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RESEARCH REPORT

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Cortical gyrification in women and men and the (missing) link to prenatal androgens

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Abstract

Previous studies have reported sex differences in cortical gyrification. Since most cortical folding is principally defined in utero, sex chromosomes as well as gonadal hormones are likely to influence sex-specific aspects of local gyrification. Classic congenital adrenal hyperplasia (CAH) causes high levels of androgens during gestation in females, whereas levels in males are largely within the typical male range. Therefore, CAH provides an opportunity to study the possible effects of prenatal androgens on cortical gyrification. Here, we examined the vertex-wise absolute mean curvature—a common estimate for cortical gyrification—in individuals with CAH (33 women and 20 men) and pair-wise matched controls (33 women and 20 men). There was no significant main effect of CAH and no significant CAH-by-sex interaction. However,

Abbreviations: CAH, congenital adrenal hyperplasia; CSF, cerebrospinal fluid; GCSE, General Certificates of Secondary Education; GM, grey matter; MRI, magnetic resonance imaging; TBV, total brain volume; TIV, total intracranial volume; WM, white matter.

there was a significant main effect of sex in five cortical regions, where gyrification was increased in women compared to men. These regions were located on the lateral surface of the brain, specifically left middle frontal (rostral and caudal), right inferior frontal, left inferior parietal, and right occipital. There was no cortical region where gyrification was increased in men compared to women. Our findings do not only confirm prior reports of increased cortical gyrification in female brains but also suggest that cortical gyrification is not significantly affected by prenatal androgen exposure. Instead, cortical gyrification might be determined by sex chromosomes either directly or indirectly—the latter potentially by affecting the underlying architecture of the cortex or the size of the intracranial cavity, which is smaller in women.

KEYWORDS
androgens, CAH, congenital adrenal hyperplasia, cortical complexity, curvature, folding, gyrification, magnetic resonance imaging, sex

1 | INTRODUCTION

The gyrification of the cerebral cortex seems to be a consequence of fitting—by way of folding—the cortical sheet into the tight intracranial space (Hofman, 1989; Zilles et al., 2013). Given that women have smaller intracranial cavities than men, higher degrees of folding might be evident in female brains. However, the underlying mechanisms of cortical folding are complex (Caviness, 1975; Llinares-Benadero & Borrell, 2019; Rademacher et al., 1993; Rakic, 1988, 1998; Rash et al., 2023; Richman et al., 1975; Rilling & Insel, 1999; Tallinen et al., 2014; Toro et al., 2008; Toro & Burnod, 2005; van Essen, 1997), and as far as sex differences are concerned, the outcomes of both post mortem and in vivo research paint a rather inconsistent picture. More specifically, some studies reported larger degrees of cortical folding—also often referred to as cortical complexity, cortical convolution or cortical gyrification (Luders & Kurth, 2020)—in female brains compared to male brains (Cui et al., 2023; Gautam et al., 2015; Luders et al., 2004, 2006), while others reported the opposite effect (Cui et al., 2023; Fish et al., 2017; Gautam et al., 2015; Li et al., 2014; Mavridis et al., 2011; Raznahan et al., 2011; Wang et al., 2016) or no sex differences at all (Im et al., 2008; Nopoulos et al., 2000; Schaer et al., 2013; Yucel et al., 2001; Zilles et al., 1988). Some of these conflicting findings might be explained by the fact that several studies did not account for sex differences in brain size, while those that did used different correction methods (e.g., scaling and residualizing).

Another unresolved question refers to the determinants of cortical gyrification. Given that most cortical folding, at least of the primary gyri and sulci, is defined in utero (Armstrong et al., 1995; Chi et al., 1977; Richman et al., 1975), sex chromosomes and/or prenatal gonadal hormones are likely to contribute to sex differences in cortical gyrification, but conclusive research in humans is missing. Certain conditions, such as congenital adrenal hyperplasia (CAH), offer an opportunity to gain further insights into the ontogeny of cortical gyrification: classic CAH causes elevated androgen exposure of female foetuses, whereas androgen levels in male foetuses are largely unchanged. Thus, if hormones—specifically foetal androgens—influence cortical gyrification, one would expect significant differences when comparing women with CAH to control women (i.e., groups with different foetal androgen levels), but not when comparing men with CAH to control men (i.e., groups with similar foetal androgen levels). In other words, there would be a sex-by-CAH interaction. In contrast, if sex chromosomes are an important contributor, one would expect significant differences when comparing women (who have XX chromosomes) to men (who have XY chromosomes), regardless of whether they are affected by CAH. In other words, there would be a main effect of sex. A third possibility would be a main effect of CAH (i.e., when comparing all individuals with CAH to all controls). In that case, cortical gyrification may be affected by aspects of the condition itself and/or by its treatment because both women and men with CAH receive supplements of glucocorticoids.

That is, classic CAH provides an opportunity to study the possible effects of prenatal androgens on cortical gyrification. Here, we analysed the largest sample to date in this field ($N = 106$) consisting of women and men with CAH ($n = 53$), who were pair-wise matched on sex, age, education and verbal intelligence to control women and men ($n = 53$). In addition to gaining insights into

determinants of cortical gyrification, our study will serve to confirm (or refute) prior reports of significant sex differences in cortical gyrification in normative samples with a high regional specificity at thousands of vertices across the lateral and medial cerebral cortex. Given that there is no consensus to date about whether it is appropriate to control for brain size when investigating cortical gyrification, we will conduct our analyses both with and without accounting for individual differences in brain size.

2 | METHODS

2.1 | Study sample

The sample consisted of 53 individuals (33 women and 20 men) with classic CAH (Merke & Auchus, 2020), aged between 18 and 46 years (mean ± SD: 30.15 ± 7.92 years), and 53 controls (33 women and 20 men), aged between 18 and 45 years (mean ± SD: 30.34 ± 7.71 years). Of the 53 individuals with CAH, 29 presented with a salt-wasting phenotype and 18 with a simple virilizing phenotype; the remaining 6 individuals with CAH did not have information on the form of the condition. All individuals were recruited in the United Kingdom through National Health Service (NHS) clinics, a national CAH support group, as well as flyers and advertisements posted in hospitals, general practice clinics and online. Individuals with CAH were pair-wise matched to controls with respect to sex, age, education and verbal intelligence, the last determined using the Advanced Vocabulary Test (Ekstrom et al., 1976). Table 1 provides descriptive statistics on age, education and verbal intelligence for each of the four subgroups (women with CAH, control women, men with CAH and control men). All participants were required to be free from neurological or psychiatric disorders and to have no contraindications to magnetic resonance imaging (MRI). Approval for the study was obtained from an NHS Research Ethics Committee and the Health Research Authority in the United Kingdom (15/EM/0532) as well as the Ethics Committee at the University of Auckland in New Zealand (020825). All participants provided their informed consent.

2.2 | Brain image acquisition and analysis

Structural T1-weighted brain images were acquired on a Siemens 3.0 Tesla Skyra system with a 32-channel head coil using the following parameters: TR = 2300 ms, TE = 2.98 ms, flip angle = 9°, matrix = 256 × 240, voxel size = 1 × 1 × 1 mm^3. All images were processed in Matlab (https://www.mathworks.com/products/matlab.html) using SPM12, version r7771 (http://www.fil.ion.ucl.ac.uk/spm) and the CAT12 toolbox, version 12.8 (Gaser et al., 2022). As previously detailed (Gaser et al., 2006; Luders et al., 2006, 2008, 2012), images underwent a series of automated steps to calculate the vertex-wise cortical gyrification. Briefly, the T1-weighted

TABLE 1 Group-specific descriptive statistics.

	Women with CAH	Control women	Men with CAH	Control men
N	33	33	20	20
Salt-wasting[a]	20	-	9	-
Simple virilizing[a]	10	-	8	-
Age (in years)	31.1 ± 8.6 [18.3–45.7]	31.8 ± 8.5 [18.3–45.3]	28.5 ± 6.6 [19.3–43.4]	27.9 ± 5.5 [19.4–40.8]
Verbal intelligence[b]	6.3 ± 2.6 [1.5–11.2]	6.3 ± 2.3 [1.8–11.0]	5.6 ± 3.4 [2.0–12.5]	6.4 ± 3.1 [−1.0–13.5]
Education[c]	4.0 ± 1.3	4.1 ± 1.3	3.8 ± 1.4	3.9 ± 1.2
GCSEs	$n = 6$	$n = 6$	$n = 4$	$n = 3$
A levels	$n = 5$	$n = 6$	$n = 7$	$n = 5$
Vocational training	$n = 6$	$n = 5$	$n = 1$	$n = 4$
Bachelor	$n = 14$	$n = 12$	$n = 5$	$n = 7$
Master	$n = 2$	$n = 4$	$n = 3$	$n = 1$

[a]Information on the form of the condition (salt-wasting vs. simple virilizing) was not available for six individuals with CAH (three women and three men).
[b]Measured using the Advanced Vocabulary Test (Ekstrom et al., 1976).
[c]Highest level obtained, coded as GCSEs (General Certificates of Secondary Education) = 2; A levels = 3; vocational training = 4; bachelor = 5; master = 6.

images were corrected for magnetic field inhomogeneities, which was followed by removing the skull, the cerebellum, and the brain stem, and by separating the hemispheres. Each hemisphere was then segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF), and the cortical surface was reconstructed using the projection-based thickness approach as implemented in CAT12 yielding a mesh of the brain's central cortical surface (Dahnke et al., 2013). Any topological defects were repaired using spherical harmonics (Yotter, Dahnke, et al., 2011). Finally, cortical gyrification was quantified at each vertex on the central surface (Gaser et al., 2022) by calculating the absolute *mean curvature* (do Carmo, 1976). To ensure comparability across brains, all individual central surfaces were spatially normalized to the 'fsaverage' template using spherical mapping (Yotter, Thompson, & Gaser, 2011). Before conducting the statistical analyses, the normalized surfaces were spatially smoothed using a 20 mm FWHM kernel. Finally, total intracranial volume (TIV) and total brain volume (TBV) were calculated (in ml) to be included as a covariate in the statistical models as indicated (details provided below). TIV was derived as the sum of GM, WM and CSF (GM + WM + CSF), whereas TBV was derived as the sum of GM and WM (GM + WM).

2.3 | Statistical analyses

All statistical comparisons were performed using a general linear model, with the smoothed mean curvature values as the *dependent* variables, group (CAH/control), sex (female/male) and the group-by-sex interaction as the *independent* variables, and age as co-variate (Analysis Stream I). In a second model, both age and TIV (as a proxy for brain size) were included as co-variates (Analysis Stream II). In a third model, both age and TBV (as an alternative proxy for brain size) were included as co-variates (Analysis Stream III). Finally, in an exploratory analysis, individuals with CAH were divided by phenotype, with group (salt-wasters/simple virilizers/controls), sex (female/male) and the group-by-sex interaction as *independent* variables and age as co-variate (Analysis Stream IV), or age and TIV as co-variates (Analysis Stream V), or age and TBV as co-variates (Analysis Stream VI). For all analyses, results were corrected for multiple comparisons by controlling the family-wise error (FWE) rate at the cluster level using a cluster-forming threshold of $p < .001$ (Friston et al., 1996) while controlling for non-sphericity (Hayasaka et al., 2004). The exact anatomical location of the resulting significance clusters (their local maxima, respectively) was determined using the Desikan Atlas (Desikan et al., 2006).

3 | RESULTS

3.1 | Analysis Stream I: Without corrections for brain size

There was no significant main effect of CAH and no significant CAH-by-sex interaction.[1] In other words, individuals with CAH did not differ significantly from controls with respect to cortical gyrification. However, there was a significant main effect of sex in five distinct regions across the lateral cortical surface, where gyrification was increased in women compared to men (see Figure 1 and Table 2). Three of these regions were located within the left hemisphere, specifically the left rostral middle frontal gyrus ($p < .001$), the left caudal middle frontal gyrus ($p = .027$) and the left inferior parietal lobe ($p = .002$). The fourth cluster ($p = .024$) was located in the right inferior frontal gyrus ($p = .024$), specifically the pars triangularis, and the fifth cluster was located in the right occipital lobe ($p = .017$). There was no region where cortical gyrification was increased in men compared to women.

3.2 | Analysis Streams II and III: With corrections for brain size

Regardless of whether we co-varied for TIV or for TBV, there was no significant main effect of CAH, no significant main effect of sex and no significant CAH-by-sex interaction.

3.3 | Exploratory Analysis Streams IV–VI: Effects of CAH subtype

Regardless of whether we co-varied for brain size or not, there was no significant main effect of group. In other words, there were no significant differences in gyrification between individuals with the salt-wasting phenotype and controls, or between individuals with the simple virilizing phenotype and controls, or between individuals with the salt-wasting phenotype and individuals with the simple virilizing phenotype.

4 | DISCUSSION

To our knowledge, this is the first study to date examining cortical gyrification in a well-matched sample of men and women with and without CAH ($N = 106$). The

[1]There was also no significant difference between CAH women and control women or between CAH men and control men.

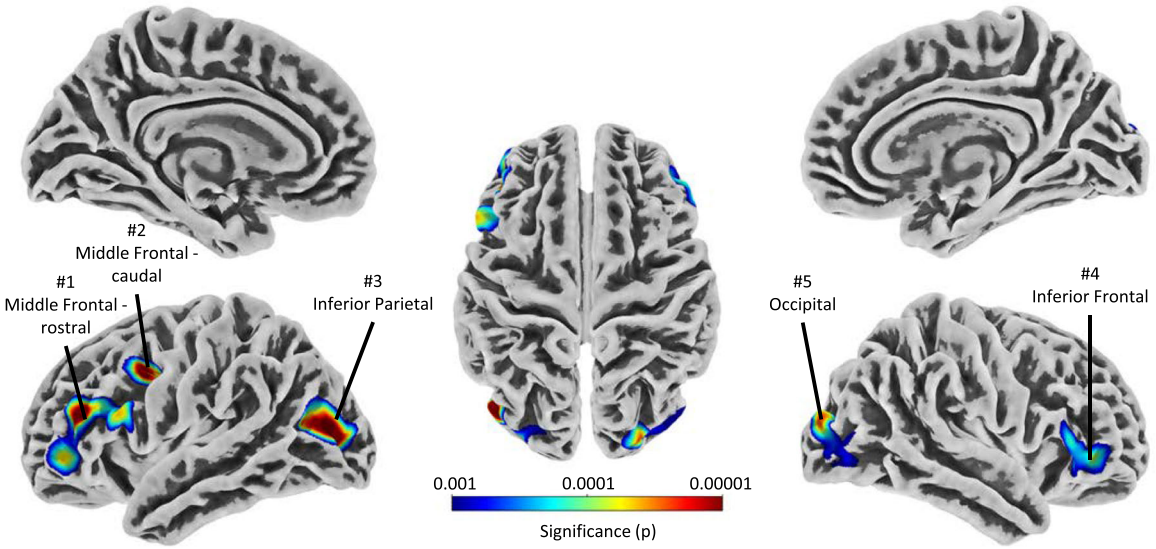

FIGURE 1 Regions of significantly increased cortical gyrification in women compared to men. Five clusters (three in the left hemisphere and two in the right hemisphere) survived corrections for multiple comparisons at the cluster level. The clusters are projected onto the 'fsaverage' template. To enhance the information on the voxel level, the colour bar encodes the uncorrected significance at $p \leq .001$. There was no region where cortical gyrification was significantly increased in men compared to women.

TABLE 2 Significant main effects of sex in cortical gyrification when co-varying for age.

Women > men			
Cluster	**Local maximum**	**Cluster extent (k)**	**Significance (*p*)[a]**
1. Left rostral middle frontal gyrus	$x = -42; y = 37; z = 19$	2,481	<.001
2. Left caudal middle frontal gyrus	$x = -39; y = 8; z = 39$	734	.027
3. Left inferior parietal lobe	$x = -36; y = -80; z = 9$	2,324	.002
4. Right inferior frontal gyrus	$x = 42; y = 40; z = -3$	1,364	.024
5. Right occipital lobe	$x = 28; y = -93; z = 16$	1,460	.017
Men > women			
None	n/a	n/a	n/a

[a]Corrected for multiple comparisons by controlling the family-wise error (FWE) rate at the cluster level.

different analysis streams (with/without brain size corrections) produced identical results with respect to the main effect of CAH and the CAH-by-sex interaction; there were no significant effects. In contrast, the analysis streams produced different results with respect to the main effect of sex: co-varying for brain size (using either TIV or TBV) resulted in a lack of a significant main effect of sex, whereas not co-varying for brain size produced five distinct regions, where cortical gyrification was increased in women compared to men.

4.1 | Sex effects versus brain size effects

The aforementioned differential effect could imply that all observed sex differences are explained by brain size differences. However, at the same time, it may be argued that brain size effects, in fact, constitute sex effects because female brains are smaller on average than male brains. In other words, accounting for brain size effects (e.g., by co-varying for brain size) may not be appropriate in this situation. Aside from this perhaps more philosophical debate, there could be a scientific reason for not co-varying because different rules apply to volumetric or voxel-based measures of GM, which scale with brain size and where corrections are crucial (Barnes et al., 2010; Sanchis-Segura et al., 2019, 2020), and to surface-based measures (e.g., cortical thickness or cortical gyrification), which are not closely linked to brain size and where corrections might not be warranted or even inappropriate (Barnes et al., 2010; Luders et al., 2006). Since there is no gold standard yet, we conducted our analyses with and

without applying corrections for brain size, and when correcting for brain size, we used two commonly used measures for brain size (TIV and TBV), so the outcomes of our analyses may serve as a frame of reference for future studies. However, given that applying corrections for brain size resulted in a lack of significant findings (i.e., no main effect of CAH, no main effect of sex, no CAH-by-sex interaction), the remainder of the discussion will place emphasis on discussing the findings when not correcting for brain size and revealing a significant main effect of sex.

4.2 | Correspondence with prior findings

With respect to the presence and direction of the observed sex effect (women > men), the current findings confirm some prior studies, which reported an increased gyrification in females compared to males in parietal regions (Gautam et al., 2015), frontal and parietal regions (Cui et al., 2023; Luders et al., 2004), or frontal, parietal, temporal and occipital regions (Luders et al., 2006). With respect to the location of the sex effect, there is a striking correspondence with the outcomes of another recent study (Cui et al., 2023) based on 204 healthy adults (127 women / 77 men): More specifically, when investigating the *gyrification index*, Cui et al. (2023) reported very similar regions where women had increased measures compared to men (see fig. 4 in Cui et al., 2023). However, not only did the aforementioned study reveal additional clusters where women had larger measures compared to men but it also observed the opposite effect in some other regions where women had smaller measures compared to men (Cui et al., 2023). There is a further spatial correspondence with the outcomes of another independent study (Luders et al., 2006) based on 60 healthy adults (30 women and 30 men): when investigating *mean curvature*, Luders et al. (2006) detected the most pronounced sex difference (women > men) within a region that includes the left rostral middle frontal gyrus (see fig. 2d in Luders et al., 2006). Additional wide-spread effects were observed in that study in all four lobes, with larger measures in female brains compared to male brains. In agreement with the current study, there was no region where female brains had smaller measures.

4.3 | Possible functional implications

Cortical gyrification scales with cortical surface area; the higher the degree of folding, the larger the surface area (Luders et al., 2006; Mota & Herculano-Houzel, 2015). Thus, the observed increased cortical gyrification in women may offset their smaller brain sizes in general (Luders & Kurth, 2020). However, the assumption of equal surface sizes is challenged by some prior reports of greater cortical surface areas overall in males compared to females, sometimes even after controlling for TBV (Fish et al., 2017; Koolschijn & Crone, 2013; Raznahan et al., 2011; Ritchie et al., 2018). It is still possible though that equal surfaces in male and female brains exist in those particular regions where the sex effect was detected, which is consistent with the notion that mental capacities in general are comparable in women and men. For a recent discussion on cortical gyrification versus cortical surface area in association with general cognitive abilities, see Mathias et al. (2020). Moreover, there may be even an excess of surface area in those regions in female brains, which could contribute to average sex differences in human behaviour, cognition and emotional functioning (Halpern, 1992; Hines, 2005; Kaczkurkin et al., 2019), as discussed elsewhere (Luders et al., 2006).

4.4 | Ontogeny of cortical gyrification

Given that the folding of the human brain mostly takes place in utero (Armstrong et al., 1995; Chi et al., 1977; Richman et al., 1975), sex chromosomes and/or prenatal exposure to gonadal hormones are likely to influence the emergence of sex differences in local gyrification. Since CAH exposes female, but not male, foetuses to elevated androgen levels prenatally, a significant difference between the two female groups (women with CAH and control women), but not between the two male groups (men with CAH and control men), would have suggested a hormonal influence on the formation of gyri and sulci. However, there was a lack of such an observation (i.e., there was no significant group-by-sex interaction and also no significant difference between CAH women and control women). Instead, we detected a significant effect of sex, which suggests that sex chromosomes are a major determinant in the ontogeny of cortical gyrification. Genes may influence gyrification directly and/or indirectly—the latter potentially by affecting the size of the intracranial cavity, which is smaller in women. Other indirect effects might be exerted through genetic influences on the cytoarchitectonic level (neurogenesis, dendritogenesis, axogenesis, myelination, etc.) as well as region- and layer-specific growth rates and expansions, factors known to contribute to the formation of gyri and sulci (Caviness, 1975; Llinares-Benadero & Borrell, 2019; Rademacher et al., 1993; Rakic, 1988, 1998; Rash et al., 2023; Richman et al., 1975; Rilling & Insel, 1999; Tallinen et al., 2014; Toro et al., 2008; Toro & Burnod, 2005; van Essen, 1997). While cortical gyrification

is mostly shaped during the third trimester of pregnancy, subsequent changes—both increases and decreases—have been reported after birth (White et al., 2010) until late adulthood (Madan, 2021). Thus, even if our findings suggest a genetic component, given the age range of our sample (18–45 years), sex chromosomes might not be the only determinant for cortical gyrification, and it is likely that non-foetal androgens or sex hormones in general as well as non-biological factors (e.g., social experience) contribute their own effects.

4.5 | Study limitation and future research

Follow-up studies, ideally comprising larger sample sizes—which could pose a bit of a challenge as CAH is a rare condition—are required to replicate the current non-effects to ensure that the study was not just underpowered to detect a significant CAH effect or a significant sex-by-CAH interaction. Likewise, future studies in big normative samples—that would not require any CAH individuals—will serve to determine if the currently observed significant sex effect (when not applying brain size corrections) was a false positive and/or if the currently observed lack of a significant sex effect (when applying brain size corrections) was a false negative.

AUTHOR CONTRIBUTIONS

Eileen Luders: Conceptualization; funding acquisition; investigation; project administration; writing—original draft; writing—review and editing. **Christian Gaser:** Methodology; writing—review and editing. **Debra Spencer:** Data curation; writing—review and editing. **Ajay Thankamony:** Data curation; writing—review and editing. **Ieuan Hughes:** Data curation; writing—review and editing. **Helen Simpson:** Data curation. **Umasuthan Srirangalingam:** Data curation. **Helena Gleeson:** Data curation. **Melissa Hines:** Conceptualization; funding acquisition; project administration; writing—original draft. **Florian Kurth:** Formal analysis; methodology; visualization; writing—original draft; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors report no competing interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data are not publicly available due to ethical restrictions imposed by the signed consent. Any reasonable request for data access should be made to the corresponding author.

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