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Changes in fMRI activation in anterior hippocampus and motor cortex during memory retrieval after an intense exercise intervention

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ABSTRACT

Strong evidence indicates that regular aerobic training induces beneficial effects on cognitive functions. The present controlled fMRI study was designed to investigate the impact of a short-term intense aerobic exercise on the pattern of functional activation during the retrieval of learned pair-associates in 17 young and healthy male adults compared to 17 matched control subjects. We further aimed to relate putative changes in hippocampal activation to postulated changes in the exercised-induced brain derived neurotrophic factor (BDNF). The supervised exercise program was performed on a bicycle ergometer and lasted six weeks, with three aerobic sessions per week.

We found profound improvement of physical fitness in most subjects indicated by the target parameter 'individual anaerobic threshold'. Significant improvements in the cognitive performance were detected in the exercise group, but also in the control group. We observed significant differences in the activation pattern of the left anterior hippocampus during the pair-associates task after the intervention. We could also show a significant positive correlation between changes in exercise-induced BDNF and left anterior hippocampal activation. Moreover, we observed the brain's motor network to be significantly stronger activated after the exercise intervention. Thus, our results suggest BDNF dependent activation changes of the hippocampus in addition to previously described structural changes after exercise.

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1. Introduction

A growing body of evidence indicates that regular aerobic training induces beneficial effects on cognitive functions (Colcombe & Kramer, 2003). Previous research has focused mainly on the relationship between physical activity and cognition regarding the following two age groups: children/adolescents and sedentary elderly people. For example, Monti, Hillman, and Cohen (2012) found that aerobic training positively influenced performance in a memory task requiring relational binding in preadolescent children. Chaddock et al. (2010) reported an association between fitness level and memory performance in preadolescent children, which was mediated by hippocampal volume. A similar association was observed in older adults during the performance of a spatial memory task (Bugg & Head, 2011; Erickson et al., 2009). The influence of aerobic exercise on cognitive functions also suggests its role in the development as well as maintenance of neuronal structures. Erickson et al. (2011) showed in a randomized controlled trial including 120 older adults that aerobic exercise training selectively increased the size of the anterior hippocampus, thus reversing age-related hippocampal volume loss by 1–2 years. The increased hippocampal volume was significantly associated with improvements in spatial memory performance. In addition to the hippocampus, Ruscheweyh et al. (2011) reported an exercise-induced increase in the gray matter volume in fronto-cingulate brain regions and an improvement in episodic memory performance in healthy elderly subjects. In a cross-sectional fMRI study on adolescents, Herting and Nagel (2013) observed marked activation differences in the hippocampus and prefrontal cortex between low-

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fit and high-fit male adolescents during verbal associative memory encoding, despite similar behavioral performance.

The time span between adolescence and old age, however, has rarely been investigated. This may be due to the fact that young adulthood is characterized by a relatively constant cognitive performance, as well as stable brain volumes (Ziegler et al., 2012). Cognitive performance across multiple domains reaches its peak level during the young adulthood (Salthouse & Davis, 2006), suggesting little flexibility for exercise-related improvements in cognitive function during this period. Nevertheless, in one of the few studies involving young adults, Stroth, Hille, Spitzer, and Reinhardt (2009) detected an improvement in a memory task performance as a result of individually adapted exercise training. Pereira et al. (2007) have provided specific evidence for improved cognitive performance in a subscore of the Rey Auditory Verbal Learning Test (RAVLT) and an increased regional cerebral blood flow (rCBF) in the dentate gyrus (DG) in young/middle-aged adults after aerobic fitness training. Here, increased rCBF in the DG was positively correlated with a training-induced increase of VO_{2max}, which is a parameter indicating cardiovascular fitness. Very recently, Alfini et al. (2016) showed a decrease in hippocampal rCBF in older master athletes after cessation of a 10-day exercise training.

In a sample of middle-aged sedentary subjects, Holzschneider, Wolbers, Roder, and Hotting (2012) investigated the effect of a six-month exercise intervention on spatial learning in a virtual maze task using fMRI. Individual fitness level modulated fMRI activations during spatial learning in a number of cortical and subcortical regions, including the hippocampus, parahippocampal gyrus, basal ganglia, occipital, temporal, frontal and cingulate regions. Exercise-induced changes in cardiovascular fitness correlated positively with changes in brain activation in the medial frontal gyrus and the cuneus.

One major link between physical activity and neuroplastic processes subserving memory and learning seems to be the expression of growth factors in the hippocampus (Cotman, Berchtold, & Christie, 2007). Specifically, it was suggested that brain derived neurotrophic factor (BDNF) plays a central role in many functional and structural processes of neuroplasticity. BDNF, a neurotrophin, is widely expressed in the brain and has been shown to influence neuronal survival, differentiation, axonal path-finding, regulation of dendritic trafficking to postsynaptic densities (Cotman et al., 2007; Nakata & Nakamura, 2007) and protection against neuronal death (Pringle, Sundstrom, Wilde, Williams, & Iannotti, 1996). However, the main function of BDNF in the adult brain is seen in enhancing synaptic transmission, facilitating synaptic plasticity and promoting synaptic growth (Lu, Nagappan, Guan, Nathan, & Wren, 2013). This neurotrophic effect is primarily mediated by the tyrosine kinase receptor B (trkB). Regarding synaptic plasticity, BDNF appears to play a central role in induction and maintenance of long-term potentiation (LTP) in the hippocampus (Cotman et al., 2007). A reduction of hippocampal BDNF levels through genetic manipulation impairs LTP (Korte et al., 1995), even when the level of trkB was manipulated (Minichiello et al., 1999).

With respect to the impact of physical exercise on BDNF secretion, Neeper, Gomez-Pinilla, Choi, and Cotman (1995), Neeper, Gomez-Pinilla, Choi, and Cotman (1996) were the first to show that voluntary exercise increased levels of BDNF messenger RNA in the hippocampus and in the caudal neocortex. Most further studies suggest that both acute and enduring aerobic exercise lead to BDNF concentration elevations (Huang, Larsen, Ried-Larsen, Moller, & Andersen, 2014). Convincing evidence for the role of BDNF in cognitive performance was shown in rodents. Mu, Li, Yao, and Zhou (1999) reported that BDNF deprivation by injection of BDNF antibodies into the rat brain affected spatial learning and memory compared to controls. In the same vein, the beneficial effect of exercise on cognitive function and on downstream systems was inhibited by blocking BDNF action in the hippocampus of rats (Vaynman, Ying, & Gomez-Pinilla, 2004). Cirulli, Berry, Chiarotti, and Alleva (2004) administered neural injections of exogenous BDNF and showed improvement in cognitive performance in rodents.

In human subjects, Erickson, Miller, and Roecklein (2012) provided compelling evidence in their review for the association between BDNF and age- as well as exercise-related changes in memory function. Whiteman et al. (2014) reported in a cross-sectional design that the performance on a recognition memory task in healthy young adults was predicted by BDNF and aerobic fitness in an interactive manner. Thus, these studies illustrate the importance of BDNF involvement in learning and memory as well as its key role in mediating exercise-induced effects.

The importance of hippocampal structures in memory formation is well documented (Milner, Squire, & Kandel, 1998). There is abundant electrophysiological data retrieved from animal research, suggesting a crucial role of the hippocampus in spatial processing and storage (Jeffery, Anderson, Hayman, & Chakraborty, 2004; O'Keefe & Burgess, 1996). This may be one reason why previous animal and human studies have often used visuospatial memory tasks to investigate the effects of physical activity on hippocampal activation. Moreover, it is known that the hippocampus establishes relationship representations using common features of episodes for flexible memory retrieval (relational processing theory (Eichenbaum, 2004)). In a meta-analysis of human fMRI studies, Spaniol et al. (2009) showed across several studies that retrieval of successfully encoded items has been associated with activations in the hippocampus, but also with lateral prefrontal, parietal, and cingulate regions.

The current controlled longitudinal fMRI study was primarily designed to investigate the impact of a short-term, intense aerobic exercise intervention on cognitive performance in young adults with average fitness, both in an established memory task outside the MRI scanner as well as on brain activation, specifically on hippocampal activation during memory retrieval. We were interested in a task that robustly shows hippocampal activation in order to investigate exercise-induced effects on the pattern of functional brain activation. For this purpose, we developed a paired-associate memory task, which measures relational memory and crucially depends on hippocampal functioning (Eichenbaum, 2004). Based on previous studies (Holzschneider et al., 2012; Pereira et al., 2007), we mainly hypothesized an exercise-induced increase of hippocampal activation during memory retrieval of previously learned paired associates, but also increased activation in regions of the fronto-cingulate circuitry.

We further expected to find exercise-induced BDNF changes to correspond with exercise-induced changes in hippocampal BOLD activation. This study is part of a large trial, investigating the effects of physical exercise on hippocampal structure, functioning and metabolism. Structural and metabolic changes of the hippocampus were reported previously (Wagner et al., 2015).

2. Methods

2.1. Subjects

Thirty-four male students were recruited from the local university to participate in the present study for a total period of 8 weeks. In the physical training condition, seventeen subjects were assigned to six weeks of controlled training intervention, including one week beforehand and one week afterwards for pre- and post-training investigations. Seventeen subjects, who were matched for age, gender, body mass index (BMI) and maximum oxygen uptake

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