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Morphological variations and cortical atrophy of the precuneus in normal aging and Alzheimer's disease

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Abstract

The precuneus is a central hub of the human brain, and its morphology displays a noticeable individual variability. It is larger in humans than in other primates, and it is affected by atrophy and hypometabolism in the early stages of Alzheimer's disease (AD). In this study, we compare its general morphology in normal aging subjects and AD patients, considering its geometry through shape analysis, and the atrophy at its boundary by quantifying the intersulcal spacing. Results suggest that the AD sample displays a reduction of the inferior regions of the precuneus, namely those that fade into the posterior cingulate and retrosplenial cortex. During aging, sulcal spacing is pronounced at the superior and posterior regions, although in the AD sample the latter change is more marked. However, these differences are associated with a remarkable individual variation and a consistent overlap between group ranges. This study stresses further the differences between the dorsal and ventral regions of the precuneus. Beyond functional factors, the dorsal areas represent a region of scarce spatial constraints, whereas the ventral regions are embedded in a complex topological environment. This structural difference must be considered when investigating cortical morphology in both normal and pathological conditions.

KEYWORDS
brain morphology, neurodegeneration, parietal lobes, shape analysis, sulcal spacing

1 | INTRODUCTION

The precuneus is an association region with a key role in integrating somatic and visual signals, merging the resulting combinations within the frame of episodic memory (Cavanna & Trimble, 2006; Margulies et al., 2009; Zhang & Li, 2012). In terms of cytoarchitectonic areas, it is part of the superior parietal lobule, roughly separated into anterior, middle, and posterior regions, which are differently involved in somatic (more anteriorly) and visual (more posteriorly) integration (Scheperjans et al., 2008). This organization is due to a longitudinal gradient involved in body–vision integration and a vertical one linking visuospatial and autonoetic functions (Bruner, 2023; Jiang et al., 2023). The precuneus is also a main hub of the whole cerebral system in terms of structural and functional connections (Hagmann et al., 2008; Van Den Heuvel et al., 2010), with a complex pattern of connectivity integrating the default mode network with different cognitive domains, including somatic perception and body awareness, vision, and attention (Cunningham et al., 2017; Dadario & Sughrue, 2023; Herbet et al., 2019; Jitsuishi & Yamaguchi, 2023; Tanglay et al., 2022). The cognitive management of awareness and attention within the frame of body cognition and episodic memory suggests that the precuneus might be central to several aspects of consciousness and the

construction of self and agency (Bruner, 2023; Cavanna, 2014; Darby et al., 2018; Freton et al., 2014; Northoff & Bermpohl, 2004).

The precuneus is particularly variable among adult humans, mainly in terms of longitudinal extension (Bruner et al., 2014; Bruner, Pereira-Pedro, Chen, & Rilling, 2017). Additionally, it also displays a noticeable variability concerning its vertical development (Bruner & Pereira-Pedro, 2020), cortical surface area (Bruner et al., 2015), and folding patterns (Bruner, Pereira-Pedro, & Bastir, 2017; Pereira-Pedro & Bruner, 2016). Finally, it is proportionally larger in humans when compared with other primates, suggesting a recent evolutionary expansion in our lineage (Bruner, Pereira-Pedro, Chen, & Rilling, 2017).

In the last decades, there has been compelling evidence suggesting that the precuneus is sensitive to neurodegenerative processes, particularly in Alzheimer's disease (AD), suffering amyloid accumulation and hypometabolism since the earliest prodromal stages of the disease (e.g., Buckner et al., 2008; Dadario & Sughrue, 2023; Grothe et al., 2016; Jacobs et al., 2012, 2013; Karas et al., 2007; Koch et al., 2018, 2022; Levin et al., 2021; Rami et al., 2014). Taking into account the high energetic load of the precuneus, its topological properties, high thermal load (metabolic heat accumulation), and vascular arrangement, it has been proposed that the recent anatomical changes of the precuneus associated with our evolution might have increased the vulnerability to structural or functional imbalances (Bruner et al., 2014; Bruner & Jacobs, 2013, 2024).

Although research on the precuneus has experienced a substantial increase in the last decade, information on its morphological variability in normal and pathological conditions is still scarce. In this study, we compared the morphology of the precuneus in a sample of AD patients and a control sample of healthy individuals of the same age. We considered both the general shape of the precuneus and the degree of atrophy at its boundaries, under the null hypothesis of no differences between samples or regions.

2 | MATERIALS AND METHODS

In this survey, we have compared MRI scans from 39 AD patients (82 ± 6 years old, age range: 69–97 years old) with a control sample of 42 healthy subjects (81 ± 5 years old, age range: 69–92 years old). The AD sample (Vallecas Alzheimer Reina Sofía—VARS study) and control sample (Proyecto Vallecas—PVAL) come from previously published studies (see Garo-Pascual et al., 2024; Sánchez-Juan et al., 2024 for more information on samples and MRI procedures). AD cases have been confirmed through neuropathological validation at autopsy. Control subjects have been followed during one decade and did not present evidence of cognitive impairment. Only the left hemisphere has been considered in this survey.

For a general descriptive comparison, we contrasted the two samples through a conventional voxel-based morphometry analysis of regional grey matter atrophy, following standard procedures implemented in the Computational Anatomy Toolbox (CAT12, https://neuro-jena.github.io/cat/) for Statistical Parametric Mapping software (SPM12, Wellcome Trust Center for Neuroimaging) that have been described in detail previously (Gaser et al., 2024). The AD and healthy control groups were compared using voxel-wise two-sample t-tests, and voxel-wise effects were corrected for multiple comparisons using the false discovery rate ($p_{FDR} < 0.05$). Subsequently, we performed two specialized analyses on the precuneus to investigate local morphological differences.

In a first study, the morphology of the precuneus was investigated through geometric morphometrics, namely by using landmark-based multivariate shape analysis (Mitteroecker & Gunz, 2009; Mitteroecker & Schaefer, 2022; Slice, 2007). For each subject, we selected the parasagittal MRI slice that displayed the most complete extension of the precuneus and used this image to build a geometrical model based on 30 bidimensional landmarks (Figure 1a). Anatomical landmarks include the dorsal boundaries of the precuneus between the postcentral and occipital cortex (dorsal endpoint of the marginal ramus of the postcentral sulcus and dorsal endpoint of the perpendicular fissure, respectively), the anterior margin of the *tentorium cerebelli*, the posterior margin of the splenium, and the flexion of the marginal ramus of the cingulate sulcus. All the other landmarks are semilandmarks positioned at equally spaced intervals between these anatomical references. In this analysis, sliding procedures to minimize the Procrustes distance or the bending energy (Gunz & Mitteroecker, 2013) have not been employed for two main reasons. First, the curves considered here are smooth and simple and do not show a complex geometry. There are several disagreements on the effect of these sliding procedures (e.g., Perez et al., 2006; Klingenberg, 2008; Shui et al., 2023; Zelditch & Swiderski, 2023) and, in this case, equally spaced landmarks are sufficient to represent the shape of the boundaries. Second, all the studies published previously on the shape variation of the precuneus have employed the same criterion, which is therefore recommended to compare the results. Beyond these outline landmarks, we also added a central landmark at the most central region of the subparietal sulcus to separate the dorsal region of the precuneus (precuneus sensu stricto) from the ventral region (gradually smoothing into the retrosplenial and posterior cingulate regions). Because of the atrophy associated with the dorsal region in both normal and pathological aging, the dorsal landmarks do not match the cortical boundaries of the precuneus but its meningeal (endocranial) outline. Also, in the case of the anterior and posterior boundaries, the landmarks have been conventionally sampled in the middle of the interposed space between the precuneus and the postcentral and occipital cortex, respectively. This approach is aimed at quantifying the original shape of the space occupied by the precuneus independently from brain mass loss.

Coordinate systems of all the subjects have been registered through Procrustes Superimposition, which includes translation to a common centroid, scaling to unitary size, and rotation to minimize the differences between corresponding landmarks (Zelditch et al., 2012). Shape variation and shape differences have been tested through Principal Component Analysis and Discrimination Analysis, computed on the covariance matrix of the shape coordinates. Landmarks were sampled with tpsDig 2.32 (Rohlf, 2017) and statistics were performed with MorphoJ 1.08.01 (Klingenberg, 2011) and PAST 4.05 (Hammer et al., 2001).

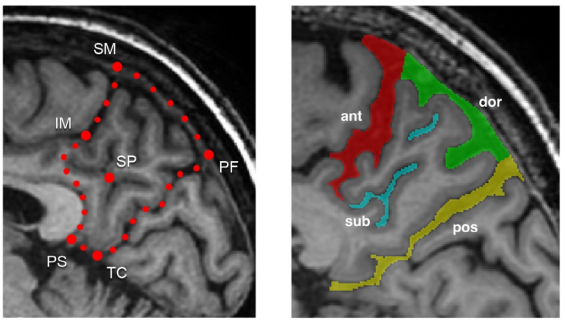

FIGURE 1 (a) The geometrical model used to delineate the shape of the precuneus. Larger dots represent anatomical references (IM, inferior marginal point; PF, perpendicular fissure; PS, posterior splenial point; SM, superior marginal point; SP, subparietal point; TC, tentorial point), whereas smaller dots represent equally spaced semi-landmarks. (b) The four regions that have been segmented to quantify the degree of atrophy of the precuneal boundaries.

A second study concerned the extension of the atrophy along the precuneus boundaries, measured as the space occupied by cerebrospinal fluid at the anterior marginal (ant), dorsal precuneal (dor), posterior occipital (pos), and subparietal (sub) regions (Figure 1b). In the same MRI section used for the previous analysis, we segmented the intersulcal space separating the boundaries of the cortex, approximately quantifying the loss of cortical mass in that region. In this case, such loss can be due to atrophy of both sides, so the method cannot distinguish the contribution of the paracentral, precuneal, and occipital regions. Because of the continuity of the intersulcal space, this measure is therefore influenced by an implicit uncertainty, due to the lack of clear boundaries. Groups and regions have been compared through Mann–Whitney tests, Pearson correlation coefficient, and Bonferroni correction. Statistics were computed with PAST 4.05 (Hammer et al., 2001). In both studies, we also tested sex differences, although the sample has a strong female predominance (74%) and hence the results of this analysis must be interpreted as preliminary.

3 | RESULTS

Complementary voxel-wise analyses showed a typical pattern of temporo-parietal cortical atrophy in the AD sample that included effects in the precuneus and particularly its ventral portion, corresponding to the posterior cingulate and retrosplenial cortex (Figure 2).

A Principal Component Analysis on the shape coordinates of the precuneus detected two main vectors of variation, explaining 37% and 22% of the total variance, respectively (Figure 3). The first component is associated with a longitudinal expansion/reduction of the precuneus. When compared with the control sample, the AD sample displays a modest shift toward lower values, namely reduced extension ($p=0.016$). The second component is associated with expansion/reduction of the ventral region, namely of the region in which the inferior part of the precuneus fades into the posterior cingulate and retrosplenial areas. When compared with the control sample, the AD sample displays a shift toward lower values, namely a reduction of this region ($p=0.0001$). A Discrimination Analysis is statistically significant (Procrustes distance: $p<0.0001$), and it identifies a reduction of the ventral part of the precuneus (including the posterior cingulate and retrosplenial regions) in the AD sample (Figure 4). Size (centroid size) only explains a minor part of the total shape changes (4%), and of the PC1 ($p=0.02$; $r^2=0.07$). A Discriminant Analysis for sex is not significant.

For what concerns the sulcal atrophy around the precuneus, in the control sample, the only significant difference after Bonferroni correction between the four regions considered here concerns the subparietal region, which displays less spacing within its boundaries when compared with the anterior, dorsal, and posterior sulcal regions (Figure 5). If Bonferroni correction is not applied, the anterior region also displays significant differences when compared with the dorsal and posterior regions, being on average less spaced. In the AD sample, significant differences concern the subparietal region (less spaced) and the posterior region (more spaced). Comparing the two samples, the only significant difference concerns the dorsal region, which is less spaced in the AD sample ($p=0.006$). However, a ternary plot showing the proportions between anterior, dorsal, and posterior spacing suggests that the AD sample also displays a distribution shifted toward larger posterior atrophy (Figure 6). In both samples, there is no correlation between atrophy and age, and the only significant correlation between the four variables deals with the positive correlation between anterior and dorsal spaces, which is more consistent in the AD sample ($p=0.0004$; $R=0.59$) than for the control sample ($p=0.05$; $R=0.40$). There is no significant difference between males and females.

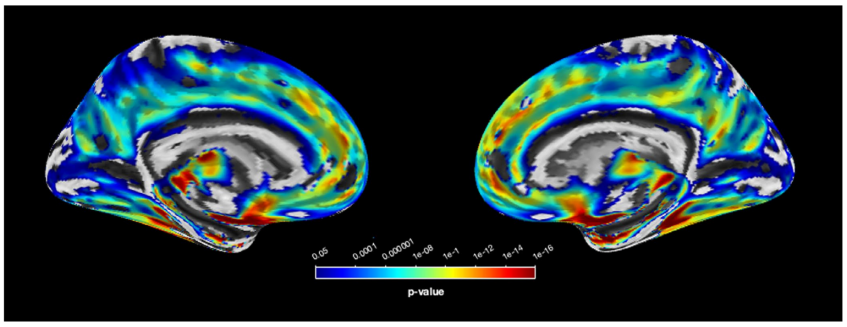

FIGURE 2 A conventional voxel-based comparison between the two samples shows, in the AD samples, a typical pattern of temporo-parietal cortical atrophy. The precuneus is particularly affected in its ventral region, which is contiguous with the posterior cingulate and retrosplenial cortex.

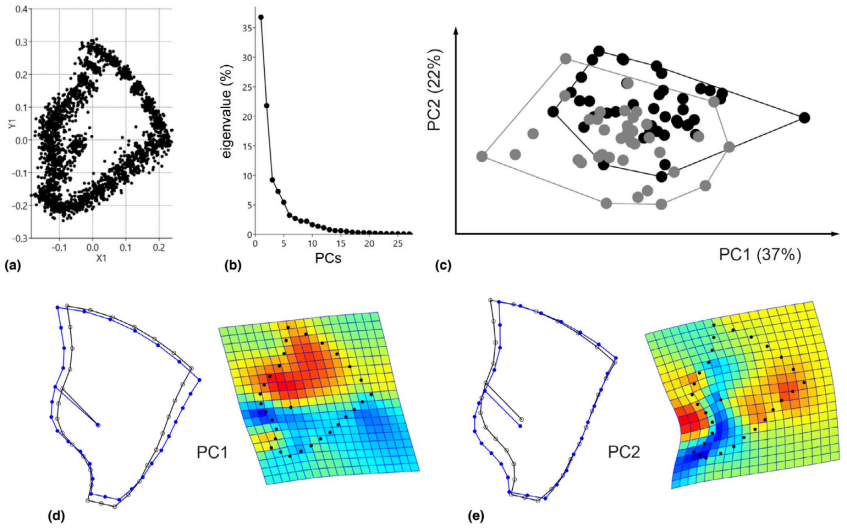

FIGURE 3 After Procrustes superimposition (a), a principal component analysis reveals two main vectors of variation (b). When compared with the control samples (black dots), the AD sample (grey dots) displays reduced values for both components (c). The first component deals with the longitudinal extension of the precuneus (d), especially in its anterior region (the deformation map displays the positive values; red: expansion; blue: reduction), whereas the second component concerns the extension of the ventral region (e) namely, in the opposite direction, the reduction of the retrosplenial areas (the deformation map displays the negative values).

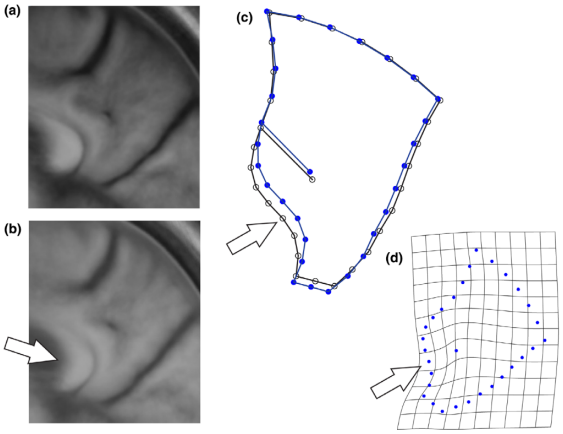

FIGURE 4 Comparing the averaged control sample (a) with the averaged AD sample (b) through density projection (intrasample scout view) after Procrustes registration, the latter is characterized by a reduced ventral region and compressed splenium. A discriminant analysis reveals, in the AD sample, the spatial reduction of the ventral region (c, d).

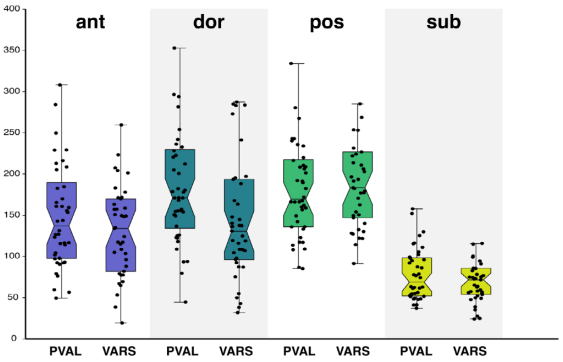

FIGURE 5 Comparing the intersulcal space at the four boundaries, the AD sample (Vallecas Alzheimer Reina Sofía—VARS) is characterized by a less spaced dorsal region and a more spaced occipital region. In the control sample (Proyecto Vallecas—PVAL), there is only a minor difference in the anterior region, which is less spaced. The subparietal region displays minimal spacing.

4 | DISCUSSION

In adult humans, the precuneus displays an outstanding morphological variation (Bruner et al., 2015; Bruner, Pereira-Pedro, & Bastir, 2017). This cortical element is particularly expanded only in our species (Bruner, Pereira-Pedro, Chen, & Rilling, 2017), and it suffers cortical damage and hypometabolic conditions in prodromal stages of AD (Buckner et al., 2008; Grothe et al., 2016; Jacobs et al., 2012, 2013; Levin et al., 2021). In this survey, we investigated the morphological differences of the precuneus between a sample of AD patients and a healthy control sample of the same age, to evidence specific morphological differences associated with normal aging and AD-related neurodegeneration.

Interestingly, within the age range considered here (70–90 years old), there is no apparent chronological trend of shape change,

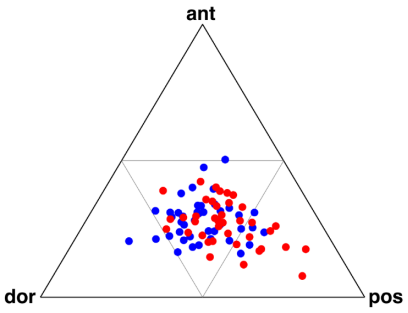

FIGURE 6 A ternary plot shows that the AD sample (red dots) displays, proportionally, more intersulcal space in the posterior region, when compared with the control sample (blue dots).

suggesting that individual variability is by far more important than age when considering the overall morphology of the precuneus. The most striking difference in the AD sample deals with a longitudinal reduction of the ventral region of the precuneus. This trait is the one leading the differences between the two sample means (discrimination analysis) and represents the second axis of general variation (PC2). At present, we interpret this difference as the result of the progressive cortical atrophy experienced by this region, generally associated with an expansion of the ventricular volume and posterior displacement of the splenium. This morphological change is in agreement with the global voxel-based comparison performed with these samples, which confirms a typical pattern of atrophy in AD subjects, in which the precuneus is damaged mostly in its inferior parts. Taking into account that this region is affected since the early stages of the disease, we can wonder whether this reduction is progressive, and if it is hence proportional to the progression of the neurodegenerative process. Future analyses may add information to test this hypothesis further.

The first axis of variation (PC1) is, nonetheless, the longitudinal extension/reduction of the dorsal region, which represents the dominant pattern also observed in normal samples, associated with the pronounced idiosyncratic variability of this region (Bruner & Pereira-Pedro, 2020). According to this component, the AD sample shows a shorter precuneus when compared with the normal aging group. The difference is, however, subtle. In this region, our model estimates the space of the precuneus independently from its current atrophy, so we cannot conclude whether this difference is due to uneven loss of cortical mass or to the original extension of the precuneus. The latter case would be particularly interesting, but it requires longitudinal studies to be properly evaluated.

The analysis of the distribution of the cerebrospinal fluid space adds to the shape analysis, suggesting that, in normal aging, the degree of atrophy is comparable at the anterior, dorsal, and posterior edges of the precuneus, albeit a bit less pronounced at the boundary with the marginal gyrus. By contrast, the AD sample displays more sulcal spacing at the perpendicular fissure, and less spacing on the dorsal surface. It remains to be evaluated whether such differences can be due to the displacement of the cortical mass, or alternatively to a larger degree of atrophy at the parieto-occipital boundary. Traditionally (and in this study too), the voxel-based analyses failed to find consistent signals of atrophy in the dorsal regions of the precuneus (see Figure 1). Nonetheless, these methods are based on a non-homologous minimization of density values, and we can wonder whether the sulcal spacing described during normal and pathological aging in these regions may introduce noise in the registration procedure. The fact that the dorsal sulcal elements are "floating" within the cerebrospinal fluid may introduce a bias in the process of normalization, mostly taking into account the absence of homology or local anatomical references.

These differences between the dorsal and ventral regions require some considerations on their respective structural environments. Indeed, the topological conditions of the dorsal and ventral areas are quite dissimilar (see Bruner, 2022; Schuurman & Bruner, 2023). The dorsal region displays a low *morphological burden*, intended as the amount of spatial constraints imposed by the surrounding cortical elements, taking into account its position and neighboring contacts (Riedl, 1978). Brain loss, therefore, simply reduces the mass of the cortical gyri, increasing the spatial gap between them, passively filled by cerebrospinal fluid. By contrast, the ventral region of the precuneus has a very different topological situation. It fades into the retrosplenial cortex, which is a midsagittal area with an outstanding spatial burden. This region has an elevated centrality (namely, it is in contact with a high number of other elements), it is integrated with the dorsal parietal regions, it experiences a pronounced heat load, and it is structurally constrained by the *tentorium cerebelli* (Bruner & Jacobs, 2024). Therefore, neuronal loss in this region is associated with a consequent spatial compression and rearrangement exerted by the surrounding tissues. Namely, beyond possible local effects of the neurodegenerative process, the dorsal and ventral regions of the precuneus display two distinct behaviors in response to atrophy: the dorsal areas become spaced and invaded by cerebrospinal fluid, whereas the ventral areas become more compressed and invaded by surrounding soft tissues. This difference is also reflected by the fact that the subparietal sulcus, bridging the dorsal and ventral regions, displays less spacing when compared with the dorsal boundaries of the precuneus, suggesting an intermediate topological condition between the low-constrained superior parietal lobule and high-constrained retrosplenial cortex. Interestingly, beyond the midsagittal plane, the other element of the human brain associated with high morphological burden is the parahippocampal gyrus (Schuurman & Bruner, 2024), which is also a crucial spot for AD (Coleman et al., 2023; Echávarri et al., 2011; Van Hoesen et al., 2000).

The atrophy of the precuneus, associated with sulcal reduction and spacing in its dorsal region, and with spatial compression in the ventral region, should also be interpreted in the light of the complex connectivity pattern of this cortical element, which is central to both the structural and functional network of the brain (Hagmann

et al., 2008). A recent review stressed the importance of the precuneus in dual default mode network systems, which is crucial in episodic memory and theory of mind (Dadario & Sughrue, 2023). Additionally, it is also part of a para-cingulate network that may have a key role in self-referential processes, and that is targeted by many neurodegenerative processes, including AD. Both diffusion tractography and anatomical dissections are currently evidencing the organization of such a complex network (e.g., Catani et al., 2017; Cunningham et al., 2017; Jitsuishi & Yamaguchi, 2023; Tanglay et al., 2022; Wu et al., 2016). The cingulum bundle and the middle longitudinal fasciculum represent major routes of connectivity in this sense. The former connects the precuneus with the frontal regions, the latter with the insular-opercular cortex and temporal regions. Additionally, the superior longitudinal fasciculus connects the precuneus with the motor cortex, and the fronto-occipital fasciculus with the frontal and visual areas. All these routes, as well as their associated functions, are targeted in aging and neurodegeneration. As mentioned, the precuneus is particularly large in humans, when compared with nonhuman primates (Bruner, Pereira-Pedro, Chen, & Rilling, 2017), and some of the connections between the precuneus and the posterior cingulate region are derived in our species (Ardesch et al., 2019). The evolutionary adjustments necessary to this structural and functional complexity may in part explain the increased vulnerability of these deep cortical areas to vascular, metabolic, or glymphatic impairments (Bruner & Jacobs, 2024).

It is important to stress that the observed differences between the AD and control samples are, nonetheless, subtle, with a noticeable overlap between their respective ranges. They reveal some underlying anatomical factors, which are anyway hardly reliable to be employed as diagnostic features. As for many neurological disorders, individual variability is outstanding, hampering a clear identification of thresholds or markers associated with specific anatomical traits.

5 | LIMITATIONS OF THE STUDY AND FURTHER RESEARCH

This analysis was aimed at investigating the shape variation of the precuneus in normal aging and AD subjects, so as to investigate macroanatomical changes associated with senescence and atrophy. The analysis is limited to the general shape of the precuneus and to the gyral spacing at its boundaries, and therefore, conclusions are restricted to these features. Future analyses could be devoted to correlating these traits with specific biomarkers, histological assessments, or etiological parameters. This analysis is also limited to the two-dimensional extension of the internal anatomy of the precuneus. Taking into account the histological continuity with the superior parietal lobule, further three-dimensional analyses of the whole region may provide a more comprehensive anatomical scenario. In all cases, longitudinal surveys are mandatory to investigate specific morphological changes independently of the individual variability that, in the case of the precuneus, is noticeable. Importantly, the precuneus is not affected similarly in all subtypes of AD, being more targeted in fronto-parietal and medial temporal lobe-sparing phenotypes (e.g., Ossenkoppele et al., 2016; Vogel et al., 2021). Future surveys should take these differences into account, relying on samples in which these subtypes can be properly assessed.

This study stresses further the differences between the dorsal and ventral parts of the precuneus, which are often pooled when making volumetric or functional analyses of this region. The dorsal areas are, in terms of cytoarchitecture, a part of the superior parietal lobule, whereas the inferior parts fade into the posterior cingulate and retrosplenial regions. Beyond crucial differences in terms of functions and connectivity, the dorsal and ventral regions are also embedded in very different topological environments, influencing their spatial and biomechanical properties. The precuneus is indeed the result of two different gradients: an anteroposterior one associated with somatic and visual integration, and a dorsoventral one associated with the integration between visuospatial and episodic functions. This double polarity is probably the key to its relevance in consciousness and awareness, a crucial factor of its morphogenetic development, and a sensitive spot of vulnerability to neurodegenerative processes.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical approval and consent to participate The BT-CIEN brain bank is an officially registered biobank by the Carlos III Research Institute (Ref: 741). BT-CIEN procedures, as well as VARS cohort patient follow-up, have been approved by local health authorities (Ref: MCB/RMSFC, Expte: 12672). Likewise, all participants of the PVAL provided written informed consent, and the project was approved by the Ethics Committee of the ISCIII, Madrid, Spain. All brain donations were carried out under informed consent by a relative or proxy, as approved by the Ethics Committee of the Carlos III Research Institute.

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