More frequent cognitive activity in late life is associated with higher brain microstructural integrity in non-demented older adults

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Target Audience: Researchers in brain MRI of aging.

Purpose: Previous research suggests that more frequent cognitive activity in late life is associated with lower rate of cognitive decline, reduced risk of cognitive impairment, Alzheimer's disease and dementia [1,2]. The underlying mechanism is thought to be that more frequent cognitive activity builds "cognitive reserve", which reduces susceptibility to brain changes and pathology [3]. Cognitive reserve has been defined as a set of structural or functional brain characteristics that protect against neuropathologic damage. The purpose of this study was twofold: a) test the hypothesis that more frequent cognitive activity in late life is associated with higher microstructural integrity in brain white matter, and b) test the hypothesis that microstructural integrity in brain white matter mediates the relation between late life cognitive activity and cognition.

Methods: A community-dwelling sample of 397 non-demented older participants of the Rush Memory and Aging Project [4] was included in this study (82±7 years of age). All participants rated their current frequency of participation in cognitively stimulating activities (late life cognitive activity, LLCA), as well as their past frequency of cognitive activity (from childhood until middle age; past cognitive activity, PCA), and the availability of cognitive resources (CR) in their home during childhood and adulthood [5]. T1-weighted MPRAGE, T2-weighted FLAIR and SE-EPI-DTI data were collected on all participants using a 1.5 Tesla MRI scanner. White matter hyperintense lesions (WMH) were automatically segmented using a support vector machine based on data from both MPRAGE and FLAIR. For the DTI data, corrections for bulk motion and distortions due to eddy-currents and field non-uniformities, B-matrix reorientation, and diffusion tensor calculation, were conducted using TORTOISE [6]. Fractional anisotropy (FA), trace of the diffusion tensor, axial (AD) and radial diffusivity (RD) were calculated in each voxel. Tract-Based Spatial Statistics was used to test for voxel-wise associations of DTI parameters with LLCA, while controlling for age, sex, level of education, the presence of WMHs, PCA and CR [7]. The null distribution was generated using the randomise tool and 5000 permutations. Differences were considered significant at $p<0.05$, Family Wise Error corrected. Threshold-Free Cluster Enhancement was used to define significant clusters. Voxels of the WM skeleton with significant associations between FA and LLCA were grouped into clusters. Mediation analysis was conducted to test for mediation of the mean FA per cluster on the association of LLCA with cognition.

Results & Discussion: Higher frequency of LLCA was associated with higher FA values in the genu and body of the corpus callosum and white matter of the left brain hemisphere (left ILF, left SLF, left arcuate fasciculus, left fornix) (Fig.1), and with lower trace, AD, and RD in the thalamus (not shown here). The laterality of the FA findings was probably due to the fact that several of the activities included in the LLCA measure involved language. The above results suggest that more frequent cognitive activity in late life is associated with higher microstructural integrity in brain white matter.

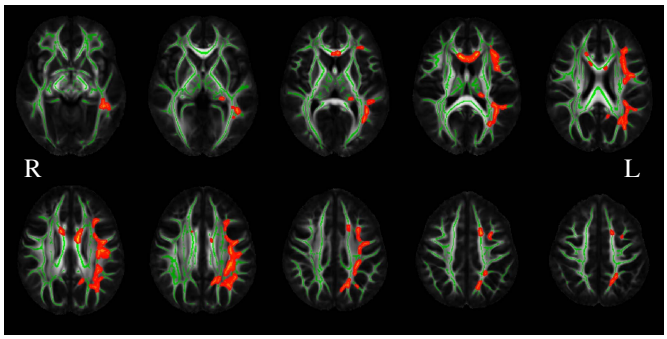

Figure 1. White matter regions with a significant positive correlation between frequency of LLCA and FA are shown in red.

Complete mediation of FA on the relation between LLCA and cognition was not present for any of the clusters. However, bias-corrected bootstrap analysis revealed partial mediation of FA in the left fornix and left hemisphere clusters on the relation between a) LLCA and semantic memory, as well as b) LLCA and perceptual speed. These findings suggest that microstructural integrity of brain white matter is only one of the factors that mediate the relation of cognitive activity in late life with cognition. This further implies that microstructural integrity of brain white matter may be one of the components of "cognitive reserve": "a set of structural or functional brain characteristics that protect against neuropathologic damage" [3].

References: [1] Wilson RS, et al. *Neurology* 2012;78:1123-1129. [2] Verghese J, et al. *J Geriatr Psychiatry Neurol* 2009;22:110-118. [3] Stern Y, *Lancet Neurol* 2012;11:1006-1012. [4] Bennett DA, et al. *Curr Alzheimer Res* 2012;9:646–663. [5] Wilson RS, et al. *J Int Neuropsychol Soc* 2005;11:400-407. [6] Pierpaoli C, et al. ISMRM 2010, p.1597. [7] Smith SM, et al. Neuroimage 2006;31:1487–1505.