting that individuals with IR and/or MetS may be unable to maintain proper vascular reactivity and effectively clear metabolites from the neuronal environment, especially during periods of high functional demand (e.g., during a cognitive task).[115] This may be a function of IR, as adults with obesity and IR show greater decreases in cerebrovascular reactivity compared to adults with obesity alone.[131] Decreased vascular reactivity may be important to the brain deficits present in IR, T2DM, and MetS. Weight loss and improvements in insulin function have been associated with improved cerebral perfusion, supporting a potential causal link.[132,133] Important to note, though, is that the latter studies were conducted in adults so their relevance to children and adolescents is unclear. An important related point is that vascular reactivity differences could affect the BOLD signal,[55] which has implications for interpretation of fMRI measures of resting state activation and task-related activation. The practice of analysing fMRI data using within subject contrasts (e.g., high calorie food response vs. low calorie food response) rather than absolute values may somewhat alleviate the impact of vascular reactivity differences between subjects in cross-sectional designs. However, it does not rule out the possibility that individual differences in global or regional neurovascular coupling resulting from obesity and MetS could contribute to observed differences in brain function.

A further mechanism of high potential relevance during development is effects of high fat diets and obesity on myelination. Myelin-specific MRI techniques (e.g., mcDESPOT[134]) may offer the potential to expand on knowledge obtained using FA measurements by providing unique information about brain structure characteristics critical for the rapid synchronization of information transfer that underlies coordinated movement and cognitive and behavioural processes. In children and adults, myelination is negatively associated with obesity.[135] Research with animal models suggests obesity may cause disruptions in essential fatty acid production such as hyperinsulinemia or other endocrine factors affecting early myelination,[136] and high fat diets may impair oligodendrocytes, which are imperative to myelin expression.[137] Further, insulin has been reported to promote myelin-producing oligodendrocytes during development.[138] Hence, it has been speculated that higher insulin concentration due to insulin resistance may alter cholesterol metabolism as demonstrated in rodent models.[139]

Another mechanism may be responsible for relationships of body weight and indicators of MetS with food-related (vs. general) cognition: changes to the striatal dopamine (DA) system. In a classic study using [^{11}C] raclopride Positron Emission Tomography (PET) imaging, in which the radioactive tracer [^{11}C] raclopride is injected and competes with endogenous DA at DA receptors thereby giving an indication of DA receptor availability, obesity in adults was associated with evidence for downregulation in striatal DA D2 receptors,[140] a finding which has been replicated in some studies but not others.[141] Obesity and insulin resistance have also been associated with decreased DA release in the NAcc in response to calories in adults,[142] suggesting abnormal reward response to caloric intake. Due to the need to limit radiation exposure in children it is not clear whether these phenomena generalize to youth. Studies in rodents subsequently showed that prolonged exposure to a high-fat, high-sugar diet increased compulsive food-seeking behaviour and downregulates DA D2 receptors.[143] These results suggest that associations between obesity and food-related cognition could be partly explained by dysregulated functioning of striatal DA D2 receptors. More recent work in rodents has supported independent effects of diet on dopamine circuits, finding that high-fat (vs. low-fat) feeding decreased striatal DA release following lipid infusion in the absence of an effect on weight.[144] Further, other studies have shown that heightened responses to food cues precede overeating and weight gain in animals who later develop diet-induced obesity and are accompanied by differences in NAcc function[145]; this suggests that relationships between diet/adiposity and DA dysfunction are likely bidirectional.

Important for this review, new evidence additionally suggests that associations between adiposity and brain reward responses to food cues may be explained by learning effects resulting from impacts of diet on glucose metabolism. For example, one imaging study in adults found that when participants consumed a noncaloric, flavoured beverage that had previously been paired with calories, NAcc response was correlated with the change in plasma glucose levels following initial consumption of the caloric version.[146] The effect was independent of explicit 'liking' ratings for the beverage, suggesting an implicit effect of glucose dynamics on brain response. This finding raises the possibility that heightened glucose responses could drive reward circuit responses to food stimuli in individuals with impaired insulin sensitivity.

6 | FUTURE DIRECTIONS

Many questions remain regarding relationships of paediatric obesity, MetS, and components of MetS with measures of cognition, brain function, and brain structure, many of which can be addressed by advancing the quality of existing studies.

Firstly, we note several opportunities to improve sampling methods, with ensuing benefits in terms of statistical power and generalizability. Small sample sizes are particularly ubiquitous in many of the extant human neuroimaging studies, increasing the likelihood that results are driven by sampling variation, decreasing replicability and compromising generalizability. Small samples are a problem for neuroimaging studies due to the multiple testing problem engendered by investigating thousands of voxels across the brain. This issue can be addressed to some degree by ROI approaches that confine the number of voxels examined; however, these approaches can present the opposite problem of Type II error due to failure to examine brain regions that play an important role in the phenomenon under study. Multi-site designs are increasingly being used to generate large paediatric imaging datasets containing structural MRI, resting state MRI and general cognitive task data.[147,148] Similar approaches may be necessary to establish generalizable findings on brain responses to food cues and food tastes. In addition, to promote the applicability of imaging findings and allow the identification of robust predictors of individual variation in responses, these studies must take care to include minority populations with disproportionately high obesity rates, which are often under-represented in imaging studies. The comorbidity of obesity and MetS[149,150] with psychiatric and neurodevelopmental disorders[151,152] (e.g., depression, attention deficit hyperactivity disorder ADHD)[153,154] also deserves further attention. For example, increasing evidence suggests that ADHD and obesity share neural and genetic underpinnings[155,156] and thus findings of studies that do not screen out individuals with ADHD symptoms may be driven in part by a subset of individuals with both obesity and ADHD symptomatology who may not be wholly representative of the larger population.[157] Measurement of eating-related phenotypes may also be important as this could influence results.[74] Complementarily, adoption across the field of best methodological and analytical practices for food-related imaging including adjustment for appropriate covariates (e.g., hunger state) as well as appropriate statistical thresholding and adjustment for multiple comparisons would also help improve the quality of research and promote robust findings. We refer the reader to[75] for a fuller discussion of statistical issues and recommended practices in food-related neuroimaging and to[158] for more general discussion of recommendations for structural and resting state imaging analysis methods.

Mechanistic understanding could also be promoted by improving or expanding collection of data on MetS components and potential mediators of effects on neurocognitive outcomes. In particular we note that researchers may be able to capitalize on already existing brain MRI protocols by adding abdominal or full body MRI to obtain high quality estimates of abdominal and/or visceral versus subcutaneous adiposity which could be leveraged for more nuanced investigation of relationships with brain and behaviour outcomes. Agreement on the definition of metabolic syndrome in children, specifically on cut-off values for blood pressure, triglycerides, and high-density lipoproteins relevant for different developmental stages, may also help to stimulate research in this area. Studies combining structural brain assessments with measures of cognition and behaviour will also be essential to illuminate the mechanistic significance of observed brain structural alterations. For instance, two analyses of the ABCD cohort reported that CT reductions in frontal cortex mediated negative associations between BMI and executive function in children.[39,40] Another study showed that FA mediated the relationship between BMI and working memory accuracy.[54] Such findings support that these structural alterations may contribute to the differences in cognitive outcomes that accompany obesity and MetS. There is also some evidence in adolescents that subtle white matter abnormalities may be associated with microvascular abnormalities (retinal arteriolar diameter).[46] Since reduced integrity of white matter tracts could compromise cognitive processing,[159] including food-related cognitive processes associated with eating behaviour, relationships between white matter integrity, cognition, food-related cognition and development of MetS merit further exploration. Further research should also examine potential metabolic mediators of effects of MetS and its components on structural and functional brain outcomes by including measures of glucose, insulin, and other appetite-related hormones including ghrelin, PYY and GLP-1.[160] Metabolomics platforms measuring products of human metabolism and broad hormone panels allowing investigation of correlations between measures may be a particularly promising approach.

Longitudinal and interventional research will also be essential to advance our understanding. The cross-sectional nature of the majority of extant reports limits the ability to draw directional conclusions and is a particular problem for paediatric studies in which the brain is still developing and one-off assessments could produce misleading results due to individual variation in growth and potentially non-linear patterns of development. Large longitudinal datasets with multiple repeated measures of obesity and metabolic markers, brain function and structure, and cognitive outcomes beginning early in childhood will be required in order to fully model inter-relationships as they unfold over time, to provide insight into potential differences in neural and behavioural processes by developmental stage, and to more fully investigate dynamic vulnerability models of obesity.[77] However, we note that longitudinal research will by itself be insufficient to illuminate mechanism. For example it is possible that brain and cognition differences drive weight gain and development of MetS, and that excess weight and Met S affect the brain and cognition, but also that another common underlying mechanism causes each of these phenomena to unfold at different stages of development. For example, there is evidence that shared genetic variation underlies population variation in both BMI and in psychopathologies with a neural basis such as ADHD.[161] Changes over time in brain/cognition and weight/MetS outcomes could therefore be jointly driven by an underlying genetic mechanism. Studies using interventional designs are therefore important to establish causal pathways. Studies of weight loss interventions such as bariatric surgery, as well as longitudinal studies of natural weight change, suggest that weight loss and improvements to insulin sensitivity can result in significant cognitive improvements, decreased activation of neural reward networks to food cues, and increased efficiency of food-related inhibitory control. However more paediatric research is needed to understand how interventions targeting MetS and obesity in children

impact cognition and brain function and if impairments associated with MetS and paediatric obesity are reversible. For example, if changes in insulin sensitivity and vascular reactivity mediate effects of MetS and its components on neurocognition then these mechanisms could form targets for biological interventions like medications to increase insulin sensitivity (e.g., metformin) or interventions focused on modifiable targets such as diet.

7 | CONCLUSIONS

To conclude, a limited but growing body of research in adolescents and children suggests that paediatric obesity, MetS, and MetS components are associated with differences in general cognition (e.g., poorer executive function and attention), food-related cognition (e.g., increased food motivation and attentional bias to food cues and decreased food-related inhibitory control), brain structure (alterations, frequently reductions, in GM volume, and alterations in WM integrity and volume), brain function (e.g., hyperactivation of food reward regions and hypoactivation of cognitive control networks in response to food stimuli) (Figure 1). However, available data are not sufficient to draw conclusions about causal mechanisms; most are instead consistent with bidirectional influences between obesity/MetS and neurocognitive outcomes. Future observational studies using longitudinal designs beginning early in life and including measures of potential mediators promise to further illuminate causal mechanisms, while intervention studies could increase mechanistic understanding as well as informing clinical practice by testing whether interventions targeted at modifiable biological or behavioural factors associated with paediatric obesity and MetS can alter brain and behaviour in a beneficial manner. Together these research approaches are likely to provide further clarity on causal relationships, biological mechanisms, and biobehavioral interventions that may help interrupt pathways between paediatric obesity and metabolic risk, and cognitive and neural dysfunction.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

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