Opposing effects on parieto-frontal white matter plasticity after demanding and undemanding working memory training: A multimodal MRI approach.

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Purpose: Our brain structure and organization can be shaped by environmental demands but the mechanisms underlying brain plasticity remain poorly understood. This is the first study to investigate plasticity of white matter microstructure by combining standard diffusion tensor imaging (DTI) with putative indices of axonal density from the composite hindered and restricted model of diffusion (CHARMED)[1] and myelin water mapping from mcDESPOT[2]. We present novel findings regarding the effects of two months of high and low capacity working memory training on microstructural properties of the cingulum and parieto-frontal fibers in the superior longitudinal fasciculus (SLF) (Fig 1).

Materials and Methods: Participants: 40 young adults were randomly allocated to either high capacity working memory training with performance related adaptive increases in task difficulty, or low capacity training with constant low level of task difficulty[3]. Working memory span performance was assessed before and after the training. **MRI:** Data were acquired using a 3T GE HDx MRI system. **T1 weighted anatomical scan** (FSPGR) (256 x 256 acquisition matrix, TR = 7.8 ms, TE = 2.9 ms, flip angle = 20, 172 slices, 1mm slice thickness, FOV = 23cm). Cardiac-gated **HARDI diffusion MRI**[4] employing an optimised 60 direction gradient vector scheme and b-value 1200s/mm^2, 60 slices (2.4mm), FoV 24 cm, matrix 96x96, TE 87ms. Images were corrected for EPI distortions and motion with re-orientation of gradient directions[5]. The tensor was estimated in each voxel using RESTORE[6], and damped Richardson-Lucy spherical deconvolution[7] was used to extract voxelwise peaks in the fibre orientational density function (fODF). **CHARMED** (TE = 126 ms, TR = 17000 ms, 45 gradient orientations distributed on 8 shells, slice thickness = 2.4mm, maximum b-value = 8700 s/mm2, SR 2.4 isotropic, acquisition time 13 min). **mcDESPOT** (spoiled gradient recalled, or SPGR, acquisitions: TE = 2.1 ms, TR = 4.7 ms, flip angles = [3, 4, 5, 6, 7, 9, 13, 18°]; balanced Steady-State Free Precession, or bSSFP, acquisitions: TE = 1.6 ms, TR = 3.2 ms, flip angles = [10.6, 14.1, 18.5, 23.8, 29.1, 35.3, 45, 60°], SR 1.7 isotropic, acquisition time 12 min) bSSFP acquisitions were repeated with and without 180 RF phase alteration to remove SSFP banding artefacts and spgr and irspgr acquisitions were used to correct B0 and B1-induced errors in the derived myelin water fraction estimates. All data were corrected for partial volume artefacts[8,9]. Deterministic tractography was performed by seeding in all voxels and following the fODF peaks using *ExploreDTI*[10]. Putative 3D pathways belonging to SLF and the cingulum (Fig. 1) were selected from the whole brain tracking results using 'waypoint' regions of interest and reproducible landmarking techniques[11,12]. Tract-specific measures of average fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), tissue volume fraction (TVF), total restricted fraction (TRF) as putative measure of axonal density and myelin water fraction (MWF) as putative index for myelin were subsequently generated.

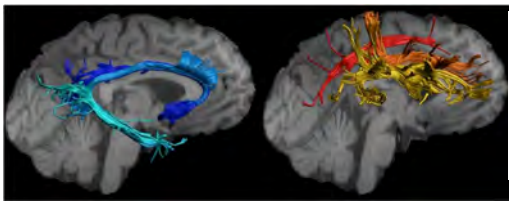

Figure 1: Sagittal view of the cingulum (left panel) and Superior Longitudinal Fasciculus (SLF) (right panel): Subgenual (dark blue), retrosplenial (blue) and parahippocampal cingulum (PHC) (light blue) as well as SLF1 (red), SLF2 (orange), and SLF3 (yellow).

Results: **High capacity training** (Fig. 2 red) led to ***increases in TRF, FA, and TVF and decreases in MD and RD*** in the right SLF1. **Low capacity training** (Fig 2 blue) led to ***decreases in TRF, FA, and TVF*** **and** ***increases in MD and RD*** in the right SLF1. Working memory span improvements in the high capacity group were positively correlated with increases in MWF across SLF and cingulum fascicles notably in the right PHC (Fig 3).

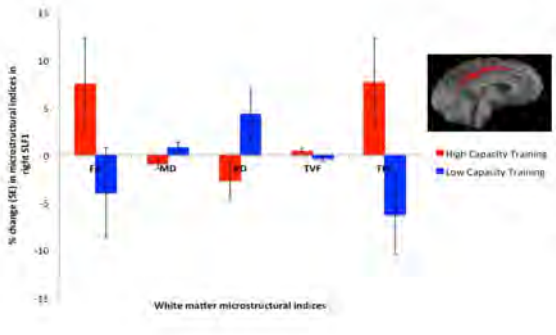

Figure 2: % change in white matter microstructure in right SLF1 in high (red) and low (blue) capacity training groups

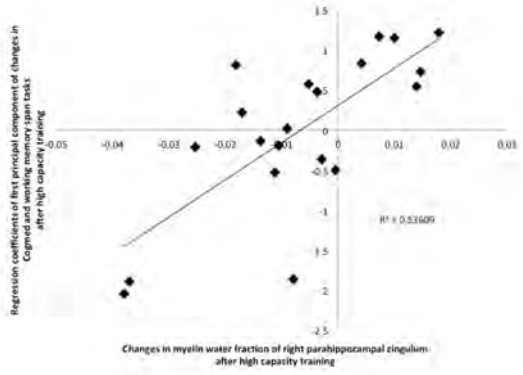

Figure 3: Positive correlation between cognitive improvements and increases in myelin water fraction in right PHC.

Conclusion: Most strikingly high and low training demands led to **opposite changes** in white matter microstructure in the right SLF1. **High capacity training** led to a pattern of changes indicative of ***increased axonal density*** and **low capacity** to a pattern indicative of ***decreased axonal density*** in the right SLF1. Increases in putative indices of myelin (MWF) across cingulum and SLF fascicles were positively correlated with improved working memory span performance, notably in the right PHC. These novel findings demonstrate training induced changes in axonal density and myelin and suggest that the intensity and nature of daily activities may critically shape an individual's cognitive capacities and underpinning brain infrastructure. These results may aid in the development of novel methods of self-improvement and the rehabilitation of age- and disease related decline.

References: [1] Assaf Y, Basser PJ (2005) *Neuroimage* 27:48-58. [2]Deoni SC (2011) *Methods Mol Biol* 711:65-108. [3]Cogmed and Cogmed Working Memory Training are trademarks, in the U.S. and/or other countries, of Pearson Education, Inc. or its affiliate(s).[4]Tuch DS et al *MRM* 48:577-82. [5]Leemans A, Jones DK (2009) *Magn Reson Med* 61:1336-49. [6]Chang et al (2005) *MRM* 53:1088-95. [7]DellAqua et al (2010) *NeuroImage.*49:1446-58. [8]Pasternak et al (2009) *Magn Reson Med* 62:717–730. [9] Bells S et al (2011) *Proc ISMRM 19th Ann Meetg, p 8076, Montreal*. [10] Leemans et al (2009) ExploreDTI *Proc ISMRM 17th Ann Meetg*, p 3537, Hawaii. [11]Jones D et al. (2013) *Neuropsychologia* 51: 67-78. [12] Thibaut de Schotten et al (2011) *Nat Neurosc* 14:1245-6.

Target audience: Cognitive neuroscientist, Imaging scientist, Psychologists, Clinicians