

Reduced age-related degeneration of the hippocampal subiculum in long-term meditators



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ABSTRACT

Normal aging is known to result in a reduction of gray matter within the hippocampal complex, particularly in the subiculum. The present study was designed to address the question whether the practice of meditation can amend this age-related subicular atrophy. For this purpose, we established the correlations between subicular volume and chronological age within 50 long-term meditators and 50 control subjects. High-resolution magnetic resonance imaging (MRI) scans were automatically processed combining cytoarchitectonically defined probabilistic maps with advanced tissue segmentation and registration methods. Overall, we observed steeper negative regression slopes in controls. The analysis further revealed a significant group-by-age interaction for the left subiculum with a significant negative correlation between age and subicular volume in controls, but no significant correlation in meditators. Altogether, these findings seem to suggest a reduced age-related atrophy of the left subiculum in meditators compared to healthy controls. Possible explanations might be a relative increase of subicular tissue over time through long-term training as meditation is a process that incorporates regular and ongoing mental efforts. Alternatively, because meditation is an established form of reducing stress, our observation might reflect an overall preservation of subicular tissue through a reduced neuronal vulnerability to negative effects of stress.

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1. Introduction

As our population ages, maintaining good cerebral health and minimizing the effects of neurodegenerative processes are becoming increasingly important. Meditation is being considered as a potential approach to counteract age-related brain decline (Pagnoni and Cekic, 2007; Luders, 2014; Marciniak et al., 2014). However, data directly addressing age effects in the framework of meditation are still sparse. Findings from research exploring associations between meditation and cerebral health without reference to aging provide encouraging supporting evidence for a beneficial effect, especially with respect to the hippocampus (i.e., one of the key structures implicated in brain aging). More specifically, a number of neuroimaging studies have revealed meditation effects in the hippocampal formation and adjoining structures, including larger gray matter volumes, as well as enhanced connectivity in hippocampal pathways (Holzel et al., 2008; Luders et al., 2009, 2011, 2012b; Murakami et al., 2012; Leung et al., 2013). Furthermore, a

recent study investigating hippocampal sub-regions using cytoarchitectonic probability maps reported more gray matter in long-term meditators within the hippocampal subiculum (Luders et al., 2013b). The latter finding is particularly interesting as the subiculum is associated with a loss of brain tissue in normal aging (La Joie et al., 2010; Thomann et al., 2013; Jiang et al., 2014). Moreover, it also plays a significant role in higher order cognitive processes (e.g., episodic memory or navigational abilities) that are known to decline with age (Verhaeghen and Salthouse, 1997; Jagust, 2013; Samson and Barnes, 2013). It is therefore important to determine whether meditation has a protective effect specific to the subiculum, which may counteract typical age-related decline. The existing data demonstrating the presence of a larger subiculum in meditators (Luders et al., 2013b) do not allow any definite conclusion. On one hand, the rate of age-related subicular atrophy might be slower in meditators than controls; on the other hand, meditators might start out with greater volumes in this region and then follow an age-related atrophy that is similar to the one in controls. Both alternatives could result in a significant group difference in subicular volume (i.e., meditators > controls) as previously observed (Luders et al., 2013b). Therefore, to shed further light on this question, the aim of this study was to investigate whether associations between age and subicular structure

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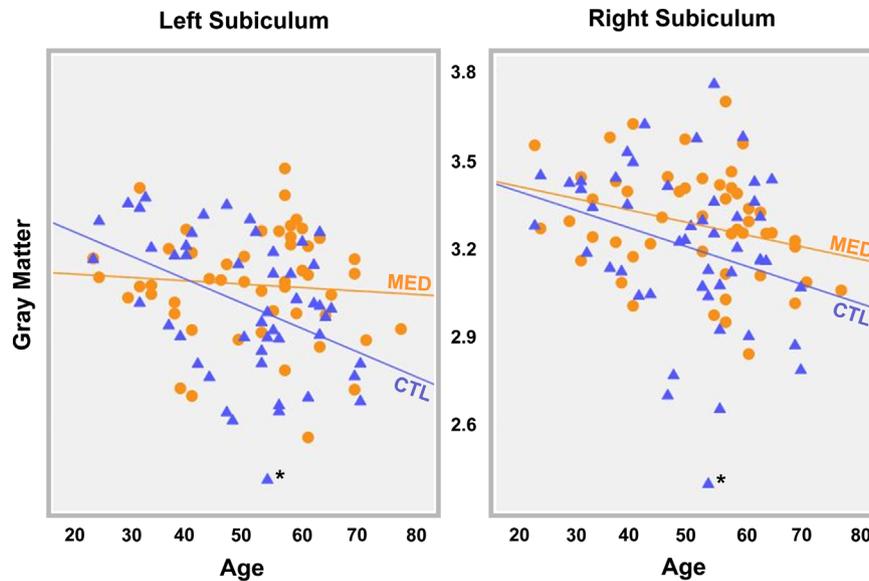


Fig. 1. Correlations between chronological age and subicular gray matter. Scatterplots and regression lines were generated separately for meditators (circles) and controls (triangles). The x-axes display age (in years); the y-axes display the probability-weighted gray matter volume (in ml). Note the flatter slope of the regression lines in meditators (MED) compared with controls (CTL), especially for the left subiculum. Removing one outlier (see asterisks) did not significantly alter the omnibus group-by-age interaction ($p=0.021$) or the group-by-age interactions for the left subiculum ($p=0.033$) or right subiculum ($p=0.59$).

differed in a large cohort of meditators and controls closely matched for age and sex.

2. Methods

2.1. Subjects and imaging

The study included 50 meditation practitioners (28 men, 22 women) and 50 control subjects (28 men, 22 women). Both groups were closely matched for age (meditators: 51.4 ± 12.8 years; controls: 50.4 ± 11.8 years) ranging from 24 to 77 years. Note that the 100 subjects of the current study are identical with samples analyzed in previous studies (Luders et al., 2012a, 2013b; Kurth et al., 2014). Meditators were newly recruited from various venues in the greater Los Angeles area. Meditation experience ranged between 4 and 46 years (mean \pm S.D.: 19.8 ± 11.4 years). A detailed overview with respect to each subject's individual practice has previously been provided (Luders et al., 2012a). Brain scans for the control subjects were obtained from the International Consortium for Brain Mapping (ICBM) database of normal adults (<http://www.loni.usc.edu/ICBM/Databases/>). The majority of subjects ($n=89$) indicated that they were right-handed; six meditators and five controls were left-handed. All subjects, meditators and controls, gave their informed consent in accordance with the policies and procedures of UCLA's Institutional Review Board. All subjects were scanned on the same site, using the same scanner, and following the same scanning protocol. Specifically, magnetic resonance images were acquired on a 1.5 T Siemens Sonata scanner (Erlangen, Germany) using an 8-channel head coil and a T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence with the following parameters: 1900 ms repetition time, 4.38 ms echo time, 15° flip angle, 160 contiguous sagittal slices, $256 \times 256 \text{ mm}^2$ field of view, $1 \times 1 \times 1 \text{ mm}^3$ voxel size.

2.2. Data processing

Data were analyzed using the SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm>) and the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm.html>), as previously described (Luders et al., 2013b). Briefly, using the same generative model, images were first corrected for magnetic field inhomogeneities and tissue-classified into gray matter, white matter, and cerebrospinal fluid. The segmentation procedure was based on maximum *a posteriori* estimations (Rajapakse et al., 1997) and used a partial volume estimation algorithm (Tohka et al., 2004) as well as a spatially adapting non-linear means de-noising filter (Manjon et al., 2010) and a hidden Markov Random Field model (Cuadra et al., 2005). The gray matter partitions were spatially normalized to the DARTEL template provided by the VBM8 toolbox using 12-parameter affine transformations as well as high-dimensional warping. The normalized gray matter segments were divided by the non-linear components of the Jacobian derived from the normalization matrix. This latter modulation step

served to preserve actual gray matter values locally, while still accounting for the individual differences in brain size (via proportional scaling).

Subsequently, the normalized gray matter volumes (encoding the local gray matter volume) were multiplied with cytoarchitectonically derived probability maps of the left and right subiculum, (encoding the local probability for this structure). The cytoarchitectonic probability maps, which are available for use in *in-vivo* image analyses (Eickhoff et al., 2005), were originally created using cell-body stained histological sections of 10 *post mortem* brains through observer-independent mapping of borders between the subiculum and its adjacent brain regions (Amunts et al., 2005). The cytoarchitectonic probability maps of the left and right subiculum are shown in the Supplementary Figure. Prior to the voxel-wise multiplication, the left and right maps of the subiculum were spatially normalized to the DARTEL template to ensure an accurate spatial match between the subiculum maps and the individual gray matter segments in DARTEL space. The multiplication of these maps with the gray matter segments yielded a voxel-wise probability-weighted measure of gray matter content within the left and right subiculum, as detailed elsewhere (Luders et al., 2013b). Finally, the voxel-wise gray matter content was multiplied with the voxel volume in mm^3 and summed up, thus yielding the gray matter volumes of the left and right subiculum for each individual brain. Note that these volumes are already corrected for inter-individual differences in brain size (given the aforementioned modulation of the gray matter segments).

2.3. Statistical analyses

First, we calculated the Pearson product-moment correlations within each group, meditators and controls, in order to determine the strength and direction of associations between chronological age and subicular gray matter. Subsequently, we tested for significant group differences (meditators vs. controls) with respect to the aforementioned correlations (group-by-age interactions). For this purpose, we used the general linear model for multivariate analyses, with the left and right subicular gray matter volumes as *dependent variables*, group as *fixed factor*, and age as *covariate*. A significant group-by-age interaction was followed by conducting appropriate *post hoc* tests for left and right subicular measures. In addition, we generated group-specific scatter plots and regression lines. Alpha was set at 0.05. All statistical analyses were conducted using SPSS20 (<http://www-01.ibm.com/software/analytics/spss/>).

3. Results

We observed negative correlations between left and right subicular gray matter and age, indicating smaller volumes in older subjects. These negative correlations were evident in controls (left subiculum: $r = -0.426$; right subiculum: $r = -0.285$) as well as in meditators (left subiculum: $r = -0.080$; right subiculum: $r = -0.286$). However, while

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