Exercise-related changes in hippocampal and white matter structures: A longitudinal MRI and serum marker study

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Target audience: Researchers interested in structural brain plasticity and structural MRI.

Purpose: In animals and humans, the brain-derived neurotrophic factor (BDNF) is known to act on the central nervous system, supporting the survival of existing neurons, and stimulating the growth and differentiation of new neurons and synapses. Several lines of research converge on the notion that physical exercise supports the protection and even restoration of the brain. What remains less clear is whether this impact of physical exercise on brain structure relates to BDNF. To address this question, we conducted a longitudinal brain MRI study on subjects who participated in an intense physical training. We compared structural MRI scans before and after the training period. In addition to BDNF, we also assessed exercise-related alterations of serum leptin, as an adiposity signal, and high-density lipoprotein (HDL) as a fat marker, as well as their relationships to possible alterations in brain structure.

Methods: Sixteen young overweight and obese volunteers (9 females, age 27.2±6.7 y, BMI 33.6±5.9 kg/m²) participated in two MRI sessions before and after a fitness course with intense physical training twice a week over a period of 3 months. In both sessions, blood from a peripheral venous puncture was withdrawn. To separate serum, blood was centrifuged at 4°C for 10 min at a relative centrifugal force of 3500 g. Finally, several serum markers were determined, including BDNF, leptin, and HDL. The exercise-related intra-individual changes of these markers was assessed using one-tailed paired t-tests with p<0.05.

In both sessions, T1-weighted images were acquired on a whole-body 3T TIM Trio scanner (Siemens, Erlangen, Germany) with a 12-channel head coil using the MP-RAGE sequence (TI/TR/TE/FA = 650/1300/3.5ms/10°). Grey matter density (GMD) images were computed using SPM8 and the VBM8 toolbox. Group analysis was performed using a flexible factorial design to investigate correlations between the individual change of serum parameters and GMD (p<0.05, family-wise error corrected) corrected on the cluster level.

Further, whole-brain diffusion-weighted (DW) images (60 directions, b = 1000s/mm², GRAPPA accel fact 2, NEX=3) were acquired from 72 axial slices with isotropic nominal resolution of 1.7 mm. For TBSS², each subject’s aligned map of fractional anisotropy was projected to a mean skeleton. In addition, we assessed the axial and radial diffusivity (λax, λrad). Correlations between the individual change of serum markers and diffusivity parameters were computed with randomization tests using a flexible factorial design (p<0.05, threshold-free cluster enhancement corrected).

Results: After the 3 months of fitness training, we observed a significant decrease of serum leptin that was significantly correlated with an increase in GMD in the left hippocampus. We also found a positive correlation between serum leptin and λax, which was expressed in the vicinity of the GMD increases of the hippocampus, but also in other brain regions including the whole corpus callosum (Fig. 1). The exercise-related decrease in serum leptin concentration was accompanied by a significant intra-individual increase in HDL serum concentrations that again correlated with the GMD increase in left hippocampus. As for serum leptin, we also detected a negative correlation between HDL concentration and λax in large brain areas including white matter regions in the vicinity of the left hippocampus (Fig. 2).

The BDNF serum concentration increased significantly in ten subjects (responders), whereas six subjects showed a moderate decrease (non-responders). The correlation analyses revealed that responders had a significantly steeper correlation between BDNF and GMD compared to non-responders (Fig. 3). In responders, but not in non-responders, a BDNF increase was accompanied by a significant GMD increase in hippocampus, insula, and cerebellar regions within the left hemisphere. Responders and non-responders differed with respect to the correlation between BDNF and λax. In responders, a BDNF increase was accompanied by a significant decrease of λax in the vicinity of hippocampus and insula.

Discussion: Previous findings suggested a relationship between leptin concentrations and brain structure, particularly in the corpus callosum in obese women, but also in the hippocampus where it seems to modulate synaptic plasticity. These findings agree with the present results. Besides the exercise-related increase in hippocampal GMD and the parallel changes of leptin and HDL, we also found a decrease of λax in various brain regions including the whole corpus callosum. Interestingly, an exercise-related increase in BDNF serum concentrations showed a positive correlation with GMD in the left hippocampus for BDNF responders. This observation is in agreement with recent results in animal studies suggesting a dependence between BDNF expression and hippocampal plasticity. The relationship between physical exercise, the increase in BDNF serum concentrations and the increase in GMD in a key region of memory encoding, namely the hippocampus, may serve as a possible explanation for growing evidence that physical exercise might improve cognitive function. Future research needs to combine physical exercise with cognitive tests to further investigate this physical-cognitive relationship.

Conclusion: The observed correlation between serum markers and brain structure, particularly in the left hippocampus, may explain previous findings showing that physical exercise improves cognitive function. Changes in brain structure may rely on BDNF and leptin-related mechanisms of neuroplasticity as observed in recent animal studies.

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