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Extensive learning is associated with gray matter changes in the right hippocampus

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Longitudinal voxel-based morphometry studies have demonstrated increases in gray matter volume in hippocampal areas following extensive cognitive learning. Moreover, there is increasing evidence for the relevance of the subiculum in the context of learning and memory. Using longitudinal FreeSurfer analyses and hippocampus subfield segmentation the present study investigated the effects of 14 weeks of intensive learning on hippocampal and subicular gray matter volume in a sample of medical students compared to control subjects not engaged in any cognitive learning activities. We found that extensive learning resulted in a significant increase of right hippocampal volume. Volume of the left hippocampus and the subiculum remained unchanged. The current findings emphasize the role of the hippocampus in semantic learning and memory processes and provide further evidence for the neuroplastic ability of the hippocampus in the context of cognitive learning.

Introduction

An increasing amount of evidence supports the notion that the brain undergoes continuous activity-dependent neuroplastic changes across the life-span. In structural imaging studies these changes have been demonstrated as a consequence of various activities, such as learning to juggle (Boyke et al., 2008; Draganski et al., 2004), learning of mirror reading (Ilg et al., 2008), learning of new color names (Kwok et al., 2011), motor exercise (Niemann et al., 2014), video gaming (Kuhn et al., 2014) or meditation (Kurth et al., 2014). Surprisingly few evidence, on the other hand, has been provided for structural changes in association with learning of abstract information (Ceccarelli et al., 2009; Draganski et al., 2006). Ceccarelli et al. (2009) explored the effects of two weeks of intensive learning and found a fronto-parietal gray matter (GM) volume increase. Draganski et al. (2006) used voxel-based morphometry at three different time points to investigate the effects of intensive learning in students preparing for their medical exam. They found a significant gray matter increase in the posterior and lateral parietal cortex bilaterally and a significant increase in the right hippocampus during the learning period which augmented even further during the subsequent semester break. The primary function of the hippocampus is clearly memory-related. The hippocampus plays a key role in the consolidation of information from short-term to long-term memory and a number of studies have shown a correlation between hippocampus volume and memory performance (Arlt et al., 2013; Avery et al., 2013; Gimenez et al., 2004; Pohlack et al., 2014; Siraly et al., 2015).

Thus, Arlt et al. (2013) and Gimenez et al. (2004) reported a correlation between left hippocampal volume and verbal working memory, Avery et al. (2013) demonstrated an association between total hippocampal volume and relational working memory and Pohlack et al. (2014) reported an association between total hippocampal volume and verbal working memory.

The hippocampus or hippocampal formation can be subdivided into several subfields (dentate gyrus, areas CA3 and CA1, entorhinal cortex and subiculum) (Amaral and Witter, 1995), out of which the subiculum constitutes one of the largest subfields and the major output structure. There is increasing evidence indicating that the subiculum is the subfield that is most strongly involved in basic memory processes and semantic learning (O'Mara et al., 2009). It receives the majority of efferent information from the CA1 region of the hippocampus thus being in a position to integrate, transfer and resolve information from other parts of the hippocampus related to learning and memory (Amaral et al., 1991; Deadwyler and Hampson, 2006).

Nevertheless, changes in gray matter volume in association with learning of semantic information have only been reported for the hippocampus formation as a whole whereas potential gray matter changes in the subiculum have not been specifically investigated up to now. Learning-related changes in gray matter volume of the hippocampus

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are most likely the consequences of synaptic or dendritic sprouting or increases in synaptic strength and neuronal growth (i.e., increases of neuronal somae and nuclei) and, as such, very small (Neves et al., 2008). Hence, high image resolution is needed to detect the aggregated effects of such changes on the macroscopic level across time. Against this background, in the present study we used FreeSurfer (http://surfer.nmr.mgh.harvard.edu) which is a software package capable of detecting sub-millimeter changes in gray matter volume. The software has a longitudinal image processing framework (i.e., FreeSurfer longitudinal). This framework is based on unbiased, robust, within-subject template creation which has been demonstrated to successfully reduce variability, avoid over-regularization and increase power to detect structural changes across time by initializing the processing in each time point with common information from the within-subject template (Reuter et al., 2012). We used this longitudinal framework to investigate the effects of intensive learning on gray matter volume and expected increases in the hippocampus and more specifically the subiculum as a consequence of learning. In addition, we investigated whether baseline gray matter volume predicted learning-associated increases in hippocampal gray matter volume. Finally, based on the above mentioned findings of an association between memory performance and hippocampus volume, we used the digit span task, an established and frequently employed working memory task, to explore whether memory performance at the first measurement time point predicted learning-associated increases in hippocampal gray matter volume. Thus, we intended to extend previous findings of a mere association between working memory performance and hippocampal volume and to explore a directed association by investigating whether working memory performance predicts hippocampal volume change. Identifying parameters which allow the prediction of neuroplastic processes on an individual basis would be of high practical use, for instance in the field of cognitive remediation and training.

Materials and methods

Subjects

We recruited 35 medical students from the Medical School of our University and 24 healthy control subject. 7 medical students and 6 control subjects dropped out after the first scan resulting in a final sample size of 28 right-handed healthy students (m:f = 14:14, mean age = 19.3 years, SD = 1.0 years) and 18 right-handed healthy control subjects (m:f = 6:12, mean age = 18.6 years, SD = 0.5 years) with no history of neurological or psychiatric disorders or other serious medical conditions. Groups were matched according to their level of education (i.e., both had the German "Abitur") and they were carefully selected regarding the amount of physical exercise and musical activities they were doing (i.e., professional athletes or musicians or subjects excessively engaged in sports or playing an instrument were not included). In both groups, T_1-weighted magnetic resonance imaging (MRI) scans were performed at two time points, TP1 and TP2 (i.e., 14 weeks after TP1). In the student group, the first scan was performed at the beginning of their first semester of medical school, the second scan was performed fourteen weeks later shortly before their first semester medical exams. During this time period the students spent on average about 190 h in class and 280 h outside of class with learning facts and information related to anatomy, chemistry, and biology.

The control subjects had recently started a voluntary social year. They were not attending any lesson or studying for any exams between TP1 and TP2.

Handedness was assessed using Annett's handedness inventory. All participants gave written informed consent to the study protocol which is in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Ethics Committee of the Technische Universität München, Medical School.

MRI acquisition

High-resolution anatomical T_1-weighted volume scans (MP-RAGE) were collected on a 3 T whole body system equipped with a 12-element receive-only head matrix coil (INGENIA, Philips). They were obtained in sagittal orientation (TR = 9 ms, TE = 4 ms, TI = 900 ms, flip angle = 8°, FOV = 240 × 240 mm^2, matrix = 240 mm × 240 mm, number of sagittal slices = 170) with an isotropic resolution of 1 × 1 × 1 mm^3.

Data analysis

We used the digit span task to assess cognitive performance and to investigate a potential association between memory performance and gray matter increase. The test consists of a forward and a backward version. In the forward version of the test, a list of random numbers is read out which the participant has to recall in the correct order. The test begins with two numbers, increasing a number at a time until two errors are committed in a row. In the backward version, participants are asked to recall the digits in backward order. Thus, the forward version mainly reflects working memory performance, the backward version assesses predominantly manipulation of stimulus material and executive processing. Memory performance was investigated using a repeated measures one-way ANOVA with digit span forward performance as the dependent variable, group as a between subject factor and measurement time point (TP1, TP2) as a within subject factor. Digit span data of one medical student and one control are missing.

Gray matter volume was assessed using the FreeSurfer software package (version 5.3.0, http://surfer.nmr.harvard.edu).

The initial processing of T1 high-resolution images includes several steps which have been described in previous papers (Dale et al., 1999; Fischl et al., 1999). Briefly, the implemented processing stream contains removal of non-brain tissue, transformation to Talairach-like space, and segmentation of gray/white matter tissue. White and gray matter boundary is tessellated and topological defects are automatically corrected. After intensity normalization and transition of gray/white matter, pial boundary is indicated by detecting the greatest shift in intensity through surface deformation. Segmented data were then parcellated into units based on gyral and sulcal structure, resulting in values for gyrification and volume. Maps were smoothed using a Gaussian kernel of 10 mm.

Subsequently, for the longitudinal processing, an unbiased within-subject template is created using robust, inverse consistent registration to estimate average subject anatomy across both measurement time points (Reuter et al., 2012). Finally, each time point is processed "longitudinally", where information from the subject-template and from the individual runs are used (see Fig. 1, for details please refer to Reuter et al. (2012)). This procedure has been demonstrated to significantly increase reliability and statistical power in longitudinal studies (Ibarretxe-Bilbao et al., 2012; Kwan et al., 2012; Reuter et al., 2012).

Then, an automated subfield segmentation of the hippocampus was performed using Bayesian inference and a probabilistic atlas of the hippocampal formation. The hippocampal subfield volumes obtained with this method have been compared to manual hippocampal subfield tracings, and reliability measures were good for the larger subfields (CA2/3, CA4/DG, subiculum) and only acceptable for the smaller ones (CA1, presubiculum, fimbria) (Van Leemput et al., 2009). Seven hippocampal subfield volumes were automatically calculated including the fimbria (white matter), presubiculum, subiculum, CA1, CA2–3, and CA4-DG fields (gray matter) as well as the hippocampal fissure (cerebrospinal fluid). The procedures for subfield segmentation have been described elsewhere (Van Leemput et al., 2009). The present analyses focus on the subiculum. To investigate the hypothesized changes in hippocampal and subicular gray matter volume, for each subject and time point,

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