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Review

Obesity-associated biomarkers and executive function in children

Alison L. Miller[1,2], Hannah J. Lee[1] and Julie C. Lumeng[1,3,4]

There is a growing focus on links between obesity and cognitive decline in adulthood, including Alzheimer's disease. It is also increasingly recognized that obesity in youth is associated with poorer cognitive function, specifically executive functioning skills such as inhibitory control and working memory, which are critical for academic achievement. Emerging literature provides evidence for possible biological mechanisms driven by obesity; obesity-associated biomarkers such as adipokines, obesity-associated inflammatory cytokines, and obesity-associated gut hormones have been associated with learning, memory, and general cognitive function. To date, examination of obesity-associated biology with brain function has primarily occurred in animal models. The few studies examining such biologically mediated pathways in adult humans have corroborated the animal data, but this body of work has gone relatively unrecognized by the pediatric literature. Despite the fact that differences in these biomarkers have been found in association with obesity in children, the possibility that obesity-related biology could affect brain development in children has not been actively considered. We review obesity-associated biomarkers that have shown associations with neurocognitive skills, specifically executive functioning skills, which have far-reaching implications for child development. Understanding such gut–brain associations early in the lifespan may yield unique intervention implications.

Executive functioning (EF) skills are a set of cognitive processes that enable conscious and subconscious control of attention and effort. As such, the executive system can shape multiple cognitive and behavioral outcomes across the lifespan, ranging from specific academic skills (1), to intelligence quotient scores (2) and overall school achievement (3). Central EF skills include working memory, problem solving, set-shifting, inhibitory control, flexible thinking, and planning. Such skills emerge rapidly during the early childhood years and continue to develop throughout later childhood and into adolescence (4). More so than simply academic knowledge, EF skills are vital for preparing children to be successful in school (5,6).

The prefrontal cortex (PFC) has traditionally been viewed as the "seat" of EF, as this region of the brain is centrally involved in the high-level, top-down control of impulses that are generated from elsewhere in the brain (e.g., the limbic system, which is typically considered more emotionally reactive). It is increasingly recognized however that there are multiple areas of the brain involved in EF (e.g., dorsolateral PFC, anterior cingulate cortex, orbitofrontal cortex, medial PFC), and that each of these brain regions have extensive functional connections to other regions of the brain (subcortical areas and brain stem), which govern the automatic processes that also shape an individual's EF profile. Although some of the brain regions associated with specific EF skills are beginning to be mapped, the nature of the executive control system is that multiple brain areas play a role in the process and there is ongoing communication among these regions.

Children's brains undergo extensive change and development during the first years of life, with continued maturation of the cortical regions responsible for top-down control of cognitive and behavioral processes continuing into adolescence (7). Importantly, not only brain structures but also neural organization and functional connectivity among brain regions change and develop over this time. As obesity tends to have its onset during early childhood when rapid brain development is occurring, considering how the biological changes associated with obesity may affect the organization of the developing brain is important. The focus of this review is on how obesity-specific biology may adversely affect multiple regions of the brain that shape the range of EF skills that are in turn critical for successful child development across domains. We focus here on gut-hormone- and adipose-tissue-mediated pathways. We do not include a review of the literature regarding diabetes and its associated biology with cognitive functioning, because it remains relatively uncommon in children, even in adolescents (8).

The multiple hormones that are secreted in order to regulate satiety and food intake are altered in the case of obesity, including in pediatric populations, and have been associated with cognition. Ghrelin (produced in the stomach) induces hunger by signaling to the hypothalamus to increase food intake (9)

[1]Center for Human Growth and Development, University of Michigan, Ann Arbor, Michigan; [2]Department of Health Behavior and Health Education, University of Michigan School of Public Health, Ann Arbor, Michigan; [3]Department of Pediatrics and Communicable Diseases, University of Michigan Medical School, Ann Arbor, Michigan; [4]Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, Michigan. Correspondence: Alison L. Miller (alimill@umich.edu)

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and low serum ghrelin is associated with obesity (10). With regard to implications for EF, experimental animal models have shown that ghrelin activates hippocampal regions relevant for learning and memory (11–13). For example, ghrelin and the activation of ghrelin receptors increase long-term memory and spatial task learning in rodents (14–17) and ghrelin-deficient mice show impaired memory (18–20). Glucagon-like peptide 1 (secreted by the intestine) is another appetite-regulating hormone that promotes satiety and decreases energy intake (21) and is reduced in obesity (22). Glucagon-like peptide 1 also signals multiple brain regions, including the hypothalamus and the PFC (23). Mice deficient in the glucagon-like peptide 1 receptor have learning and memory deficits (24–26). The possibility of using glucagon-like peptide 1 as a mechanism to reduce the likelihood of neurodegenerative conditions such as Alzheimer's disease in humans has been proposed (27–29).

It has also become clear in recent years that fat tissue itself (adipose tissue) is metabolically active. It produces various substances with a wide range of obesity-associated biological functions, and communicates with multiple tissues and organ systems, including the brain, to regulate metabolism. Such substances include adipokines (fat-derived proteins) such as leptin, and proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha. C-reactive protein is also triggered by fat cells (adipocytes) and rises in response to inflammation. These adipose-tissue generated substances are also associated with EF skills.

Leptin is produced almost exclusively by fat cells (adipocytes) and signals the brain to reduce food intake (9). Receptors for leptin are found throughout the brain. Most obesity research focuses on the role of leptin in the hypothalamus for appetite regulation, but leptin may also influence other brain functions. Leptin has been linked to cognition and memory processing (30–35) and acts in brain regions involved with memory and reward, such as the hippocampus, cortex, and cerebellum (36). Short-term leptin infusion in mice improves memory and learning (32,33) and leptin has been found to be important for brain development (37). Serum leptin is positively correlated with percentage of body fat, and is higher in obese individuals, including children (38,39).

Adipose tissue chronically activates the inflammatory response by producing abnormal levels of adipose tissue-derived proteins (proinflammatory cytokines), even in children (40). Thus, as with leptin, obesity-driven biological features can be present very early in life. Such inflammation can have profound effects in multiple brain areas critical for effective cognitive functioning (41,42). Systemic inflammation has been associated with reduced spatial learning and memory skills in experimental rodent models (43–45). Obesity-induced inflammation can also directly interfere with synaptic communication in the hippocampus (46).

In sum, the hormones that function to regulate metabolism also appear to make significant contributions to cognitive processing, particularly the skills such as working memory and learning that are key elements of EF. Further, contributions of adipose tissue itself to reduced cognitive functioning have been identified. In the case of obesity, there is dysregulation of both appetite-regulating hormones and the substances produced by adipose tissue, resulting in multiple obesity-related biomarkers that can potentially adversely affect EF skills. Notably, such biomarkers are also present in obese children. If obesity-related biology is impairing the cognitive skills that should be developing during early childhood, this could have significant adverse consequences for young children who experience early-life obesity. Although biomarkers of obesity have been implicated in cognitive decline among older adults (47,48), this association is virtually unexamined in children. How such biomarkers may uniquely contribute to shaping neurobiology and EF skills early in the lifespan should be considered.

Importantly, our current understanding of the mechanistic associations of obesity-related biology through hormone- and adipose-tissue-mediated pathways is based on animal models; there is a paucity of research on these processes in humans and almost none in children. However, the few available human studies also consistently suggest that obesity is associated with cognitive deficits (49–53). Most of this work is focused on the end of the lifespan, with multiple studies documenting associations of obesity with Alzheimer's disease (47,48,54) and reduced cognitive skills in aging populations (52). Some work has identified similar associations across the adult lifespan, specifically that overweight and obese adults performed more poorly on verbal interference and attention tasks (55) and verbal memory tasks (56), and that higher BMI was associated with slower performance on measures of processing speed and memory (digit span; 57). In longitudinal work, midlife obesity was associated with later poorer executive function performance among men in the Framingham Heart Study (49) and central obesity was associated with poorer memory and visual-motor executive function skills among the middle-aged offspring of this sample (58). Importantly, a growing number of brain imaging studies have shown reduced blood flow and metabolic activity in the PFC among obese adults (59,60); a recent review noted consistent findings of reduced brain volume in relation to adiposity indicators among adults over 40 y of age (61). Overweight among young adults was also associated with reduced gray matter density in the hippocampus and cerebellum (62), regions that are important for EF. Obese adolescents also demonstrated reduced EF as well as reduced volume in the orbitofrontal cortex (63). Furthermore, human studies have linked elevated leptin (64) and inflammatory markers (65), as well as visceral fat (66,67) with reduced neurocognitive functioning. Taken together, evidence from human studies of adults suggests that relevant brain regions are associated with obesity; identifying whether biologically-mediated pathways are present in children is an important future research direction.

Childhood obesity has been associated with poor school performance in multiple studies (68–70). Findings may reflect in part difficulties in EF, although school performance is at best a very distal indicator of EF skills. Not all studies have found such associations (53,71–73), possibly due to measurement or design issues that have not allowed for an examination

of more proximal mechanisms of association. Recent reviews have identified associations between adiposity and a range of neurocognitive skills, including EF (53,72,74,75) and several studies have linked weaknesses in specific aspects of EF with obesity in children (76,77). Studies to date have been limited by their use of correlational and cross-sectional designs, small sample sizes, samples that have low rates of obesity or are exclusively of obese and overweight youth, and/or by using BMI as the only indicator of adiposity. Understanding whether underlying obesity-associated biological mechanisms are responsible for some of these associations is important. If such biological changes are identifiable early in development, perhaps even prior to the onset of obesity, there may be additional opportunities to act early to deter the effects of such biological processes on cognitive skills. Indeed, if the obesity–EF associations described in this review are confirmed in future research, then much more detailed investigation of the underlying brain structures and specific neurophysiological mechanisms of association will be needed.

Finally, considering intervention implications, some have suggested that cognitive deficits may in part explain the limited success to date of cognitive-behavioral therapies to reduce obesity and manage weight among obese and overweight youth (72,73,78,79). Additional evidence supporting this perspective is that a few experimental studies (mostly clinical weight loss trials) have found that when obesity decreases, cognitive skills increase (80). A recent review suggested lifestyle interventions to reduce obesity could improve school achievement, but effects were small (81). If it is the case that the biology of obesity itself is impairing children's EF and thus their abilities to engage in or benefit from obesity prevention and treatment approaches, different therapeutic approaches may need to be developed to aid these children not only to reduce their obesity, but also to enhance their EF skills. Future research should test a potential causal role of obesity and its associated biology in having an adverse impact on EF in children.

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