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The Role of Sport Involvement in Reducing Depressive Symptoms via Changes to Hippocampal Structure: Next Steps for Research in Developing Samples

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Experiencing depressive symptoms in childhood is related to risk of developing a unipolar depressive disorder later in life. Depression in young people increases the likelihood of negative long-term outcomes, such as poor physical health, relationship quality, and vocational achievement and an increased risk of suicide. Depression accounts for the greatest burden of disease in this age group (1). As such, identifying risk factors and prevention and/or early intervention strategies for depression in young people is essential for ultimately lessening the burden associated with this mental illness.

Recommended first-line treatments (e.g., cognitive behavioral therapy) for depressed youths have only modest effects (2), highlighting the need for more effective alternative or adjunct therapies. Exercise is a promising candidate for the treatment of depression because exercise has been linked to reductions in depressive symptoms in young people across a number of studies (3). One mechanism by which exercise might influence depression is through its impact on the developing brain and in particular its impact on the hippocampus. Rodent studies have consistently demonstrated that aerobic exercise can increase the rate of synaptic plasticity, neurogenesis, angiogenesis, and the circulation of important neurotrophic factors in the hippocampus. Studies in humans have also found exercise to be associated with growth in hippocampal volume [see Den Ouden *et al.* (4)]. Importantly, reduced hippocampal volume is one of the most robust findings in depression (5). As such, treatments or interventions that have targeted effects on the hippocampus have intuitive appeal.

In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Gorham *et al.* (6) tested whether exercise influences depressive symptoms via hippocampal volume in young people. They examined cross-sectional links between sport participation, hippocampal volume, and depressive symptoms in a U.S. nationwide sample of 4191 children 9 to 11 years of age from the Adolescent Brain and Cognitive Development study. Several different sport and nonsport activities were assessed in order to test whether the effects were likely driven by exercise per se or were instead driven by certain aspects of sport involvement. While sports involvement was positively correlated with hippocampal volume in both males and females, sports involvement was indirectly associated with lower depressive symptoms via larger hippocampal volume only in males. The effects were not evident for nonsport activities, suggesting that exercise (rather than social interaction in general) is critical. However, these same effects were not found for "individual sport" involvement, suggesting that exercise may have extra benefit when performed in a social or team environment. Finally, the effects were specific to depression (i.e., greater exercise was not associated with decreased anxiety).

The findings of Gorham *et al.* (6) represent an important contribution to our knowledge of a potentially effective intervention for depressed youth and its related neurobiological mechanism. However, there are a number of aspects of the research that require additional investigation to strengthen the implications. Gorham *et al.* (6) highlight a number of critical directions for future research, including 1) longitudinal research to better investigate directionality of associations (important, given that the research was cross-sectional, and as such it is possible that depressive symptoms might lead to reduced hippocampal volumes and reduced sport participation); 2) the investigation of puberty, particularly given the gender differences found; 3) the investigation of social factors (e.g., competitiveness) that may moderate associations; and 4) the inclusion of measures of physical fitness, to help tease apart physical from other (e.g., social, stress) effects.

There are two additional points that may be helpful both in the interpretation of these findings and in considerations for future research: brain development and hippocampal subregions.

The brain is developing rapidly during childhood and adolescence. Nonlinear patterns of hippocampal volume change have been found, such that hippocampal volumes increase in childhood and then decrease, with peaks apparent in early to mid-adolescence (7). Several studies of children and adolescents have shown that various environmental factors and indices of mental health are related to patterns of hippocampal development [e.g., Whittle *et al.* (8)]. For example, reduced growth of the hippocampus has been prospectively associated with depression onset in adolescents (8). In addition, these studies suggest that investigating only cross-sectional associations likely limits the meaningful interpretation of findings (8). For example, longitudinal imaging data could establish whether sport involvement is associated with consistently larger volumes across development or with an altered growth pattern.

The investigation of longitudinal volume change is particularly important for structures like the hippocampus where development is characterized by nonlinear trajectories with peaks (e.g., inverted-U shaped curves). In Gorham *et al.*'s

SEE CORRESPONDING ARTICLE ON PAGE 484

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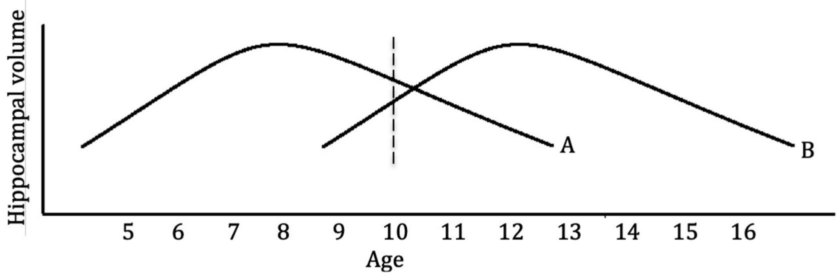

Figure 1. Schematic illustration of two scenarios where peak hippocampal volumes are reached at approximately 8 years of age (trajectory A) and at 12 years of age (trajectory B). If hippocampal volume is measured at approximately 10 years of age (dashed line), larger volume may represent reduced volumetric reduction (A) or greater volumetric growth (B).

study (6), it is possible that larger cross-sectional volumes in individuals with greater sports involvement reflects greater volumetric growth or reduced volumetric decline, respectively, depending on whether measurement occurred before or after the "peak" (Figure 1). It is also possible that sports involvement affects the age at which one reaches his or her peak, effectively shifting the growth trajectory such that it may be described as more or less "mature." As such, longitudinal research would allow for better disentangling of individual developmental trajectories. In summary, while the cross-sectional findings reported by Gorham *et al.* (6) are intriguing, longitudinal investigation will be important to understand the effects of sports participation on hippocampal structure and depression in the context of dynamic neurodevelopment occurring in childhood and adolescence.

The hippocampus is a structurally and functionally heterogeneous region that includes the hippocampus proper (i.e., cornu ammonis [CA]), the dentate gyrus (DG), the entorhinal cortex, and the subiculum, presubiculum, and parasubiculum. Based on cytoarchitecture, the hippocampus proper can be divided in four subregions: CA1, CA2, CA3, and CA4, although some consider CA4 part of the DG. Localizing effects of exercise/sport involvement within the hippocampus may provide clues as to the mechanisms at play. Preclinical studies have shown that aerobic exercise is associated with volume increases primarily in the DG, the site where postnatal neurogenesis is known to be largely restricted. Human studies have also found aerobic exercise to be associated with pronounced increases in the hippocampal head where the DG is located [see Den Ouden *et al.* (4)]. The DG is particularly vulnerable to stress because it has a high density of multipotent stem cells, and cell proliferation can be hampered by exposure to glucocorticoids (9). As such, exercise effects on DG may primarily reflect cell proliferation (potentially via a buffering or protective effect against stress).

However, other research has found that exercise affects the hippocampus proper (4). Structural changes in this hippocampal subregion may be more likely to occur owing to angiogenesis, synaptic plasticity, or changes in glial cell density. While the findings are mixed regarding the specific hippocampal subregions implicated in depression, the structure of CA regions have been suggested to be altered earlier in the course of depression, whereas the DG may be more likely to be affected with illness progression (10). Further work investigating whether the volume of specific hippocampal subregions mediates the association between sport involvement and depression will facilitate a better understanding of the specific cellular mechanisms involved.

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Article Information

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