Title: Handedness and Other Variables Associated with Human Brain Asymmetrical Skew

Abbreviated title: Handedness and Brain Asymmetry

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Abstract

The average human brain is characterized by a global left-right asymmetry of shape, including a well-known 'torque' on the fronto-occipital axis, and less-studied differences on the dorsal-ventral axis. Torque has been claimed to be human-specific. However, the functional significance and developmental mechanisms underlying the global aspects of brain anatomical asymmetry are unknown. Here we used a registration-based approach with respect to a symmetrical template, to carry out the largest-ever analysis of global brain asymmetry in magnetic resonance imaging data. Three population datasets were used, the UK Biobank (N = 21,389), Human Connectome Project (N = 1,113) and BIL&GIN (N = 453). At the population level, there was an anterior and dorsal skew of the right hemisphere, relative to the left. Variances of this skew on the anterior-occipital and dorsal-ventral axes were largely independent, but both measures were associated with handedness, as well as various regional grey and white matter metrics. Both skew measures also showed heritabilities of 5%-10%, and four potential loci were identified in genome-wide association scanning. Several phenotypic variables related to early life experiences, cognitive functions, or mental health showed associations with the skew measures. These results provide replicable associations of global brain structural asymmetry measures with left-handedness, as well as insights into molecular genetic and early life factors which may contribute to brain asymmetry.

Keywords: brain asymmetry; global brain asymmetry; brain torque; handedness; genetics; lateralization

Introduction

A counter-clockwise twist of the whole brain along the anterior-posterior axis, i.e. the fronto-occipital torque, has been widely reported in humans since observations in the middle of the 20th century (e.g., (Galaburda et al. 1978b; Kong et al. 2018; LeMay 1976; Watkins et al. 2001; Weinberger et al. 1982; Yakovlev & Rakic 1966; Zilles et al. 1996); see (Toga & Thompson 2003) for a review). This global twisting is manifested by several features, including a more anteriorly protruding right frontal lobe (frontal petalia) and posteriorly protruding left occipital lobe (occipital petalia), a so-called "bending" of the right frontal and left occipital lobes across the midline, and relative increases in the dimensions (e.g., volume and width) of the right frontal and left occipital poles (Toga & Thompson 2003).

Torque has been suggested to be a human-specific feature of the brain, through comparative work with chimpanzees (Xiang et al. 2019; Xiang et al. 2018). There is also evidence for alterations of torque in cognitive and neuropsychiatric disorders, including developmental stuttering (Mock et al. 2012), dyslexia (Pieniadz et al. 1983), schizophrenia ((Crow 1997; Luchins & Meltzer 1983; Maller et al. 2017); but see (Chapple et al. 2004)), attention-deficit/hyperactivity disorder (Shaw et al. 2009), and depression (Fullard et al. 2019; Maller et al. 2014). While the sample sizes were not large in these previous studies (e.g., 37 cases and 44 controls in (Maller et al. 2017); 231 cases and 68 controls in (Fullard et al. 2019)), and further replication is needed, these results suggest that the global brain asymmetry pattern may reflect an optimal organization, and deviation from it might serve as a biomarker of brain dysfunction.

Besides torque on the anterior-occipital axis, asymmetry on the dorsal-ventral axis has also been reported, but less consistently or well described. An early study reported that the left hemisphere was shifted dorsally relative to the right (Best 1986), but recent work found the opposite pattern, i.e. the left hemisphere shifted significantly downward relative to the right (Xiang et al. 2019). Again, this latter pattern was reported to be human specific, in comparison to chimpanzees (Xiang et al. 2019). Variation in the 'vertical' asymmetry has not previously been linked to behavioural differences, or disorder risk, as far as we are aware.

It was posited in 1874 that "difference of [brain] structure of necessity implies difference in function" (Jackson 1874). However, it has proven surprisingly difficult to link brain structural asymmetries to lateralized functions (Batista-Garcia-Ramo & Fernandez-Verdecia 2018; Bishop 2013; Josse et al. 2003; Tzourio-Mazoyer & Mazoyer 2017). For example, handedness is one of the most clearly evident functional lateralization, such that in the general population roughly 90% of people are right-handed, and 10% left-handed (de Kovel et al. 2019; Peters et al. 2006). In a series of studies based on X-Ray Computed Tomography (CT), LeMay and colleagues reported that the right occipital lobe was more often wider than the left in left-handers, which was the opposite of that found in right-handers (Galaburda et al. 1978a; Le May & Kido 1978; LeMay 1976; LeMay 1977). Some researchers have even attempted to use the asymmetrical anatomy of skull endocasts to infer handedness in hominins (Holloway 2015; LeMay 1976; Smith 1925).

However, other investigations of the relationship between handedness and features of global brain asymmetry, including more recent ones with up-to-date methodology, have produced inconsistent or negative findings (Chiu & Damasio 1980; Kertesz & Geschwind 1971; Koff et al. 1986; Narr et al.

2007). It has therefore been noted that handedness and global brain asymmetry might not be associated at all, and in any case, their relationship is clearly far from absolute (Chiu & Damasio 1980; LeMay 1992; Narr et al. 2007; Steele 2000). Several MRI studies of regional structural asymmetries that may partly reflect global asymmetry, such as cortical thickness asymmetry of frontal and occipital regions, have also failed to find associations with handedness (Good et al. 2001; Herve et al. 2006; Kong et al. 2018; Watkins et al. 2001). Overall, the mixed results may reflect differences in many factors, including limited imaging quality in early studies, statistical power related to small sample sizes, and potential biases when measuring global asymmetry, perhaps especially for manual approaches. A large-scale survey using high-resolution imaging, and objective analysis, is therefore needed to understand the relevance of global brain asymmetry to handedness.

Population-level, average left-right differences of global brain anatomy suggest a genetic-developmental program that is inherently lateralized (de Kovel et al. 2017; de Kovel et al. 2018; Francks 2015; Ocklenburg et al. 2017). Torque has been observed in fetal brains by the second trimester of pregnancy (Weinberger et al. 1982), as have other region-specific brain asymmetries (Francks 2015), which further supports a genetic influence. McShane et al. reported left-right differences of occipital petalia and width that were related to ethnic origin, suggesting genetic contributions to variability (McShane et al. 1984). A recent, large-scale population study indicated a torque-like pattern of cortical thickness asymmetry, with frontal regions being generally thicker on the left hemisphere, and occipital regions thicker on the right (Kong et al. 2018). In the same study, twin- and family-based analysis found heritabilities of up to 15-20% for some of these regional cortical thickness asymmetry measures, for example in the lateral occipital and rostral middle frontal regions, which again suggests that genetic variability may affect global brain asymmetries. A study of vervet monkeys (Fears et al. 2011) also reported heritabilities of 10%-30% for measures of global brain asymmetry, which were methodologically very similar to those used in the present study, i.e. based on skewing brain MRI data in order to register to a symmetrical template (see below).

Regardless of the heritability findings, the specific genes involved in global brain asymmetry remain unknown. Early life factors that are known to influence handedness such as birthweight and multiple birth (de Kovel et al. 2019; Heikkila et al. 2018) could also contribute to global brain asymmetry, but this has not previously been studied in large population data.

Here, we present the largest-ever analysis of global brain asymmetry, in three independent datasets: the UK Biobank (N = 21,389), Human Connectome Project (HCP, N = 1,113) and BIL&GIN (N = 453, roughly balanced for left/right handedness). First, the two components of global brain asymmetry, i.e. the horizontal and vertical asymmetry skews, were extracted from brain MRI data for each individual, to capture global left-right differences along the anterior-posterior and dorsal-ventral axes. The reliability of these two measures was confirmed using a test-retest dataset from the HCP (N = 30). Next, we investigated the relationships of horizontal and vertical skews with handedness in each of the datasets. Then, we estimated the heritabilities of the horizontal and vertical skews using twin data in the HCP, and genome-wide genotype data in the UK Biobank. We also ran genome-wide association scans (GWAS) for the horizontal and vertical skew measures, using UK Biobank, to identify individual genetic loci that affect global brain asymmetry. Finally, we used extensive phenotypic data in the UK Biobank, including early life factors, psychosocial factors, regional grey and white matter

measures derived from the brain MRI, and variables related to cognitive functions and health, to explore other potential correlates of global brain asymmetry.

Materials and Methods

Datasets

UK Biobank. Data were obtained from the UK Biobank as part of research application 16066, with Clyde Francks as the principal applicant. This is a general adult population cohort. The data collection in the UK Biobank, including the consent procedure, has been described elsewhere (Sudlow et al. 2015). Informed consent was obtained by the UK Biobank for all participants. For this study, we used data from the October 2018 release of 21,389 participants' brain T1-wighted MRI data, after bias field correction and brain extraction (i.e. *T1_unbiased_brain.nii.gz*) (Alfaro-Almagro et al. 2018). The median age of the 21,389 subjects was 63 years, range 44 to 80 years, and 11,236 subjects were female. Handedness was assessed based on responses to the question: "*Are you right or left handed?*" with four response options: "*Right-handed*", "*Left-handed*", "*Use both right and left equally*", and "*Prefer not to answer*". Those who preferred not to answer were excluded for association analysis of global brain asymmetry with handedness, leaving 19,059 right-handers, 2,001 left-handers, and 324 'ambidextrous' with brain asymmetry measures. We also made use of genome-wide genotype data for single nucleotide polymorphisms (SNPs) as described previously (Bycroft et al. 2018), as well as other phenotypic data, including early life factors, psychosocial factors, regional grey and white matter measures that had already been derived from the brain imaging images, and variables related to cognitive functions and health. Information on these additional phenotype measures are available via the Data Showcase on the UK Biobank website (https://www.ukbiobank.ac.uk/).

Human Connectome Project. The HCP comprises 1,113 individuals with MRI data (606 females, age range 22-37 years at the time of scanning) of varying ethnicities (https://humanconnectome.org/). The HCP contains 143 monozygotic twin pairs and 85 dizygotic twin pairs, as well as unrelated individuals. Brain structure images, after bias field correction and brain extraction (i.e., files of type *T1w_acpc_dc_restore_brain.nii.gz*) (Glasser et al. 2013) were used for each subject. The strength of hand preference had been assessed with the Edinburgh Handedness Inventory (Oldfield 1971), resulting in scores ranging from -100 (strong left-hand preference) to 100 (strong right-hand preference). In addition, a test-retest dataset of MRI data acquired from 30 subjects was provided in the HCP project (i.e., HCP Retest) (20 females, age ranges from 22-35 years at the scanning time).

BIL&GIN. BIL&GIN ((Mazoyer et al. 2016); $N = 453$; 232 females, age ranges 18-57 years at the scanning time). A high resolution T1-weighted MRI image was used for each individual, and brain images after bias field correction and brain extraction (implemented in *FreeSurfer* v5.3; surfer.nmr.mgh.harvard.edu) were used. Unlike the UK Biobank and HCP which had natural population proportions of right-handers, BIL&GIN participants had been selected to be roughly balanced for handedness (248 right-handers and 205 left-handers), based on responses to the options: "*right-handed, left-handed, or forced left-handed*". The strength of hand preference had again been assessed with the Edinburgh Handedness Inventory (Oldfield 1971), resulting in scores ranging from -100 (strong left-hand preference) to 100 (strong right-hand preference).

Global Asymmetry Measurement from T1-weighted Brain Images

A registration-based approach was used for global asymmetry measurement (Fig. 1), similar to that previously used in a study of vervet monkeys (Fears et al. 2011). Specifically, for each individual participant, an affine transformation was applied to align the T1-weighted brain image (in native space) to the target template image (in the standard MNI space), and an affine transformation matrix was generated as an output. Image processing tools of *flirt* and *avscale* from FSL (version 5.0.10; fsl.fmrib.ox.ac.uk) were used for this analysis. The transformation matrix captures information about global shape differences between individual brain images and the target image, including scaling and skewing with respect to each axis. While the scaling factors are related to individual brain size, the skewing factors indicate the amount of global twisting to match the template. In order to measure left-right asymmetries, a left-right symmetrized template was used (i.e., ICBM 2009c Nonlinear Symmetric template). Here, we focused on skewing in the transverse (horizontal) and coronal (vertical) planes, to measure the two global asymmetry components, i.e. with respect to the frontal-occipital and dorsal-ventral axis, respectively (Fig. 2). A positive horizontal skew is closely akin to typical torque, i.e. the protrusions of the right frontal and left occipital regions, which has been reported as the average asymmetry pattern in the human brain (see Introduction). In contrast, a negative horizontal skew indicates a reversal of the typical pattern, with the left frontal and right occipital regions protruding. Similarly, a positive vertical skew indicates an overall twisting downward of the left hemisphere and upward of the right hemisphere, while a negative vertical skew indicates the opposite pattern.

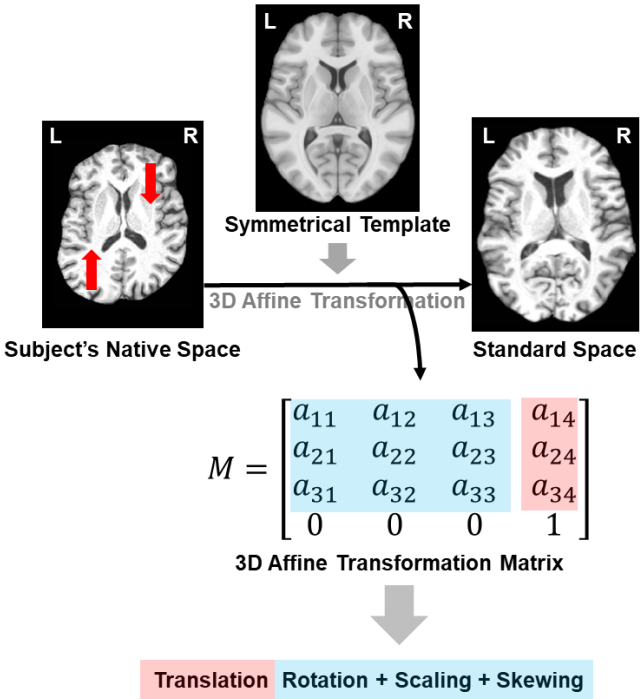

Fig. 1. A registration-based approach for estimating global asymmetry skewing. The transformation matrix from the registration procedure captures information about the position alignment (i.e., translation and rotation) as well as scaling, and the amount of skewing during registration. Red arrows indicate the direction in which the native space image is shifted during image registration. Transverse sections are shown, which illustrate the horizontal skew process.

Test-Retest Reliability of Global Asymmetry Measures

The HCP Retest data allowed us to quantify test-retest reliability of the two global asymmetry metrics. Intraclass correlation coefficients (ICC) were calculated using IBM SPSS 20 (Model: Two-Way Mixed; Type: Consistency), where the ICC is conceptualized as the ratio of between-subjects variance to total variance. The ICC is a value between 0 and 1, where 1 indicates perfect reliability (i.e., the within-subject variance is 0).

Association of Global Brain Asymmetry with Handedness

Association analyses of the horizontal and vertical skew measures were performed for each dataset separately, as per the availability of specific handedness measures and co-variables. In the UK Biobank, the asymmetry differences between handedness groups (-1=left, 0=both, 1=right, treated as a continuous variable) were assessed with linear regression models adjusted for sex, age, nonlinear age (z-transformed square of the age, $zage^2$), the first ten principal components (PCs) which capture genome-wide population structure in the genotype data (as made available by the UK Biobank (PC1-10)) (Bycroft et al. 2018), and several technical variables related to imaging (Alfaro-Almagro et al. 2018): imaging assessment center (binary), scanner position parameters (continuous X/Y/Z), and signal/contrast-to-noise ratio in T1 (continuous). To explore which handedness group differences mainly contributed to the results, we repeated the analyses with each pair of handedness groups (i.e., right-handers vs. left-handers; right-handers vs. both-handers; and both-handers vs. left-handers). To exclude possible outliers in asymmetry measures, we excluded subjects above/below 4 standard deviations from the mean, separately for the horizontal and vertical skew measures. In addition, analyses were repeated when additionally adjusting for brain volume (i.e., grey+white volume) and the brain-size related scaling factors indicated in Figure 1. Python's *pandas* (pandas.pydata.org) and *statsmodels* (www.statsmodels.org) packages were used for these analyses.

In the HCP dataset, asymmetry differences related to the strength of hand preference (ranging from -100 to +100, see above) were examined with linear regression models, adjusting for sex, age, nonlinear age ($zage^2$), '*Acquisition*' (a variable to control for possible scanner status differences across the study period of several years), and 'Race' (a variable given this label in the HCP data, to capture ethnicity). Analyses were repeated when additionally adjusting for brain volume ('*FS_IntraCranial_Vol*', intracranial volume estimated with FreeSurfer,) and the brain-size related scaling factors indicated in Figure 1. The HCP dataset included twins and siblings, and we therefore used Permutation Analysis of Linear Models (PALM, version alpha111) (Winkler et al. 2014) from FSL (version 5.0.10), which has a specialized function for accounting for possible non-independence caused by family structure. For this we used 10,000 permutations and calculated 2-tailed p values.

In the BIL&GIN dataset, asymmetry differences related to the strength of hand preference (again ranging from -100 to +100, see above) were examined with linear regression models, adjusting for sex, age, and nonlinear age ($zage^2$). Analyses were repeated when additionally adjusting for brain volume (again intracranial volume estimated with FreeSurfer) and the brain-size related scaling factors indicated in Figure 1. Python's *pandas* and *statsmodels* packages were used.

Heritability Estimation

In the UK Biobank, 550,192 autosomal, directly genotyped SNPs with minor allele frequencies (MAF) > 0.01, genotyping rate >0.95 and Hardy-Weinberg equilibrium (HWE) $p>1\times10^{-6}$ were used to build a genetic relationship matrix (GRM) using GCTA (version 1.26.0) (Yang et al. 2011). We excluded samples with a genotyping rate of <98% and a kinship coefficient higher than 0.025 based on this GRM, resulting in a sample size of 17,221. Genome-based restricted maximum likelihood (GREML) analyses using GCTA were performed to estimate the SNP-heritabilities for the horizontal and vertical skew measures, after residualizing for the covariate effects of sex, age, $zage^2$, the first ten principal components capturing genome-wide genetic structure (Bycroft et al. 2018), and several technical variables related to imaging as mentioned above. SNP-based heritability is a measure ranging from 0 to 1 which indicates the extent to which variation in a trait is influenced by the combined effects of variations at SNPs distributed over the genome (Vinkhuyzen et al. 2013). Bivariate analyses (Lee et al. 2012) were also run in GCTA, to investigate the SNP-based genetic correlations between the two global asymmetry measures. Genetic correlation analysis measures the extent to which variability in a pair of traits is influenced by the same genetic variations over the genome.

In addition, we also estimated SNP-based heritability of the two global asymmetry measures in the UK Biobank data using GWAS summary statistics for each measure (see below), using the LDSC package (https://github.com/bulik/ldsc) (Finucane et al. 2015).

Heritability could also be estimated in the HCP dataset, as it included monozygotic and dizygotic twin pairs, as well as unrelated individuals (see above). We estimated the heritability of each global asymmetry component using variance-component analysis implemented in SOLAR (Almasy & Blangero 1998). Briefly, each asymmetry component was entered as a dependent variable into separate linear mixed-effects models, which included fixed effects of sex, age, and nonlinear age ($zage^2$), and a random effect of genetic similarity, whose covariance structure was determined by the pedigrees. Genetic similarity for MZ pairs is coded as 1 as they share 100% of their DNA sequence, whereas DZ twins and siblings are coded as 0.5 as they share on average 50%, while unrelated individuals are coded as zero. Maximum likelihood-based bivariate variance decomposition analysis was also applied, again using SOLAR, to estimate the genetic correlation of the two global asymmetry measures.

Genome-wide Association Scans

Imputed SNP genotype data (bgen files; imputed data v3 – release March 2018) were extracted for the samples with global brain asymmetry measures (N =18,057), and SNP-level statistics were then computed within this set using QCtools (v.2.0.1). We excluded SNPs with a minor allele frequency below 0.001, Hardy-Weinberg p-value below 1×10^{-7} or imputation quality INFO scores below 0.7 (the latter as provided by the UK Biobank with the imputed data (Bycroft et al. 2018)), which resulted in 15,120,452 SNPs genome-wide. GWAS was performed with BGENIE (v.1.2) (Bycroft et al. 2017) for each of the residualized global asymmetry measures separately (after accounting for the same covariate effects as for SNP heritability analysis, above), using imputed genotype dosages and an additive model. Manhattan plots and QQplots were made using the "qqman" R package (Turner 2018), and regional association plots were made using LocusZoom (Pruim et al. 2010). We applied the widely-used threshold p value of 5e-08 to assign significance in the context of genome-wide multiple

testing, which accounts for the number of SNPs tested in a modern GWAS study, and the correlation structure between SNPs in European ancestry populations (Hoggart et al. 2008; Panagiotou et al. 2012).

Gene-wise and Gene-set Analyses

The summary statistics from each GWAS were loaded into the annotation and analysis platform FUMA (v1.3.4b) (Watanabe et al. 2017). We then derived gene-level association statistics using MAGMA (v1.07) (de Leeuw et al. 2015), as implemented in FUMA and using the default settings. In brief, the gene-wise test summarizes the degree of association between a phenotype and all SNPs within a given gene (de Leeuw et al. 2015). A significance threshold of $p < 2.532e\text{-}6$ (i.e., 0.05/19747) was applied to correct for multiple testing across all protein coding genes (Ensembl version v92; n = 19,747). The gene-level association statistics were in turn used to perform gene-set enrichment analysis, again using MAGMA, for curated gene sets and gene ontology (GO) terms (Ashburner et al. 2000) (n = 10676) obtained from MsigDB (v6.2) (http://software.broadinstitute.org/gsea/msigdb), and Bonferroni correction was performed. This approach tests whether the genes in a given set show, on average, more evidence for association with the trait in question than the rest of the genes in the genome for which scores could be calculated, while accounting for non-independence of SNPs due to linkage disequilibrium (LD).

Other Variables Associated with Global Brain Asymmetry

The UK Biobank dataset includes many variables, including early life factors, psychosocial factors, derived imaging traits, and variables related to cognitive functions and health. We ran a Phenome-wide Association Scan (pheWAS) analysis for each global asymmetry component, to screen for other associated variables besides handedness and genetic data. We used the package PHEnome Scan Analysis Tool (PHESANT) (Millard et al. 2017), which enables comprehensive phenome scans to be performed across all data fields in the UK Biobank. PHESANT uses a rule-based method to automatically determine how to test each variable. The decision rules start by assigning each variable as one of four types: continuous, ordered categorical, unordered categorical, or binary. A description of PHESANT's automated rule-based method is given in detail elsewhere (Millard et al. 2017). PHESANT then estimates the bivariate association of an independent variable of interest (in our case either horizontal or vertical brain asymmetry) with each dependent variable in the dataset. Dependent variables with continuous, binary, ordered categorical, and unordered categorical data types, are tested using linear, logistic, ordered logistic, and multinominal logistic regression, respectively. Prior to testing, an inverse normal rank transform is applied to variables of the continuous data type. All analyses were adjusted for covariates as in the handedness association analyses (see above).

We corrected for multiple testing using Bonferroni correction, with a significance threshold determined by dividing 0.05 by the number of tests performed, separately for the horizontal and vertical asymmetry measures as independent variables. We also looked up the results for some variables of particular interest in relation to global brain asymmetry (see Results), which did not necessarily survive multiple testing correction over all phenotypes tested, in which case we report the nominal P values. In addition, we visualized our results as D3.js graphs using tools included in the

PHESANT package, and made the graphs online for easy access (https://github.com/Conxz/gbaphewas). This enables comparison of the identified associations with results for other, possibly related variables.

Finally, as language is a prominently lateralized and human-specific function (Gazzaniga 2009; Price 2012), we ran association analyses between the two global asymmetry components and a set of behavioral performance measures related to language, which were available in the HCP dataset. The tasks included the Penn Word Memory Test, Language Task for fMRI, and the NIH Toolbox Oral Reading Recognition Test and Picture Vocabulary Test (Barch et al. 2013). PALM was again used for accounting for family structure in the statistical analyses (see above). Multiple testing was corrected using the Bonferroni method (corrected $p < 0.05$).

Results

Global Brain Asymmetry in the UK Biobank, HCP, and BIL&GIN datasets

We extracted two global asymmetry components for each individual. A positive score for horizontal skew indicates a global pattern in which the right hemisphere is shifted anteriorly relative to the left, while a negative score indicates that the left hemisphere is shifted anteriorly relative to the right (see Fig. 2 and Supp. Fig. 1 for examples). Note that the skew is calculated as a global feature, not a feature of any particular slice (Supp. Fig. 1). Similarly, a positive score for vertical skew indicates a global shift downwards of the left hemisphere relative to the right, while a negative vertical skew indicates the opposite pattern (Fig. 2, Supp. Fig. 2). Both asymmetry components showed almost perfect reliability (horizontal skew: $ICC = 0.989$; vertical skew: $ICC = 0.977$) as indicated in the test-retest dataset (Fig. 2; HCP Retest, $N = 30$).

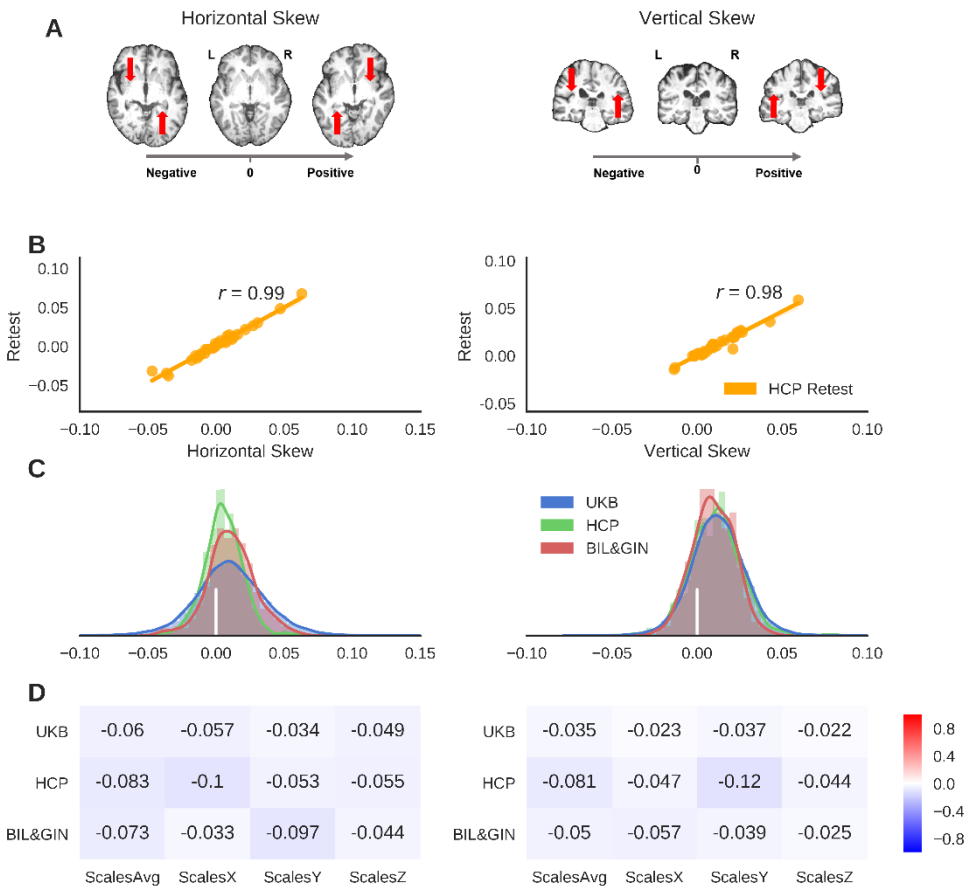

Fig. 2. Global brain asymmetry: the horizontal and vertical skews. (A) Examples of the human brain with different asymmetry skew scores. The right-pointing grey arrow indicates the axis of the skew scores from negative to positive. The red arrows indicate the skewing needed for each brain during image registration (i.e., registration of the native space brain to a symmetrical template). (B) Scatter plots of the asymmetry skews in the HCP Retest dataset, with the Pearson correlation coefficients. (C) Distributions of the asymmetry skew scores in the three datasets: UK Biobank in blue, HCP in green, and BIL&GIN in red. The vertical bar in white indicates the position of zero skewing. (D) The Pearson correlation coefficients of the asymmetry skew scores with brain size-related scaling factors in the three-dimensions (ScalesX/ScalesY/ScalesZ) and their average (ScalesAvg).

The average values of both asymmetry components were positive in the three independent datasets (Fig. 2), confirming a population-level pattern of global asymmetry. For horizontal skew, the average pattern involved protrusions of the right frontal and left occipital regions (UK Biobank: $N = 21{,}389$, *Mean* =0.0105, *Std* = 0.025; HCP: $N = 1113$, *Mean* = 0.0054, *Std* = 0.014; BIL&GIN: $N = 453$, *Mean* = 0.011, *Std* = 0.017). One sample t-testing indicated a significant difference of each dataset mean from zero (UK Biobank: $t(21{,}388) = 60.00$, $p < 5.00\text{e-}100$; HCP: $t(1112) = 12.56$, $p = 5.96\text{e-}34$; BIL&GIN: $t(452) = 14.14$, $p = 7.68\text{e-}38$). The population average horizontal skew matches the widely-observed features of brain torque (e.g., frontal/occipital petalia) in the human brain (See Introduction and e.g. Thompson et al., 2003).

Regarding the vertical asymmetry skew, the sample means were again all positive (UK Biobank: *Mean* = 0.0122, *Std* = 0.0156; HCP: *Mean* = 0.011, *Std* = 0.015; BIL&GIN: *Mean* = 0.0097, *Std* = 0.012), indicating an average pattern involving downward skewing of the left hemisphere relative to the right. Again the means were significantly different from zero in each dataset (UK Biobank:

$t(21{,}388) = 114.59$, $p < 5.00e\text{-}100$; HCP: $t(1112) = 24.48$, , $p < 5.00e\text{-}100$; BIL&GIN: $t(452) = 16.96$, $p = 2.90e\text{-}50$). Notwithstanding the average asymmetry patterns, the distributions of the vertical and horizontal skews showed considerable individual differences, with e.g. 33% of participants showing a reversal compared to the average horizontal pattern, and 20% showing a reversal compared to the average vertical pattern, in the UK Biobank dataset (Fig. 2). The horizontal and vertical skews showed very low correlations with brain-size-related scaling factors in the three datasets (Fig. 2): UK Biobank ($|r|$s < 0.06), HCP ($|r|$s < 0.12), and BIL&GIN ($|r|$s < 0.10). Therefore, global brain asymmetries are largely independent of brain size. Also, the two asymmetries showed low correlations with each other, and these were inconsistent in strength and direction among the three datasets: UK Biobank (r = 0.126), HCP (r = -0.170), BIL&GIN (r = -0.030), such that the two components of global brain asymmetry appear largely independent in their variabilities.

Global Brain Asymmetry and Handedness

We found significant associations between handedness (left coded as -1, N = 2001; ambidextrous coded as 0, N = 324; right coded as 1, N = 19059) and both asymmetry components in the UK Biobank (Fig. 3; horizontal skew: t = 5.13, p = 2.99e-07; vertical skew: t = -7.52, p = 5.84e-14). These were mainly contributed by group differences between left-handers and right-handers (horizontal skew: t = 5.00, p = 5.70e-07, d = 0.120; vertical skew: t = -7.56, p = 4.35e-14; d = 0.182). These results show that right-handers, compared with left-handers, are more likely to show skew along the anterior-posterior axis in the same direction as the population average pattern (i.e., more positive horizontal skew scores). However, on the dorsal-ventral axis, left-handers are more likely to show skew in the same direction as the population average pattern (i.e., more positive vertical skew scores). In addition, a difference was found when comparing vertical skew between left-handers and ambidextrous participants (t = -2.04, p = 0.041), while no other comparisons between handedness groups showed significant effects (ps > 0.15).

The HCP dataset confirmed the asymmetry differences related to left and right hand preference. Here, a continuous index of the strength of hand preference was available, from -100 (left) to 100 (right), and the analysis accounted for family structure (see Methods). Again, horizontal skew was positively associated with right-hand preference (Z = 3.30, p = 0.0021), and vertical skew was positively associated with left-hand preference (Z = -3.83, p = 0.0002) (Fig. 3).

The BIL&GIN dataset further confirmed the finding with respect to vertical skew, i.e. this was again positively correlated with increased left-hand preference, t = -3.33, p = 0.00095 when using the hand preference scale from -100 to 100, and t = -3.61, p = 0.00035 when using a binary handedness assessment, see Methods (Left: N = 205; Right: N = 248). However, in this dataset, the association of hand preference with horizontal skew was not significant, t = 0.77, p = 0.44 for the continuous hand preference scale, and t = 0.81, p = 0.42 for binary handedness. Nonetheless, the direction of this non-significant association in BIL&GIN was consistent with the UK Biobank and HCP datasets. The BIL&GIN dataset provided only 35% power to detect the association of horizontal skew with handedness at alpha 0.05, according to the effect size of this association in the UK Biobank (Cohen's d = 0.120). The non-significant association between horizontal skew and handedness in BIL&GIN is therefore likely to be a power issue, due to relatively limited sample size (whereas for the association

with vertical skew, BIL&GIN provided 61% power at alpha 0.05, in relation the UK Biobank effect size $d = 0.182$).

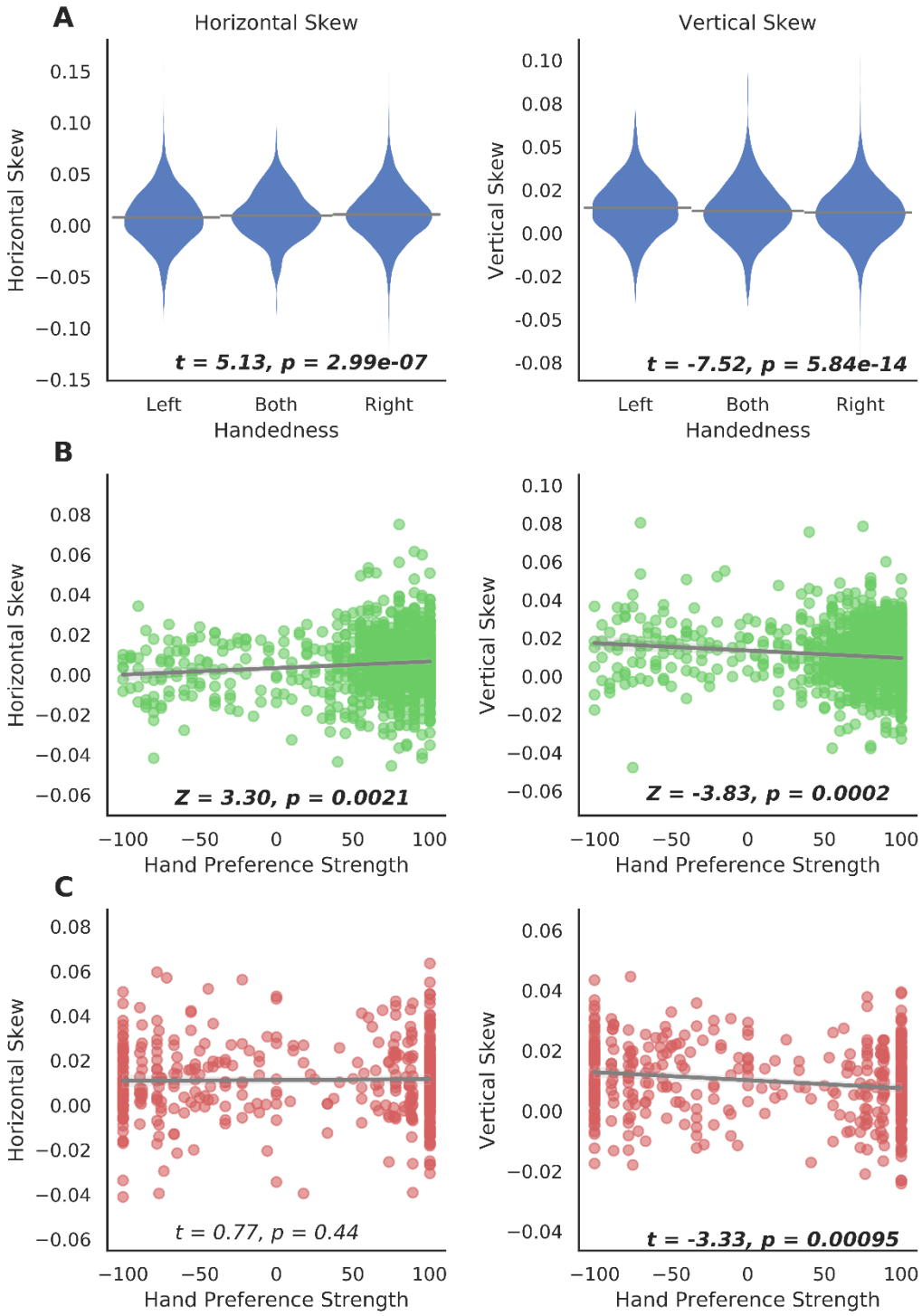

Fig. 3. Global asymmetry skews and hand preference. (A) Differences in global asymmetry measures between handedness groups in the UK Biobank. (B) Scatter plots of global asymmetry measures and hand preference strength in the HCP. (C) Scatter plots of global asymmetry measures and hand preference strength in BIL&GIN. Note that the statistical tests of association were based on analyses with covariate effects being controlled for, whereas data are plotted here without adjusting for covariates, for display purposes.

When adjusting vertical skew for horizontal skew, and vice versa, the associations of both asymmetry variables with hand preference remained very similar (UK Biobank, three handedness groups, horizontal skew, t = 5.93, p = 2.99e-09; vertical skew, t = -8.09, p = 6.24e-016: HCP, horizontal skew, Z = 2.69, p = 0.011; vertical skew, Z = -3.32, p = 0.0006: BIL&GIN, hand preference strength, horizontal skew, t = 0.67, p = 0.50; vertical skew, t = -3.57, p = 0.00039). This indicates that handedness is primarily associated independently with the two asymmetry variables, rather than with any shared variance between them.

In the UK Biobank, there was a significant association between handedness (including left, ambidextrous and right groups) and one of the brain-size-related scaling factors (i.e., ScalesY: scaling in the anterior-posterior direction, t = -3.65, p = 0.00026). However, this association did not replicate in the HCP (ts<1) or BIL&GIN datasets (ts<1 except for ScalesZ: scaling in the superior-inferior direction, t = 1.75, p = 0.08). Moreover, when controlling for these scaling factors related to brain size, associations between hand preference and the global asymmetries remained unchanged (UK Biobank, three handedness groups, horizontal skew, t = 5.16, p = 2.51e-07; vertical skew, t = -7.65, p = 2.17e-14; HCP, horizontal skew, Z = 3.38, p = 0.0014; vertical skew, Z = -3.60, p = 0.0004; BIL&GIN, hand preference strength, horizontal skew, t = 0.89, p = 0.38; vertical skew, t = -3.38, p = 0.00079).

Heritability Estimation and Genetic Correlation

In the UK Biobank, low SNP-based heritabilities of around 5% were found for horizontal skew (h^2 = 5.4%, se = 0.033, p = 0.048 with GCTA; h^2 = 4.9%, se = 0.025, p = 0.051 with LDSC) and vertical skew (h^2 = 4.5%, se = 0.033, p = 0.082 with GCTA, h^2 = 5.2%, se = 0.024, p = 0.032 with LDSC). In the HCP dataset, which included twins, both global asymmetry measures showed relatively higher heritabilities: horizontal skew h^2 = 9.1%, p = 0.041; vertical skew h^2 = 10.1%, p = 0.030. These findings suggest that genetic variability influences global brain asymmetry, but that most of the variance is not genetic.

Similarly, handedness showed a low heritability in both the UK Biobank (h^2 < 0.001) and the HCP (h^2 < 0.001), which is in line with previous analyses of the UK Biobank (e.g., (de Kovel et al. 2019)). No significant genetic correlations of hand preference with global asymmetries were observed in either the UK Biobank or HCP datasets (ps > 0.10), indicating that genetic factors for global brain asymmetries and handedness are largely or wholly independent.

Scaling factors showed high heritabilities in both the UK Biobank (ScalesAvg: h^2 = 72.5%, se = 0.036; ScalesX: h^2 = 56.2%, se = 0.037; ScalesY: h^2 = 47.5%, se = 0.036; ScalesZ: h^2 = 60.2%, se = 0.036) and the HCP (ScalesAvg: h^2 = 92.1%, se = 0.0096; ScalesX: h^2 = 85.5%, se = 0.018; ScalesY: h^2 = 85.0%, se = 0.018; ScalesZ: h^2 = 86.6%, se = 0.016), which was expected because of the high heritability of brain size (UK Biobank: h^2 = 72.3%, se =0.037 ; HCP: h^2 = 87.8%, se = 0.015). There were no significant genetic correlations between these scaling factors and the global brain asymmetry measures (ps > 0.10), except for a consistent negative genetic correlation between horizontal skew and ScalesX (scaling in the left-right axis) (UK Biobank: r_g = -0.303, se = 0.159, p = 0.0157; HCP: r_g = -0.291, se = 0.156, p = 0.0341). Thus some of the same genetic variability which contributes to a wider brain may also result in a more positive horizontal skew (e.g., anterior shift of the right hemisphere).

Genome-wide Association Scans of Global Brain Asymmetry Measures

We ran GWAS for each of the two global brain asymmetry components. The distributions of *p*-values did not reveal evidence of inflation of test-statistics (horizontal skew: λ= 1.0091; vertical skew: λ=1.0058) (for QQ-plots see Supplemental Fig. S3). One locus was significantly associated with horizontal skew, and three loci with vertical skew, using a genome-wide significance threshold of 5e-8, although each of these loci only just surpassed the threshold (Fig. 4, S4).

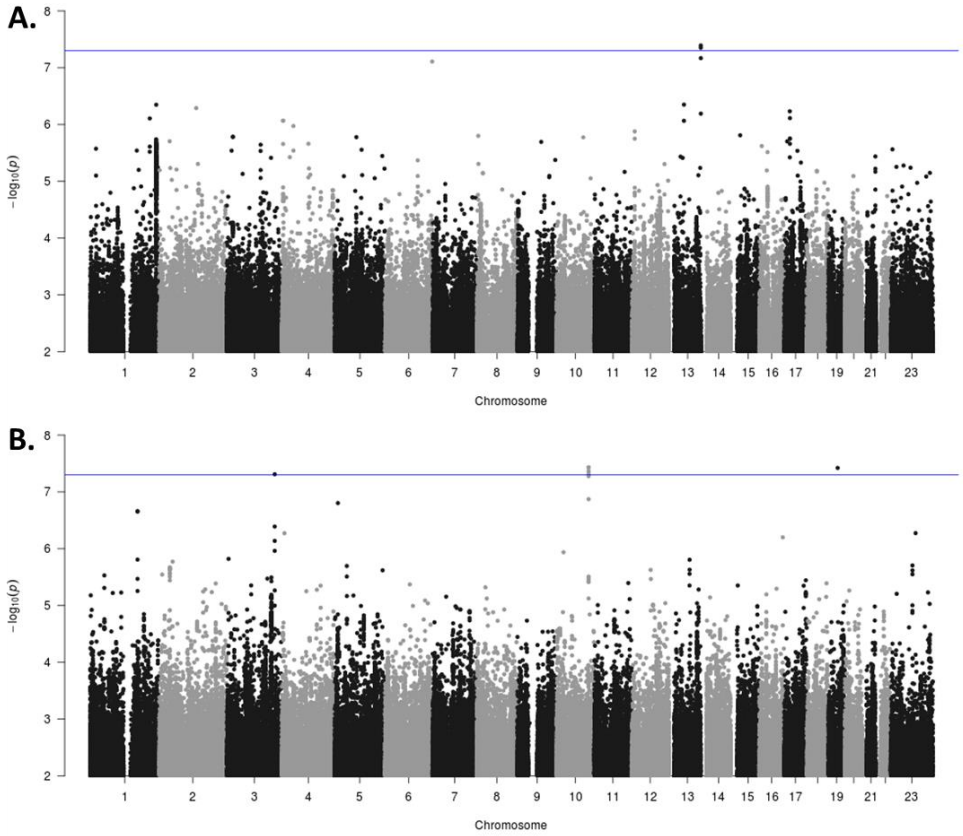

Fig. 4. Manhattan Plots for GWAS analyses. (A) Horizontal skew. (B) Vertical skew. Blue lines indicate the threshold for genome-wide significance (p < 5e-08).

Regarding the horizontal component, the only significant locus was on chromosome 13 (lead SNP rs139309608: T/A, MAF(T)=0.17%, additive effect of T allele t = -5.49, p = 4.01e-08; Table S1), located within an intron of *TMEM255B* (transmembrane protein 255B). Additional SNPs in high LD with this SNP, or with association p values less than 5e-7 elsewhere in the genome, are listed in Table S1.

Regarding the vertical component, the three genome-wide significant loci (lead SNPs) were rs576289 (chr.10, A/G, MAF(A)=3.36%, additive effect of increasing A alleles t = 5.51, p =3.64e-08), rs138596065 (chr.19, GC/G, MAF(GC)=8.28%, additive effect of increasing GC alleles t = -5.50, p =3.74e-08), and rs17759085 (chr.3, T/C, MAF(T)=19.90%, additive effect of increasing T alleles t = -5.46, p =4.83e-08). These three lead SNPs are located in introns or intergenic regions, within or close to the genes *RNU7-165P* (RNA, U7 small nuclear 165 pseudogene), *DPY19L3* (dpy-19 like C-mannosyltransferase 3), and *SPATA16* (spermatogenesis associated 16), respectively. Additional SNPs

in LD with these lead SNPs, or with association *p* values below 5e-7 elsewhere in the genome, are listed in Table S2.

After adjusting the global asymmetry measures for brain size, the four genetic associations (one for horizontal skew and three for vertical skew) remained significant (*p*s < 5e-08) (Table S3). None of these four loci were associated with left-handedness in recently published GWAS results for this trait in the UK Biobank (*p*s > 0.15) (de Kovel et al. 2019) (note that the GWAS analysis for handedness made use of over 300,000 UK Biobank participants, regardless of whether brain MRI data was available) (Table S3).

Gene-wise and Gene-set Analyses

At the gene-level, MAGMA analyses revealed four additional genome-wide significant associations with horizontal skew (threshold $p < 2.532e-6$, i.e., 0.05/19747 protein coding genes). These were *SEZ6L2* (chr.16, seizure related 6 homolog like 2: $Z = 5.06$, $p = 2.07e-07$), *ASPHD1* (chr.16, aspartate beta-hydroxylase domain containing 1: $Z = 4.84$, $p = 6.4e-07$), *SLC5A8* (chr.12, solute carrier family 5 member 8: $Z = 4.72$, $p = 1.20e-06$), and *HEATR6* (chr.17, HEAT repeat containing 6: $Z = 4.68$, $p = 1.42e-06$). There were two genes significantly associated with vertical skew: *FAM117B* (chr.2, family with sequence similarity 117 member B: $Z = 4.80$, $p = 7.86e-07$) and *B3GALNT1* (chr.3, beta-1,3-N-acetylgalactosaminyltransferase 1: $Z = 4.76$, $p = 9.48e-07$).

At the gene-set level, no enrichment of association signals survived multiple testing correction for either horizontal or vertical asymmetry ($p < 0.05$, Bonferroni-corrected). Gene sets showing uncorrected enrichment *p* values less than 0.005 are shown in Table S4 and S5. These include '*GO_bp:go_corpus_callosum_development*' for horizontal asymmetry, $p = 0.00089$, which is potentially relevant given that interhemispheric connectivity via the corpus callosum may influence brain laterality (Karbe et al. 1998), and "*GO_bp:go_microtubule_bundle_formation*" for vertical asymmetry, $p = 0.0012$, potentially relevant to left-right patterning of the visceral organs in various organisms (e.g., (Chang et al. 2011)).

Additional Measures Associated with Global Brain Asymmetry

In the UK Biobank dataset, we ran pheWAS analysis to search for other variables associated with the horizontal or vertical components of global brain asymmetry. The pheWAS analysis included 2645 tests per asymmetry component. Note that some variables tested might only be considered as phenotypes in a very broad sense, such as country of birth, or home area population density.

For each of the two global asymmetry components, the pheWAS QQ plot is shown in Fig. S5, and the full results and an interactive visualization can be found at https://github.com/Conxz/gbaphewas. There were 354 associations below the Bonferroni corrected threshold of 1.89e-05 (0.05/2645) for horizontal skew, and 178 associations for vertical skew. The overwhelming majority (346 out of 354) for horizontal skew were associations with other structural brain imaging variables, e.g., diffusion brain MRI - "*Mean MO in cingulum hippocampus on FA skeleton (left)*": $N = 19385$, $beta = -0.19$, $p = 7.40e-155$, and T1 structural brain MRI - "*Volume of grey matter in Parahippocampal Gyrus, posterior division (right)*": $N = 21389$, $beta = 0.11$, $p = 2.4e-55$. For horizontal skew, there were also 4 significant cognitive function variables, under the categories of pairs matching and fluid intelligence,

plus 1 mental health variable related to depression, as well as "*Country of birth*": most positive score in '*Wales*', least in '*Republic of Ireland*', and two sociodemographic variables ("*Age completed full time education*"; "*Home area population density*" with "*England/Wales - Urban - less sparse*" as baseline: most positive score in '*England/Wales - Hamlet and Isolated Dwelling - less sparse*', least in '*Scotland - Other Urban Area*') (Table 1).

Table 1. pheWAS results for horizontal skew, showing only the results that were significant after multiple testing correction. Please see Table S6 for all of the imaging variables.

FIELD ID	DESCRIPTION	CATEGORY	N	BETA	P
25000-25920	**346 brain imaging variables**	**Brain MRI – Imaging**	**19385-21389**	**-**	**-**
398	Number of correct matches in round	Pairs matching - Cognitive function	21005	-0.17	< 1.00E-155
4935	FI1 : numeric addition test	Fluid intelligence - Cognitive function	7517	-0.0056	< 1.00E-155
20244	Pairs matching completion status	Pairs matching - Cognitive function online	11387	-0.021	6.28E-116
20131	Number of correct matches in round	Pairs matching - Cognitive function online	11383	0.0065	4.01E-08
20518	Recent changes in speed/amount of moving or speaking	Depression - Mental health	15580	-0.047	1.29E-144
1647	Country of birth	Early life factors	21379	NA	1.15E-05
845	Age completed full time education	Education - Sociodemographics	11706	-0.085	2.89E-06
20118	Home area population density	Location - Sociodemographics	21206	NA	1.69E-82

Regarding the vertical asymmetry component, again the significant associations were mostly (169 out of 178) with brain imaging variables, e.g., Diffusion brain MRI - "*Mean L1 in cerebral peduncle on FA skeleton (right)*": $N = 19385$, $beta = 0.13$, $p = 2.39e\text{-}93$ and T1 structural brain MRI - "*Volume of grey matter in Occipital Pole (right)*": $N = 21389$, $beta = -0.048$, $p = 7.45e\text{-}15$. There were also significant associations with 6 cognitive performance variables related to pairs matching, reaction time, fluid intelligence and symbol digit substitution, 1 mental health variable related to depression, 1 early life factors ("*Country of birth*": most positive score in '*Wales*', least in 'Northern Ireland'), and 1 sociodemographic variable ("*Home area population density*" with code '*England/Wales - Urban - less sparse*' as baseline: most positive score in '*England/Wales - Village - less sparse*', least in '*Scotland - Accessible Small Town*') (Table 2).

Table 2. pheWAS results for vertical skew, showing only the results that were significant after multiple testing correction. Please see Table S7 for all of the imaging variables.

FIELD ID	DESCRIPTION	CATEGORY	N	BETA	P
25000-25920	**169 brain imaging variables**	**Brain MRI – Imaging**	**19385-21389**	**-**	**-**
398	Number of correct matches in round	Pairs matching - Cognitive function	21005	-0.03	< 1.00E-155
403	Number of times snap-button pressed	Reaction time - Cognitive function	21013	0.016	< 1.00E-155
4935	FI1 : numeric addition test	Fluid intelligence - Cognitive function	7517	0.082	< 1.00E-155
20245	Symbol digit completion status	Symbol digit substitution - Cognitive function online	11483	-0.1	< 1.00E-155
20131	Number of correct matches in round	Pairs matching - Cognitive function online	11383	-0.0089	< 1.00E-155
20244	Pairs matching completion status	Pairs matching - Cognitive function online	11387	0.0021	1.50E-35
20518	Recent changes in speed/amount of moving or speaking	Depression - Mental health	15580	-0.049	< 1.00E-155
1647	Country of birth	Early life factors	21379	NA	7.55E-80
20118	Home area population density	Location - Sociodemographics	21206	NA	3.09E-82

We looked further into the pheWAS results for brain imaging variables. Forty-four regional grey matter volumes showed significant associations (after multiple testing for all phenotypes tested) with horizontal skew, which together formed a global anterior-posterior "torque" pattern: right frontal and left occipital volumes positively correlated with horizontal skew, while left frontal and right occipital regions negatively correlated with horizontal skew (Fig. 6). This confirms that torque manifests not only as a relative shifting of the hemispheres, but also as interhemispheric regional imbalances of grey matter volume (Kong et al. 2018). Six regional grey matter volumes showed significant associations with vertical skew, again with a clearly complementary interhemispheric pattern: left inferior, medial temporal and occipital regions correlated positively with vertical skew, while the homologous regions in the right hemisphere showed negative correlations with vertical skew (Fig. 6). Similarly, both horizontal skew and vertical skew showed significant associations with properties of various white matter tracts widely distributed across the brain, and more importantly, these associations were usually in opposite directions for the contralateral tracts (see Fig. S6, S7).

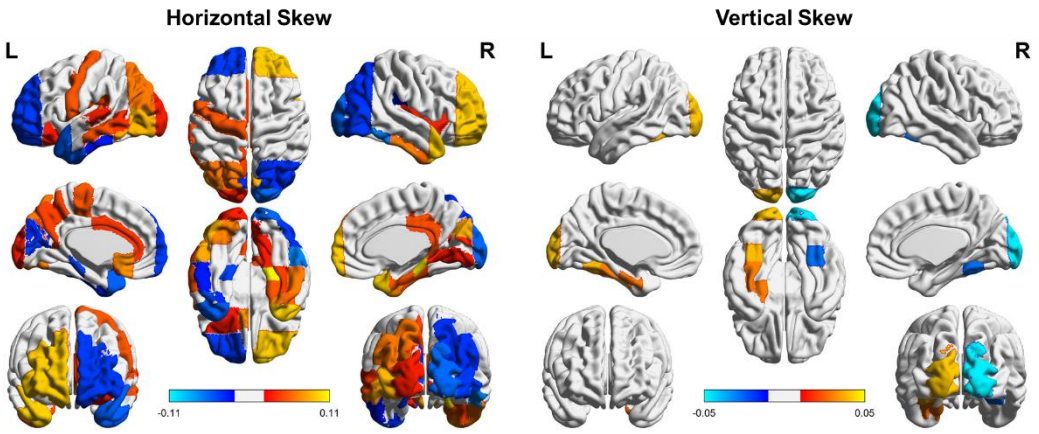

Fig. 6. Associations of global asymmetry components with regional grey matter volumes. Red-yellow indicates a positive association; blue indicates a negative association.

Certain early life factors have been shown to influence handedness in the UK Biobank, including birthweight, multiple birth, breastfeeding, and country of birth (de Kovel et al. 2019). Maternal smoking was not found to influence handedness in the UK Biobank (de Kovel et al. 2019), although has been implicated in handedness by other studies (e.g. (Dragovic et al. 2013)). We looked specifically into the pheWAS results for these early life factors, for the two global brain asymmetry measures. In addition to country of birth as already mentioned above, breastfeeding (N = 17055, *beta* = 0.069, p = 0.00013) and maternal smoking (N = 18798, *beta* = -0.038, p = 0.018) showed nominally significant associations with vertical skew, while other associations were not significant (ps > 0.05).

Finally, analysis of behavioral measures related to language in the HCP showed a positive correlation between horizontal skew and oral reading recognition performance (Z = 3.37, p = 0.00075, permuted p = 0.0023), such that individuals with more positive horizontal skew showed better oral reading recognition ability. No significant genetic correlation was observed between these measures, based on twin analysis in the HCP (p = 0.54). In addition, we found no significant associations with other behavioral measures in the HCP (ps > 0.10).

Discussion

Here, we present the largest-ever analysis of global brain shape asymmetry, i.e., the horizontal and vertical asymmetry skews, in three independent datasets. At the population level, there was an anterior and dorsal skew of the right hemisphere, relative to the left. The population variances of these skews were largely independent, but both were associated with handedness, as well as various regional grey and white matter metrics. Both skews also showed heritabilities of 5%-10%, and four significant loci were identified in genome-wide association scanning. Several phenotypic variables related to early life experiences, cognitive functions, and mental health showed significant associations with the skew measures.

Global Brain Asymmetry

We measured the anterior-posterior and superior-inferior aspects of global left-right asymmetry in the human brain, using three population datasets and an automated, registration-based approach. The approach contrasts with older, manual methods for evaluating global asymmetry, or approaches using regionally restricted frontal and/or occipital hemispheric differences as proxies for overall torque (e.g., (Barrick et al. 2005; Bear et al. 1986; Fullard et al. 2019; LeMay 1976; Maller et al. 2014; Van Essen et al. 2012). Rather, the registration-based approach of the present study allowed an automatic and objective assessment of global asymmetry based on skewing transformation of the brain as a whole. This provides a truly global measure of left-right asymmetry in the human brain. Moreover, the skew metrics in the present study showed high test-retest reliability.

We found population-level asymmetrical skews on both the horizontal and vertical axes. The average horizontal skew pattern was consistent with previously-observed features of brain torque in the human brain, involving a more anteriorly protruding right frontal lobe and posteriorly protruding left occipital lobe (i.e., frontal/occipital petalia), and relative increases in the dimensions (e.g., volume and width) of the right frontal and left occipital poles (see (Toga & Thompson 2003) for a review).

The horizontal skew may also relate to a population-level, frontal-occipital asymmetry gradient in regional cortical thickness, recently reported in a large-scale study (Kong et al. 2018). Indeed, we also observed in the present study that individual differences in horizontal skew showed positive correlations with grey matter volumes of right frontal and left occipital regions, and negative correlations with left frontal and right occipital regions, again in line with previously described features of brain torque (Toga & Thompson 2003).

The mean population-level asymmetry pattern in the vertical plane, i.e. along the inferior-superior axis, involved an overall twisting of the left hemisphere downward, and right hemisphere upward. This aspect of global brain asymmetry has not been described consistently in the literature, but we found it to be replicable in the three independent cohorts of this study. Our findings are also consistent with another recent report that the left-occipital pole is shifted significantly downward relative to the right, on average (Xiang et al. 2019). We found that individual differences in vertical skew correlated positively with grey matter volumes of left inferior temporal regions and the occipital pole, while correlating negatively with the homologous regions of the right hemisphere.

Both components of global brain asymmetry showed significant associations with numerous, widely distributed regional brain imaging measures and white matter tracts. On the one hand, this suggests that global asymmetry is not simply a spatial displacement of the left and right hemispheres with respect to one another, but also relates to structural differences between the two hemispheres, and thus likely indicates functionally meaningful hemispheric differences. On the other hand, the widely distributed regional associations with both components of global brain asymmetry indicate pervasive hemispheric differences affecting many regions and structures from front to back, and top to bottom. In addition, given that the global asymmetry measures correlated with both regional grey matter volumes and white matter properties, our analysis does not support a previous suggestion that brain torque is driven by white but not grey matter (Allen et al. 2003).

An aspect that was inconsistent across datasets in the present study was the relationship between individual differences in the horizontal and vertical components of global asymmetry. Specifically, a positive correlation of 0.13 was found in the UK Biobank, but a negative correlation of similar magnitude was observed in the HCP, and no correlation was present in the BIL&GIN. While further investigations with comparably large sample sizes to the UK Biobank are needed, these results suggest that the two components of global asymmetry vary largely or wholly independently of each other. The absence of genetic correlation between the two components further supported this independent nature. Therefore, separate consideration of these two aspects of global brain asymmetry will be important in future studies of functional significance or underlying mechanisms.

As abnormal brain asymmetry patterns have been reported in a variety of cognitive and neuropsychiatric disorders, including dyslexia (Pieniadz et al. 1983), Alzheimer's disease (Thompson et al. 1998), attention-deficit/hyperactivity disorder (Shaw et al. 2009), autism (Eyler et al. 2012), obsessive-compulsive disorder (Kong et al. 2019), and mood disorders (Liu et al. 2016; Yucel et al. 2009), the two measures of global asymmetry used in the present study might usefully be analyzed in future studies of these disorders. For example, the HCP dataset showed a positive correlation between horizontal asymmetry and oral reading recognition ability in our analysis. In the UK Biobank, there were significant associations of both horizontal and vertical brain skew with a depression-related

variable, '*Recent changes in speed/amount of moving or speaking*'. This may be consistent with previous reports of altered occipital bending in major depression (Fullard et al. 2019; Maller et al. 2014). In general, these findings suggest that variation in global brain asymmetry can affect lateralized functions. Moreover, the automated measurement of global asymmetry that we have employed here is feasible for large-scale meta-analysis-based studies of brain disorders, such as those carried out within consortia such as ENIGMA (http://enigma.ini.usc.edu/) (Thompson et al. 2019; Thompson et al. 2014).

Global Brain Asymmetry and Handedness

We found significant associations between both horizontal and vertical skews with handedness, or the strength of hand preference. On average, left-handers showed relatively lower horizontal asymmetry scores than the right-handers, i.e. reduced asymmetry along the anterior-posterior axis, and higher vertical asymmetry scores, i.e., increased asymmetry along the dorsal-ventral axis. The effect sizes were small, e.g. in the UK Biobank Cohen's $d = 0.12$ for the handedness association with horizontal skew, and $d = 0.18$ for vertical skew. However, particularly in the large UK Biobank dataset, the significance levels were unambiguous (p value as low as 5.00e-14 for handedness with vertical skew).

As regards the horizontal component, previous results with regard to handedness have been mixed, with some reports finding an association (Galaburda et al. 1978a; Le May & Kido 1978; LeMay 1976; LeMay 1977), and others not (Chiu & Damasio 1980; Kertesz & Geschwind 1971; Koff et al. 1986; Narr et al. 2007). All three of our datasets showed the same direction of effect for the association between handedness and horizontal skew, although limited statistical power to detect this effect in the BIL&GIN dataset ($N = 453$) is likely to explain that the association was not significant in this specific dataset. For the vertical skew, the association with handedness was again consistent in direction across all three datasets, and also significant in all three. The association of handedness with the vertical component of global brain asymmetry is a novel finding, as far as we are aware.

Given the small effect sizes in our study, it is clear that inferring the handedness of individuals from their global brain asymmetry is unlikely to be possible. Anatomists and anthropologists have long noted a potential link between left-handedness and brain asymmetry, which was initially considered to involve localized thinning and protrusions of the skull, such that attempts have even been made to use skull endocasts to infer the evolution of handedness in hominins (Holloway 2015; LeMay 1976; LeMay 1992; Smith 1925). For example, based on their asymmetrical shapes, a skull from Gibraltar and the 'Peking man' were suggested to be from right-handed individuals, while a skull from London was suggested to have been from a left-handed individual (for a review, see (LeMay 1992)). Unfortunately, relationships between brain structural and functional asymmetries are clearly far from absolute, as evidenced by the present study, as well as others (e.g., (Chiu & Damasio 1980; Koff et al. 1986; Narr et al. 2007)).

We found no significant genetic correlations between either aspect of global brain asymmetry and handedness in the UK Biobank or HCP datasets. This suggests that genetic factors influencing global brain asymmetry are largely dissociable from those affecting handedness, and therefore that environmental factors, such as early life experiences, may play a more predominant role in causing the

associations of handedness with global brain asymmetry measures. However, both handedness and global brain asymmetry measures are weakly heritable to begin with, so that detecting genetic correlation between them in the current sample sizes might have been unlikely.

Development of global brain asymmetry

Thus far we know little about the developmental mechanisms which lead to brain asymmetry. Best (1986) proposed a 3D lateralized neuro-embryologic growth gradient, including a "rearward and dorsal" twist of the left hemisphere and a "forward and ventral" twist of the right hemisphere. However, the dorsal-ventral twist was based only on a preliminary observation at the time (Dooling et al. 1983), and our observations of adults in the present study show an opposite direction, i.e. a ventral twist of the left hemisphere, and a dorsal twist of the right. However, the typical adult brain asymmetries are the endpoint of a dynamic developmental process that also plays out through childhood and adolescence, and may involve some reconfiguration (Shaw et al. 2009). Possible mechanisms may include inter-hemispheric differences in neural pruning (Fullard et al. 2019), axon tension (Van Essen 1997), and/or ventricular cerebrospinal fluid (CSF) volume (Maller et al. 2014) during neural development.

Establishing the genetic origins of brain asymmetry would help elucidate the developmental origins of this trait, as well as potentially its evolution, and the neural basis of functional lateralization. In the present study, we found heritabilities of 5%-10% for the two global brain asymmetry measures in the UK biobank and HCP datasets. This is lower than the 10%-30% heritabilities reported in a previous study of vervet monkeys using a similar registration-based approach (Fears et al. 2011), which might suggest a species difference in the degree of genetic control of global brain asymmetry (Xiang et al. 2019). Moreover, our GWAS analyses revealed 4 genome-wide significant loci (1 for horizontal skew, 3 for vertical skew) and 6 genome-wide significant protein-coding genes (4 for horizontal skew and 2 for vertical skew), although all of these findings only just surpassed thresholds for defining genome-wide significance, and require replication in future datasets as they become available. In total, our analysis implicated 10 novel candidate genes for affecting global brain asymmetry, which were *FAM117B* (chr.2), *B3GALNT1* (chr.3), *SPATA16* (chr.3), *SLC5A8* (chr.12), *RNU7-165P* (chr.10), *TMEM255B* (chr.13), *ASPHD1* (chr.16), *SEZ6L2* (chr.16), *HEATR6* (chr.17), and *DPY19L3* (chr.19). Variants of some of these genes may associate with disorders that can be accompanied by altered brain asymmetry and/or reduced linguistic abilities. For example, *FAM117B* was one of the genes deleted in an individual with a learning disability, moderate intellectual disability, and autistic features (Roberts et al. 2014). A coding variant in *SEZ6L2* has been associated with autism (Kumar et al. 2009), and a polymorphism within *DPY19L3* has been associated with bipolar disorder (Smith et al. 2009). Unfortunately our bioinformatic analysis of the GWAS results did not identify higher-level biological pathways that might be affected. This kind of analysis is likely to benefit from the future availability of even larger sample sizes.

As the heritabilities of both global asymmetry measures were low in our analyses, then non-genetic factors seem likely to also influence them. Early life factors such as birth weight, being part of a multiple birth, and breastfeeding, have been shown to correlate with handedness (de Kovel et al. 2019). In the present study, while we did not find any significant associations between global brain

asymmetries and early life factors after correction for multiple testing, two nominally significant associations were observed with vertical asymmetry: maternal smoking and breastfeeding. In addition, country of birth was significant even after correction for multiple testing in phenome-wide association analysis. We speculate that there are aspects of prenatal and perinatal behaviour or care that differ systematically between the countries of the United Kingdom and can affect brain shape development, but population-genetic differences may also be involved, as may environmental influences later in life. These findings will require follow-up in independent datasets.

Summary

In sum, the present study used automated, registration-based measurement of the horizontal and vertical components of global brain asymmetry, both of which showed high test-retest repeatability. With the largest-ever analyses, we revealed two average asymmetry patterns at the population level: one global asymmetry along the anterior-posterior axis, and one along the dorsal-ventral axis. Furthermore, we clarified the relationships between global brain asymmetries and handedness, linking brain structural asymmetries to one of the most clearly evident functional lateralizations, although the effect sizes were small. Moreover, the global brain asymmetry measures showed heritabilities of 5%-10%, and genetic analyses revealed 10 candidate genes affecting them. These results provide further evidence for the functional significance of brain asymmetry, and suggest that genetic factors play a role - though not a determining one - in its development.

Ethics statement

This study utilized de-identified data from the baseline assessment of the UK Biobank, a prospective cohort of 500,000 individuals (age 40-69 years) recruited across Great Britain during 2006-2010. The protocol and consent were approved by the UK Biobank's Research Ethics Committee. Data from the Human Connectome Project was approved by the Institutional Review Boards associated with that project. The BIL&GIN study was approved by the local ethics committee (CCPRB Basse-Normandie).

Data Availability

For use of UK Biobank data, application must be made via http://www.ukbiobank.ac.uk/register-apply/. The Human Connectome Project data are available via https://www.humanconnectome.org/. The BIL&GIN data sharing is based on a collaborative model: http://www.gin.cnrs.fr/BIL&GIN.

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