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Discussion

Does intensity or youth affect the neurobiological effect of exercise on major depressive disorder?☆

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ABSTRACT

The purpose of this commentary is to discuss the different neurobiological effects of exercise on major depressive disorder (MDD) in children and adolescents and to provide additional explanations to this well written systematic review. This commentary highlights the effects of exercise on the hypothalamic-pituitary-adrenal (HPA) axis, which plays a crucial role in MDD. We address the questions of whether age and different exercise intensities may provide additional information on the neurobiological effects of acute or chronic exercise on MDD. Previous findings clearly suggest that the etiology of MDD is complex and multifaceted, involving numerous neurobiological systems, which are additionally influenced by these two factors.

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Schuch et al. (2016) composed a well written and interesting systematic review examining the relationship between exercise and major depressive disorders (MDD) from a neurobiological perspective. We know from studies, including a large number of subjects, that exercise does have a positive impact on depression (Wegner et al., 2014a), for which different mechanisms have been previously suggested including neurobiological changes (Helmich et al., 2010) as well as psychological factors such as self-efficacy, emotional activation, or emotion regulation (Bartholomew et al., 2005; Lawlor and Hopker, 2001). It is new and interesting that these neurobiological mechanisms are systematically reviewed. In their

review, Schuch et al. (2016) included twenty studies representing 1353 people with MDD. One main finding was that the number of studies and their limitations presented within the review preclude a more definitive conclusion of the underlying neurobiological explanations for the antidepressant effect of exercise in people with MDD. They close their abstract with the recommendation that trials should utilize appropriate assessments of neurobiological markers to further clarify the potential mechanisms associated with the antidepressant effects of exercise. The authors of this commentary agree with Schuch et al. (2016) although we see two main problems in this review pointing to age and intensity of exercise, which moderate the strength of the exercise effect on MDD from a neurobiological perspective. Although, the review by Schuch et al. (2016) contains the factor age, it did not focus on children and adolescents but only on adults and the elderly. Because the first incidence of depression occurs in childhood, with a prevalence rate of 2.7% (Merikangas et al., 2010), and with symptoms dramatically increasing in adolescence (prevalence rate above 8%; Avenevoli et al., 2015) this is a relevant age group to target in terms of prevention and early

☆ Commentary in response to the article *Neurobiological effects of exercise on major depressive disorder: A systematic review* by Schuch et al. (2016) published in *Neuroscience & Biobehavioral Reviews*.

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intervention (Kessler et al., 2005). Tümer et al. (2001), for example, found that the genetic responses of exercise training of aged animals differed from the young especially in the substantia nigra a part of the basal ganglia also important in depression. Thus, there is a difference between juvenile and adult depression, with potentially different neurobiological concomitants of the effect exercise has on brain regions that have been associated with MDD. The results of qualitatively high studies on the impact of chronic exercise on depression for children and adolescents suggest a smaller effect compared to adult samples (Wegner and Budde, in press). This needs to be added to the review by Schuch et al. (2016).

It was previously argued that glucocorticoid regulation, for example, in response to physical exercise affects emotional states and depressive symptoms (Erickson et al., 2003). The regulation of the hypothalamic-pituitary-adrenal (HPA) axis as a main target in the antidepressive effect of exercise, however, is dependent on the intensity of exercise, which the authors of the review underestimated. Lamego et al. (2015), for example, conducted a review on the acute and chronic effects of aerobic exercise on the cortisol levels in individuals with depression. However, no relationship for the impact of exercise on the concentration of this biomarker was found. One important moderating factor not controlled in this review was intensity, although other variables such as type of exercise adopted, duration of the session, and frequency of weekly sessions may also be responsible for these null effects. Although, the review by Schuch et al. (2016) contains the factor intensity, this information is only covered in Table 1 (Summary of acute studies) while it was not focused on later in the article. However, this information is important. It is relevant for chronic as well as for acute studies. The take home message from different studies in children, adolescents, and adults dealing with the effect of acute bouts of exercise on the HPA axis activity and reactivity is that the effects depend on the duration and intensity of exercise, and on training status of the subjects (Budde et al., 2015, 2010a, 2010b, 2010c; Lamego et al., 2015).

This leads us to a further moderating factor for the reactivity of the HPA axis: age. In agreement with findings in studies examining adults, adolescents in late pubertal stages show a similar reactivity of the HPA-axis resulting in cortisol increases in response to acute bouts of exercise (Budde et al., 2015). However, we do not see this cortisol pattern in healthy children in response to the same protocol (Budde et al., 2010c). Studies with laboratory stressors show that cortisol responses increase with age and pubertal status over the transition toward adulthood (Gunnar and Quevedo, 2007). From studies with 15–16-year-old healthy adolescents we know that a 12 min exercise bout with an intensity of 70–85% of the maximum heart rate (HR_{max}) led to an increase in cortisol levels contrasted to a group exercising with moderate intensity (50–65% HR_{max}) (Budde et al., 2010a, 2010b). A recent study investigated how cortisol levels of healthy adolescents at the age of 14 react to different stressors (Wegner et al., 2014b). In this study, exercise was induced by running 15 min at a medium intensity level of 65–75% HR_{max} . Other than the psychosocial stressor, the acute bout of physical exercise was not able to significantly increase cortisol levels. These results confirm the threshold phenomenon for adults (Hill et al., 2008) also in adolescents in late pubertal stages and indicate that the concentration of cortisol after acute bouts of exercise is intensity-dependent.

For adults it has previously been shown that the HPA axis is hyperactive in depressed patients (Nestler et al., 2002; Southwick et al., 2005). Although, HPA dysfunction is already associated with depression in childhood, previous research has shown that this association becomes stronger with advancing age (Guerry and Hastings, 2011) making it sometimes hard to find strong links in a very young population. The results obtained from Gispen-de Wied et al. (2000), for example, reveal that the cortisol output

after an acute physical challenge was the same in depressed and non-depressed adolescent patients and healthy controls. Thus, the mediation of the link between exercise and depressive symptoms through HPA axis activity or reactivity in children and adolescents is at least questionable.

Finally, results from meta-analyses on the mental health effect of exercise in depressed children and adolescents on average show smaller positive effects (Ahn and Fedewa, 2011; Craft and Landers, 1998) than meta-analyses for adult samples (Rebar et al., 2015). Overall, the existing findings regarding the positive effects of exercise on depression point to a strong involvement of the HPA axis. However, the mediating effect seems to be age- and intensity-dependent. Future studies need to identify the optimum trade-off between intensity and duration, type of exercise, and level of training in various ages, in order to compare the effects of exercise on depression from a neurobiological perspective.

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