Compositive morphological alterations in healthy ageing, mild cognitive impairment and Alzheimer's disease: An MANCOVA study

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Introduction: Differentiation early Alzheimer's disease (AD) from healthy ageing remains challenging in clinical practice. Magnetic resonance imaging (MRI) has been used to study the morphological alterations of brain during ageing and disease progression in AD. However, previous studies have mainly focused on the individual structural changes that may profoundly interact with one another [1, 2]. This study aims to explore the compositive brain structural alterations using Multivariate analysis of covariance (MANCOVA) and its potential in differentiating mild cognitive impairment (MCI) converted and AD from healthy ageing.

Materials and Methods: 152 subjects were included and categorized into groups of healthy young, healthy elderly, MCI and AD (Table 1). Data of the last 3 groups were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database. High resolution Magnetic Resonance T1 weighted images covering the entire brain were obtained through MPRAGE sequence with a 3T Scanner (Siemens, Magnetom TRIO, Erlangen, Germany) and a 32-channel head coil. The typical imaging parameters were TR/TE=1900/2.53ms, FA=9, FOV=256×256, and in plane resolution = 1mm×1mm×1mm. FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) was used to parcellate the cerebral cortex into 34 gyral-based regions-of-interest (ROIs) for the entire brain (Table 2). Surface area, mean curvature index, cortical thickness, and subjacent WM volume were calculated for each ROI as morphological indices. MANCOVA was performed to compare the indices collectively firstly among the 4 groups, then among the last 3 groups; age and gender were introduced as covariates. ANOVA was then applied to compare individual index among 4 groups, followed by sensitivity analysis to evaluate whether one single index could be the major contributor affecting the whole results. Multiple testing corrections were conducted to control the false discovery rate (FDR) at a significance level of 0.05 for all the analyses. All the statistical analyses were performed using SPSS (Version 17.0, SPSS Corp., Chicago, USA).

Results: There was no age difference among groups of healthy elderly, MCI and AD (F=2.26, P=0.11). All the 34 gyral regions were found significantly different among 4 groups and the last 3 groups by MANCOVA with FDR correction (Fig 1A). With regards of individual index, 3 gyral regions (23, 28, 31) were statistically significant for Surface area by ANOVA (Table 2, Fig 1B), 13 regions (2, 3, 4, 6, 9, 10, 13, 15, 21, 22, 23, 28, 33) for the mean curvature index (Table 2, Fig 1C), 25 regions (2, 3, 5, 6, 9, 10, 14, 15, 16, 17, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 30, 31, 32, 33, 34) for WM volume (Table 2, Fig 1. E), 33 out of 34 regions (whole cerebrum except Pericalcarine Sulcus) for cortical thickness (Table 2, Fig 1D). Global structural alterations remained significantly different among 4 groups by sensitivity analysis (Fig 1F) performing MANCOVA with exclusion of cortical thickness.

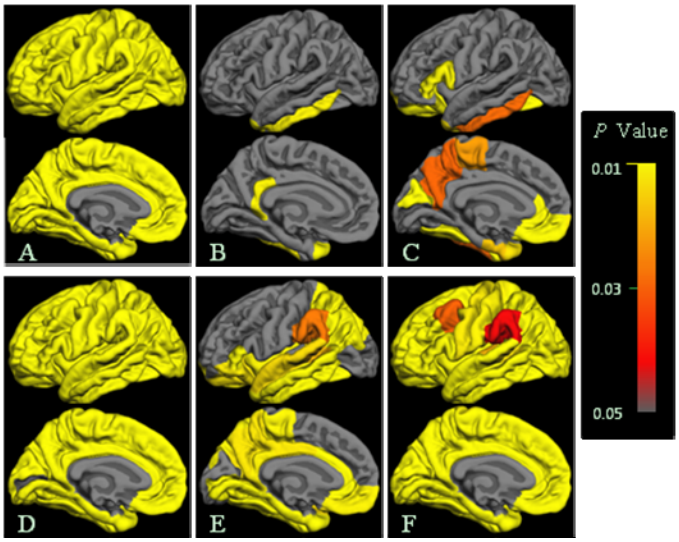

Fig 1. Gyral based Significance mapping of MANCOVA and ANOVA.
A. Collective comparison of 4 indices of MANCOVA among 4 groups and the last 3 groups.
B.C.D.E. ANOVA of single index comparison among 4 groups
F. MANCOVA sensitivity analysis with thickness excluded among 4 groups

Table 1 – Demographic information of subject groups

Group	N	Sex (M/F)	Age
Healthy young	36	18 / 18	29.92±10.25
Healthy eldly	44	23 / 21	76.11±6.55
MCI	39	27 / 12	75.44±7.31
AD	33	17 / 16	77.88±7.51

Table 2 — Parcellated gyral-based regions of interests

No.	Gyral Regions	No.	Gyral Regions
1	Caudal middle frontal gyrus	18	Lateral occipital gyrus
2	Lateral orbito frontal gyrus	19	Pericalcarine sulcus
3	Medial orbito frontal gyrus	20	Banks of superior temporal sulcus
4	Pars opercularis	21	Entorhinal cortex
5	Pars orbitalis	22	Fusiform gyrus
6	Pars triangularis	23	Inferior temporal gyrus
7	Rostral middle frontal gyrus	24	Lingual gyrus
8	Superior frontal gyrus	25	Middle temporal gyrus
9	Frontal pole	26	Parahippocampal gyrus
10	Paracentral lobulus	**27**	Superior temporal gyrus
11	Postcentral gyrus	28	Temporal pole
12	Precentral gyrus	29	Transverse temporal gyrus
13	Cuneus	30	Caudal anterior cingulate
14	Inferior parietal gyrus	31	Isthmus cingulate
15	Precuneus	32	Posterior cingulate
16	Superior parietal gyrus	33	Rostral anterior cingulate
17	Supramarginal gyrus	34	Insula

Discussion & Conclusion: In comparison with single index assessment, collective analysis of MANCOVA revealed global rather than region specific structural alterations that was age independent and differed significantly among healthy ageing, MCI and AD patients. Interaction of the single morphological indices led to the overlap in the heterogeneous regional alteration indexed by surface area, curvature, cortical thickness and subjacent white matter volume. Cortical thickness distinguished the most regional morphological alterations but was found not to be a major marker contributing to the global structural alteration among the aforementioned groups. Collective structural analysis with MANCOVA proved to be effective in differentiating MCI, AD and healthy ageing, which may potentially be useful for disease management in clinical practice.

References

1. Im K et al. NeuroImage. 2008; 43: 103-113
2. Ohnishi T et al. AJNR. 2001; 22: 1680-1685