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CORTICAL THICKNESS ALTERATIONS IN ALZHEIMER'S PROGRESSIVE MEMORY IMPAIRMENT CONTINUUM: A NETWORK PERSPECTIVE

ALZHEIMER'İN İLERLEYİCİ BELLEK BOZUKLUĞU SÜREKLİLİĞİNDE KORTİKAL KALINLIK DEĞİŞİMLERİ: AĞ PERSPEKTİFİ

Gözde KIZILATEŞ EVİN[1,2], Ali BAYRAM[3], Elif KURT[3], Emre HARI[4], Çiğdem ULAŞOĞLU YILDIZ[3], Hakan GÜRVİT[5], Tamer DEMİRALP[4]

[1]İstanbul University, Graduate School of Health Sciences, İstanbul, Türkiye
[2]İstanbul University, Hulusi Behcet Life Sciences Research Laboratory, Neuroimaging Unit, İstanbul, Türkiye
[3]İstanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Neuroscience, İstanbul, Türkiye
[4]İstanbul University, İstanbul Faculty of Medicine, Department of Physiology, İstanbul, Türkiye
[5]İstanbul University, İstanbul Faculty of Medicine, Department of Neurology, Behavioral Neurology and Movement Disorders Unit, İstanbul, Türkiye

ORCID IDs of the authors: G.K.E. 0000-0001-5518-6015; A.B. 0000-0002-6588-3479; E.K. 0000-0003-1956-575X; E.H. 0000-0002-8329-5507; Ç.U.Y. 0000-0003-1849-0055; H.G. 0000-0003-2908-8475; T.D. 0000-0002-6803-734X

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ABSTRACT

Objective: Alzheimer's Progressive Memory Impairment Continuum (PMIC) is typically the clinical reflection of the neurofibrillary tangle (NFT) spread of Alzheimer's disease (AD), which starts with subtle memory complaints of subjective cognitive impairment (SCI), passes through objectifiable memory problems of the amnestic mild cognitive impairment (aMCI), and finally reaches the dementia stage of multiple cognitive deficits with an amnestic core (ADD). This study evaluated the patterns of cortical thickness changes across the PMIC, using a network perspective to unravel structural and functional disruptions.

Material and Methods: The study included 88 participants: 21 with mild ADD, 34 with aMCI, and 33 with SCI. Clinical and neuropsychiatric evaluations were conducted, followed by structural MRI scanning for cortical thickness measurements. Vertex-wise cortical thickness analyses were conducted using ANCOVA. Age, gender, and education were covariates.

Result: The results showed significant cortical thinning across the PMIC, with more pronounced reductions in the ADD group. The cortical thinning overlapped with the Default Mode Network (DMN), Ventral Attention Network (VAN), and Frontopari-

ÖZET

Amaç: Alzheimer'ın İlerleyici Bellek Bozukluğu Sürekliliği (İBBS), Alzheimer hastalığında (AH) nörofibriler yumak (NFY) yayılımının klinik yansımasıdır. Bu süreç, subjektif kognitif bozukluk (SKB) olarak bilinen hafif bellek şikayetleriyle başlayıp, amnestik hafif kognitif bozukluk (aHKB) olarak adlandırılan belirginleşmiş bellek problemlerine, nihayetinde amnestik bir çekirdekle karakterize edilen çoklu kognitif bozuklukları içeren demans aşamasına (AHD) ulaşır. Bu çalışma, İBBS boyunca kortikal kalınlık değişim paternlerini ağ perspektifiyle değerlendirerek yapısal ve fonksiyonel bozulmaları ortaya çıkarmayı amaçlamıştır.

Gereç ve Yöntem: Bu çalışmaya, 21 hafif AHD, 34 aHKB ve 33 SKB olmak üzere 88 katılımcı dahil edilmiştir. Klinik ve nöropsikiyatrik değerlendirmeler yapıldıktan sonra, kortikal kalınlık ölçümleri için yapısal MRG taraması gerçekleştirilmiştir. Verteks-temelli kortikal kalınlık analizleri ANCOVA kullanılarak yapılmıştır. Yaş, cinsiyet ve eğitim kovaryet değişkenlerdi.

Bulgular: Sonuçlar, İBBS boyunca anlamlı kortikal incelme olduğunu ve bu incelmenin AHD grubunda daha belirgin olduğunu göstermiştir. Kortikal incelme Olağan Durum Ağı (ODA), Ventral Dikkat Ağı (VDA) ve Frontoparyetal Ağ (FPA) ile örtüşmektedir.

Corresponding author/İletişim kurulacak yazar: Gözde KIZILATEŞ EVİN – gozde.kizilates@gmail.com

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etal Network (FPN). The comparison between the SCI and aMCI groups revealed no significant difference.

Conclusion: Cortical thinning was evident across different stages of PMIC, with more extensive thinning in later stages. The observed network-wide pattern of atrophy that AD-like deterioration affects broader neural systems rather than isolated regions. The findings highlight the importance of a network-based approach to understand AD-related structural changes and the potential for future research to integrate multimodal imaging to explore functional connectivity alongside structural atrophy.

Keywords: Alzheimer's disease, mild cognitive impairment, structural magnetic resonance imaging, cortical thickness

SKB ve aHKB grupları arasındaki karşılaştırmada anlamlı bir fark bulunamamıştır.

Sonuç: Kortikal incelme, IBBS'nin farklı evrelerinde belirgindir ve özellikle ileri evrelerde daha yaygın görülmektedir. Ağ genelinde gözlemlenen atrofi paterni, AH-benzeri bozulmanın yalnızca izole bölgeleri değil, daha geniş sinir sistemlerini etkilediğini göstermektedir. Bulgular, AH ile ilişkili yapısal değişiklikleri anlamak için ağ tabanlı bir yaklaşımın önemini vurgulamakta ve yapısal atrofinin yanı sıra fonksiyonel bağlantısallığı keşfetmek için gelecekteki araştırmalara çoklu modalite görüntülemeyi entegre etme potansiyeline dikkat çekmektedir.

Anahtar Kelimeler: Alzheimer hastalığı, hafif kognitif bozukluk, yapısal manyetik rezonans görüntüleme, kortikal kalınlık

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative process causing progressive cognitive impairment. The initiating event is the accumulation of amyloid during the pre-clinical stage. The clinical stages start with the formation and spread of the hyperphosphorylated tau-containing neurofibrillary tangles (NFTs) (1). In the most common AD phenotype, which constitutes 90% of cases (typical AD), the transentorhinal and entorhinal limbic cortices are the initial targets of NFTs corresponding to the I and II Braak and Braak stages, followed by progressive spread along the nodes of the episodic memory neural network, comprising the intrinsic hippocampal circuitry and the larger Papez circuit of the paralimbic cortices, corresponding to Braak and Braak III and IV stages. Finally, neocortical spread starts with stage V and is completed in stage VI by the invasion of virtually all the association cortices (2, 3). Clinically, this spread pattern manifests as an insidious onset progressive memory impairment. Stages I-II are the pre-clinical stage of the disease continuum, which comprises cognitively normal (CN) individuals and those with subjective cognitive impairment (SCI), who have subjective memory complaints but normal performance in neuropsychological testing (4). The mid-stages III-IV generally correspond to the amnestic subtype of mild cognitive impairment (aMCI) stage, where memory impairment, isolated or accompanied by other cognitive deficits with lesser severity can be demonstrated. Activities of daily living (ADLs) must be preserved during the MCI stage (5-7). aMCI was shown to be double the risk of conversion to dementia in a 3-year long longitudinal study, which found the overall rate as 29% (8). Therefore, we deemed aMCI as the representative of the mid-stage along the AD continuum. Finally, the neocortical stages V-VI correspond to the dementia stage, where multiple cognitive deficits with an amnestic core are severe enough to cause ADL impairment. This dementia subtype is typical for AD and is called probable AD dementia (ADD). This particular progression of cognitive impairment leading to dementia can be named as "progressive memory impairment continuum (PMIC)", which in the presence of positive biomarkers can also be named as "Alzheimer's continuum." Early recognition of Alzheimer's continuum-related SCI and MCI is crucial for timely interventions, as these stages offer a potential window for disease-modifying treatments before irreversible neuronal damage occurs (4, 9-12).

Complementing these neuropathological and clinical stages, structural magnetic resonance imaging (sMRI) is widely used to detect and quantify brain atrophy associated with AD. Among the key imaging biomarkers assessed by sMRI, cortical thickness is particularly relevant. Cortical thinning, especially in regions such as the entorhinal cortex, hippocampus proper and its sub-sectors, and temporoparietal areas, is one of the earliest detectable structural changes in individuals at risk for AD (13). Studies have shown that cortical thinning is strongly correlated with both the clinical progression of cognitive decline and the presence of AD pathology, such as tau and amyloid deposition. Cortical atrophy is particularly pronounced in patients transitioning from MCI to ADD. By measuring cortical thickness changes, sMRI provides valuable insights into the disease's progression and can be used to predict MCI progression to ADD (14, 15).

In the progression of ADD, alterations in the intrinsic connectivity networks (ICNs) connectivity patterns of the brain play a critical role in the clinical and pathological manifestations of the disease. Two of the most well-studied networks that show disrupted connectivity are the Default Mode Network (DMN) and the Salience/Ventral Attention Network (SN/VAN), although other networks such as the Frontoparietal Network (FPN) and Hippocampal-Cortical Networks are also affected. Early disruptions in DMN connectivity are linked to amyloid pathology in pre-clinical AD. It was shown that not only amyloid positivity as detected by amyloid PET imaging leads to DMN connectivity disruptions in CN individuals as severe as those with ADD, being mere APOE-ε4 carrier in CN individuals with negative amyloid status causes the same DMN connectivity disruption (16, 17). Longitudinal studies have also revealed a progressive shift in the balance

of within-network and inter-network connectivity, particularly within the DMN and hippocampal networks, which deteriorates over time. At the same time, compensatory increases in inter-network connectivity between the DMN and VAN are observed in the early phases of the disease, followed by a global decrease in network integration as the disease advances (18).

In this study, we aimed to evaluate and discuss patterns of cortical thickness changes from a network perspective along the continuum of AD, providing a more integrated understanding of structural and functional disruptions.

MATERIALS AND METHODS

Participants

This study included a total of 88 patients, comprising 21 with mild ADD, 34 with aMCI, and 33 with SCI, all of whom were followed up at the Behavioral Neurology and Movement Disorders Unit of the Department of Neurology, Istanbul University, Istanbul Faculty of Medicine. All participants were thoroughly informed about the study. Written informed consent was obtained before the clinical evaluation. Detailed neuropsychiatric evaluations were conducted, and study groups were determined based on scores from the Clinical Dementia Rating (CDR), the Mini-Mental State Examination (MMSE), and the Free and Cued Selective Reminding Test (FCSRT) (19-22). Additionally, all participants' FLAIR and T2-weigthed structural MRI images were reviewed by an expert neurologist for the presence of hyperintensities. The ADD group included patients diagnosed with very mild and mild AD according to the NIA-AA criteria, while the aMCI group included patients diagnosed based on Petersen's criteria (23-25). The SCI group comprised individuals with self-reported memory complaints (26). The criteria of the groups are detailed in Table 1. The exclusion criteria for the study included significant neuropsychiatric disorders such as major depression or schizophrenia, systemic diseases or unstable medical conditions, neurological comorbidities, a history of stroke or head injury, and white matter hyperintensities with Fazekas scores ≥1 on clinical MRI examinations. The study protocol was approved by the Clinical Research Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (Date: 09.09.2022, No: 16). This study was conducted according to the ethical principles of the latest version of the Declaration of Helsinki.

Table 1: The criteria for determining study groups

Group	CDR	SOB	FCS-RT-TFR
ADD	0.5 or 1	≥2 (very mild ADD) or 1 (mild ADD)	-
aMCI	0.5	0.5 or 1	≤24
SCI	0	-	>24

ADD: Alzheimer's disease dementia, aMCI: Amnestic mild cognitive impairment, SCI: Subjective cognitive impairment, CDR: Clinical Dementia Rating, SOB: Sum of Boxes, FCSRT-TFR: Free and Cued Selective Reminding Test-Total Free Recall

MRI acquisition

The MRI data were collected at Hulusi Behçet Life Sciences Research Laboratory, İstanbul University using a 3 Tesla MRI system (Phillips, Achieva, Best, The Netherlands) with a 32-channel SENSE head coil. T1-weighted MRI images were acquired with 3D FFE (Fast Field Echo) sequence with the following parameters: TR/TE (ms) = 8.3/3.8, flip angle = 8°, FoV = 220×240 mm, 1 mm^3 isotropic voxels, 180 axial slices.

Preprocessing and cortical thickness estimation

Cortical surfaces from high-resolution T1-weighted images were extracted using the Computational Anatomy Toolbox (CAT12, version 12.9 (r1932), Structural Brain Imaging Group, University of Jena, https://neuro-jena.github.io/cat/) within Statistical Parametric Mapping (SPM12, r7771, Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, United Kingdom, https://www.fil.ion.ucl.ac.uk/spm/) run with MATLAB (R2022b; MathWorks, Natick, MA, USA).

A fully automated approach of CAT12 enables the cortical thickness estimation and the central surface reconstruction of the grey matter (GM) in a single step. This method uses tissue segmentation to determine the distance from the white matter (WM) to the cortical surface, then projecting the local maxima, representing the cortical thickness, onto the outer GM voxels based on neighbour relationship. This projection-based thickness (PBT) technique effectively manages sulcal blurring and partial volume effects without requiring explicit sulcal reconstruction (27).

All T1 images were corrected for bias-field inhomogeneities, automatically segmented into GM, WM, and CSF (28), and spatially aligned to a Montreal Neurological Institute standard space (MNI-152 template) using the Diffeomorphic Image Registration Algorithm (DARTEL) within SPM12 (29). The cortical thickness values were also estimated for each hemisphere. All data appeared to be of good quality, so all participants' data were used for cortical surface reconstructions. After subject-level thickness estimation, group-level analysis was performed. For group comparisons, the subject-specific results were transformed into a common space and smoothed with a 15-mm Gaussian kernel (30, 31).

Statistical analysis

The vertex-wise thickness was analysed with the General Linear Model (GLM) as part of the statistical inference using CAT12. A one-way ANCOVA model was created. Age, gender, and education were covariates. A cluster

forming threshold at $p_{uncorr}<0.001$ and the cluster level threshold at $p_{FWE\text{-}corrected}<0.05$ were applied.

Statistical analyses of the demographic data were conducted using SPSS 26.0 (IBM SPSS Corp., Armonk, NY, USA). Age, education, gender, and MMSE and FCSRT-TFR scores were compared among the study groups. Age was analysed using ANOVA, while education, MMSE, and FCSRT-TFR scores were compared using the Kruskal-Wallis test. Gender distribution among the groups was assessed using a chi-square test. Post hoc t-tests were performed using a 0.05 alpha threshold. The Bonferroni correction was applied for multiple comparisons.

RESULTS

Demographic and clinical results

Age, gender, and education did not differ statistically, but there were significant differences in MMSE and FCSRT-TFE scores among the groups (Table 2). Post-hoc analyses revealed that there was a significant reduction in both MMSE and FCSRT-TFR scores from SCI to ADD among the 3 groups ($p<0.005$).

Cortical thickness comparisons

According to the ANCOVA results, widespread cortical thinning was observed among the groups in the cortical areas overlapping with DMN, VAN, and FPN (Figure 1). The cluster size, peak F value, and MNI coordinate of the statistically significant clusters are listed in Table 3.

Post hoc comparisons revealed a significant decrease in the cortical thickness in individuals with ADD compared with those with aMCI and SCI. The mean cortical thickness value of the aMCI group was lower than that of the SCI group, however this difference was not statistically significant (Figure 2).

DISCUSSION

This study investigated the surface-based morphometry analysis along the PMIC. The study revealed a widespread reduction in the cortical thickness among subjects diagnosed with ADD, aMCI, and SCI. These decreases corresponded to the VAN, FPN, and DMN regions of Yeo's 7-network atlas (32). Moreover, pairwise comparisons between the groups showed that this reduction was significantly greater in ADD than in aMCI and SCI.

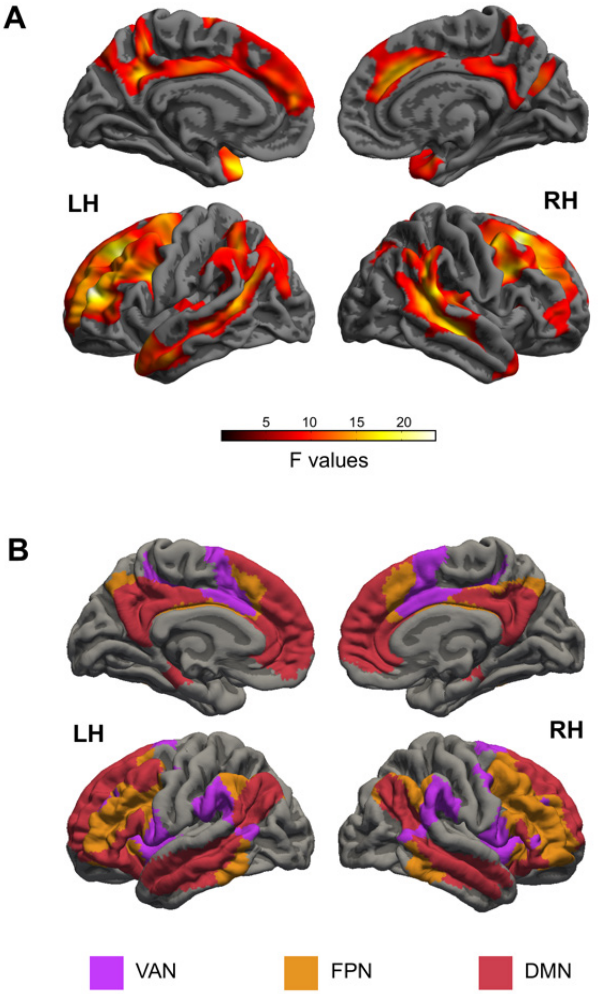

Figure 1: A) The areas with significant cortical thickness differences among the groups (cluster forming threshold at $p_{uncorr}<0.001$, the cluster level threshold at $p_{FWE\text{-}corrected}<0.05$). **B)** Yeo 7-Network Template maps comprising VAN, FPN and DMN. LH: Left Hemisphere, RH: Right Hemisphere, VAN: Ventral Attention Network, FPN: Frontoparietal Network, DMN: Default Mode Network

Table 2: Demographical and clinical characteristics of the groups

	ADD (n=21)	aMCI (n=34)	SCI (n=33)	Comparison
Age	67.43±9.938	63.79±7.176	63.12±8.019	F=1.921[a], p=0.153
Gender (F/M)	10/11	13/21	22/11	χ^2=5.554[b], p=0.062
Education	10.86±4.629	10.94±4.936	13.12±4.722	χ^2=2.911[c], p=0.233
MMSE	23.33±3.799	27.91±1.712	28.94±1.391	χ^2=37.315[c], p<0.001
FCSRT-TFR	8.14±7.255	18.35±4.389	30.85±4.424	χ^2=68.957[c], p<0.001

[a]One-way ANOVA test, [b]Pearson's Chi-Square test, [c]Kruskal-Wallis test, F: Female, M: Male, MMSE: Mini-Mental State Examination

Table 3: Clusters with cortical thickness differences among groups

Cortical areas	Hemisphere	Cluster p value	Cluster size	Peak F value	MNI coordinates (x y z)
Superior frontal Rostral middle frontal Inferior parietal Superior parietal	L	<0.0001	11476	23.73171	-22 22 41
Inferior parietal Supramarginal Superior temporal Middle temporal	R	<0.0001	4285	17.28386	65 -37 18
Superior frontal Rostral middle frontal Caudal middle frontal	R	<0.0001	3393	21.96116	23 19 51
Precuneus Posterior cingulate Isthmus cingulate	R	<0.0001	941	12.79864	20 -69 26
Pars opercularis Pars triangularis Insula	R	0.0083	223	12.96585	38 18 10
Precuneus	R	0.0173	191	9.51841	8 -49 63
Superior parietal	R	0.0260	173	9.45733	21 -68 41

MNI: Montreal Neurological Institute, L: Left, R: Right

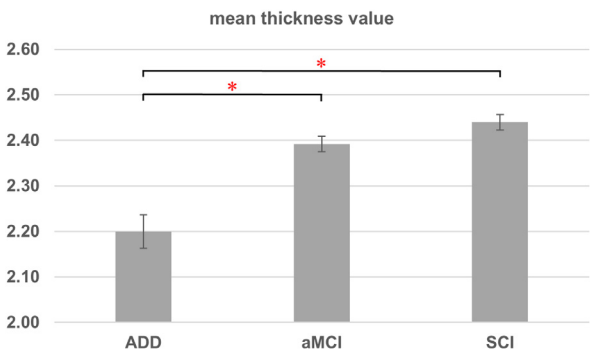

Figure 2: Mean thickness values of all significant clusters. Error bars show the standard error of the thickness values (Significance threshold *p<0.001). ADD: Alzheimer's disease dementia, aMCI: Amnestic mild cognitive impairment, SCI: Subjective cognitive impairment

Many studies have explored cortical thickness changes in AD using ROI-based or surface-based morphometry approaches, highlighting significant patterns of localised atrophy. Dickerson et al. indicated that specific regions of the brain, particularly the ventromedial temporal and inferior parietal cortices, reveal cortical atrophy even in individuals with very mild AD. This regional atrophy correlated with clinical measures of memory impairment,that specific areas may serve as biomarkers for distinguishing different stages of cognitive decline. This suggests that these areas are among the first to be affected by the disease, even before more pronounced symptoms appear (14).

Additionally, Vogt et al. demonstrated significant cortical thickness reductions in individuals with ADD, particularly in the bilateral frontal, parietal, and temporal regions, as well as in the limbic areas, compared to healthy individuals and those with MCI. The cortical thickness comparison between the MCI group and controls indicated no significant difference (33).

Montal et al. reported that healthy control subjects demonstrated increased cortical thickness in middle temporal gyrus, precuneus, and superior parietal areas, indicating preserved structural integrity in the early stages. In contrast, individuals with MCI progressing to ADD show significant atrophy in critical areas such as the middle temporal gyrus, indicating early neurodegenerative changes. Furthermore, patients with dementia exhibit widespread cortical atrophy across multiple regions, reflecting the advanced and progressive nature of neurodegeneration in AD (34).

Moreover, Bakkour et al. investigated the cortical signature of thinning associated with MCI and its predictive value for the progression to mild AD dementia. The study found that the thickness of the medial temporal lobe showed the best performance to predict the progression. Additionally, the mean thickness of the AD-signature regions also performed well (35).

The findings we obtained are consistent with previous research in the literature; however, a network-based interpretation of cortical thickness alterations may provide

a more comprehensive understanding than a strictly regional approach. Specifically, our analysis revealed that the observed cortical thickness reductions were predominantly distributed across the three neural networks. This pattern indicates that neurodegenerative changes in AD may manifest not as isolated focal atrophy but rather as network-wide disruptions that reflect the vulnerability of particular ICNs to the underlying pathophysiology.

Although this study did not directly address functional changes within networks, previous literature highlights the critical role of disrupted functional connectivity in the DMN, VAN, and FPN as underlying features of AD, contributing to its cognitive symptoms. The DMN is crucial in ageing-related fMRI studies because it contains brain areas linked to AD, where amyloid buildup is first observed, even in individuals showing no symptoms (36-39). Greicius et al. was one of the first to identify that the DMN activity was disrupted in ADD as compared to CN individuals (40). Villemagne et al. showed that amyloid deposition as detected by PET was particularly evident in midline cerebral structures, which are also the major hubs of DMN, and during follow-up they observed that cognitive decline was weakly correlated with amyloid burden in patients with ADD and MCI and in CN individuals (41). Onoda et al. revealed that resting-state functional connectivity between the anterior cingulate cortex and bilateral insula, regions linked to SN, decreases with age (42). Berier et al. demonstrated that AD is linked not only to a reduction in connectivity within individual networks but also to decreased correlations between different networks. This pattern of decline becomes more pronounced as the disease progresses, reflecting a broader disruption in the functional integrity of brain networks (43). Moreover, Nebizadeh et al. reported that lower functional connectivity correlates with tau spread (44).

Our findings support the existing literature by demonstrating that reduced cortical thickness accompanies the diminished connectivity observed across these networks. This suggests a parallel relationship between cortical atrophy and decreased network connectivity, potentially reflecting the broader impact of neurodegenerative processes on the anatomical and functional integrity of the brain.

Future research could benefit from a multimodal approach by examining the relationship between cortical thickness alterations and functional network changes. This integrated analysis would offer a more comprehensive perspective, potentially elucidating how structural atrophy corresponds to disruptions in functional connectivity and contributes to the progression of neurodegenerative processes. Such an approach could provide deeper insights into the mechanisms linking anatomical and functional network changes in cognitive decline.

CONCLUSION

This study demonstrates that cortical thinning occurs across the PMIC, from SCI to aMCI and ADD, with more pronounced reductions in the later stages. The observed cortical atrophy is not restricted to specific brain regions but is distributed across key networks, including the DMN, VAN, and FPN. This network-wide pattern of cortical thinning indicates that AD impacts broader neural systems, potentially underlying the cognitive and functional deficits seen in affected individuals. Our findings emphasise the importance of a network-based approach to understanding the structural changes associated with AD. Future research should incorporate multimodal imaging techniques to explore the relationship between structural atrophy and functional connectivity disruptions, which may offer deeper insights into the mechanisms driving neurodegenerative processes.

Ethics Committee Approval: Ethics committee approval was received for this study from the İstanbul University, İstanbul Faculty of Medicine (Date: 09.09.2022, No: 16).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Author Contributions: Conception/Design of Study- G.K.E., A.B., E.H., H.G., T.D.; Data Acquisition- E.K., Ç.U.Y.; Data Analysis/Interpretation – G.K.E., A.B.; Drafting Manuscript- G.K.E., A.B., E.K., E.H., Ç.U.Y.; Critical Revision of Manuscript- H.G., T.D.; Final Approval and Accountability- G.K.E., A.B., E.K., E.H., Ç.U.Y., H.G.; Supervision- H.G., T.D.

Conflict of Interest: The authors have no conflict of interest to declare.

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