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Training induces changes in white-matter architecture

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Although experience-dependent structural changes have been found in adult gray matter, there is little evidence for such changes in white matter. Using diffusion imaging, we detected a localized increase in fractional anisotropy, a measure of microstructure, in white matter underlying the intraparietal sulcus following training of a complex visuo-motor skill. This provides, to the best of our knowledge, the first evidence for training-related changes in white-matter structure in the healthy human adult brain.

The learning of a new skill relies on changes in brain function. This functional plasticity can be accompanied by structural changes in the gray matter of the human brain[1]. Such gross changes in gray-matter structure could reflect underlying cellular events, including synaptogenesis and dendritic arborisation[2,3]. In contrast, longitudinal, experience-dependent white-matter changes have not previously been reported in healthy humans. However, evidence from animal studies suggests that white matter could alter with experience or training. For example, the amount of neuronal activity along an axon modulates its degree of myelination[4,5] and marked cortico-cortical rewiring has been observed in response to training[6] or rehabilitation[7].

Diffusion tensor imaging (DTI) provides measures of white-matter microstructure in the human brain. DTI is sensitive to the hindrance of water diffusion resulting from local tissue boundaries. Fractional anisotropy, a DTI-derived quantitative measure of the directional dependence of water diffusion, reflects anatomical features of white matter, such as axon caliber, fiber density and myelination[8].

Cross-sectional studies have shown that inter-individual variation in white-matter microstructure, as indexed by fractional anisotropy, reflects behavioral variation[9,10]. Moreover, fractional anisotropy variation correlates with differences in experience, such as the amount of childhood piano practice[11]. Such cross-sectional studies, however, can never confirm a causal role of experience on white-matter structure, as it is possible that common genetic factors influence both white-matter structure and the propensity to train.

We used DTI to measure white-matter changes and voxel-based morphometry (VBM) to measure gray-matter changes in a longitudinal study of individuals learning a new visuo-motor skill: juggling. We obtained informed consent from 48 healthy adults and placed them into either a training group ($n = 24$) or an untrained control group ($n = 24$). The training group was scanned before (scan 1) and after (scan 2) a 6-week training period and following a subsequent 4-week period without juggling (scan 3) (**Supplementary Methods**). After training, all subjects could perform at least two continuous cycles of the classic three-ball cascade (**Supplementary Fig. 1**).

We fitted a diffusion tensor model to DTI data to create whole brain maps of fractional anisotropy that we compared between time points using tract-based spatial statistics (TBSS; **Supplementary Methods**). Comparisons between scan 2 and scan 1 in the trained group revealed significant training-related increases in fractional anisotropy in white matter underlying the right posterior intraparietal sulcus (IPS; $P < 0.05$, corrected, $t_{max} = 4.57$, $x = 31$, $y = -59$, $z = 31$; **Fig. 1**). We carried out a series of *post hoc* tests to probe this difference further and found that it was specific to the trained group and remained elevated relative to baseline after a 4-week period without juggling (**Supplementary Results** and **Supplementary Fig. 2**).

To explore the possibility that learning is associated with colocalized white-matter/gray-matter changes, we tested for gray-matter density changes using VBM (**Supplementary Methods**). Following juggling training, gray-matter density increased significantly in the medial occipital and parietal lobe in cortical regions overlying the white matter area of significant fractional anisotropy increase ($P < 0.05$, corrected, $t_{max} = 6.22$, $x = -10$, $y = -70$, $z = 36$; **Fig. 2**). Again, we carried out a series of *post hoc* tests and found that this increase was specific to the trained group and continued after the 4-week period without juggling (**Supplementary Results**, **Supplementary Figs. 3** and **4**, and **Supplementary Table 1**).

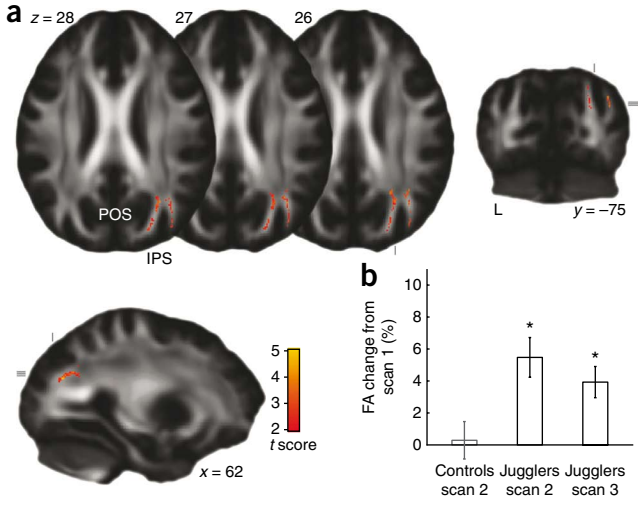

Figure 1 Fractional anisotropy increases after juggling training. (**a**) Colored voxels represent clusters (corrected $P < 0.05$) of significant fractional anisotropy increase from scan 1 to scan 2, superimposed on the mean fractional anisotropy map. POS, parieto-occipital sulcus. (**b**) Mean fractional anisotropy (FA) change from scan 1 in the cluster shown in **a**. Error bars represent standard errors. * indicates significance relative to baseline at $P < 0.05$.

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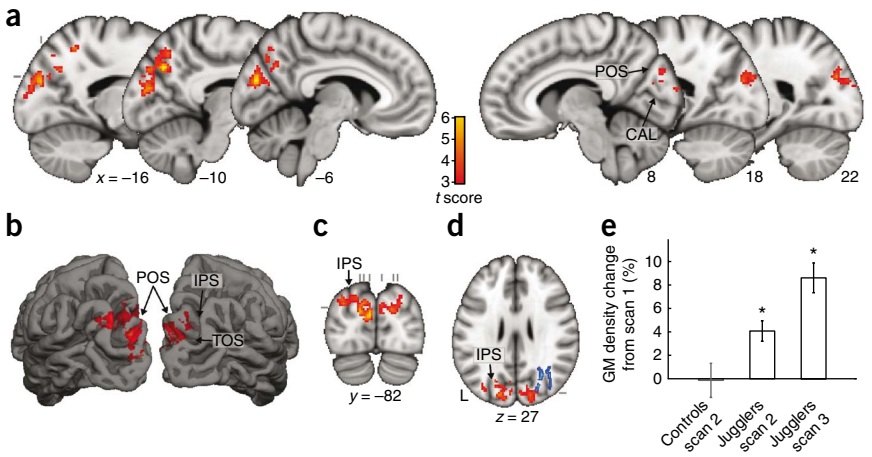

Figure 2 Gray-matter density increases after juggling training. (**a**–**d**) Red and yellow voxels represent clusters ($P < 0.05$, corrected) of significant gray-matter density increase from scan 1 to scan 2, superimposed on the Montreal Neurological Institute template. Sagittal (**a**), coronal (**c**) and axial (**d**) slices, and a surface rendering (**b**) are shown. The white-matter changes (blue, thickened for visibility) are shown in **d** for comparison. CAL, calcarine sulcus; TOS, transverse occipital sulcus. (**e**) Mean gray-matter (GM) density changes from scan 1 in the clusters shown in **a**–**d**. Error bars represent standard errors. * indicates significant at $P < 0.05$ relative to scan 1.

Juggling is a complex motor skill that requires accurate bimanual arm movements, grasping and visual tracking in the periphery, precisely those functions in which the apparently structurally altered brain regions specialize (**Supplementary Discussion**). In general, structural changes did not correlate significantly with training progress or the performance level reached after the juggling period, consistent with previous reports[12,13] (left hemisphere: level, $r = 0.076$, $p = 0.7$; progress, $r = 0.28$; $p = 0.19$; right hemisphere: level, $r = 0.064$, $p = 0.8$; progress, $r = 0.18$, $p = 0.40$), although we did find a restricted effect at the peak voxel for our gray matter analysis (**Supplementary Results** and **Supplementary Fig. 5**). The absence of a strong and widespread relationship between performance and structural changes suggests that the majority of structural changes might be more closely related to the amount of time spent training (which was kept constant in this study) than to the training outcome.

Despite the close spatial proximity of gray-matter and white-matter regions showing training-related changes, we did not find any correlation between the magnitude of gray-matter and white-matter changes across subjects. This, along with the markedly different time courses of gray-matter and white-matter change, suggests that relatively independent structural changes occur in these different tissue types. Future studies could use varying training regimes and longer periods of observation to more fully characterize the complex dynamics of gray-matter and white-matter change with learning.

Biological interpretation of changes in imaging measures is challenging (see **Supplementary Discussion** for interpretation of gray-matter changes). Fractional anisotropy in part reflects white-matter properties such as axon caliber and myelination[8]. Changes in these properties might underlie behavioral improvements by altering conduction velocity and synchronization of nervous signals[14]. Previous reports suggest that electrical activity in an axon could regulate its myelination over a time course of days to weeks[4,5]. Activity-dependent myelomodulation, which would be expected to influence fractional anisotropy, is therefore a potential mechanism by which the functional properties of white matter are affected by experience. Changes in other structural features of the white matter, such as axon diameter (which could itself be regulated by myelin[14]) or packing density, could also underlie the results found here.

In summary, we provide, to the best of our knowledge, the first evidence for experience-dependent changes in white matter microstructure in healthy human adults. Although neuroimaging techniques such as DTI provide opportunities for whole-brain studies in living human subjects, the measures derived from magnetic resonance imaging are indirect and their interpretation is complex. Therefore, future studies using cellular and biochemical techniques are required to determine the biological basis of the observed changes.

Note: Supplementary information is available on the Nature Neuroscience website.

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AUTHOR CONTRIBUTIONS

J.S. and H.J.-B. designed the study. J.S. and M.C.K. collected and analyzed the data. H.J.B. supervised the project. T.E.J.B. provided assistance with data analysis and interpretation. J.S. wrote the manuscript and all of the authors edited the manuscript.

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