Zamani, Jafar, Sadr, Ali and Javadi, Amir-Homayoun (2022) *Comparison of cortical and subcortical structural segmentation methods in Alzheimer's disease: A statistical approach.* Journal of Clinical Neuroscience, 99 . pp. 99-108. ISSN 0967-5868.

Comparison of Cortical and Subcortical Structural Segmentation Methods in Alzheimer's Disease: a Statistical Approach

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Running title: Structural Segmentation in Alzheimer's Disease

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Abstract

Background. Automated segmentation methods are developed to help with the segmentation of different brain areas. However, their reliability has yet to be fully investigated. To have a more comprehensive understanding of the distribution of changes in Alzheimer's disease (AD), as well as investigating the reliability of different segmentation methods, in this study we compared volumes of cortical and subcortical brain segments, using HIPS, volBrain, CAT and BrainSuite automated segmentation methods between AD, mild cognitive impairment (MCI) and healthy controls (HC).

Methods. A total of 182 MRI images were taken from the minimal interval resonance imaging in Alzheimer's disease (MIRIAD; 22 AD and 22 HC) and the Alzheimer's disease neuroimaging initiative database (ADNI; 43 AD, 50 MCI and 45 HC) datasets. Statistical methods were used to compare different groups as well as the correlation between different methods.

Results. The two methods of volBrain and CAT showed a strong correlation (p's<0.035 Bonferroni corrected for multiple comparisons). The two methods, however, showed no significant correlation with BrainSuite (p's>0.820 Bonferroni corrected). Furthermore, BrainSuite did not follow the same trend as the other three methods and only HIPS, volBrain and CAT showed strong conformity with the past literature with strong correlation with mini mental state examination (MMSE) scores.

Conclusion. Our results showed that automated segmentation methods HIPS, volBrain and CAT can be used in the classification of HC, AD and MCI. This is an indication that such methods can be used to inform researchers and clinicians of underlying mechanisms and progression of AD.

Keywords: volumetric T1-MRI; atrophy; automatic segmentation; dementia; volBrain; CAT; BrainSuite; HIPS

1 Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disease, contributing to 60-70% of dementia cases [1]. One important characteristic of AD is a significant loss of neurons and synapses, resulting in brain shrinkage and atrophy. Structural changes have been shown to be one of the earliest biomarkers that can be used in the diagnosis of AD, and mild cognitive impairment (MCI). Much effort has been devoted to find patterns of changes in the structure of different brain areas that can be reliably used for diagnosis of AD and MCI.

Earlier investigations relied mostly on manual segmentation of brain areas requiring a great deal of expertise and time. Therefore, the majority of the focus has been devoted to changes in the hippocampus due to its distinct structure. It has been shown that a loss in hippocampal volume can be an indication of AD. Further investigations have looked at subfields of the hippocampus, showing a nonuniform rate of neuroplasticity due to their specialisation [3]. For example, it has been shown that NFT begin in the medial temporal region and exhibit a characteristic distribution pattern across subfields, starting in the CA1 and later spreading to subiculum, CA2, CA3 and CA4/Dentate Gyrus [4].

With the development of semi- and fully-automated segmentation methods, however, it has now become easier and faster to segment not only the hippocampal area, but also other brain areas [5–9]. HIPpocampus subfield Segmentation (HIPS) [10], volBrain [11], Computational Anatomy Toolbox (CAT) [12,13], BrainSuite [14,15] and FreeSurfer [16] are some of the commonly used semi- and fully-automated methods. These methods, however, are still under development [17]. For example, CA1 segmentation in the FreeSurfer v5.3 was partially included in the subiculum [18] potentially explaining why the CA1 field was reported to be insensitive to AD pathology in some [19] but not all [20]. Similar findings have recently raised questions and concerns regarding the accuracy and consistency of these methods [21]. Therefore, it is important to investigate the accuracy of these methods further [22].

Benefiting from the computational power of automated methods, analysis of a large number of brain images has become more feasible. Large datasets of brain scans such as Minimal Interval Resonance Imaging in Alzheimer's Disease (MIRIAD) [23], and the Alzheimer's disease neuroimaging initiative database (ADNI) [24,25] public databases of Alzheimer's magnetic resonance imaging (MRI), offer a great opportunity to have a more comprehensive approach to the underlying mechanism and progression of AD. It also facilitates multisite studies to form a more accurate understanding of the disease.

Mini mental state examination (MMSE) is one of the commonly accepted measurements of cognitive ability, in particular in clinical settings. This measure has been widely used in classification of AD. For example, MIRIAD classifies participants with score between 12 and 26/30 as AD and those higher than 26/30 as healthy control. There is huge body of literature showing correlation between MMSE score and brain atrophy [26].

The aim of this study was to investigate the reliability of four automated segmentation methods of volBrain, CAT and BrainSuite for segmentation of the whole brain, and HIPS for segmentation of subfields of hippocampus, which belongs to the same analysis tool as volBrain. We used images belonging to MIRIAD. Correlation of the volume of each brain area with MMSE scores are also investigated. To investigate the reliability of the three methods volBrain, CAT and BrainSuite, the correlation of their common brain areas is also reported.

2 Material and Methods

2.1 Subjects

Our data analysis is based on data from 182 participants from two databases of Minimal Interval Resonance Imaging in Alzheimer's Disease (MIRIAD) (https://www.ucl.ac.uk/drc/research/research-methods/minimal-interval-resonance-imaging-alzheimers-disease-miriad) [23] , and the Alzheimer's disease neuroimaging initiative database (ADNI) (http://adni.loni.usc.edu) [24,25]. For details of the demographics please see Supplementary Table 1.

2.2 Magnetic Resonance Imaging (MRI)

Data was extracted from MIRIAD, and ADNI databases. All of the MIRIAD subjects underwent MRI scanning on a 1.5 T Signa scanner (GE Medical Systems, Milwaukee, WI, USA). T1-weighted volumetric images were obtained using an inversion recovery prepared fast spoiled gradient echo sequence with acquisition parameters time to repetition = 15 ms, time to echo = 5.4 ms, flip angle = 15°, TI = 650 ms, a 24-cm field of view and a 256×256 matrix, to provide 124 contiguous 1.5-mm thick slices in the coronal plane (voxels $0.9735 \times 0.9735 \times 1.5$ mm^3) [23]. Brain structural T1-weighted MRI data with 256×256×170 voxels and 1×1×1 mm^3 voxel size were extracted for ADNI subjects. ADNI data were obtained using an echo-planar imaging sequence on a 3T Philips MRI scanner.

2.3 Methods

HIPS and volBrain; The volumes of Cerebrospinal fluid (CSF), white matter (WM), grey matter (GM), brain hemispheres, cerebellum and brainstem were obtained using volBrain pipeline [11]. This method is based on an advanced pipeline providing automatic segmentation of different brain structures from T1 weighted MRI, Supplementary Figure 1. The preprocessing is based on the following procedure: (1) a denoising step with an adaptive non-local mean filter, (2) an affine registration in the Montreal Neurological Institute (MNI) space, (3) a correction of the image inhomogeneities, and (4) an intensity normalisation. (5) Afterwards, MRI images are segmented in the MNI space using non-local patch-based multi-atlas method. Images were corrected for intensity inhomogeneity, and the images were segmented into brain/non-brain using a semi-automated technique (MIDAS). The non-local means filter was applied to each pixel of the image by computing a weighted average of surrounding pixels using a robust similarity measure that takes into account the neighbouring pixels surrounding the pixel being compared. This segmentation method is based on the idea of non-local patch-based label fusion technique, where patches of the brain image to be segmented are compared with those of the training library, looking for similar patterns within a defined search volume to assign the proper label. HIPS and volBrain are used for segmentation of the hippocampus subfields and the rest of the brain, respectively [10].

CAT; Computational Anatomy Toolbox (CAT) is a powerful package for brain T1-MRI data segmentation, Supplementary Figure 2. It is a voxel base estimation method. The CAT preprocessing steps are as follows: (1) spatial registration to a template, (2) tissue segmentation into grey, white matter and CSF, and (3) bias correction of intensity non-uniformities. (4) Finally, segments are extracted by scaling the amount of volume changes based on spatial registration, so that the total volume of grey matter in the modulated image remains the same as the original image. For correction of the orientation and size of the brain, non-linear registration methods are applied to the image. Projection-based thickness (PBT) method is used for calculation of the cortical thickness and central surface. Spatial-adaptive non-local means (SANLM) and classical Markov random field (MRF) were used for image denoising. Adaptive Maximum a Posterior (AMAP) method was used for segmentation.

BrainSuite; BrainSuite is an open-source software tool that enables largely automated cortical surface extraction from MRI of the brain, Supplementary Figure 3. BrainSuite includes automatic cortical surface extraction, bias field correlation, cerebrum labelling, and surface

generation features. Also, this toolbox is used in tractography and connectivity matrix calculation in diffusion imaging data [14].

2.4 Statistical Analysis

Independent-sample t-tests are run to compare the volume of different brain areas between the AD and HC, AD and MCI, and MCI and HC groups for volBrain, CAT and BrainSuite for the whole brain, and HIPS for the hippocampus subfields. Bivariate-correlation analyses are also run to investigate the relationship between volume and MMSE scores for all four segmentation methods. Correlational analyses are run between the common brain areas in volBrain, CAT and BrainSuite to investigate the relationship between the three methods. Bonferroni correction is applied to account for multiple comparison by reduction of the p threshold.

3 Results

Using three automatic segmentation methods CAT, volBrain and BrainSuite, we segmented the whole brain, and using HIPS we segmented the hippocampus. For details of the values for each of the segmentation methods, see Supplementary Data for ADNI and MIRIAD databases. Using independent-sample t-tests we compared the volumetric data for AD and HC, AD and MCI, and MCI and HC for each segment. Supplementary Figures 4-7 show sample output images for one AD patient and one HC participant. Furthermore, we investigated the correlation of volumetric data with MMSE scores in AD and HC, AD and MCI, and MCI and HC groups.

CAT segmentation method returned data for 63 distinct brain areas. This method highlighted many brain areas that are significantly different between the AD and HC, AD and MCI, and MCI and HC groups, Table 1. In particular fusiform gyrus, parahippocampal gyrus, hippocampus, entorhinal cortex, amygdala, temporal gyri, thalamus, nucleus accumbens, insula, caudate and precuneus were significantly different. Importantly, the size of all these brain areas showed a strong correlation with MMSE scores. For further details see Supplementary Figures 8-10.

=== Table 1 ===

volBrain segmentation method returned data for eight distinct brain areas. In particular the amygdala, hippocampus, nucleus accumbens, thalamus and caudate were significantly different between the AD and HC, AD and MCI, and MCI and HC groups, Table 2. Again, the

size of all these brain areas showed a strong correlation with MMSE scores. For further details see Supplementary Figure 11-13.

=== Table 2 ===

BrainSuite segmentation method returned data for 50 distinct brain areas. In contrast to CAT and volBrain, this method highlighted only six brain areas that are significantly different between the AD and HC, AD and MCI, and MCI and HC groups, Table 3. These brain areas included temporal gyri, third ventricle, supramarginal gyrus and angular gyrus. Similar to previous segmentation methods, all these brain areas showed strong correlation with MMSE scores. For further details see Supplementary Figures 14-16.

=== Table 3 ===

HIPS segmentation method returned data for the whole hippocampus and five of its subfields: CA1, CA2-CA3, CA4/Dentate Gyrus, Subiculum and strata radiatum/lacunosum/moleculare (SR-SL-SM). All these areas showed a significant difference between the AD and HC, AD and MCI, and MCI and HC groups, Table 4. The size of hippocampus and all its subfields showed strong correlation with MMSE scores. For further details see Supplementary Figure 17-19.

=== Table 4 ===

To investigate the relationship between the three whole-brain segmentation methods CAT, volBrain and BrainSuite, we ran correlational analysis, Table 5. Seven brain areas were common between these methods: nucleus accumbens, amygdala, caudate, globus pallidus, hippocampus, putamen and thalamus. CAT and volBrain showed strong correlation for nucleus accumbens, amygdala, caudate, hippocampus and thalamus. Two brain areas globus pallidus and putamen were not significantly correlated. These brain areas did not show significant difference between the AD and HC, AD and MCI, and MCI and HC groups either. BrainSuite, however, showed no significant correlation with either of the other two segmentation methods. For further details see Supplementary Figures 20-22.

=== Table 5 ===

4 Discussion

We used HIPS automated method to segment the subfields of hippocampus, and CAT, volBrain and BrainSuite automated methods to segment the whole brain using T1 weighted MRI data. Our results showed that all subfields of hippocampus in the Alzheimer's Disease (AD) and

mild cognitive impairment (MCI) groups were significantly smaller than those of the healthy control (HC) group. The atrophy of all subcomponents of hippocampus were correlated with the MMSE measure. Quite a large portion of cortical and subcortical areas in the brain were also smaller in the AD, and MCI groups as compared to the control group, as evident from CAT and volBrain segmentation results. The shrinkage in these brain areas mostly showed a strong correlation with MMSE measure. BrainSuite failed to discriminate between the two groups. While CAT and volBrain shows a strong correlation, BrainSuite did not show any significant correlation with CAT and volBrain.

With the advancement of computational methods, fine-grain analysis of the brain areas is more feasible. Earlier methods relied heavily on manual segmentation of the brain areas, which was extremely time demanding and also required a great level of expertise. Therefore, the majority of the analysis was limited to brain areas with more distinct structure, such as the hippocampus. Many semi- and fully-automated segmentation methods have been developed. While these methods have been used more commonly in recent years, the reliability and accuracy of these methods was yet to be fully studied. We used four pipelines of HIPS [10], volBrain [11], CAT [12,13] and BrainSuite [14]. In this study we evaluated their reliability by looking at their ability to discriminate between AD and HC, AD and MCI, and MCI and HC groups with ADNI and MIRIAD databases, whether a correlation existed between them, their correlation with MMSE scores, and comparing their results with past literature. Our results showed strong reliability of HIPS, volBrain and CAT. These methods have been successfully applied to brain images from those with AD and MCI [27].

BrainSuite, however, underperformed greatly. For example, it failed to accurately segment the hippocampus, thalamus and amygdala to show a significant difference between the two groups. While this automatic segmentation method has been used frequently in past research [28], its application has been mostly limited to the processing of brains with no atrophy [29], as well as detection of gross segments such as tumours [30]. Given that early AD is so difficult to recognise, being able to detect atrophy represents a crucial aspect to diagnosing AD earlier and consequently providing such subjects with better preventative measures, thus helping to ensure an extended period of higher quality of life for these individuals. This highlights the importance of validation studies such as ours to gain a greater understanding of the applications and limitations of different methods [31], especially considering the greater accuracy and speed identified with our method.

The volume of the hippocampus is considered as an important biomarker for AD and has been included in recently proposed research diagnostic criteria. It has been shown that the hippocampal atrophy estimated on anatomical T1 weighted MRI can help in classifying the different stages of AD. Confirming past literature, our results showed that the hippocampus volume significantly differed between AD and the HC, MCI and HC.

Histological studies have shown that lesions are not uniformly distributed within the hippocampus. Neuronal loss results in a reduction of the thickness of the layers richer in neuronal bodies, while the loss of synapses results in the reduction of the layers poorer in neuronal bodies and these changes are stage-dependent [32]. Our results, however, failed to differentiate the contribution of these subfields in AD; they all showed significant reduction in size, compared to the control group. This effect could be because our AD group consisted of those with later stages of AD. The contribution of different subfields of the hippocampus is more visible in those with MCI [33].

While the contribution of atrophy in the hippocampus has been widely studied, the role of atrophy in the rest of the brain in AD is less clear [17]. An important contributing factor is that the boundaries of the hippocampus are easier for human operators or automated algorithms to recognise than other brain areas such as the amygdala, entorhinal cortex or thalamus [17]. Due to methodological advances, however, it is now possible to measure atrophy across the entire cortex with good precision. Our results from CAT and volBrain methods showed strongly significant differences between many brain areas such as the amygdala, thalamus, nucleus accumbens, insula and caudate. These findings are in-line with past literature showing similar differences in these brain areas [17].

There is a growing body of literature showing a correlation between cognitive decline and brain atrophy. For example, it has been shown that basal forebrain changes are correlated with cognitive decline in MCI and AD patients, as measured with recall task and MMSE, as well as healthy participants that later progressed to AD. Atrophy of other brain areas such as lateral and medial parietal cortex, as well as lateral temporal cortex have also been shown to have a correlation with cognitive decline [34]. Our results showed a strong correlation between brain atrophy and cognitive decline as measured by MMSE. All brain areas that were significantly different between the AD and the control group showed a significant correlation with MMSE, except for the caudate (CAT $p = 0.001155$, volBrain $p = 0.005091$, Bonferroni corrected statistic not significant). While the effect of shrinkage of the caudate in AD is not very clear, there is some evidence that caudate volume has a correlation with MMSE measures, although

not as strongly as other brain areas such as the thalamus [35]. An important consideration is that atrophy in the left caudate has a stronger role in AD, as compared to the right caudate [36]. Our analysis combined both the left and right caudate, which may have led to this inconsistency between our results and previous literature.

Although AD commonly presents as an amnestic syndrome, there is significant heterogeneity across individuals, which is accompanied by different atrophy patterns [26]. For example, while those with more language difficulties might exhibit greater atrophy in temporal or parietal regions, those with more visual difficulties might have greater atrophy in posterior cortical regions [37]. Availability of the automated systems offers many opportunities, such as the ability to analyse a large number of brain images with reasonable time and expertise. This is in particular very appealing, considering the increased number of large datasets such as MIRIAD and ADNI. Automated systems can go through the collection and aggregate data from a wide range of participants, healthy and patients to gain a greater understanding of AD. Methods with advanced accuracy and speed can analyse such banks with accuracy such that their applicability to clinical settings is inevitable with ongoing technological and practical advancements. This is important considering the heterogeneity of the disease and its progression.

Another application of automated systems is in clinical settings. By the time of diagnosis, rapid ongoing atrophy is already far advanced. Early diagnosis of AD in MCI stage can help with deceleration of the progression of the disease. This is particularly important as there are modifiable factors that can help with brain health. Therefore, a massive effort has been devoted to the development of diagnostic methods to enable researchers and clinicians to detect AD and MCI and cases with potential progression to AD, as early as possible. For the development of preventive strategies, it is important to predict future brain atrophy, as this may aid in identifying which individuals with normal cognition are more susceptible of progressing to later stages of AD [38]. Clinician's reliance on their own expertise and subjective judgements arises from caution held over automated systems due to their lower performance. However, with recent developments and methods, automated systems can provide additional information to clinicians, enabling them to have a greater understanding of the progression of the atrophy [39]. Some of these methods have already received approval from different licensing bodies such as CE (European conformity) and FDA (food and drug administration, USA) approval. These methods, however, come with some limitations such as speed of processing, expensive licences, or requirement of other specialised software. This study is another step to evaluate freely available analytical tools to achieve an ideal analysis pipeline, suitable for researchers

and clinicians. Ultimately, such work serves to aid clinicians in their diagnoses of future MCI and thus AD, as well as to help improve the preventative measures taken to help secure a greater quality of life for subjects with AD. Clinicians still rely heavily on subjective judgement, which requires great expertise. Agreeing with the reviewer, clinicians use automated segmentation methods very cautiously due to their poor performance. Therefore, development of methods such as the one suggested in this study can pave the way for further application of automated methods in clinical settings.

Availability of the reliable automated segmentation methods enables researchers and clinicians to have a greater understanding of the underlying mechanisms and the progression of the AD. This will allow them to attempt to prevent or decelerate the progression of the disease more effectively. This rate can be helpful to have a more informed understanding whether an individual with MCI will later progress to AD or not. The output of automated segmentation methods can also be used in training of intelligent classification methods such as those using artificial neural networks and support vector machines, which has shown promising results [40]

The purpose of this article was not to identify the superiority of any particular automatic segmentation method over another, but to solely highlight possible limitations and applications of four commonly used segmentation methods. We proposed that CAT, volBrain and HIPS are methods that can robustly operate on brain images with significant atrophy and can be used in research and clinical settings. BrainSuite, however, should be used with caution for brain images with atrophy.

Authors' Contribution

JZ analysed the data. ZJ and AHJ interpreted the results. JZ and AHJ wrote the manuscript. JZ, AHJ and AS revised the manuscript.

Conflict of Interest

Authors claim no conflict of interest.

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