A longitudinal study of the corpus callosum size and shape in early Alzheimer's disease

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TARGET AUDIENCE:
Researchers interested in neuroimaging biomarkers of Alzheimer's disease (AD) progression.

PURPOSE:
The number of longitudinal studies of the corpus callosum (CC) size and shape is very limited. We studied the time rate of change of the size (area) and shape (circularity) of the mid-sagittal cross-section of the CC in normal aging and early AD by using MRI scans of the same subjects at two time points.

METHODS:
Subjects: We used images in the OASIS longitudinal database[1] from 75 normal controls (NC), 51 mild cognitively impaired (MCI) and 21 mild AD (AD) right-handed subjects aged 60-96, scanned twice approximately two years apart. Subjects were grouped solely by their Clinical Dementia Rating (CDR) (NC: CDR=0, MCI: CDR=0.5, AD: CDR=1). Imaging: Scans were 3D sagittal MPRAGE volumes of matrix size 256x256x128, voxel size 1x1x1.25 mm^3, TR=9.7 ms, TE=4.0 ms, TD=200 ms, TI=20 ms, and flip angle 10°, using a 1.5T Vision scanner (Siemens, Erlangen, Germany).
CC Measurements: The Automatic Registration Toolbox (ART) module 'yuki' (www.nitrc.org/projects/art) was used to automatically segment the CC and measure its total area (A), perimeter (P), and sub-areas according to the Hampel parcellation scheme[2] (Fig. 1). Circularity (CIR) was calculated as $4\pi A/P^2$ as a measure of CC shape.
Statistical Analyses: Rates of change were estimated using the following mixed effects model:

$$\Delta = \beta_1 delay + \beta_2 delay \times I_{MCI} + \beta_3 delay \times I_{AD} + \epsilon$$

where delay is a random effect (time between baseline and follow-up scans), Δ represents the change over time (follow-up minus baseline) in a parameter (e.g., CIR), and I_{MCI} and I_{AD} are indicator functions (1 if the subject belongs to the group and 0 otherwise). Note that an intercept term was not included since no change would be expected if there is no delay.

RESULTS:
Time rates of change in total CC, splenium, and genu area, and CIR are shown in Table 1. '*' indicates rates that were significantly negative. The total area or genu rates were not significantly different between groups. The splenium rates were different in NC vs. AD ($p<10^{-3}$) and MCI vs. AD ($p<10^{-3}$). For CIR, all three group comparisons were significant (Fig. 2): NC vs. MCI ($p<0.024$), NC vs. AD ($p<10^{-4}$), MCI vs. AD ($p<10^{-3}$).

DISCUSSION:
Our results indicate that normal aging involves reduction in the size of the genu (red in Fig. 1), while AD progression in early stages of overt symptoms is also associated with accelerated atrophy of the splenium (blue in Fig. 1). However, the most sensitive marker of both normal aging and AD progression proved to be the CC circularity which decreased significantly with time. In addition, the rates of decrease in CIR were significantly different between the three groups (Fig. 2).

CONCLUSIONS
Decreases in splenium area and circularity in time can be used as informative biomarkers along with other measures such as CSF chemical markers, neuropsychological tests, and other imaging markers (e.g., PET) for earlier AD diagnosis. They can also be used as objective markers of group stabilization in clinical trials of drugs that aim to slow AD progression.

REFERENCES:
1 Marcus DS, et al. Open Access Series of Imaging Studies: Longitudinal MRI data in nondemented and demented older adults. J Cog Neur 2010;22:2677-84.
2. Hampel H, et al. In vivo imaging of region and cell type specific neocortical neurodegeneration in Alzheimer's disease. J Neural Transm 2002;109:837-55.
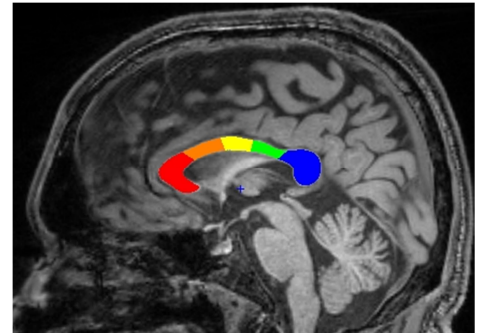
Fig 1: Automatic CC segmentation using 'yuki'. Colors show the Hampel sub-regions.

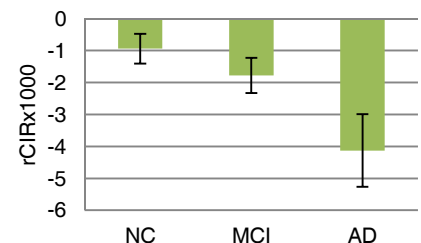| Table 1: Time rate of change of CC size and shape.			
	NC	MCI	AD
Total area (mm^2/yr)	-1.50±1.56	-3.2±1.86*	-4.07±3.54*
Splenium (mm^2/yr)	-0.25±0.51	-0.95±0.59*	-2.91±1.31*
Genu (mm^2/yr)	-0.81±0.71*	-1.61±0.84*	-2.04±1.70*
Circularity (1/yr)	-0.94±0.47*	-1.78±0.55*	-4.13±1.14*
Error cited is 95% CI. *Significantly negative rates (p<0.05)			

Fig. 2: Rates of change of CIRx1000 (yr^{-1}). Error bars indicate the 95% CI.