MRI-Based Volumetry of Medial Temporal Lobe Possibly Predicts the Cognitive Decline in Alzheimer's Disease

H. Wang[1], L. Shu[1], J. Xie[2], H. Zhang[1], D. Zhang[1]

[1]Peking University Institute of Mental Health, Beijing, 100083, China, People's Republic of, [2]Department of Radiology, The Third Hospital Affiliated with Peking University, Beijing, 100083, China, People's Republic of

Purpose

With the prospect of disease-modifying drugs, reliable diagnosis of Alzheimer's disease (AD) at its earliest stages is increasingly important, because treatment effects may be most beneficial before the pathological progress is well advanced. A major clinical challenge is the objective, non-invasive tracking of biomarkers of neuronal and functional deterioration. Most previous neuroimaging studies reported that the amygdalohippocampal atrophy is associated with the onset and progression of AD. Measures of the volumes and rates of atrophy of these structures therefore should be a sensitive means of detecting the earliest changes in the disease [1, 2]. Given this premise, we hypothesized that dynamic medial temporal lobe atrophy could predict the progression of AD. Therefore, in this pilot longitudinal study, we used quantitative MRI techniques to investigate the role of MTL volumetry in predicting the cognitive decline among AD patients.

Methods

Eighteen patients meeting NINCDS-ADRDA criteria of probable AD (68 ± 8 years, 7 men, 11 women) were recruited for this 2-year follow-up study. All subjects provided their informed consent prior to entering the study. At baseline and 2-year after the baseline, all subjects underwent an MRI scanning and neuropsychological assessment. All MRI scans were performed on a 1.5-Tesla Siemens Magnetom MRI Scanner (Siemens Medical, Germany). Spin echo sequence was used to acquire the oblique coronal T1-weighted images (T1WI). The slices were perpendicular to the long axis of hippocampus (TR/TE = 500ms/15ms, matrix 256 x 256, slice thickness = 5mm, no gap). The oblique coronal T1WI covered the hippocampus, amygdala, and parahippocampal gyri (PHG). On the oblique coronal T1WI, the volumes of hippocampus, amygdala, and PHG were obtained as described previously [3]. The amygdala-hippocampal complex (AHC) combined the structure of hippocampus and amygdala. Briefly, an experienced investigator (intrarater reliability ICC = 0.98) obtained the ROIs of hippocampus, amygdala and PHG and calculated the volumes with an in-built program. The normalized volumetric ratio (NVR) to intracranial volume (ICV) was used for analysis. The cognitive function was assessed with the Mini-mental State Examination (MMSE), Wechsler Memory Scale-R (WMS-R), and AD Assessment Scale – Cognitive subscale (ADAS-Cog).

The percentage of change of each end-point measurement from the baseline measurement was used for statistical analysis. Paired sample t test was used to compare the difference between the baseline and end-point measurements. Correlation analysis was used to examine the relationship between the changes in cognitive function with the changes in normalized MTL volumes. Three-level regression analysis was deployed to investigate the utility of baseline measurements in predicting the change of cognitive function. In the first level, subjects' demographic background (age, education) was entered; in the second level, the baseline cognitive measurement was entered; and in the third level, the baseline normalized volumes of MTL regions were entered.

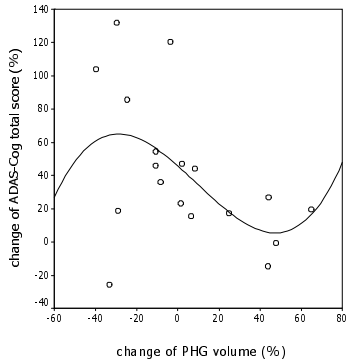

Figure 1. Curvilinear effects of PHG volumetric change on the change of ADAS-Cog total score among AD patients during 2-year follow-up examinations.

Table 1. The models predicting the change of the total score of MMSE, WMS-R and ADAS-Cog among AD patients in a 2-year follow-up (n = 18)

	MMSE change percentage			WMS-R change percentage			ADAS-Cog change percentage		
model	B	SE B	β	B	SE B	β	B	SE B	β
Background									
age	0.90	0.85	0.23	0.75	0.52	0.35	-0.73	1.22	-0.13
education	-12.43	7.08	-0.45	-3.11	3.84	-0.21	21.80	11.77	0.53
Cognitive measurement									
$MMSE_0$	2.02	1.72	0.31						
$WMS\text{-}R_0$				-0.29	0.43	-0.21			
$ADAS\text{-}Cog_0$							0.32	0.91	0.11
Normalized volume									
$hippocampus_0$	-155.28	63.00	-0.759*	-37.06	25.63	-0.33	42.11	66.19	0.14
$amygdala_0$				-12.26	31.68	-0.13	-145.93	78.15	-0.56
PHG_0	-31.95	26.70	-0.42	-2.72	13.64	-0.07	101.25	40.57	0.906*
AHC_0	102.88	54.96	0.77						

* $p < 0.05$ The subscript 0 indicates the baseline measurements.

Results

We observed a significant reduction of normalized hippocampal volume after 2-year follow-up ($p < 0.05$). The change of normalized volume of amygdala, PHG, and AHC was not statistically significant ($p > 0.05$). The total score of MMSE, WMS-R, and ADAS-Cog decreased significantly at 2 years after the baseline ($p < 0.001$).

As shown in Fig. 1, there was a curvilinear relationship between the change of ADAS-Cog total score and the change of normalized PHG volume ($R^2 = 0.25$, $p < 0.05$), suggesting the advanced PHG atrophy might be associated with the cognitive impairment in AD. The models predicting the changes in the score of MMSE, WMS-R, and ADAS-Cog are summarized in Table 1. It clearly shows that the baseline normalized hippocampal size is a significant predictor of the change in MMSE score, suggesting the baseline hippocampal size might be associated with the advanced cognitive decline in AD. Also, the baseline normalized PHG volume has a significant predictability for the change of ADAS-Cog total score. This further adds evidence that the advanced PHG atrophy is possibly related to the cognitive decline in AD.

Discussion

There are two major findings from this pilot study. Firstly, we observed a curvilinear effect of PHG volumetric change on the cognitive change measured with ADAS-Cog. The middle portion of the curve exhibits the ADAS-Cog score increases with the reduction of PHG volume, suggesting within this limit, the advanced PHG atrophy may be associated with the cognitive decline. The reason for the changing trend of such relationship at both ends of the curve remains unclear. One possible explanation is that beyond the optimal range of PHG volume, the PHG might be functionally overloaded or underloaded, and its capacity to modulate the cognitive function might be confounded by other brain structure-behavior associations. Secondly, our results show that baseline hippocampal size is a significant predictor for the change of MMSE score, and the baseline PHG size for the change of ADAS-Cog total score. These findings add more evidence that the baseline MTL volumetry is possibly useful to predict the cognitive decline in AD. Prior studies have produced equivocal findings concerning the advantage of MRI structural measures in tracking the progression of AD [4, 5]. Further longitudinal investigations with a larger sample, and on the therapeutic effect of AD drugs are certainly warranted. If the outcome is positive, it may be implicated that the structural technique could be used to monitor the progression of AD with or without AD drug treatment.

References

1. Jack CR, Jr., et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology 1999; 52:1397-403.
2. Chetelat G, Baron JC. Early diagnosis of Alzheimer's disease: contribution of structural neuroimaging. Neuroimage 2003; 18:525-41.
3. Wang H, et al. Diagnostic utility of neuropsychological performance and quantitative MRI-based measurement in Alzheimer's disease. Alzheimer Dis Assoc Disord 2004; 18:163-170.
4. Laakso MP, et al. Hippocampus in Alzheimer's disease: a 3-year follow-up MRI study. Biol Psychiatry 2000; 47:557-61.
5. Fox NC, et al. Presymptomatic cognitive deficits in individuals at risk of familial Alzheimer's disease. A longitudinal prospective study. Brain 1998; 121 (Pt 9):1631-9.