

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

Karsten Mueller¹, Harald E Möller¹, Franziska Busse¹, Annette Horstmann^{1,2}, Jörn Lepsiem¹, Matthias L Schroeter^{1,3}, Matthias Blüher^{2,4}, Michael Stumvoll⁴, Arno Villringer^{1,3}, and Burkhard Pfeifer^{1,3}

¹Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany, ²Integrated Research and Treatment Center (IFB) Adiposity Diseases, Leipzig, Germany, ³Day Clinic for Cognitive Neurology, University Hospital Leipzig, Germany, ⁴Department for Internal Medicine, University Hospital Leipzig, Germany

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 synapses¹. Several lines of research converge on the notion that physical exercise supports the protection and even restoration of the brain². 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-induced 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 In both sessions, blood from a peripheral venous puncture was withdrawn.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 in order to investigate correlations between the individual change of serum parameters and GMD ($p < 0.05$, family-wise error³ corrected on the cluster level).

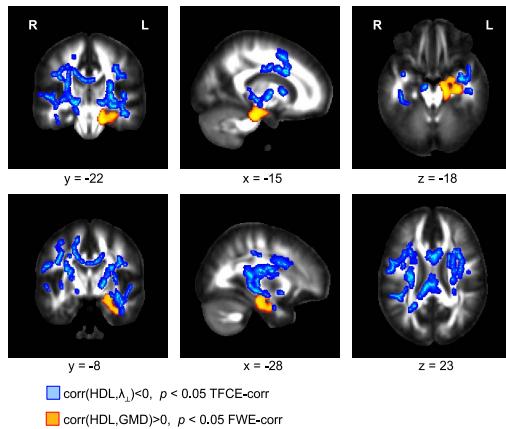


Fig. 2. Correlation between GMD and HDL. An exercise-related significant HDL increase correlated with a GMD increase in the hippocampus (orange). This HDL increase was accompanied by a decrease of λ_{\perp} (blue).

Discussion: Previous findings suggested a relationship between leptin concentrations and brain structure, particularly in the corpus callosum in obese women⁷, but also in the hippocampus where it seems to modulate synaptic plasticity^{8,9}. 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 λ_{\perp} 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^{10,11} 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.

Acknowledgement: Partly funded through Helmholtz Alliance ICEMED—Imaging and Curing Environmental Metabolic Diseases.

References: ¹Binder DK, *Growth Factors* 2004;22:123–31, ²Voss W, *Trends Cogn Sci* 2013;17:525–44, ³Nichols TE, *Stat Methods Med Res* 2003;12:419–46, ⁴Smith S, *NeuroImage* 2006;31:1487–505, ⁵Nichols TE, *Hum Brain Mapp* 2002;15:1–25, ⁶Smith S, *NeuroImage* 2009;44:83–98, ⁷Mueller K, *PLoS ONE* 2011;6:e18544, ⁸Shanley LJ, *Nat Neurosci* 2002;5:299–300, ⁹Harvey J, *Prog Lipid Res* 2006;45:369–78, ¹⁰O’Callaghan R, *Behav Brain Res* 2007;176:362–66, ¹¹Ding Q, *Neuroscience* 2011;192:773–80.

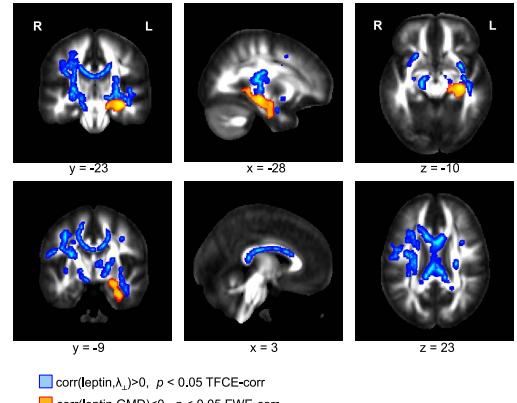


Fig. 1. Leptin-dependent correlations of parameters of grey and white matter structure. Exercise-related decreased serum leptin levels were accompanied by an increased GMD in the hippocampus (orange). A significant positive correlation between leptin and λ_{\perp} was observed in several white matter regions (blue).

Further, whole-brain diffusion-weighted (DW) images (60 directions, $b = 1000$ s/mm², GRAPPA accel fact 2, NEX=3) were acquired from 72 axial slices with isotropic nominal resolution of 1.7 mm. For TBSS⁴, each subject’s aligned map of fractional anisotropy was projected to a mean skeleton. In addition, we assessed the axial and radial diffusivity (λ_{\perp}). Correlations between the individual change of serum markers and diffusivity parameters were computed with randomization tests⁵ using a flexible factorial design ($p < 0.05$, threshold-free cluster enhancement corrected)⁶.

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 λ_{\perp} , 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 λ_{\perp} 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 as 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 also differed with respect to the correlation between BDNF and λ_{\perp} . In responders, a BDNF increase was accompanied by a significant decrease of λ_{\perp} in the vicinity of hippocampus and insula.

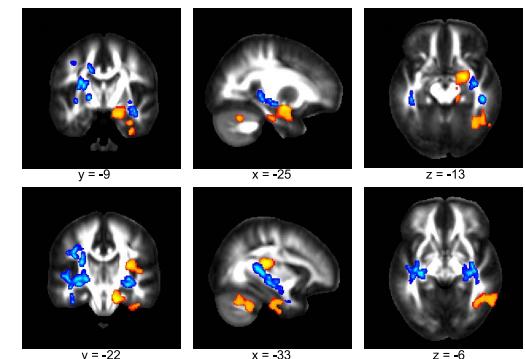


Fig. 3. Structural brain differences between BDNF responders and non-responders. Responders showed a significantly steeper correlation between BDNF and GMD compared to non-responders (orange). Responders and non-responders also differ with respect to the correlation between BDNF and λ_{\perp} (blue).