TITLE

The adhesio interthalamica as a neuroanatomical marker of structural differences in healthy adult population

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ABSTRACT

The adhesio interthalamica (AI) is a small midline brain structure that connects the left and right thalamus. According to *in vivo* data, between 2.3% to 22.3% of the general population lack the AI, and the question of whether this absence is more prevalent in males than in females is a matter of debate. Despite the existence of these demographic figures, it remains unclear how this distinctive feature affects healthy people, or what specific anatomic profile is related to the presence or absence of the AI. The aim of this study was to investigate whole brain gray matter (GM) volumetric differences depending on the presence or absence of the AI. A total of 240 healthy adult volunteers completed one MRI scanning session. After the AI assessment, the data from 110 participants were included in the final sample, of which 12.9% of the participants (n=31) presented complete AI absence vs. 32.9% of participants (n=79) who presented complete AI presence. Then, whole-brain group comparison analysis revealed that the absent AI brain, compared to the present AI brain, was associated with lower GM volume in the premotor cortex, inferior frontal gyrus, and anterior temporal cortex. Interestingly, neuroscience research has linked emotional and cognitive control brain processing to the latter two regions. The importance of these findings lies in providing a neuroanatomical profile for the absent AI brain in healthy human adults.

KEYWORDS

CAT12; gray matter; adhesio interthalamica; voxel-based morphometry; frontal cortex; individual differences

INTRODUCTION

Different studies investigated brain anatomy and its relationship with individual differences, thus providing more and more details about the structural organization of the human brain, targeting either its generalities or its particularities. Despite all the advances made, some brain structures have received less attention and interest from the scientific community, and so they have been investigated less. This is the case of the adhesio interthalamica (AI), a region close to the thalamus, about which little is known regarding its anatomical correlates and functional role.

From an anatomical perspective, the AI is considered a small brain structure because its anterior-posterior length extends for ~1cm (see **Figure 1**), and it is formed by nerve cells and nerve fibers (Gray, 1918). When present, the AI usually communicates the two parts of the thalamus, a subcortical structure formed by two large ovoid masses located in each brain hemisphere. Surrounding the internal medullary lamina of the thalamus are the diverse thalamic nuclei, which can be classified as lateral, medial, and anterior masses (Hendelman, 2006). The AI is in contact with the midline nucleus of the medial mass and specifically connects the medial surface of the thalamus, which forms the higher part of the lateral wall of the third ventricle. The dorsomedial nucleus and the intralaminar nuclei, formed by the centromedian and the parafascicular inter alia, are other thalamic nuclei found next to the AI.

Some of the research related to AI has been carried out in order to describe individual differences in the general population, thus generating some demographic data. Postmortem studies have shown that the AI is absent in approximately 15-25% of healthy humans (Samra & Cooper, 1968); however, *in vivo* studies using magnetic resonance imaging (MRI) increased the variability of this proportion to a range between 2.3% and 22.3% (Trzesniak et al., 2016). Regarding sex differences, some studies have found that the AI is more frequently absent in males than in females (Allen & Gorski, 1991; Borghei et al., 2020; de Souza Crippa et al., 2006; Malobabić et al., 1987; Nopoulos et al., 2001; Samra & Cooper, 1968), although other studies failed to find any significant differences (Damle et al., 2017; Erbağcı et al., 2002; Haghir et al., 2013; White et al., 2013).

Very little research has been carried out in healthy populations with the objective of investigating the role of the AI. A recent exploratory study by Borghei et al. (2020) used the data on 402 healthy brains from the Human Connectome Project database. The authors found that AI absence was associated with negative emotional function, inhibition, and attention processes. Additionally, the authors suggested that AI presence was predicted by sex, loneliness, and inhibition. In this line, a previous study found that the size of the AI positively mediated the relationship between age and attentional scores, as measured by the Continuous Performance Test–Identical Pairs (Damle et al., 2017). On the other hand, much more literature involves clinical populations, such as schizophrenia (Ceyhan et al., 2008; Ettinger et al., 2007; Haghir et al., 2013; Nopoulos et al., 2001; Takahashi, Suzuki, Nakamura, et al., 2008; Takahashi, Suzuki, Zhou, et al., 2008; Trzesniak, Kempton, Busatto, de Oliveira, et al., 2011), temporal epilepsy (Trzesniak et al., 2016), or bipolar disorder (Landin-Romero et al., 2015; Takahashi et al., 2010). Overall, these studies have reported that the AI is less prevalent and smaller in individuals with the aforementioned pathologies. These results point out the relevance of the AI in proper emotional and control functioning. In other words, they show that AI anomalies, including its complete absence, are broadly correlated with a wide variety of psychological disorders.

Although there are some previous functional studies, the consequences for the brain structural organization of having or not having AI have not been described in the healthy population so far. Therefore, in the present research, an exploratory whole-brain voxel-based morphometry (VBM) analysis approach was used to investigate the possible differences in gray matter (GM) brain volume in a sample of 240 healthy individuals. Structural neuroimaging data from participants with complete present AI or complete absent AI were used to configure two experimental groups. We were interested in comparing the GM volume of the groups and determining which other brain regions were related to the two distinctive AI profiles. Predictably, we expected that participants with an absence of the AI would show reduced regional volume in the medial area of the thalamus where the AI is located. In addition, we hypothesized that, due to thalamo-cortical anatomical interactions and the AI's association with emotional and cognitive control processes, between-group differences would be located in cortical areas that usually manage these functions.

MATERIALS AND METHODS

Participants

In the present study, participants were 240 right-handed healthy volunteers (125 females) with an age range between 18-46 years old (mean age = 21.76; SD = 3.42). They were recruited from the student population of the Universitat Jaume I through poster advertisements and word of mouth. None of them had a previous psychiatric or neurological diagnosis. Informed consent was obtained from each participant before participation, and they received monetary compensation for their time and effort. The research project was approved by the Ethical Committee of the Universitat Jaume I.

MRI acquisition

Anatomical MRI data were acquired using a 1.5 T Siemens Avanto scanner (Erlangen, Germany). High-resolution T1-weighted gradient-echo pulse sequences (MPRAGE) were acquired, covering the whole brain of all the participants (TE = 3.8 ms, TR = 2200 ms, flip angle = 15º, matrix = 256 x 256 x 160, voxel size = 1 mm^3). Participants were placed in a supine position in the MRI scanner, and their heads were immobilized with cushions to reduce involuntary motion. Furthermore, participants were asked to minimize head movement. All the scanner acquisitions were performed in parallel to the anterior commissure-posterior commissure plane (AC-PC).

Image Preprocessing

The Computational Anatomy Toolbox (CAT12; v12.6 (r1450); www.neuro.uni-jena.de/cat/) for the Statistical Parametric Mapping (SPM12) package (v7487; Wellcome Department of Imaging Neuroscience, London, UK; www.fil.ion.ucl.ac.uk/spm/), run in the Matlab R2015b environment (v8.6; www.mathworks.com), was used to conduct the VBM analysis. The preprocessing procedure implemented in CAT12 is an extension of the unified segmentation approach, which includes initial registration, bias correction, and segmentation in a unified model (Ashburner & Friston, 2005). The preprocessing steps were: 1) segmentation of the images into GM, white matter (WM), and cerebrospinal fluid (CSF); 2) registration to a standard template provided by the International Consortium of Brain Mapping (ICBM); 3) DARTEL normalization to the Montreal Neurological Institute (MNI) template; and 4) modulation by the "affine + nonlinear" components derived from spatial normalization. After these steps, the total

intracranial volume (TIV) was estimated as the sum of the GM, WM, and CSF volumes to correct for different head sizes and volumes across participants. Prior to second-level analysis, a data quality check was carried out to assess the homogeneity of the GM tissue, and no outliers were identified. Finally, brain images were spatially smoothed using an 8-mm full width at half maximum Gaussian kernel.

AI assessment

All cases were evaluated by two trained researchers who served as independent evaluators. We refer the reader to **Table 1** for a summary of the AI assessment results. The evaluators visually inspected participants' preprocessed MRI data using MRIcron software to determine the presence or absence of the AI. The method consisted of identifying the coronal slices where the thalamus is visible and then counting the number of slices lacking the AI. If it was not possible to identify the AI on three or more slices, the participant's data were classified as having a complete absence of AI; the opposite case was fulfilled by participants with a complete presence of AI (Takahashi, Suzuki, Zhou, et al., 2008). Cases not classified as complete AI absence or presence were recorded as partial AI because this structure was only visible in slice 1 or slice 2. The assessment of the AI length consisted in identifying the number of coronal slices in which the AI was present, then multiplying this value by the slice thickness MRI acquisition value (1 mm). The results related to the AI length are summarized in **Table 2**.

Demographic analysis

IBM SPSS Statistics (v25) software was used to determine whether there were any statistically significant differences in age or sex between the experimental groups by means of the Student t-test. In addition, with the aim of investigating sex and age differences, a two-sample t-test was used to perform within-group comparisons in the absent AI group or in the present AI group.

Neuroimaging analysis

Second-level statistical analyses were performed using the SPM12 package to test whole-brain anatomical differences related to the presence or absence of the AI. Two-sample t-tests comparing the experimental groups were conducted. Specifically, to test our predictions, two statistical contrasts were used: 1) to determine brain regions with higher GM volume in the Present AI group (Present AI group > Absent AI group); 2) to find

brain regions with higher GM volume in the Absent AI group (Absent AI group > Present AI group). The model included the variable group as covariate of interest and TIV as covariate of no interest, whereas the threshold masking in each contrast was set at 0.12. The statistical inference was applied by using threshold-free cluster enhancement (TFCE; Smith & Nichols, 2009), included in the CAT12 toolbox, establishing the critical threshold to control the family-wise error (FWE) at $p < 0.05$ (5000 permutations). This method is based on a nonparametric approach, which provides some advantages over parametric methods, such as better control for nonstationary smoothing and eliminating the need for a cluster-forming threshold (Li et al., 2017).

RESULTS

AI assessment and demographic results

The evaluation of the 240 cases yielded the classification of participants into four groups (see Table 1). A total of 31 participants (18 male) had a complete absence of the AI (Absent AI group). Absence of the AI was significantly more common in males than in females ($t_{30} = 15.76$, $p < 0.001$), and significant differences in age were also found in this group ($t_{30} = 37.9$, $p < 0.001$). The second group was composed of 79 participants (29 male) who had a complete AI (Present AI group); in other words, they had no coronal slices where the GM band connecting the thalami could not be identified. Presence of the AI was significantly more common in females than in males ($t_{78} = 29.92$, $p < 0.001$) and, as in the Absent AI group, significant differences in age were found ($t_{78} = 70.03$, $p < 0.001$). Finally, some cases were classified as partial AI because it was possible to distinguish this structure in some but not all of the cortical slices. In the subsequent VBM analysis, the Absent AI group was compared with the Present AI group in order to make a clear distinction between presence and absence of the AI. The two-sample t-tests showed that there were significant differences in sex ($F_{108} = 0.802$, $p = 0.042$), but no significant differences in age, between these groups ($F_{108} = 0.48$, $p > 0.05$).

Table 1: Sample's demographic details and participants' classification into experimental groups.

Group	**Total**	**Percentage**	**Sex**		**Age**
			Female	Male	(Mean age)
Absent AI*	31	12.9%	13	18	22.32
Present AI*	79	32.9%	50	29	21.15
1 slice	75	31.3%	37	38	22.3
2 slices	55	22.9%	25	30	21.58

*Groups entered in the VBM analysis.

Table 2: Prevalence and length of the AI in the entire sample.

	N	**AI absent**	**AI length (mm)**
		N	Mean (SD)
All sample	240	31	13.79 (3.23)
Females	125	13	14.13 (2.96)
MAles	115	18	13.43 (3.48)

VBM analysis results

As expected, the two-sample t-test contrast testing differences in GM volume in the Present AI group compared to the Absent AI group (Present AI group > Absent group) revealed lower GM volume in the medial area of the thalamus where the AI is located in participants with absence of the AI. In addition, participants with absence of the AI showed lower GM volume in the left inferior frontal gyrus, the left premotor cortex, and the right anterior temporal pole (see details in **Table 2** and **Figure 2**). No statistically significant differences were found in the opposite contrast (Absent AI group > Present AI group).

Table 3: Brain regions associated with lower GM volume in the absent AI group. Contrast: Present AI group > Absent AI group. The results were corrected for multiple comparisons using a threshold set at $p < 0.05$ FWE via TFCE.

Brain Region	Hemisphere	Brodmann's Area	MNI coordinates	Cluster Size *k*	p-value FWE-corr
AI			0 -10 2	1503	0.001
Inferior frontal gyrus	Left	48/44	-52 12 4	436	0.027
Premotor	Left	6	-54 6 24	171	0.042
Anterior Temporal Pole	Right	36	22 10 -38	113	0.045

$p < 0.05$ FWE via TFCE.

On the other hand, motivated by the differences observed between the distributions of the sexes in both groups, we conducted further analyses in order to assess differences by sex and the presence or absence of the AI. Thus, we performed an interaction analysis by means of a 2 × 2 ANCOVA (Sex × AI Group). Results showed a significant positive interaction effect in the Anterior Cingulate Cortex (ACC; BA32) and left insula (BA48). All the details and results can be found in the **Supplementary Information**.

DISCUSSION

In the present study, structural neuroimaging data were used to investigate brain anatomical differences associated with the absence or presence of the AI, a small structure connecting the left and right thalamus. Little is known about the implications of lacking the AI in the healthy population. Using an exploratory approach, we confirmed our expectations by using VBM analysis. Whole-brain GM volume comparisons showed significant between-group differences in the brain area located between the thalami; the absent AI group had less GM volume where the AI is usually located. In addition, our findings also showed that these participants presented lower regional volume in the left premotor cortex, left inferior frontal gyrus, and right anterior temporal cortex.

In this study, 12.9% of the participants were found to lack the AI. This percentage is similar to the results reported in other studies with healthy populations (Ceyhan et al, 2008; Erbağcı et al, 2002; Haghir et al, 2013). In addition, we also replicated the result

showing that the AI is usually absent more in males than in females (Allen & Gorski, 1991; Borghei et al., 2020; de Souza Crippa et al., 2006; Malobabić et al., 1987; Nopoulos et al., 2001; Samra & Cooper, 1968). Interestingly, among participants with complete AI presence, the prevalence is higher in females than in males.

As mentioned above, to investigate the brain anatomical profile associated with absent AI, we used whole-brain VBM analysis to compare participants with completely present AI with participants with completely absent AI. Participants lacking the AI also have lower GM regional volume in the left premotor cortex, left inferior frontal gyrus, and right anterior temporal cortex. The differences in these cortical regions may be related to the proximity of the AI to medial thalamic nuclei because these nuclei are connected to these cortical areas. The dorsomedial thalamic nuclei project to the prefrontal cortex (Abril Alonso, 2001; Buchsbaum et al., 2006; Crossman & Neary, 2007; Eckert et al., 2012; Haber & Calzavara, 2009; Hendelman, 2006; Klein et al., 2010; Perea Bartolomé & Ladera Fernández, 2004). Additional connections to the orbitofrontal cortex (Haber & Calzavara, 2009; Klein et al., 2010), and to subcortical structures such as the caudate nucleus (Eckert et al. 2012), have been described. Meanwhile, the centromedian and parafascicular nuclei form a main part of the intralaminar nuclei and are close to the AI. These nuclei are connected to the primary motor cortex, cortical association areas, anterior insula/frontal operculum, and subcortical areas, such as striatal areas (the putamen and the pallidum), hippocampus, and amygdala (Haber & Calzavara, 2009; Eckert et al. 2012). The AI is spatially close to the midline, which in turns shows connectivity with striatal areas, the cingulate gyrus, the amygdala, and basal nuclei (Haber & Calzavara, 2009; Hendelman, 2006; Abril Alonso, 2001).

Literature relating cognitive function to thalamic nuclei is scarce; however, recent studies suggest that some thalamic regions - especially the dorsomedial portion - are involved in executive functions such as behavioral flexibility and attention shifting (see Halassa & Kastner, 2017). These reports are not surprising, given that the thalamus exerts control on cortical-subcortical processes through thalamocortical loops (Borghei et al., 2020; Pessoa, Medina, Hof, & Desfilis, 2019). Indeed, our results highlight the relationship between the AI and the left inferior frontal gyrus, in line with the connectivity profile of the medial thalamic nuclei, as both the intralaminar and dorsomedial nuclei have multiple connections with prefrontal areas (Abril Alonso, 2001; Buchsbaum et al., 2006;

Crossman & Neary, 2007; Eckert et al., 2012; Haber & Calzavara, 2009; Hendelman, 2006; Klein et al., 2010; Perea Bartolomé & Ladera Fernández, 2004). The same connectivity scenario is found when studying the projections of other nuclei close to the AI, such as the centromedian and parafascicular, which have projections to primary motor cortex, premotor areas, and association areas of the frontal lobe (Haber & Cazavara, 2009). These connections would support our findings because these areas are found to have less GM volume in participants lacking the AI (i.e. left premotor cortex and left inferior frontal gyrus).

In addition to the premotor cortex and inferior frontal gyrus, our results indicate differences in the right anterior temporal cortex. Regarding the relationship between the AI and temporal areas, one study performed with mesial temporal lobe epilepsy patients linked absence of the AI to lower scores on verbal memory and executive function tests. Authors posited that AI absence has clinical significance and lies behind neurodevelopmental alterations in this disorder (Trzesniak et al., 2016). Consequently, we believe that a functional association may exist between the AI and some temporal lobe areas. Supporting our hypothesis, on the one hand, previous investigations on schizophrenia and different mood disorders have related the absence of the AI to psychiatric dysfunction (e.g. Ceyhan et al., 2008; Landin-Romero et al., 2015; Trzesniak, Kempton, Busatto, Oliveira, et al., 2011), indicating a possible relationship between the AI and a vast range of emotional (e.g. depression or anxiety; Buckley et al., 2009) and cognitive domains (e.g. attention, executive function, or working memory; Carter et al., 2008). On the other hand, research performed with healthy populations has also linked the size of the AI to attention differences (Damle et al., 2017) and lower inhibition in participants without the AI (Borghei et al., 2020). Moreover, Borghei and colleagues (2020) related the AI to loneliness, which is usually linked to the temporal anterior lobe, and to attention, which is associated with the premotor area and the inferior frontal cortex. Considering all this evidence, along with our results connecting the AI and the thalamus to brain areas linked to social behavior, affective, and cognitive control processes, may lead us to think that the AI plays an important role in these processes (i.e., Dixon, 2015; Erika-Florence, Leech, & Hampshire, 2014; McGuire & Botvinick, 2010; McTeague et al., 2017; Swick, Ashley, & Turken, 2011; Albein-Urios et al., 2013; Buhle et al., 2014; Muhlert & Lawrence, 2015; Olson, Plotzker, & Ezzyat, 2007). Supporting our claims, recent reviews highlight the relevance of the thalamus in these domains (Gao et al., 2019;

Halassa & Kastner, 2017). The thalamus has been widely established as a "relay-station" between cortical and basal ganglia structures (the so-called "cortico-basal ganglia-thalamo-cortical loop"; Haber, 2014; Pessoa, 2017; Pessoa et al., 2019). Therefore, anatomical differences in thalamic structures would be related to individual differences, not only in motor and sensory processes - as classically defined -, but also in higher-order cognitive functions.

Some potential limitations must be considered before concluding. On one hand, a 1.5T scanner was used to acquire the images and, therefore, may present a limited spatial resolution. In this regard, the AI structure was considered present when it could be clearly located - as a gray matter bridge - on three or more slices in both the coronal and axial views. Using this criterion to assess the presence of AI could be considered conservative, but it makes a clear distinction when classifying subjects. This approach has also been used in previous published works that used a 1.5T scanner and similar imaging parameters to ours (Ceyhan et al., 2008; de Souza Crippa et al., 2006; Haghir et al., 2013; Takahashi et al., 2010; Takahashi, Suzuki, Nakamura, et al., 2008; Takahashi, Suzuki, Zhou, et al., 2008; Trzesniak et al., 2016). Nevertheless, the results obtained from different MRI scanners (e.g., 1.5T, 3T, or more) should be interpreted cautiously. On the other hand, only self-reported assessments were used to evaluate the participants' health status (e.g., previous psychiatric or neurological diagnosis), which may lead to inaccuracies. Subsequently, the findings reported in this study should be considered preliminary, and further studies would be needed to confirm and extend our results.

To our knowledge, this is the first brain anatomy report that shows whole-brain GM volume differences in healthy individuals due to the presence or absence of the AI. Adults lacking the AI also have lower regional volume in the medial area of the thalamus, as well as in the left inferior frontal gyrus, the left premotor cortex, and the right anterior temporal pole. Because of the proximity of the AI to the medial thalamic nuclei, and taking into account the projections of these nuclei, the AI may be functionally related to emotional and cognitive control processes. Further neuroimaging studies are need to directly investigate the involvement of the AI in higher-order cognitive functions.

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FIGURES

Fig 1 Examples of sagittal (right), coronal (middle), and axial (left) T1-weighted MRI images showing a brain without (a; green circle) and with (b; blue circle) the adhesio interthalamica (AI)

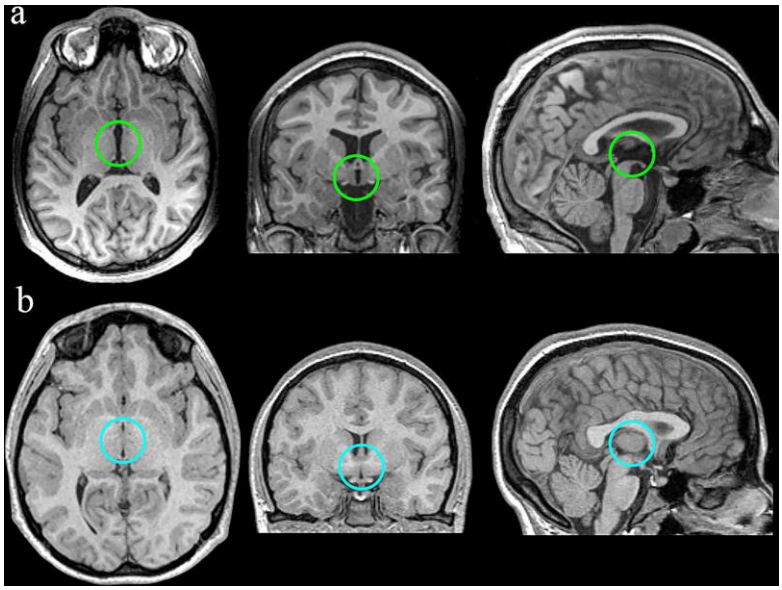

Fig 2 Brain areas with lower GM volume in the Absent AI group. Contrast: Present AI group > Absent AI group. Results were corrected for multiple comparisons using a threshold set at $p < 0.05$ FWE via TFCE. Color bar represents TFCE-values