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The relationship between the 2D:4D ratio and lateral preference in a Ghanaian population

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Abstract

Prenatal androgen exposure has suggested to be associated with lateral preferences in humans as per the Geschwind-Behan-Galaburda (GBG) theory, the Sexual Differentiation Hypothesis (SDH) and the Callosal Hypothesis (CH). The 2D:4D ratio is the putative marker of prenatal androgen exposure. The study aimed to determine the relationship between the 2D:4D ratio and lateral preferences. The study was cross-sectional from May to June 2021 that involved 206 participants (females = 112, males = 94), aged between 18 to 32 years. Computer-assisted analysis was used to measure the right (2D:4DR) and the left (2D:4DL) digit ratios while lateral preferences were measured using the Lateral Preference Inventory (LPI) questionnaire. The females' 2D:4DL was significantly higher than males with a medium effect size ($p = 0.033$, $d = 0.29$). The odds that a male would have a preference for the left ear was greater relative to a female [AOR = 2.330 (95%CI: 1.034-5.251)]. There was a significant correlation between right-eye laterality and the 2D:4DR in females ($r = -0.589$, $p = 0.030$). Also, left-foot laterality significantly correlated with the 2D:4DL in males ($r = 0.693$, $p = 0.046$). Prenatal androgen exposure, as indexed by the 2D:4D ratio may be associated with lateral preferences of the eye in females and the foot in males. Further studies are however recommended.

Keywords: *The 2D:4D ratio, Prenatal androgen exposure, Lateral preference, The Lateral Preference Inventory (LPI) questionnaire, Ghana*

1. Introduction

The suggestion that prenatal androgen or testosterone (PT) exposure may impact human development and behavior was suggested by Phoenix *et al*. (1959) which is now regarded as the organizational hypothesis. Human digit lengths and their ratios are impacted by PT exposure with high PT exposure leading to masculinized (typical-male) while low PT exposure may result in feminized (typical-female) digit ratios (Manning *et al*., 1998). The ratio of the second-to-fourth (2D:4D) digit is the most sexually dimorphic trait among the digit ratios in humans, with males exhibiting lower values than females on average (Hönekopp andWatson, 2010). The 2D:4D ratio is the putative marker of PT and Prenatal Oestrogen (PE) exposure, as hormonal manipulations in humans are unethical (Manning, 2002). Support for the effect of PT and PE exposure on the 2D:4D ratio have been demonstrated in animal experiments and studies in mother-offspring

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pairs (Huber *et al*., 2017; Lutchmaya *et al*., 2004; and Zheng and Cohn, 2011). Also, studies among persons with conditions of hyper-androgynization or complete androgen insensitivity have suggested the possible role of PT in the ontogenesis of human digits (Brown *et al*., 2002; and Van Hemmen *et al*., 2017). However, these observations are not universal as meta-analytic studies indicate that effect sizes may be small (Hönekopp and Watson, 2010; and Richards *et al*., 2020). Some authors have even critiqued that the 2D:4D ratio is not a suitable marker of PT exposure (Leslie, 2019).

Despite the lack of consensus on the observations of Manning *et al*. (1998), the 2D:4D ratio has been associated with brain lateralization or functional cerebral asymmetries due to variation in neural function between the left and right cerebral hemispheres (Hausmann and Burt, 2018). Three prominent theories or hypotheses: (1) the Geschwind-Behan-Galaburda (GBG) theory, (2) the Sexual Differentiation Hypothesis (SDH) and (3) the Callosal Hypothesis (CH) have linked PT exposure to cerebral lateralization in males and females. The GBG proposed that high PT exposure is significantly associated with left-hand preference as PT enhances the development of the right hemisphere of the fetal brain relative to the left (Geschwind and Galaburda, 1985a and 1985b). On the contrary, the CH posits that high PT exposure leads to exon loss, smaller corpus callosum, reduced interhemispheric connectivity, and thereby increasing the odds of right-hand preference, at least in males (Witelson and Nowakowski, 1991). Similar to the GBG, the SDH proposed that sexual differentiation is mediated by PT exposure as left-hand preference is more frequent among males than females (Hines and Shipley, 1984). The GBG, the SDH and the CH have been subjected to reviews by many authors with varying outcomes, but are still popular among scientists (Chura *et al*., 2010; McManus and Bryden, 1991; McManus *et al*., 1988; and Papadatou-Pastou *et al*., 2020a). The 2D:4D ratio is still widely regarded as the putative marker of PT or PE exposure while lateral preference is still widely regarded as a measure of cerebral lateralization in humans (Richards *et al*., 2021).

There are within and between population variabilities in the 2D:4D ratio and lateral preferences due to genetic, environmental and sociocultural factors, which does not allow for the generalization of study outcomes (Richards *et al*., 2021; and Warrington *et al*., 2018). Testing of the GBG, the SDH and the CH with regards to the 2D:4D ratio are few in Sub-Saharan African populations including Ghana (Abubakar *et al*., 2018; and Aminu *et al*., 2018). The study aimed to test these theories or hypotheses regarding lateral preferences of the hand, foot, eye, and ear and their relationship with the 2D:4D ratio in a Ghanaian population.

2. Materials and methods

2.1. Study design and setting

The study was cross-sectional and was conducted between May and June 2021 among students of the University for Development Studies (UDS), Tamale. The University for Development Studies is the major university in the northern part of Ghana and it is located in the largest city in that part of the country. The Tamale campus of UDS is one of the many campuses of the university and the largest. The Tamale campus is host to various programs including the Doctor of Medical Laboratory Science program, Pharmaceutical Sciences, Nutritional Sciences, Nursing, Medicine, Medical Imaging and Education (UDS, 2020).

2.2. Participants

The study participants included females (n=112) and males (n=94), aged between 18 and 32 years. The target population was first stratified by sex before selection using a non-probability sampling technique. Participation was voluntary and was not restricted by the program of study, cultural group or religion. The selected participants were devoid of finger or hand injuries and without any known endocrine disorder that may have affected their digit ratios.

2.3. Variables

The dependent variables were the right (2D:4DR), left (2D:4DL) and the difference between the right and the left (Dr-l) digit ratios. The independent variables were the lateral preferences of the hand, foot, eye and ear. Also, playing a role as a leader previously or at the time of sampling was included as an independent variable. The descriptive variables were sociodemographic variables such as age, cultural group, height, weight and BMI.

3. Data sources and measurements

3.1. Digit measurements

The digit or finger lengths of the participants were measured using a computer-assisted program [GIMP v2.10.22 (www.gimp.org)]. The participant removed all objects such as rings from their fingers before the palmar surface of each hand was placed on the flatbed surface of an Hp 2620 series Desk jet scanner (HP Inc. CA 94304 United States). The participant's second to fifth fingers was held parallel and the tip of the middle finger aligned with the wrist and elbow (Allaway *et al*., 2009). The palm and fingers were then scanned, together with the participant's study unique identifier, at a resolution of 150 dpi. The scanned images were then exported to GIMP for analysis. Finger lengths were measured from the mid-point of the most proximal flexion crease to the tip of each finger using a mouse-assisted caliper.

Measurements were taken twice by one observer at a week's interval. The intraclass correlation coefficients (two-way mixed, single measures with absolute agreement) were found to be 0.98 and 0.97 respectively for the right (2D:4DR) and the left (2D:4DL) digit ratios. The two measurements were then averaged to obtain the final value. The right-left difference or directional asymmetry (Dr-l) was calculated. Information regarding a participant's leadership role before or at the time of sampling was also documented.

3.2. Lateral Preference Inventory questionnaire

The lateral preference of the hand, foot, eye and ear were assessed using the Lateral Preference Inventory (LPI) questionnaire (Coren, 1993). The LPI is a 16-item inventory with four subscales for assessing preferences for the hand, foot, eye and ear. The LPI is the most comprehensive laterality inventory questionnaire that assesses four different laterality variables simultaneously within 2 to 3 min. From experiments, the LPI has been shown to have a concordance of at least 92% with self-reported behavioral traits for all four subscales (Porac and Coren, 1981). In the LPI, data are simply scored for each four-item scale as (R-L), where R is the number of "right" responses and L is the number of "left. " The total score for each subscale goes from –4 to 4. A negative value is considered as being 'left-sided, a positive value is considered as being 'right-sided and zero denotes both left or right (ambilateral). Also, a –4 means consistent left-sidedness and 4 means consistent right-sidedness for any index. The strength of laterality increases from 1 to 4 for right-sided laterality and from –1 to –4 for left-sided laterality. The LPI has been used in a previous study (Polemikos and Papaeliou, 2000).

3.3. Statistical analysis

The data were collected onto a Microsoft Excel spreadsheet before statistical analysis in SPSS (v23) and GraphPad Prism (v8). The continuous variables were checked for outliers while the normality was assessed using the Shiro-Wilk test. Descriptive statistics were performed for each variable and were presented as mean ± SD for parametric variables and frequency (%) for categorical variables. The differences between mean values were determined using the student *t*-test (unpaired, 2-tailed). A participant's sex was dummy coded (female= zero,male= one) as well as the laterality (right = zero, left = one, both = two) before logistic regression analysis. In the logistic regression analyses, each variable was entered simultaneously with the cultural group variable into the same model and the effect sizes were reported as Adjusted Odds Ratios (AOR) and the 95% confidence intervals (CI). The differences in mean values and odds ratios were presented in the equivalents of standardized mean differences (Cohen's *d*) (Fritz *et al*., 2012).The correlation between digit ratios and lateral asymmetries were determined using Spearman rank correlation. All the statistical analyses were two-tailed at a significance level of $p < 0.050$.

3.4. Ethical considerations

The study complied with the guidelines regarding human subject studies as contained in the 1964 declaration of Helsinki and its later amendments. The study was approved by the institutional review board of the UDS. Participation in the study was voluntary and informed consent was obtained from all the participants.

4. Results

4.1. General characteristics

The general characteristics of the study population are shown in Table 1. The study population was 206 with females forming 54.4% and the rest were males (45.6%). The study population was aged between 18 to 32 years with a mean ± SD age of 22.6 ± 2.61 years. Participants who plaid a leadership role previously or at the time of sampling were the minority (36.2%). The majority of the participants had preferences for the right hand (92.7), right foot (83.1%), right eye (69.4%) and right ear (58.5%).

Table 1: General characteristics of the study population

Variable	**Descriptive statistics**
Age(years)	22.6 ± 2.61
Female	112(54.4)
Male	94(45.6)
Cultural group	
Mole-Dagomba	61(29.7)
Akan	62(30.4)
Others	88(39.9)
Leadership role	
No	131(63.8)
Yes	75(36.2)
Hand preference	
Right	190(92.7)
Left	9(4.6)
Both	7(2.6)
Foot preference	
Right	171(83.1)
Left	20(10.1)
Both	15(6.8)
Eye preference	
Right	142(69.4)
Left	36(17.7)
Both	28(12.9)
Ear preference	
Right	120(58.5)
Left	51(25.2)
Both	35(16.3)

Table 1 (cont.)	
Variable	**Descriptive statistics**
Height (cm)	167.2 ± 8.82
Weight (kg)	61.9 ± 9.94
BMI (kg/m^2)	22.0±2.95
2D:4DR	0.94±0.034
2D:4DL	0.94±0.036
Dr-l	-0.001±0.027
Note: Results were presented as mean ± SD for continuous and frequency (%) for categorical variables.	

4.2. Differences in male and female variables

From Table 2, the mean ± SD 2D:4DR of the females was 0.94 ± 0.035 while that of the females 0.93 ± 0.033. The mean ± SD 2D:4DL of the females and the males were 0.94 ± 0.036 and 0.93 ± 0.034 respectively. The females' 2D:4DL was significantly higher than the males with a medium effect size (p = 0.033, d = 0.29). The odds that a male would have a preference for the left ear was greater relative to a female [AOR = 2.330 (95%CI: 1.034-5.251)].

Table 2: Comparison of male and female lateral preferences, leadership role and digit ratios

Variable	**Female**	**Male**	**AOR (95%CI)/*p*-value**	***d***
Leadership role				
No	72(54.6)	59(45.4)	1	
Yes	44(58.2)	31(41.8)	0.898(0.452-1.785)	–0.06
Hand preference				
Right	108(57.1)	82(42.9)	1	
Left	4(42.9)	5(57.1)	1.053(0.197-5.619)	0.03
Both	5(75.0)	2(25.0)	0.465(0.045-4.813)	–0.42
Foot preference				
Right	103(60.2)	68(39.8)	1	
Left	8(40.0)	12(60.0)	1.743(0.554-5.484)	0.31
Both	6(40.0)	9(60.0)	2.206(0.574-8.475)	0.44
Eye preference				
Right	86(60.8)	56(39.2)	1	
Left	19(53.8)	17(46.2)	1.148(0.462-2.854)	0.08
Both	10(36.8)	18(63.2)	2.733(0.963-7.759)	0.55
Ear preference				
Right	77(64.0)	43(36.0)	1	
Left	21(40.5)	20(59.5)	2.330(1.034-5.251)*	0.47

Table 2 (Cont.)

Variable	Female	Male	AOR (95%CI)/*p*-value	*d*
Both	19(54.2)	16(45.8)	1.344(0.517-3.490)	0.16
Digit ratios				
2D:4DR	0.94 ± 0.035	0.93 ± 0.033	0.103	0.29
2D:4DL	0.94 ± 0.036	0.93 ± 0.034	0.033	0.29
Dr-l	–0.003 ± 0.026	–0.000 ± 0.027	0.460	0.11

Note: Results were presented as mean ± SD for parametric variables and frequency (%) for categorical variables. Differences in means were determined by the student *t*-test (unpaired, 2-tailed). Each independent variable and cultural group variable were entered into the same logistic regression model to obtain the adjusted odds ratios (AOR) and their 95% confidence intervals. The differences were also presented as standardized mean difference (Cohen's *d*): similar ($d <$ 0.20), small ($0.20 \leq d < 0.50$), moderate ($0.50 \leq d < 0.80$), and large ($d \geq 0.80$).

4.3. Association between male and female variables with the 2D:4D ratio

From Figure 1, the strength of right-eye laterality increased with increasing 2D:4DR among females [r = (–) 0.589, p = 0.030], while the strength of left-foot laterality increased with decreasing 2D:4DL among males [r = (+) 0.693, p = 0.46]as shown in Figure 3. It should be noted that the strength of the right- and the left-sided laterality increases from 1 to 4 and –1 to –4 respectively. The correlation graphs were plotted using the negative scores for left-sided laterality to distinguish them from the right-sided laterality. And as such the sign of the correlation coefficient (*r*) is rather the reveres when interpreting the results, i.e., a negative correlation coefficient (–) is interpreted as increasing strength of left-sided laterality while a positive value denotes a decreasing strength in left-sided laterality.

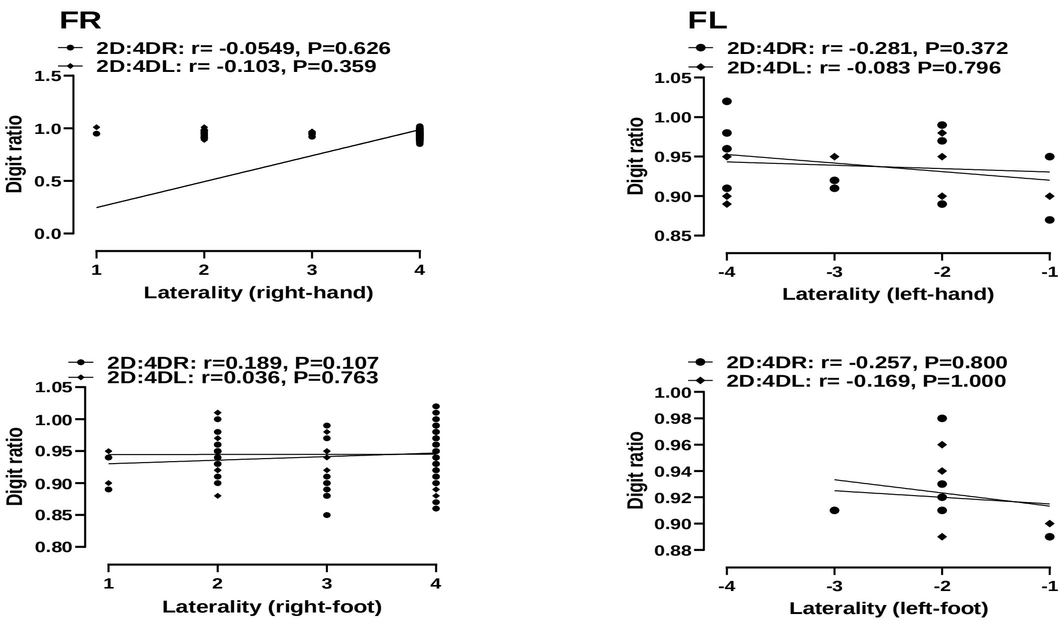

Figure 1: Spearman correlation plots show the relationship between right-sided (FR), left-sided (FL) laterality and the right (2D:4DR) and the left (2D:4DL) digit ratio among females. It should be noted that the strength of the right- and the left-sided laterality increases from 1 to 4 and -1 to -4 respectively. The correlation graphs were plotted using the negative scores for left-sided laterality to distinguish them from the right-sided laterality. And as such the sign of the correlation coefficient (r) is rather the reveres when interpreting the results i.e., a negative correlation coefficient (-) is interpreted as increasing strength of left-sided laterality while a positive value denotes a decreasing strength in left-sided laterality. FR=female right hand, FL=female left hand, R=right, L=left

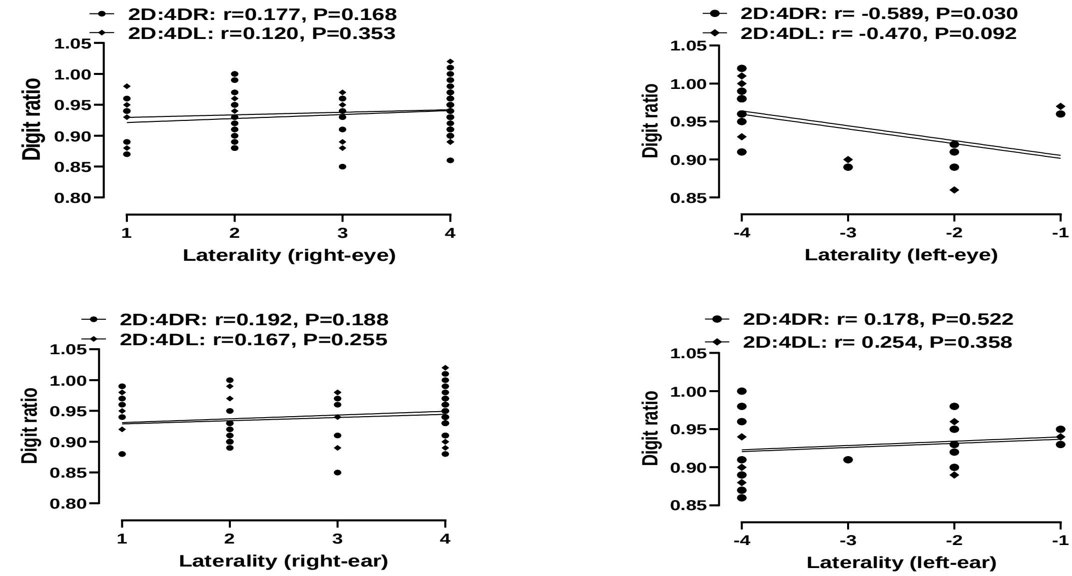

Figure 1: (Cont.)

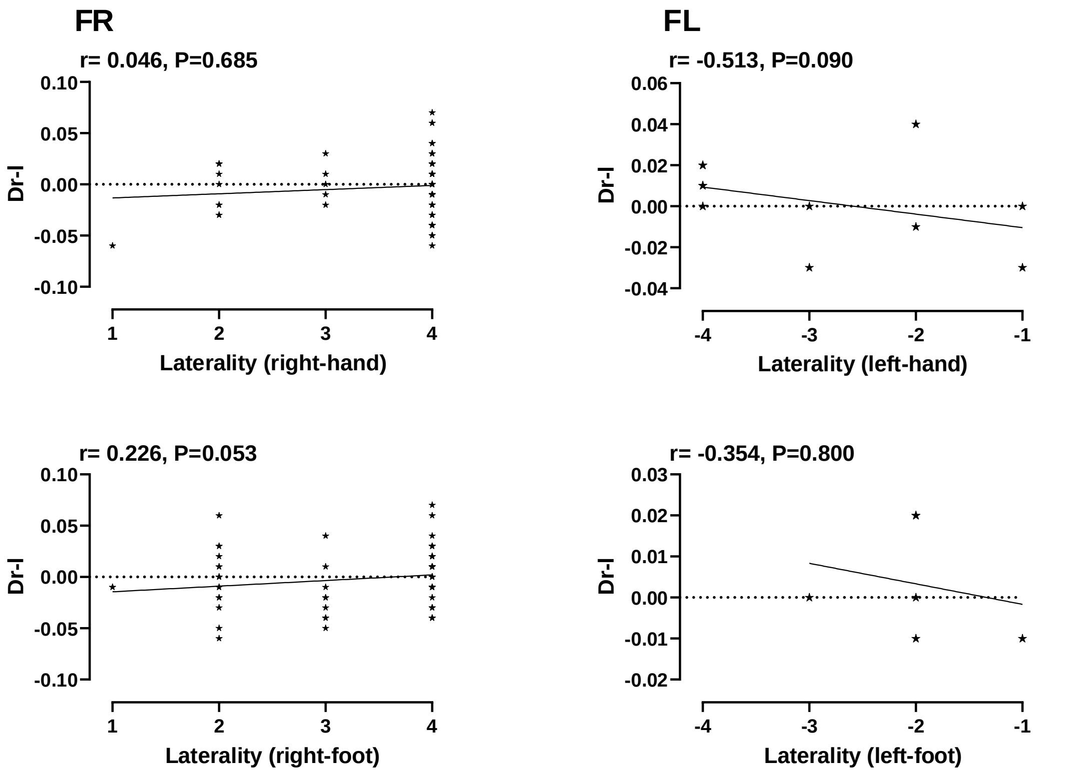

Figure 2: Spearman correlation plots show the relationship between right-sided (FR), left-sided (FL) laterality and the 2D:4DR ratio asymmetry (Dr-l) among females. It should be noted that the strength of the right- and the left-sided laterality increases from 1 to 4 and -1 to -4 respectively. The correlation graphs were plotted using the negative scores for left-sided laterality to distinguish them from the right-sided laterality. And as such the sign of the correlation coefficient (r) is rather the reveres when interpreting the results i.e., a negative correlation coefficient (-) is interpreted as increasing strength of left-sided laterality while a positive value denotes a decreasing strength in left-sided laterality. FR=female right hand, FL=female left hand, R=right, L=left

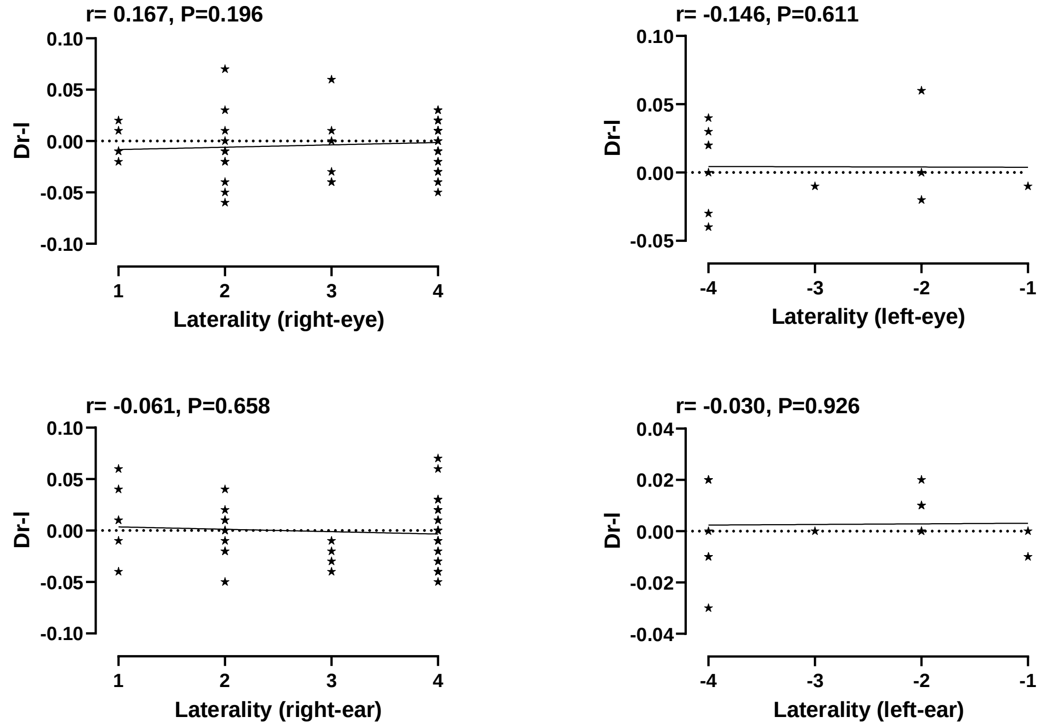

Figure 2: (Cont.)

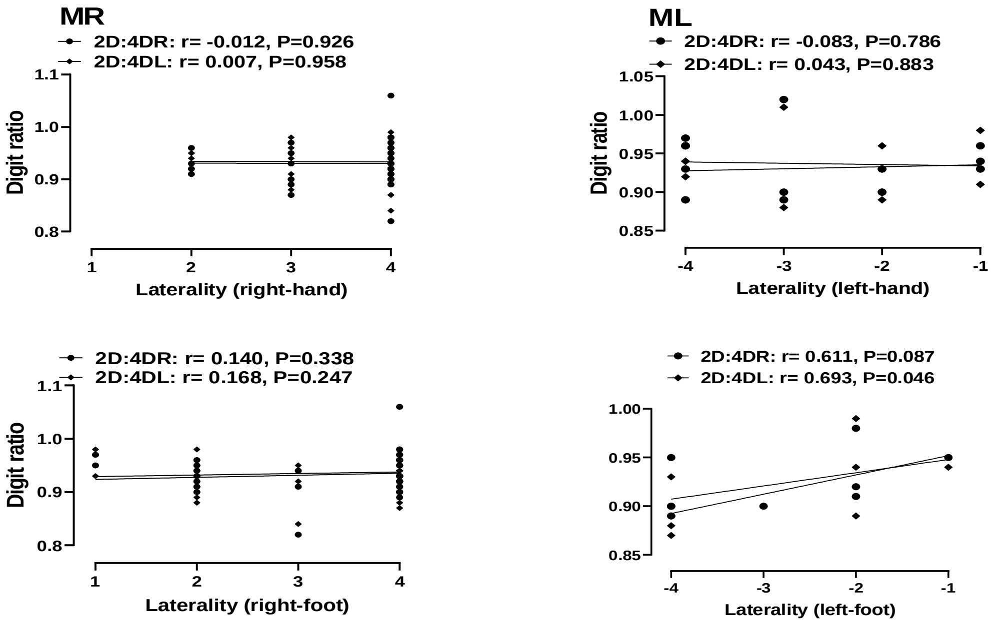

Figure 3: Spearman correlation plots show the relationship between right-sided (MR), left-sided (ML) laterality and the right (2D:4DR) and the left (2D:4DL) digit ratio among males. It should be noted that the strength of the right- and the left-sided laterality increases from 1 to 4 and -1 to -4 respectively. The correlation graphs were plotted using the negative scores for left-sided laterality to distinguish them from the right-sided laterality. And as such the sign of the correlation coefficient (r) is rather the reveres when interpreting the results i.e., a negative correlation coefficient (-) is interpreted as increasing strength of left-sided laterality while a positive value denotes a decreasing strength in left-sided laterality. MR=male right hand, ML=male left hand, R=right, L=left

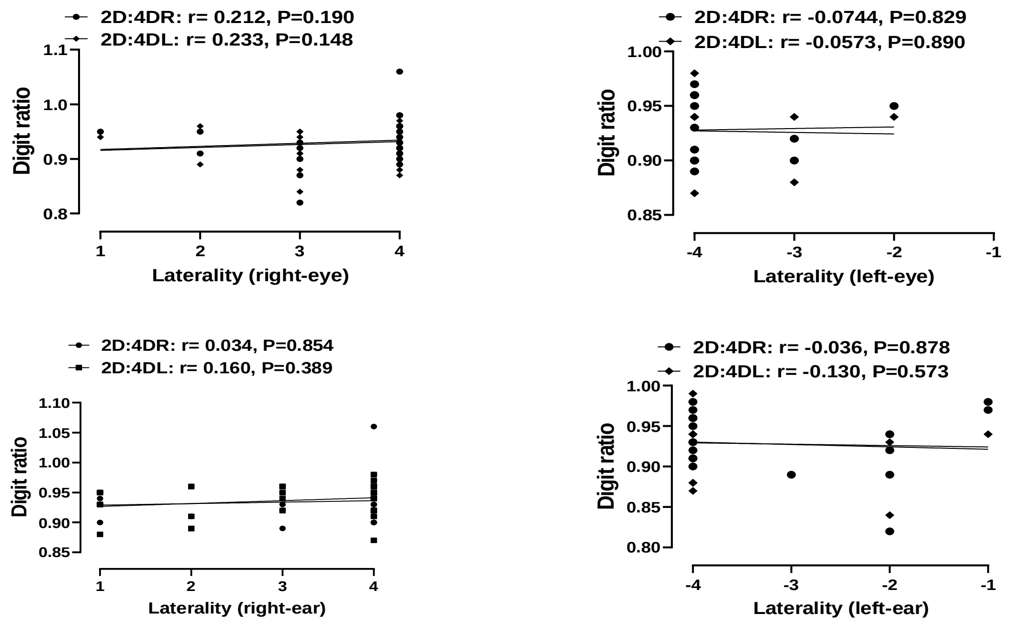

Figure 3: (Cont.)

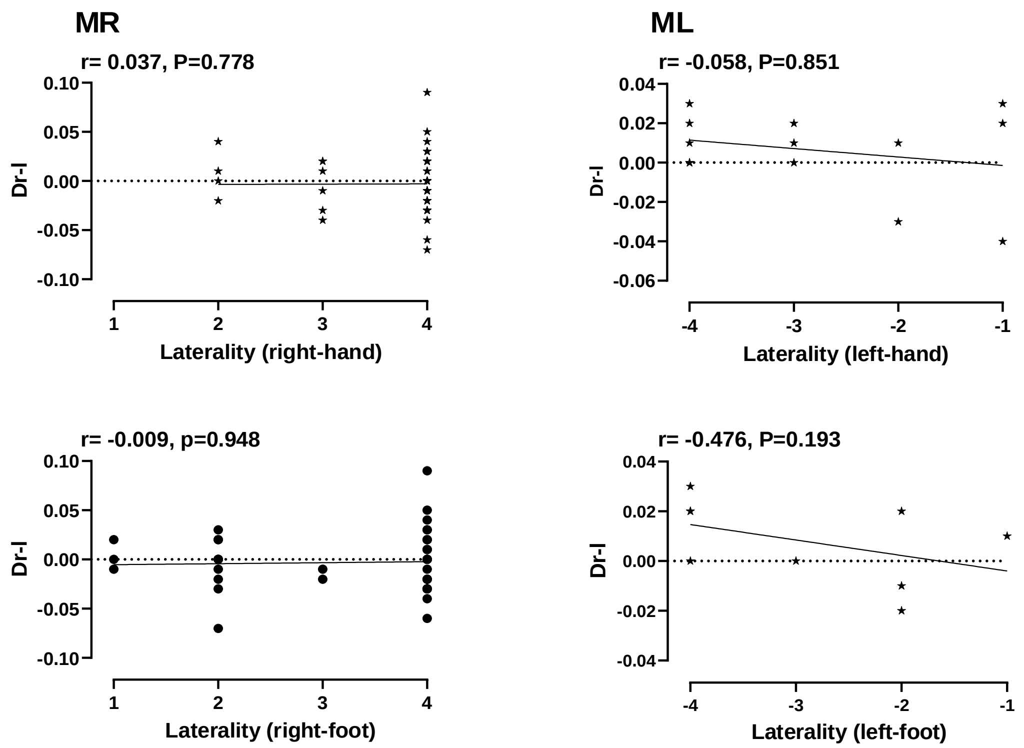

Figure 4: Spearman correlation plots show the relationship between right-sided (MR), left-sided (ML) laterality and the 2D:4DR ratio asymmetry (Dr-l) among males. It should be noted that the strength of the right- and the left-sided laterality increases from 1 to 4 and -1 to -4 respectively. The correlation graphs were plotted using the negative scores for left-sided laterality to distinguish them from the right-sided laterality. And as such the sign of the correlation coefficient (r) is rather the reveres when interpreting the results i.e., a negative correlation coefficient (-) is interpreted as increasing strength of left-sided laterality while a positive value denotes a decreasing strength in left-sided laterality. MR=male right hand, ML=male left hand, R=right, L=left

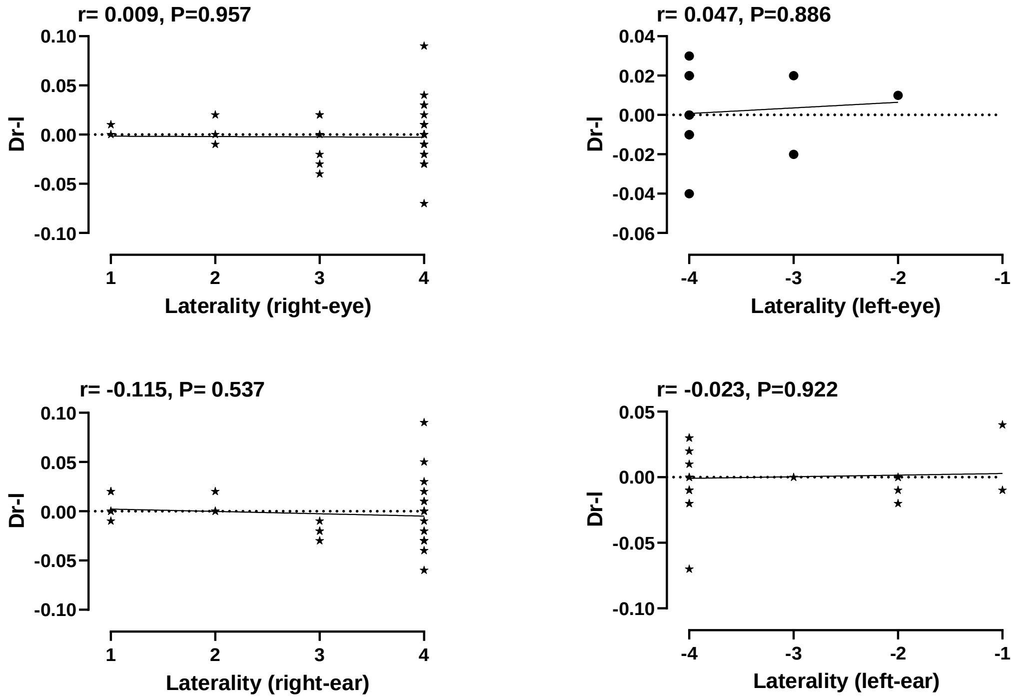

Figure 4: (Cont.)

5. Discussion

The study aimed to test the GBG theory, the SDH and the CH in a Ghanian population concerning the 2D:4D ratio. The 2D:4DL of the females was significantly higher than the males. The majority of the participants had a rightward preference in the hand, foot, eye and ear. It was observed that males had significant left-ear laterality compared to females. Also, the strength of right-eye laterality among females increased with increasing 2D:4DR while among males, the strength of left-foot laterality increased with decreasing 2D:4DL.

The findings of this study are supported by the SDH and partly by both the GBG theory, and the CH. The observations are in line with the findings from previous studies (Beaton *et al*., 2011; Jackson, 2008; Lust *et al*., 2011; Manning and Peters, 2009; Stoyanov *et al*., 2009; and Voracek *et al*., 2006) but differ from others (Richards *et al*., 2021). Also, a meta-analytic study has reported a significant association between left-hand preference with low 2D:4DR, high 2D:4DL and low Dr-l although the effect sizes were small in magnitude (Richards *et al*., 2021).

Sexual differentiation could have accounted for the male-female differences in digit ratio and ear laterality. According to the SDH, the frequency of left-hand laterality is more common among males than females. This male-female difference may be attributed to PT exposure that differentially promotes the development and function of the right hemisphere of the brain, thereby increasing the odds of left-hand or left-sided laterality (Papadatou-Pastou *et al*., 2008; and Papadatou-Pastou *et al*., 2020b). Also, it has been demonstrated that the fourth digit (4D) has more testosterone and oestrogen receptors and therefore more sensitive to PT and PE exposure than the second digit (2D). Since PT promotes while PE inhibits chondrocyte proliferation, males tend to have longer 4D than 2D (low 2D:4D) relative to females (Zheng and Cohn, 2011).

The correlation between left-foot laterality and the digit ratio is supported partly by the concept of the GBG theory. According to the GBG, the brain of the developing fetus is surrounded by high levels of androgens. The levels of these androgens are affected by genetic and environmental variabilities (Ypsilanti *et al*., 2008). These androgens, including testosterone, leads to a reduction in functional and neuroanatomic development of the left hemisphere of the brain (particularly the posterior regions) relative to the right, thereby promoting left-sided laterality and increased frequency of left-hand preference (Geschwind and Galaburda, 1985a and 1985b). The delayed growth of the left hemisphere of the brain is due to neural migration disruption and the subsequent neural dislocation, abnormalities in the architecture and atypical cerebral lateralization in the cortex (Ypsilanti *et al*., 2008). In extension, left-foot preference may also be explained by the GBG theory due to the dominance of the right hemisphere of the human brain which may confer some special talents to some particular individuals (Geschwind and Galaburda, 1985a).

Although the Colossal hypothesis pertained to hand preference and PT exposure, at least in males, indirectly, it may affect the laterality of the human eye and ear too (Witelson and Nowakowski, 1991). The corpus callosum in primates has many parts that are differentially affected by PT exposure. Specific regions of the callosum are responsible for transmitting specific information. The transfer of motor information is by the anterior mid-body while the posterior mid-body transfers somatosensory information. Also, the isthmus is responsible for the transfer of auditory information while the splenium is responsible for transferring visual information (Lust *et al*., 2011). Studies have shown that the callosal size and symmetry are affected by PT exposure in boys, with boys having a right ear advantage which was found to be significantly correlated with amniotic fluid testosterone levels (Chura *et al*., 2010). Higher amniotic fluid testosterone indicated reduced ability to report digits from the left ear in a left-focused condition, a reflection of poor information transfer from the left ear among boys. Increased axonal loss during fetal development in males may be responsible for the male-female differences in the isthmus of the callosum, and hence differences in functional asymmetry (Ypsilanti *et al*., 2008). These findings suggest that PT exposure modulates heritable variation of human lateralization, particularly for the ear, at least in boys (Chura *et al*., 2010; and Lust *et al*., 2010).

The present study has some strengths: (1) this study is probably the first to test, in a Ghanaian population, the GBG theory, the SDH, the CH using lateral preference (hand, foot, eye, ear) and the 2D:4D ratios as proxy-markers of cerebral lateralization and PT exposure respectively. In this study, digit ratios were measured by computer-assisted analysis, which is a more precise method compared to photocopies or physical measurements (Allaway *et al*., 2009). However, the study is limited by sample size (as compared to meta-analysis) which does not allow for the generalization of the results.

6. Conclusion

In conclusion, PT exposure (as indicated by the 2D:4D ratio) maybe associated with foot and eye laterality in males and females respectively. These pieces of evidence are in support of the GBG theory, the SDH, and the CH. Further studies involving larger sample sizes are, however, recommended.

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Conflicts of interest

The authors declare no competing or financial interest

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