Heliyon 10 (2024) e28957

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Analysis of brain structural covariance network in Cushing disease

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ARTICLE INFO

Keywords:
Cushing's disease
Structural covariance networks
Graph theoretical analysis
Gray matter volume

ABSTRACT

Background: Cushing disease (CD) is a rare clinical neuroendocrine disease. CD is characterized by abnormal hypercortisolism induced by a pituitary adenoma with the secretion of adrenocorticotropic hormone. Individuals with CD usually exhibit atrophy of gray matter volume. However, little is known about the alterations in topographical organization of individuals with CD. This study aimed to investigate the structural covariance networks of individuals with CD based on the gray matter volume using graph theory analysis.

Methods: High-resolution T1-weighted images of 61 individuals with CD and 53 healthy controls were obtained. Gray matter volume was estimated and the structural covariance network was analyzed using graph theory. Network properties such as hubs of all participants were calculated based on degree centrality.

Results: No significant differences were observed between individuals with CD and healthy controls in terms of age, gender, and education level. The small-world features were conserved in individuals with CD but were higher than those in healthy controls. The individuals with CD showed higher global efficiency and modularity, suggesting higher integration and segregation as compared to healthy controls. The hub nodes of the individuals with CD were Short insular gyri (G_insular_short_L), Anterior part of the cingulate gyrus and sulcus (G_and_S_cingul-Ant_R), and Superior frontal gyrus (G_front_sup_R).

Conclusions: Significant differences in the structural covariance network of patients with CD were found based on graph theory. These findings might help understanding the pathogenesis of individuals with CD and provide insight into the pathogenesis of this CD.

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https://doi.org/10.1016/j.heliyon.2024.e28957
Received 18 August 2023; Received in revised form 27 March 2024; Accepted 27 March 2024
Available online 3 April 2024

1. Introduction

Previous research has established that an abnormal increase in adrenocorticotropic hormone (ACTH) might cause endocrine dysfunction of a hypothalamic–pituitary–adrenal axis (HPA axis) [1]. CD is a typical ACTH-secreting pituitary adenoma, which is clinically manifested with moon face, purple striae, hypertension, and osteoporosis [2]. Therefore, CD is a unique pathophysiological model for studying the consequences of chronic hypercortisolemia on the structural and functional changes in the brain [1,3]. Individuals with CD always suffer from neurocognitive and neuropsychiatric symptoms due to these abnormal structural and functional changes in the brain [4,5]. A considerable amount of literature has been published on CD in the last decade. These studies have provided important information on the etiology of abnormal increase in ACTH levels. Surprisingly, the underlying mechanism of brain injury caused by CD have not been closely examined.

Recently investigators have examined the effects of ACTH on the structure and function of the brain in individuals with CD by diverse imaging modalities [6,7]. Starkman et al. showed a decreased hippocampal volume in individuals with CD, which indicated that the abnormal increase in the ACTH level could alter brain structure [8]. The existing body of research on functional magnetic resonance imaging (fMRI) suggests that the limbic network (LIM), default mode network (DMN), and executive control network (ECN) were more susceptible to ACTH [6,9]. Moreover, data from several studies suggest that there was a widespread reduction in the fractional anisotropy (FA) values and an increase in the mean diffusivity (MD) by diffusion tensor imaging (DTI) [10]. Till now, many research has tended to focus on several special brain regions rather than the structural and functional changes in the brain of individuals with CD by using graph theoretical analysis (GTA).

Brain is a complex network, which is organized by a large number of different regions that each have their own task and function, but who are continuously sharing information with each other efficiently. Structural covariance refers to the relations of morphological properties in brain areas across individuals [11]. Based on gray matter volume or cortical thickness, the covariance network can be utilized to assess brain functions [12]. This method has been widely used to study the pathogenic mechanism of other nervous system diseases [13–15]. Additionally, by studying the entire brain rather than one particular structure, this method can help understand potential variations in the development of brain networks.

The topological characteristics of the brain network, which is composed of a number of nodes (brain regions) and edges (correlation), can be examined using the effective technique of graph theory analysis [16]. The organization of the human brain's large-scale network, which is connected by nodes and edges, has been studied using graph theory [17]. Numerous studies have demonstrated the aberrant topological characteristics of neurological disorders [18,19]. The brain volume morphology covariance network and graph theory analyses might offer a thorough knowledge of the impact of hypercortisolism on brain function in individuals with CD, given the gray matter atrophy with continuous exposure to an abnormal increase in the ACTH levels in these individuals. The current study looked at how structural covariance network analysis might be used to examine how ACTH can impact individual with CD brain activity. Additionally, using a graph theory analysis and the structural covariance network, the topological characteristics of patients with CD were examined.

2. Methods

2.1. Participants

In this study, a total of 61 CD patients (43.95 ± 11.96) and 53 HCs (48.59 ± 17.28) with matched age and education were included. All the patients provided informed consent. The inclusion criteria for the patients in the CD group were as follows: (a) patients with ages between 18 and 60 years and (b) those with previously reported positive imaging tests for pituitary abnormalities [20]. The exclusion criteria were as follows: (a) patients with a history of drug or alcohol abuse, (b) patients with a history of traumatic brain injury and neurological conditions, and (c) patients with contraindications for undergoing an MRI scan and left-handedness. In accordance with 2008 Endocrine Society guidelines, CD was identified in patients who had similar clinical symptoms, increased 24 h urine free cortisol (UFC) levels, bilateral petrosal sinus sampling, and no impaired circadian regularity of cortisol secretion [3]. This study was approved by the Research Ethics Committee of Ruijin Shanghai Hospital.

2.2. Imaging data acquisition

Three-dimensional (3D) T1-weighted images were acquired in the sagittal plane, yielding 196 continuous slices with of voxel. The imaging parameters were: repetition time (TR) = 5.552 ms; echo time (TE) = 1.752 ms; field of view (FOV) = 256×256 mm^2; flip angle (FA) = 12°; slice thickness = 1.0 mm with no interslice gap; matrix = 256×256; NEX = 1, bandwidth = 244.141 Hz; and a scan time of 3 min and 11 s.

2.3. Imaging preprocessing

All subjects' structural T1 images were processed with FreeSurfer (Version 7.2.0) software [21]. The quality control analysis of

FreeSurfer reconstruction included the automatic detection of recon-all processing errors and visual inspection for segmentation, intensity normalization, and skull stripping errors. The FreeSurfer offers a surface-based approach for estimating cerebral surface gray matter volume. All image preprocessing computation described in this study were conducted in subject native space. After obtaining individual gray matter volume, it was finally resampled into the common fsaverage template and smoothed using a 15-mm full width at half maximum (FWHM) Gaussian kernel. The gray matter volume was extracted using aparc.a2009s atlas [22], which includes 148 regions of interest (ROIs). The average gray matter volume was calculated for the ROI of each subject in both groups. After that, Pearson's correlation coefficients for each ROI were determined.

2.4. Network metrics

The structural covariance network was established using a variety of network graph metrics. The following metrics were calculated: global efficiency, small world parameters (normalized Cp γ, normalized Lp λ, and small wordless σ), local efficiency, and modularity (Q). The node metric included degree centrality (DC). The network metrics were computed using the GRETNA toolkit [23]. The network of individuals with CD and HCs underwent a descriptive analysis for the spatial distribution of brain hubs. If a brain area's or node's DC was 2 SD higher than the network, it was considered a hub region [24].

2.5. Statistical analyses

All the statistical analyses were performed using SPSS software (version 22.0; Inc., Chicago, IL). Differences in gender distribution between the two groups were determined using a chi-square test, while the differences in age and education level were determined using between-group *t*-tests for means. Based on the global properties of network matrices between the CD and HC groups, significance analyses were performed using a two-sample *t*-test, and multiple comparisons were corrected using FDR and q-value was set to 0.05 for significant level of multiple comparison. The significance level was set to $P < 0.05$ for each network feature. Prism 8 and MATLAB (MathWorks, Natick, MA, United States) were used for all the network statistical analyses.

3. Results

3.1. Demographic and clinical data

The clinical and demographic characteristics of the patients and controls are listed in Table 1. There were no significant differences between patients and HCs in terms of age, gender, and education level (More information about brainnetwork construction can be seen in Fig. 1).

3.2. Topological properties of morphology covariance networks

In the gray matter volume network, the γ- and σ-values of individuals with CD, between the sparsity of 0.05–0.50, were greater than healthy control [25]. This indicated that the individuals with CD possessed small-world features. However, the σ- and γ-values of individuals with CD over the sparsity of 0.05–0.50 were higher (Fig. 2). In the gray matter volume network, individuals with CD showed an increase in global efficiency (CD = 0.5905 ± 0.1215, HC = 0.5705 ± 0.1250; Fig. 2), while there were no significant differences in local efficiency between the two groups.

Table 1
Demographics and clinical data of participants.

	Cushing Disease (n = 61)	Controls (n = 53)	P Value
Age (y)	43.95 ± 11.96	48.59 ± 17.28	0.102[b]
Sex	4/15	7/15	0.328[a]
No. of Women	52	36	
Education (years)	12.74 ± 3.27	12.67 ± 3.67	0.878[b]
Duration of illness (years)	65.89 ± 72.37	–	–
Plasma Cortisol (12am) (ug/dl)	21.16 ± 13.04	–	
Plasma Cortisol (4pm) (ug/dl)	21.38 ± 8.74	–	
Plasma Cortisol (8am) (ug/dl)	26.06 ± 14.11	–	
UFC_(21-111μg/24 h)	659.87 ± 357.29	–	
ACTH_ (7.0–65.0 pg/ml)	103.30 ± 68.26	–	

Data are means and standard deviation unless otherwise noted. All of the scores are raw values. The comparisons of demographic between groups were performed with Mann-Whitney *U* test. $P < 0.05$ indicated a significant difference. UFC: Urinary Free Cortisol; ACTH: adrenocorticotropin.

[a] Chi-squre test was used for calculated.

[b] Mann-Whitney *U* test was used for calculated.

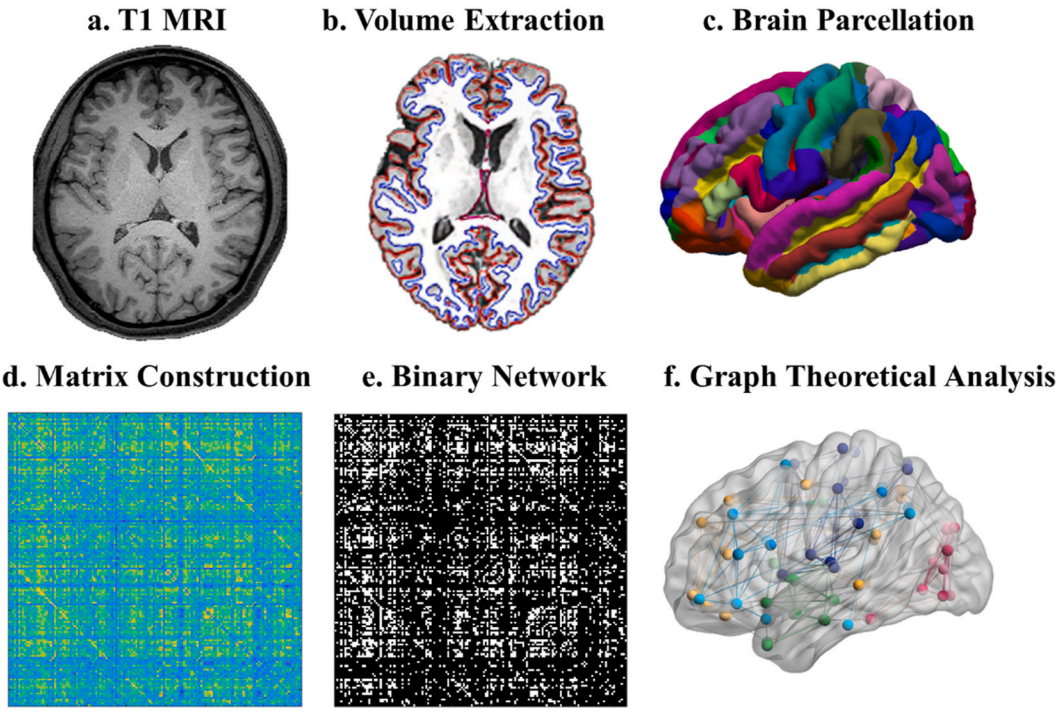

Fig. 1. Flow chart of imaging processing, network construction and graph theoretical analysis. (a) Structural images (T1) of CD patients and HCs were collected to construct structural covariance network. (b) For each T1 image, gray matter volume was first extracted using Freesurfer. (c) Each cortical stiffness map was then divided into different numbers of regions according to aparc.a2009s atlase. (d) Subsequently, covariance networks were constructed by calculating the Person's correlation coefficients of each region pairs. (e) A sparsity-based procedure was further used to threshold each covariance network into a series of binary networks. (f) Graph theoretical analysis were utilized to characterize the topological organization of CD patients' and HCs' structural covariance network. CD: Cushing disease, HCs: healthy controls.

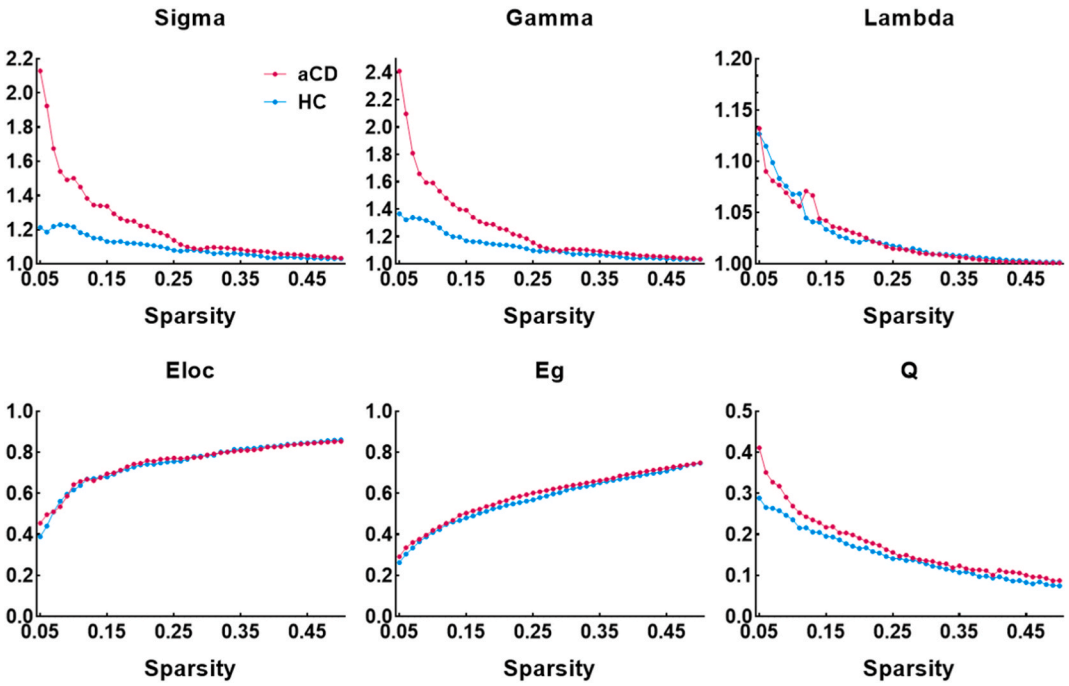

Fig. 2. Changes in global network metrics as a function of network density in the aCD group and the HC group. aCD: active Cushing disease, HCs: healthy controls.

3.3. Network hubs

For the individuals with CD, the hub nodes were G_and_S_cingul-Ant_L, G_insular_short_L, G_orbital_L, and G_front_sup_R, while those for healthy controls were G_orbital_L, G_temp_sup-Lateral_R, and G_temporal_middle_R (Fig. 3, Supplement Table 1).

4. Discussion

To the best of our knowledge, this study was the first to use graph theory to assess the structural covariance network that was built based on the volume of gray matter in individuals with CD. When compared to HCs with age, gender, and education matching, individuals with CD demonstrated a greater global efficiency of the gray matter volume-based covariance. Moreover, the results showed that the individuals with CD had increased Q as compared to that in the HCs. Additionally, both the individuals with CD and the HCs demonstrated small-world properties. However, those of individuals with CD were higher as compared to HCs. As compared to HCs based on DCs, individuals with CD were also reported to have different hubs.

4.1. ACTH and changes in brain volume

It was first suggested that hypercortisolemia could cause structural alterations in the brain in 1992, when a study found that the hippocampus volume of CD was lower than HCs [8]. Since then, numerous studies have shown structural changes in the brain, especially in some specific brain regions of individuals with CD, and the patients with longer illness duration have revealed more severe brain atrophy [26]. A study has reported a decrease in the prefrontal cortex (PFC) and cerebellum volume of individuals with CD [27]. Moreover, researchers used the methods of automatic volumetric segmentation or voxel-based morphometry and showed a decrease in the gray matter volume in individuals with CD [28]. The biological cure using the transsphenoidal surgery of individuals with CD can improve structural changes in the brain caused by excess cortisol even in a short time [29]. After transsphenoidal surgery, Toffanin et al. [30] showed an effective reduction in the volume of the hippocampus head, which suggested that the hippocampus head might be more sensitive than the hippocampus body and tail. Chronic hypercortisolemia exposure may impair learning and memory, which may be related to hippocampal volume atrophy; the learning and memory recovered with biological treatment. Although several researches have looked at the relationships between ACTH and anatomical changes in the brain, the mechanism of brain injury is still not fully understood.

4.2. Changes in cortical structural networks in individuals with CD based on graph theory

Graph theory was used in this study to find substantial differences between HCs and individuals with CD in the structural covariance network of gray matter volume. The small-world properties of networks showed lower path lengths and greater cluster efficiency, which maximizes information flow in a complex network while minimizing wire costs [31]. In line with our earlier research, the brain structural networks showed the small-world properties; however, the small-worldness index sigma (σ) significantly increased in the individuals with CD [32]. Despite the conservation of small-world properties in individuals with CD, the γ (Gamma) was higher across the range of sparsity, suggesting higher segregation in the brain of individuals with CD. This suggested more extensive linkages between nearby brain regions in individuals with CD. Furthermore, higher γ and Q in individuals with CD suggested that the network's regular structure: a balance between local specialization and global integration had been disturbed. Other structural covariance networks in patients with neurological and mental diseases have also been reported to exhibit this phenomenon. Additionally, research

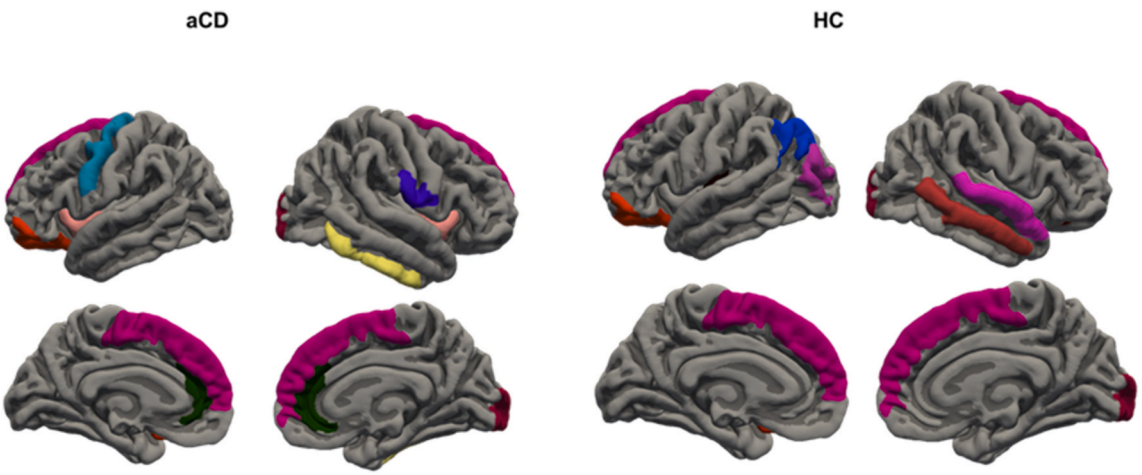

Fig. 3. Network hubs based on degree centrality in HCs and the aCD group. aCD: active Cushing disease, HCs: healthy controls.

suggested that less consistency between distant nodes in emotional processing may be connected to the shifting of the regular network in the brain structural covariance network of MDD patients [14]. This may help to explain why individuals with CD have a variety of emotional and cognitive function impairments. Local efficiency denotes a brain region's capacity to exchange information with its nearby brain regions, whereas global efficiency shows the capacity of the complex network as a whole. In the current investigation, individuals with CD had higher global efficiency as compared to HCs, indicating greater connectivity between nearby brain regions. The higher integration reflects greater synchronization with brain regions, belonging to other communities [33]. Additionally, greater global efficiency suggests that individuals with CD brain networks are more capable of exchanging information in an efficient manner. This phenomenon has previously been reported in other neurological and mental diseases, including alcoholism and Alzheimer's disease [34]. To the best of our knowledge, higher segregation and integration were reported for the first time in the brain networks of individuals with CD. This might be because chronic glucocorticoid exposure-induced brain atrophy is a resolvable form of brain atrophy, suggesting that it is not accompanied by a decrease in neurons or neuron death.

4.3. Altered hubs in gray matter volume in the structural covariance networks of individuals with CD

Hub refers to the brain regions with high DC, which can control the flow of information and interact with many other nodes [35]. The network of individuals with CD and HCs underwent a descriptive analysis for the spatial distribution of brain hubs. If a brain area's or node's DC was 2 SD higher than the network, it was considered a hub region [24]. Although hubs play an important role in the brain network, they are highly vulnerable to being attacked in disease progression [36]. Here, a distinct distribution of hubs was observed between the individuals with CD and HCs. Among HCs, the hubs were comparable to the previously reported brain network, while among individuals with CD, they were mainly found in G_insular_short, G_and_S_cingul-Ant, and G_front_sup. The hubs of front_sup are mainly distributed in the default mode network, which mainly maintains normal brain functional activities under a resting state [37]. A previous study reported that CD was associated with abnormal functional connectivity in the default mode network as compared to that in HCs [9]. Moreover, researchers reported that the volume of cingul-Ant and front_sup decreased in individuals with CD and was associated with changes in hormone levels [29]. The hubs of cingul-Ant and G_insula is mainly distributed in the limbic system, which plays an important role in emotional responses and control. This might explain why individuals with CD are often accompanied by cognitive and emotional dysfunction. Moreover, an increase in functional connectivity between the limbic network and default mode network was observed in the resting state fMRI of individuals with CD [7]. The hubs of G_insular_short, G_and_S_cingul-Ant, and G_front_sup indicated that these nodes might play important coordination roles in whole-brain networks and might be a compensatory response to chronic exposure to cortisol.

5. Limitations

This study has several limitations. First, this was a cross-sectional study, long-term follow-up on patients experiencing chronic high cortisol stimulation was needed in future. Second, cognitive and emotional information of individuals with CD was lacking, future studies with this information are essential to investigate network topology of individuals with CD. Moreover, BMI - related information might also be needed to study the relationship between weightiness and brain network topology.

6. Conclusions

In conclusion, high integration and high segregation of structural covariance networks were observed for individuals with CD, based on gray matter volume with graph theoretical analysis. Additionally, compared to healthy controls, individuals with CD have various network hubs, and these varied hubs may be one of the important factors affecting cognitive and emotional problem.

Ethical approval/informed consent

This study was approved by the Medical Ethics Committee of Shanghai Ruijin hospital (2019–221). All procedures performed were in accordance with the ethical standards of the institutional committee.

Funding sources

This study was supported by grants from Science and Technology CommissionFoundation of Shanghai (21JM0010202 and 21JM0010200), the National Natural Science Foundation of China (8217070113, 82000751, 32271359), Shanghai Sailing Program (20YF1438900).

Statement of written consent

Written consent was obtained from each patient or subject after a full explanation of the purpose and nature of all procedures used.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author, but they are not publicly

available due to privacy restrictions.

CRediT authorship contribution statement

Can-Xin Xu: Software, Data curation, Conceptualization. **Linghan Kong:** Methodology, Investigation, Data curation. **Hong Jiang:** Visualization, Validation, Project administration. **Yue Jiang:** Validation, Resources, Project administration. **Yu-Hao Sun:** Validation, Supervision. **Liu-Guan Bian:** Writing – review & editing, Writing – original draft, Funding acquisition. **Yuan Feng:** Writing – review & editing, Software, Funding acquisition. **Qing-Fang Sun:** Writing – review & editing, Writing – original draft, Visualization, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28957.

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