EDITORIAL COMMENT

Obesity Is Associated With Structural and Functional Brain Abnormalities: Where Do We Go From Here?

Obesity is a global epidemic and leading cause of preventable death (1). As in other Western countries, the prevalence of obesity among adults in the United States is high (35.9%), with 15.5% of the population having a body mass index (BMI) of 35 kg/m^2 or greater and 6.3% having a BMI of 40 kg/m^2 or greater (2). In addition to premature mortality, obesity is associated with a host of medical complications, including Type 2 diabetes mellitus, metabolic syndrome, and cancer (3,4). In addition to their well-known medical consequences, the metabolic abnormalities that span the spectrum from uncomplicated obesity to metabolic syndrome and ending up in Type 2 diabetes mellitus are also linked to cognitive deficits and impairments of brain structure and function (5–13). However, the mechanisms for these brain impairments are not understood.

Two articles in this issue provide an exploration of brain correlates of obesity (14,15). First, using diffusion tensor imaging of the brain, Verstynen et al. (14) demonstrate that increasing BMI is associated with decreased microstructural integrity in a multitude of white matter tracts after accounting for age and sex. Importantly, these associations offer a potential mechanism linking physical health and cognitive health. Although these links are a useful point of departure, the associations between obesity and brain health are etiologically quite complex. As suggested by these authors, the pathways linking increasing BMI to decreasing white matter integrity could include low-grade inflammation, insulin resistance, dyslipidemia, and elevated blood pressure but may also include reductions in endothelial integrity and vascular reactivity, as well as hypothalamic-pituitary-adrenal axis dysregulation. In addition, it is also possible that more lipids enter the brain in the context of obesity (16), thereby potentially causing increased oxidative stress. As recently reported by this group, increased exercise and fitness can be neuroprotective (17), particularly for the hippocampus. Therefore, brain health is likely the result of a balance between damaging and protecting influences, and measures of physical activity/fitness and diet, which could moderate the relationships between obesity and brain health, should also be included in future efforts.

The second study by Gonzales and colleagues (15) reports BMI-associated increases in occipitoparietal gray matter myo-inositol (mI)-creatine (Cr) ratios, as ascertained by single-voxel proton spectroscopy. In addition, the BMI-associated reductions in cognitive performance, memory in particular, were mediated by the mI/Cr ratio. Increased mI/Cr ratios have been previously reported in patients with diabetes and/or hypertension. Importantly, this study controlled for age, fasting glucose levels, and hypertension, suggesting that their findings may be uniquely related to BMI. The authors speculate that perhaps the increased mI/Cr ratios reflect or indicate microglial activation (inflammation) and osmotic regulation disturbance as potential mechanisms associating increases in BMI with lower cognitive performance. When considered together with the findings of Verstynen et al. (14), these two studies help to further the development of useful noninvasive neurobiological markers that may prove useful to ascertain the effectiveness of behavioral and pharmacological interventions intended to protect the brain from metabolic conditions that accompany obesity.

With that said, the studies reported in this issue of *Psychosomatic Medicine* only demonstrate the associations between current BMI status and specific brain imaging measures. Moreover, although they are provocative, these studies remain mostly hypothesis generating because of their cross-sectional designs and narrow focus. Future prospective longitudinal study designs, where each person serves as his/her own control, will further contribute to our understanding of cause and effect throughout development and aging. Such longitudinal studies also attenuate the influence of genetic and other effect modifiers. Finally, multiple potential mechanisms for the observed relationships between obesity, neural changes, and neurocognitive dysfunction have been hypothesized and are important to consider here. It is quite likely that the mechanisms linking obesity-associated metabolic dysregulation (including insulin resistance) with brain health largely overlap with those that have been fairly well characterized as in peripheral tissues. Therefore, to understand the impact of obesity on brain, it would make sense to explore these pathways first. The leading candidates would be abnormalities in brain vascular reactivity, neuroinflammation, and oxidative stress. The remainder of this commentary will review the potential role of vascular reactivity as an example of how the multifactorial interactions between overweight, altered metabolism, and neurocognitive processes can be investigated.

The damaging effects of obesity and insulin resistance on brain integrity are partly dependent on vascular reactivity abnormalities (18). When a region of the brain is activated (as when performing a cognitive task), there is increased synaptic activity in that region, resulting in a drop in interstitial glucose levels (the primary substrate for brain metabolism), which normally results in compensatory regional vasodilatation (19). Although the triggers for the vasodilatation remain unclear (see Iadecola (20) for review), we do know that, in obesity-associated insulin resistance, there are impairments in endothelial-dependent vasodilatation (21,22). Vascular reactivity is key to maintain energy-dependent processes, such as regional

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brain activation by clearing the metabolic "waste" produced by neuronal activity (carbon dioxide, excess lactate, other metabolites, heat, etc) (19). Consequently, individuals with obesity-associated insulin resistance may not maintain an optimal neuronal environment, particularly during periods of high energy demand by particular brain circuitries (e.g., cognitive or emotional control networks). We propose that this dysfunction, when coupled with other potentially damaging influences such as inflammation, hypothalamic-pituitary-adrenal axis dysregulation, or increased oxidative stress, may damage the brain. Prospective longitudinal human studies should first ascertain whether the cognitive deficits and/or structural brain abnormalities associated with obesity are driven by brain vascular reactivity (assessed using transcranial Doppler and/or magnetic resonance imaging arterial spin labeling methods). Furthermore, we should then determine whether these relationships can be modified by interventions (weight loss, exercise, pharmacological insulin sensitization, or reduction of inflammation) that improve the vascular response. Based on this conceptual model, appropriate animal models can be designed to further understand these mechanisms at a level that is not possible in human work. Such research could in turn lead to important targets for behavioral and pharmacological interventions in humans, particularly those at risk for premature neurocognitive decline.

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