Possible Determinants of Brain Volumetric Alterations in Alzheimer's Disease

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Abstract: Several neuroimaging studies used the severity of specific regional atrophy for the grading of dementia. Finally, these studies suggested that hippocampus and total brain volume atrophy were the most critical finding in AD (Alzheimer's Disease). Among the new methods, MRI-Cloud (Magnetic Resonance Imaging-Cloud) is a recently developed free, automated web-based tool that performs automated segmentation and quantification of multiple MRI modalities and provides a platform to characterize anatomy.With its ability to analyze multiple modalities in the same anatomical framework this novel volumetric analysis system offers a multi-atlas fusion approach and provides a significant improvement in segmentation accuracy in comparison to the single-atlas based analysis methods. Here we retrospectively analyzed brain volumes of 50 AD patients with the aim to compare the changes brain regional changes of Alzheimer's patients linked to the degree of disease severity by using the novel MRI-Cloud measurement method. We have shown that AD patients exerted significant atrophy related to the disease severity although age, cognitive status, and sex differences were not determinants of the severity of AD.

Key words: Alzheimer's disease, MRI-Cloud, brain volume.

1. Introduction

AD (Alzheimer's disease) is characterized by the accumulation of amyloid plaques and neurofibrillary tangles that eventually lead to brain atrophy [1]. Several risk factors including TBI (traumatic brain injury), stroke and mood disorders have been shown to play a critical role in AD pathogenesis [2-5]. In the neuroimaging literature, it is stated that enlargement in the ventricles [6, 7] is a reliable sign of brain atrophy which is more common in the temporal lobe and the hippocampus. Furthermore, several studies indicated that there is a relationship between the degree of temporal lobe atrophy and the severity of dementia [8]suggesting the predictive role of brain imaging in the dementia prognosis. Thus, volumetric MRI (magnetic resonance imaging) has become a key role in diagnosis, research and clinical trials in dementia [9]. Finally, these studies have indicated that cognitive decline is strongly linked with brain and atrophy when it comes to key memory regions in AD pathogenesis,

such as hippocampus, temporal lobe and the cingulate gyrus [10-12]. Additionally, several neuroimaging studies used the severity of specific regional atrophy, such as, hippocampus and lateral ventricle, for the grading of dementia. Despite using different methods, these studies together suggested that hippocampus and total brain volume atrophy was the most critical finding in the AD [13-16]. Relatedly, decreased cortical thicknesses in temporal and parietal regions was strongly associated with AD [17, 18] suggesting the role of cortical thinning in neurodegenerative changes such as neuronal cell loss associated with Alzheimer's pathology [19]. More recently, new methods have been developed to identify morphological brain networks in individual patient based on structural MRI data [20, 21]. MRI-Cloud (www.MRICloud.org) [22, 23] is a recently developed free, automated web-based tool which performs automated segmentation and quantification of multiple MRI modalities and provides a platform to characterize anatomy (using T1 high-resolution-weighted images for volumetric

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analysis), white matter (using DTI (diffusion tensor images)), and resting-state functional connectivity, built on structure-based analysis. MRI-Cloud is a good example of the new knowledge-based approach that provides several advanced features. For instance, it can analyze all these modalities in the same anatomical framework, and facilitate the integration of information from multiple domains in a biologically meaningful set of structures. Thus, a number of studies have revealed that this novel volumetric analysis system offers a multi-atlas fusion approach that provides a significant improvement in segmentation accuracy compared to the single-atlas based analysis methods. Therefore, this imaging tool meets the requirements for a neuroimaging tool that is widely applicable to large-scale multimodal processing [22, 23]. Furthermore, the reliability and accuracy of MRI-Cloud for whole-brain segmentation, based T1-WIs, have been extensively validated [23-29]. Also, the test-retest reproducibility of MRI-Cloud structural quantification has shown that the reproducibility for T1-volumetric analysis was significantly higher than that obtained using other well-established methods such as Free Surfer and CONN-SPM, suggesting that it serves also a reliable tool for the interpretation of structure-based MRI studies, such volumetric measurements [23].

In our study, we aimed to compare the changes that may occur in the brain regions of Alzheimer's patients according to the degree of Alzheimer's by using the MRI-Cloud measurement method, which has not been used on MRI of Alzheimer's patients before.

2. Materials and Method

A total of 50 AD patients diagnosed by a neurologist with the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition) have been recruited in the retrospective study. We have screened the patients' cognitive status and radio imaging on the hospital records. MRI, MMSE (mini-mental status examination) [30], and dementia

severity staged on the CDR (Clinical Dementia RatingScale) are recorded.This study was performed at the Radiology, Neurology and Anatomy Department in Alanya Alaaddin Keykubat University, Alanya Training and Research Hospital. Informed consent (written) was delivered by their legal guardians for all patients.

The MMSE evaluated (5-10 min) the cognitive function with several cognitive domains: temporal and spatial orientation, working and immediate memory, attention, calculus, naming of objects, repetition of a sentence, execution of commands, comprehension, and writing task execution, comprehension and verbal task execution, planning, and praxis. This patient-based tool scored each correct answer from zero to a maximum of 30 points. A lower score has pointed to impaired cognition in individuals. The patients who had MMSE $\leq$ 26 have been enrolled in the study [31].

The CDR provides a means to categorize people with dementia according to stages. A score of 0 would indicate no dementia, a score of 0.5 is very mild dementia, whereas a score of 1, 2, or 3 would indicate mild, moderate, or severe dementia [32]. Six areas are covered, i.e., memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care.

2.1 Neuroimaging

Neuroimaging procedure was performed using a 1.5TMRI device (GE, SIGNA Explorer, General Electric, Milwaukee, US). Structural images were acquired using 3D T1 FSPGR (fast spoiled gradient recalled acquisition in the steady-state) sequence in the sagittal plane, using this parameter: TE =1.7ms, TR =5.95ms, flip angle =12°, acquisition matrix =256 × 256, FOV =256 × 256 mm^2, number of slices =170
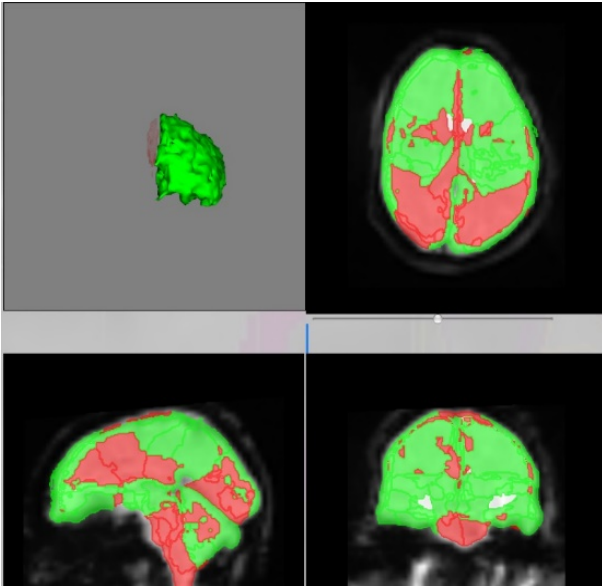
Fig.1 Axial, coronal and sagittal MRI-Cloud image of a patient.

and slice thickness =1.0mm. After the scanning procedure, volumetric image data were downloaded and transferred to a personal computer and processed to create header (HDR) and image (IMG) analyze formats using software (DTIS tudio). Saved HDR and IMG files of patients were uploaded to a free web-based module (www.mricloud.org) which is an automatic volumetric analysis system that works remotely through a web interface and provides reliable and consistent volumetric information of any submitted case. MRI Cloud provides a fully automated cloud service for brain parcellation of MPRAGE images based on Multiple Atlas Likelihood Fusion algorithm, JHU multi-atlas inventories with 286 defined structures, and an Ontology Level Control technology (https://mricloud.org). The atlas used for the processing of our data was the Adult_286labels_ 10atlases_V5L. The programme was designed to perform ROI-based image quantification for any type of brain MRI data (Fig. 1).

2.2 Statistical Analyses

Patients' clinical characteristics were presented as mean and SD (standard deviation) for continuous variables. Statistical analysis was done using the SPSS (Statistical Product and Service Solutions) package, version 21.0. The main variables in the study showed normal distribution (Kolmogorov-Smirnov test). Differences between the two groups (CDR 1 and 2) on the mean of brain areas, ages were assessed for significance using the Mann-Whitney U test. The frequencies of categorical variables were compared using Pearson χ^2 test, when appropriate. The level of significance for all comparisons was set at 0.05 (5%). MRI images of retrospectively scanned patients were divided into regions defined in the MRI-Cloud program and their specific measurements were performed.

3. Results

In this retrospective study, 30 male and 20 female AD patients have constituted the total sample size. While 28 participants were in stage of CDR 1, 22 were in CDR 2. Clinic and demographic data are summarized in Table 1.

There were no significant differences in age, gender, and MMSE in CDR groups. Table 2 shows the brain areas are significantly different between the groups (Mann-Whitney U test, $p<0.05$).

Table 1 Demographic and clinic features of the patients.

	All (n=50)	CDR 1 (n=28)	CDR 2 (n=22)	p
Age	69.10 (8.2)	70.21 (7.5)	69.36(6.7)	0.65
Male	70.2 (8)	71.05 (6.2)	70 (5.3)	
Female	68 (9.1)	69.52 (8.5)	68.52 (8)	
MMSE	17.62 (4.5)	19.45 (2.7)	15.53 (4.65)	0.56

$p<$ 0.05: significant; Mann-Whitney U test and Pearson correlation test; CDR: Clinical Dementia Rating; MMSE: Mini-Mental State Examination; n: Number of patients.

Table 2 The comparison of brain areas between CDR groups(mm^3).

Variable	CDR 1 (*n*=28)			CDR 2 (*n*=22)			*p*
Left side	Mean	SD	SE	Mean	SD	SE	
CerebralNucli_L	12457,83	5793,142	1207,954	9854,313	1638,987	409,7467	0.01
BasalForebrain_L	3752,174	2628,56	548,0927	2615,375	411,0166	102,7542	0.00
Mesencephalon_L	5756,826	2287,654	477,0089	4713,438	658,0552	164,5138	0.00
WhiteMatter_L	242686,5	74118,94	15454,87	211775	23496,24	5874,06	0.01
BasalGang_L	10630,7	5426,266	1131,455	8616,563	1419,948	354,987	0.01
Cerebellum_L	59855,78	14446,82	3012,37	48221,5	24402,25	6100,563	0.02
Pons_L	8527,87	2446,441	510,1182	17996,5	22286,25	5571,563	0.00
Putamen_L	4895,043	3725,769	776,8765	3384,375	662,6613	165,6653	0.00
Right side	Mean	SD	SE	Mean	SD	SE	
Diencephalon	8531,087	2766,361	576,8261	7284,625	1069,576	267,394	0.04
CerebralNucli_R	12396,39	4556,576	950,1119	10450,75	1638,082	409,5205	0.04
WhiteMatter_R	242005	76232,35	15895,54	212293,8	21432,51	5358,128	0.00
BasalGang_R	10492	4069,36	848,5202	9102,813	1484,195	371,0486	0.04
Cerebellum_R	60070,39	13171,56	2746,46	48270,25	24018,08	6004,519	0.02
Pons_R	8954,783	2256,682	470,5506	18855,31	22804,85	5701,213	0.00
Putamen_R	4851	3348,645	698,2408	3574,875	648,0661	162,0165	0.02

Mann-Whitney *U* test, *p*< 0.05: significant; CDR: Clinical Dementia Rating.

4. Discussion

It is widely known that there are several external and internal factors responsible for brain atrophy and neurodegeneration [2, 33-36]. Although critical clinical signs and biomarker changes indicate neuronal injury and neurodegeneration [37, 38], a pinpoint regional diagnosis was difficult until the development of novel neuroimaging methods, which enabled us to look inside the black box [39, 40]. These novel methods also link critical biomarker changes and the positive clinical signs with regional brain pathology [41, 42]. In this respect, many dynamic neuroimaging methods have enabled the evaluation of simultaneous brain changes related to disease, such as FDG-PET [43, 44].However, these methods have many disadvantages (i.e., radiation exposure and expense). Hence, these methods are not easy to apply in a simple clinical setting, which is a crucial blockage for systematic clinical research [45]. MRI, however, is an exception with its both dynamic and static properties. For instance, although MRI seems to be a static method, it can give us important clues regarding the neurodegenerative process if evaluated longitudinally.

Our study showed that atrophic changes in several brain regions were significantly correlated with disease severity as determined by CDR. Based on previous findings showing increased atrophy in advanced AD stages, this finding was not surprising.

For instance, some recent studies reported that the rate of whole-brain atrophy in AD is between 1% and 4% per year. In comparison, the rate of atrophy varies between 0.3% and 0.7% per year in people of similar age without AD [46], while regional brain atrophy has been defined for the frontotemporal type of dementia [47-49]. Also, in some MRI studies of early-stage Alzheimer's patients, significant volumetric reductions in the hippocampus, entorhinal cortex, posterior cingulate gyrus, amygdala, and parahippocampal gyrus have been reported [50]. Despite some inconsistencies, reporting no significant difference between total brain volumes [6], increased third ventricle volumes of Alzheimer's patients indicating hemispheric atrophy was a consistent

finding of AD. Thus, a recent study by Caspers et al. [51] applying AD Neuroimaging Initiative in 1,330 patients, found that most of the 1,323 patients with brain atrophy also had significant temporoparietal atrophy.

In conclusion, we have shown that AD patients exerted significant atrophy related to the disease severity. Beyond suggesting the role of volume alterations in AD, our findings also indicate that specific brain volume changes might indicate disease severity since age, cognitive status, and sex differences were not determinants of CDR. Further studies with larger sample sizes combined with multimodal imaging and cognitive tests are warranted.

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