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Volumetric and Morphometric Analysis of Pineal and Pituitary Glands of an Indian Inedial Subject

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Keywords
Ayurveda · Siddha · Survive on sunlight · Level set active contours · Neurohormonal morphology

Abstract
Background: Inedia (Latin for "fasting") is the ability of a person to live without consuming food and water and to sustain solely by prana, the vital life force in Hinduism. According to Ayurveda, sunlight is one of the main sources of prana, and some practitioners believe that it is possible for a person to survive on sunlight alone. ***Purpose:*** In this study, we report the unusual sizes and volumes of both the pineal and pituitary glands in a subject with inedia state for nearly 70 years. ***Methods:*** The pineal and pituitary glands were located in the MRI of the subject from coronal, axial, and sagittal images. Segmentation of the pineal and pituitary glands was performed using level set active contours method. ***Results:*** The overall volume, size, and shape of the glands were calculated as 38.7604 mm^3 for the pineal gland and 272.552 mm^3 for the pituitary gland and compared with that of the normal volumes (94.2 ± 40.65 mm^3 and 320–718 mm^3, respectively). ***Conclusion:*** It was found that the subject has significantly low pineal and pituitary volumes, which fall under the category of normal young child and we could show that the neurohormonal morphology of inedia subject is within childhood range.

Introduction

Pineal and pituitary glands are very important neuroendocrine organs. The main hormone secreted by the pineal gland is melatonin, but the pineal also produces a number of other hormones, including arginine vasoto-

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cin. The pineal gland modulates gonadal activity, mediates responses to light, and alters pigment coloration. The pituitary gland hangs from the bottom of the hypothalamus at the base of the brain and sits in a small cavity of bone above the roof of the mouth. The pituitary gland consists of the anterior, intermediate, and posterior lobes which are connected to the hypothalamus by the hypophyseal stalk. Axons from the PVN and SON of the hypothalamus project through the infundibulum to terminate in the posterior lobe, which consists of neural tissue. The anterior and intermediate lobes of the pituitary consist of endocrine tissue, which receives hormonal stimulation from the hypothalamus through the blood vessels of the hypophyseal portal system in the pars tuberalis of the hypophyseal stalk. The pituitary gland produces 10 hormones: 6 from the pars distalis, 2 from the pars nervosa, and 1 from the pars intermedia, while j8-endorphin is secreted from the pars intermedia and the pars distalis.

The size of the pineal and pituitary glands is related to its function or the abnormality [1]. Reference data for the normal pineal volume [2] and pituitary volume [3] have been reported.

In this study, we report the unusual size of the volumes of both pineal and pituitary glands in a subject with inedia (ability of a person to live without food and water for longer duration) for nearly 70 years. The motivation for this study is to find possible mechanisms of inedial state in humans that might lead to techniques inducing inedial state. From the MRI morphometric and volumetric analysis of pineal and pituitary glands, it was found that the subject has significantly low pineal and pituitary volumes which falls under the category of normal young child (5–10 years old). It can sustain in the inedial state for longer duration if the pineal and pituitary volumes are low and if the brain does not age in coordination with the body. In addition, no reference data have been established on the relation between inedia and low pineal and pituitary volumes; earlier studies have shown that there is no significant relationship between the total pineal volume and the age of the subject [4].

Our conjecture is that the subject's brain resembles that of a person in the age group of 5–10 years, although his body is aging over the course of time his brain still continues to function as a normal young child. From the morphometric and volumetric analysis of pineal and pituitary glands, it was found that the subject has significantly low pineal and pituitary volumes, which falls under the category of normal young child.

Methods

Subject

The study was conducted on an 82-year-old male subject who claims to have been in the state of inedia for the past 70 years. The subject weighed 35 kg and was 158 cm in height.

Image Acquisition

In this study, we used MRI modality to analyze the evolving size of pineal and pituitary glands. The brain study was conducted on Philips Achieva MRI system with a magnetic field strength 3.0 T. Thin sections of MRI data was obtained using transverse and sagittal 3D volumetric T1 weighted TFE gradient echo. The width and height of the image was 250 × 250 mm. Depth = 146.40 mm, voxel size = 1.04 × 1.04 × 0.60 mm, resolution = 0.960 pixels/mm. The file format was DICOM. The scanning sequence and scanning variant were GR and MP, respectively. The spacing between slices was 0.6 mm. The slice thickness was 1.2 mm. The receiving coil type was SENSE-NV-16. FOV = 24.0 × 24.0 cm, matrix size = 250 × 250, pixel bandwidth = 209.709, and imaging frequency = 127.792 Hz.

Medical Image Processing

The raw data were processed using the MRIcron software (which is an open source software tool kit used for medical image processing, especially for MRI data) with voxel size 1.04 × 1.04 × 0.60 mm. Multi Planar Reformation was performed to obtain the coronal, sagittal, and axial views (Fig. 1). The windowing and contrast factors were suitably adjusted to obtain a clear visibility of the pineal gland.

Segmentation of Medical Data

Medical image segmentation is used to solve a wide range of biomedical research problems: cancer detection, brain morphology, treatment planning, robot-guided surgery, etc. Segmentation is a valuable tool which exerts an important influence on neuroimaging research. In today's medical imaging scenario, robust tools are available, ranging from manual to semiautomatic to automatic segmentation, which provides high efficiency and accuracy for segmenting anatomical structures. Open-source segmentation and registration tools are becoming very popular these days, which enable researchers to develop a fast prototyping model. Active contour level set segmentation algorithm is a robust and elegant tool with high specificity and good accuracy [5]. In this study, we have used Insight Segmentation and Registration Tool Kit (ITK-SNAP) for segmentation of pineal gland. ITK is one such popular open source tool which is highly accurate and efficient for medical image segmentation, funded under the Visible Human Project by the US National Library of Medicine [6], which implements level set active contour segmentation. The scope of this study is limited to the segmentation of pineal and pituitary glands.

Insight Segmentation and Registration Tool Kit

The overall volumes of pineal and pituitary glands and statistics of the intensity of pixels for each segmented structure was calculated using ITK-SNAP 1.1 build version with Microsoft VC++ Express Edition Compiler. ITK-SNAP [5] is an open source tool kit, used extensively in academic and industrial environments, built on ITK C++ classes. The processed MRI data in DICOM format were

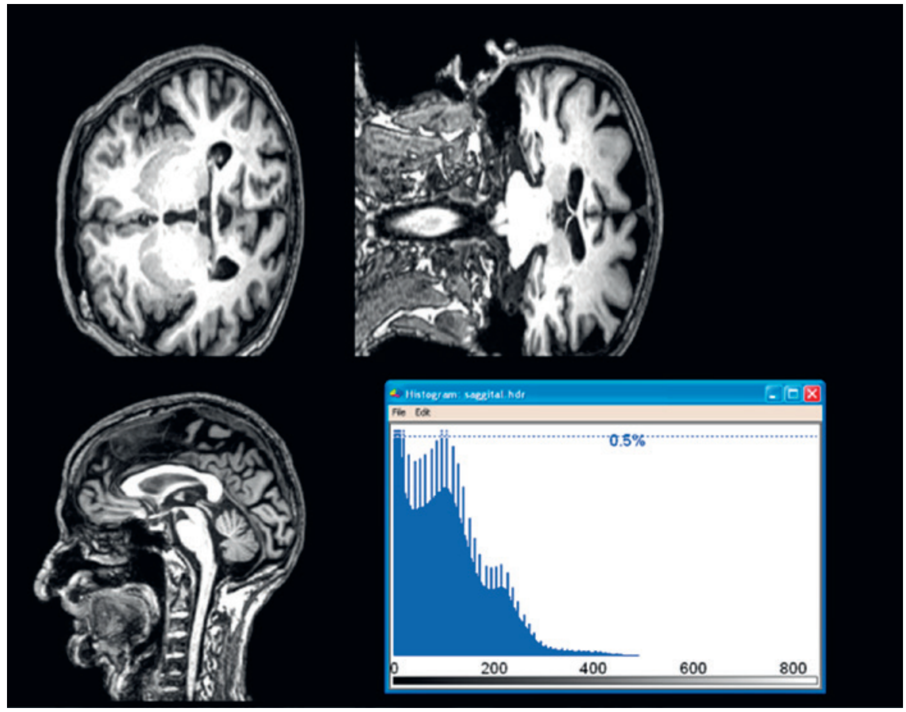

Fig. 1. Multiplanar reformation of the raw MRI data with histogram.

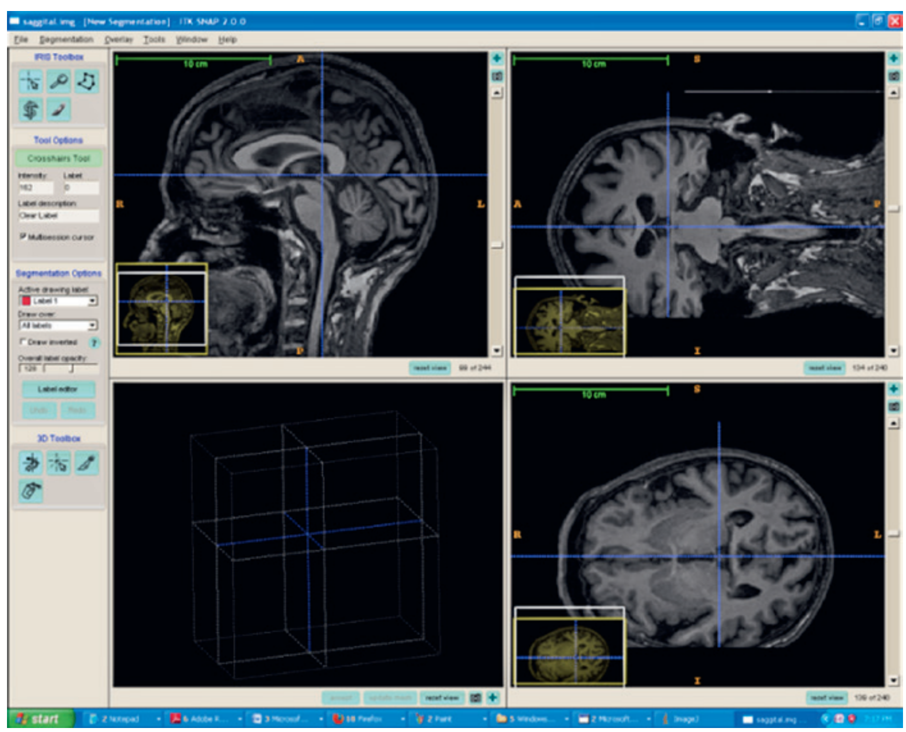

Fig. 2. GUI of ITK-SNAP showing MRI data in sagittal, coronal, and axial views.

loaded to the ITK-SNAP (Fig. 2) tool kit and the segmentation operation was performed to segment the pineal gland. Segmentation method adopted here is 3D level set active contour. SNAP provides a set of tools to make segmentation of volumetric data simpler and faster. SNAP can be used in 2 different modes: manual segmentation and semi-automatic segmentation. The manual mode is used for segmentation using hand contouring and for cleaning up the results of automatic segmentation; many brain research laboratories use manual delineation as the technique of choice for image segmentation. In the semi-automatic mode, a powerful level set seg-

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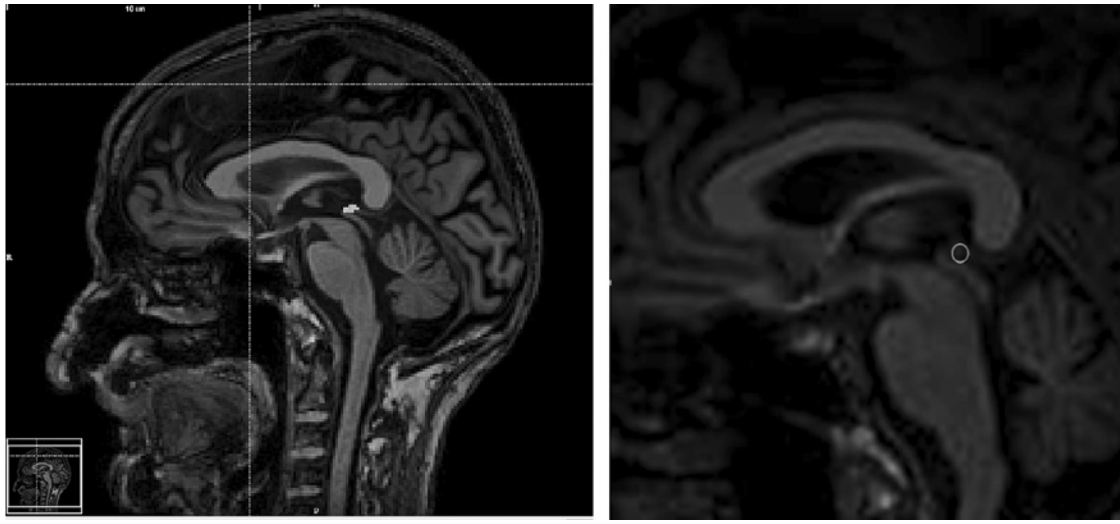

Fig. 3. Pineal gland marked in red on the sagittal section of the subject's MRI data.

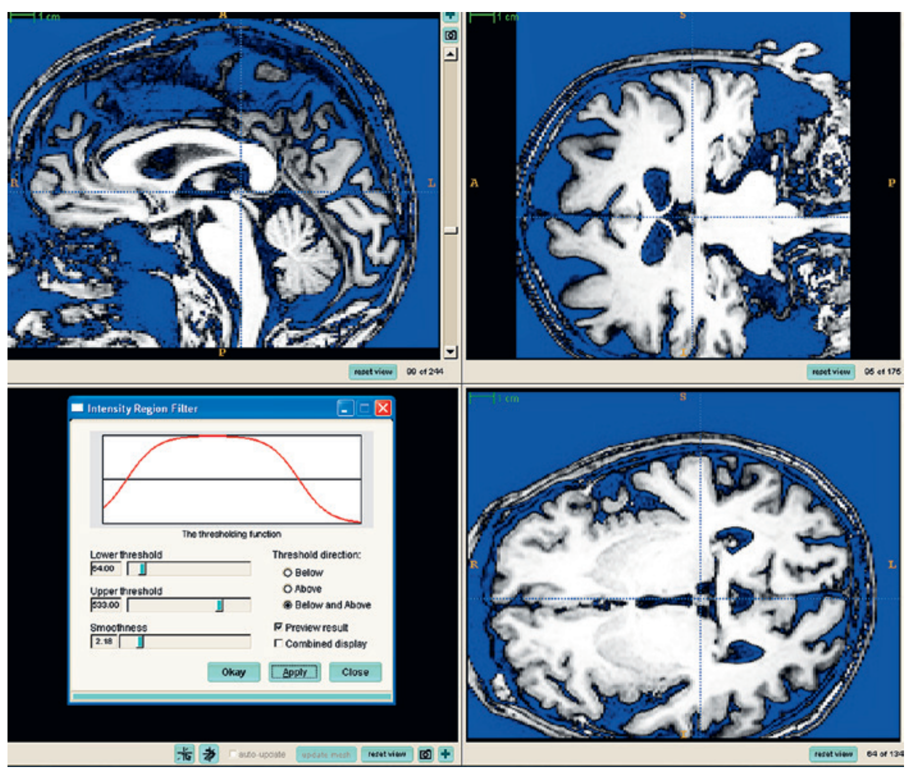

Fig. 4. Selection of upper and lower threshold in the GUI of ITK-SNAP after performing cubic interpolation.

mentation algorithm is used to segment anatomical structures in 3 dimensions. ITK-SNAP has the ability to compute segmentation operation with region competition snakes and edge-based snakes.

Computation of Pineal Gland and Pituitary Gland Volumes

The overall pineal gland and pituitary gland volume was computed using semi-automatic segmentation algorithm, embedded in ITK-SNAP. The region/tissue of interest was selected (Fig. 3). The data were resampled using cubic interpolation method. The upper threshold, lower threshold, and smoothness parameters were adjusted appropriately to enable high accuracy and specificity for the segmentation of pineal gland (Fig. 4). Level Set Active contour (snakes) algorithm was used to control the snake evolution or the movement of snakes in the pixel regions pertaining to the pineal gland and pituitary gland. The algorithm groups the pixels corresponding to pineal gland and pituitary gland into a particular class in all the slices of MRI data and calculates the volume in cubic mm.

ITK SNAP adopts level set active contour model [7–9] as shown below:

$$A_t\,(t,u) = F_{\mathrm{in}ternal} + F_{\mathrm{ext}ernal}$$

where $A(t,u)$ represents the contour at time t, with u being the variable value that is influenced by a duration of time t. $F_{\mathrm{internal}} + F_{\mathrm{external}}$ are the 2 forces acting on the contour.

Computation of external forces by Caselles method is modeled in the following form:

$$C_t\,(t,\,u) = (\alpha g_I + \beta k g_I + \gamma \nabla g_I.N)N$$

The modulating weights are represented by α, β, and γ parameters, respectively. k represents the mean value of the contour.

In Caselles method of level set active contour computation, the calculation of the external forces is done from the gradient magnitude of the intensity of pixels. N represents the contour normal and g_I denotes the normalized gradient magnitude function of image I

$$g_{I = f_{\mathrm{map}}}\left(\frac{\| \nabla (G_\sigma * I) \|}{\max \| \nabla\,(G_\sigma * I) \|}\right)$$

$$f_{\mathrm{map}}\,(x) = \frac{1}{(1 + (x\,/\,v)^l}$$

G_s *I represents the convolution operation with a Gaussian kernel. V, σ, λ are the user-defined parameters.

The 3D volume rendering of the segmented pineal gland and pituitary gland structures was performed using marching cubes algorithm in visualization tool kit [10, 11]. Visualization tool kit is independent of open source tool kit with C++ core. ITK-SNAP utilizes visualization tool kit application programming interface for surface and volume rendering and meshing display.

Previous Work

Findings Related to Pineal Gland

Several radiological case studies are available where researchers have done rigorous analysis on the volume of pineal gland in normal and abnormal subjects. An extensive study conducted on pineal volume in healthy young adults by [2] reports that the mean pineal volume in the case of male adults with no cysts was estimated to be 89.21 ± 28.78 mm^3 and the true pineal volume in healthy adults was reported to be 94.2 ± 40.65 mm^3. A study pertaining to the evolving size of the pineal gland [1] reports that the size of the pineal gland was 26.9 ± 12.4 mm^3 (mean ± SD) in subjects with age greater than 2 years, and in patients with age ranging from 2 to 20 years the volume was observed to be 56.6 ± 27.6 mm^3 (mean ± SD).

A statistical study [12] on 80 human cadavers aimed at comparing the length, height, width, and volume of pineal gland with overall body weight, height, and age, reports that the average pineal volume was highest (158.34 ± 43.17 mm^3) in the age group of 31–40 years, the lowest mean volume (109.90 ± 37.50 mm^3) was reported in the age group of 41–50 years; in the age group of less than 30 years, the pineal volume was found to be 131.47 ± 41.42 mm^3 and in those with age greater than 50 years the pineal volume was 124.97 ± 39.79 mm^3. In weight-related measures, the volume of pineal gland was observed to be highest in subjects with body weight less than 60 kg (140.08 ± 49.63 mm^3), least in subjects with body weight greater than 80 kg (105.67 ± 39.48 mm^3), and the pineal volume was found to be 130.79 ± 63.97 mm^3 in subjects with body weight ranging from 61 to 70 kg and 114.26 ± 47.09 mm^3 in subjects with body weight ranging from 71 to 80 Kg. In the height-related measurements, the pineal volume was observed to be lowest in subjects with height ranging from 171–175 cm (100.84 ± 47.71 mm^3), highest in subjects with height ranging from 165 to 170 cm (145.69 ± 72.32 mm^3), in subjects with height less than 165 cm the pineal volume was found to be 138.74 ± 52.89 mm^3 and in subjects with height greater than 175 cm the pineal volume was reported to be 111.18 ± 32.71 mm^3.

Findings Related to Pituitary Gland

Whole pituitary volume has been reported by Takano et al. [13] as 0 years = 132.6 ± 39.6, 1–4 years = 212.7 ± 44.1, 5–9 years = 309.9 ± 54.9, 10–14 years = 423 ± 110.3, 15–19 years = 586.2 ± 149.8 mm^3. Ikram et al. [3] reports the pituitary volume of male subjects in the 3 age groups: in the first decade the volume was observed to be 116 ± 62 mm^3 ($p = 0.491$), in the second decade, the volume was found to be 268 ± 118 mm^3 ($p = 0.079$), and in the third decade the volume was found to be 309 ± 117 mm^3 ($p = 0.731$). Under the age of 19 years, pituitary gland volume was strongly correlated with age ($r = 0.46$, $p < 0.0001$), compared to that of older (20–35 years) subjects (0.06, $p = 0.76$) [14].

A study conducted by Ju et al. [15] on 33 human cadavers (23 were male cadavers in the age group of 23–87 years and 10 were female cadavers in the age group of 28–76 years) reports that in the anterior lobes the mean width, length, and height of the pituitary gland were found to be 14.3 ± 2.1, 7.9 ± 1.3, 6.0 ± 0.9 mm and 8.7 ± 1.7, 2.9 ± 1.1, 5.8 ± 1.0 mm in posterior lobes, respectively. Ertekin et al. [16] estimated the volume of 6 male pituitary glands with an age range of 35–66 years, using stereoscopic approaches such as point counting (582.14 ± 140.16 mm^3), planimetry (610.08 ± 133.17 mm^3), and elliptical formula (390.99 ± 105.46 mm^3).

Results

Volumetric and Morphometric Analysis of Pineal Gland

The pineal gland segmentation was performed in coronal, axial, and sagittal section views of the subjects' MRI data (Fig. 5; subset (a) shows pineal gland marked in sagittal section, subset (b) shows pineal gland marked in coronal section, subset (c) shows pineal gland marked in axial section, and subset (d) shows volume rendered image of pineal gland).

Table 1 shows the details of the volume of pineal gland computed from the MRI segmentation. The mean volume is 148.741 mm^3 with a SD of 34.745 mm^3.

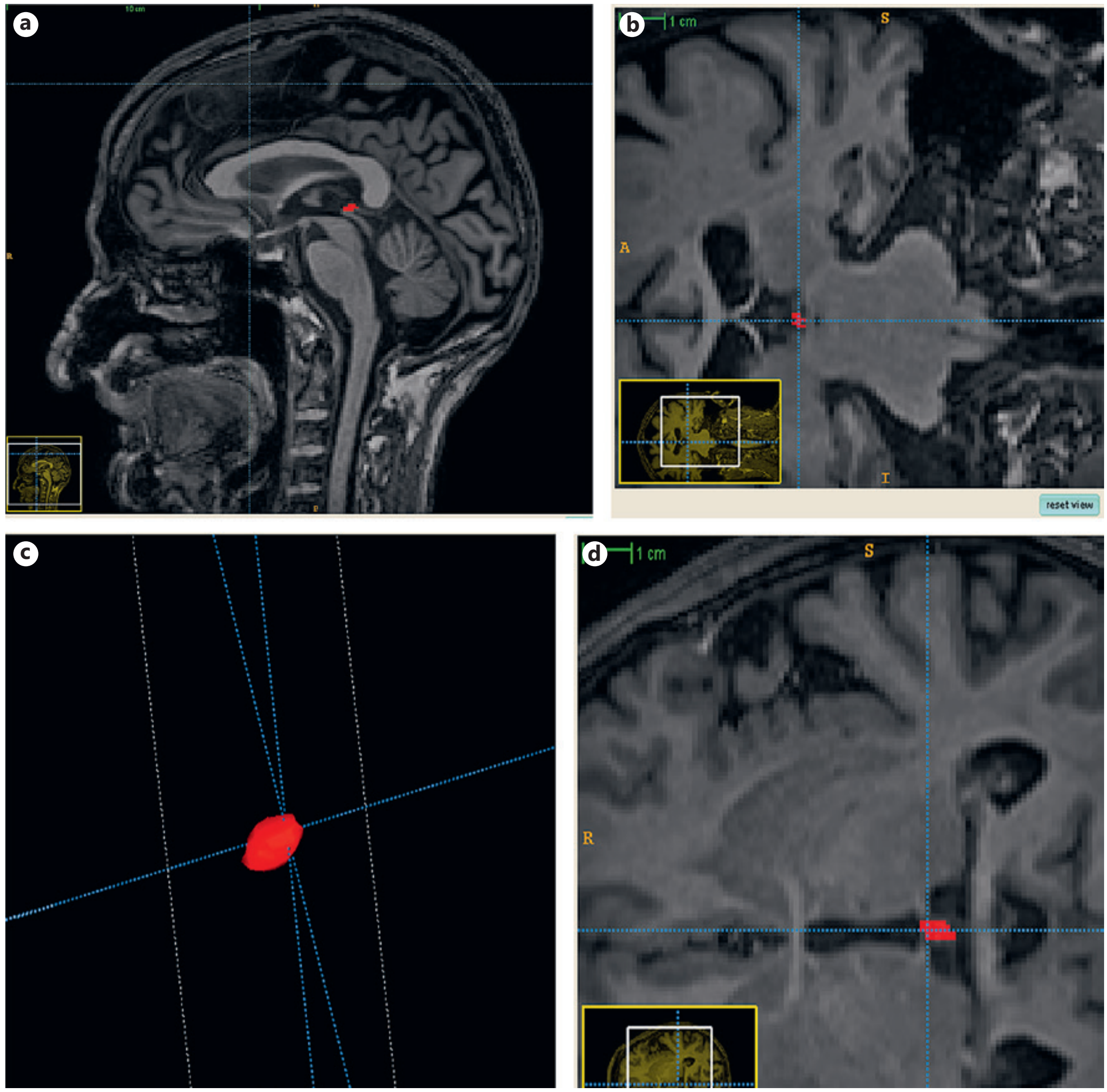

Fig. 5. Segmentation of pineal gland. **a** Pineal gland marked in sagittal section. **b** Pineal gland marked in coronal section. **c** Pineal gland marked in axial section. **d** Volume rendered image of pineal gland.

Table 1. Volume and statistics table of the pineal gland

S. No.	Number of voxels	Volume of voxels, mm^3	Mean	SD
1	58	38.7604	148.741	34.745

Figure 6 shows the morphometric parameters of pineal gland. Subset (a) shows the height of the pineal gland on T1 weighted sagittal section, subset (b) shows the length of the pineal gland on T1 weighted sagittal section, and subset (c) shows the width of the pineal gland on T1 weighted axial section.

The maximum values of length (4.8 mm), width (4.27 mm), and height (3.8 mm) of pineal gland are shown in Table 2.

The head circumference (C) was calculated based on the ellipsoidal assumption of the shape of the head when it is viewed axially, as shown in Figure 7. In this study, we used the Ramanujan's approximation formula to calculate the circumference of the head.

$$C \approx \pi\left[3(a+b) - \sqrt{(3a+b)(a+3b)}\right]$$

Table 2. Maximum length, width, and height of pineal gland

S. No.	Maximum pineal length, mm	Maximum pineal width, mm	Maximum pineal height, mm	Subject's weight, kg	Subject's height, cm	Subject's head circumference, mm
1	4.8	4.27	3.8	35		506.566

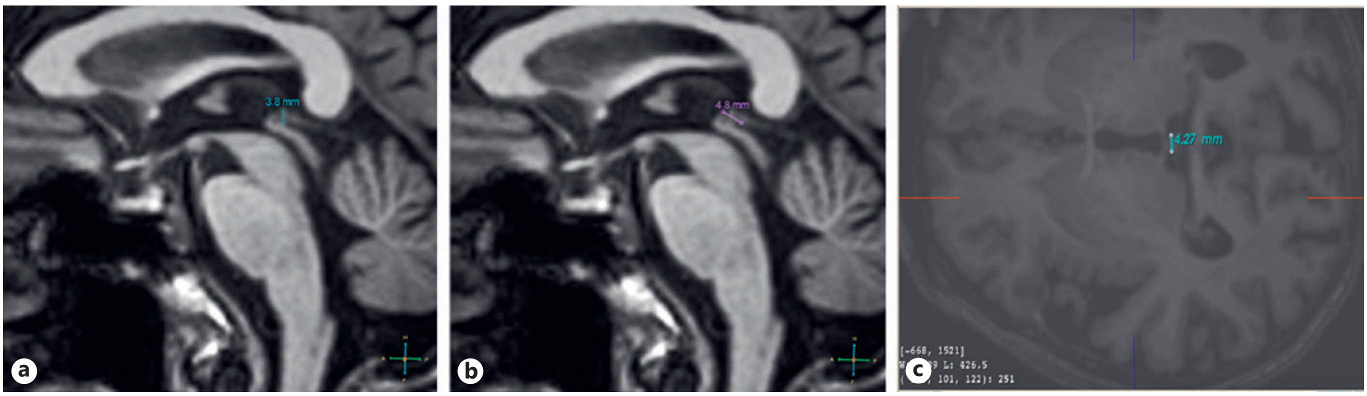

Fig. 6. Morphometric parameters of pineal gland. **a** Height of the pineal gland on T1 weighted sagittal section. **b** Length of the pineal gland on T1 weighted sagittal section. **c** Width of the pineal gland on T1 weighted axial section.

Fig. 7. Area of head.

Volumetric and Morphometric Analysis of Pituitary Gland

Not only is the pineal gland of the subject measured, but also the pituitary gland. Figure 8 shows the segmentation of the pituitary gland, subset (a) shows the pituitary gland marked in the sagittal section, subset (b) shows it in the coronal section, subset (c) shows it in the axial section, and subset (d) shows the volume rendered image of the pituitary gland.

Table 3 shows the details of the volume of pituitary gland computed from the MRI segmentation. The mean volume is 264.412 mm^3 with a standard deviation of 58.537 mm^3.

Figure 9 shows the morphometric parameters of the pituitary gland, such as the height (subset a), length (subset b), and width (subset c) of the pituitary gland on T1 weighted axial section.

The maximum values of length (10.00 mm), width (10.5 mm), and height of pituitary gland (4.7 mm) are shown in Table 4.

Discussion

The pineal gland volume (38.7604 mm^3) of the inedia subject is much smaller than the normal adult volume 94.2 ± 40.65 mm^3. The height, width, and length of the pineal gland is small (3.8, 4.27 and 4.8 mm) compared to the morphometric findings reported by Sun et al. [2] (3.85, 6.92, 6.64 mm). Compared to the subject's age, his pineal volume is less; when compared to age

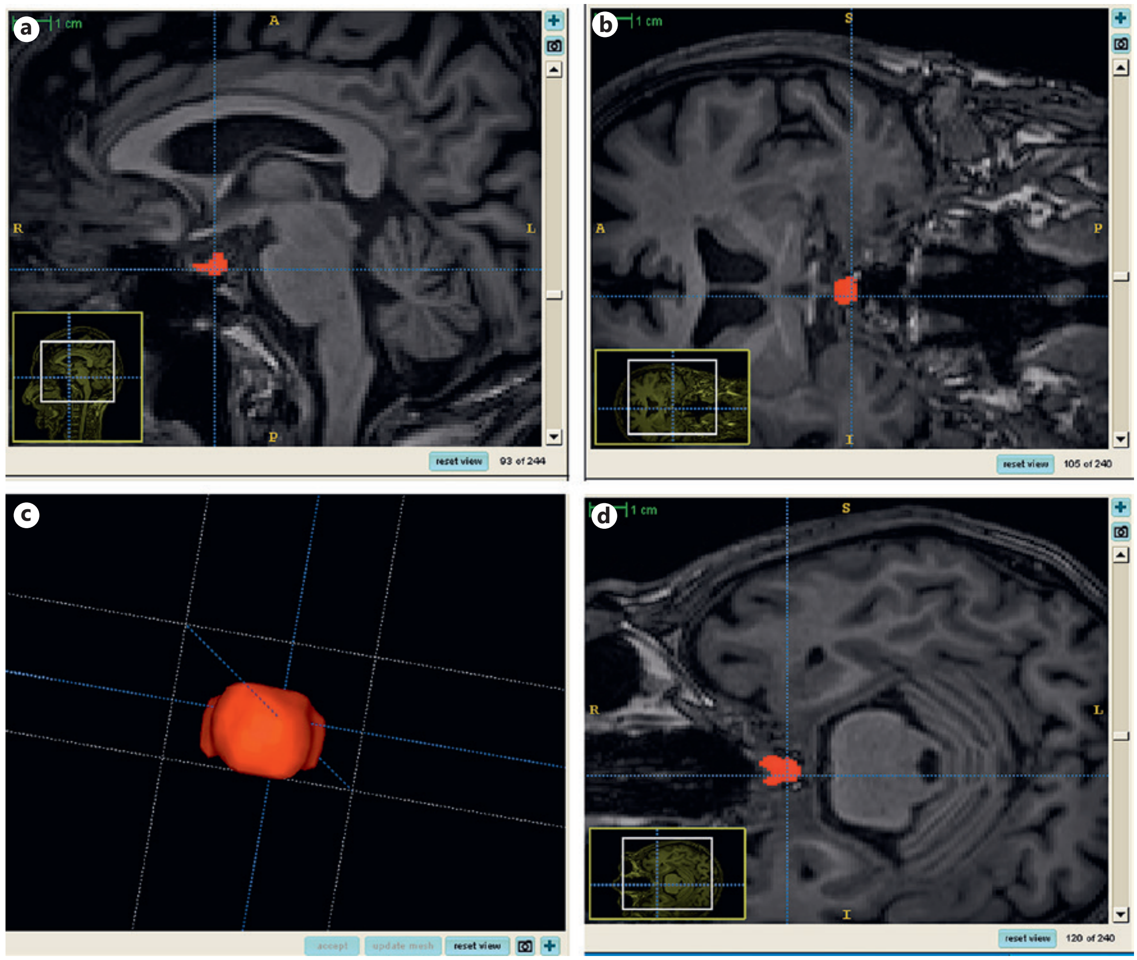

Fig. 8. Segmentation of the pituitary gland. **a** Pituitary gland marked in the sagittal section. **b** Pituitary gland marked in the coronal section. **c** Pituitary gland marked in the axial section. **d** Volume rendered image of the pituitary gland.

Table 3. Volume and statistics table of the pituitary gland

S. No.	Number of voxels	Volume of voxels, mm^3	Mean	SD
1	434	272.552	264.412	58.537

and corresponding volume of healthy young adults and the circumference of head, the pineal volume is less in size. The pituitary volume (272.552 mm^3) of the inedia subject is less compared to the normal pituitary volume, which is around 390.99 mm^3 [16]. The height, width, and length of pituitary gland (4.7, 10.5, 10.00 mm) of the inedia subject is small compared to the normal findings on Korean adults reported by Ju et al. [15] (8 mm in length, 14 mm in width, and 6 mm in height).

A previous study by Fink et al. [17] determined the volume of pituitary gland and its height in normal children within 10 years of age. When we compared our results with this study we found that our results were similar, that is, our calculated pituitary volume (272.552 mm^3) is found normally in male children with age range of 6–8 years and our calculated pituitary height of 4.7 mm corresponds to the volume of 272.552 mm^3 in the volume versus pituitary height graph. Thus, the size of pituitary and pineal glands of the inedia subject falls in the range of 5–10 years in a normal child.

The purpose of this study is to put forth a hypothesis that the humans can sustain in the inedial state for longer duration if the pineal and pituitary volumes are low and

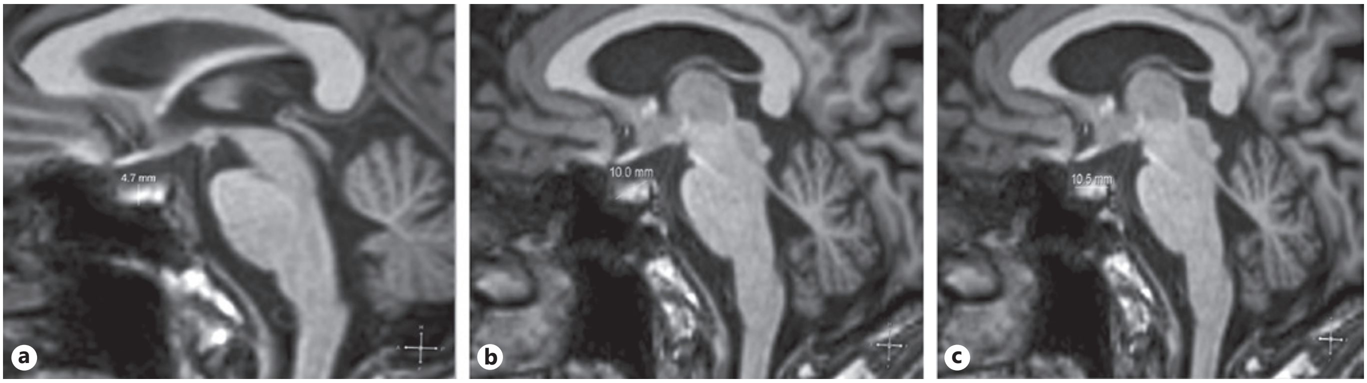

Fig. 9. Morphometric parameters of the pituitary gland. **a** Height of the pituitary gland on T1 weighted sagittal section. **b** Length of the pituitary gland on T1 weighted sagittal section. **c** Width of the pituitary gland on T1 weighted axial section.

Table 4. Maximum length, width, and height of pituitary gland

S. No.	Maximum pituitary length, mm	Maximum pituitary width, mm	Maximum pituitary height, mm	Subject's weight, kg	Subject's height, cm	Subject's head circumference, mm
1	10.00	10.5	4.7	35	158	506.566

if the brain and its neuroendocrine morphology does not age along with the body. In addition, no reference data have been established on the relation between inedia and low pineal and pituitary volumes; earlier studies have shown that there is no significant relationship between the total pineal volume and the age of the subject [18].

From the morphometric and volumetric analysis of pineal and pituitary glands, it was found that the subject has significantly low pineal and pituitary volumes which falls under the category of normal young child.

Our observation is that the subject's brain resembles that of a person in the age group of 5–10 years, although his body is aging over the course of time his neuroendocrine morphology and functions still continues to remain as that of a normal young child. Although it is tempting to conclude that our hypothesis is true, due to the lack of clinical and hormonal profile of the inedia subject, we could only say that the neurohormonal morphology of inedia subject is within childhood range.

Disclosure Statement

We declare that we do not have any financial or other relationships that might lead to a conflict of interest. The manuscript complies with ICMJE guidelines.

Author Contribution

Both authors have contributed equally to this work.

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