Gender differences in cortical complexity

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Cortical complexity, a measure that quantifies the spatial frequency of gyrification and fissuration of the brain surface, has not been thoroughly characterized with respect to gender differences in the human brain. Using a new three-dimensional (3D) analytic technique with magnetic resonance imaging, we found greater gyrification in women than men in frontal and parietal regions. Increased complexity implies more cortical surface area, which may offset gender differences in brain volume and account for behavioral gender differences.

The normative literature documents larger brains in men than in women, leading some scientists to propose that compensation mechanisms might have developed in smaller female brains during human evolution. Findings of regionally increased neuropil[1] and neuronal densities[2], especially in the cortex, as well as higher gray matter percentages[3] in females, support the idea of brain size–related neuronal compensation. We investigated whether regional increases in cortical folding (cortical complexity) are present in females, which could have a compensatory effect by increasing cortical surface area. Different cortical complexities in men and women are likely, given that brain expansion is partly constrained by the size of the intracranial cavity during neurodevelopment[4], and average skull sizes in females are smaller than in males.

We examined cortical complexity in a well-matched sample of healthy men (n = 30; 25.5 ± 4.7 years, mean ± s.d.) and women (n = 30, 24.3 ± 4.4 years), who gave informed written consent according to institutional guidelines (Ethics Committee of the University of Magdeburg). High-resolution spoiled gradient-echo (SPGR) T1-weighted magnetic resonance images (256 × 256 × 124 matrix, 0.98 × 0.98 × 1.5 mm voxel size) were obtained on a 1.5-tesla scanner (General Electric) and preprocessed using manual and automated procedures. After applying a radio-frequency bias field correction[5] and 12-parameter linear transformations into ICBM-305 stereotaxic space[6], we extracted 3D cortical surfaces[7] and used validated anatomic protocols[8] to identify and manually outline 16 cortical surface sulci in each hemisphere (www.loni.ucla.edu/NCRR/Protocols/SulcalAnatomy.html). Intra- and inter-rater reliability was established as previously described[8]; the 3D root-mean-square distance was <2 mm, and on average <1 mm, for all landmarks within and between raters.

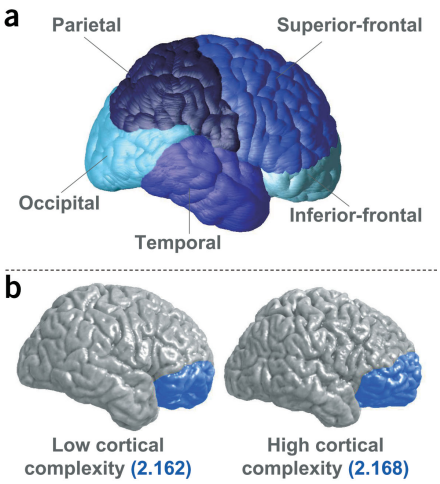

Figure 1 The cerebral cortex. (**a**) The parcellation of the cortical surface into five lobar regions in each hemisphere. (**b**) Examples show low (2.162) and high (2.168) cortical complexity indices as measured from the right inferior frontal lobe region of two different individuals.

Next, we used cortical pattern matching methods[9] to identify homologous cortical regions between subjects based on the sulcal landmarks. Briefly, the manually derived sulcal landmarks are used as anchors to drive the surrounding cortical surface anatomy of each individual into correspondence. A 3D vector deformation field was computed that associates the same cortical surface locations in each subject with reference to the average anatomical pattern of the entire study group. The manually delineated sulcal landmarks were used again later, to divide each 3D cortical surface model into five distinct cortical regions of interest within each hemisphere, including the frontal (superior and inferior), temporal, parietal and occipital lobes (**Fig. 1a**).

Finally, the cortical complexity, which reflects the frequency of sulcal and gyral convolutions in these distinct neuroanatomic regions, was estimated as described previously[10] (**Supplementary Figure 1**). To compare cortical complexity values between males and females and examine interactions with gender and hemisphere, we used repeated-measures ANOVAs, with hemisphere as a within-subjects factor.

Statistical comparisons of cortical complexity values (**Table 1**) revealed significantly greater cortical complexity in women compared to men in the superior-frontal ($F_{1,58}$ = 8.71, P < 0.005) and parietal lobes ($F_{1,58}$ = 10.38, P < 0.002). A trend for hemisphere-by-sex interaction was present for the inferior-frontal lobe ($F_{1,58}$ = 4.25, P < 0.044), with follow-up analyses revealing significantly greater

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Table 1 Cortical complexity values and statistics

Lobar region	Complexity: males, mean (s.e.m.)	Complexity: females, mean (s.e.m.)	Males CI, min–max	Females CI, min–max	Cohen's *d*	Power
Inferior frontal						
Right*	2.16188 (0.00107)	2.16817 (0.00123)	2.15969–2.16406	2.16565–2.17070	**0.996**[a]	0.940
Left	2.15706 (0.00329)	2.15517 (0.00192)	2.15034–2.16377	2.15124– 2.15910	n.s.	n.s.
Superior frontal						
Right*	2.16801 (0.00126)	2.17340 (0.00187)	2.16544–2.17059	2.16957–2.17724	*0.615*	0.609
Left*	2.16580 (0.00131)	2.17329 (0.00236)	2.16312–2.16849	2.16846–2.17812	*0.717*	0.760
Temporal						
Right	2.15921 (0.00062)	2.16080 (0.00100)	2.15794–2.16047	2.15877–2.16284	n.s.	n.s.
Left	2.15783 (0.00076)	2.16116 (0.00200)	2.15628–2.15938	2.15707–2.16525	n.s.	n.s.
Parietal						
Right*	2.16202 (0.00082)	2.16726 (0.00116)	2.16033–2.16370	2.16489–2.16962	**0.952**	0.967
Left*	2.16585 (0.00076)	2.16840 (0.00111)	2.16429–2.16741	2.16612–2.17068	0.487	0.327
Occipital						
Right	2.16557 (0.00081)	2.16850 (0.00121)	2.16392–2.16721	2.16602–2.17099	n.s.	n.s.
Left	2.16888 (0.00141)	2.17024 (0.00118)	2.16600–2.17176	2.16782–2.17266	n.s.	n.s.

[a]According to Cohen[15], an effect size of $d = 0.8$ constitutes a large effect (bold), $d = 0.5$ a medium effect (italic), and $d = 0.2$ a small effect.

*Regions with significant differences between men and women. n.s., differences not significant between males and females.

complexities in the right hemisphere in females compared to males ($F_{1,58} = 14.87$, $P < 0.001$). No lobar region showed significantly greater cortical complexity in men. The proportion of variance accounted for by gender differences was medium or large for four out of the five significant results reported (**Table 1**). Examples of low and high regional complexities are provided in **Figure 1b**.

Statistical analyses also revealed significant differences between the hemispheres, with higher complexities in the left parietal ($F_{1,58} = 3.54$, $P < 0.001$) and left occipital cortices ($F_{1,58} = 9.90$, $P < 0.003$), as well as in the right inferior-frontal cortices ($F_{1,58} = 20.62$, $P < 0.001$;), relative to counterparts in the opposite brain hemisphere.

Gender-related differences in sulcal and gyral convolutions have not been observed in previous studies, due to limitations in the use of 2D measures and/or postmortem data[11,12]. Here, by applying sophisticated 3D parametric mesh-based techniques, we found gender-specific differences in cortical complexity that might be associated with differential function, given that cortical folding patterns are influenced by the underlying cytoarchitecture and reflect neural connectivity[13,14]. Gender-specific cortical complexities may thus contribute to gender-specific abilities and/or behavioral differences, and increased complexities in females may also compensate for their smaller brain volumes or constitute part of the anatomical substrate that supports some of the cognitive skills in which women tend to outperform men. Different cortical complexities in male and females brains support the hypothesis that brain volume tends to be inversely proportional to folding complexity, possibly as a result of developmental constraints on brain expansion. In addition, gender- and hemisphere-specific rates of brain maturation may partly account for present findings of sexual dimorphism in gyral complexity and fissuration asymmetry, where different spatial frequencies of gyrification and fissuration in the left and right hemisphere might reflect a hemisphere-specific brain organization possibly related to functional specializations.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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1. Rabinowicz, T. *et al. J. Neuropathol. Exp. Neurol.* **61**, 46–57 (2002).
2. Witelson, S.F., Glezer, I.I. & Kigar, D.L. *J. Neurosci.* **15**, 3418–3428 (1995).
3. Gur, R.C. *et al. J. Neurosci.* **19**, 4065–4072 (1999).
4. Van Essen, D.C. *Nature* **385**, 313–318 (1997).
5. Sled, J.G., Zijdenbos, A.P. & Evans, A.C. *IEEE Trans. Med. Imaging* **17**, 87–97 (1998).
6. Woods, R.P., Grafton, S.T., Watson, J.D., Sicotte, N.L. & Mazziotta, J.C. *J. Comput. Assist. Tomogr.* **22**, 153–165 (1998).
7. MacDonald, D., Avis, D. & Evans, A. *Proc. Int. Soc. Opt. Eng.* **2359**, 160–169 (1994).
8. Sowell, E.R. *et al. Cereb. Cortex* **12**, 17–26 (2002).
9. Thompson, P.M., Woods, R.P., Mega, M.S. & Toga, A.W. *Hum. Brain Mapp.* **9**, 81–92 (2000).
10. Thompson, P.M., Schwartz, C., Lin, R.T., Khan, A.A. & Toga, A.W. *J. Neurosci.* **16**, 4261–4274 (1996).
11. Nopoulos, P., Flaum, M., O'Leary, D. & Andreasen, N.C. *Psychiatry Res.* **98**, 1–13 (2000).
12. Zilles, K., Armstrong, E., Schleicher, A. & Kretschmann, H.J. *Anat. Embryol. (Berl.)* **179**, 173–179 (1988).
13. Roland, P.E. & Zilles, K. *Trends Neurosci.* **17**, 458–467 (1994).
14. Caviness, V.S. *Science* **189**, 18–21 (1975).
15. Cohen, J. *Statistical Power Analysis for the Behavioral Sciences* pp. 25–27 (Hillsdale, New York, 1988).