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Brain handedness associations depend on how and when handedness is measured

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Hand preference is ubiquitous, intuitive, and often simplified to right- or left-handed. Accordingly, differences between right- and left-handed individuals in the brain have been established. Nevertheless, considering handedness as a binarized construct fails to capture the variability of brain-handedness associations across different domains or activities. Further, hand-use changes across generations (e.g., letter writing vs. texting) such that individuals of different ages live in different environments. As a result, brain-handedness associations may depend on *how* and *when* handedness is measured. We used two large datasets, the Human Connectome Project-Development (HCP-D; *n* = 465; age = 5–21 years) and Human Connectome Project-Aging (HCP-A; *n* = 368; age = 36–100 years), to investigate generational differences in brain-handedness associations. Nine items from the Edinburgh Handedness Inventory were associated with resting-state functional connectomes. We show that brain-handedness associations differed across the two cohorts. Moreover, these differences depended on the way handedness was measured. Given that brain-handedness associations differ across handedness measures and datasets, we caution against a one-size-fits-all approach to neuroimaging studies of this complex trait.

Keywords Handedness, Functional connectivity, Life-span, Development, Aging

A preference for using one hand over another—or handedness—is a complex trait with well-studied neural correlates. Differences in the language[1–5], motor[6–8], and somatosensory[9–11]networks have been consistently reported when comparing right- and left-handed individuals. For example, left-handed individuals exhibit more bilateral activation of brain regions during language tasks, suggesting a greater reliance on the right hemisphere for language processing[4]. The corpus callosum, which connects the two hemispheres, may be larger in left-handed individuals, indicating increased interhemispheric communication[12,13]. Recent work further suggests that differences related to handedness extend beyond localized regions to widespread functional connectivity differences[14–16], potentially affecting every canonical brain network[17–19]. Characterizing brain-handedness associations is crucial for human neuroscience. Historically, left-handed individuals have been excluded from neuroimaging studies[20]. Detailed characterization and nuanced understanding of brain-handedness associations are needed to study and include left-handed individuals in future research. Nevertheless, although brain-wide differences in functional connectivity have been demonstrated[19], previous studies were limited to children and adolescents[14,16]. They showed substantial contributions from prefrontal and cerebellar networks. Both are linked to development[16,21,22], possibly influencing results. Thus, there is a need to elucidate further the contributions of other factors affecting brain-handedness associations by examining how generational, maturational, and environmental differences affect more fine-grain, granular measures of handedness.

While individual differences in handedness are partly attributable to genetic factors[5,23], environmental factors play an essential role in shaping the expression of handedness[24–26]. For example, cultural preferences have historically encouraged right-hand dominance[27]. In some instances, young children were mandated to use their right hand for writing, using cutlery, and performing everyday tasks despite their natural preferences[28–30]. Moreover, although left-handed individuals comprise ~ 10% of the population[27], evidence suggests that rates of left-handedness have increased in recent years, perhaps due to growing tolerance of variation in this trait[31].

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These observations point to a generational effect[32–34], where individuals of different ages live in different environments[24–26]. A related challenge concerns the definition of handedness. Although it is often considered a binarized construct, such a definition fails to capture the variability of handedness preferences across domains or activities[32]. One may prefer to write with their right hand but throw a ball with their left. This heterogeneity is captured by validated handedness questionnaires, such as the Edinburgh[35–37], the Annett[38], and many others[39–41]. These generate ordinal or dimensional sum scores from items that span the full breadth of handedness use. Despite this rigor, the test-retest reliability of handedness scores changes over time[42], suggesting the environment's role in shaping hand preferences. As a result, brain-handedness associations may depend on *how* and *when* handedness is measured.

In the present study, we used two large datasets, the Human Connectome Project-Development (HCP-D; $n = 465$; age = 5–21 years) and Human Connectome Project-Aging (HCP-A; $n = 368$; age = 36–100 years), to investigate handedness preferences and brain-handedness associations across different generations of participants. We hypothesized that brain-handedness associations would differ across these generations for multiple different measures of handedness. Significant results would highlight that the environment (or, more specifically, the change in the environment across different age groups) influences brain-handedness associations. First, we investigated group differences between pairs of granular measures of handedness on a behavioral level. We then investigated group differences in brain-handedness associations. Finally, we compared how brain-handedness associations differed for every granular measure of handedness between cohorts. Our findings show that, although the covariance among granular handedness measures was similar between the datasets, brain-handedness associations differed significantly. These results are attributable to generational[32–34], environmental[24–26], and maturation[43,44] factors that shape brain-handedness associations. Given that brain-handedness associations differ across handedness measures and datasets, we caution against a one-size-fits-all approach to neuroimaging studies of this complex trait, as results will ultimately depend on how and when handedness is measured.

Methods

Datasets: Human Connectome Project-Development (HCP-D) & Human Connectome Project-Aging (HCP-A)

We analyzed behavioral and neuroimaging data from the Human Connectome Project (HCP) Lifespan Studies[45–48]. The Human Connectome Project-Aging (HCP-A; brain and behavior $n = 368$, behavior only $n = 724$) was used as the older cohort. Data were obtained from two separate populations. Table 1 summarizes each dataset's participant population and handedness preference. We used resting state fMRI scans obtained from 3T Siemens scanners of 10 min in length. Scans that contained head motion exceeding 0.1 mm were excluded.

Behavioral measures of handedness

Measures of handedness were determined from individuals' self-reported preferences for their dominant hand using nine items from the Edinburgh Handedness Inventory[49]. The following nine items were assessed: writing, throwing, scissors-use, toothbrush-use, using a knife without a fork, spoon-use, sweeping (using a broom),

	HCP-D[45–47]		HCP-A[46,48]	
	Behavioral	**Brain**	**Behavioral**	**Brain**
Sample size	488	465	724	368
Age	16.16 ± 3.12 Range: 11–21.92	15.12 ± 3.77 Range: 8.08–21.92	60.35 ± 15.73 Range: 36–100	56.34 ± 13.48 Range: 36–100
Sex (M/F)	255/233	252/213	406/318	195/173
Handedness Sum Score (normalized)	63.96 ± 43.98 IQR = 55.56–88.89	60.91 ± 41.90 IQR = 55.56–88.89	50.37 ± 37.27 IQR = 50–75	63.69 ± 53.25 IQR = 61.11–100
Writing	78.14 ± 60.67 IQR = 100–100	78.49 ± 60.17 IQR = 100–100	75.79 ± 63.59 IQR = 100–100	73.21 ± 66.56 IQR = 100–100
Throwing	73.92 ± 54.05 IQR = 50–100	75.60 ± 51.08 IQR = 50–100	74.41 ± 55.78 IQR = 100–100	70.83 ± 58.95 IQR = 50–100
Scissors	76.30 ± 55.24 IQR = 100–100	76.02 ± 55.03 IQR = 100–100	78.07 ± 52.97 IQR = 100–100	74.55 ± 58.08 IQR = 100–100
Toothbrush	67.20 ± 59.84 IQR = 50–100	68.39 ± 57.43 IQR = 50–100	66.55 ± 64.01 IQR = 50–100	62.65 ± 67.11 IQR = 50–100
Knife (no fork)	69.36 ± 56.77 IQR = 50–100	68.98 ± 56.45 IQR = 50–100	71.31 ± 58.68 IQR = 50–100	70.24 ± 61.88 IQR = 87.50–100
Spoon	69.43 ± 60.98 IQR = 50–100	70.69 ± 58.63 IQR = 50–100	68.28 ± 60.90 IQR = 50–100	62.35 ± 65.70 IQR = 50–100
Broom	23.46 ± 73.40 IQR = −50–100	24.08 ± 74.13 IQR = −50–100	41.66 ± 71.36 IQR = 0–100	37.20 ± 73.10 IQR = 0–100
Match	75.51 ± 52.75 IQR = 100–100	75.92 ± 52.71 IQR = 100–100	73.96 ± 58.53 IQR = 100–100	72.17 ± 61.63 IQR = 100–100
Box	49.59 ± 58.82 IQR = 0–100	49.08 ± 59.24 IQR = 0–100	53.17 ± 60.53 IQR = 0–100	50.00 ± 63.12 IQR = 0–100

Table 1. Dataset description and demographics.

lighting a match, and opening a box. Individuals responded using a 5-point Likert scale, ranging from 1 = *Always left* to 5 = *Always right*, to indicate their hand preference for each item. Our handedness sum score was simply a summation of all nine values for each subject to determine overall handedness (unless specified otherwise). Participants who rated indifferent, sometimes, or always left were classified as left-handed. In contrast, those who rated they were sometimes or always right were classified as right-handed. A comprehensive breakdown of the number of subjects endorsing each Likert scale value for handedness measures can be found in Table S1 and Table S2 for the HCP-D and HCP-A, respectively.

Preprocessing and generating connectomes

The HCP-D and HCP-A datasets were analyzed with identical processing pipelines. Structural scans were first skull-stripped using an optimized version of the FMRIB's Software Library (FSL)[50]pipeline[51]. Functional images were motion-corrected using SPM12[52]. All further analyses were performed using BioImage Suite[53]. Several covariates of no interest were regressed from the data, including linear and quadratic drifts, mean cerebral-spinal-fluid (CSF) signal, mean white-matter signal, and mean gray matter signal. For additional control of possible motion-related confounds, a 24-parameter motion model (including six rigid-body motion parameters, six temporal derivatives, and these terms squared) was regressed from the data. The data were temporally smoothed with a Gaussian filter (approximate cutoff frequency = 0.12 Hz).

Nodes were defined using the Shen 268-node brain atlas[54], which includes the cortex, subcortex, and cerebellum as described in prior work. The atlas was warped from MNI space into single-subject space via a series of linear and non-linear transformations calculated using a previously validated algorithm[55] implemented in BioImage Suite. Mean time courses for each of the 268 nodes were calculated (i.e., averaging the time courses of all constituent voxels). Node-by-node pairwise correlations were computed, and Pearson correlation coefficients were Fisher z-transformed to yield symmetric 268×268 connectivity matrices, in which each matrix element represents the connectivity strength between two individual nodes (i.e., 'edge').

Correlations for behavioral measures

Pairwise correlations for handedness items were calculated using Spearman's correlation (ρ). These values were then plotted on a heat map to demonstrate how similar handedness granular measures were to others. Correlations were compared between datasets. Correlation coefficients were converted to z-scores, and p-values were subsequently calculated using a z-test.

Identifying significant edges and nodes between handedness

We separately assessed edge-wise t-tests between left-handed and right-handed participants for the HCP-D and HCP-A datasets. We used the Network-Based Statistics (NBS)[56] to identify components where functional connectivity was significantly associated with handedness while controlling for the family-wise error rate (component-determining threshold $Z = 1.96$, 2-tailed, $K = 5000$ permutations). Age, sex, and head motion were additionally used as covariates to control for these differences. NBS is analogous to cluster-based correction and solves the statistical problem of multiple comparisons in a whole-brain connectivity analysis. In NBS, the largest fully connected network of suprathreshold edges, or "component," is identified within a connectome, and its extent is defined as the number of edges it comprises.

Whole brain effect sizes

Thresholding based on significance can negatively affect interpretations and understanding of a study[53,57]. For example, one cluster of edges may be just over the significance threshold and one just under. Visualizing the first but not the second over-emphasizes a minor difference, making the groups appear more different than they are. Using effect sizes is a complementary approach that examines all edges based on the magnitude of associations with handedness rather than only significant ones. As effect size measures, like Cohen's d, are standardized, they are comparable across different analyses. We calculated effect sizes using Cohen's d for handedness separately for the HCP-D and the HCP-A datasets. To help put these whole-brain differences into a comparable context, we compared our effect sizes relative to sex differences, which have been known to have large effect sizes and are tightly controlled for in fMRI studies[58,59]. Effect sizes for sex were calculated using only primarily right-handed individuals relative to each granular measure. Cohen's d was then calculated for the difference between male and female participants (based on self-reported sex).

Differences between whole brain effect size

Edge-wise z-tests were computed between the HCP-D and HCP-A effect sizes to explore edge-wise differences between cohorts. These z-scores were then thresholded at p-values of below 0.05 to visualize edges in a connectome that were deemed significantly different between the two cohorts and subsequently visualized on 3D brain plots using BioImage Suite.

Correlations and variance explained for effect sizes

Correlations for each behavioral measure were calculated using Pearson's r between each measure to quantify the similarities of the effect size distributions for pairs of granular measures of handedness. These values were then squared to give variance explained (r^2) and these r^2 were subsequently plotted on a heat map to demonstrate how similar effect size maps for each handedness granular measure were to one another.

Results

Behavioral correlations

When assessing the covariance of individual Edinburgh Handedness Inventory (EHI) items, we found that most items were significantly correlated for both the HCP-D (Fig. 1A) and the HCP-A cohorts (Fig. 1B). Although patterns of Spearman correlations (ρ) were similar between the two generations ($r = 0.85$ between correlation

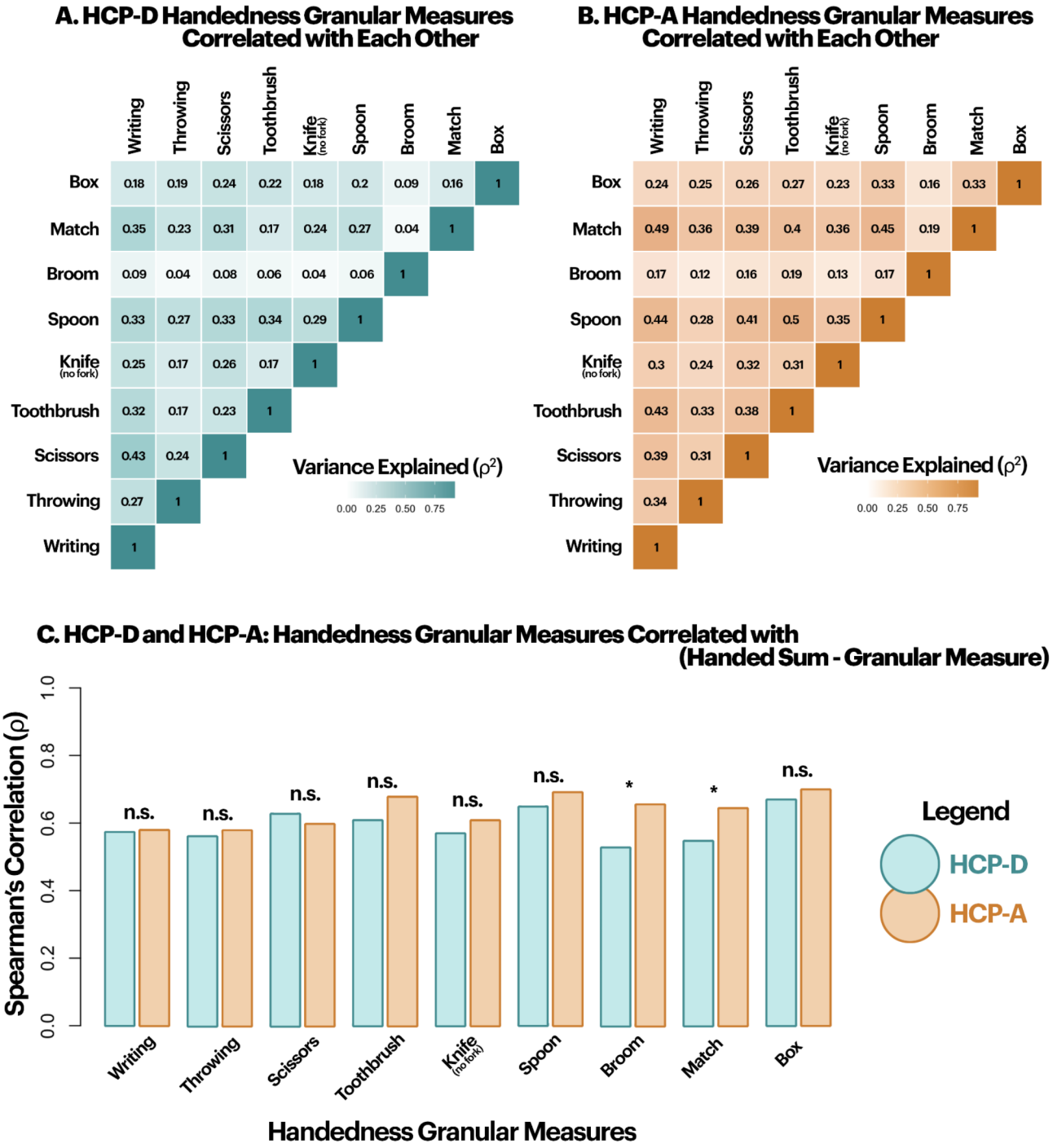

Fig. 1. Behavioral correlations between pairs of granular measures of handedness and the sum score. (**A**) Spearman's variance explained between pairs of granular measures of handedness for the HCP-D. (**B**) Spearman's variance explained between pairs of granular measures of handedness for the HCP-A. (**C**) Granular measures of handedness correlated with the handedness sum score minus that particular granular measure. Spearman's correlations (ρ) for the HCP-D are displayed in blue and HCP-A in orange. The significance between pairs of correlations between the HCP-D and HCP-A are denoted above each handedness granular measure.

matrices), the lower correlations exhibited between specific pairs and measures—for instance, between sweeping (Broom) and other granular measures—indicate not all granular measures of handedness are meaningful. Nevertheless, 28 out of 36 pairs of correlations were significantly stronger in the HCP-A cohort than among the younger HCP-D cohort when p-values were calculated to compare the strengths of these correlations (Fig. S1). These differences were further validated by performing significance tests between pairs of measures of handedness (Table S3, S4). These results suggest that the EHI measures captured similar information for each cohort.

As the current gold standard for measuring handedness utilizes a sum score of EHI items, we investigated how well a given item performed relative to the sum score. Spearman's ρ's were calculated between each granular measure and the handedness sum score, minus that particular granular measure, separately for the two cohorts (Fig. 1C). In general, correlations between handedness sum score and any given item were comparable between the two datasets, with the HCP-A dataset showing marginally stronger correlations (n.s.) than for the HCP-D cohort.

Brain-handedness associations

Out of the 35,778 total edges in a connectome, 5.5% and 6.27% were identified as statistically ($p < 0.05$, corrected) different for right- and left-handed groups in the HCP-D cohort, respectively. In the HCP-A cohort, 4.39% and 4.96% of edges were significant ($p < 0.05$, corrected) for right- and left-handed groups, respectively. In each group, differences were widespread and complex, with contributions from every node and canonical brain network (Fig. 2).

Interestingly, a region that emerged across analyses is the cerebellum. Patterns of brain-handedness associations differed between the two cohorts (Fig. 2). More edges and nodes within the cerebellum were observed in the HCP-D (edges in cerebellum for handedness L, R: 30.37%, 32.08%) than in the HCP-A (edges in cerebellum for handedness L, R: 24.30%, 25.68%). In contrast, group differences in the HCP-A are more

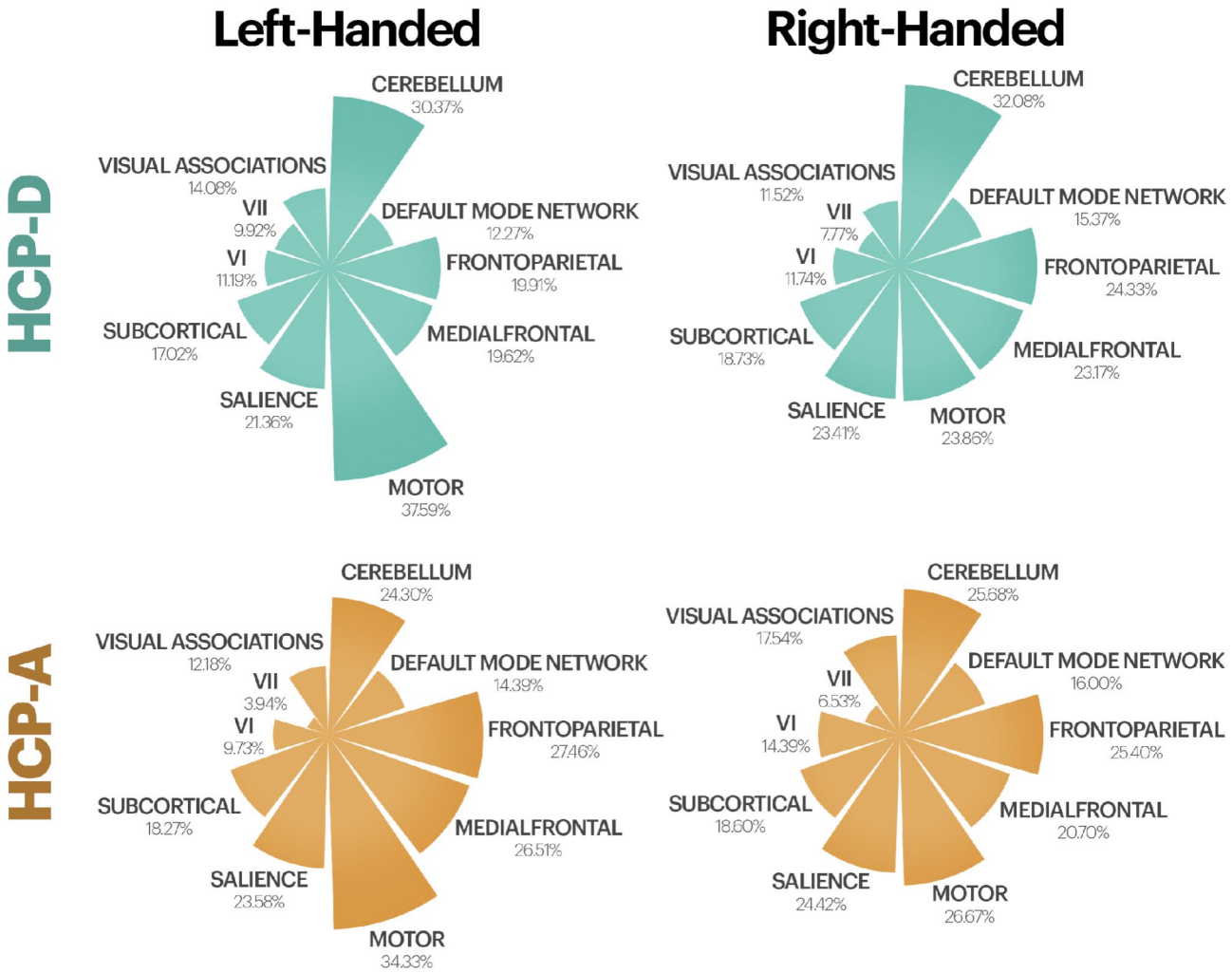

Fig. 2. A comprehensive breakdown of where significant nodes and edges are allocated in NBS group differences for handedness for the HCP-D and HCP-A separately. Circular bar plots represent the percentage of edges connecting within and between respective networks.

confined within cortical regions, as evidenced by lower percentages of significant edges connecting within and between the cerebellar networks.

In addition, patterns between handedness preferences also emerged as a larger percentage of significant edges were connected within and between the motor network for left-handed groups (HCP-D: 37.59%, HCP-A: 34.33%) than in right-handed groups in both cohorts (HCP-D: 23.86%, HCP-A: 26.67%) (Fig. 2).

Next, we explored differences between right-handed males and females to benchmark meaningful handedness differences[61]. The neural correlates of self-reported sex are widely studied[63–66]and often controlled for in fMRI studies[58,59]. Since sex differences in handedness have been shown in previous literature[31,67,68], only right-handed subjects, as defined by their composite handedness sum scores, were included in our calculations of effect size differences between males and females. The effect size distribution for handedness was wider than for sex for the HCP-A (f-stat = 1.46, p-value < 0.001), indicating that handedness generally exhibited larger effect sizes than sex. In contrast, no significant differences between effect sizes were noted for the HCP-D.

Moreover, in comparing NBS results for sex and handedness, a comparable percentage of significant edges could also be attributed to connections within and between the prefrontal regions in both the HCP-D (edges in prefrontal for handedness L, R: 39.14%, 37.79%; and sex M, F: 33.82%, 31.01%) and the HCP-A (edges in prefrontal for handedness L, R: 35.79%, 34.97%; and sex M, F: 33.39%, 29.53%). Differences detected by NBS were specific to handedness given that when head motion and sex were used as covariates to regress out these effects (Fig. S2), results remain correlated with those in which age were regressed out (Fig. 3). To further illustrate these similarities, 3D brain plots of edge and node allocations were compared (Fig. S3). Nevertheless, these results are less surprising given the rich literature demonstrating prefrontal differences in sex[60–62], handedness[3–5], and across developmental trajectories more broadly.

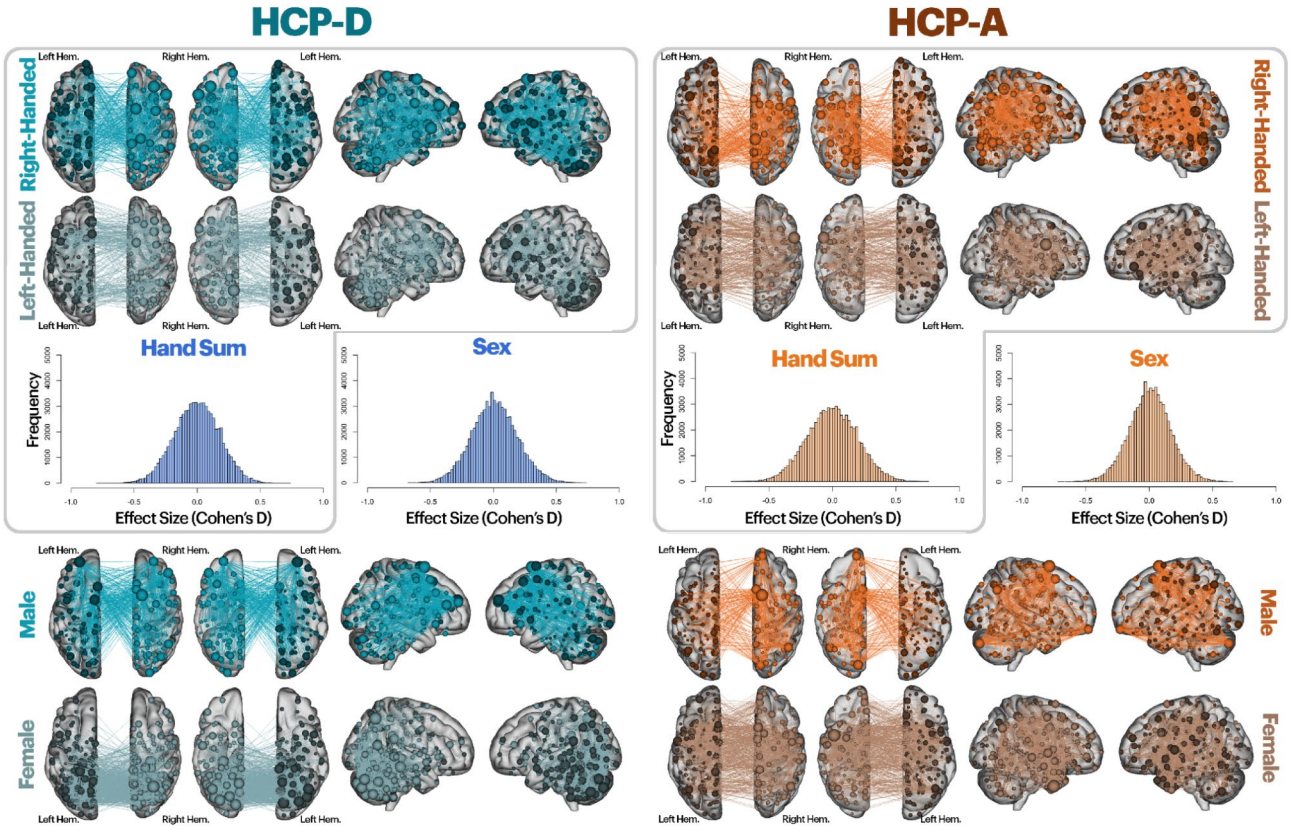

Fig. 3. **Handedness vs. Sex**: Boxed: Edges significantly different between left- and right-handed groups were identified based on the handedness sum score. Effect sizes were then calculated for all 35,778 edges and shown on a histogram. This procedure was performed separately for the two cohorts with the HCP-D (on the left in blue) and the HCP-A (on the right in orange). Unboxed: Edges significantly different between right-handed males and females were identified based on self-reported sex. Effect sizes were then calculated for all 35,778 edges and shown on a histogram. This procedure was performed separately for the two cohorts with the HCP-D (on the left in blue) and the HCP-A (on the right in orange). Thresholds for 3D brain visualizations (thresholded at a minimum number of significant edges connected to a specific node) were as follows: [HCP-D] right-handed: 35, left-handed: 35, male: 80, female: 75 [HCP-A] right-handed: 25, left-handed, 25, male: 60, female: 50.

Exploring effect sizes in granular measures

Within a dataset, when effect size distributions for all individual handedness items were compared by cohorts and with the handedness sum score (Fig. S4), similar distributions were observed except for opening a box and broom use. The box and broom-use items had smaller effect sizes than the handedness sum score overall. Komolgorov-Smirnov test statistics were performed to compare the effect size distribution between the two cohorts (Table S5). All distributions were significantly different, with the HCP-A generally being wider (i.e., larger effects are observed in the HCP-A).

Comparing brain-handedness associations between cohorts

We formally compared the brain-handedness associations between cohorts, using edge-wise z-tests (Fig. 4). Widespread differences in brain-handedness associations between the HCP-D and the HCP-A cohorts for the handedness sum score were observed. These differences account for 12.5% of edges (out of 35,778). While results were widespread across the brain, a large cluster of edges was located in posterior regions. Differences were also calculated between left- and right-handed groups based on individual handedness items (Fig. 4: periphery). While measures such as throwing, scissors-use, knife-use, writing, and match-use had significant edges that were comparable to or higher than that of the handedness sum score (10.88%, 11.06%, 12.79%, 10.2%, and 14.2%, respectively), not all measures demonstrated as large of differences between the two cohorts. As expected based on our earlier results (Fig. S4), box opening and broom use were associated with a lower percentage of significant edges at 6.31% and 3.87%, respectively. When we explored the percentage of overlap between each handedness item and the handedness sum score, these values ranged from 1.24% (broom-use) to 7.18% (writing), indicating that the functional correlates of a given item differ across the cohorts. In other words, while differences in brain-handedness associations between the cohorts exhibit widespread patterns, each granular measure still has distinct differences.

Although differences in significant edges and nodes between cohorts varied by measures of handedness, these edges are located in posterior regions, particularly the cerebellum. In particular, the handedness sum score exhibited the largest differences between cohorts within the cerebellar regions (Fig. 4: bottom), where 25.77% of all edges differed between cohorts were located in the cerebellum.

Examining covariance of brain-handedness effect sizes

To explore how similar the brain-handedness associations were across EHI items, we correlated effect size maps (Fig. S2) for all pairwise item combinations (Fig. 5). In HCP-D, effect size maps were weakly correlated or uncorrelated, except for toothbrush-use, scissors-use, throwing, and writing. In contrast, all item-level effect size maps were strongly correlated in HCP-A. In other words, for HCP-A, edges that show a strong correlation with one EHI item tend to show strong correlations with other EHI items. For HCP-A, these correlation patterns (Fig. 5B) resemble the behavioral variance explained (Fig. 1B). In contrast, HCP-D does not show this pattern. These results were further validated by significance tests between pairs of correlations (Table S6, S7).

To consolidate the relationship between behavioral preferences and brain networks, a confirmatory visualization to illustrate couplings between brain-handedness associations (Fig. 5A and B) and behavioral explained variances (Fig. 1A and B) between pairwise EHI items was conducted (Fig. S5). As anticipated, brain-behavior correlations were weaker in the HCP-D ($r = 0.29$) than in the HCP-A ($r = 0.81$) dataset ($z = 3.41$, p-val < 0.01). These results suggest that—although, behaviorally, younger cohorts may have similar covariance between different items—the underlying functional organization of the brain for each item appears distinct.

Discussion

This study investigated brain-handedness associations across multiple granular measures of handedness and how these associations differ across generations. Importantly, brain-handedness associations differed across the two cohorts. Further, these differences depended on the way handedness was measured. Our results, first and foremost, suggest that the question "Are you right—or left-handed?" may be oversimplified for brain-handedness associations. Brain-handedness associations likely depend on how and when handedness is measured and are attributable to environmental[24–26], maturation[43,44], and generational[32–34] effects.

Overall, an age-by-environment interaction[69] gives rise to generational effects[70,71] where individuals of different ages live in different environments. Older individuals may have been more adept at using their right hands overall since older generations were more likely forced to use their right hands[28,72]. The percentage of left-handed individuals has increased as these cultural influences change. Similarly, handwriting is less common in younger generations as digital communication increases. Brain-handedness associations change due to these environmental differences, allowing the brain to perform modern hand-use more efficiently. These changes are likely similar to neuroplastic changes observed when individuals learn hand motor skills[73,74] and when they can no longer use their dominant hand[75]. Overall, our results indicate that brain-handedness associations are attributable to age-by-environment interactions and, subsequently, generational effects.

While it is tempting to infer that brain-handedness associations for an individual do not change over time, the test-retest reliability for handedness measures is imperfect[76], indicating that handedness preferences may change over time[77]. Thus, it is essential to consider that EHI scores reflect an individual's preference at a given time, and it can not be concluded that results will remain the same for future time points. These observations and our results strongly suggest that brain-handedness associations are only partly attributable to genetic factors[5,23]. Cultural preferences are another environmental factor that shapes brain-handedness associations[78,79]. Western and Eastern cultures have been known to impose right-handedness on children from a very young age[24,25,27]. This practice further affects how individuals from these cultures exhibit handedness preference changes later on[80]. Studies surrounding cultural changes offer a unique opportunity to more clearly disentangle the interactions

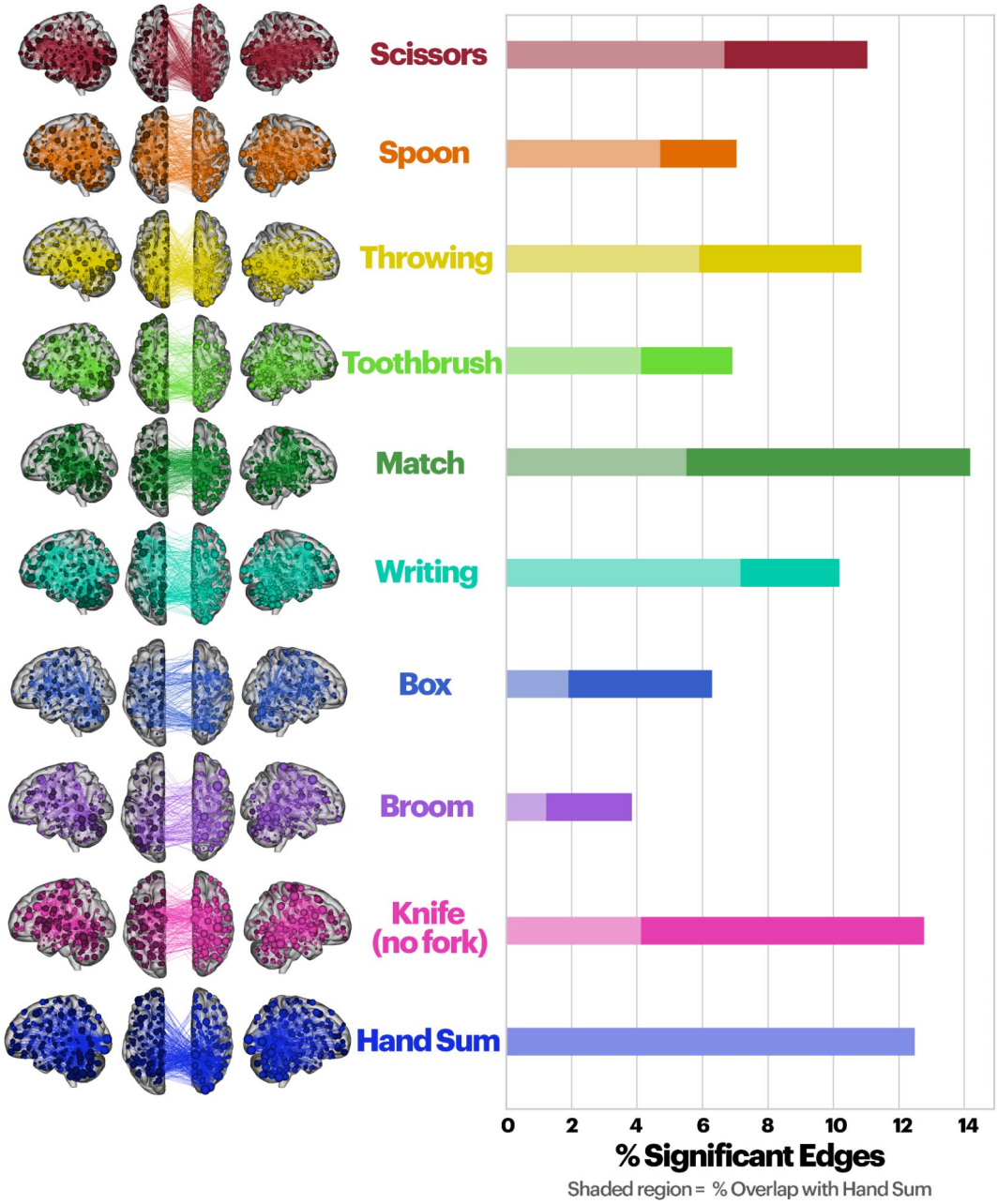

Fig. 4. **Edges and nodes significantly differ between the HCP-D and the HCP-A.** 3D brain plots on the left were thresholded (minimum number of edges connected to specific node to be visualized) for interpretability at 35 for spoon-use, 55 for throwing, 35 for toothbrush-use, 70 for match-use, 50 for writing, 35 for box opening, 25 for broom-use, 70 for knife-use (no fork), and 55 for scissors-use. The percentage of significant edges for each granular measure ($p < 0.05$) and the percentage of overlapping edges with the handedness sum score are displayed in a horizontal bar plot to the right of the 3D brain plots. For the percent of overlap with the handedness sum score, all edges that yielded significance for both the granular measure and the sum score were summed up and calculated as a percentage of the whole connectome. The percent of edges overlapped with the handed sum score for each granular measure is shown as the shaded regions on the bar plots.

between genetics, epigenetics, and the environment. Nonetheless, for these studies to be successfully conducted, we would require data to be collected from many different countries and cultures.

Our studies shed light on traditional neuroscience theories on brain lateralization and dominance, such as the Hemispheric Encoding/Retrieval Asymmetry (HERA) model[81]. This model proposes that the left and right hemispheres of the brain are functionally different in memory encoding and retrieval systems. Hypotheses on functional differences in brain lateralization are not only limited to memory but also extend to differences in specialization towards creativity[82], broader cognitive skills[83], and, more pertinent to differences in handedness, differences in language specialization[84,85]. In addition, recent human neuroimaging studies have demonstrated

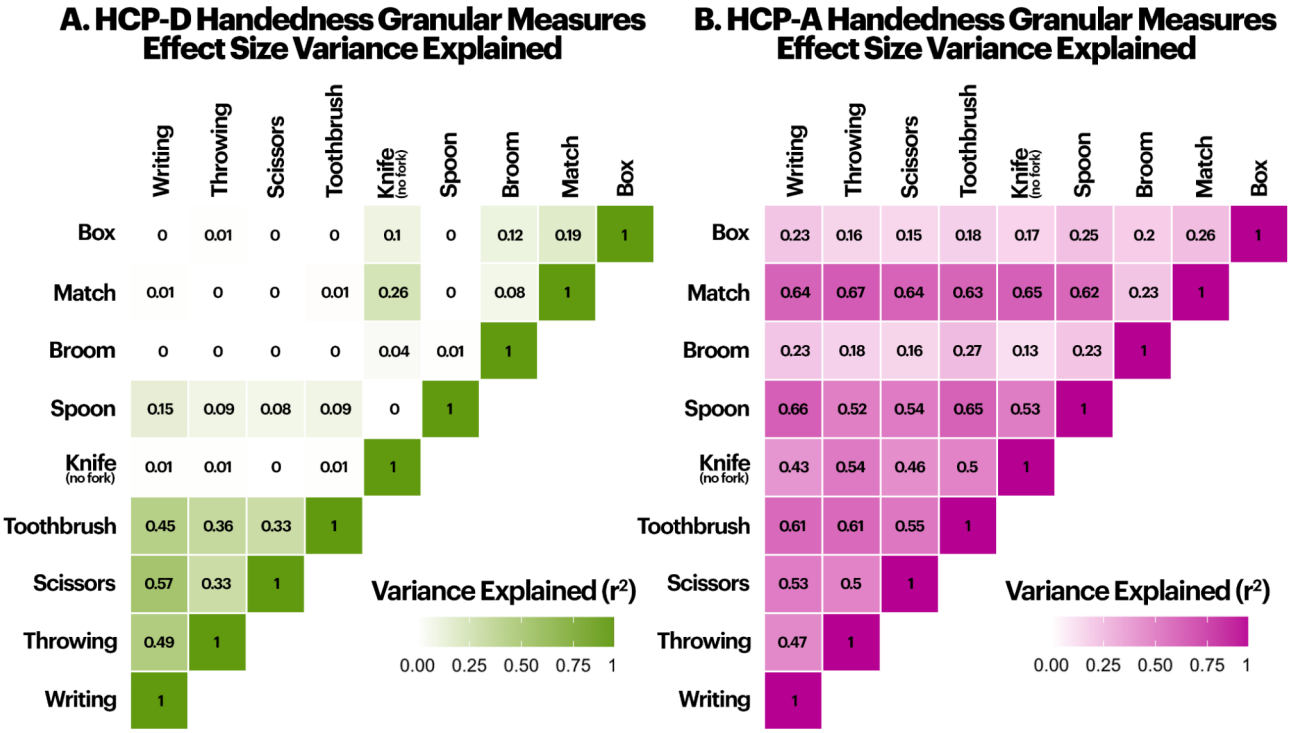

Fig. 5. Effect size variance explained for all granular measures of handedness calculated separately for the two cohorts Correlations between brain-handedness effect size maps for pairs of specific granular measures shown for HCP-D (left) and HCP-A (right).

that these trends in lateral specialization are heritable[29]. Our current studies support brain lateralization theories proposed by the HERA model and extend to the possibility that these models may change as different generations become more open to diversity in handedness preferences. While these models have provided a baseline for understanding brain laterality, our results further allow us to add nuance. They probe into how these models may adapt and change in response to whole-brain differences in brain-handedness associations over generations. Numerous studies have shown that regions responsible for language in the brain are located in different parts of the brain for left-handed individuals[2,86–89]. However, brain laterality models may be worth revising to consider the nuances that change over generations as brain-handedness associations change and adapt to how future generations utilize their hands.

While we initially thought that age could contribute to handedness preferences over time, the discrepancies in variance explained in our developmental cohort between behavioral preferences (Fig. 1A) and brain correlates (Fig. 5A) suggest otherwise. The developmental cohort identified handedness preferences behaviorally from a young age (Fig. 1A) despite longer timelines required for brain-behavior associations (Fig. 5A) to follow. Thus, differences are attributable to a combination of generational and maturational effects. However, due to the limited number of left-handed individuals in each cohort, differences between developmental and generational effects could be further explored. More left-handed individuals would allow for detailed matching on motion or narrower age bins to explore both developmental and generational effects.

Generational and maturational effects also explain patterns of similarity between the cohorts. Specific measures, such as writing and throwing, are taught in schools from a very young age, and the maturation of preferences and brain circuits to support them can form at earlier time points. Yet others, like knife-use, broom-use, and lighting a match, would be less common behaviors in a younger cohort. For instance, lighting matches are less relevant in current times given that younger children are not lighting matches and newer generations have other alternative methods (e.g., lighters or vaping). Therefore, brain-handedness associations for certain measures may not be particularly informative in a younger cohort due to lower engagement rates. Conversely, scissors-use correlations are marginally higher for HCP-D than HCP-A, which may be because younger cohorts are more actively using scissors in classroom activities. Additionally, we cannot account for all individual differences of participants. For instance, athletes train to utilize their hands or perform motor movements with more nuance than the general population. Training and using hands for specific tasks will moderate brain-handedness associations.

To disentangle generational and maturational effects, longitudinal studies over different generations are likely needed to map out generational effects fully. Nevertheless, collecting data over decades is a difficult task. Using two harmonized cohorts collected at different ages is a reasonable starting point to understand how brain-handedness associations change. Similarly, animal studies offer the possibility of longitudinal studies across lifespans, and greater experimental manipulations exist. However, animals do not have the same motor capacities as humans and cannot self-report handedness preferences beyond pure observations. Thus, studies of

brain-handedness associations in animal models cannot address these questions. Longitudinal datasets (such as the Adolescent Brain Cognitive Development Study[90]) may represent a starting point for further investigations.

While our study broadly showed differences in brain-handedness associations depending on how and when handedness is measured, there are a few notable limitations. First, there has long been speculation that the EHI may not be the most effective method of measuring handedness[91]. Still, the EHI remains the most comprehensive measure available. Secondly, although we utilized an adult-derived atlas to parcellate our brain data in both the developmental and aging cohorts, the same parcellations needed to be utilized to compare results consistently across the two cohorts. Moreover, inconsistent atlases may further introduce various biases. Adult parcellations are routinely used in studies focusing only on adolescents and children[92–96]. Accordingly, we used an adult atlas on brain data in the developmental cohort to maintain comparison consistency. Nonetheless, future studies could utilize individualized atlases that retain correspondence between two groups while accounting for differences. Lastly, resting-state fMRI data can potentially emphasize or deemphasize the effects of handedness. On the one hand, task data would allow us to test brain-handedness associations more precisely. However, doing so would require the acquisition of task-based data on handedness tasks, limiting our ability to obtain large amounts of data to power our statistical analyses, given how rare left-handed individuals are in the population. Large datasets that specifically test motor and handedness functions are limited to specific age ranges[97], limiting investigations of generational effects. Future studies could leverage task-based functional connectivity to explore these brain-handedness associations more precisely.

In conclusion, we examine brain-handedness associations from multiple measures across an extensive age range. We demonstrated that not all handedness measures are equal, and each measure exhibits associations and cohort differences. Differences in brain-handedness associations depend highly on when and how handedness is measured. Regardless of mechanisms, brain-handedness associations differ by when they are measured and are also nuanced by the generation in which a particular individual was raised in.

Data availability

Data from the Human Connectome Project-Development and Human Connectome Project-Aging are publicly available on the National Institute of Mental Health Data Archive (NDA) [https://nda.nih.gov/].Requests to access data from these datasets can be made by filing Data Use Agreements and Data Use Certifications directly through NDA.

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Author contributions

L.T. and D.S. conceptualized, designed, curated and processed data, conducted analyses, and wrote manuscript. M.W. contributed in study design, data visualization, and provided comments. C.H., C.F., and B.F.T. provided processed data and provided comments.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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