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Research report

Cortical gyrification and its relationships with cortical volume, cortical thickness, and cognitive performance in healthy midlife adults

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HIGHLIGHTS

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- Inter-relationships examined between cortical gyrification, cortical volumes, and cortical thickness in a large middle-aged sample of adults.
- Positive gyrification–volume relationships and negative gyrification–thickness relationships found in the cortex.
- Positive gyrification–cognition relationships found in the lateral frontal cortex, which were independent of cortical volume and thickness contributions.
- Sex differences in cortical gyrification minute after taking total brain volumes into account.

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ABSTRACT

Across species, greater cortical gyrification, or folding of the cortex, has been shown to be associated with higher cognitive abilities and is thought to reflect an evolutionary process aimed at maximizing the number of cerebral computational units while minimizing the energy and communication costs of larger brains. Relatively little is known about the significance of individual variation in gyrification in humans and how it relates to other aspects of cerebral structure and function. In the current study, we examined relationships between cortical gyrification and (i) cortical volume, (ii) cortical thickness, and (iii) executive functions. Participants were middle-aged healthy adults (44–48 years old, $n = 396$) in a community-based sample. T1-weighted 3D structural magnetic resonance imaging scans were acquired in a Fast Field Echo sequence. Cortical gyrification, volume, and thickness were measured through the semi-automated software FreeSurfer. Results showed that cortical gyrification was strongly and positively related to cortical volume, but was negatively related to cortical thickness in many regions of the cortex. In addition, frontal gyrification was positively related to performance in working memory and mental flexibility tasks. These results support the view that greater cortical gyrification is related both to bigger brain volumes and better cognitive function, but not to greater cortical thickness. The results provide evidence of functional relevance of cortical gyrification development, and show that it can be a useful index to investigate structure–cognition relationships.

Q5 1. Introduction

Q6 A striking characteristic of the cerebral cortices is their convoluted structure, with the cortex folding upon itself inside the cranial cavity. This feature is known as cortical gyrification. Evolutionary studies as well as studies investigating the development of gyrification in animals have identified several important drivers of gyrification including increase in cortical area and increase in the number of neurons and intra-cranial volume (ICV) [1–6]. Cortical gyrification begins early in development and continues into adulthood. The development of major gyri begins in gestation, and smaller gyri continue to develop until the first year of birth [4,7] and beyond.

1.1. How does gyrification occur?

The factors leading to cortical folding are thought to be forces generated early during brain development through processes that

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change brain volume. These processes include both neurogenesis and development of dendrites and supporting structures which increase volume, as well as processes that decrease brain volume, such as pruning, and programmed cell death [2]. The 'random buckling' theory [8] suggested that forces that contribute to the regional folding of the cortex are largely dependent on local influences of cell division and cell death. Some experimental studies in animals support this view by showing that alteration to programmed cell death leading to increased cell numbers can result in formation of extensive additional cortical folding, for instance in cultures grown ex vivo [9] as well as in developing chicken embryos [2].

However, more recent views suggest that the forces along axons and glial fibers act as major drivers for the creation of cortical folds by pulling at more distant parts of the cortex. Van Essen [10] proposed that tension along interconnected fibers would result in functionally similar regions coming together during the development of the cortex so that the length of the fiber between such regions is as short as possible. Such regions would create outward folds or gyri. In contrast, inward folds or sulci are formed as a result of the forces that create outward folds—the sulci form in regions in between gyri; and as a consequence, regions with less interconnectedness are more susceptible to be situated in inward folds [10]. Measurement of tensions along the axons in animal models support this view [10]. Others [3,11], have more recently proposed that the factors of early-life cellular events which increase of cortical surface area inside the skull could explain the generation of forces along axonal fibers and also dictate cortical folding. In their computer simulations, they showed that the initial assumptions of a limiting ICV, combined with increases in cell numbers in a cortex that was 'elastic' (able to bend/fold) and 'plastic' (hold on to the shape after folding) generated cortical models that were structurally similar to the human gyrified cortex. Hence, they suggest that differential expansion of cortical layers in different regions of the cortex could also lead to differences in regional folding [3,11].

1.2. Why is the cortex gyrified?

Toro and colleagues [11], using 3-D automated methods have found that gyrification is strongly and positively associated both with brain size and cortical surface area. In addition, increases in cortical surface area have been found to be strongly and positively associated with increased cortical curvature in young adults [12]. The cortical surface area in primates is accordingly, much larger than that of rodents [13] and in humans the cortical surface is known to increase up to 3-fold between birth and adulthood [14]. One possible advantage of such increases in cortical gyrification through increase in surface area is to increase the computational capacity of the brain. Accordingly, species with increased gyrification demonstrate increased cognitive capacity. For example, a rodent cortex, which has relatively low levels of gyrification [15], also lacks many of the specific cortical functional areas present in the gyrified primate cortex. Similarly, the associative cortices such as the prefrontal regions, which are implicated in higher order cognition, also have one of the highest levels of gyrification in humans and in primates [5,16]. Hence, if the increase in cortical area associated with increased folding is related to increases in cortical function then it may be expected that cortical gyrification should be positively related, with both cortical volume and cognitive performance, especially in the prefrontal cortices.

Surprisingly, Toro and Burnod [3] in their computer simulations of cortical folding development models found that thicker cortical sheets lead to less cortical convolutions. A possible advantage of having thinner cortices in conjunction with a large cortical surface area could be the preservation of optimum white matter fiber length and effective cortico-cortical communication. Such underlying fibers form the basis of communication between all the gyral regions as well as between the cortex and the sub-cortical regions. Keeping thickness at a minimal level might serve to keep the outermost cortical cell layer within the shortest possible distance from surrounding regions, and to keep the length of the connecting fibers at a minimum. In this case, cortical gyrification would be negatively related to cortical thickness. More recently, in a lifespan sample, Hogstrom and colleagues [17] found that cortical surface area and cortical volume was positively related to gyrification but negatively related to cortical thickness. The authors interpreted these results as being consistent with the notion that gyrification maximizes the cortical surface and facilitates brain connectivity and functional development although they did not test any associations with brain function.

Furthermore, there is limited evidence that individual differences in cortical folding in humans may be related to cognitive function. Previous research has reported mixed findings. Some have found that young females, but not males, have a positive correlation between cortical folding and IQ that are especially prominent in the prefrontal regions [18]. Others have found lower gyrification of prefrontal regions in those with global cognitive impairment [19] and in schizophrenia [20].

Similarly, it is unclear whether gyrification is sexually dimorphic. Earlier studies detected no differences in gyrification between males and females [5,21]. However, more recent investigations have found mixed results with one suggesting young females (mean age 25) have higher cortical folding [12,22], and another finding no such differences in a much larger sample [17]. Although cross-sectional studies have found that sex differences in cortical measures such as cortical volume and thickness are inconsistent and can vary through the lifespan [23,24], cortical gyrification differences (if any) have not been reported in epidemiological samples of midlife adults.

Hence, although past research has produced important insights into the development and topography of cortical gyrification, it is still unclear whether variability in gyrification in humans is functionally significant. Previous studies have been somewhat limited in their capacity to detect functional differences by their relatively small sample sizes (ranging between 37 and 65), which might have provided limited statistical power to detect associations in other parts of the cortex besides the frontal cortex or in males. Moreover, the extent to which small samples are representative of the broader population is also open to question. Though this limitation was addressed in the study by Hogstrom et al. with a sample size of 322, this study assessed individuals across a very broad age range (20–85 years) and did not investigate associations between cortical gyrification and cognitive function.

1.3. Current study

In light of the available evidence, the aims of the current study were to (1) investigate the association of cortical gyrification with cortical thickness and brain volume; (2) investigate sex differences in cortical gyrification and (3) investigate the associations between cortical gyrification and cognitive performance, after taking cortical volume and cortical thickness into consideration. As the primary interest of the study was investigating the inter-relationships between cortical volume, thickness, and gyrification—cortical surface area is not examined in the current study.

It was hypothesized that cortical volumes would be positively, and cortical thickness negatively, associated with gyrification. Based on prior findings of volume- and thickness-cognition relationships in the frontal cortex using an executive function battery in this population [25], it was also hypothesized that gyrification would be positively associated with cognitive performance in the frontal cortex. No specific hypotheses were made on sex differences in cortical gyrification, due to the inconsistent and limited available literature.

2. Methods

2.1. Sample selection

Participants were drawn from the Personality and Total Health (PATH) Through Life Study. The PATH study consists of participants randomly recruited from the electoral roll living in Canberra, in the Australian Capital Territory and the adjacent city of Queanbeyan. The project includes three age-cohorts with individuals between the age groups of 20–24, 40–44, and 60–64 who are followed up every four years. Data were collected on cognitive function, socio-demographic variables, depression, anxiety and psychosocial risk factors. Further details on the PATH study have been published previously [26]. Approval for the study was obtained from the human research ethics committee of the Australian National University and University of New South Wales.

This study concerns the second wave of data for the middle aged (MA) participants; therefore they were between the ages of 44–48. The initial sample included 431 participants who completed the MRI scans.1 scan was lost during acquisition and 34 scans were deemed unsuitable for semi-automated analyses due to excessive motion. Total sample size was 396. Previous publications from this sample have included investigation of cognition–structure relationships in frontal cortical volumes and thickness [27] and analyses of sex differences in cortical thickness [27].

2.2. Scan parameters

Participants were scanned on a 1.5 T Philips Gyroscan scanner (ACS-NT, Philips Medical Systems, Best, the Netherlands) for three-dimensional (3D) structural T1-weighted MRI in coronal orientation and Fast Field Echo sequence yielding contiguous slices with thickness of 1.5 mm. The in-plane spatial resolution of the contiguous coronal slices was 1.016 mm × 1.016 mm/pixel. About midway through the study, the original Philips scanner (scanner A) was replaced with an identical Philips scanner (scanner B) for reasons beyond the researchers' control. The first 163 participants were scanned with field of view = 256 mm × 256 mm and matrix size = 256 × 256, flip angle = 8°, TR = 8.84 ms, and TE = 3.55 ms. The remaining 268 participants were scanned with field of view =256 × 256 mm and matrix size = 256 × 256, flip angle = 8°, and TR = 8.93 ms and TE = 3.57 ms to improve image quality. There were no differences in age, years of education, or ICV between the subjects scanned in the two scanners (results published previously [25]), but more men were inadvertently scanned in scanner A than in scanner B.

2.3. Image processing and obtaining cortical measures

MR images were analyzed through a set of automated tools, FreeSurfer v4.3.0 (http://surfer.nmr.mgh.harvard.edu). FreeSurfer allows for automatic reconstruction of the cortical surface using T1-weighted MR images. Major steps during image analyses include removal of non-brain tissue, automated Talairach transformation, subcortical and cortical matter segmentation, intensity correction, and delineation of gray/white/pial boundaries [28,29]. After the formation of cortical models, deformable procedures are applied including cortical inflation, registration to a spherical atlas, and parcellation of the cerebral cortex into gyral and sulcal units [30].

Brain structure measures for cortical volume, thickness, and gyrification were obtained through semi-automated segmentation tool, FreeSurfer. Cortical thickness maps were created using both signal intensity and continuity information from the 3D volume from MR images where thickness was calculated as the closest distance from a pial to white matter boundary at each vertex [29]. Reliabilities for cortical thickness measures obtained using FreeSurfer have been previously described [31]. After initial processing by FreeSurfer, all MRI scans were visually checked slice by slice to ensure that there was no mis-registration of gray and white matter voxels; scans were corrected and reprocessed if errors were detected and rechecked visually a second time. The most common reasons for reprocessing were inclusion of the dura in the middle temporal lobe and labeling of remaining bone tissue as gray matter after incomplete skull stripping, around the temporal lobe. Approximately 10% of scans in each cohort were found to contain errors during manual checking and were reprocessed a second time.

Thickness maps were spatially smoothed with a Gaussian kernel with a half maximum width of 10 mm. Maps were then averaged across participants using a spherical aligning method for cortical folding patterns. To measure gyrification, the current study used 3-D methods of gyrification to measure local gyrification index, which was computed in the FreeSurfer software with a MATLAB add-on package, and provided an index of cortical folding with respect to regional structural variance in gyri and sulci. This process has been described in detail by Schaer and colleagues [16]. Briefly, cortical gyrification was measured as a ratio of the area on the outer surface to the area on the pial surface. During this initial calculation of gyrification index, a fixed radius of 25 mm was used at each point so that the surveyed area was able to take into consideration the number of sulci and gyri and therefore, the local variation in cortical folding of the region [16]. In later stages during statistical analyses using FreeSurfer, a smaller FWHM of 5 mm was selected as appropriate for smoothing of gyrification maps.

2.4. Cognitive measures

A cognitive battery was administered to the participants during the PATH interview preceding the MRI acquisition. Episodic memory was measured with the first list of the California Verbal learning Test for both immediate and delayed recall [32]. Simple and choice reaction times were measured and the procedure has been explained in detail elsewhere [33]. Verbal working memory was measured through the Digits-Backwards span (DB), a subtest of the Wechsler memory scale [34], information processing speed and attention were measured through the Symbol-Digit Modalities Test (SDMT) [35], and mental flexibility and executive control were measured through the Trail Making Tests A and B. The cognitive tests utilized in the study are widely used in neuropsychological examinations and their test–retest reliabilities have been previously reported by other studies (for EM see [36], for DB see [37], for SDMT see [38], and for Trails A and B see [39]). Missing data (<5%) for cognitive measures were imputed using the EM algorithm from SPSS.

In the interest of reducing the number of statistical tests, a number of cognitive measures were combined. A reaction time (RT) measure was computed by averaging z-scores for simple and choice reaction times. A measure of mental flexibility was produced by computing the ratio of Trails A/Trails B [40,41]. An index of episodic measure was computed by averaging the highly correlated ($r \sim 0.84$) z-scores of immediate and delayed recall. *Z*-scores for DB and SDM were used individually as measures of working memory and speed-of-processing. Thus, in total five cognitive domains were tested: namely, episodic memory, processing speed, working memory, mental flexibility, and reaction time.

2.5. Statistical analyses

Using general linear modeling (GLM), cortical gyrification was measured across groups, and all analyses were conducted using the in-built statistical analyses engine in FreeSurfer to identify significant vertex clusters. Surface analyses were conducted for each hemisphere separately.

Correlations with cortical volume and thickness were investigated through General Linear Modeling (GLM). To investigate the first aim, GLM was conducted by using the inbuilt statistical engine in FreeSurfer, and cortical gyrification values were regressed on (i) cortical volume, (ii) cortical thickness (added as per-vertex regressor), and (iii) cognitive measures. During these analyses, cortical gyrification was the dependent variable while cortical volume was the independent variable of interest. These analyses were repeated with cortical thickness as the independent variable. Finally, each of the cognitive variables were independent variables, while cortical gyrification was the variable of interest and these analyses included years of education as an additional covariate. All analyses were controlled for ICV, age, and sex. For these analyses conducted on the whole brain, significant values have been reported after removing the effects of all covariates and after setting the threshold of detection of false discovery rate (FDR) corrections at $p < 0.01$, consistent with prior publication with cortical thickness [24].

To examine frontal gyrification–cognition relationships, similar analyses were undertaken where cognitive scores were regressed on cortical gyrification, with covariates that included ICV, age, and sex. In an attempt to compare cognition–gyrification relationships with those previously published for cortical thickness and volume in this sample [27], these sets of analyses were controlled for multiple comparisons using the permutation method provided in FreeSurfer. A 1000 permutations were conducted and the statistical threshold was set at $p < 0.01$.

3. Results

Sample characteristics are presented in Table 1 and show that women did not differ from men on age or incidence of diabetes or smoking but did on average have smaller intra-cranial, gray and white matter volumes. Women also had lower prevalence of hypertension and had fewer years of education (although years of education was high for both groups).

3.1. Relationships between cortical gyrification, volume and thickness

Cortical gyrification in the whole sample was positively associated with cortical volume in most regions of the cortex. However, there were also regions where cortical gyrification was not strongly correlated with cortical volume including the superior frontal cortex and tips of the frontal and occipital poles. In addition, cortical gyrification at the tip of the temporal poles showed negative relationships with volume. Fig. 1(i)–(iv) show these volume-cortical gyrification relationships after controlling for age and sex and correcting for multiple comparisons at FDR $p < 0.01$. The effect of scanner change was tested as a nuisance variable, and no significant differences were observed in the results. This variable was thus removed from further analyses.

Relationships between cortical gyrification and cortical thickness were in the opposite direction to those detected with cortical volume. Cortical thickness of multiple regions in the middle frontal cortex, superior and middle temporal cortex, orbitofrontal cortex, inferior parietal cortex and many regions in the anterior and middle cingulate areas were significantly and negatively associated with cortical gyrification. Conversely, in many regions in the superior frontal, inferior temporal, medial and superior parietal, and most of the occipital cortex, cortical thickness showed little or no significant associations with cortical gyrification. In addition, some cortical regions showed positive relationships between cortical gyrification and cortical thickness. These were almost exclusively located in the left hemisphere and included the middle frontal gyrus and posterior parietal gyrus as well as the superior frontal and posterior parietal regions. Fig. 2(i)–(iv) shows the thickness–cortical gyrification relationships after controlling for ICV, age, and sex and correcting for multiple comparisons at FDR, at $p < 0.01$. Uncorrected results for cortical thickness and gyrification correlations are presented in Supplementary Fig. 1. Not controlling for ICV produced essentially identical results.

Supplementary Fig. 1 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbr.2015.03.018.

3.2. Sex differences in gyrification

Males showed overall higher cortical gyrification in most areas of the cortex, $p < 0.001$. However, this difference was significantly attenuated after controlling for cortical volume and only small areas in the superior temporal lobes remained significant. In contrast, after controlling for cortical volume, females showed higher gyrification than males in left medial parietal regions (Fig. 3). All analyses were repeated after co-varying for hypertension and diabetes. Results were essentially identical to those obtained without co-varying for these two factors. Sex-by-age interactions were also tested, but did not reach statistical significance.

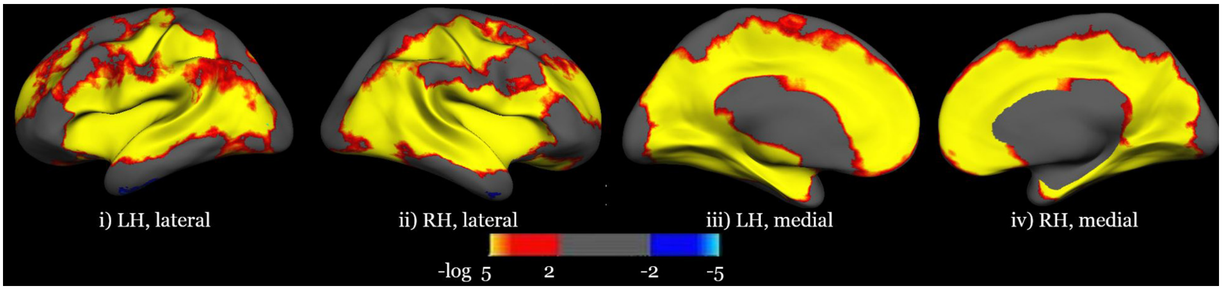
3.3. Relationships between gyrification and cognition

Associations between frontal cortical gyrification and cognitive indices were assessed using GLM in FreeSurfer after controlling for ICV, age, and sex. Education did not make any significant contributions to the results, so was not included in the final model. To make these results comparable with prior published findings [27], analyses were then corrected for multiple comparisons using permutation testing with 1000 iterations and thresholded at $p < 0.01$. While significant raw correlations were obtained for EM, SDMT, and RT before controlling for ICV, only those between gyrification and DB and TAB survived corrections after controlling for ICV. The

Table 1
Demographic and brain variables for study participants and group differences using ANOVA.

Demographic variables	Males	Females	*p* Values
Sample size	174	222	–
Age, years (SD)	46.67 (1.49)	46.73 (1.37)	0.702
Education, years (SD)	14.95 (2.14)	14.39 (2.26)	0.017
Diabetes (yes/no)[a]	3/169	5/214	0.716
Hypertension (yes/no)[a]	65/109	40/182	0.012
Smoking (Never/Past/current smoker)[b]	98/52/24	115/75/33	0.635
Intracranial volume (mean, SD)	1.664 (0.12)	1.456 (0.11)	<0.001
Total cortical gray matter (mean, SD)	0.473 (35.24)	0.420 (32.27)	<0.001
Total cortical white matter (mean, SD)	0.487 (52.50)	0.420 (41.00)	<0.001

[a] Data missing for some participants: diabetes (6) hypertension (1).
[b] Chi-squared test conducted.



Q13 **Fig. 1.** Association between cortical volume and gyrification after controlling for age and sex, corrected at FDR $p < 0.01$. Color codes represent strength of significance with warm colors for positive associations and cool colors for negative associations. LH: left hemisphere: RH: right hemisphere (For interpretation of the references to color in figure legend, the reader is referred to the web version of the article.)

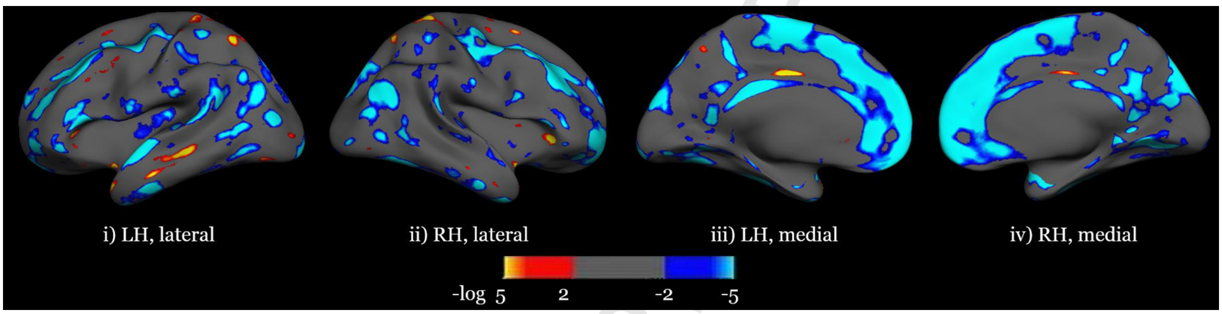


Fig. 2. Association between cortical thickness and gyrification after controlling for age and sex, corrected at FDR $p < 0.01$. Color codes represent strength of significance with warm colors for positive associations and cool colors for negative associations. LH: left hemisphere: RH: right hemisphere (For interpretation of the references to color in figure legend, the reader is referred to the web version of the article.)

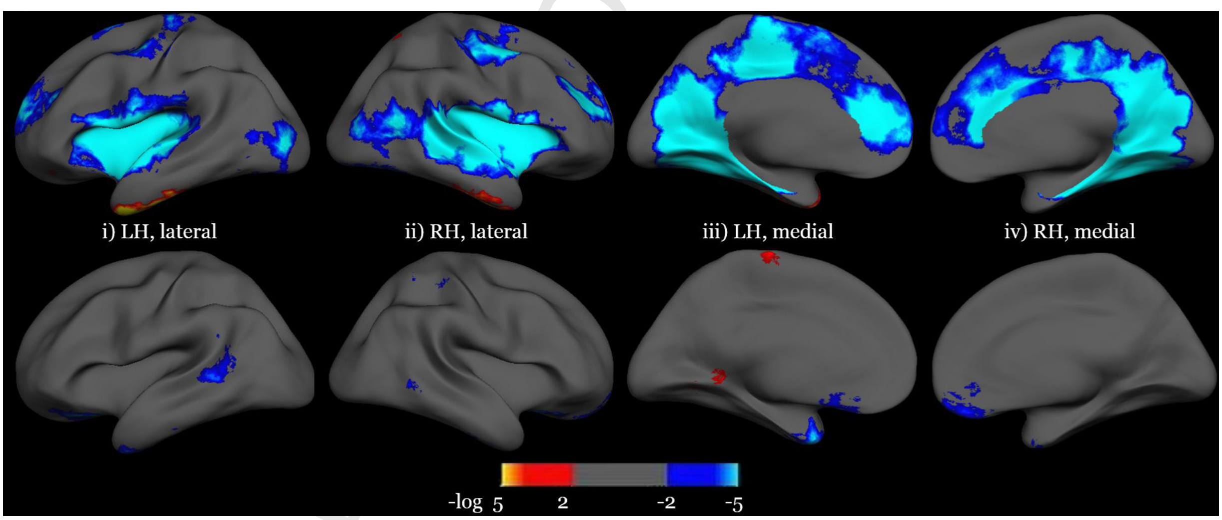


Fig. 3. Differences in gyrification before controlling for cortical volume (Top Panel) and after controlling for cortical volume (Bottom panel). Color codes represent strength of significance with warm colors for regions where females have higher gyrification than males and cool colors for regions where males have higher gyrification than females. LH: left hemisphere: RH: right hemisphere (For interpretation of the references to color in figure legend, the reader is referred to the web version of the article.)

significance maps are shown in Fig. 4. Higher gyrification of the medial frontal cortex was positively correlated with better DB scores in both the right and the left hemispheres. Similarly, positive relationships were observed with TAB where better performances on the TAB (shorter times) were related to greater gyrification in superior frontal and the medial frontal cortex.

3.4. Correlations between gyrification and cognitive performance after controlling for cortical thickness

Because of the strong negative relationships found between cortical thickness and gyrification, additional analyses were undertaken to investigate structure–cognition relationships between cognitive indices and gyrification measures after controlling for cortical thickness. The results obtained before and after controlling for cortical thickness were very similar and no significant changes in the relationships between the structural and cognitive measures were observed.

4. Discussion

Using a large midlife sample, our results suggest that cortical gyrification development is positively related to volume expansion, but this expansion also operates under the constraints of keeping

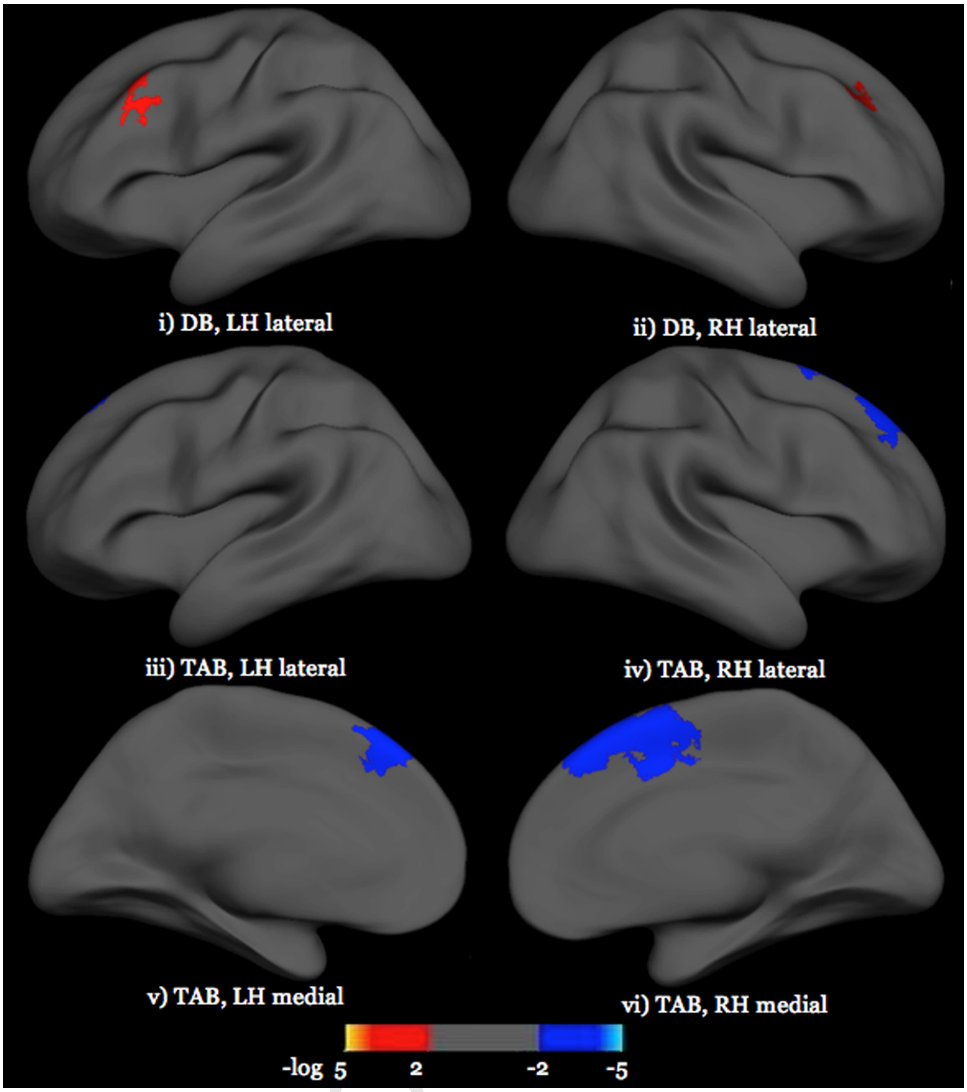


Fig. 4. (i–vi) Associations between frontal gyrification and cognitive performance controlling for ICV, age and gender and controlling for multiple comparisons at $p < 0.01$. ICV: Intra-cranial volume, DB: Digit-backwards span, TAB: Trails A and B, LH: left hemisphere, RH: right hemisphere. Correlations in red denote positive relationships, and those in blue denote negative relationships between cognitive function and cortical gyrification (For interpretation of the references to color in figure legend, the reader is referred to the web version of the article.)

cortical thickness at a minimal level. Furthermore, greater gyrification of the lateral frontal cortex was found to be related to better executive functions independent of cortical volume, sex, and age. Taken together, the results provide evidence on the important functional relevance of cortical gyrification on cortical development and suggest that higher gyrification is related to better cognitive function and larger brain volume, but thinner cortices.

Our results are consistent with previous inter-species and comparative studies of animals, which show that cortical volume increases more rapidly than cortical thickness in relation to brain size. Research has found that when head size across species is plotted against cortical thickness, there are minimal increases in cortical thickness with increases in volume [11,42,43]. It has also been known for more than two decades that the six-layered cortex is more-or-less constant in mammals with widely differing brain sizes [44]. Finally, negative relationships between cortical thickness and both cortical surface area and gyrification has also been previously reported in a lifespan sample [17]. Here, we have shown that this relationship is independent of age and sex in healthy middle-aged adults, even when extremely narrow-age ranges are considered. Combined with the results where more gyrification was related to better cognitive functioning, results support the likely role of increases in functionality of the cerebral cortex to be a driver of increases in cortical gyrification; with opposite roles for cortical brain volume and cortical thickness. The implication of our findings in the context of higher brain volumes and thinner cortices are detailed next.

First, the negative relationship between gyrification and thickness is most likely related to both space constraints and brain functionality. Besides allowing increase of neuronal numbers within a limited space, another way to increase brain functionality would be to improve efficiency of cortical communication. If the brain were conceptualized as a sphere, then the minimum distance for white matter fibers to travel from the inside (i.e., from sub-cortical regions) to the outer regions would be along the radial length. Decreasing cortical thickness could shorten the distance of the white matter fibers running between adjacent brain regions, and increase the efficiency of cortical communication. Smaller cortico-cortical distances not only aid rapid communication, they also increase the overall efficiency of cortical signaling by reducing energy expenditure. Measurement of axonal radii and fiber lengths through histological studies in biological systems show that the length and the volume occupied by these structures are at an optimal ratio in terms of distance traveled and time taken to propagate cortical signals [45]. Hence, with consideration to the evolutionary pressures that dictate larger brain volumes and favor tangential expansion, an expanding cortex would quite possibly limit increases to thickness, as increments to *both* these factors would not be feasible. Thus, although increases in cortical cell numbers and increases in brain growth can, in theory, lead to both increases in gyrification and surface area, such increases in reality seem to favor tangential (i.e., along the surface of the cortex) rather than radial expansion (cortical thickness).

Secondly, these findings contribute to evidence consistent with the idea that cerebral gyrification is central to the fine-tuning of the human brain computational efficiency. Research in comparative brain anatomy shows that increases in neuronal numbers are associated with smaller increases in brain volume (and cortical surface area) in primates [13] than in rodents [46]. In other words, cognitively more complex species showed *smaller* increases in volume with increase in neuronal numbers; specifically, an 11-fold increase was found in primates versus a 35-fold increases in rodents for every 10-fold increase in neuronal number [46]. This ability of “packing in neurons” into the least amount of space has most likely contributed to increased cognitive abilities in primates [47]. Hence, the huge energy expenditure by the human brain, a large proportion of which is consumed by neurons, is sustainable because this increase most likely provides substantial benefits in cognitive function and efficiency.

In addition, the significant positive relationships between executive functions and increased gyrification strongly support the functional importance of gyrification. These relationships also survived corrections for cortical volume and thickness and were independent of age and sex, suggesting that despite sharing a large proportion of variance with volume and thickness, there is a unique relationship between cognitive function and cortical gyrification in the lateral frontal cortex. Our results in this population are also relevant in the context of cognitive aging, as there are indications that the cognitive difficulties that are observed in older adulthood are related to brain [48] and cognitive health [49,50] much earlier in the lifespan. Given the age-related vulnerability of the frontal cortex to volume decrease and its important role in cognitive aging, it is of value to document if prefrontal gyrification relates to cognitive function, especially in a midlife population who are still under-investigated in the literature. The results support the role of the frontal lobes in working memory, mental flexibility, and processing speed and to our knowledge, this is the first study to report significant relationships between cortical gyrification and cognitive function in an epidemiological sample with healthy midlife adults.

Finally, the strong relationship between gyrification and brain volumes was highlighted when sex differences were investigated in the two age groups. Males had higher gyrification than females in frontal, occipital and medial regions and women had higher gyrification in the temporal regions (Fig. 3, top panel) but these differences largely disappeared after taking brain volumes into consideration (Fig. 3, bottom panel). These results suggest that while sex differences exist in gyrification with males showing marginally higher gyrification than women, this association is largely due to males having larger brain volumes in many cortical regions. Hence, our results suggest that after taking into account brain volumes, only minute sex differences in gyrification are present in midlife adults. These results are consistent with the lifespan results reported by Hogstrom, Westlye et al. [17], but not consistent with previous results reported on young adults, where females were seen to have significantly higher gyrification compared to males [18]. Previous cross-sectional studies utilizing large sample sizes have also reported inconsistent sex differences in cortical volume and thickness [24,51] suggesting that previously documented differences could also be influenced by sample characteristics and cohort effects. Furthermore, it is possible that sex differences in cortical structures are inconsistent and prone to differ with age and that age has an evolving role in such differences. Longitudinal follow-up of these adults is needed to assess if sex differences in cortical gyrification change over time.

Our results have implications on future studies on human cortical structure and function. The structure–function relationships observed for the lateral frontal cortex suggest that gyrification is a useful marker for lateral frontal cortex structure and function in healthy adults and future studies could test whether controlling for cortical gyrification could provide additional information in a sample of different ages (young adults, or older adults) where structure–cognition relationships might be more robust. Also, while the interest of the current study lay on the structure–cognition relationships for the frontal cortex, our results suggest that such relationships can also be tested for other regions of the cortex and could be an important extension of this work. Finally, one environmental factor that could have an effect on the development of gyrification is diet. For instance, the addition of lipids to the developing cortex in mice resulted in increased growth and gyrification of the cortex ex vivo [52], probably due to reductions in cell death that normally occurs during neural pruning [9,52]. These findings suggest that other factors known to favorably affect brain growth early in development, such as increased education and better nutrition [53] could affect gyrification in humans, and future studies could address these considerations as a possible covariate.

4.1. Limitations

We did not investigate differences in white matter structure and their possible relationship with cortical gyrification. The underlying brain structure supporting the folding of the cortex initially during development is white matter scaffolding which can influence gyrification through axonal fiber tension, future studies should consider this in relation to variations in white matter structure with age. We did not investigate relationships between gyrification and cortical surface area in our study as it was beyond the scope of the current study. Nonetheless, since it is a brain metric intrinsically related to gyrification, volume, and thickness, future studies should investigate the influences of surface area on these measures. Also, in our study, age-by-sex interactions for cortical gyrification did not survive corrections for multiple comparisons due to the narrow age range design of the sample. Our results are similar to others [54] who have also reported that age-by-sex interactions are minimized in such samples. Finally, as mentioned before, longitudinal follow-up of both the participants in this cohort would allow for adequate measurement of change in cortical gyrification with time.

5. Conclusions

The results of this study add to our understanding of how cortical folding as measured through cortical gyrification is associated with cortical volume, thickness, and cognitive performance. We demonstrated that cortical gyrification is positively associated with brain volume and largely negatively associated with cortical thickness measures, independent of age and sex. Cortical gyrification was also found to be positively related to cognitive function in midlife adults. Our results provide evidence on the functional relevance of cortical gyrification on cortical development and suggest that higher gyrification is related to better cognitive function and larger brain volume, but thinner cortices, and does not differ by sex in healthy midlife adults.

Authors' contribution

Prapti Gautam: Statistical analysis.

Declaration of ethics

The manuscript does not contain clinical studies or patient data.

As mentioned in the manuscript, approval for the study (for data examined in the manuscript) was obtained from the human research ethics committee of the Australian National University and University of New South Wales. All research subjects provided written consents to be in the study.

Conflict of interest

The authors declare that they have no conflict of interest.

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