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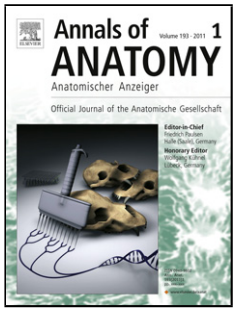

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PII: S0940-9602(17)30026-2
DOI: http://dx.doi.org/doi:10.1016/j.aanat.2017.02.003
Reference: AANAT 51138

To appear in:

Received date: 5-12-2016
Revised date: 30-1-2017
Accepted date: 21-2-2017

Please cite this article as: Bruner, Emiliano, Pereira-Pedro, Ana Sofia, Chen, Xu, Rilling, James K., Precuneus proportions and cortical folding: a morphometric evaluation on a racially diverse human sample.Annals of Anatomy http://dx.doi.org/10.1016/j.aanat.2017.02.003

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Precuneus proportions and cortical folding: a morphometric evaluation on a racially diverse human sample

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Abstract. Recent analyses have suggested that the size and proportions of the precuneus are remarkably variable among adult humans, representing a major source of geometrical difference in midsagittal brain morphology. The same area also represents the main midsagittal brain difference between humans and chimpanzees, being more expanded in our species. Enlargement of the upper parietal surface is a specific feature of *Homo sapiens*, when compared with other fossil hominids, suggesting the involvement of these cortical areas in recent modern human evolution. Here, we provide a survey on midsagittal brain morphology by investigating whether precuneus size represents the largest component of variance within a larger and racially diverse sample of 265 adult humans. Additionally, we investigate the relationship between precuneus shape variation and folding patterns. Precuneus proportions are confirmed to be a major source of human brain variation even when racial variability is considered. Larger precuneus size is associated with additional precuneal gyri, generally in its anterior district. Spatial variation is most pronounced in the dorsal areas, with no apparent differences between hemispheres, between sexes, or among different racial groups. These dorsal areas integrate somatic and visual information together with the lateral elements of the parietal cortex, representing a crucial node for self-centered mental imagery. The histological basis and functional significance of this intra-specific variation in the upper precuneus remains to be evaluated.

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Keywords: parietal lobes; geometric morphometrics; brain morphology; brain shape; sulcal patterns; subparietal sulcus.

Introduction

Precuneus proportions represent a major source of brain morphological variability among adult humans (Bruner et al., 2014a), with spatial changes associated with increase/decrease in its cortical surface area (Bruner et al., 2015a). Precuneus dimensions are also the main difference between human and chimpanzee midsagittal brain morphology, with humans exhibiting marked expansion of this medial parietal element (Bruner et al., 2016). The precuneus is part of the superior parietal lobules, and it is positioned medially between the somatosensory cortex and the occipital cortex, corresponding to Brodmann area 7 (see Spasojević et al. 2004; Cavanna and Trimble, 2006; Margulies et al., 2009). In adult humans its sagittal aspect has an average height of 36 mm and average length of 37 mm, and it is delimitated inferiorly by a parasagittal fold, the subparietal sulcus, with an average width of 14 mm (Bruner et al., 2015b; Pereira-Pedro and Bruner, 2016). The right precuneus is generally larger than the left one, and the morphological correlation between the two hemispheres is generally modest, in terms of size, shape, and sulcal patterns. Its upper areas are involved in visuo-spatial integration, imagery, autonoesis, egocentric memory, and many different tasks integrating spatial, chronological, and social relationships, while the lower areas are contiguous with a crucial node in the Default Mode Network (Cavanna and Trimble, 2006; Margulies et al., 2009; Zhang and Li, 2012; Utevsky et al., 2014). Parietal cortex is sensitive to both genetic (Chen et al., 2012) and environmental (Quallo et al., 2009) effects, and the origin of this morphological variation among adult humans is not known. Furthermore, there is no apparent correlation with basic standard psychometric scores (Bruner et al., 2015a), although precuneus variations have been related to creative thinking (Chen et al., 2015).

Although it has traditionally been interpreted as a single cortical element, modern mapping of the precuneus shows a parcellation into many distinct sub-areas, (Zilles and Palomero-Gallagher, 2001; Scheperjans et al., 2008; Glasser et al., 2016). In terms of anatomy, information is lacking on the histological basis and functional significance of precuneus variation. In terms of morphology, it remains to be established to what extent variability in precuneus shape is associated with anatomical factors (volume and sulcal patterns) and with genetic variability. In this study, we extend the previous morphological analyses on precuneus morphology in humans (Bruner et al. 2014, 2015; Pereira-Pedro and Bruner, 2016) in two

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directions. First, we test midsagittal brain variation in a wider human sample including different racial groups. Second, we evaluate whether precuneus shape is associated with variations of its folding scheme.

Materials and Methods

Sample and digital imaging

We analyzed MRI data from 265 adults (126 men and 139 women) with diverse ancestral backgrounds (self-reported race; Table 1). All subjects were healthy adults from the Emory University community between the ages of 18 and 22 (mean and standard deviation = 20.7 ± 2.2 years for men, and 20.5 ± 1.3 years for women). Subjects underwent MRI scanning at Emory University on a 3 Tesla Siemens Trio MRI scanner (Siemens Medical System, Malvern, PA, USA) with a 12-channel parallel imaging phase-array coil. Foam cushions were used to minimize head motion. All procedures were carried out in accordance with protocols approved by the Emory University Institutional Review Board (IRB# 000007905). Our current study uses only the T1-weighted structural MRI images, which were acquired using a 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence with a GRAPPA (Generalized Autocalibrating Partially Parallel Acquisitions) factor of 2. The T1 scan protocol, optimized for 3 Tesla, used the following imaging parameters: a repetition time/inversion time/echo time (TR/TI/TE) of 2600/900/3.02 ms, a flip angle of 8°, a volume of view of 256×256×176 mm3, a matrix of 256×256×176, and isotropic spatial resolution of 1.0×1.0×1.0mm3, one average. Total T1 scan time was approximately 5 min.

For each subject, brain volume and precuneus volume were estimated. Brain volume includes the whole brain mass, while precuneus volume includes only the cortical gray matter. Cortical reconstruction and volumetric segmentation were automatically performed with Freesurfer v5.3.0 (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 1999, 2002, 2004). Parcellation of the cerebral cortex into units (including the precuneus) was performed with respect to gyral and sulcal structure, based on the Desikan-Killiany cortical atlas (Desikan et al., 2006; Fischl et al., 2004). Brain volume was estimated in FMRIB Software Library (Smith et al., 2004) after removing the skull using Brain Extraction Tool (Smith, 2002). The functional and architectural boundaries between the precuneus, posterior cingulate cortex and retrosplenial cortex are generally blurred, and the current Freesurfer parcellation, based on the Desikan-Killiany cortical atlas (Desikan et al., 2006), includes areas below the subparietal sulcus (Fig. 1a). Precuneus relative volume was computed as the ratio between precuneus cortical volume (summed hemispheres) and brain volume. Shape comparison between humans and

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chimpanzees pointed to the anterior-superior parietal area as the possible localization of spatial differences (Bruner et al., 2016). Therefore, we also calculated the geometrical area included between the margin of the cingulate gyrus and the upper border of the perpendicular scissure (ASPA, Anterior-Superior Precuneus Area) to evaluate the contribution of this specific district (Fig. 1b).

Shape analysis

MRI images of all subjects were first aligned to a human brain template (MNI-152) using rigid body linear registration with 6 degree of freedom (DoF) so that all individual brains had a standard orientation and the sagittal plane was parallel to the interhemispheric fissure of the brain. Each individual brain was then visualized in FSLVIEW and snapshots were taken of the sagittal slice that is 6.0 mm lateral from the mid-sagittal slice in both hemispheres. This specific slice was chosen to cut through the middle thickness of the medial parietal cortex. We sampled 16 two-dimensional landmarks from the same sagittal slice for each hemisphere, as to consider the geometry of the midsagittal brain elements (Fig. 1c). The landmark configuration includes the center of the genu, the center of the splenium, the center of the thalamus, the center of the quadrigeminal lamina, the anterior border of the optic chiasm, the central sulcus, the marginal ramus of the cingulate sulcus, the marginal/precuneal notch, the midpoint of the subparietal sulcus, the external and internal extremes of the perpendicular sulcus, and the occipito-cerebellar fissure (internal occipital protuberance). Four semi-landmarks were sampled as equally distant points along the frontal (3 landmarks) and occipital (1 landmark) profiles. The configuration was similar to that used in the previous study (Bruner et al., 2014a), with some minor differences like the addition of the central sulcus and of the middle point of the subparietal sulcus. The central sulcus is useful to separate the conventional territories of the frontal and parietal lobes. This landmark is useful to delimitate the posterior area of the paracentral lobule, which is regarded as part of the superior parietal cortex (Scheperjans et al. 2008). The subparietal sulcus is a highly variable fold of the precuneus, which may be connected with the outer surface, with the marginal ramus of the cingulate sulcus, or even with the parieto-occipital fissure (Pereira-Pedro and Bruner, 2016). Although its morphology is highly variable between individuals and between hemispheres, the localization of a middle point is easy and practical, because it establishes an inferior boundary for the precuneus. The marginal notch is a minor flexion of the marginal ramus, generally identifiable through additional short folding elements which can be in some cases associated with longer precuneal sulci.

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Coordinates were registered through Procrustes superimposition (Fig. 1d). This registration translates all the specimens to a common centroid (average coordinate value), scales the coordinate systems to unitary size by normalizing the centroid size value (square root of the sum of squared distances of a set of landmarks from their centroid) and rotates the configurations as to minimize the distance between corresponding landmarks (Bookstein, 1991). Coordinates were used to compute a principal component analysis following the principles and methods of geometric morphometrics (Zelditch et al., 2004). Coordinates were also used to analyze the distribution of all the interlandmark distances (Euclidean Distance Matrix Analysis; Lele and Richstmeier, 1991) as to calculate their coefficients of variation.

We also evaluated the morphological modularity of the precuneus, that is to what extent the landmarks forming the precuneal geometry (see Fig. 4d) display an internal correlation which is stronger than the rest of the coordinates. Integration and modularity are hierarchical concepts based on different degree of reciprocal or shared influences among biological processes and traits, aimed at localizing functional, structural, genetic, and morphogenetic units within a given anatomical system (Cheverud, 1996; Mitteroecker and Bookstein, 2007). Integrated anatomical areas display high covariance and shared patterns of variation, while non-integrated anatomical systems are formed by independent elements influenced by distinct factors (Klingenberg, 2009). A module is a group of elements which show a higher degree of reciprocal variation when compared with other elements or with other groups. Modularity within the current configuration of landmarks was tested taking into consideration the relative degree of correlation between adjacent partitions by using the Escouffier coefficients, comparing the value of multiple correlations of the medial parietal geometry (from the retrosplenial cortex to the upper parietal profile) with the distribution of the values obtained for all the other possible combinations with similar parameters (Klingenberg, 2009, 2013).

Sulcal pattern

The precuneus displays a highly variable sulcal pattern, which is apparently not associated with the thickness of the cortical folding (Pereira-Pedro and Bruner, 2016). Additional sulci (precuneal sulci) can increase the sulcal complexity, being connected or not to the main central fold (subparietal sulcus). Precuneal sulci, and associated additional precuneal gyri, are more frequent anteriorly, although in some cases they can be found toward the posterior (occipital) boundary. Here, we evaluate whether the presence of additional gyri are associated with variation of the precuneus geometry, considering three morphotypes (Fig. 2): absence of

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additional gyri (type I), partial additional gyrus (type II), and complete additional gyrus (type III).

Statistics

The study was performed on the whole sample of 530 hemispheres as well as on 265 mean values obtained after averaging the left and right hemisphere for each individual. Left and right sides display a high correlation of their covariance matrices ($p < 0.0001$; $R = 0.98$), and the only asymmetry, as evidenced by the current configuration, is a very minor difference in the retrosplenial space, smaller in the right hemisphere because of relatively larger occipital length. However, the two analyses gave the same multivariate results, so here we present only the study on averaged shapes, except the sulcal analysis which was performed on all hemispheres independently. Because of small sample size for some ancestry groups, inferential statistics were only computed for the three largest groups, namely African, European, and Asian ancestry. Morphometrics were computed by using PAST 2.17c (Hammer et al., 2001) and MorphoJ 1.06a (Klingenberg, 2011). Differences have been tested through permutation tests.

Results

Volumes and metrics

Precuneus cortical volume averages 10.4 ± 1.2 cc (interquartile 9.6-11.2; coefficient of variation 12%), and represents 1.4 ± 0.1% of the whole brain volume (Table 2). Brain volume is correlated with precuneus volume ($p < 0.0001$; $r = 0.74$) and with ASPA ($p < 0.0001$; $r = 0.40$) but not precuneus relative volume ($p = 0.49$). ASPA is also correlated to precuneus volume ($p < 0.0001$; $r = 0.48$) and modestly to precuneus relative volume ($p < 0.0002$; $r = 0.23$). Precuneus volume is correlated to precuneus relative volume ($p < 0.0001$; $r = 0.61$). Males have larger values than females for all absolute variables ($p < 0.0001$), but there is no difference between sexes for relative precuneus volume ($p = 0.72$). Analyzing sex differences by analysis of covariances, there are no differences in means ($p = 0.74$) or slopes ($p = 0.39$) when comparing precuneus volume with brain volume. In contrast, males have larger ASPA at a given brain size ($p = 0.04$), despite no difference in slope ($p = 0.64$). This result suggests that males have relatively larger upper precuneal extension when compared with females, when brain size variation is taken into account. Comparisons between ancestry groups reveals differences in precuneus volume (Europe > Asia > Africa; $p < 0.0001$), and precuneus relative volume (Asia = Europe > Africa; $p < 0.001$). A similar situation is found when comparing precuneus volume and

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brain size covariance, with the three groups showing the same slopes ($p = 0.99$) but with African sample showing smaller mean ($p = 0.001$). However, average differences are minimal, overlap is extensive, and mean group-wise values for the relative volume only differ by between 1.4% and 1.5%. Differences for ASPA are significant when comparing European and African ancestry (smaller in the second group; $p = 0.04$), but neither differed from the Asian sample. The proportion of the upper precuneus area (ASPA divided for brain volume) did not differ among ancestry groups and, taking into account brain size, analysis of covariance reveal same slopes ($p = 0.77$) and means ($p = 0.91$) for the anterior-superior precuneus extension.

Analyzing the mean and standard deviation of all the inter-landmark distances and computing their coefficients of variation, most diameters display values between 4% and 11%, except five distances associated with precuneus and with the deep posterior (retrosplenial and cerebro-cerebellar) districts, showing values of 13-21% (see Fig. 4f).

Shape variation

The overall midsagittal shape variation is correlated with midsagittal centroid size ($p < 0.0001$), although the correlation explains only 2.9% of the variance, through a pattern characterized by precuneus dilation and occipital bulging (Fig. 3a). A discriminant analysis between males and females on the whole shape coordinates is significant ($p = 0.002$) and associated with a more dolichocephalic (flattened) braincase in the former group (Fig. 3b). This pattern is able to correctly classify 75-78% of the specimens after cross-validation. Comparing the three main ancestry groups, Asians display a morphological difference from the other two groups which is significant according to Mahalanobis distance ($p < 0.001$ and $p = 0.001$ for African and European ancestry, respectively) and significant/marginal according to Procrustes distance ($p = 0.003$ and $p = 0.07$ for African and European ancestry, respectively). The difference mainly separates Asian from African ancestry because of the brachycephalic proportions of the former group (Fig. 3c). As for sex variation, differences are apparently due to the form of the braincase rather than local changes of specific brain areas. Although the separation is significant, a cross validation shows that differences are subtle, with large overlap between the two groups, and a discrimination function based on coordinates is able to classify correctly only 56% of the individuals with African ancestry and 60% of the individuals with Asian ancestry.

The principal component analysis shows a morphospace which is not characterized by few distinct patterns, but instead by a set of components with a smooth and gradual decrease of explained variance (Fig. 4a). Only the first vector displays a marked separation in terms of variance (24%), and after the fifth vector the eigenvalues are not even above a threshold of

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random variation. Such structure of the multivariate space reflects scarce integration of the overall geometrical system, due to many local and independent factors influencing the global spatial distribution of the midsagittal brain elements (Bruner et al., 2010). Therefore, we only consider the first component here, which is supposed to represent a reliable biological vector of variation. This first axis of variation is strictly associated with the relative proportion and shape of the precuneus (Fig. 4b,c). The upper part of the precuneus undergoes a longitudinal dilation/compression, without any patent shape change in the other districts, except a spatial shift of the frontal and occipital volumes due to the lengthening of the parietal space.

This principal component is not correlated with brain volume ($p = 0.29$), is slightly correlated with precuneus volume ($p = 0.01$; $R = 0.15$) and relative precuneus volume ($p = 0.02$; $r = 0.14$), and moderately correlated with ASPA ($p < 0.0001$; $r = 0.40$). There are neither sexual ($p = 0.50$) nor racial ($p = 0.38$) differences for PC1 values.

The modularity analysis shows that the landmarks forming the medial parietal geometry (Fig. 4d) do not show a higher correlation when compared with the rest of the coordinates ($p = 0.55$), suggesting that it does not represent a separate morphological module. In contrast, its lower parts and the posterior subcortical areas represent the most integrated module that is, using the same modularity parameters, the group of landmarks showing the higher internal cohesion (Fig. 4e).

Sulcal analysis

The analysis of all 530 hemispheres shows that in 54% of the cases there is an incomplete additional gyrus, in 43% of the cases there is a complete additional gyrus, and only on 3% of the cases there is no additional folding. There is no difference in sulcal patterns between males and females according to a Chi-square test. In contrast, the right hemisphere shows more incomplete gyri (61%) and the left hemisphere shows more complete gyri (50%). Racial differences are significant ($p = 0.05$): individuals with African ancestry show more absence of additional gyri, more complete additional gyri, and less frequent incomplete gyri. Individuals with European ancestry display the opposite patterns, showing an increase of the frequency of incomplete gyri (62%). The presence of additional gyrus is not associated with brain volume ($p = 0.18$), but both ASPA ($p = 0.00004$) and PC1 (toward larger precuneus; $p = 0.0004$) increase from no additional gyrus, to incomplete additional gyrus, to complete additional gyrus (Fig. 5). The difference is more marked between no additional gyrus and incomplete additional gyrus, while it is less pronounced between the latter and complete additional gyrus ($p = 0.01$). Shape analysis discriminates between absence and presence of gyrus ($p = 0.0001$ for both Procrustes distance and Hotelling T), but is less decisive to discriminate between complete and

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incomplete gyrus (p = 0.01 and 0.15 for Procrustes distance and Hotelling T). In this case cross-validation is able to classify only 54% of the specimens. In all comparisons, the shape difference among sulcal types is associated with precuneus expansion.

Discussion

Morphometrics and precuneus variation

The size of the precuneus is highly variable among adult humans, representing the main source of shape variation in midsagittal brain geometry, largely because of its longitudinal extension (Bruner et al. 2014, 2015a). Past morphological analyses on these cortical districts were based on samples including about one hundred specimens with homogeneous ancestry. In this study we extend the analysis to a larger sample, including individuals from various racial groups. We also use a configuration of landmarks able to separate the areas above the subparietal sulcus, and the posterior district of the paracentral lobule. Finally, we also evaluate to what extent this morphological variation is associated with specific sulcal patterns.

As for earlier analyses, variation in midsagittal brain shape is not characterized by few global morphological patterns, probably because it is influenced by many local and independent factors (Bruner et al., 2010; Gómez-Robles et al., 2014). The allometric effect is minor, at least when dealing with adult phenotype. Nonetheless, the shape of the precuneus represents a consistent trait influencing individual variability and generating a consistent vector of variation (24% of the variance), as described in previous studies. Because of the difficulties associated with MRI imaging and brain landmarking, reproducibility of these results is crucial. To date, precuneus form has been confirmed to be the main source of midsagittal brain variation among adult humans in a local European sample (Bruner et al., 2014a), in a biomedical sample (Bruner et al., 2015b), and in an anthropological sample with distinct racial groups (this study), three studies in which landmarking was performed by independent observers. This shape variation is not due to brain size differences. It is weakly correlated (r = 0.15) with absolute and relative precuneus volume as calculated according to traditional neuroanatomical templates, which include lower areas fading into the posterior cingulate and retrosplenial cortex. On the other hand, this shape component is moderately correlated with the size of the superior and anterior precuneus areas (r = 0.40). Brain volume and precuneus relative volume are not correlated, confirming that changes in the precuneus proportions in general do not depend upon brain size. The size of its superior areas is only modestly correlated to the whole precuneus absolute and relative size, suggesting that other parts of the segmented volumes (the posterior and inferior areas) may vary independently. In this study, in addition to *shape*

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analysis we also computed a *form* analysis based on Euclidean Distance Matrix, showing that all the superior and anterior boundaries of the precuneus include the most variable inter-landmark distances. This result, based on absolute values and not on registered/normalized coordinates, further substantiates marked individual variability of this district. Indeed, the current geometrical models points at these areas as the origin of the spatial differences. At the same time, the configuration of landmarks used in this study stresses further that the inferior and posterior areas are not involved in the dominant spatial pattern of variation, as also observed for the human-chimpanzee comparison (Bruner et al., 2016). The modularity analysis further suggests independence between superior and inferior medial geometry. The posterior part of the paracentral lobule is not implicated in the main pattern of shape differences, although it too is highly variable.

Sex differences in the precuneus are largely due to general brain size differences. The relative precuneus volume is similar in males and females, and the scaling between brain volume and precuneus volume shows a shared allometric trajectory. Males have slightly larger anterior-superior precuneus extension when brain size is considered, although the individual variation is remarkable and group differences are subtle. Current psychometric evidence suggests that males perform better than females on visuospatial cognitive tasks (e.g., Gur et al., 2000; Sacher et al., 2013), however the anatomical group-difference found in this study is minimal and with extensive overlap. The distribution of males and females along the main shape pattern (precuneus expansion/reduction) is similar, and the overall midsagittal brain differences are due to brachycephalic-dolichocephalic neurocranial variation, more than to actual differences in brain proportions. A similar situation can be described for the ancestry groups: there is no difference among racial groups for the distribution along the main shape vector (precuneus expansion/reduction), and global shape differences are due to brachycephalic (Asian ancestry) and dolichocephalic (African ancestry) cranial architectures, without apparent localized changes of specific brain areas. Dolichocephalic-brachycephalic neurocranial variations (i.e., relatively longer and narrow skulls vs relatively shorter and wider skulls), can probably result from distinct morphogenetic processes (Zollikofer and Ponce de León 2002) but, in any case, they are likely to be influenced by cranial constraints (Lieberman et al., 2000; Bastir and Rosas, 2016) and not by specific patterns of brain growth and development. The African group displays smaller precuneus volume when brain size is taken into account, but the proportional difference is very minor, and overlap among racial groups is extensive. The fact that the same group does not show differences in the extension of the dorsal proportions suggests that this variation of the precuneus, if confirmed, should be associated with differences in the other precuneus areas, approaching the subparietal sulcus

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or the retrosplenial/cingulate cortex. As a cautionary note, it must be observed that these results are based on self-reported race rather than genealogic or genetic data.

The analysis of the sulcal patterns add to the current knowledge on precuneus anatomical variation. The folding patterns associated with the subparietal sulcus are highly variable, without a clear association with fold size, sex, or hemispheric asymmetry (Pereira-Pedro and Bruner, 2016). Although the height of the precuneus can influence the outer brain form, the variations of the folding scheme likely have no effects on the external brain outline (Pereira-Pedro and Bruner, 2016). According to the results presented in this study, most individuals (97%) display at least one additional folding branch, associated with complete or incomplete precuneal sulci. Such additional gyri are slightly associated with longer precuneus, and with the main pattern of shape variation described for the midsagittal brain morphology. The difference is more marked between specimens with or without additional gryri, but there is also a minor difference between specimens with incomplete and complete additional gyrus. Therefore, although the relationship is not stringent, larger precuneus size is partially associated with additional longitudinal folding. Of course, the polarity of this relationship cannot be evaluated with the current data, and additional folding can be the cause or else the consequence of cortical area expansion. Recent empirical and experimental models suggest that folding is largely due to geometrical mechanical adjustments between volume and surface growth (Tallinen et al., 2016). Therefore, an additional gyrus can be the cause of the cortical expansion, or else a mechanical consequence passively induced by the growth of a larger surface.

There are no sex differences in the folding pattern, but the left side seems to shows more frequently complete additional gryri. This is counterintuitive when considering that the right side is generally larger, but a similar result was found in a different sample, showing more precuneal sulci in the left hemisphere (Pereira-Pedro and Bruner, 2016). Nonetheless, sex and asymmetry patterns for these areas are still not clear, and there are still contrasting results which require further investigation (Zhang and Li, 2013; Bruner et al., 2015a). Similarly, the racial trend, which associates African ancestry with increasing frequency of absent and complete additional folds, cannot be easily interpreted. Critically, the minor sex and racial differences reported here could be due to either genetic or environmental factors.

It is worth noting that all these relationships reveal modest ($R \approx 0.15$), or moderate ($R \approx 0.40$) correlations. The large individual variability makes trends weak and, even in the most consistent cases, minimally predictive. Such large individual variation may be due multiple factors influencing the final phenotype and idiosyncratic features. It is nonetheless suggestive that, as trends and patterns, these relationships can be found even when considering adult

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individuals of the same species. The same rules are likely to be stronger when dealing with ontogenetic or inter-specific variation.

Precuneus variation and cortical areas

This study further suggests that the dorsal areas of the precuneus may represent a relevant source of individual variability. The width of the precuneus is extremely small when compared with its length and height (Pereira-Pedro and Bruner 2016), and its variation largely deals with its longitudinal extension, in particular with the extension of its dorsal parts. The fact that sex, race, and size do not exert a major influence on these differences suggests that individual factors contribute to this pattern of midsagittal brain variability. Cranial architecture (in particular the dolichocephalic-brachycephalic axis) displays sexual and racial trends, which are not associated with the main pattern of variation and precuneus proportions. Therefore, precuneus expansion/reduction seems not affected by the general cranial proportions. Increase/decrease of a cortical surface is unlikely to be a passive consequence of "space filling" after cranial adjustments, and hence we must assume that it is associated with expansion/reduction of specific histological components. These areas display a remarkable cytoarchitectonic individual variation (Scheperjans et al. 2008). Although we know that precuneus variation is associated with surface extension, we ignore the exact anatomical nature of these changes, or the functional and morphogenetic process involved. The parietal areas mature very early during ontogeny (Gogtay et al., 2004), but they are also exceptionally sensitive to later influences of training (Quallo et al. 2009). Despite shared genetic factors (Chen et al., 2012), we currently ignore to what extent the precuneus variation is the result of innate or environmentally shaped differences. We also ignore whether precuneus morphological variation is due to difference in neuron size or density, connections, or non-neuronal cerebral components (e.g., glia, vascular elements, etc.).

The precuneus is generally labeled as Brodmann area 7, but its cytoarchitectonic parcellation is currently under investigation, revealing a finer degree of complexity (Scheperjans et al. 2008). Although our geometrical model cannot discriminate among specific sub-areas of the precuneus, it suggest that the morphological variation is associated with a district which, according to the cytoarchitectonic probabilistic map of Scheperjans et al. (2008), spatially matches areas 7A and 7P. Area 7A is the largest among those described for the superior parietal cortex, it is the most variable between individuals, and extends from the medial (interhemispheric) fold to the outer superior parietal lobule. Therefore, it is a good candidate for further anatomical surveys. Interestingly, while the medial part of the precuneus

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represents a connection hub in most primates, the external part may have hub properties only in humans (Li et al., 2013).

In terms of functions, it remains to be established whether these morphological changes are actually associated with cognitive or metabolic variations. Area 7A is particularly associated with functions dealing with self-centered mental imagery and attentional processes (Scheperjans et al. 2008). In general, the dorsal areas of the precuneus are more connected with somatosensory and motor cortex (dorsal anterior) and visual cortex (dorsal posterior), representing a crucial node for visuospatial integration, while the ventral areas are more connected with the frontal and cingulate cortex, acknowledging functions associated with episodic memory and self-representation (Lou et al, 2004; Zhang and Li, 2012; Bzdok et al., 2015). A preliminary survey with traditional psychometric tests failed to reveal any apparent difference associated with precuneus size (Bruner et al., 2015a). Nonetheless, due to the several functional and cognitive processes in which the precuneus is involved (Cavanna and Trimble 2006; Margulies et al. 2009; Zhang and Li, 2012), assessments must be based on more extensive and specialized approaches. Grey matter increase and functional homogeneity of the right precuneus is positively correlated with verbal creative thinking ability (Chen et al., 2015). It is worth noting that visuospatial functions, body perception and self-awareness are crucial also for social relationships (Hills et al., 2015; Maister et al., 2015; Peer et al., 2015), and precuneus cortical reduction is one of the few grey matter alterations associated with autism (Via et al., 2011).

Our shape analysis also confirms that the dorsal areas of the precuneus and the inferior ones should be considered separately when dealing with individual variation. The analysis of modularity adds further evidence to the hypothesis of a morphological integration between lower precuneus, retrosplenial and posterior cingulate areas, splenium, and posterior subcortical elements, as described in another sample (Bruner et al., 2014a). Also functional mapping suggests a distinction between dorsal and ventral precuneus, with the ventral areas more connected with those same regions evidenced by a shared modular structure (Zhang and Li, 2012). This ventral part is also the one possibly more involved in the Default Mode Network and connected with the angular gyrus, while the dorsal areas are less involved in the default mode and more connected with the rest of the parietal cortex, namely with parasagittal elements (not included in this study) like the intraparietal sulcus and the supramarginal gyrus. The spatial correlation between lower precuneal landmarks, retrosplenial cortex and posterior subcortical areas, provides therefore an interesting convergence between geometrical patterns and connectivity schemes.

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A final issue concerns metabolism. The precuneus represent a highly metabolically active area, which is positioned close to the thermal core of the brain (the geometric area of maximum heat accumulation according to the spatial pattern of heat dissipation) and in a crucial vascular district (Sotero and Iturria-Medina 2011; Bruner et al. 2014b). Its involvement in metabolic dysfunctions and Alzheimer's disease therefore raises questions about possible functional consequences (Zhang and Li, 2012; Bruner and Jacobs 2013). It is worth noting that the inferior areas of the precuneus is part of (Utevsky et al., 2014) or is contiguous with (Bzdok et al., 2015) crucial connection hubs, including relevant nodes of the Default Mode Network which are shared among primates, introducing issues bridging functional and structural levels of brain organization (Raichle et al. 2001; Hagmann et al., 2008; Meunier et al. 2010; Van den Heuvel et al. 2016). As mentioned, the superior parietal lobules may present some human specific connection nodes (Li et al., 2013) and might represent an outer extension of the area 7A of the precuneus (Scheperjans et al., 2008).

Conclusions

For many years, information on human parietal cortex was limited, and we still lack many details of its neuroanatomical organization (Zilles and Palomero-Gallagher, 2001). Its areas are currently under investigation based on functional and structural properties, but there is much disagreement on its parcellation, homology, functions, and boundaries. The current study further points to the precuneus as a main factor of intra-specific human brain variation. Its relative extension is not dependent on size, sex, or race, suggesting individual factors associated with shared genetic or environmental effects. It remains to be investigated what structural and histological elements are involved in generating this spatial change, and if these are associated with specific functional issues. A rounded braincase is a specific trait of *Homo sapiens* (Lieberman et al., 2002; Gómez-Robles et al., 2017), largely due to enlarged parietal bones and lobes (Bruner et al., 2014b). A globular braincase in *Homo sapiens* is due to a morphogenetic endocranial stage which is specific of our species, occurring either before (Ponce de León et al., 2016) or after (Gunz et al. 2010) birth. This stage is absent in chimpanzees and other living apes (Neubauer et al. 2009; Scott et al. 2014), and enlargement of the precuneus is also a major difference distinguishing human from chimpanzee midsagittal brain morphology (Bruner et al., 2016). Both intra-specific and inter-specific geometrical models point to the same anterior and dorsal areas of the precuneus, roughly corresponding to area 7A, associated with visuospatial integration and self-centered mental imagery (Scheperjans et al. 2008). Visuospatial integration combines egocentric representations with

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spatial, chronological, and social abilities (Land, 2014; Peer et al., 2014). Taking into account the importance of technology and visual imagery in our species, we should evaluate whether visuospatial capacity and extended cognitive abilities may have been enhanced along our evolutionary lineage (Iriki 2006; Iriki and Taoka 2012; Bruner and Iriki, 2016). Area-specific analyses will be necessary to evaluate further the neuroanatomical changes associated with both intra- and interspecific variation of the parietal districts, taking into account parcellation schemes which include both functional and structural territories (Glasser et al., 2016).

Acknowledgments

We thank Dr. JiuQuan Zhang (MD/PhD) for help in landmark sampling. EB is funded by the Spanish Government (CGL2015-65387-C3-3-P) and by the Italian Institute of Anthropology. ASPP is funded by the Atapuerca Foundation. This study was supported by National Institute of Mental Health (R01 MH084068-01A1).

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Table 1. Sample

	N
Sex	
Males	126
Females	139
Ancestry	
Africa	57
Europe	94
Asia	84
Hispanic	16
Mixed	12
Native American	1
Unknown	1
TOT	265

Table 2. Precuneus volume per group

	Precuneus volume (cc)					**Precuneus volume (%)**				
	Males	*Females*	*Europe*	*Africa*	*Asia*	*Males*	*Females*	*Europe*	*Africa*	*Asia*
Mean	11.0	9.9	10.9	9.7	10.5	1.43%	1.44%	1.44%	1.39%	1.46%
St. Dev	1.1	1.1	1.2	1.1	1.2	0.12%	0.12%	0.10%	0.11%	0.13%
25th	10.1	9.2	10.0	8.9	9.7	1.40%	1.40%	1.40%	1.30%	1.40%
Median	10.9	9.8	10.8	9.7	10.5	1.40%	1.40%	1.40%	1.40%	1.50%
75th	11.8	10.7	11.8	10.5	11.2	1.50%	1.50%	1.50%	1.50%	1.50%

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Captions

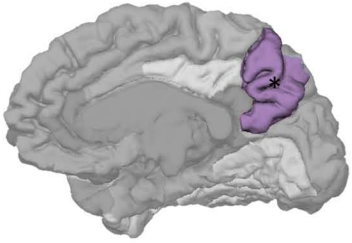
Figure 1. Precuneus volume was calculated according to the Freesurfer parcellation template (a), and its anterior-posterior area was calculated between the marginal ramus of the cingulate sulcus and the perpendicular scissure (b). Midsagittal shape was analyzed with a configuration of 16 bi-dimensional landmarks (c), superimposed by Procrustes registration (d).

Figure 2. Three sulcal patterns were considered: with no additional gyrus (Type I), with incomplete additional gyrus (Type II) and with complete additional gyrus (Type III).

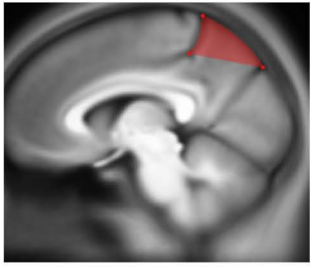
Figure 3. Shape variation includes a minor allometric component (a; blue wireframe: larger brain sections), sexual differences (b; blue wireframe: males), and racial differences, mostly between African ancestry and Asian ancestry (c; blue wireframe: Asian group).

Figure 4. Principal Component Analysis shows four vectors above the threshold of random eigenvalue (red line), with the first component explaining 24% of the variance (a). This component is strictly associated with increase/decrease of the upper precuneus proportions, here showed though wireframe (b) and thin-plate spline deformation grid with deformation map (c; red: geometric dilation). The landmarks forming the parietal medial districts, from the retrosplenial cortex to the upper parietal profile (d; white dots) do not display a modular correlation. Instead, its lower areas and the posterior subcortical areas represent a more integrated unit (e). Taking into account all the raw interlandmark distances, the ones showing the larger coefficient of variation (13-21%) are associated with the upper parietal and restrosplenial districts (f).

Figure 5. Boxplots show the distribution of the three sulcal types along the first Principal Component (PC1): no additional gyrus (NG), incomplete additional gyrus (IG), and complete additional gyrus (CG). Wireframe shows shape difference after discrimination analysis from specimens without additional gyrus to specimens with complete additional gyrus. The two MRI images are computed as the densitometric superimpositions of the 20 specimens with highest and lowest PC1 values, showing the actual extent of the precuneus variation associated with this shape vector. Note that larger precuneus is associated with an additional precuneal sulcus. No other morphological change is apparently associated with this vector.



a



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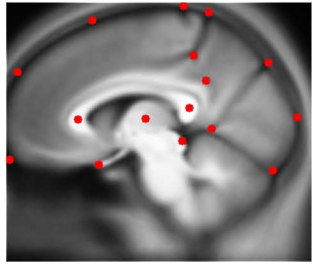

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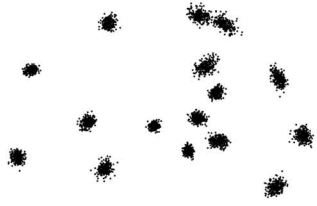

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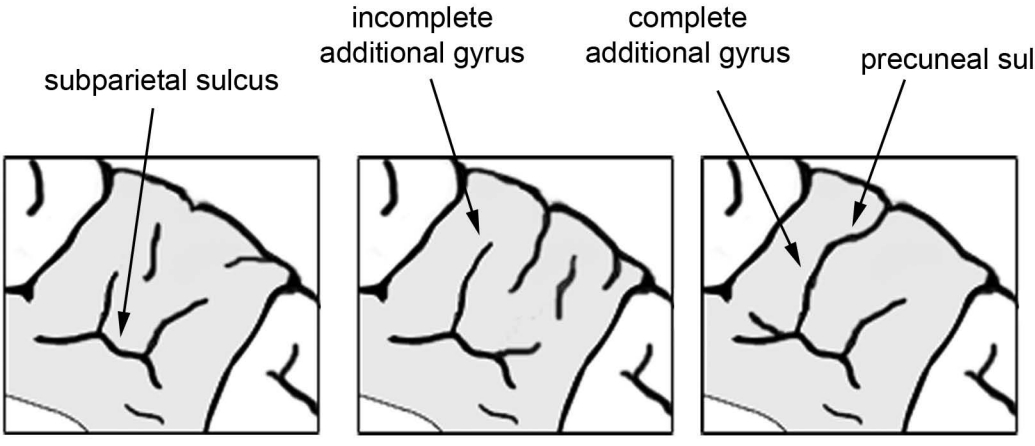
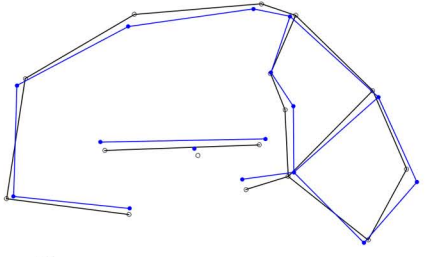

subparietal sulcus
incomplete additional gyrus
complete additional gyrus
precuneal sulcus
Type I
Type II
Type III



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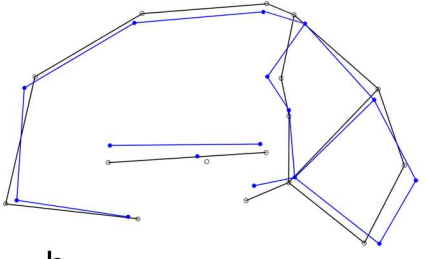

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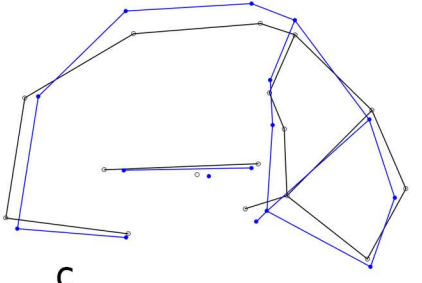

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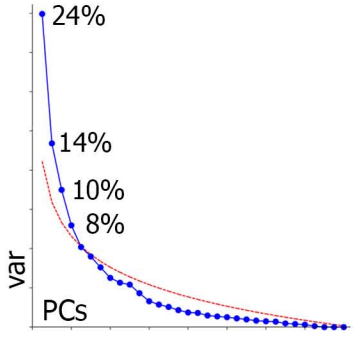

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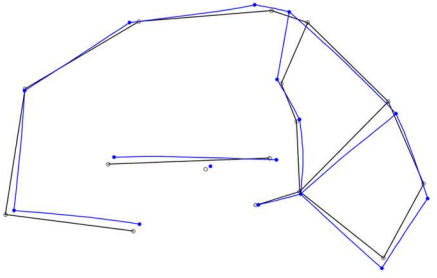

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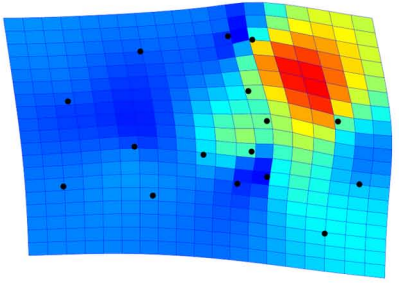

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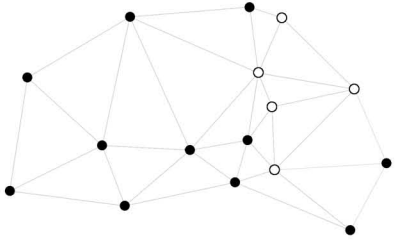

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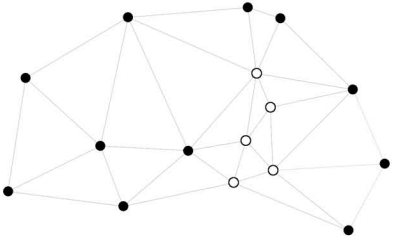
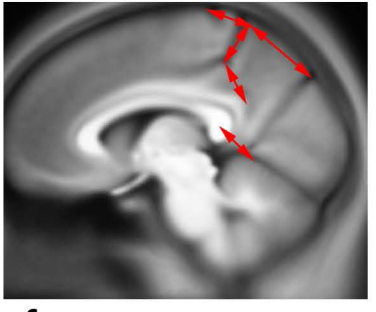


e



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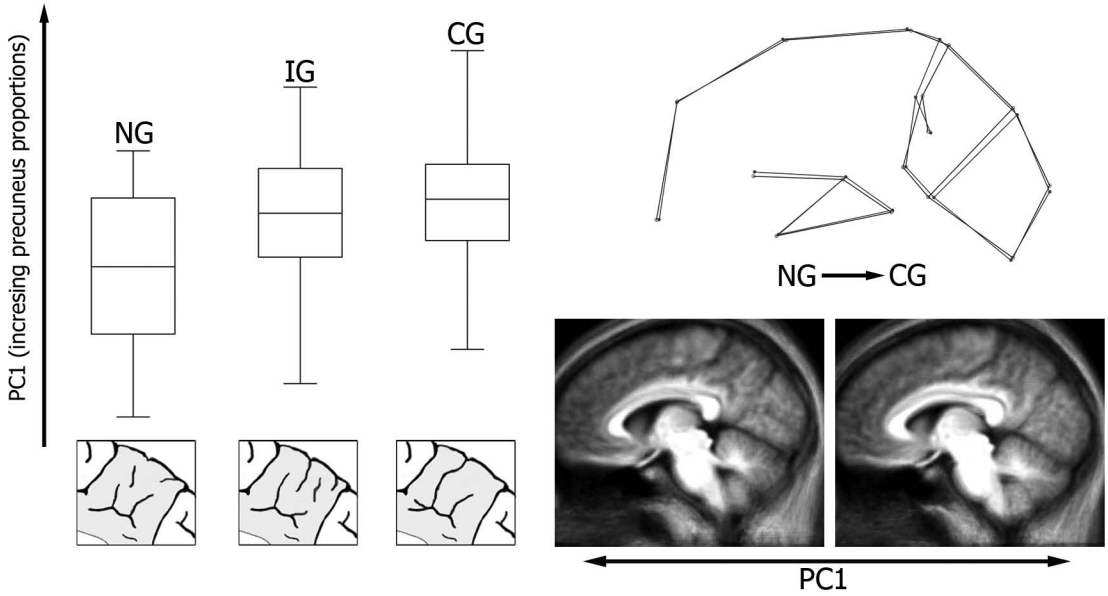
PC1 (incresing precuneus proportions)
NG
IG
CG
NG → CG
PC1