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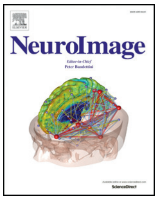

Changes in fitness are associated with changes in hippocampal microstructure and hippocampal volume among older adults

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ABSTRACT

This study investigates the effects of fitness changes on hippocampal microstructure and hippocampal volume. Fifty-two healthy participants aged 59–74 years with a sedentary lifestyle were randomly assigned to either of two levels of exercise intensity. Training lasted for six months. Physical fitness, hippocampal volumes, and hippocampal microstructure were measured before and after training. Hippocampal microstructure was assessed by mean diffusivity, which inversely reflects tissue density; hence, mean diffusivity is lower for more densely packed tissue. Mean changes in fitness did not differ reliably across intensity levels of training, so data were collapsed across groups. Multivariate modeling of pretest–posttest differences using structural equation modeling (SEM) revealed that individual differences in latent change were reliable for all three constructs. More positive changes in fitness were associated with more positive changes in tissue density (i.e., more negative changes in mean diffusivity), and more positive changes in tissue density were associated with more positive changes in volume. We conclude that fitness-related changes in hippocampal volume may be brought about by changes in tissue density. The relative contributions of angiogenesis, gliogenesis, and/or neurogenesis to changes in tissue density remain to be identified.

Introduction

During the last decade, evidence has been accumulated documenting beneficial effects of exercise in preserving cognitive abilities as well as brain structure and function in older adulthood (for reviews, see, e.g., Bherer et al., 2013; Erickson et al., 2015; Hötting and Röder, 2013). The hippocampus has attracted much attention because some of the most compelling evidence for positive effects of fitness on cognition has been found for this brain region, in both animal and human studies. The hippocampus is a small brain region located in the medial temporal lobes, which plays a major role in spatial and contextual memory formation (Squire et al., 2004). It is one of the first brain regions affected by age-related atrophy and has been associated with age-related disorders such as Alzheimer's disease (Barnes et al., 2009). On the other hand, the hippocampus is one of two brain regions for which the potential for neurogenesis is preserved into late adulthood (Eriksson et al., 1998; Spalding et al., 2013). Specifically, the hippocampus is responsive to exercise in animal models (Kronenberg et al., 2003; van Praag et al., 1999).

Multiple studies point to stable or even increased hippocampal volumes after completing 3–12 months of physical exercise interventions (Erickson et al., 2011; Maass et al., 2015; Niemann et al., 2014), using either manual segmentation or automated subcortical segmentation procedures for the MR images. However, the cellular mechanisms underlying these volumetric changes remain largely unknown. Some insight can be gained from animal studies showing that animals with access to running wheels as opposed to those held in standard cages show increased capillary density, and produce new neurons (for reviews, see Kempermann, 2012; Thomas et al., 2012; Voss et al., 2013).

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Consistent with the animal literature, Pereira et al. (2007) demonstrated that after 3 months of exercise in middle-aged human adults, changes in fitness correlated with increases in dentate gyrus cerebral blood volume (CBV), and by extrapolating from animal data, claimed that these changes are related to neurogenesis. A recent study replicated this finding in older adults, reporting associations among changes in fitness, hippocampal perfusion, and volume of the hippocampal head in the context of a 3-month fitness intervention program (Maass et al., 2015). At the cellular level, these observations may reflect either dilation of existing blood vessels or angiogenesis.

Parameters derived from diffusion tensor imaging (DTI) may shed additional light on underlying changes in brain microstructure. DTI measures the diffusion of water molecules within tissue and is commonly used to determine white matter integrity (Bammer, 2003; Beaulieu, 2002). DTI can also be applied to gray matter, where it likewise provides information on how freely water molecules can diffuse through tissue. When many barriers (mostly cell membranes) are present, that is, when the tissue is densely packed, mean diffusivity (MD) would be low, and vice versa. In this way, DTI can complement volumetric measures with information on tissue (or barrier) density (cf. Lövdén et al., 2013). Thus, in the case of exercise-induced volumetric increases that are accompanied by increases in the bulk of membranes, including potentially angiogenesis, gliogenesis, or neurogenesis (hyperplasia), we would expect to observe an increase in barrier density, that is, a decrease in mean diffusivity as opposed to unchanged diffusivity, which would be more consistent with a mere hypertrophy of cells that were already present before the intervention. Tian et al. (2014) provided initial evidence for such an association between higher fitness and lower hippocampal MD, showing that the amount of self-reported exercise activities predicts lower MD in medial temporal lobe (and cingulate cortex) about 10 years later in very old adults.

The present study investigates whether hippocampal tissue changes as captured by MD potentially mediate the association between fitness changes and changes in hippocampal volumes. Latent difference modeling (McArdle and Nesselroade, 1994; cf. Raz et al., 2005), a variant of structural equation modeling (SEM), was used to represent individual differences in changes before and after the intervention. This method greatly reduces the problem of unreliability in the measurement of longitudinal change by using identical sets of more than one observed variable to define equivalent latent constructs at each measurement occasion, and then computing difference scores on the basis of these latent constructs. In doing so, the method effectively separates variance at the construct level from measurement-specific variance and error, and generates difference scores that are more reliable than difference scores based on observed variables (cf. McArdle and Nesselroade, 1994). To this end, we examined the covariance of change in fitness, hippocampal MD, and hippocampal volume in the context of a fitness intervention study with healthy sedentary older adults. Elderly participants were randomly assigned to either of two levels of fitness-training intensity. Before and after the 6-month training phase, participants performed a maximal graded exercise test to assess their training-related fitness improvements, and underwent T1-weighted and diffusion-weighted MR imaging. We hypothesized: (a) a negative association between changes in fitness and changes in MD, in that an increase in fitness would lead to lower diffusivity in the hippocampus, thus reflecting higher tissue density, and (b) a negative association between changes in MD and changes in volume, in that greater decrements in diffusivity, again reflecting more positive changes in tissue density, would lead to more positive changes in volume.

Materials & methods

Participants

Seven hundred and twenty-three community-dwelling older adults were contacted via local newspaper advertisements; from this initial pool, fifty-seven individuals were enrolled in the study. Participants met the following inclusion criteria: (1) age between 59 and 75 years; (2) physical inactivity prior to study enrollment (metabolic rate < 40 based on the Freiburg Questionnaire of physical activity in German, Frey et al., 1999); (3) MMSE score ≥ 26; (4) free of neurological, psychiatric, or cardiovascular diseases; (5) right handedness; (6) no contraindication for heart-rate controlled exercise training (e.g., beta blockers); and (7) suitability for an MR environment (e.g., no magnetic implants, claustrophobia). During training, three participants dropped out due to health issues unrelated to the study, and two dropped out due to motivational issues, resulting in an effective final sample of fifty-two participants who completed the intervention (mean age = 66.0 years, SD = 4.36, age range = 59–74 years; 20 men). Participants gave informed written consent to the study procedure, which was approved by the Ethics Committee of the German Psychological Society (DGPs), and were paid for study participation. Study adherence was incentivized with a bonus system.

Design

Before (pretest) and after (posttest) the 6-month aerobic fitness intervention, as well as another six months after completing the intervention (maintenance), participants underwent a comprehensive assessment distributed over six testing sessions including a battery of questionnaires, cognitive tests, and motor tests as well as cardiovascular fitness assessment and an MR session. A mock scanner session was also included prior to the very first MR assessment to familiarize participants with the MR procedure.

Training

After completing the pretest assessment, participants were randomly assigned to either of two training regimens, high intensity (HI) or low intensity (LI). Groups were counterbalanced for age, sex, years of education, digit-symbol, and MMSE scores.

Participants in both groups came to the lab to exercise on stationary bikes. During the first three weeks, participants exercised twice a week, with each session lasting 25 min in the first week, 40 min in the second week and 55 min in the third week. After the third week, participants trained three times a week for 55 min each session. For the HI group, training intensity was calibrated to result in a heart rate at 80 % of the individual's ventilatory anaerobic threshold (Wasserman et al., 1990), as determined from a maximal graded exercise test at pretest. The LI group exercised at a constant resistance of 10 W irrespective of heart rates. During the last 21 sessions, 5 intervals of 2 min each were integrated after 20 min of training in order to further increase variance in fitness gains. Whereas the LI group only increased the cadence in these time windows from 60–70 to 80–90 cycles/min, the HI group also increased the intensity to a resistance corresponding to 110 % of the individual's ventilatory anaerobic threshold. To adapt intensity levels, heart rate was centrally and automatically monitored using the training software custo cardio concept (custo med GmbH, Ottobrunn, Germany). A staff member additionally controlled compliance for each participant and each training session. Participants exercised in groups of up to six persons at a time. Groups were not separated by intensity level, and participants were informed about differences between the two training regimens only after the termination of the study.

Cardiovascular fitness assessment

Aerobic fitness was assessed using a maximal graded exercise test on a cycle ergometer. The test started at 10 W, increased to 25 W after 2 min followed by 25 W increments every 2 min until total exhaustion or signs of cardiac or respiratory distress. A sports physician continuously monitored the cardiogram, oxygen uptake, heart rate, and blood pressure. As outcomes of the fitness assessment, four parameters

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