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Invited Commentary | Nutrition, Obesity, and Exercise

Neuroinflammation and Obesity in the ABCD Study

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The Adolescent Brain Cognitive Development (ABCD) Study is currently the second-largest brain imaging study in the world, with more than 11 000 participants followed for at least 10 years, including biennial multimodal magnetic resonance imaging (MRI) assessments. The UK Biobank brain imaging substudy is even larger, with more than 100 000 individuals scanned but with a much wider age range. Beyond the true longitudinal design, the ABCD Study stands out in terms of its unique focus on youths rather than adults. The initial ABCD cohort was recruited at age 9 or 10 years and will be followed until at least age 19 or 20. The focus on youths between the ages of 9 and 16 poses some special challenges, simply as a function of the rate of age-related changes occurring within the body and brain. The rate of overall change is high, but likewise the degree of variability between individuals is greater within this phase of the lifespan than almost any other.

Using the first 2 waves of imaging data available within the ABCD Study, Adise et al[1] have introduced an important set of findings to the increasingly extensive literature on brain health correlates of obesity. Specifically, they found that indices of neuroinflammation derived from MRI in the ABCD Study may signal and may be signaled by indices of adiposity. Although the associations are not large in magnitude, they may nonetheless be important if they confer ongoing, cumulative fuel to support a recursive cycle that unfolds over time. An analogy is the case of cigarette smoking.[2] When predicting mortality risk from time spent smoking, small effects over a few years may produce more substantial risk over a multidecade exposure period, assuming that risk is cumulative. Because obesity without treatment is often lifelong, a very wide exposure window would exist; therefore, small effects within a 1- to 2-year period examined in the study by Adise et al may translate into highly consequential impacts over a decade or two of cumulative influence. The ABCD data will provide an opportunity to test this hypothesis when the study concludes and the final wave of data become available in or around 2027.

In our own work with the ABCD Study data, we employed latent variable modeling to test the cross-lagged associations between adiposity and cognitive function in waves 1 to 3.[3] We found similar cross-lagged effects involving adiposity and cognitive task performance, with evidence for bidirectionality across a number of different task types. In this case, we made use of both the waist circumference and body mass index (BMI) data.[4] Evidence for bidirectional influence was strongest for executive function, whereas episodic memory and achievement indices (reading, vocabulary, phonologic processing) all showed primarily cognition-to-adiposity associations prospectively. Only processing speed appeared to be predicted by adiposity prospectively. One critical difference between the 2 studies was the focus on different parts of the brain as regions of interest. For theoretical reasons, Adise et al[1] examined subcortical structures, whereas Sakib et al[3] examined neocortical regions of interest; however, both are theoretically meaningful areas, and they work in concert to determine when and how obesogenic behavior is expressed. The reasons for this are 2-fold: First, there is theoretical precedent for suggesting that the lateral prefrontal cortex is linked to cognitive control networks that are critical for top-down regulation of appetite, particularly in the presence of calorie-dense foods and permissive cues for consumption. Second, both lateral prefrontal regions and midbrain reward centers are mediated by dopamine signaling, with substantial projections from the latter to the former. As such, lateral and midbrain reward systems are functionally interlinked in the eating context.[4,5]

With respect to adiposity metrics, BMI is the most well established but there are other options. For instance, waist circumference—which is available in the ABCD dataset—may be more predictive

of gold-standard dual-energy x-ray absorptiometry (DEXA)–measured fat mass in youths.[6] In the case of Adise et al,[1] there is a missed opportunity to explore the proposed research question more thoroughly by using waist circumference to validate the BMI findings. In other datasets involving different age groups, there is evidence of bidirectional association between adiposity and cognitive function, using DEXA as the measure of the former,[7] and this underscores the utility of looking beyond BMI when quantifying weight status.

In theory, the causal status of a bidirectional association between adiposity and neuroinflammation (or other brain health metrics) can be examined in the context of clinical trials. Evidence from randomized clinical trials suggests that glucagon-like peptide-1 receptor agonist medications impact neuroinflammation.[8] Likewise, there are several other pharmacologic options that affect inflammation without impacting obesity, such as nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, and corticosteroids. With the right design and outcomes, it would be theoretically possible to examine causal effects bidirectionally to further support the groundwork laid by Adise et al[1] using this observational research design.

As acknowledged by Adise et al,[1] there are some ambiguities with respect to understanding the meaning of the metrics generated by the imaging modality. For instance, as the authors noted, the metrics may indicate the presence of neuroinflammation but more specifically the density of glial cells. Glial cells indeed participate in the inflammatory response; but without being able to differentiate among different types of glial cells, there is inherent ambiguity in what the present findings truly represent. Microglia and astrocytes are clearly implicated in neuroinflammation, but there is less of an established role for oligodendrocytes. Adise et al also pointed out that there is a possibility that synaptic pruning might be indicated by inflammation. Finally, it is worth noting that age effects might not be fully controlled by statistical procedures used here, and it could be argued that the differences in brain region structural parameters reflect naturally occurring variability in growth rates within the brain itself across individuals.

With these caveats in mind, the work of Adise et al[1] is important and will no doubt stimulate future investigation. With additional waves of data becoming available, there will be opportunities to examine the proposed bidirectional effects more comprehensively within the ABCD Study and within the context of other datasets available internationally.

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