Relation of Corpus Callosum Commissural System Volume and its Projection Regions to Volume of White Matter Lesion Load and Whole Brain Atrophy with Age in Healthy Adults

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Introduction: We analyze the degree of age-related atrophy changes of the corpus callosum during normal aging in healthy subjects and its relationship with white matter lesion load and whole brain atrophy. Previous studies have suggested that there is substantial axonal loss in the normal-appearing white matter, but there was no correlation between age and corpus callosum size in healthy subjects. Corpus callosum atrophy has been suggested as a putative marker for the loss of intracortical-projecting neocortical association neurons in Alzheimer's disease[1] and Interhemispheric Dysfunction in Relapsing-Remitting Multiple Sclerosis[2]. It has been claimed that the human corpus callosum shows sex differences, and in particular that the splenium (the posterior portion) is larger in women than in men[3]. The relationship between callosal atrophy and degree of white matter lesions evaluated by MRI is unclear. Magnetic resonance images of 217 normal individuals were analyzed to assess whether or not the loss of volume in the corpus callosum and parts thereof is related to white matter lesion load and whole brain atrophy.

Methods: A total of 217 subjects from previous studies of normal aging and control subjects from various studies were included (mean age = 61.04, 139 women). Most participants above 60 did not have any memory impairment (Box Score 0.0)[4]. Dual-echo axial MRI images of the brain (1.5 T) were acquired. Image analysis comprised an automated tissue segmentation into the intracranial cavity (ICC) and subclasses of white matter (WM), gray matter (GM), cerebrospinal fluid (CSF), and WM signal abnormalities (WMSA)[5,6,7,8]. Brain parenchymal fraction (BPF) was defined as BPF=(1-CSF)/ICC. Corpus callosum (CC) measures were obtained from Mid-sagittal T_1-weighted MRI scans. Briefly, total callosal area was obtained by manually tracing the outer edge of the corpus callosum on the midsagittal slice by using 3D Slicer software (Surgical Planing Lab, Brigham&Women's Hospital, Boston, MA) on a workstation (Apple), as described elsewhere. The outline of the corpus callosum was divided into five subareas corresponding to sub-regions of the corpus callosum (C1 indicates the rostrum; C2, the anterior truncus; C3, the middle truncus; C4, the posterior truncus; and C5, the splenium) based on the Witelson scheme[9]. Tissue volumes were normalized by the ICC for analysis. Correlation analysis between volumetric variables was performed.

Results: After correction for ICC, healthy subjects demonstrate age-related CC atrophy. Interestingly, total CC area as well as BPF (data not shown) did not correlate significantly with WMSA load. Total CC area did show moderate correlation with brain atrophy (table). All segments of the CC also had moderate correlation with brain atrophy. The most prominent age-related decrease in CC area was in the CC1 and CC4 segments, resulting in a moderately significant correlation of total CC and age. The degree of the WMSA load correlated moderately only for loss in middle sections of the CC (CC2, CC3, CC4) (the midbody connects the motor, sensory and auditory cortices). CC volume loss may be an important determinant of axonal loss and therefore of late age cognitive impairment and disability.

Table. Correlation (Pearson) between volumetric CC measurements, WMSA and BPF.

Variables*	**Age**		**BPF**		**WMSA**	
	corr	**p**	**corr**	**p**	**corr**	**p**
Total CC	-0.135	0.048	**0.330**	**<0.001**	-0.072	0.288
CC1	**-0.211**	**0.002**	**0.349**	**<0.001**	-0.008	0.902
CC2	-0.087	0.204	**0.291**	**<0.001**	**-0.148**	**0.029**
CC3	-0.015	0.831	**0.188**	**0.006**	**-0.146**	**0.032**
CC4	**-0.210**	**0.002**	**0.328**	**<0.001**	**-0.159**	**0.019**
CC5	0.01	0.886	**0.179**	**0.008**	0.006	0.929

- normalized by icc.

Discussion: Age related callosal atrophy is discrete, but does not colocalize with CC segments in which WMSA volume appears to be a determinant of CC segmental area in the CC. Loss of commissural fibres in aging might have different etiologies, that are not always associated with WMSA. More detailed WMSA distribution analysis will be required to further understand the relationship between WM disease and regional callosal atrophy.

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