Sex Differences of the Brain Structural Adaptation to Hypoxic Environment

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Abstract

Background: Different physiological and pathological patterns have been found in the two sexes at high altitude. However, sex differences in brains remain unknown. Methods: T1-weighted MRI scanned in 61 Tibetan males and 68 Tibetan females aged 17-23, and Freesurfer was used to detect brain structures. Neuropsychological tests were also performed. Matched lowland Han subjects were controls. Results: Both Tibetan and Han males had larger global gray matter (GM) volume and white matter volume than females, while Tibetan but not Han female brains contained a larger proportion of GM than male brains. Tibetan females had significant smaller regional GM volume in the left rostral middle frontal gyrus, pars opercularis, and right caudal middle frontal gyrus, and moreover, GM volume in the left pars opercularis positively correlated with digit span score. However, Tibetans females had significantly thicker cortices in the left rostral middle frontal gyrus, left pars triangularis, right rostral middle frontal gyrus, and right pars triangularis than males and cortical thickness in these regions negatively correlated with altitude. In Tibetan females but not males, the negative correlation of cortical thickness with altitude has been testified by global analysis. Conversely, Han subjects showed discrepant sex differences in brains with Tibetans, showing larger regional GM volume and thicker cortices in different brain areas. Conclusion: A distinct pattern of sex differences exists between Tibetan and Han brains. Female brains may be more tolerable to hypoxia. Sex differences in the brains of Tibetans may be related to different neuropsychiatric performances in the two sexes.

Background

Different adaptation patterns have been found in the two sexes exposed to high-altitude (HA) environment. Females were thought to cope better with hypoxia than males due to higher hypoxic ventilation response [1]. At HA, females have lower hemoglobin levels [2], less nocturnal periodic breathing [3, 4], less fat mass loss [5], and higher systolic and diastolic pressures [6] than males. Females have greater incidence of acute mountain sickness but lower risk of chronic mountain sickness than males [7-9].

Sex-based differences of brain functions in response to stress have been reported [10-12]. Hypoxic stress is the dominant environmental factor at HA. The brain is one of the heaviest consumers of oxygen in the body and thus is inevitably suffered from hypoxia. There is evidence that sex influences all levels of brain in the extension of brain damages, mechanisms of damages, behavioral outcomes, and treatment efficacies in the neonatal hypoxic-ischaemic models [13-15]. Sex-specific cerebral cortices, moleculars, densities of nerve cells, neuroplasticities, iron contents, and cerebral hemodynamic changes were also found in the hypoxic populations [16-18]. Clinical data and animal studies confirmed sex differences in hypoxic-ischaemic outcomes, including emotions [19-21], cognitions [22], and attention domains. Females showed better neurological outcomes after traumatic brain injury [23, 24]. Sex differences have also been reported in the protection of brain after posthypoxic hypothermia [25] and poly polymerase-1 knockout [26]. Moreover, sex differences in the brain energy metabolism have been demonstrated in animal model of neonatal hypoxia-ischemia [27]. Altogether, these studies suggest that females are more tolerable to hypoxia.

A lot of documents have revealed sex differences in the brain architecture at normoxic environment. The most consistent observations are that males have larger global brain volumes than females [28] and female brains contain a larger proportion of gray matter (GM) than male brains [29, 30]. However, sex differences in the GM volume have been reported to be variable in the literature. In different studies, males showed larger regional GM volumes in a large number of brain regions, including the amygdala, hippocampus, anterior parahippocampal gyrus, precuneus, putamen, temporal pole, and posterior and anterior cingulate cortices. On the contrary, females showed larger regional GM volumes in the frontal pole, inferior and middle frontal gyri, pars triangularis, parietal operculum, anterior cingulate cortex, insular cortex, Heschl's gyrus, parahippocampal gyrus, lateral occipital cortex, thalamus, and precuneus [28, 31]. Sex differences in the cortical thickness (CT) have also been reported to be inconsistent and cover a large number of brain regions. Females have thicker cortices than males in the superior and inferior frontal gyri, superior parietal gyrus, postcentral gyrus, parietal lobe, and superior and posterior temporal gyri [32-34]. In addition, a study showed males had thicker temporal and frontal cortices than females [35].

Based on the above data, we hypothesized that hypoxia could have differently exerted its effects on native male and female brain developments at HA. In view of the allelic variations of EGLN1, EPAS1, and PPARA have been identified as the genetic loci related to HA adaptation [36, 37], it is reasonable to consider that the genetic variation in Tibetans may also account for discrepant pattern of sex differences existed between Tibetan and Han brains. For this purpose, Tibetan college students, who were born and raised on the Qinghai-Tibetan Plateau, were recruited in the present study. In addition, Han college students at lowlands were recruited as controls.

Results

Physiological measurements

Demographic information and physiological characteristics of Tibetans and Han population are showed in Table 1. Only 53 Han students (25 males; 28 females) attended physiological and behavioral tests. Tibetan males had higher blood hemoglobin than Tibetan females.

Neuropsychiatric characteristics

Neuropsychiatric characteristics of HA Tibetans and Han population are showed in Table 2. There were higher scores in Wechsler Memory Scale subset digit serial accumulation and forward digit span in Tibetan males than Tibetan females.

Global brain volume

Tibetan males had significantly larger global GM volume ($p < 0.001$) and global white matter (WM) volume ($p < 0.001$) than females, (Fig. 1A). However, Tibetan female brains contained a larger proportion of GM volume than males ($p = 0.043$) (Fig. 1B).

Han males had significantly larger global GM volume ($p < 0.001$) and global WM volume than females ($p < 0.001$) (Fig. 1C). No significant difference in the proportion of GM volume between males and females was detected (Fig. 1D).

Tibetan males had a larger proportion of GM volume than Han males ($p = 0.031$); Tibetan females had a larger proportion of GM volume than Han females ($p = 0.008$).

Regional cortical GM volume

Tibetans females had significant smaller regional GM volume in the left rostral middle frontal gyrus, pars opercularis, and right caudal middle frontal gyrus than males (Fig. 2). There was no significantly larger cortical GM volume in females than males.

Han females had significantly larger regional GM volume in the right precentral gyrus and left postcentral gyrus than males (Fig. 2).

GM volume in the left pars opercularis in Tibetan males and females had a significant positive correlation with forward digit span score (Fig. 3).

Regional CT

Tibetan females had significantly thicker cortices in the left rostral middle frontal gyrus, left pars triangularis, right rostral middle frontal gyrus, and right pars triangularis than males (Fig. 4). There was no significantly thicker cortex in males than females.

Han females had significantly thicker cortices in the left lateral occipital cortex, precentral cortex, superior frontal gyrus, and rostral middle frontal gyrus as well as right lateral occipital cortex and superiortemporal gyrus than males (Fig. 4).

In Tibetan females, CT values in the left rostral middle frontal gyrus, left pars triangularis, right rostral middle frontal gyrus, and right pars triangularis had significant negative correlations with altitude (Fig. 5). No significant correlation between CT value and altitude existed in Tibetan males.

Correlation of global CT with altitude

Global analysis showed that, in Tibetan females, CT had negative correlation with altitude in the right lateral orbitofrontal gyrus, caudal middle frontal gyrus, and inferior parietal cortex and the left medial orbitofrontal gyrus, superior parietal cortex, superior frontal gyrus, and pars triangularis (Fig. 6). There were no significant correlation between CT value and altitude in Tibetan males.

Discussion

Our study revealed that Tibetan males had larger brains than Tibetan females in both global GM volume and WM volume, which was consistent with that found in lowlanders such as the Germans, Americans, Koreans, Swiss, and Australians [28] as well as in our present Chinese Han subjects. Tibetan females had a larger proportion of GM volume than males, which was also found in previous studies on lowlanders [29, 30] but not in our present study on Han subjects. Moreover, Tibetan females had smaller regional cortical GM volume than males, with GM volume in the left pars opercularis in males and females had a significant positive correlation with forward digit span performance. In contrast, Tibetan females had larger regional CT than males, and moreover, in females, CT values in these regions had significant negative correlations with altitude.

In our study, the accurate brain sites showing sex differences of CT were different between Tibetans and Han subjects, but they were all within the regions found in the Germans aged 24.3 ± 4.3 years [38], Koreans aged 19-36 years [32], and Americans aged 7-87 years [33], with significantly thicker cortices in females. In our study, although we got an opposite results in regional GM volume between Tibetans and Han, but the smaller regions in Tibetan females and the larger regions in Han females all overlapped and were consistent with the regions found in the Germans aged 20-30 years [39]. In addition, the regions that showed higher CT in the right superior temporal gyrus and left occipital lobe in our Han subjects also showed larger GM volume in America females aged 25.1 ± 4.5 years [40]. In the present study, we have also analyzed brain structural differences between Han males and Tibetan males and brain structural differences between Han females and Tibetan females, and the results showed that the sex differences of brains were consistent with that found in our previous study in Tibetans and Han subjects [41].

Our study found that Tibetan females had significantly thicker regional CT than males and the correlation of regional CT with altitude existed in female but not male Tibetans by both regional and global analyses. (1) Firstly, these results suggest that HA environmental factors may affect easily on brain developments in female residents. In agreement with our results, depression and anxiety behaviors have been observed to increase with altitude in female but not male rats [21]. In our previous study on sea-level residents after 4-week exposure on the Qinghai-Tibet Plateau, both males and females showed significant increases in cerebral iron deposition in the deep nuclei of brains, while the increased proportion of females (4%) was greater than males (2%) [17]. Baum et al. [42] found that chronic intermittent hypoxia induced a higher Fosb gene expression in females than in males, reflecting stronger neuroplastic dynamics. (2) Secondly, these results suggest that females may have a better capacity to adapt to hypoxia. Some clinic and experimental data support this suggestion. When both male and female rats were reared at an altitude, red blood cell count, haematocrit, and plasma erythropoietin levels were lower in females than in males [43]. A lot of laboratory studies showed that female animals with cerebral hypoxia-ischemia were less adversely affected relative to comparably injured males [14, 22, 44]. Clinical data also suggests females with cerebral hypoxia-ischemia exhibited less severe behavioral deficits compared to males [19]. Cohort studies have demonstrated a higher vulnerability in males towards neonatal ischemic and/or hypoxic-ischemic injury. Male brains are poorly repaired after neonatal hypoxia-ischemia, and males have an increased incidence of long-term cognitive deficits [45]. Female resistance to hypoxia can explain the lower female total mortality rate in infancy, childhood and adulthood [46].

Several studies have reported sexual dimorphism of the proportion of major cranial tissue compartments in the brain. In our study, Tibetan females showed a larger proportion of GM volume than males, which was consistent with the findings in the Americans [29] and Germans [30]. However, consistent with our findings in Han subjects, two studies failed to detect any sex differences in the Americans [47, 48]. Others observed both higher GM and WM proportions in males (reviewed by Luders Toga [49]). Moreover, in our study, both Tibetan males and females had a larger proportion of GM volume than Han males and females. Taken together, these differences may be due to racial factor.

Allelic variation of natural selective genes for HA adaptations may account for discrepant pattern of sex differences exists between Tibetan and Han brains. Genome-wide scans has reported evidence for positive natural selection at the Egl nine homolog 1 (EGLN1), endothelial PAS domain-containing protein 1 (EPAS1), and peroxisome proliferator-activated receptor alpha (PPARa) loci in the Tibetan on Qinghai-Tibet Plateau [36, 37]. All of these genes are associated with the hypoxia-inducible transcription factor (HIF) pathway. EPAS1 gene encodes the HIF-2α subunit of HIF complex. Variation at the EGLN1 locus is associated with protection against polycythemia in Tibetans at HA [37], and single nucleotide polymorphism at the EPAS1 locus is associated with hemoglobin levels in Tibetans [36, 50]. EPAS1 plays an important role in vascular remodeling [51]. HIF-2α also mediates the transcriptional activation of EPO expression in astrocytes, and thus promotes astrocytic paracrine-dependent neuronal survival during ischemia [52]. EGLN1 through encoding HIF prolyl 4-hydroxylase 2 (PHD2) plays a critical role in glucose metabolism [53]. PHD2 deficiency induces vascular remodelin [54]. PHD is highly expressed in the cortex [55]. It is shown to regulate synaptic density and alter cell migration [56] and is involved in axon rewiring following a brain injury by regulating neurite elongation of cortical neurons [57]. PPARa is involved in neuronal proliferation, differentiation, and apoptosis [58].

The greater capacity for females to adapt to hypoxia may be related to the effects of circulating estrogen and progesterone. These two hormones have been shown greater in the females living at HA than the females who resident at lowlands [59]. The resistance of females to ischemia is acquired after puberty [60] and is lost after menopause, which is in accordance with the protective effects of estrogen [61]. Exogenous administration of estrogen has been shown to reduce ischemia-induced cerebral injury [62], and the protective effect may be through preventing neuron death [62] and related to its antioxidant properties [63]. Estrogen can also increase regional cerebral blood flow (CBF) [64-66] and correlates directly with CBF velocity [67]. Females have higher CBF compared with males in the left inferior frontal gyrus, bilateral middle temporal gyri, and left superior temporal gyrus [68, 69]. In addition, in the animal models of neonatal hypoxia-ischemia, males were more sensitive to mitochondrial dysfunction, with the increased mitochondrial permeability on the inner and outer membranes leading to a high amount of released proteins as compared to females [27]. Taken together, the increased blood sex hormones, increased CBF, and relatively little mitochondrial permeability may contribute to female resistance to hypoxia. Females also have a better capacity to adapt to cold. For example, the vascular response to coldness at HA was smaller in females compared with males [70]; cold decreased the fatigue index of a sustained 2-min maximal voluntary contraction in males but not in females [71]; a significant benefit of temperature reduction in hypoxia ischemia was found in females but not in males [72].

In our study, sex differences of brains were found in the young adult residents at HA, which could be different from that in children or older peoples, as age-associated changes are sex-specific. A study has shown that men experienced greater volume decrement across age-groups than women, particularly in the dorsolateral prefrontal regions [73]. Another MRI studied on healthy adults aged range 18-80 years showed that the greatest amount of atrophy in elderly men was in the left hemisphere, whereas in women age effect was symmetric [74].

In our study, females showed significant decreases of GM volume in the left pars opercularis and pars triangularis of Broca's area, and GM volume in the left pars opercularis in Tibetans had a significant positive correlation with forward digit span performance. Previous study has found an association between the impaired forward digit span performance and the ischemia in pars opercularis [75]. Moreover, stimulation of left Broca's area interfered with digit span, producing significantly more item than order errors [76]. Forward digit span is a kind of verbal phonological short-term memory. MRI studies on articulatory suppression indicated that pars opercularis was involved in phonological short term-memory [77, 78]. Patients, who had a disability to make phonological judgements, showed lesions in the left Broca's area [79]. Therefore, the decreased GM volume of left pars opercularis of Broca area may be associated with poor phonological short term-memory in Tibetan females.

In comparison with Han population, both Tibetan males and Tibetan females had lower scores in almost all items of behavioral tests. Considering all the behaviors were originally designed for the test of Han population and cultural difference between Tibetans and Han population is real, we cannot reach the conclusion that the Tibetans performed worse than Han population.

The limitation in our study is that the inter-ethnic differences in brain structures can be large. We cannot draw a conclusion that gene and developmental environment which one dominantly determined the different pattern of sex differences between Tibetan and Han brains. Brain morphological differences between populations of different origins have been found in the early neonate life [80] and in adults in terms of whole brain and region-specific volume [81-83]. Our previous study has revealed that, compared with Han subjects living at lowlands, Tibetans living on the Qinghai-Tibetan Plateau were associated with structural modifications in cortical thicknesses, curvature, and sulcus [39]. Therefore, the global brain differences between these two populations may underlie the different pattern of sex differences between Tibetan and Han brains.

Conclusion

In agreement with Han and other population Tibetan males have larger brains than females. Female brains have a larger proportion of GM than males in Tibetans but not in Han subjects. Moreover, sex differences in the brain volume and cortical thickness in Tibetans showed a distinct pattern with that in Han subjects. Genetic and environmental factors may work together to influence the HA brains. Our results support the hypothesis that females had a better capacity to adapt to hypoxia. In Tibetans, female brain developments seem to be more tolerable to HA environmental factors. Sex differences of regional brain volumes in Tibetans may be related to different neuropsychiatric performances in the two sexes.

Methods

Subjects

Sixty-one Tibetan males and 68 Tibetan females (freshmen or sophomore) were recruited from Xizang University at Lasa (3650 m), China. They originally lived at altitude of 3119-4642 m on the Qinghai-Tibetan Plateau, and were born and raised at HA without any prior descent to lowlands or ascent to higher altitudes. Their ancestors are all native Tibetans. In addition, 73 healthy female and 54 male Han college students (male: 19.9 ± 1.9; female: 19.2 ± 1.8), who have been living at lowlands, were recruited from Xiamen University at Xiamen (China) as controls. Male and female students do not differ in college enrollment scores. All subjects were not smokers, and were excluded if they had a past history of mountain sickness, neurological disorder, or head injury. Procedures were fully explained, and all subjects provided written informed consent before participating in the study. The experimental protocol was approved by the Research Ethics Review Board of Xiamen University.

Physiological measurements

Physiological measurements included heart rate, blood pressure, hematological measure, and arterial oxygen saturation (SaO_2). Blood samples were taken in the morning between 07:00 and 07:30 h.

Neuropsychological tests

Subjects were given the following tests: (1) The Chinese revised version of Wechsler Memory Scale [84] provided measurements of visual and verbal memory functions, including digit serial accumulation, digit span forward and backward task, accumulation, figural memory, visual recognition, visual reproduction, and touch. The procedures of above tests have been described in our previous study [85]. (2) Rey–

Osterrieth Complex Figure (ROCF) assessed short- and long-term visual memory and visuoconstructional ability. Subjects were presented with a ROCF on a paper (21 × 29.7 cm) and asked to copy it. Immediately following completion of the copy trial, the figure was removed and subjects were asked to reproduce the figure from memory (testing for immediate recall). Twenty minutes after the last exposure to the figure, subjects were asked to reproduce the figure from memory again (delayed recall). Two scores (maximum score = 36) were derived from the immediate recall and delayed recall. (3) Beck Anxiety Inventory assessed the severity of anxiety.

MRI data acquisition

Brain images were obtained on two Tim Trio 3T scanners (Siemens, Erlangen, Germany). Tibetans were scanned at the MRI Center in Tibet Autonomous Region People's Hospital at Lasa, and Han subjects were scanned at the MR Imaging Center, First Affiliated Hospital of Xiamen University at Xiamen. A 3D structural MRI was acquired using a T1-weighted MPRAGE sequence: TR/TE = 5000/298 ms, FOV = 240 × 256 mm^2, average = 1, matrix = 256 × 240, voxel size = 1 × 1 × 1 mm^3, slice thickness = 1 mm. Conventional 2D T1 and T2 images were also acquired for any incidental findings. The data analysis was conducted by two researchers who were blind to the status of the subjects.

FreeSurfer analysis

FreeSurfer (version 510; http://surfer.nmr.mgh.harvard.edu) was used for analyses of CT and cortical GM volume. The process consisted of the removal of non-brain tissue, mapping to Talairach-like space, and segmentation of the GM-WM and pial boundaries. These maps of measurements were obtained by reconstructing representations of the GM/WM boundary and the white boundary to the GM/cerebrospinal fluid boundary and then calculating the closest distance from those surfaces at each vertex on the tessellated surfaces. Areal maps obtained here were along with the methods described by Joyner et al. [86] and Palaniyappan et al. [87]. All subjects' images were resampled to the FreeSurfer default common surface template using a high-resolution surface-based averaging technique that aligned cortical folding patterns. Finally, the surface data were spatial smoothed using a Gaussian kernel of 8 mm full-width at half-maximum.

GM volume, WM volume, and CT were compared using Independent-Samples t-test, with age as covariates. Moreover, for GM and WM volumes analyses, we also test the sex differences using intracranial volume as covariate. The statistical parametric map was generated at $p < 0.05$ (FDR corrected for multiple comparisons).

Statistical analysis of demographic variables

All analyses were conducted using SPSS19.0. Independent-Samples t-test was used to measure between-group neuropsychological differences. Statistical significance was set at $p < 0.05$.

To analyze the correlations of GM volume and CT values with altitude and neuropsychological behaviors, the GM volume and CT values were extracted from each individual's normalized maps. Moreover, the global correlations of CT with altitude were also analyzed. Statistical significance was set at $p < 0.05$, with age and education as covariates.

Abbreviations

HA: high-altitude; GM: gray matter; CBF: cerebral blood flow; CT: cortical thickness; WM: white matter; ROCF: Rey–Osterrieth Complex Figure.

Declarations

Ethics approval and consent to participate

The experimental protocol was approved by the Research Ethics Review Board of Xiamen University.

Consent for publication

Not applicable.

Availability of data and material

Presented in the main manuscript.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JZ conceived of the research question, CF and JZ designed the study and created experimental protocols, CF, CZ, YZ, WY, JL and collected the data, CF and CZ analyzed the data, JZ wrote the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Demographic information and physiological characteristics of Tibetans and Han population

	Tibetan		*Han*		*p1*	*p2*
	Males	*Females*	*Males*	*Females*		
	61	68	25	28	-	-
mean ± SD)	20.0 ± 1.1	19.8 ± 0.9	21.2 ± 1.0	20.9 ± 1.6	0.083	0.152
ears) (mean ± SD)	12.8 ± 0.5	12.7 ± 0.5	13.5 ± 0.5	13.3 ± 0.5	0.183	0.209
ndex (mean ± SD)	19.5 ± 2.1	20.1 ± 2.0	19.8 ± 2.4	20.3 ± 1.6	0.185	0.163
(mean ± SD)	4040.9 ± 374.4	3943.2 ± 275.2	576.7 ± 235.4	607.2 ±185.1	0.087	0.405
sure	117.8 ±7.7	111.3±9.8	126.9±11.9	110.1±12.0	0.276	0.732
ssure	68.4±8.1	67.6±7.6	81.7±10.1	75.1±10.0	0.964	0.867
n saturation	93.2±1.8	91.3±3.9	98.2±0.5	98.4±0.8	0.070	0.137
	64.1±9.4	73.9±8.9	68.6±8.4	71.9±11.8	0.058	0.320
	166.3±11.9	140.6±16.5	151.5 ±7.2	132.1 ±8.3	0.048	0.468
	46.8±3.6	41.5±4.0	45.6±1.9	40.8±2.3	0.846	0.332
)	95.1	94.1	4	0	-	-
alcoholics	None	None	None	None	-	-

$p1$: Tibetan males vs. females; $p2$: Han males vs. females

Table 2 Neuropsychiatric characteristics of Tibetans and Hans

	Tibetan		Han			
Tests	*Males*	*Females*	*Males*	*Females*	*p1*	*p2*
Mental control						
Digit serial accumulation	8.1 ± 3.0	7.1 ± 2.9	12.3±1.8	11.2±2.3	0.029	0.313
Backward task	11.5 ± 1.3	11.6 ± 1.9	14.3±0.7	14.0±0.6	0.330	0.198
Accumulation	11.1 ± 1.8	10.7 ± 1.5	13.2±0.8	12.7±1.0	0.094	0.253
Figural memory	10.9 ± 1.7	10.7 ± 1.5	11.6 ± 1.8	12.2±1.0	0.228	0.599
Visual recognition	10.4 ± 2.3	10.5 ± 2.1	11.0± 1.9	9.8±2.2	0.419	0.841
Visual reproduction	11.4 ± 1.4	11.1 ± 1.3	12.5 ± 1.2	12.3±1.1	0.128	0.783
Touch	12.2 ± 3.1	11.4 ± 2.2	16.1± 2.2	16.3±2.5	0.055	0.219
Digit span Forward task	13.6 ± 2.3	12.7 ± 2.4	17.1± 1.8	17.2±1.9	0.027	0.931
Rey-Osterrieth Complex Figure test						
Immediate recall	25.3 ± 6.7	24.5 ± 6.0	27.4 ± 5.8	28.1±4.2	0.251	0.211
Delayed recall	25.9 ± 6.2	24.6 ± 6.8	27.4 ± 5.6	28.9±4.7	0.141	0.401
Beck Anxiety Inventory score	29.3 ± 6.8	30.3 ± 7.1	25.2 ± 3.4	25.1±3.7	0.209	0.594

*p*1: Tibetan males vs. females; *p*2: Han males vs. females

Figures

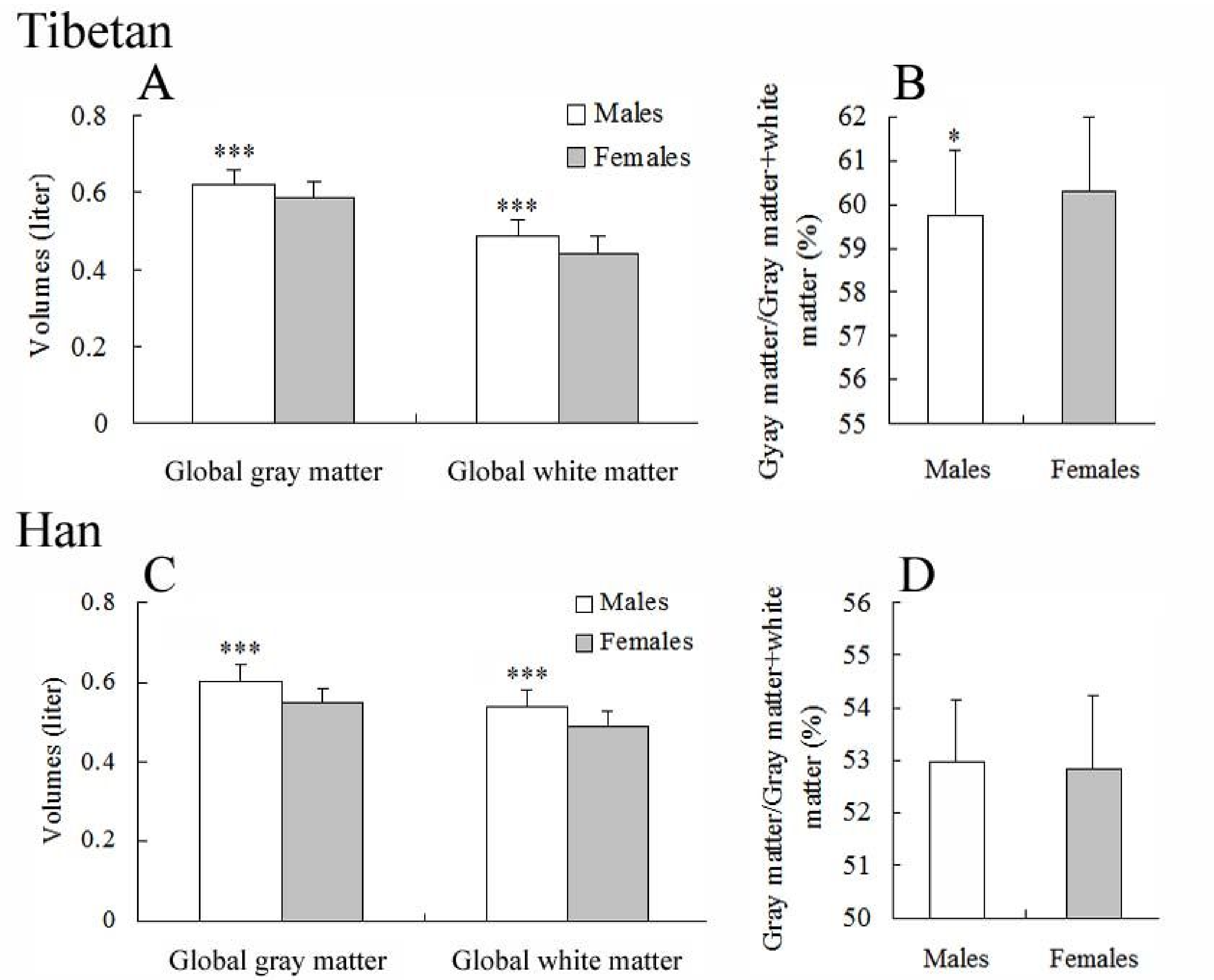

Figure 1

(A) Sex differences in brain volumes. Global brain volumes and percentage of gray matter/gray matter + white matter in Tibetans (A and B) and in Han population (C and D). *, $p < 0.05$; ***, $p < 0.001$.

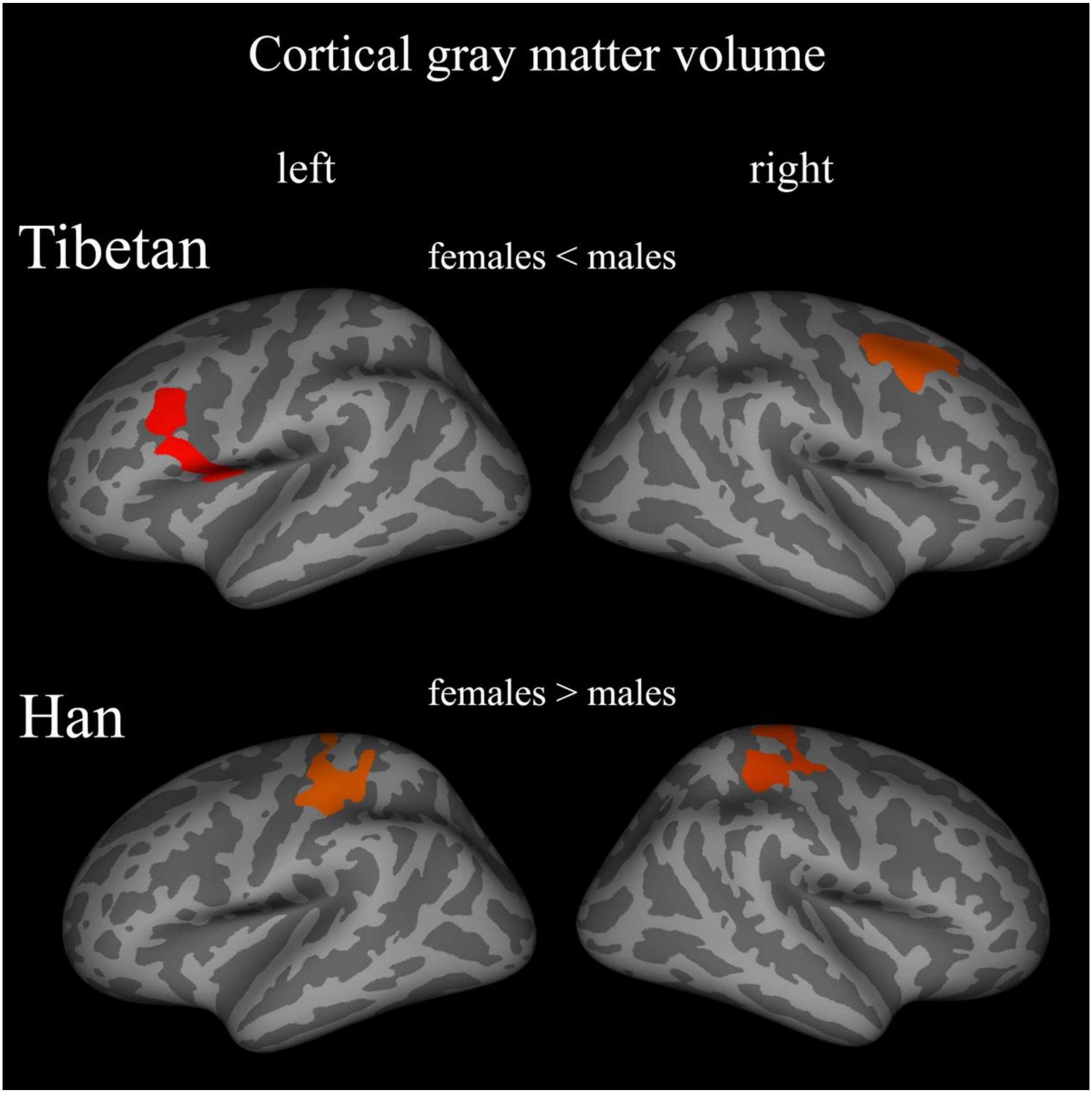

Figure 2

Colored regions showing significant sex differences of cortical gray matter volume.

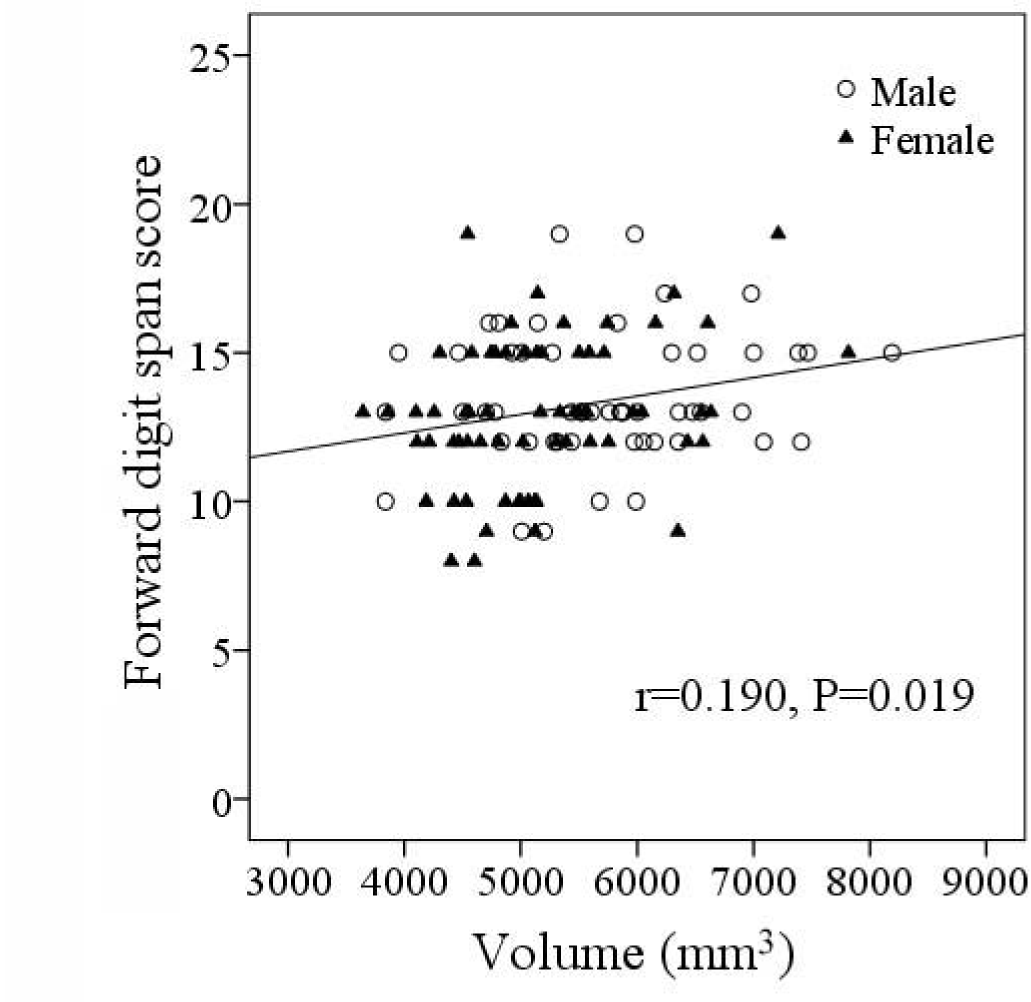

Figure 3

Correlation between gray matter volume in the left pars opercularis and forward digit span performance in Tibetan males and females.

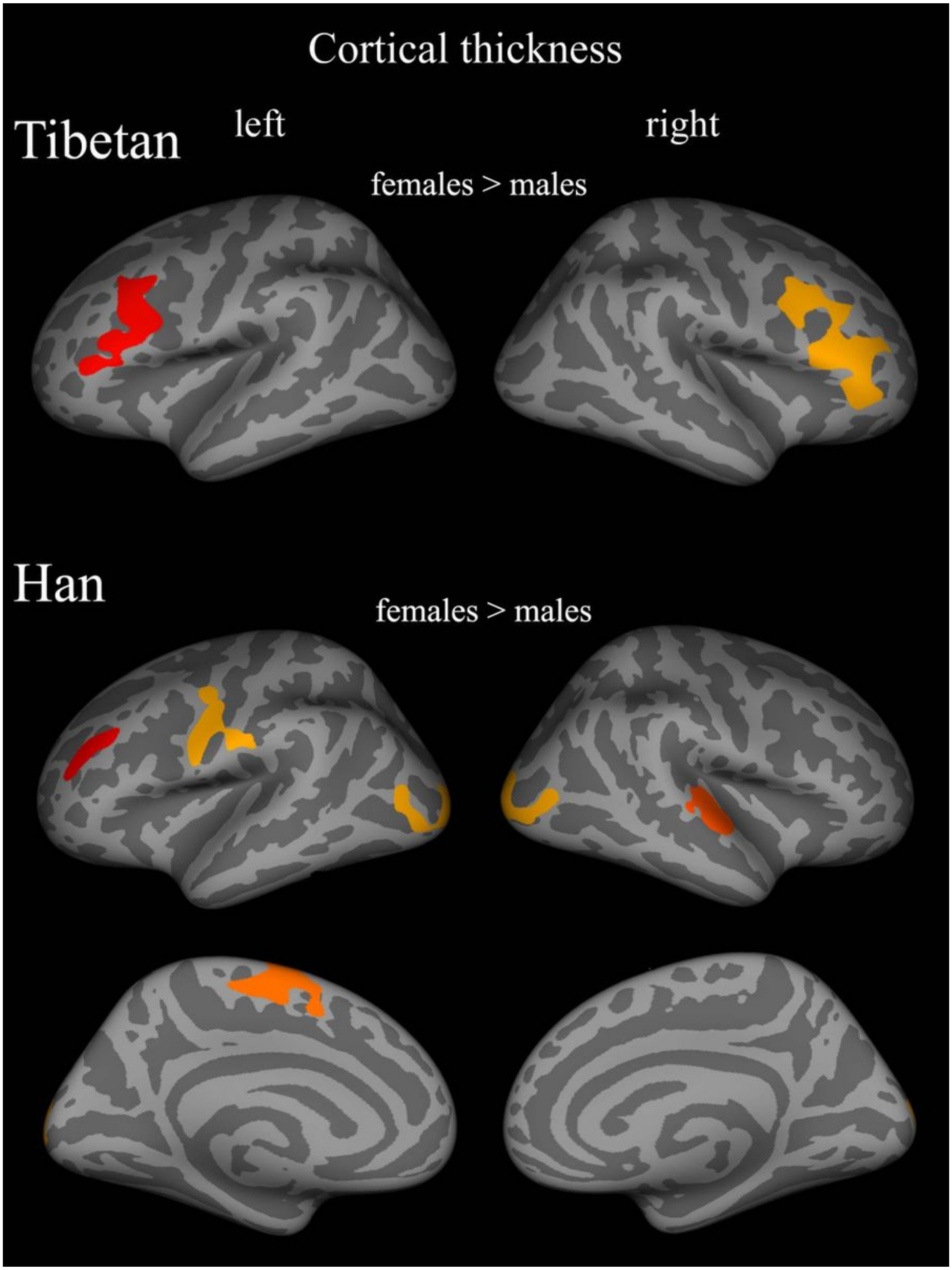

Figure 4

Colored regions showing higher cortical thickness in females than males.

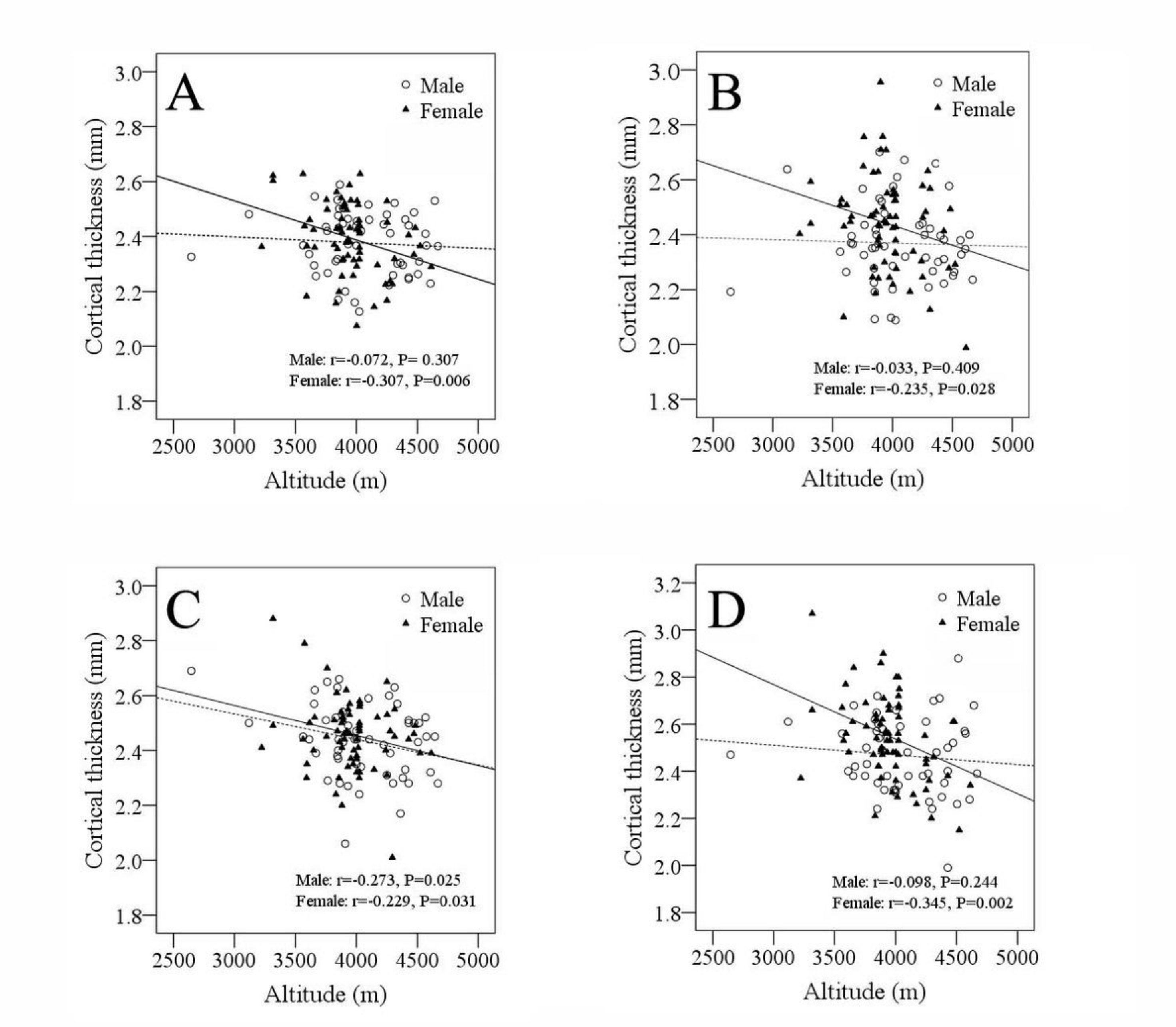

Figure 5

Correlations of cortical thickness values with altitude in Tibetan males and females. (A) left rostral middle frontal gyrus; (B) left pars triangularis; (C) right rostral middle frontal gyrus; (D) right pars triangularis.

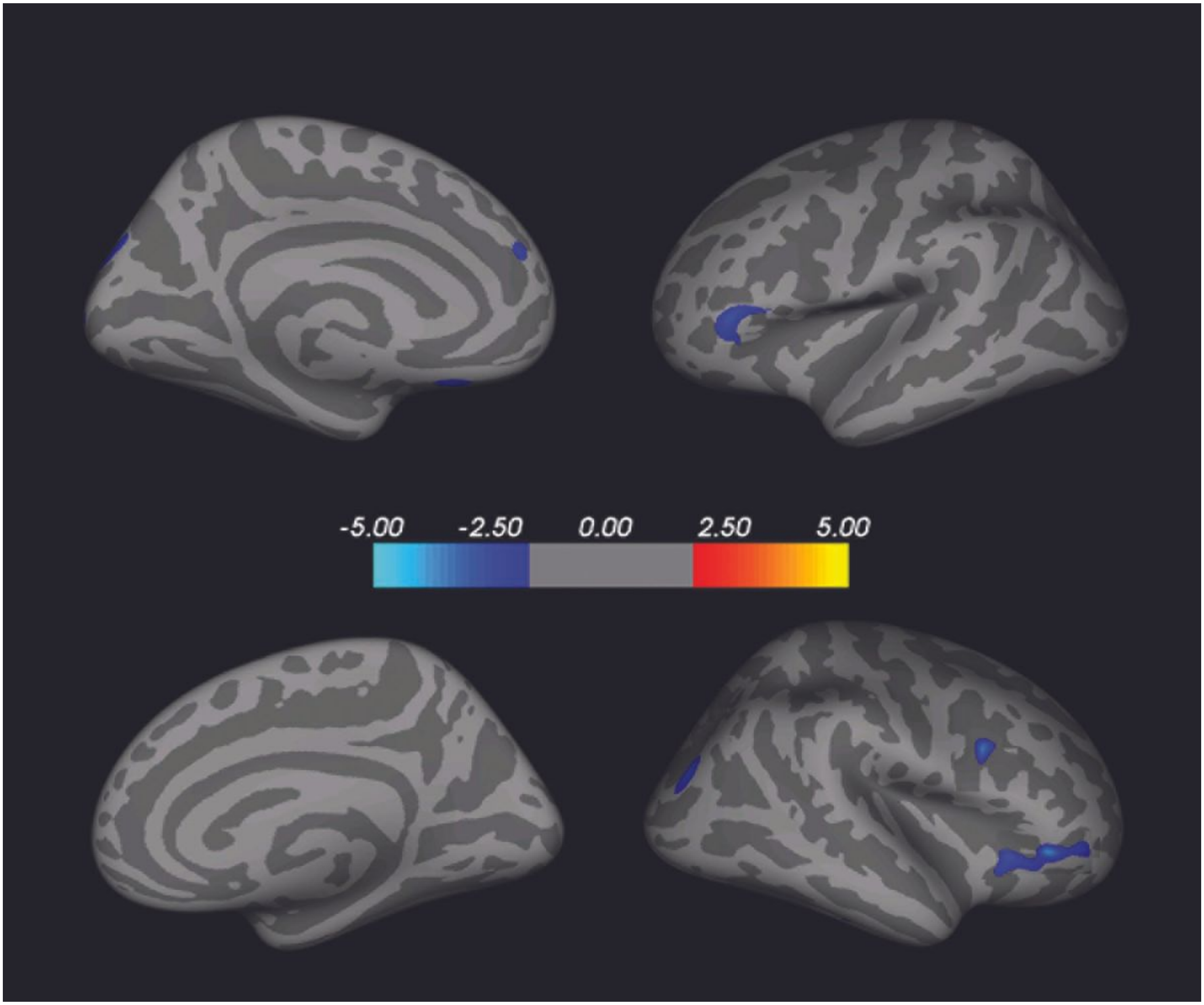

Figure 6

Global correlations of cortical thickness values with altitude in Tibetan females. Blue indicates significant negative correlation.