Quantitative multidimensional phenotypes improve genetic analysis of laterality traits

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Abstract

The heritability of handedness, the most commonly investigated lateralised phenotype, has been consistently estimated to be ~25%. Handedness is linked to brain asymmetries such as hemispheric dominance for language and it has been associated to psychiatric and neurodevelopmental disorders. Here, we investigated the genetics of handedness as well as foot and eye preference and their relationship with neurodevelopmental phenotypes. Parental left-side preference increased the chance of an individual to be left-sided for the same trait, with stronger maternal than paternal effects ($n \leq 4{,}042$ family trios from the Avon Longitudinal Study of Parents and Children (ALSPAC)). By regressing out effects of sex, age, and the first two ancestry-informative principal components, we transformed categorical phenotypes (right, mixed, left) into quantitative measures for single nucleotide polymorphism (SNP) based heritability (SNP-h^2). We found moderate SNP-h^2 for transformed measures of hand (.21) and foot (.28) but negligible SNP-h^2 for eye preference (.02) or the untransformed categorical measures ($n \leq 5{,}931$). Genomic and behavioural structural equation modelling (SEM) in ALSPAC and a twin cohort from Hong Kong ($n = 366$) identified a shared genetic factor contributing to hand, foot, and eye preference, but no independent effects on individual phenotypes. Higher polygenic risk scores (PRS) for ADHD and genetic predisposition towards lower IQ and educational attainment (EA) were associated with left hand preference. This finding supports the idea of a right-handedness advantage on neurodevelopmental outcomes. This is the largest study conducted to date for multiple lateralised measures in the same individuals. Our analysis demonstrates how quantitative multidimensional laterality phenotypes are better suited to capture the underlying genetic component than simple left/right binary traits.

Keywords: left/right asymmetry, laterality, ALSPAC, ADHD, intelligence, educational attainment, neurodevelopment, PRS, structural equation modelling

Introduction

The two halves of the human brain differ in function and structure underpinning hemispheric specialisation for cognition, perception, and motor control [1]. For example, language is predominantly processed in the left hemisphere in the majority of individuals [2] and the *planum temporale*, a brain structure critical for language processing, typically shows a pronounced structural leftward asymmetry [3]. Several forms of neurodevelopmental disorders have been associated with atypical laterality. For example, *planum temporale* asymmetry is often reduced or reversed in individuals affected by dyslexia [4,5], schizophrenia [6], or autism spectrum disorder (ASD) [7]. While by themselves, these findings offer no information on whether reduced laterality is a consequence or cause of neurodevelopmental dysfunction [8], the finding that atypical laterality of language processing in infants is associated with poorer reading skills in childhood suggests that atypical laterality might be a risk factor for dyslexia [9].

The most commonly studied lateralised trait is handedness. Worldwide, around 10% of the general population are left-handed and as many as 9% are mixed-handed with slight geographical variation [10], likely influenced by cultural factors [11]. Meta-analyses have confirmed higher rates of left- or non-right-handedness in individuals affected by neurodevelopmental disorders such as ASD [12] and schizophrenia [13]. A genetic influence on handedness has been inferred from family and adoption studies [14]. For instance, the probability of left-handedness is increased in children with one left-handed parent (19.5%) and even more so in children with two left-handed parents (26.1%) compared to a baseline probability (two right-handed parents) of ~10% [15]. Twin studies reported slightly higher rates of concordance in monozygotic (MZ) compared to dizygotic (DZ) twins [16,17] and provided heritability estimates of around .25 for handedness [18,19]. Similar estimates have been reported in children with Chinese ancestry both for a quantitative measure of relative hand skill (.22) and for hand preference (.27) [20].

Family studies have suggested differential effects of fathers and mothers to their offspring's handedness. A stronger maternal than paternal effect was found in 459 biologically related parent-offspring trios [21]. This finding has been supported in a sample of 292 biologically related parent-offspring trios [22] and a similar trend was observable in an adoption study where children of left-handed biological mothers were more likely to be left-handed (n = 40, 15%) than children of right-handed biological mothers (n = 389, 8%). This effect was not found in fathers or adoptive parents [23]. A maternal effect on non-right-handedness was also found in a sample of 592 families (n = 1,528 individuals), where a paternal effect on handedness and footedness was only detectable in males [24].

A recent large-scale genome-wide association study (GWAS; n ~ 2M) estimated that up to 6% of the variance in left-handedness and up to 15% of the variance in ambidexterity are explained by common genetic markers, respectively [25]. In this GWAS, as in most large-scale laterality studies, handedness was assessed as hand preference for writing, which is the most accessible and straightforward measure. This leads to three categories: right, left or both. The "both" category identifies individuals who can write equally well with the right and left hand,

referred to as ambidextrous. However, a single task cannot identify mixed-handed individuals who prefer different hands for different activities. Instead, self-report questionnaires such as the Edinburgh Handedness Inventory [26] assess the preferred hand for several manual activities such as writing, throwing, and cutting and therefore capture both mixed-handed and ambidextrous individuals. A GWAS on brain imaging parameters (n = 32,256) revealed that genetic markers associated with structural brain asymmetries overlapped with markers previously associated with writing hand preference [27]. Moreover, genetic factors involved in brain asymmetry overlap with neurodevelopmental and cognitive traits such as ASD, schizophrenia, educational attainment (EA) [27] and intelligence (IQ) [28]. These data suggest a general mechanism for the establishment of left-right asymmetry which is also important for neurodevelopmental outcomes. Therefore, the analysis of other lateralised preferences beyond handedness will contribute to the understanding of such general mechanisms.

Foot and eye preference have received considerably less attention than handedness, even though associations with neurodevelopmental disorders have been reported for these phenotypes as well. We previously found a higher prevalence of non-right-footedness in neurodevelopmental and psychiatric disorders including schizophrenia, dyslexia, and depression (n_{cases} = 2,431; $n_{controls}$ = 116,938) [29]. Smaller studies point to higher rates of left eye preference in schizophrenia (n_{cases} = 88; $n_{controls}$ = 118[30]; n_{cases} = 68; $n_{controls}$ = 944[31]) and ASD (n_{cases} = 37; $n_{controls}$ = 20) [32]. Warren et al. reported heritability estimates for foot and eye preference to be .12 and .13, respectively in 584 Mexican-American families [33]. Suzuki et al. provided heritability estimates for foot preference in a sample of n = 956 Japanese twins that ranged from .08 to .24 across different methods of foot preference assessment (.08 for tracing a line, .20 for kicking a ball, .24 for stamping the ground) [34]. Analysis of 1,131 Japanese twin pairs (11-12 years of age) revealed that having one left-footed parent increased the probability of being left-footed (OR = 2.5) [35]. These studies support a genetic component for foot and eye preference although there is variability in heritability estimates probably as a result of small sample sizes. Overall, these investigations have been conducted in moderately sized samples.

Here, we performed the largest heritability study conducted to date for multiple side preferences in the same individuals. We investigated the heritability of hand, foot, and eye preference as well as their relationship. First, we examined family trios from the Avon Longitudinal Study of Parents and Children (ALSPAC) (n_{hand}= 3,888, n_{foot} = 4,042, n_{eye} = 3,419) to test for maternal, paternal, and combined parental effects on offspring side preferences on the phenotypic level. Second, for unrelated children in ALSPAC ($n \leq$ 5,931), we estimated SNP-h^2 for hand, foot, and eye preference on the level of single items used to assess side preferences. Third, we performed multivariate Genetic-relationship-matrix structural equation modelling (GRM-SEM) to test for shared and independent genetic factors among hand, foot, and eye preference. Fourth, estimates obtained from GRM-SEM were compared with heritability estimates obtained from behavioural SEM in a classical twin design in a cohort of school children from Hong Kong (n = 366 twin children) [20]. Finally, we used polygenic risk score (PRS) analysis to test for an association between laterality and neurodevelopmental outcomes based on the hypothesis of a non-right disadvantage.

Materials and Methods

Cohorts

ALSPAC: ALSPAC is a population-based longitudinal cohort. Pregnant women living in Avon, UK, with expected dates of delivery from 1st April 1991 to 31st December 1992 were invited to take part, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age [36,37]. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/).

Hong Kong: Study participants were recruited from the Chinese-English Twin Study of Biliteracy, a longitudinal study of primary school twin children starting in 2014 [38]. Participating children were recruited from Hong Kong primary schools and had Cantonese as their native language. Language and cognitive ability tests have been conducted for over four waves with a one-year interval between assessments. Laterality data were collected during the second wave of assessment.

Participants and phenotypes

ALSPAC: Laterality phenotypes for children were assessed at 42 months based on maternal report. For mothers and fathers, laterality was assessed as self-report. Hand preference was assessed using eleven items for mothers and fathers (writing, drawing, throwing a ball, holding a racket, cleaning teeth, cutting with a knife, hammering, striking a match, using an eraser, dealing cards, threading a needle) and six items for children (drawing, throwing, colouring, holding a toothbrush, cutting, hitting). Foot preference was assessed using four items for mothers and fathers (kicking a ball, picking up a pebble, stepping on an insect, stepping onto a chair) as well as children with slightly different wording (kicking a ball, picking up a stone, stamping on something, climbing a step). Eye preference was assessed using two items for mothers and fathers (looking through a telescope, looking into a dark bottle) as well as children (looking through a hole, looking through a bottle). All items were rated on a 3-point scale (left, either, right). In order to develop a score where the lowest values indicate left-sidedness and the highest values indicate right-sidedness, “left”-responses were coded as 1, “either”-responses were coded as 2 and “right”-responses were coded as 3 and a mean value was calculated from the number of non-missing responses for each participant. Summary items for hand, foot, and eye preference were created by recoding these mean variables (parents’ hand preference: left when scoring < 1.50, mixed when scoring ≥ 1.5 and ≤ 2.6, right when scoring > 2.6; children’s hand preference: left when scoring < 2.00, mixed when scoring ≥ 2.00 and ≤ 2.75, right when scoring > 2.75; parents foot and eye preference: left when scoring < 1.75, mixed when scoring ≥ 1.75 and ≤ 2.50, right when scoring > 2.50; children foot

and eye preference: left when scoring < 2.00, mixed when scoring ≥ 2.00 and ≤ 2.50, right when scoring > 2.50).

Hong Kong: The overall sample comprised *n* = 366 twin children (183 twin pairs) with a mean age of 8.67 years (SD = 1.23). This sample included 81 monozygotic pairs (37 male pairs and 44 female pairs) and 102 dizygotic pairs (21 male pairs, 19 female pairs, and 62 opposite-sex pairs). Twin zygosity of same-sex twins was determined by genotyping small tandem repeat (STR) markers on chromosomes 13, 18, 21, X and Y by Quantitative Fluorescence-Polymerase Chain Reaction (QF-PCR).

Hand, foot, and eye preference were assessed using a modification of the Edinburgh Handedness Inventory (EHI) [26]. The questionnaire was translated into Chinese and included six hand preference items (writing, drawing, holding scissors, brushing teeth, chopsticks, spoon), one foot preference item ("Which foot do you prefer to kick with?") and one eye preference item ("Which eye do you prefer to see things?"). All items were read to participants by a trained research assistant as described in detail previously [20]. Self-reported responses were coded on a 5 point scale (i.e. always left, usually left, no preference, usually right, always right). To make items comparable to ALSPAC, each item was recoded as 1 (usually left or always left), 2 (no preference) or 3 (usually right or always right). A mean score was generated for hand preference items that was recoded to a summary item according to the ALSPAC data (< 2.00: left, >= 2.00 and =< 2.75: mixed, > 2.75: right).

Genotype quality control (QC)

ALSPAC: Children's genotypes were generated on the Illumina HumanHap550-quad array at the Wellcome Trust Sanger Institute, Cambridge, UK and the Laboratory Corporation of America, Burlington, NC, US. Standard QC was performed as described elsewhere [39]. In total, 9,115 children and 500,527 SNPs passed QC filtering.

Hong Kong: Genotyping was performed using Illumina Human Infinium OmniZhongHua-8 v1.3 Beadchip at the Prenatal Genetic Diagnosis Centre and the Pre-implantation Genetic Diagnosis laboratory in the Prince of Wales Hospital and The Chinese University of Hong Kong, Hong Kong SAR. Standard quality control measures were carried out. Genetic variants with missing rate >10%, minor allele frequency < 0.01 and with significant deviation from Hardy-Weinberg equilibrium ($p < 1 \times 10^{-6}$) were excluded. Individuals with genotyping rates < 90% and outlying heterozygosity rates were excluded. In total, 293,2071 SNPs passed QC filtering.

Family study

Logistic regression analyses were performed in the ALSPAC cohort, using parental sidedness (right, mixed, left) as a predictor and child sidedness (right coded as 0, left coded as 1) as the dependent variable (mixed-sided children were excluded from this analysis). We included parent-child trios with complete phenotypic data on the summary items for hand, foot or eye preference after excluding one of each twin pair (*n* = 113) and children with physical

disabilities (n = 65) or sensory impairments (n = 50), resulting in a sample size (number of trios) of n_{hand} = 3888, n_{foot} = 4042 and n_{eye} = 3419.

Three separate analyses were performed for each laterality phenotype, one using maternal sidedness as a predictor (right coded as 0, mixed coded as 1, left coded as 2), one using paternal sidedness as a predictor (coded as for mothers) and one using both parents' sidedness as a predictor (coded as 0 = two right-sided parents, 1 = one mixed-sided parent, 2 = one left-sided parent, 3 = two mixed-sided parents, 4 = one mixed- and one left-sided parent, 5 = two left-sided parents).

To assess the reliability of maternal reports, we performed a chi-square test of independence between hand preference for drawing (left/right) assessed by maternal report at age 3.5 and self-reported hand preference for writing at age 7.5 (mean = 7.52 years, SD = 0.16) (n = 2899).

Phenotypic analysis

Unrelated children (genetic relationship < 0.05) with genome-wide genetic and phenotypic data were selected for Genome-wide Complex Trait Analysis (GCTA) [40]. The same sample was used for phenotypic analysis. Sample sizes varied from n = 4630 (foot used to pick up a pebble) to n = 5931 (summary item for hand preference).

Summary items for hand, foot, and eye preference and 12 single items (right coded as 0, mixed coded as 1, left coded as 2) were residualised for sex, age in weeks, and the two most significant ancestry-informative principal components (calculated using Plink v2) and inverse rank-transformed to achieve a normal distribution (Figure S1A). This resulted in quantitative laterality phenotypes in which being left-sided, being female, and younger age are associated with higher scores. Phenotypic correlations between rank-transformed laterality items (three summary items and 12 single items) were calculated with Pearson correlation after FDR correction for 105 comparisons using the Benjamini Hochberg method [41].

Genome-wide Complex Trait Analysis

SNP-h^2 was calculated for the transformed summary items (3) and single items (12) using restricted maximum-likelihood (REML) analysis in GCTA [42], which compares phenotypic similarity and genotypic similarity based on a genetic-relationship matrix (GRM) in unrelated individuals. A GRM was estimated based on directly genotyped SNPs for unrelated children (genetic relationship < 0.05, n = 5956) using GCTA. As a comparison, SNP-h^2 was calculated for the untransformed items in a categorical approach for the three summary items and 12 single items using sex, age and the two first ancestry-informative principal components as covariates. We estimated SNP-h^2 separately for left-sidedness (left vs. right, excluding mixed-sided individuals) and mixed-sidedness (mixed vs. right, excluding left-sided individuals).

Structural equation modelling (SEM)

We applied Genetic-relationship-matrix structural equation modelling (GRM-SEM) [43] to quantify shared and unique genetic factors among laterality phenotypes. This method has

recently been used to study genetic associations among language and literacy skills in the ALSPAC cohort [44]. Equivalent to heritability analysis in twin research, GRM-SEM partitions phenotypic variance/covariance into genetic and residual components, but estimates genetic variance/covariance based on genome-wide genetic markers. We used the same GRM described for GCTA SNP-h^2 (based on directly genotyped SNPs for n = 5956 unrelated children using GCTA). A GRM-SEM was fitted using the grmsem library in R (version 1.1.0) using all children with phenotypic data for at least one phenotype. Multivariate trait variances were modelled using a saturated model (Cholesky decomposition). GRM-SEM was also used to estimate bivariate heritability, i.e. the contribution of genetic factors to the phenotypic covariance).

Heritability of laterality phenotypes was additionally estimated using a classical twin design which compares the similarity of monozygotic (MZ) twins to that of dizygotic (DZ) twins. Since MZ twins share nearly all their genetic variants, whereas DZ twins share on average 50% of their genetic variants, any excess similarity of MZ twins over DZ twins is the result of genetic influences. This method partitions phenotypic variance into that due to additive genetic (A), shared environmental (C) and non-shared environmental influence (E). The variance attributed to each component can be estimated using the structural equation modelling (SEM) technique and the proportion of variance explained by the genetic influence (A) is termed heritability. Before SEM analysis was conducted, each summary laterality variable (right coded as 0, mixed coded as 1, left coded as 2) was residualised for sex, age and the two most significant ancestry-informative principal components (calculated using Plink v2). The residualised scores were further inverse-rank transformed to achieve a normal distribution (Figure S1B). Then we fit a multivariate ACE model to the transformed scores of three phenotypes (hand, foot, and eye preference) and compared ACE with its constrained models, such as the AE model. The multivariate genetic analyses were performed using the OpenMx software package 2.18.1 [45]. The script was adapted from the International Workshop on Statistical Genetic Methods for Human Complex Traits [46].

Polygenic risk scores (PRS)

We conducted PRS analyses to assess associations between psychiatric and neurodevelopmental conditions (ASD, ADHD, bipolar disorder (BIP), and schizophrenia (SCZ)) and laterality phenotypes. Based on genetic overlap previously reported for structural brain asymmetry with EA [27] and IQ [28], we also conducted PRS analyses for these phenotypes. PRS analyses were performed for hand and foot preference (which showed significant SNP-h^2) using PRSice 2.3.3 [47]. Summary statistics for ASD [48], ADHD [49], BIP [50], and SCZ [51] were accessed from the Psychiatric Genomics Consortium (PGC) website (https://www.med.unc.edu/pgc/data-index/). Summary statistics for IQ [52] and EA [53] were accessed from the Complex Trait Genetics (CTG) lab website (https://ctg.cncr.nl/software/summary_statistics), and the Social Science Genetic Association Consortium (https://www.thessgac.org/data), respectively.

PRS were derived from LD-clumped SNPs (r^2 >= 0.1 within a 250 kb window) as the weighted sum of risk alleles according to the training GWAS summary statistics. No covariates were included as phenotypes had been corrected for age, sex and ancestry-informative principal components. Results are presented for the best training GWAS *p*-value threshold (explaining maximum phenotypic variance) as well as GWAS *p*-value thresholds of .001, 0.05, .1, .2, .3, .4, .5, and 1. Results were FDR corrected for multiple comparisons (six training GWAS × two target phenotypes × nine *p*-value thresholds = 108 comparisons) using the Benjamini-Hochberg method [41].

Data preparation and visualization were performed using R v.4.0.0. All analysis scripts are available through Github (https://github.com/Judith-Schmitz/heritability_hand_foot_eye).

Results

Parental effects

We analysed $n \leq 4{,}042$ family trios from the ALSPAC cohort to determine Odds Ratios (ORs) for children being left-sided based on parental sidedness. Mean ages of mothers, fathers, and children was 32.54 (SD = 4.42), 34.42 (SD = 5.60) and 3.55 (SD = 0.07) at the time of assessment, respectively. We classified parents as left/mixed/right-sided based on the summary items (Table 1) and tested the effect of having one or two parents in each category on children's sidedness. For this analysis, children were classified as left/right-sided (Table 1, mixed-sided children were excluded from analysis).

1 *Table 1: Descriptive results of side preferences of mothers, fathers, and children (ALSPAC) included in parental effects analyses.*

		Mothers			**Fathers**			**Children**			
								Girls		**Boys**	
	n_{total}	**Left (%)**	**Mixed[1] (%)**	**Right (%)**	**Left (%)**	**Mixed[1] (%)**	**Right (%)**	**Left(%)**	**Right(%)**	**Left(%)**	**Right(%)**
Hand	3888	299 (7.7%)	123 (3.2%)	3466 (89.1%)	320 (8.2%)	195 (5.0%)	3373 (86.8%)	225 (5.8%)	1722 (44.3%)	306 (7.9%)	1635 (42.1)
Foot	4042	250 (6.2%)	470 (11.6%)	3322 (82.2%)	328 (8.1%)	1086 (26.9%)	2628 (65.0%)	176 (4.4%)	1811 (44.8%)	294 (7.3%)	1761 (43.6%)
Eye	3419	685 (20.0%)	317 (9.3%)	2417 (70.7%)	638 (18.7%)	407 (11.9%)	2374 (69.4%)	328 (9.6%)	1330 (38.9%)	366 (10.7%)	1395 (40.8%)

2 *[1] The "mixed" category includes mixed-sided and ambidextrous individuals.*

3

We ran logistic regression analyses on child hand, foot, and eye preference using combined maternal and paternal sidedness in the respective phenotype as predictors (Figure 1). Having one left-sided parent increased one's chances to be left-sided for hand, foot, and eye preference. This effect increased for all three phenotypes if both parents were left-sided. The strongest effect was found for footedness, where the probability of being left-footed increased with an OR of 8.16 (95% CI = [3.41; 19.16]) when both parents were left-footed. Having two left-handed parents resulted in an increased probability of left-handed offspring with an OR of 4.24 (95% CI = [1.78; 9.47]) and having two left-eyed parents resulted in an increased probability of being left-eyed with an OR of 1.76 (95% CI = [1.19; 2.57]).

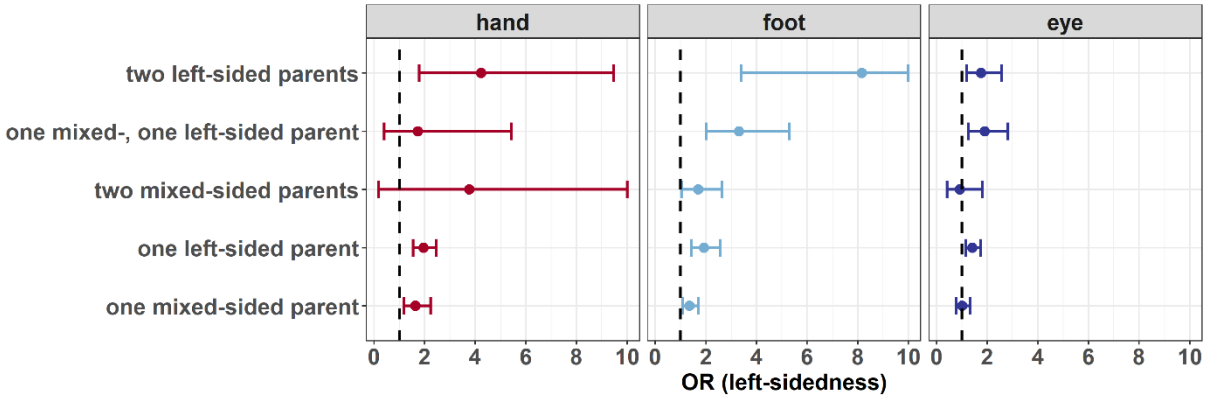

Figure 1: Parental effects on child sidedness. *ORs [95% CI], resulting from logistic regression analysis, are based on a baseline probability (two right-sided parents) of 13.2% for left-handedness, 10.2% for left-footedness and 21.8% for left-eyedness. Upper limits of CIs are capped at 10.*

Next, we differentiated the maternal and paternal effects. We ran logistic regression analyses on child hand, foot, and eye preference using maternal and paternal sidedness in that respective phenotype as predictors, individually (Figure 2, upper panel). Again, the strongest effect was found for foot preference. Maternal left-footedness increased the probability of left-footed offspring with an OR of 3.03 (95% CI = [2.21; 4.11]). Paternal left-footedness also increased the probability of left-footed offspring, albeit to a lesser degree (OR = 1.60; 95% CI = [1.15; 2.17]). A similar pattern but with slightly smaller effects was observed for hand preference. There was only a weak maternal effect and no evidence of a paternal effect on eye preference. Overall, the results suggest slightly stronger maternal than paternal effects on hand, foot, and eye preference.

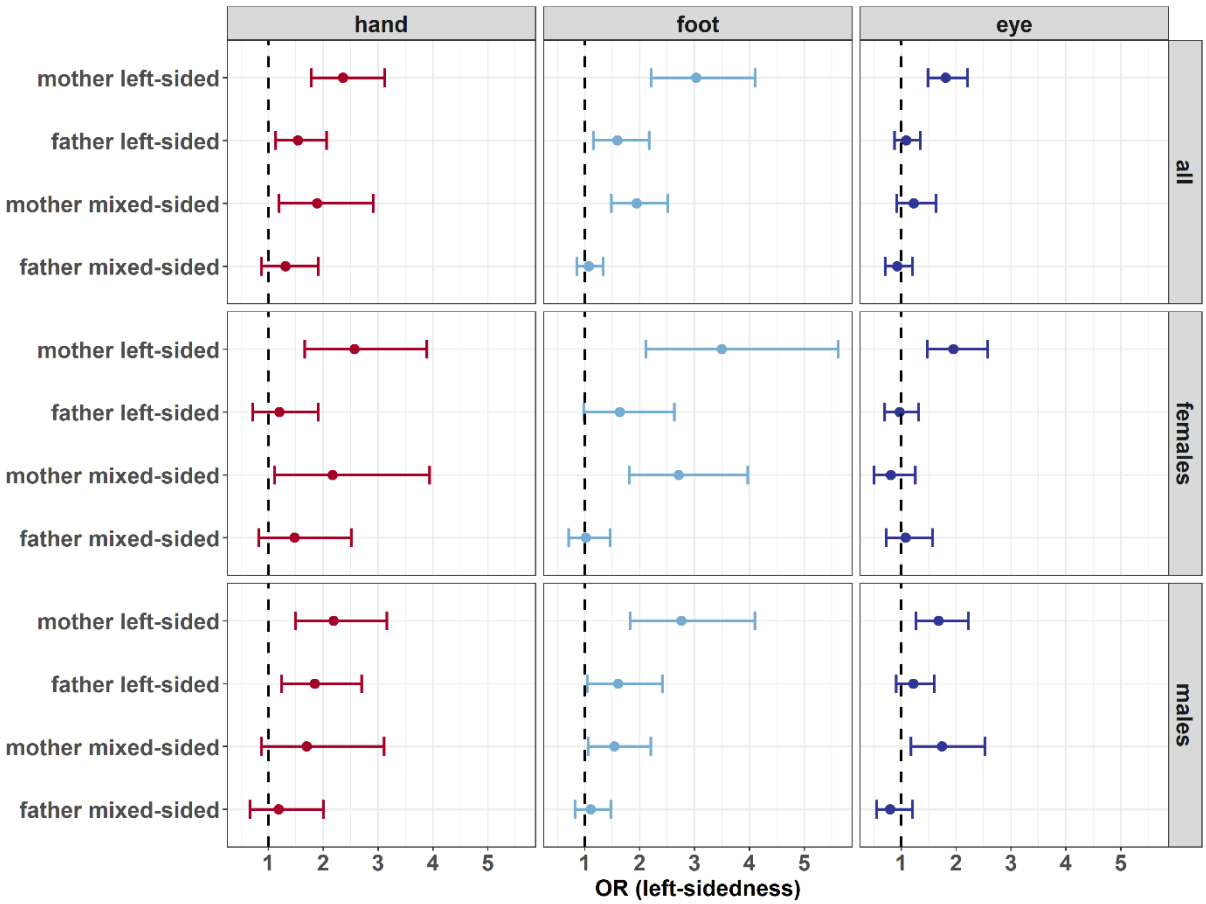

Figure 2: Maternal and paternal effects on child sidedness. ORs [95% CI] were calculated from logistic regression analysis of maternal and paternal sidedness. *The top panel reports results for all children (n_{hand} = 3888, n_{foot} = 4042 and n_{eye} = 3419) and the lower panels presents the results split by the offspring's sex, with females in the middle panel (n_{hand} = 1947, n_{foot} = 1987 and n_{eye} = 1658) and males in the lower panel (n_{hand} = 1941, n_{foot} = 2055 and n_{eye} = 1761).*

We then reran the analysis separately for girls (Figure 2, middle panel) and boys (Figure 2, lower panel) to test for sex effects. Maternal left-sidedness had similar effects on the hand, foot, and eye preference of their daughters and sons (shown by overlapping CIs). However, paternal left-handedness influenced left-handedness in boys (OR = 1.85; 95% CI = [1.24; 2.70]) but not in girls (OR = 1.20; 95% CI = [0.72; 1.91]). This effect was also found for foot preference (boys: OR = 1.61; 95% CI = [1.04; 2.41]; girls: OR = 1.64; 95% CI = [0.98; 2.63]). Maternal mixed-sidedness did have an effect on left-handedness in girls (OR = 2.17; 95% CI = [1.11; 3.94]), but not in boys (OR = 1.70; 95% CI = [0.87; 3.11]). An opposite trend was observed for maternal mixed-eyedness which had an effect on left-eyedness in boys (OR = 1.74; 95% CI = [1.18; 2.53]), but not in girls (OR = 0.81; 95% CI = [0.50; 1.26]). Again, there was no evidence for an effect of paternal mixed-sidedness on either phenotype.

The hand preference for drawing used here, collected at 3.5 years of age, was strongly associated with the hand preferred for writing collected later (7.5 years), $X^2_{(1)} = 2567.2$, $p < 2.2 \times 10^{-16}$. Among the 2534 children showing a right hand preference at age 3.5, 6 (0.2%)

showed a left hand preference for writing at age 7.5. Among the 365 children showing a left hand preference at age 3.5, 30 (8.2%) showed a right hand preference for writing at age 7.5, suggesting that a large proportion of individuals showed stable hand preference and the reliability of the measure used here.

Phenotype transformation

Phenotypic correlation and genomic analyses (SNP-h^2 estimates, GRM-SEM and PRS analysis) were performed in unrelated children from the ALSPAC cohort ($n \leq 5931$). The absolute numbers and percentages of children with left, mixed and right side preference for the three summary items are shown in Table 2.

Table 2: Children with left, mixed and right side preference for each phenotype in the ALSPAC cohort (unrelated children) and in the Hong Kong cohort (twin children).

	ALSPAC				**Hong Kong**			
	n	**Left**	**Mixed[1]**	**Right**	***n***	**Left**	**Mixed**	**Right**
Hand preference	5931	637 (10.7%)	1342 (22.6%)	3952 (66.6%)	366	24 (6.6%)	84 (23.0%)	258 (70.5%)
Foot preference	5860	579 (9.9%)	1103 (18.8%)	4178 (71.3%)	366	31 (8.5%)	108 (29.5%)	227 (62.0%)
Eye preference	5650	839 (14.8%)	1563 (27.7%%)	3248 (57.5%)	365	96 (26.3%)	114 (31.2%)	155 (42.5%)

[1] *In ALSPAC, the "mixed" category includes mixed-sided and ambidextrous individuals.*

In the Hong Kong twin sample, multivariate behavioural SEM analysis was performed on hand, foot, and eye preference ($n \leq 366$). In contrast to foot and eye preference, which had been assessed using only one item, hand preference was assessed using multiple items, so the "mixed" category" could have potentially included ambidextrous and mixed-sided individuals. However, none of the children was identified as being ambidextrous (i.e. selecting "either" on all non-missing items, Table 2).

As described in detail in the methods, the items (three summary items and 12 single items in the ALSPAC cohort, three items in the Hong Kong cohort) were residualised for sex, age and ancestry (Figure S1) to achieve normally distributed phenotypes with higher scores indicating a tendency towards left-sidedness, being female, and younger age.

Phenotypic correlations

Phenotypic correlations for the three transformed summary items on hand, foot, and eye preference and twelve transformed single items were assessed in a sample of unrelated children in ALSPAC. The sample size varied from n_{pick} = 4630 to n_{hand} = 5931 (Table S1) depending on data availability. All laterality items showed positive correlations after FDR correction for 105 comparisons (Figure S2). The single item that best captured the summary measure was "hand used to draw" for hand preference (r = .84, $t_{(5920)}$ = 118.77, $p < 2.2 \times 10^{-16}$), "foot used to stamp" (r = .80, $t_{(5765)}$ = 101.83, $p < 2.2 \times 10^{-16}$) for foot preference, and "eye used to look through a hole" for eye preference (r = .96, $t_{(5613)}$ = 275.21, $p < 2.2 \times 10^{-16}$). Summary measures were intercorrelated with r = .59 ($t_{(5857)}$ = 56.25, $p < 2 \times 10^{-16}$) between hand and foot preference, r = .43 ($t_{(5639)}$ = 36.22, $p < 2 \times 10^{-16}$) between foot and eye preference and r = .39 ($t_{(5647)}$ = 31.97, $p < 2 \times 10^{-16}$) between hand and eye preference.

In the Hong Kong cohort, correlations between hand, foot, and eye preference were significant after FDR correction for three comparisons. Specifically, correlation coefficients were r = .34 ($t_{(356)}$ = 6.87, $p = 3 \times 10^{-11}$) between hand and foot preference, r = .26 ($t_{(355)}$ = 5.13, $p = 5 \times 10^{-7}$) between foot and eye preference and r = .16 ($t_{(355)}$ = 3.01, p = .003) between hand and eye preference (Figure S3). Thus, correlation coefficients were lower in the Hong Kong cohort compared to ALSPAC.

SNP-h^2

SNP-h^2 of transformed laterality phenotypes was tested using GCTA REML in unrelated children in the ALSPAC cohort. SNP-h^2 ranged from .00 (SE = 0.06, p = .500) for "eye used to look through a bottle" to .42 (SE = 0.06, $p = 8 \times 10^{-13}$) for "hand used to cut" (Figure 3, Table S1). Among the summary measures, foot preference showed the highest heritability estimate (SNP-h^2 = .29, SE = 0.06, $p = 6 \times 10^{-8}$), followed by hand preference (SNP-h^2 = .21, SE = 0.06, $p = 9 \times 10^{-5}$). There was no significant SNP-h^2 for eye preference (SNP-h^2 = .02, SE = 0.06, p = .387).

For comparison, we estimated SNP-h^2 for the untransformed categorical items for left-sidedness (left vs. right, Figure S4A) and mixed-sidedness (mixed/ambidextrous vs. right, Figure S4B). SNP-h^2 for left-sidedness ranged from .00 (SE = 0.08, p = .500) for "foot used to climb a step" to .13 (SE = 0.07, p = .031) for "hand used to cut", which was the only item showing significant SNP-h^2 (Figure S4A, Table S2). SNP-h^2 for mixed-sidedness ranged from .00 (SE = 0.06, p = .500) for the handedness summary item to .12 (SE = 0.06, p = .031) for "hand used to draw" (Figure S4B, Table S3). "Hand used to draw" and "hand used to throw" (SNP-h^2 = 0.11, SE = 0.06, p = .037) were the only items showing significant SNP-h^2.

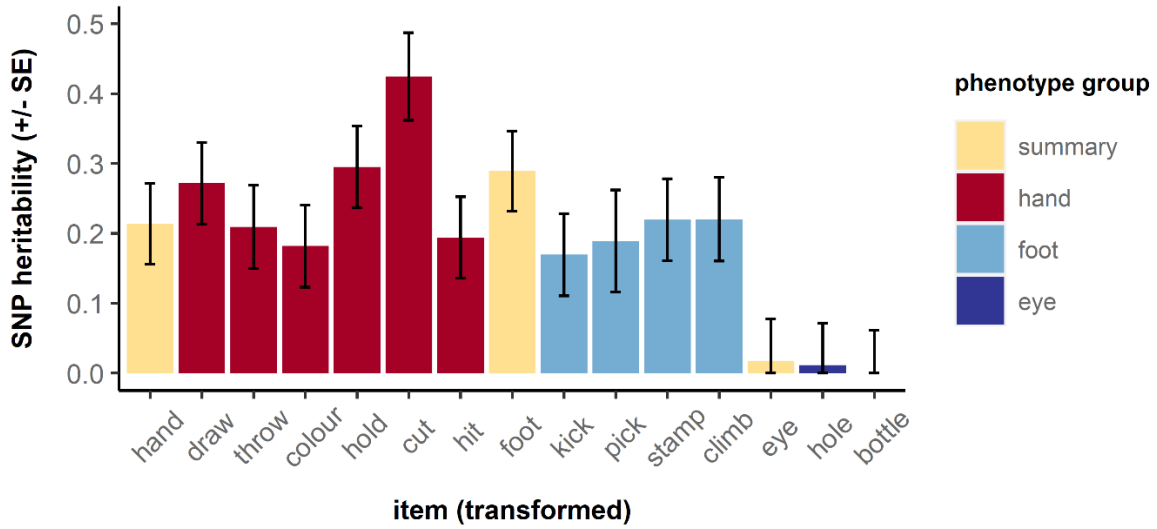

Figure 3: SNP-h^2 estimates for transformed laterality measures. *Summary items for hand, foot and eye preference are shown in yellow, followed by the corresponding single items. The estimates were calculated using GCTA REML. Bars represent standard errors. Sample sizes range from n_{pick} = 4630 to n_{hand} = 5931 depending on data availability.*

Structural equation modelling (SEM)

Multivariate GRM-SEM analysis was performed on the transformed summary items for hand, foot, and eye preference in unrelated children in ALSPAC (n_{hand} = 5931, n_{foot} = 5860, n_{eye} = 5650; Figure 4A). The squared path coefficient of genetic factor A1 explains genetic variance in hand preference (a_{11}) and genetic variance that is shared with foot (a_{21}) and eye preference (a_{31}). A single genetic factor (A1) explained 11.84% of the phenotypic variance in hand preference (path coefficient a_{11} = 0.34, SE = 0.06, $p = 1.3 \times 10^{-9}$), 21.30% of the phenotypic variance in foot preference (path coefficient a_{21} = 0.46, SE = 0.05, $p = 3.1 \times 10^{-18}$) and 6.86% of the phenotypic variance in eye preference (path coefficient a_{31} = 0.26, SE = 0.06, $p = 1.6 \times 10^{-5}$). All other path coefficients were non-significant. This suggests that one shared genetic factor (A1) contributes to a general left/right directionality across all three phenotypes while it was not possible to identify other genetic factors that would contribute to the residual variance in individual phenotypes.

Bivariate heritability analysis confirmed that shared genetic influences accounted for a significant component of the observed phenotypic correlation between summary measures (Figure S2). Specifically, it was 42.4% of the correlation between hand and foot preference (r = .59, bivariate heritability: .42, SE = 0.08, $p = 4.5 \times 10^{-8}$), 41.1% of the correlation of between foot and eye preference (r = .43, bivariate heritability: .41, SE = 0.09, $p = 1.4 \times 10^{-5}$) and 38.8% of the correlation between hand and eye preference (r = .39, bivariate heritability: .39, SE = 0.09, $p = 3.8 \times 10^{-5}$).

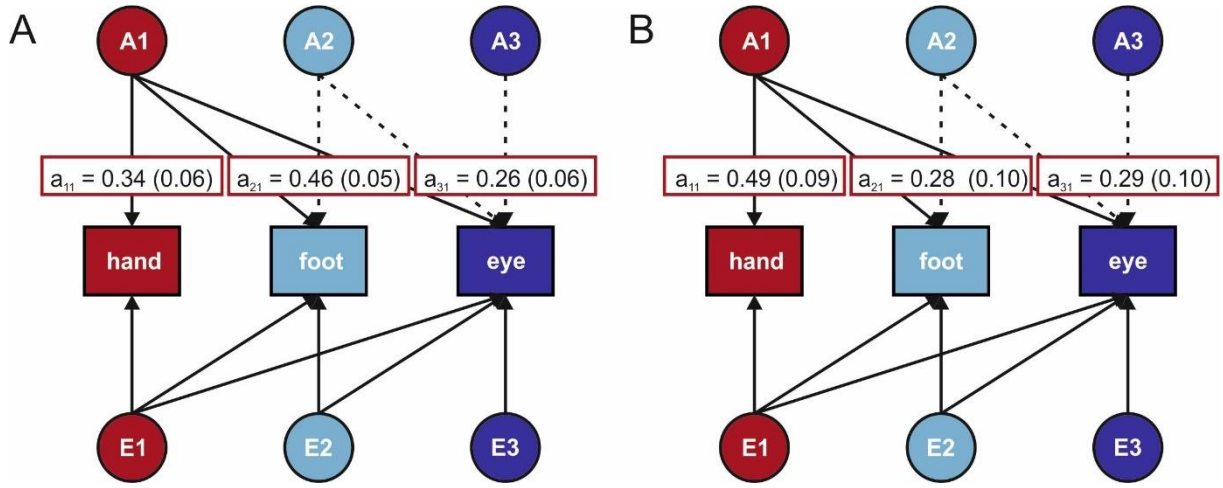

Figure 4: Results of multivariate SEM analyses between laterality phenotypes. *A) Results of GRM-SEM analysis in the ALSPAC cohort. B) Results of behavioural SEM analysis in the Hong Kong cohort. Circles on top and bottom indicate genetic (A) and environmental (E) factors, respectively. Coloured boxes indicate the phenotypes (hand summary, foot summary, eye summary). Solid lines indicate significant path coefficients, dotted lines indicate non-significant path coefficients. The white boxes indicate path coefficients and standard errors (SE) for significant genetic factors. The contour of the white boxes indicates the genetic factor (A1 in all cases).*

In the Hong Kong twin sample, a multivariate behavioural SEM analysis was performed on hand, foot, and eye preference (n_{hand} = 366, n_{foot} = 366, n_{eye} = 365, Figure 4B). A single genetic factor (A1) explained 23.48% of the phenotypic variance in hand preference (path coefficient a_{11} = 0.49, SE = 0.09, p = .001), 8.03% of the phenotypic variance in foot preference (path coefficient a_{21} = 0.28, SE = 0.10, p = .018) and 8.32% of the phenotypic variance in eye preference (path coefficient a_{31} = 0.29, SE = 0.10, p = .016). All other path coefficients were non-significant. In accordance with results for the ALSPAC cohort, this suggests the presence of a genetic factor (A1) contributing to left/right asymmetry across phenotypes.

PRS analysis

Considering the link between laterality and neurodevelopmental disorders [12,13] and EA [27], we reasoned that shared genetic pathways could influence these different outcomes. Therefore, we tested whether we could identify associations between the laterality phenotypes that showed significant SNP-h^2 (i.e. hand and foot preference) with PRS for neurodevelopmental and psychiatric traits, EA, and IQ. Results for the best p-value threshold (explaining the maximum phenotypic variance) are reported in Table 3. Full results for all p-value thresholds are reported in Table S4 and shown in Figure S5. Polygenic risk for ADHD was positively associated with hand preference after FDR correction for multiple comparisons, indicating that higher genetic risk for ADHD is associated with the tendency to prefer the left hand. PRS for EA and IQ were negatively associated with hand preference, suggesting that genetic predisposition towards higher EA and IQ are associated with the tendency to prefer the right hand. There was no evidence for an effect of any training GWAS PRS on foot preference.

Table 3: Analysis of PRS for neurodevelopmental (ADHD, ASD, BIP, SCZ) and cognitive measures (EA, IQ) on laterality summary items (hand and foot preference).

Training GWAS	Target phenotype	*p*-value threshold	# SNPs	PRS R^2	ß	SE	p_{FDR}
ADHD	**hand**	**.0914**	**26347**	**0.22%**	**515.54**	**142.52**	**.017**
ADHD	foot	5×10^{-8}	12	0.09%	-3.69	1.60	.082
ASD	hand	.0003	419	0.03%	-16.02	11.98	.466
ASD	foot	.0026	1960	0.07%	-61.62	30.74	.157
BIP	hand	.0132	8089	0.04%	-105.52	66.31	.303
BIP	foot	.0001	471	0.03%	-16.63	12.14	.450
SCZ	hand	.0408	21523	0.03%	-145.61	118.49	.538
SCZ	foot	.0010	3233	0.06%	53.54	28.79	.206
EA	**hand**	**.0247**	**22959**	**0.16%**	**-1988.41**	**644.91**	**.020**
EA	foot	5×10^{-8}	629	0.02%	-71.37	61.13	.563
IQ	**hand**	**.0161**	**16538**	**0.21%**	**-1301.84**	**368.06**	**.017**
IQ	foot	.0087	12264	0.04%	-482.21	303.67	.303

Significant results after FDR correction are highlighted in bold.

p-value threshold: p-value threshold applied to training GWAS that results in the maximum variance explained in the target phenotype (hand or foot preference)

 # SNPs: number of SNPs included in PRS after application of the respective p-value threshold

PRS R^2: Variance explained by PRS in %

ß: Estimate for regression weight

SE: Standard error of estimate for ß

p_{FDR}: p-value after FDR correction. Values below .05 indicate an association after FDR correction for 108 comparisons

Discussion

We investigated the heritability of hand, foot, and eye preference using multiple approaches. To the best of our knowledge, this is the largest study conducted to date for multiple laterality measures in the same individuals. Behavioural (Figures 1,2) and genomic analyses (Figure 3) suggest moderate heritability for hand and foot preference, while heritability for eye preference was negligible. Multivariate analyses in ALSPAC and an independent twin sample from Hong Kong suggested that a common genetic factor contributes to the shared variance in handedness, footedness, and eyedness, while there was no evidence for genetic factors explaining independent variance of individual phenotypes (Figure 4). PRS analysis for traits previously linked to handedness showed that higher polygenic risk for ADHD is associated with the tendency to prefer the left hand, while genetic liability towards higher IQ and EA is associated with the tendency to prefer the right hand. In contrast, no significant PRS results were detected for foot preference (Table 3).

Our analysis of family trios (n_{hand} = 3888, n_{foot} = 4042 and n_{eye} = 3419) showed that the probability of being left-sided increased for any left-sided parent on the same trait, with stronger effects for hand and foot, rather than eye preference (Figure 1). The probability of being left-handed increased to 20.6% (OR = 2.0) and 36.0% (OR = 4.2) when having one left-handed and two left-handed parents, respectively. These results are in line with a previous large-scale report by McManus and Bryden [15], who reported increases to 19.5% (OR = 2.3) and 26.1% (OR = 3.4) for the same conditions, considering that the baseline left-handedness in their study was lower (9.5%) than in the ALSPAC cohort (11.7%). The higher prevalence of left-handedness in ALSPAC is explained by a well-documented generational effect, likely due to discontinuation of stigma and cultural pressures [54]. We observed the strongest parental effect on foot preference. While one left-footed parent resulted in an increase in left-footed offspring that is comparable to handedness (16.40% left-footed offspring, OR = 1.9), two left-footed parents resulted in a probability of 45.45% to be left-footed (OR = 8.2). This result is consistent with what has been reported previously in a sample of Japanese twins [35].

We found a stronger maternal than paternal effect for all three traits. This is in line with previous studies which focussed mainly on handedness [15,21–24]. We also found paternal effects on hand and foot preference (but not eye preference) which reached statistical significance only when considering father-son pairs. Previously, Tran et al. [24] reported paternal effects on handedness and footedness only in males, in line with our results, but did not find any evidence for maternal effects on footedness. Parental effects could be explained with sex-linked genetic or parent-of-origin effects. For example, the imprinted *LRRTM1* gene was found to be associated with handedness under a parent of origin effect [55]. Parent of origin effects might be more wide-spread than appreciated, but their detection requires family samples as opposed to the most commonly used singleton cohorts. Few examples of parent-of-origin effects have been reported, for example for language-related measures[56–58]. As laterality questionnaires for children have been completed by their mothers, a possible limitation of the current study is the possibility that laterality is biased towards maternal hand, foot, and eye

preference. Even though close family members have been shown to correctly report an individual's handedness [59,60], it remains unclear if this is the case for foot or eye preference. In our data, we have confirmed high reliability of the hand preferred for drawing assessed using maternal report at age 3.5, as it was strongly associated with self-reported hand use for writing at the age of 7.5 years. Overall, 0.2% of initially right-handed children and 8.2% of initially left-handed children switched hand preference by the age of 7.5 years. These figures are in line with previous reports of 8.6% of children switching hand preference between kindergarten and grade 2, mostly from left- to right-handedness [61]. However, even in the absence of methodological biases, children's lateral preferences might be more similar to their mothers' due to greater maternal than paternal impact on children in early life [15]. Overall, this analysis supports a genetic component underlying these laterality traits and highlights specific maternal vs paternal and daughters vs sons patterns.

For genomic analyses, we transformed the categorical phenotypes (right, mixed, left) into a quantitative measure by regressing out the effects of sex, age, and the first two ancestry-informative principal components [44] (Figure S1). Using these transformed phenotypes, SNP-h^2 estimates for the three summary items for hand, foot, and eye preference were .21, .29, and .02, respectively ($n \leq 5931$; Figure 3). The heritability estimate for hand preference is similar to what has been reported in twin studies (.25) but higher than what has been reported from categorical GWAS performed in adults (.06 for left-handedness, .15 for ambidexterity) [25,62,63]. Although we can not compare our phenotypes directly, we did not observe higher heritability for ambidexterity compared to left-handedness using categorical measures in ALSPAC: We found SNP-h^2 estimates of .08, .03, and .00, for left-handedness, left-footedness, and left-eyedness, respectively (Figure S4A). Standard errors for the categorical measures were high, resulting in non-significant heritability estimates. For the three summary items of mixed-sidedness, all SNP-h^2 estimates were .00 (Figure S4B). In contrast, the transformed phenotypes regard laterality as a continuum from right to left, with higher values in females compared to males to correct for the fact that males are more often left-handed than females [64]. Using these transformed phenotypes, we found a comparable heritability estimate from behavioural SEM for hand preference in the Hong Kong cohort (.24), which is similar to the heritability estimates reported for a categorical measure of writing hand (.27) and a quantitative measure of relative hand skill (.22) for this cohort previously [20]. Overall, our analysis shows that the transformed phenotypes are better suited to detect the genetic component underlying lateralised traits than binary phenotypes.

Heritability estimates differed substantially between items used to measure hand, foot, and eye preference (Figure 3). We found the highest heritability estimate of .42 for "hand used to cut" (with a knife). As in other studies [65,66], this item showed the weakest phenotypic correlation with the other questionnaire items (r = .70, Figure S2), suggesting that there is something specific about this item that makes it more suitable for genetic analyses. While "hand used to cut" showed no significant heritability in a Mexican-American sample [33], it was also the most heritable item in a Japanese study (.32) [34]. The fact that the summary item for hand preference did not yield the highest SNP-h^2 estimate for hand preference is in line with

Warren et al. [33] who found no significant heritability (.07) for a composite trait of nine handedness items. The authors claimed that summary items such as the laterality quotient obtained by the EHI [26] have reduced value to determine genetic factors involved in laterality, which is in line with our results for handedness.

Heritability estimates for foot and eye preference in the Hong Kong cohort (.08 for both phenotypes, Figure 4) differed considerably from estimates obtained from the ALSPAC cohort. Lower heritability estimates for foot and eye preference (.12, .13) compared to writing hand preference (.16) have also been reported in a study of Mexican-American families [33]. The higher SNP-h^2 for the summary item for foot preference (.29) compared to single items in ALSPAC (ranging from .17 to .22, Figure 3) suggests that in contrast to handedness, multiple items might better capture a genetic component for footedness. One possible interpretation is that multiple items will allow identifying the mixed-footed individuals rather than ambidexterity. Similar to the results obtained by Suzuki et al. [34], the item "foot used to kick a ball", which is often used as the only assessment item in footedness studies, does not seem to be the optimal choice to investigate heritability of laterality. We previously showed that measuring footedness in terms of kicking results in a similar prevalence of left-footedness [29] compared to inventories such as the Waterloo footedness questionnaire (WFQ) [67] or lateral preference inventory (LPI) [68]. However, as kicking is often only assessed in one trial, the prevalence of mixed-footedness is systematically lower in studies using kicking to assess footedness [29]. Equally the low SNP-h^2 for eye preference in ALSPAC could reflect the poor quality of this phenotype. In essence, the two items (looking through a hole and looking through a bottle) are very similar tasks which might be more difficult to assess and report accurately. Overall, there is not one correct measure for laterality items however our results demonstrate the importance of reporting data for individual items in addition to the aggregates.

All transformed laterality items showed positive correlations on the phenotypic level (Figures S2,S3). In line with previous studies [33], correlations were strongest within laterality dimensions and stronger between handedness and footedness items than between eyedness items with others. Previous research has shown a tendency towards a higher probability of left-sided lateral preferences in left-handers. For example, 60% of left-handers and 3% of right-handers are left-footed [29] and 57% of left-handers and 35% of right-handers are left-eye dominant [69]. These patterns suggest that a common dimension of left/right asymmetry underlies hand, foot, and eye preference [70]. We tested this hypothesis with multivariate GRM-SEM analysis, which supported the presence of one shared genetic factor explaining variance in hand, foot, and eye preference, but no unique genetic factors explaining independent variance for individual phenotype (Figure 4A). This finding was confirmed using multivariate SEM in an independent twin sample from Hong Kong (n = 366, Figure 4B). In the ALSPAC cohort, bivariate heritability analysis suggested that around 40% of the phenotypic correlation is due to shared genetic effects.

Atypical laterality has been reported across multiple psychiatric and neurodevelopmental disorders [4–7,12,13]. We tested whether PRS for four neurodevelopmental disorders (ASD, ADHD, BIP, SCZ) and two cognitive measures (EA and IQ) have any relevance for laterality traits. An association between laterality and psychiatric disorders, especially schizophrenia [6,71], has long been debated. However, in the current study, we found no evidence for an association of any laterality phenotype with PRS for SCZ or BIP, thus not supporting a genetic association with psychiatric traits. Instead, PRS for ADHD were associated with a tendency towards left hand preference, while PRS for IQ and EA were associated with a tendency towards right hand preference (Table 3, Table S4, Figure S5). This same trend that we observed for hand preference (i.e. low genetic risk for ADHD and genetic predisposition towards higher IQ and EA associated with the tendency to report the right hand) has been reported for reading ability in previous studies [72–74]. Overall, our results hint towards a role of handedness in cognitive rather than psychiatric traits. A possible explanation for this specific link with handedness is its association with language lateralisation [2]. It has been suggested that the higher prevalence of human right- than left-handedness has arisen from a left-hemispheric dominance for manual gestures that gradually incorporated vocalisation [75]. Indeed, right-handers produce more right- than left-handed gestures when speaking [76]. This would suggest that foot and eye preference are phenotypically secondary to hand preference, as has been suggested previously [77].

In summary, using family, genomic, and twin analyses, we found moderate heritability for hand and foot preference and negligible heritability for eye preference with specific estimates varying between items. Stronger maternal than paternal effects on all phenotypes highlight the necessity of examining parent-of-origin effects on the genetic level in future studies. Genomic and behavioural SEM analyses support a shared genetic factor involved in all three phenotypes without independent genetic factors contributing to foot and eye preference. PRS analysis highlights an association of hand preference with cognitive traits, providing suggestive evidence for an association of left hand preference with reading ability that requires further investigation in future studies. These results are underpinned by the transformation of the laterality measures into quantitative phenotypes which might add resolution to genetic analyses.

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