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Localizing the Thickness of Cortical Regions to Descriptor the Vital Factors for Alzheimer's Disease Using UNET Deep Learning

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Abstract. Alzheimer's disease (AD) stands as a formidable global health challenge, impacting millions of lives. Timely detection and localization of affected brain regions are pivotal for understanding its progression and developing effective treatments. This research introduces a cutting-edge approach to address these critical concerns. Traditionally, exploring the influence of AD on the human brain has been a complex task. Existing methods often face limitations in accurately localizing the most affected brain regions, impeding our understanding of the disease's focal impact. Additionally, the need for efficient and precise cortical thickness analysis techniques has driven the quest for innovative solutions. In this paper, we proposed the DL+DiReCT method, a high-precision strategy that integrates deep learning-based neuroanatomy segmentations with Diffeomorphic Registration-based Cortical Thickness (DiReCT). This approach streamlines the measurement of cortical thickness, enabling rapid and precise localization of AD-affected regions within the brain. Our method significantly contributes to enhancing our understanding of the localized effects of Alzheimer's disease. Our extensive study, involving 434 subjects from the ADNI dataset and rigorous data augmentation and optimization, has yielded remarkable outcomes. This approach has far-reaching implications for discerning the specific regions of the brain affected by AD, shedding light on their consequences for essential physiological factors.

1 Introduction

The human cerebral cortex, a thin strip of gray matter forming the outermost layer of the brain, naturally diminishes in thickness with age [1].

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This process is known to accelerate in neurodegenerative diseases, including dementia [2]. It is well-established that cortical thickness rapidly decreases in cases of dementia. Alzheimer's disease, for instance, typically initiates within the cortex before extending into the temporal lobe, followed by its progression to other brain regions in a well-defined sequence during the later stages of the disease [3]. Several studies have demonstrated that cortical thickness can serve as an alternative marker for fundamental pathological changes [4, 5].

Registration-based solutions rely on segmenting the tissue compartments of white matter (WM) and gray matter (GM). Assuming that WM/GM interfaces share a common topology, a thickness map is derived from the distance between corresponding points [6]. An open-source implementation of the DiReCT cortical thickness algorithm in ANTs is available as part of the ANTs cortical thickness pipeline. It applies DiReCT to the segmentation derived from Atropos, an atlas-based segmentation method [7].

Regarding neuroanatomy segmentation, many recent publications have shown the superiority of DL over traditional methods [8]. We assume that registration-based thickness measures benefit from more accurate and reliable parcellation than typically available from atlas-based methods. Therefore, we propose DL+DiReCT: a deep learning-based neuroanatomy segmentation, including cortical parcellation followed by DiReCT to directly extract cortical thickness measures from T1-weighted magnetic resonance imaging (T1w). We have demonstrated its reliability through extensive validation experiments on the ADNI dataset, showcasing its capability to detect regional atrophy patterns in Alzheimer patients. Cortical parcellation is one of the methods contributing to identifying the most affected brain region, which directly affects vital factors associated with that brain area [9]. The brain is divided into several regions, 32 parts [10], responsible for many vital factors that could be affected if the region is damaged due to the progression of Alzheimer's disease in that area.

2 Material and methods

Brain structure localization has been performed using a number of methodologies, including statistical shape model-based methods, atlas-based localization, spatial relation-based localization, manual localization, and deep learning-based detection strategies [11,12]. Manual localization procedures involving brain structures need the expertise of professional operators, including radiologists [13].

2.1 Deep learning Anatomy Segmentation

Deep Learning (DL) is considered a promising technique for the analysis of medical images, with image segmentation currently being the most prevalent application of DL in neuroimaging [14]. However, adopting deep neural networks for advanced tasks such as extracting biomarkers or directly predicting diagnoses faces a challenge due to the lack of interpretability, especially in clinical applications where model confidence and result traceability are essential.

This study employed the UNet DL model for neuroanatomy segmentation, a pivotal component in our innovative DL+DiReCT method [15]. The UNet architecture, structured with interconnected convolutional blocks, was trained on a dataset comprising 434 T1-weighted MRI images. Supervised learning utilized Free-Surfer 6.0 to achieve segmentation of Gray Matter (GM) and White Matter (WM). To enhance the granularity of our analysis, we further divided brain regions into 32 distinct parts based on a segmentation protocol established in prior work [16] see Fig. 2. This segmentation protocol leveraged state-of-the-art deep learning algorithms. The comprehensive dataset and segmentation strategy aimed to capture intricate nuances in neuroanatomy, providing a solid foundation for subsequent cortical thickness analysis. The training process involved rigorous optimization, and the resultant UNet model demonstrated proficiency in accurately delineating neuroanatomical structures. Subsequently, the DL+DiReCT method seamlessly integrated the UNet-based anatomy segmentation with Diffeomorphic Registration-based Cortical Thickness (DiReCT) analysis, see Fig**. 1**. The proposed method was applied to a three-dimensional ADNI dataset. The hippocampal volumes (AD/MCI vs. NC) are then compared using a boxplot. Effect size (Cohen's d) Would give an indication of how much each part is affected; the large effect size represents more affected.

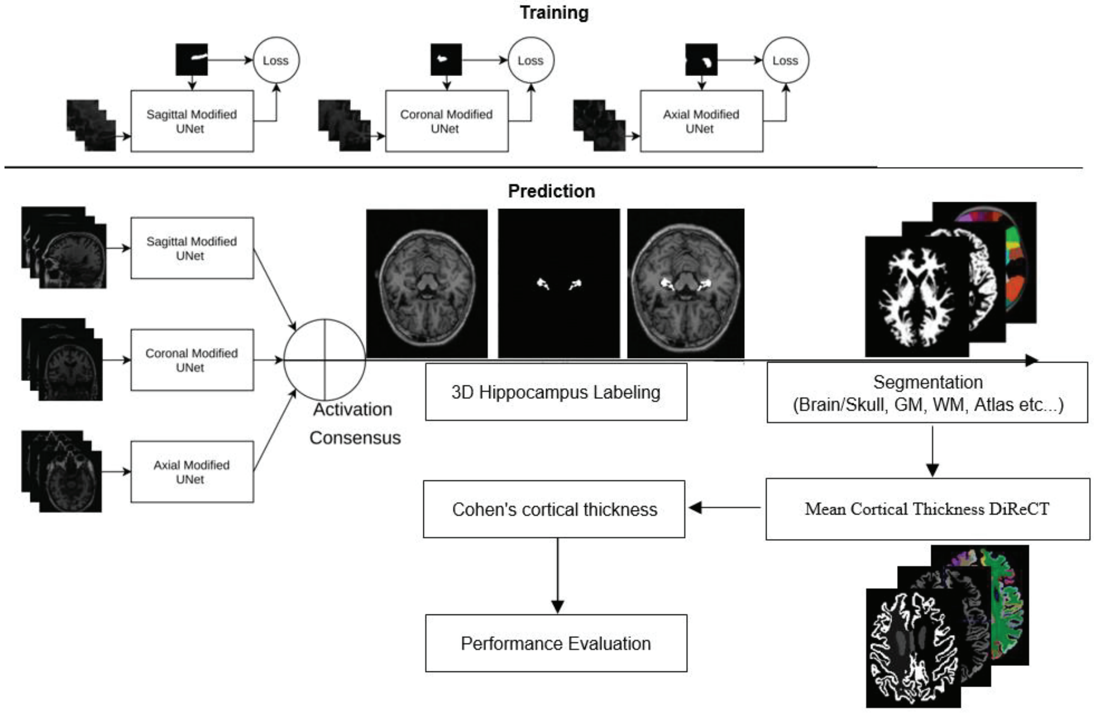

Fig. 1. Strategy of the proposed method of segmentation and DiReCT cortical thickness.

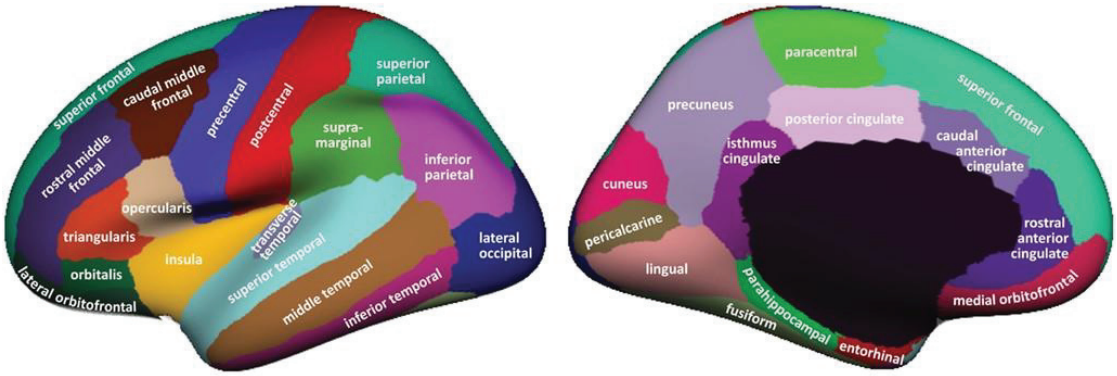

Fig. 2. The 32 cortical regions are the most common anatomical regions [16].

2.2 Cortical thickness UNet DiReCT

The probability maps obtained from the UNet segmentation are used as input to DiReCT. The cortical thickness of the brain regions is calculated to obtain the magnitude of Cohen's effect that would give an indication of how much each part is affected. Knowing the extent to which each part is affected contributes to knowing the vital factors associated with the part of the brain that is most affected, where it is considered large effect size are more affected region, see Fig. 3.

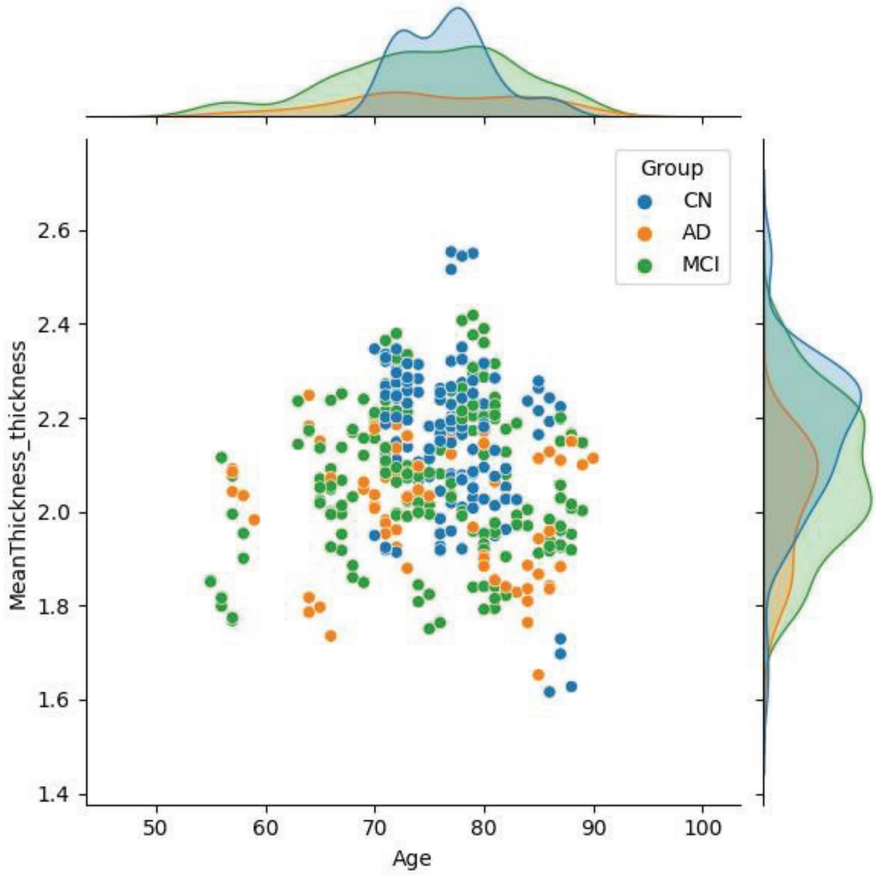

Fig. 3. Global mean cortical thickness [mm] against age for the three stages of Alzheimer

2.3 Results and Discussions

The proposed DL+DiReCT method was applied to a comprehensive three-dimensional ADNI dataset. In order to assess the impact on hippocampal volumes, a comparison was conducted between Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) groups versus Normal Control (NC) subjects. The outcomes were vividly illustrated using boxplots, providing a visual representation of the differences in hippocampal volumes across these groups. Effect sizes, quantified using Cohen's d, were calculated to gauge the magnitude of the impact on each segmented brain region. A larger effect size indicated a more pronounced influence, offering a nuanced understanding of the relative severity of the impact on different parts of the brain. The application of Cohen's d served as a valuable metric for discerning the extent to which each brain region is affected, contributing to a more comprehensive characterization of the localized manifestations of Alzheimer's disease.

The segmentation results obtained through the UNet deep learning model were systematically compared with Free-Surfer, a well-established tool in neuroanatomy segmentation. The evaluation, measured through median Dice coefficients, demonstrated remarkable accuracy in delineating brain tissue. Specifically, the median Dice coefficients achieved an impressive 0.97 for WM and 0.95 for GM. The Dice coefficients, reflecting the degree of overlap between the segmented regions and ground truth, signify a high level of concordance between the UNet-based segmentation and Free-Surfer. These outstanding results underscore the efficacy of our UNet model in accurately capturing intricate neuroanatomical structures. To contextualize our segmentation performance, DICE was calculated and compared with relevant works in the field. Our method's superior performance, as indicated by the high Dice coefficients, positions it as a state-of-the-art approach in neuroanatomy segmentation.

$$DICE = \frac{2\sum_i^N p_i g_i}{\sum_i^N {p_i}^2 + \sum_i^N {g_i}^2}$$

Where: N sums run voxels of segmentation $pi \in P$, and the ground truth volume $gi \in G$.

The proposed DL+DiReCT method was employed to calculate cortical thickness across different stages of Alzheimer's disease, utilizing Cohen's d as a metric for effect size. The resulting cortical thickness maps, as illustrated in Fig. 4, provide a comprehensive visualization of the localized impact on various brain regions. Cohen's d facilitated a nuanced understanding of the magnitude of cortical thickness alterations, with larger effect sizes indicating more significant impacts. Focuses on the specific measurement of cortical thickness in the hippocampus across different stages of Alzheimer's disease. This dedicated analysis sheds light on the region-specific variations in cortical thickness, contributing valuable insights into the progressive nature of the disease within this critical brain structure. The application of Cohen's d in conjunction with visual representations enhances our ability to discern and quantify the severity of cortical thickness changes, providing a detailed characterization of Alzheimer's disease progression.

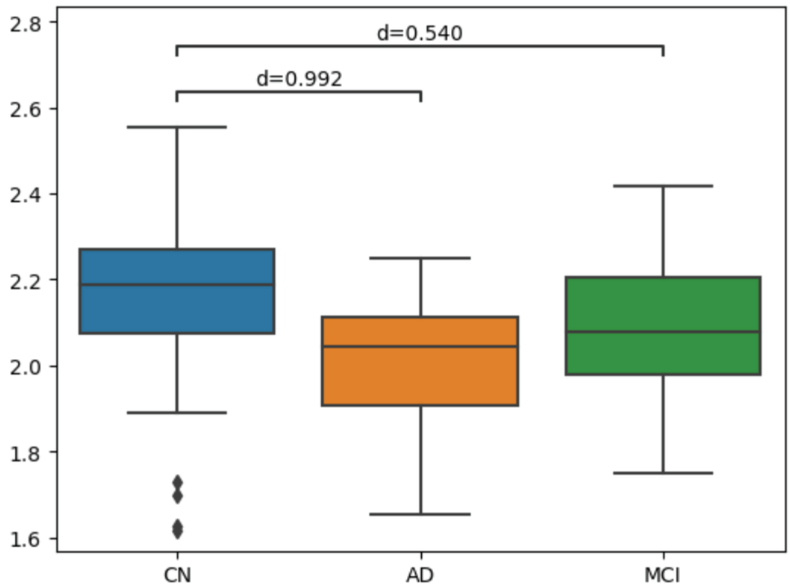

Fig. 4. Cortical thickness of the Alzheimer stages Cohen's size.

Fig**. 6** 6 provides a visual representation of the cortical thickness detection process in conjunction with the original brain image. This visualization showcases the integration of the DL+DiReCT method in detecting and measuring cortical thickness across the entire brain.

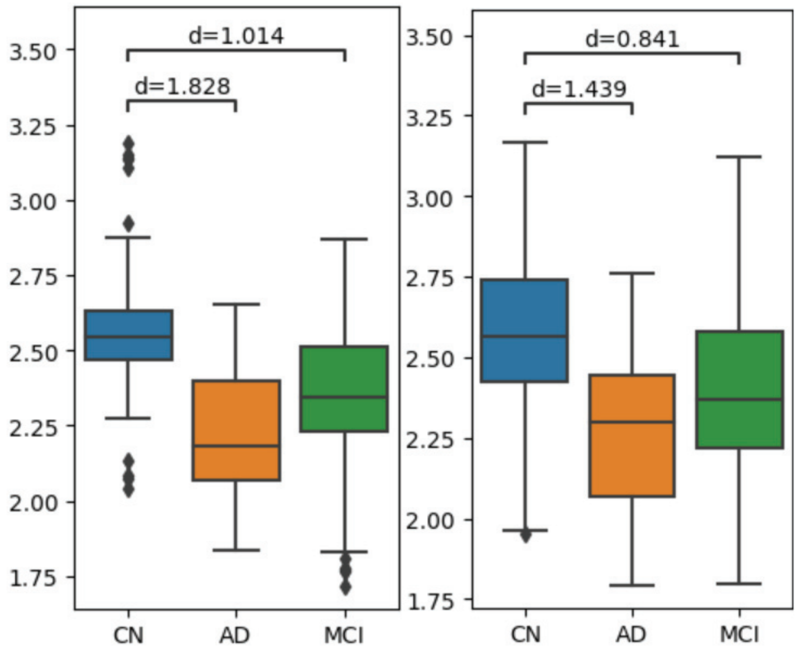

Fig. 5. Cortical thickness of Left Hippocampus and Right Hippocampus for Alzheimer's stages.

By overlaying the cortical thickness information onto the original brain image, the intricate patterns and variations in cortical thickness become apparent.

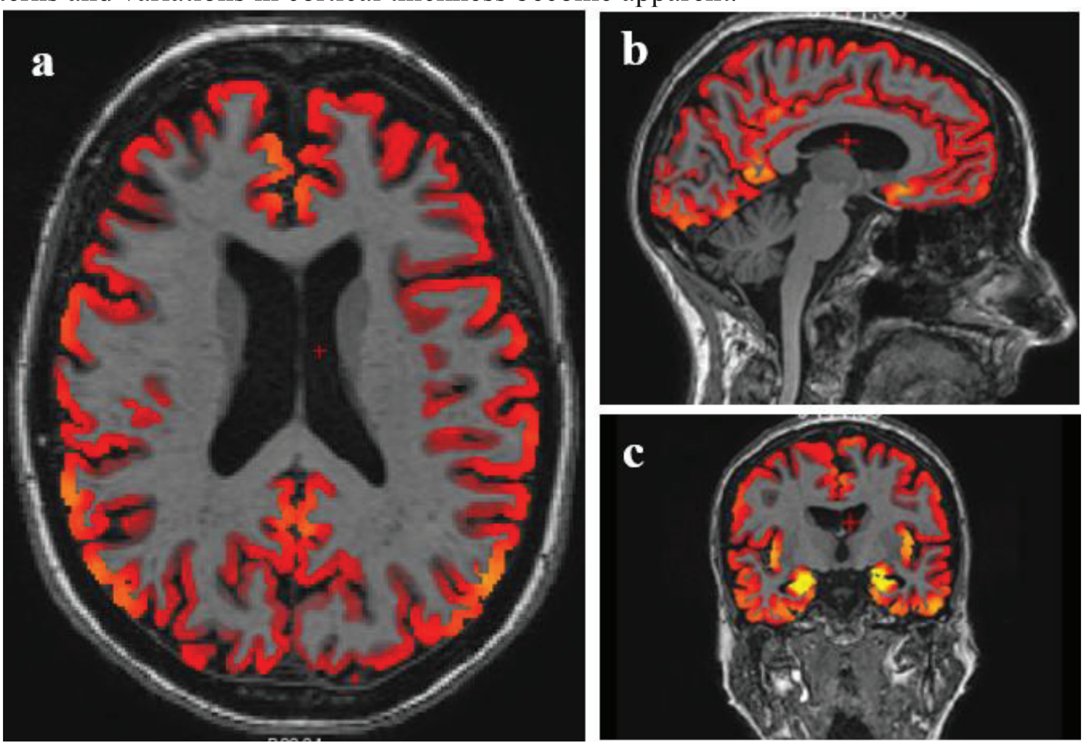

Fig. 6. Visualization of the cortical thickness with the original image, (a) Coronal slice, (b) Sagittal slice, and (c) Axial slice.

Table 1 presents a comprehensive comparison of Dice coefficients obtained through the segmentation process using the UNet deep learning model. Our results are juxtaposed with findings from previous studies, providing a benchmark for the performance of our segmentation methodology. The Dice coefficients serve as a quantitative measure of the segmentation accuracy, reflecting the degree of overlap between the segmented regions and the ground truth. The comparison showcases the efficacy of our UNet-based segmentation, highlighting its superior performance when compared to established methods in the field. This quantitative assessment, presented in Table 1, reaffirms the robustness of our segmentation approach and positions it as a state-of-the-art method for neuroanatomy segmentation, contributing to the advancements in accurate brain tissue delineation.

Table 1. Calculated validation DICE results of our work and compare with related.

Ref.	Method	DICE
Isensee et al. 2018 [17]	3D UNet	0.86
Thyreau et al. 2018 [18]	Hippodeep	0.85
Roy et al. 2019 [19]	QuickNat	0.80
Carmo et al. 2021 [20]	E2DHipseg	0.90
Proposed	UNet + DiReCT	0.95

The cortical thickness of the brain regions was calculated by Cohen size, and the affected areas were compared as shown in Table 2, where it is considered that large effect sizes are more affected regions. As expected, the dementia groups have, on average, a thinner cortex than the healthy (CN) shown in Table 2.

Table 2. Mean cortex thickness for Alzheimer's disease stages.

Group	Age	Mean Thickness
CN	76.660000	2.164460
MCI	74.621359	2.097808
AD	75.324675	2.015164

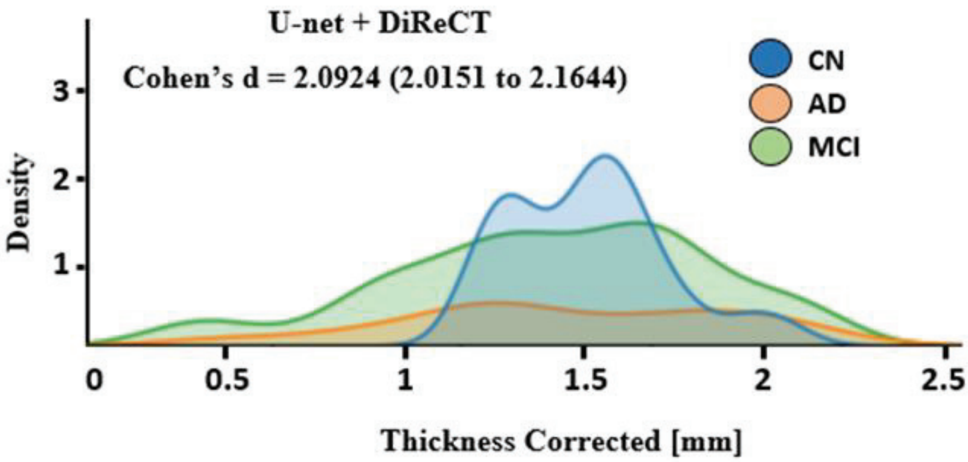

Fig. 7. Density diagrams of the corrected global mean thickness, depicting the size of the effect (Cohen's d) between HC, MCI, and AD.

Table 3. Region of Interest (ROI)

Method	ROI average
Free Surfer 6.0	1.402%
ANTs	3.149%
UNet + DiReCT	1.287%

The categorization of affected regions based on effect size in Table 4 offers a pragmatic insight into the nuanced variations in cortical thickness across the brain, contributing to a more targeted understanding of the disease's impact on specific brain regions. Table 3 categorizes regions with a large effect size, indicative of more pronounced alterations in cortical thickness. The consideration of effect size serves as a valuable indicator for the relative severity of impact across different brain regions. This comprehensive assessment further refines our understanding of the localized manifestations of Alzheimer's disease, pinpointing regions that are particularly susceptible to cortical thickness changes.

Table 4. A sample cortical thickness [mm] of the brain regions of the proposed method

Subjects		Image1	Image2	Image3	Image4
Lingual	Lift	0.6738570	0.6237830	0.5382350	0.5671290
	Right	0.6382950	0.6578570	0.5301410	0.5046190
Caudal Middle Frontal	Lift	0.4924505	0.4726962	0.5046647	0.5178191
	Right	0.4646207	0.4594334	0.5267705	0.5045786
Para Hippocampal	Lift	0.6420116	0.6297252	0.6045252	0.4302070
	Right	0.6750260	0.7013940	0.5184135	0.5030450
Middle Temporal	Lift	0.7177250	0.6780165	0.7052521	0.5867494
	Right	0.5901585	0.5604476	0.6690766	0.5349538
Precentral	Lift	0.5784770	0.5911390	0.5678920	0.5665920
	Right	0.5889970	0.6179320	0.5924940	0.5868410

Image1: 002_s_0413_140657, Image2: 002_S_0413_I64551, Image3: 005_S_0324_I32777, Image4: 005_S_0814_I85469

3 Conclusion

In conclusion, our research introduces a transformative approach for the precise localization and measurement of cortical thickness in Alzheimer's disease using the DL+DiReCT method. Leveraging the power of UNet deep learning for neuroanatomy segmentation and DiReCT for cortical thickness analysis, our method demonstrates superior accuracy, as evidenced by high Dice coefficients in comparison to traditional segmentation methods. The application of Cohen's d allows for a nuanced understanding of the impact of Alzheimer's disease on cortical thickness across various brain regions. Our findings, showcased in **Fig.** 4, Fig. 5, and **Fig. 6**, provide a comprehensive visualization and measurement of cortical thickness alterations, enabling researchers and clinicians to discern localized manifestations within the context of the original brain anatomy. Table 1 consolidates our segmentation results with previous studies, affirming the robustness of our UNet-based segmentation approach.

Additionally, Table 2 and Table 4 categorize affected brain regions based on large effect sizes, offering valuable insights into regions more susceptible to cortical thickness changes. The DL+DiReCT method significantly advances the field by not only improving our understanding of Alzheimer's disease progression but also by providing a practical tool for diagnosis and research. This innovative methodology contributes to the identification of vital factors affected by regional damage, paving the way for more targeted interventions and personalized treatment strategies. In summary, our research offers a comprehensive framework for studying Alzheimer's disease at a localized level, bringing us closer to a more precise, insightful, and effective approach to diagnosis, management, and research in the realm of this debilitating condition.

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