Disentangling the normal aging from the pathological Alzheimer's disease progression on structural MR images.

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Background. The brain atrophy observed in patients affected by Alzheimer's disease (AD) is the contribution of a normal aging process plus an AD-specific pathological matter loss. Being able to differentiate these complementary atrophy factors is fundamental to isolate and quantify the pathological AD-related structural changes, and might represent a reliable disgnostic measure, especially at prodromal stages of the disease. We propose a method based on non rigid-registration to identify the brain atrophy component specific to the clinical condition, after extraction and removal of the morphological changes described by the normal aging process.

Methods. We chose the structural MRIs for 37 healthy subjects positive to CSF Aβ42 ($<$ 192 pg/ml, Aβ+), 86 patients with mild cognitive impairment (MCI) converters to AD, 110 stable MCI, and 134 AD. For each subject, a "virtual aging" component is defined as the closest point with respect to the longitudinal deformation modeled for the healthy aging of a group of 63 normal subjects negative to the CSF Aβ42 (Aβ-) [1]. Once removed the aging component, the remaining specific morphological changes were analysed group-wise, in order to characterize the atrophy patterns at the different clinical stages. The clinical relevance of the group-specific atrophy component was verified on the discrimination between clinical groups. For this purpose, we identified in selected regions (hippocampi, medial temporal lobes (MTL), posterior cingulate (PC), and ventricles) the areas of higer/lower divergence associated to the specific deformation component of each clinical group. These areas represent the locations of the highest modeled structural expansion/contraction with respect to the predefined reference, and were used as reference for the linear discriminant analysis by leave-one-out cross validation (500 iterations).

Results. The virtual age estimated with respect to the healthy Aβ- longitudinal deformation is shown in Figure 1. Even though the considered groups did not significantly differ for age, the estimated virtual age significantly increases

* Data used in preparation of this article were obtained from the Alzheimers Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at:www.loni.ucla.edu/ADNI/Collaboration/ADNI_Authorship_list.pdf

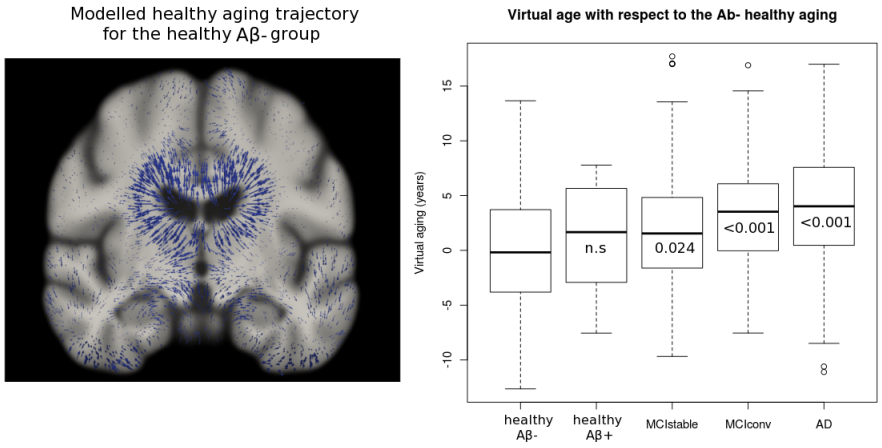

Fig. 1: Left: Normal aging trajectory modeled for the group of Aβ- healthy subjects. Right: Average virtual age estimated for the clinical groups with respect to the normal aging. The estimated virtual ages describes statistically significant older brains (standard t-test, p-value in the boxes) as the clinical condition moves towards the pathological state.

when moving towards the pathological condition. Once removed the healthy aging component, the average morphological changes specific for the clinical groups are shown in Figure 2. We notice that the change in the clinical condition is associated with larger and more intense structural changes indicating more intense expansion/contraction phenomena mapping to ventricles, temporal poles and hippocampi. Table 1 shows the classification results for the discrimination MCI stable vs converters, and AD vs healthy controls. The best results provided by the classifier were: specificity 84%, sensitivity 91%, for AD vs healthy controls, and specificity 63%, sensitivity 67% for MCI stable vs converters (all results significantly different from pure chance $p < 0.001$ McNemar test).

Conclusions. We propose a method to decompose the brain atrophy into complementary components: aging and AD specific. These components identify the different clinical stages, and suggest that more advanced AD stages are associated to both "virtually older" brains and increased specific morphological changes that are not related to the normal aging. These results provide new insights that can lead to new understandings of the AD dynamics, and to novel diagnostic techniques for the early detection of the disease.

References

1. Lorenzi, M., Ayache, N., Frisoni, G.B., Pennec, X.: Mapping the effects of Aβ_{1-42} levels on the longitudinal changes in healthy aging: hierarchical modeling based on stationary velocity fields. In: MICCAI. pp. 663–670. LNCS, Springer (2011)

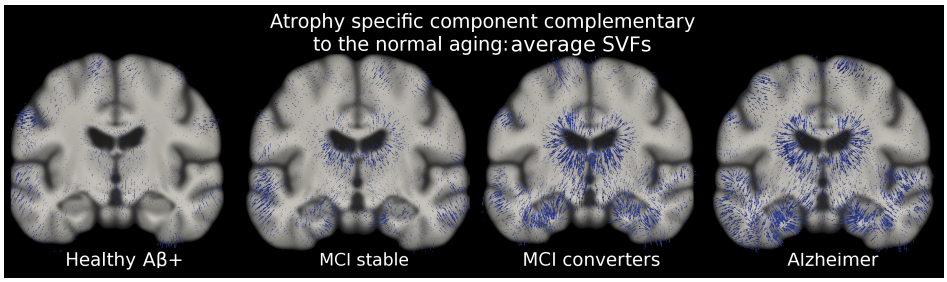

Fig. 2: Average specific deformation component not related to normal aging. MCI converters and AD patients show the more pronounced pattern of morphological changes mapping mainly to ventricles, temporal poles, entorhinal cortex and hippocampi.

AD vs $Ctrls$	Sens	Spec	PPV	NPV
All features	91	84	85	90
MTL (-)	86	81	85	82
MTL (+)	73	77	76	74
Hippocampi (-)	77	71	75	73
Hippocampi (+)	77	63	73	67
Ventricles (+)	65	69	68	66
Ventricles (-)	68	69	69	68
PC (-)	58	59	59	59
PC (+)	59	50	54	54
MCI_{conv} vs MCI_{stable}	Sens	Spec	PPV	NPV
Hippocampi (+)	67	63	64	65
PC (+)	47	74	64	58
PC (-)	58	58	58	58
Ventricles (-)	58	56	57	57
MTL (+)	57	57	57	57
Ventricles (+)	61	43	52	52
All features	54	54	54	54
MTL (-)	53	51	52	52
Hippocampi (-)	55	47	51	51

Table 1: Regional classification accuracy for the discrimination AD vs $Ctrls$, and MCI_{conv} vs MCI_{stable}, ordered by discriminative power. The analyzed features are the positive and negative divergence (+ and -) in the regions of interest (hippocampi, ventricles, posterior cingulate, and medial temporal lobes), which represent the amount of pathological changes not described by the healthy aging.