Large-scale differences in functional organization of left- and right-handed individuals using whole-brain, data-driven analysis of connectivity

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Abstract

Handedness influences differences in lateralization of language areas as well as dominance of motor and somatosensory cortices. However, differences in whole-brain functional connectivity (i.e., functional connectomes) due to handedness have been relatively understudied beyond pre-specified networks of interest. Here, we compared functional connectomes of left- and right-handed individuals at the whole brain level. We explored differences in functional connectivity of previously established regions of interest, and showed differences between primarily left- and primarily right-handed individuals in the motor, somatosensory, and language areas using functional connectivity. We then proceeded to investigate these differences in the whole brain and found that the functional connectivity of left- and right-handed individuals are not specific to networks of interest, but extend across every region of the brain. In particular, we found that connections between and within the cerebellum show distinct patterns of connectivity. To put these effects into context, we show that the effect sizes associated with handedness differences account for a similar amount of individual differences in the connectome as sex differences. Together these results shed light on regions of the brain beyond those traditionally explored that contribute to

differences in the functional organization of left- and right-handed individuals and underscore that handedness effects are neurobiologically meaningful in addition to being statistically significant.

1. Introduction

Left-handed individuals comprise approximately 10% of the population (Faurie and Raymond, 2004). This rare event in the population is believed to be due to the development of language lateralization in the left hemisphere, giving rise to a primarily right-handed population (Corballis, 2003). The association between language lateralization and handedness have been well studied (Ocklenburg et al., 2014; Knecht et al., 2000). Additionally, brain differences between left- and right-handed individuals extend beyond language lateralization that include differences in the motor and the somatosensory networks (Jang et al., 2017). Neuroimaging studies have begun to highlight these differences using both functional activation (Luders et al., 2010; Jörgens et al., 2007; Grabowska et al., 2012; Nenert et al., 2017) and morphometry (Kertesz et al., 1990; Margiotoudi et al., 2019; Rosch et al., 2018). Even so, these types of studies do not address how brain regions interact and, therefore, may give an incomplete picture of the brain correlates of handedness. Functional connectivity analysis using functional magnetic resonance imaging (fMRI) is a powerful tool to characterize group differences exhibiting temporal synchrony of activity among brain regions. While there have been some functional connectivity studies of handedness (Kirsch et al., 2018; Pool et al., 2015; Li et al., 2015), these are limited to specific networks chosen *a priori* and potentially fail to capture a complete picture of the connectivity profiles of handedness (Luders et al., 2010; Jörgens et al., 2007; Grabowska et al., 2012; Nenert et al., 2017).

In this study, we utilize resting-state fMRI data, functional connectivity analyses, and cluster-based inference (Zalesky et al., 2010) to identify differences between left- and right-handed individuals using both hypothesis-based (e.g., networks of interest) and data-driven (e.g., whole-brain) approaches across two large datasets. For the hypothesis-based analyses, we define *a priori* networks of interest based on previous literature to investigate connectivity differences in the motor (Hatta 2007), somatosensory (Jung et al., 2008), and language (Szaflarski et al., 2012; Wiberg et al., 2019) networks. For the data-driven analyses, we calculate whole-brain functional connectomes (i.e., a functional connectivity matrix containing pair-wise connections from all brain regions) using a 268-node functional brain parcellation (Shen et al., 2017) and investigate connectivity across the whole brain. As handedness preferences are well-established by 5 years of age (Nelson et al., 2014), we chose to investigate connectivity differences between left- and right-handed individuals using data from two developmental datasets (Alexander et al., 2017; Satterthwaite et al., 2016), the Healthy Brain Network (HBN) and the Philadelphia Neurodevelopmental Cohort (PNC).

First, we performed cluster-based inference on our primary dataset, the HBN, establishing robust patterns of connectivity differences in the motor, somatosensory, and language networks. We then estimated the generalizability of these results to the PNC. Given the consistency of results and to increase power for whole-brain analyses, we combined

these datasets to examine differences across the connectome and perform exploratory investigations of differences for cerebellar edges. Overall, these results demonstrate that wide-spread differences in functional organization, spanning the whole-brain, exist between left- and right-handed individuals. Thus, it may be important to account for handedness in functional connectivity studies, in particular for studies involving neuropsychiatric disorders, where left-handed individuals are disproportionately represented (Hirnstein and Hugdahl, 2014).

2. Methods

2.1. Overview

We begin by using a primary dataset, the Healthy Brain Network (HBN), to explore differences between left- and right-handed individuals within networks of interest using functional connectivity to acknowledge previous literature and show these results in the context of functional connectivity. We then show that differences between left- and right-handed individuals within our primary dataset generalizes to other datasets, such as the Philadelphia Neurodevelopmental Cohort (PNC). After combining these datasets to maximize statistical power, we subsequently explore differences in handedness using functional connectivity across the whole brain. Our secondary analyses on the cerebellum are subsequently derived from interesting patterns and results that emerge from the whole brain analyses.

2.2. Primary dataset: Healthy Brain Network (HBN)

For the primary analyses, connectomes were generated from resting-state scans obtained from the Healthy Brain Network (HBN) (Alexander et al., 2017). All resting-state scans are 10 minutes long using Siemens Scanners at four different sites around the New York greater metropolitan area: Staten Island, Cornell University, City University of New York, and Rutgers University. After excluding subjects for missing scans/data and excessive motion (> 0.25 mm), 817 subjects remain (right-handed individuals: 713, left-handed individuals: 104). Subjects' ages ranged from 5 to 22 (Fig. S1), where 148 subjects had no diagnosis and 669 had some diagnosis of learning disorders or symptoms of psychiatry. Edinburgh Handedness Questionnaire (EHQ) scores were used as a measure of the extent subjects were left- or right-handed. Scores ranged from −100 to 100 where −100 is considered an extremely left-handed individual and 100 is considered an extremely right-handed individual, (histogram: Fig. S2).

2.3. Secondary dataset: Philadelphia Neurodevelopmental Cohort (PNC)

To demonstrate that our results generalize to other large datasets, we used data from the Philadelphia Neurodevelopmental Cohort (PNC) (Satterthwaite et al., 2016, 2014) by following the same preprocessing pipelines used with HBN. All resting-state scans are 6 minutes long using a single 3T Siemens TIM Trio whole-body scanner with the VB17 revision of the Siemens software. All participants were scanned at the University of Pennsylvania in Philadelphia, PA. After excluding subjects for missing scans/data and excessive motion (> 0.25 mm), 776 subjects remain (right-handed individuals: 660, left-handed individuals: 116). Subjects' ages ranged from 8 to 23 yrs (Fig. S1) and measures of

handedness were based on self-reports of dominant hand to complete another finger tapping task in the dataset (data not used in our analyses).

2.4. Preprocessing and generating connectomes

Both the HBN and PNC datasets were analyzed with identical processing pipelines. Structural scans were first skull stripped using an optimized version of the FMRIB's Software Library (FSL) (Smith et al., 2004) pipeline (Lutkenhoff et al., 2014). Functional images were motion corrected using SPM12. All further analyses were performed using Bioimage Suite (Joshi et al., 2011). 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 (Shen et al., 2013), which includes the cortex, subcortex, and cerebellum as described in prior connectome predictive modeling work (Finn et al., 2015). 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 (Scheinost et al., 2017), implemented in BioImage Suite. Resting-state connectivity was calculated on the basis of the 'raw' task time courses (Greene et al., 2020), which emphasizes individual differences in connectivity (Jiang et al., 2020). This involved computation of the mean time courses for each of the 268 nodes (i.e., averaging the time courses of all constituent voxels). Node-by-node pair-wise correlations were computed, and Pearson correlation coefficients were Fisher z-transformed to yield symmetric 268×268 connectivity matrices, in which each element of the matrix represents the connectivity strength between two individual nodes (i.e., 'edge').

2.5. Networks of interest analyses

First, we examined the motor, somatosensory, and language networks in the HBN using EHQ as a continuous measure of handedness, where scores ranged from −100 (extremely left-handed) to 100 (extremely right-handed). Based on previous literature on differences in handedness (Jörgens et al., 2007; Jung et al., 2008; Joliot et al., 2016; Foundas et al., 1998; Pool et al., 2014; Gorrie et al., 2008; Falk 1980; Meguerditchian et al., 2012; Longcamp et al., 2005; Amunts et al., 2000), we defined three networks of interest: motor, somatosensory, and language using the Brodmann Areas that were reported for each publication (Table 1). This approach was chosen over using canonical resting-state networks because it allows for a more direct comparison to previous results and most canonical resting-state networks do not include a language network and do not include the motor and somatosensory networks as separate networks. Visualizations for where these nodes are located on a 3D brain are shown in Fig. S3. Connectomes were partitioned into matrices that only contained edges that stem from a node of interest or edges between nodes of interest.

2.6. Generalization to the PNC

Next, using the network of interest approach, we then looked at how well results based on data from the HBN generalized to other datasets of similar populations by using data from the PNC. Differences between left- and right-handed groups were estimated in the PNC and resulting differences were quantitatively compared to the HBN results.

We investigated the relationship between the HBN and PNC results at both the edge- and node-level. For the edge-level, we counted the number of significant edges that appeared in both analyses (i.e., overlapping edges). The significance of the overlapping edges was determined with the hypergeometric cumulative density function (Rosenberg et al., 2016), which returns the probability of drawing up to x of K possible items in n drawings without replacement from an M-item population. In other words, this approach calculates the probability of finding the number of overlapping from two independent analyses by chance. Given the large number of possible edges (> 35,000), finding overlapping edges when randomly sampling two sets of ~1000 edges is rare. This was implemented in Matlab as: $p = 1\text{-hygecdf}(x, M, K, n)$, where x equals the number of overlapping edges, K equals the number of connections in the HBN network of interest, n equals the number of connections in the PNC network of interest, and M equals the total number of edges in the matrix (35,778). At the node-level, node degree–defined as the number of significant edges for each node–was calculated and correlated between the HBN and PNC results.

2.7. Combined whole-brain analyses: HBN and PNC

For all remaining analyses, we combined data from the HBN and PNC. To address incongruencies in handedness measures between the datasets, we binarized EHQ scores such that subjects who scored below 0 were considered primarily left-handed and above 0 were considered primarily right-handed. No subject had an EHQ score of exactly 0.

2.8. Identifying significant edges and networks

For both the networks of interest and the whole-brain analyses, differences between left- and right-handed groups were estimated using Network-Based Statistics (NBS) (Zalesky et al., 2010) (component-determining threshold $z = 1.96$, 2-tailed, $K = 5000$ permutations). NBS is analogous to cluster-based correction and provides a solution to the statistical problem of massive multiple comparisons in a whole-brain connectivity analysis. In NBS, using the difference between left- and right-handed individuals, the largest fully connected network of suprathreshold edges, or "component", is identified and its extent defined as the number of edges it comprises. Finally, these calculations are repeated for 5000 iterations in which subjects' group assignments are randomly permuted to create a null distribution for the expected component size due to chance.

To visualize these results, we plotted edges and nodes on two visualizing modalities: ball-stick figures on 3D brains and circle plots. Due to the complicated nature of our results and the high number of edges in a connectome, some results have had to be thresholded for interpretability. Thresholds work by only visualizing edges connected to nodes that have minimum x number of connections to them.

To help summarize the complex nature of our results, we categorized significant edges as (1) located within the left or right hemisphere and (2) as between hemisphere edges. Chi-squared tests were used to compare these distributions.

2.9. Whole brain effect sizes

Due to such widespread differences in the whole brain connectivity between left- and right-handed individuals, we quantified the effect size via Cohen's D of the connectivity differences between left- and right-handed individuals for all edges. To help put these whole-brain differences into 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 (Gaillard et al., 2021; Rippon et al., 2014). Effect sizes for sex were calculated using only right-handed individuals. Cohen's D was then calculated for the difference between male and female participants (based on self-reported sex).

2.10. Secondary: cerebellar analyses

Based on our whole-brain results, we performed a set of secondary analyses restricting comparisons to cerebellar connections in an analogous manner as our network of interest analyses. In doing so, we subsetted our connectomes to only include nodes within and between the cerebellum and removed all other values. Differences between left- and right-handed groups were estimated using NBS (Zalesky et al., 2010) (component-determining threshold $z = 1.96$, 2-tailed, $K = 5000$ permutations) for each separately.

2.11. Controlling for confounding factors in datasets

We conducted additional analyses using NBS with partial correlations to control for sex (Tables S1 and S2) and age (Tables S3 and S4) in the HBN and PNC datasets. We also controlled for scan sites (Table S5) and clinical diagnoses (Table S6) in the HBN. Pearson correlations were calculated between matrices of significant edges identified by NBS alone and NBS partial correlations controlling for each factor.

3. Results

3.1. Networks of interest analyses: HBN

3.1.1. Motor—Within the motor network (Fig. 1A), two clusters consisting of 227 edges (of greater connectivity in right-handed individuals) and 195 edges (of greater connectivity in left-handed individuals) show significantly different ($p < 0.05$, two-tailed, corrected) connectivity between groups out of a total of 4042 possible edges. Interhemispheric connections between both sides of the motor strip exhibited a mix of greater and weaker connectivity for left-handed individuals compared to right-handed individuals. However, edges between the motor areas and other regions of the brain show distinct patterns between the two groups. In right-handed individuals, edges of greater connectivity relative to left-handed individuals, are scattered throughout the brain across all anatomical regions. Notably, the majority of these edges are between-hemisphere edges relative to within-hemispheres (between: (136/227 edges or 59.9%; within: 91/227 edges or 40.0%; $x^2 = 4.31$, $p = 0.038$; Fig. S4).

In contrast, a majority of edges exhibiting greater connectivity in left-handed individuals are within-hemisphere edges, between-hemisphere edges were generally confined to motor-motor edges (between: 82/195 edges or 42.0%; within: 113/195 edges or 58.0%; X^2 = 2.64, p = 0.104; Fig. S4). Neither group exhibit edges confined to a specific hemisphere (left-handed: X^2 = 1.79, p = 0.181; right-handed: X^2 = 1.42, p = 0.233; Fig. S4). Perhaps most interestingly, we observe a bundle of edges of greater connectivity in left-handed individuals between the right motorstrip and the ipsilateral cerebellum, in alignment with the known roles for the cerebellum in motor control and adjustments (Gao et al., 1996). Yet, canonical motor-cerebellar circuits point towards contralateral connections (i.e., the right motor strip connects to the left cerebellum).

3.1.2.   Somatosensory—Similar patterns are observed for the somatosensory network (Fig. 1B) with two clusters consisting of 127 edges (of greater connectivity in right-handed individuals) and 88 edges (of greater connectivity in left-handed individuals) exhibiting significantly different (p < 0.05, corrected) connectivity between left-handed and right-handed groups out of a total of 2108 edges. Neither group exhibit edges lateralized to a specific hemisphere (left-handed: X^2 = 2.22, p = 0.136; right-handed: X^2 = 0.04, p = 0.841; Fig. S4). For edges of greater connectivity in right-handed individuals, the majority are between-hemisphere edges relative to within-hemispheres (between: 80/127 edges or 63.0%; within: 37/127 edges or 37.0%; X^2 = 7.81, p = 0.005; Fig. S4).

For edges of greater connectivity in left-handed individuals, the majority are within-hemisphere edges relative to between-hemispheres (between: 29/88 edges or 33.0%; within: 59/88 edges or 67.0%; X^2 = 5.27, p = 0.022; Fig. S4). However, of the contralateral edges identified as greater connectivity in left-handed individuals, the majority are edges stemming from the parietal networks to the contralateral cerebellum on both sides. This could be partly due to the previous phenomena explained in the motor network. Studies have also shown that the cerebellum has somatosensory representation (Takanashi et al., 2003), accounting for the synchronous activity observed in both populations, but particularly in left-handed individuals.

3.1.3.   Language—Finally, for the language network (Fig. 1C), two clusters consisting of 337 edges (of greater connectivity in right-handed individuals) and 325 edges (of greater connectivity in left-handed individuals) display significantly different (p < 0.05, corrected) connectivity between the two groups out of a total of 6138 edges. Similarly to the patterns observed in the motor and somatosensory networks, the connectivity of cerebellum is notable. Bundles of edges, exhibiting greater connectivity in left-handed individuals, between both frontal lobes to the ipsilateral cerebellum are present. Additionally, bundles of edges with greater connectivity in right-handed individuals are observed between nodes in the right parietal lobe and both hemispheres of the cerebellum.

In contrast to the motor and somatosensory networks, no differences in the distribution of between and within-hemisphere edges in right-handed individuals is observed (between: 165/337 edges or 49.0%; within: 172/337 edges or 51.0%; X^2 = 0.05, p = 0.823; Fig. S4). However, similar to the motor and somatosensory networks, a majority of edges exhibiting greater connectivity in left-handed individuals are within-hemisphere edges relative to

between-hemispheres (between: 133/325 edges or 40.9%; within: 192/325 edges or 59.1%; $X^2 = 5.22$, $p = 0.022$; Fig. S4) with between-hemisphere edges primarily located between the parietal lobes. Neither group exhibit edges lateralized to a specific hemisphere (left-handed: $X^2 = 3.40$, $p = 0.065$; right-handed: $X^2 = 1.17$, $p = 0.279$; Fig. S4).

We observe that nodes with the largest number of edges for right-handed individuals (i.e., hubs) are located in both parietal lobes. Surprisingly, given the lateralization of language to the left hemisphere in right-handed individuals, the largest hubs are located in the secondary language regions in the right parietal lobe. In contrast, left-handed individuals show hubs of significantly greater connectivity in the right hemisphere homologue of Broca's area (Duffau et al., 2008). Overall, while right-handed individuals showed more widespread connectivity throughout the language networks, these edges appear to form hubs in the parietal lobe. Additionally, the cerebellum is differentially connected to the language network between the two groups. In particular, frontal-cerebellar connections were more prominent for left-handed individuals and parietal-cerebellar connections were more prominent for right-handed individuals.

For all networks of interest, similar results were obtained using the EHQ as a continuous or binary variable (EHQ < 0 = left-handed individuals, EHQ > 0 = right-handed individuals) (Fig. S5) and controlling for various demographic factors (e.g., age, sex) (Tables S1-S6). Overall, these results build upon previous work showing differences in activation patterns in networks of interest such that these differences are also observable in patterns of connectivity for all networks.

3.2.   Generalization of networks of interest results to the PNC dataset

Using the network of interest approach, we then looked at how well results based on data from the HBN generalized to other datasets of similar populations using data from the PNC (Fig. S6). We observed similar patterns of group differences in the HBN and PNC datasets as evidenced by the number of overlapping edges and the correlation of nodal degree between the two sets of results. All resulting networks of group differences were significant between the two analyses at the edge-level ($p < 0.05$; Fig. S7: top row; with the exception of the network of greater edges for left-handed individuals in the motor network) and at the node-level (all r's > 0.54, all p's < 0.001). Quantitatively, in the motor network, a fraction of edges connecting the right motorstrip and ipsilateral cerebellum are present in the PNC as well. Whereas in the somatosensory network, similar crossing patterns connecting somatosensory nodes with contralateral cerebellum nodes are observed. Overlapping edges in the language network continue to highlight the importance of the cerebellum in connectivity differences between the two groups. Notably, the measures of handedness between the HBN and PNC were conducted differently as the HBN utilized EHQ scores which ranged from −100 to 100 while the PNC was based on self-reported measures of dominant hand for a hand tapping task. Despite differences in behavioral measures, similar patterns of connectivity were repeatedly identified as significantly different between left- and right-handed groups. This highlights the robustness and generalizability of these results.

3.3. Whole-brain analyses: HBN and PNC

After having established that observed differences between left- and right-handed groups in the HBN generalize to the PNC, we combined the two datasets to increase our sample size and statistical power for whole-brain analyses. To harmonize the handedness measures in the HBN and PNC, we binarized EHQ scores to make them consistent with the PNC, such that individuals with a score below 0 were classified as primarily left-handed and individuals with a score above 0 were classified as primarily right-handed.

Despite previous literature, widespread connectivity was observed across the whole brain between left- and right-handed groups (Fig. 2A), beyond those in the networks of interest. Two clusters consisting of 1600 edges (of greater connectivity for left-handed individuals) and 1450 edges (of greater connectivity for right-handed individuals) exhibit significantly different ($p < 0.05$, corrected) connectivity between the two groups. Similar to the networks of interest analyses, cerebellar connections are prominent (left-handed individuals: 39.69% significant edges; right-handed individuals: 31.78% significant edges; Fig. 2B). We observe a large proportion of edges exhibiting greater connectivity for right-handed individuals between the right cerebellum and the left prefrontal regions. In contrast, edges of greater connectivity for left-handed individuals were more localized to connections between the cerebellum and posterior regions (e.g., the occipital and parietal lobes). Results are similar when controlling for various demographic factors (e.g., age and sex for both HBN and PNC; scan sites and clinical diagnoses for HBN) (Tables S1-S6).

Edges of greater connectivity for right-handed individuals were more *lateralized* within the left hemisphere (within left hemisphere: 423 edges; within right hemisphere: 324 edges; x^2 = 6.46, p = 0.011; Fig. S9), consistent with the theory of left-hemisphere dominance in right-handed individuals (Hécaen and Sauguet, 1971). However, edges of greater connectivity for left-handed individuals were not *lateralized* to either hemisphere (within left hemisphere: 353 edges; within right hemisphere: 411 edges; x^2 = 2.20, p = 0.138; Fig. S9), consistent with the observation of a mix of left- and right-hemisphere dominance, or even right-hemisphere dominance, in left-handed individuals. No differences in the distribution of between- and within-hemisphere edges in left- or right-handed individuals are observed (left-handed individuals between: 836/1600 edges or 52.3%; within: 764/1600 edges or 47.8%; X^2 = 1.62, p = 0.203; right-handed individuals between: 732/1450 edges or 49.8%; within: 737/1450 edges or 50.2%; X^2 = 0.01, p = 0.920; Fig. S9).

The largest proportion of edges that differed between left- and right-handed individuals were localized to the prefrontal lobe (left-handed individuals: 33.56% significant edges; right-handed individuals: 48.93% significant edges; Fig. 2B), consistent with our network of interest results, where expressive language processing nodes (e.g., Broca's region) and secondary motor nodes are located. Surprisingly, but in line with Fig. 2A, the cerebellum contained the second largest amount of edges that differed between the two groups (left-handed individuals: 39.69% significant edges; right-handed individuals: 31.78% significant edges; Fig. 2B). These results were consistent when normalizing the number of edges within each network (Fig. S10). Of the 3079 edges that were identified as significantly different between the two groups at the whole-brain level, only 16.95% were also initially identified as significant using the networks of interest analysis. Overall, this observation suggests

that functional connectivity differences between left- and right-handed individuals span the whole brain–rather than being localized to specific networks as suggested by previous literature (Knecht et al., 2000; Jung et al., 2008).

Effect sizes for connectivity differences between left- and right-handed groups ranged from −0.3 to 0.3, consistent with the observation that brain-behavior associations tend to have low to medium effect sizes (Noble et al., 2020). Broadly, the effect sizes observed for sex differences in whole-brain functional connectivity were of a similar magnitude as the effect sizes observed for handedness differences (Fig. 3) with no significant differences between the two distributions of effect-sizes being observed. Together, these results suggest that handedness differences account for a similar amount of individual differences in the connectome as sex differences, and underscore that the handedness effects are neurobiogically meaningful in addition to being statistically significant.

3.4. Cerebellum

Given the striking contribution of the cerebellum to the networks of interest (Fig. 1) and whole-brain group differences (Fig. 2) as well as the relatively unexplored functional differences in the cerebellum between left- and right-handed groups (Kavaklioglu et al., 2017), we further investigated cerebellar differences in functional connectivity using our networks of interest approach.

Within the cerebellar network (Fig. 4), clusters consisting of 463 edges (of greater connectivity in right-handed individuals) and 558 edges (of greater connectivity in left-handed individuals) exhibit significantly different ($p < 0.05$, corrected) connectivity between the two groups. Left-handed individuals show large bundles of edges with significantly greater connectivity between the cerebellum and the motor strip and somatosensory areas, consistent with results for the motor and language networks (Fig. 1). Interestingly, edges of greater connectivity for left-handed individuals are generally confined towards the posterior regions of the brain, whereas edges of greater connectivity for right-handed individuals are generally confined to the frontal regions. Results are similar when controlling for various demographic factors (e.g., age, sex) (Tables S1-S4). Edges of greater connectivity in right-handed individuals are mostly between-hemisphere edges rather than within hemispheres (between: 274/463 edges or 59.2%; within: 189/463 edges or 40.8%; $X^2 = 7.69$, $p = 0.006$; Fig. S11) and are more *lateralized* within the left hemisphere (within left hemisphere: 126 edges; within right hemisphere: 63 edges; $^2 = 14.86$, $p < 0.001$; Fig. S11). No differences in the distribution of edges of greater connectivity in left-handed individuals were observed (between: 284/558 edges or 50.9%; within: 274/558 edges or 49.1%; $X^2 = 0.09$, $p = 0.76$; within left hemisphere: 132 edges; within right hemisphere: 152 edges; $^2 = 0.71$, $p = 0.40$; Fig. S11).

4. Discussion

Using functional connectomes from two large open-source datasets (the Healthy Brain Network and Philadelphia Neurodevelopmental Cohort), we show that differences in the functional organization between groups of primarily left- and primarily right-handed individuals are found not only in previously identified functional networks, but in every

brain region with a strikingly large amount of differences for edges incident to the cerebellum. These results are summarized in Fig. 5. We began by investigating differences in networks of interest, as established by previous activation studies, to show that these differences can also be detected by functional connectivity. We then show that these differences also robustly generalized across datasets. In a combined sample from both datasets, we show that differences in functional connectivity between left- and right-handed individuals are present across the whole brain. In particular, to emphasize the significance of these differences, we compared the distribution of effect sizes to those from self-reported sex. Handedness differences exhibit similar effect sizes as sex differences, suggesting handedness may be a factor researchers should control for in future large-scale connectome studies. Finally, while previous studies have focused on the cortex (Amunts et al., 2000; Jung et al., 2003), we find that the most striking differences between left- and right-handed groups are edges located within and between the cerebellum. Together, these results characterize fundamental differences in the functional connectome associated with handedness.

4.1. Whole brain analyses: going beyond regions of interest

Deviating from traditional region and network of interest approaches, our whole-brain results emphasize that differences between left- and right-handed groups are wide-spread across the whole brain rather than localized to a few regions and networks. Indeed, only 16.95% of edges from the whole-brain results were identified as significant using the networks of interest analysis. The widespread nature of our results is also in contrast to emerging morphometric studies of handedness, which similarly report sparse, localized differences between the two groups (Sha et al., 2021). It is possible that these large-scale differences in functional connectivity are not likely observable in fixed anatomical structures.

4.2. Cerebellum

A majority of handedness work had previously focused on differences in the cortex (Pool et al., 2014; Foundas et al., 1998; Corballis 2003; Amunts et al., 2000; Amunts et al., 1996; Dassonville et al., 1997; Kim et al., 1993). Yet, the cerebellum demonstrated the second largest number of significant edges of networks evaluated in the data-driven, whole-brain analysis (the prefrontal lobe, which includes several of our networks of interest, contained the largest number of significant edges). While the prefrontal cortex and its corresponding network showed the greatest number of significant edges, this was not surprising due to previous literature showing differences in regions such as language, motor, and somatosensory, all of which are included in our canonical definitions of prefrontal regions. Only a few studies have explicitly studied the cerebellum in regards to handedness (Rosch et al., 2018; Kavaklioglu et al., 2017). Perhaps this result is not surprising given the cerebellum's role in motor control (Paulin, 1993; Ebner and Pasalar, 2008) and the association of motor control and handedness (Amunts et al., 2000; Pool et al., 2014). Nevertheless, most of the significant edges do not involve the motor cortex, congruent with our results showing more significant edges in the cerebellum and prefrontal regions, rather than a solely motor region (Buckner, 2013).

4.3. Effect sizes: controlling for handedness in large studies

Given the magnitude of effect sizes in neuroimaging and clinical and social factors associated with sex differences (Helpman et al., 2017), sex is routinely controlled for in neuroimaging studies (Gaillard et al., 2021; Rippon et al., 2014). The similarity between the effect size magnitude of handedness differences and sex differences in functional connectivity underscores the importance of potentially accounting for these functional differences. Future studies that include a large number of left-handed individuals may need to control for handedness in a similar manner as other covariates, such as sex. One caveat might be that left-handed individuals are relatively rare (around 10% of the population (Faurie and Raymond, 2004)). Many functional connectivity studies may not have a sufficiently large sample of left-handed individuals to properly estimate these effects. However, potential differences in the connectome should not be used to justify excluding left-handed individuals from a study. Best practices in maintaining representative samples necessitates the inclusion of left-handed individuals (Jack and A Pelphrey, 2017). Nevertheless, the best approach for accounting for handedness differences in the connectome remains to be determined.

4.4. Functional connectivity relative to other brain studies of handedness

In line with previous results from activation, morphometric, neuropsychological, and lesion (Vargha-Khadem et al., 1985) studies, we found that functional connectivity incident to the motor, somatosensory, and language networks differed between primarily left- and primarily right-handed individuals. While our results build upon this previous work, differences in functional connectivity do not necessarily translate to observed differences in brain activation (Tomasi et al., 2014) or structure. For instance, one may expect large functional connectivity differences in Broca's and Wernicke's areas (Ocklenburg et al., 2014; Foundas et al., 1998) based on previous work in activation studies regarding lateralization differences in language between left- and right-handed individuals. Yet, we found the largest number of significantly different edges clustered in the right-hemisphere, located in secondary language processing regions of the temporoparietal junction (in right-handed individuals). The lack of one-to-one translation of results between functional connectivity and activation likely holds in the other direction, too. In other words, the lack of differences in functional connectivity does not imply that activation patterns in Broca's or Wernicke's areas between left- and right-handed individuals during a language task would be the same. Even so, left-handed individuals show a mix of left and right language dominance, while right-handed individuals mostly show right dominance. As we cannot access language dominance in either sample, language dominance could affect our results. For example, left-handed individuals with right dominance for language may show different connectivity patterns than left-handed individuals with left dominance.

Nevertheless, patterns of within- and between-hemisphere edges also appear to be consistent across all three networks of interest, suggesting our results may be robust to the lateralization of language dominance.

4.5. Strengths

There are several notable strengths of our study. First, we used two large open-source datasets, allowing for a large sample of left-handed individuals ($n = 220$), the application of whole-brain approaches and the ability to investigate generalization/replication of results across study designs. Without the large sample size and whole-brain analyses, important results (e.g., the widespread nature of handedness differences and the large handedness differences in cerebellum) may not have been discovered. Similarly, generalizing results from the HBN to the PNC highlight their robustness, especially considering the different handedness measures across the datasets.

4.6. Limitations

Nevertheless, there are several notable limitations of our study. First, while all of our analyses are based on the same procedure and thresholds using NBS, it is important to note that running NBS on a subsetted connectome as opposed to the whole connectome will select different edges as a result. For instance, an edge that is initially identified as significant based on a subsetted connectome (like in our networks of interest) may not be identified as significant when using the entire connectome (like in our whole brain analysis). Second, in defining our networks of interest, we based our definitions on differences in activation patterns shown in previous studies (Jung et al., 2008; Jörgens et al., 2007; Hepper et al., 2005). These previous studies have typically reported their results in the context of Brodmann areas, where our connectomes are parcellated based on a 268-node functionally defined atlas. Thus, we manually identified nodes that overlapped with these Brodmann areas, however, due to the differences in the Shen atlas and the Brodmann areas, our networks of interest may not have captured the exact regions that were reported in previous studies. The choice of which atlas to use for analysis is not simple. To our knowledge, none of the existing atlases have been designed to differentiate between left- and right-handed individuals, which could bias any connectome-based results of handedness. As more knowledge is uncovered on the functional differences between left- and right-handed individuals, given the large effect sizes of differences in handedness (Fig. 3), constructing different atlases based on handedness or incorporating individualized atlases (Laumann et al., 2015; Gordon et al., 2016; Kong et al., 2019, 2021) that account for the functional topology of an individual subject are logical next steps. Third, in our whole-brain analysis, we were limited to binarizing EHQ scores in the HBN for harmonization with the PNC handedness measure. While we could have explored a third group of ambidextrous individuals in the HBN, we were limited by: (a) the fact that there is no gold standard for the range of scores in the EHQ to classify an ambidextrous group (Edlin et al., 2015) and (b) the PNC's measures of handedness being a forced-choice self report of handedness. Because of the variability and range in EHQ scores, we chose to conduct our initial analyses on the HBN and subsequent generalization/harmonization to the PNC. Finally, to address handedness interactions with sex and age, we repeated all NBS analyses using partial correlation to control for these factors (sex: Table S1, age: Table S3) as well conducting analyses for the two datasets separately (sex: Table S2, age: Table S4). These results robustly demonstrate that while sex and age are potential confounding factors, our results remain unchanged as the same significant edges are identified with and without controlling for these factors. Additionally, we also controlled for scanning site and clinical diagnoses for

the HBN, since this population was scanned across multiple sites and contained many individuals with clinical diagnoses as well as an imbalance of diagnoses across handedness (site: Table S5, diagnoses: Table S6). Similarly, the same significant edges were robustly identified as significant with or without controlling for scanning site and clinical diagnoses. The results from the HBN also generalized well to the PNC, which has significantly less clinical diagnoses and were collected on a single scanner.

4.7. Conclusions

In sum, we show that differences in the functional connectome associated with handedness are distributed across the brain, including previously unreported differences associated with the cerebellar network. Future directions include investigations into sex-handedness interactions (Levy and Reid, 1978; Amunts et al., 2000; Kertesz et al., 1990; Papadatou-Pastou et al., 2008) (as majority of left-handed population consists of males (Chapman and Chapman, 1987)), into a third ambidextrous group, and into potential interactions between handedness and psychiatric diagnoses (as non-right handedness is overrepresented in various psychiatric disorders, namely schizophrenia (Hirnstein and Hugdahl, 2014)). As the observed differences show meaningful effect sizes, future studies may need to consider accounting for handedness. This work serves as a starting point to account for handedness in functional connectivity studies, in particular for studies involving neuropsychiatric disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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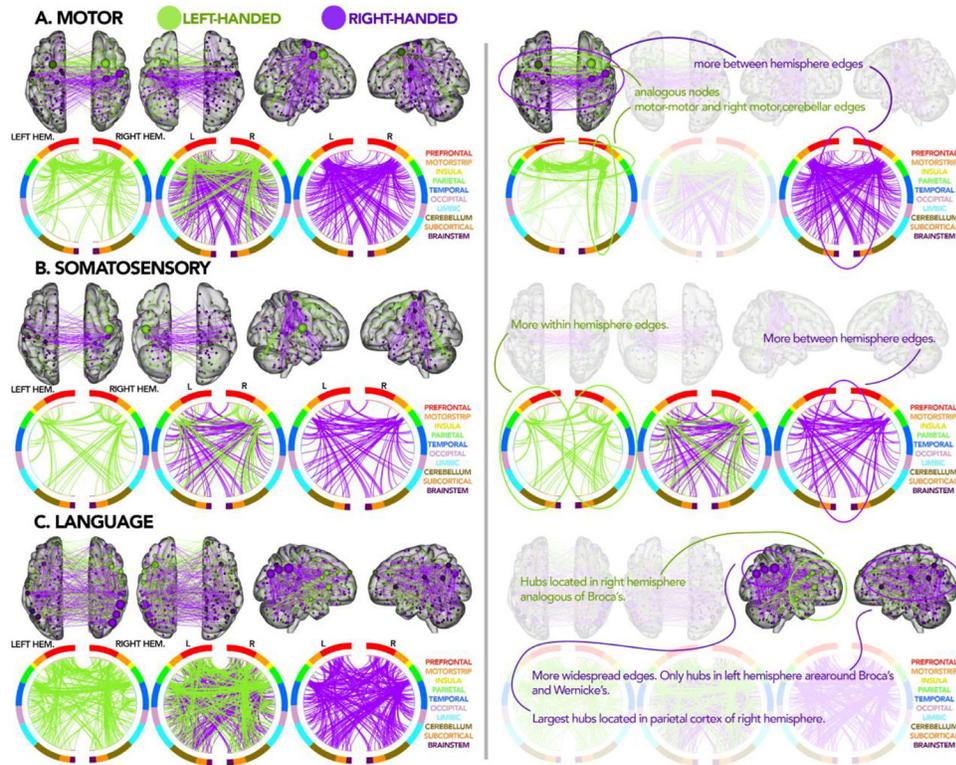
Fig. 1.

Brain and circle plots for each of the a priori defined networks in the HBN dataset. Edges that are greater for left-handed individuals are shown in green while edges that are greater for right-handed individuals are shown in purple. Results are identical for the left and right panels. The right panel shows additional annotations to simplify and demonstrate our points. Top row for each section shows significant edges drawn on an anatomical 3D brain with nodes sized based on the number of significant edges identified. Bottom row for each section shows circle plots where the left and right hemispheres are depicted as left and right semi-circles, respectively. The middle circle plot shows an overlay between left- and right-handed individuals. Nodes are color-coded by anatomical region constructed based on the Shen atlas, each line depicts a significant edge identified through NBS. Legend for which anatomical region each color represents is shown next to the circle plots. Each section shows results for each network of interest: (A) motor (p-val: 0.027), (B) somatosensory (p-val: 0.024), (C) language (p-val: 0.005).
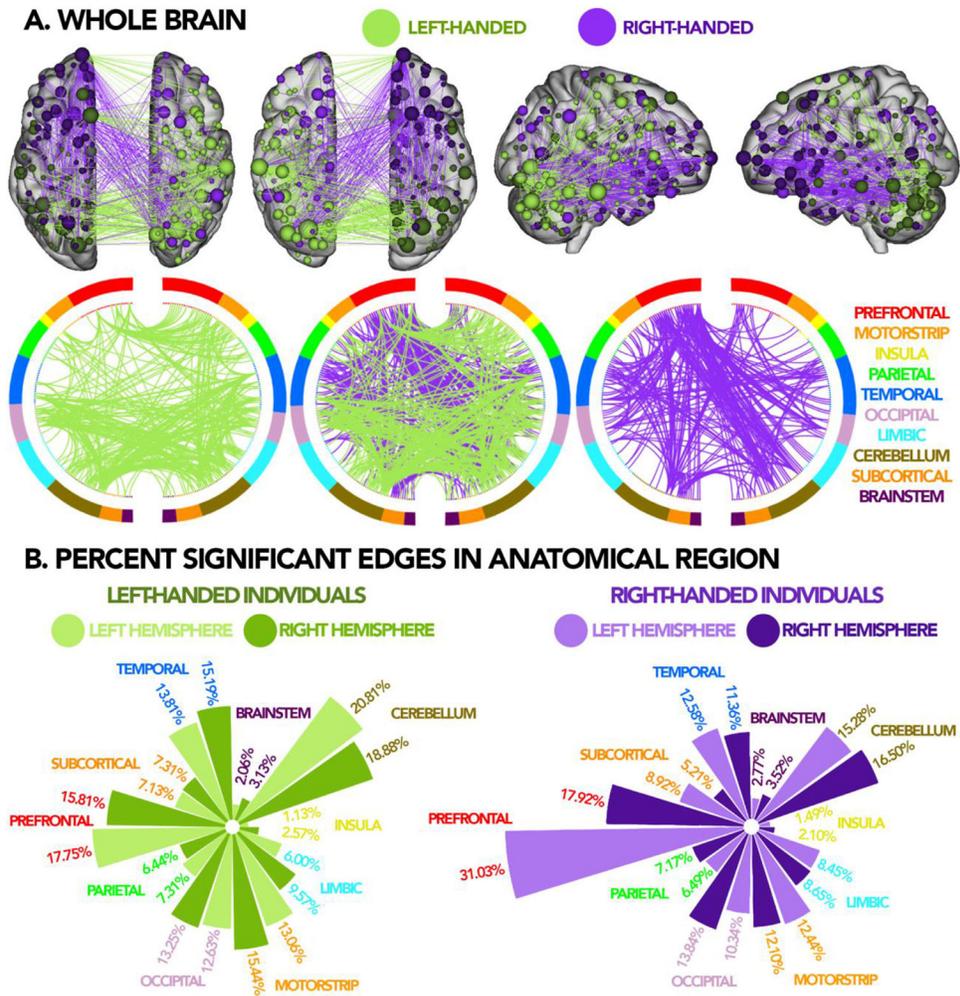
Fig. 2.
(A) Brain and circle plots for the entire connectome (p-val = 0.0018), both plots were thresholded at a degree threshold of 50 for visualization. Brain plots with varying thresholds are shown in SI (Fig. S8). Results for left-handed individuals are shown in green while results for right-handed individuals are shown in purple. Top row shows significant edges drawn on an anatomical brain with nodes sized based on the number of significant edges identified. Bottom row shows circle plots where the left and right hemispheres are depicted as left and right semi-circles, respectively. The middle circle plot shows an overlay between groups. Nodes are color-coded by anatomical regions constructed based on the Shen atlas, each line depicts a significant edge identified through NBS. (B) Circular bar graph quantifying the percent of significant edges in each anatomical network corresponding with the circle plots in 2A split by left and right hemispheres, for left and right-handed groups.
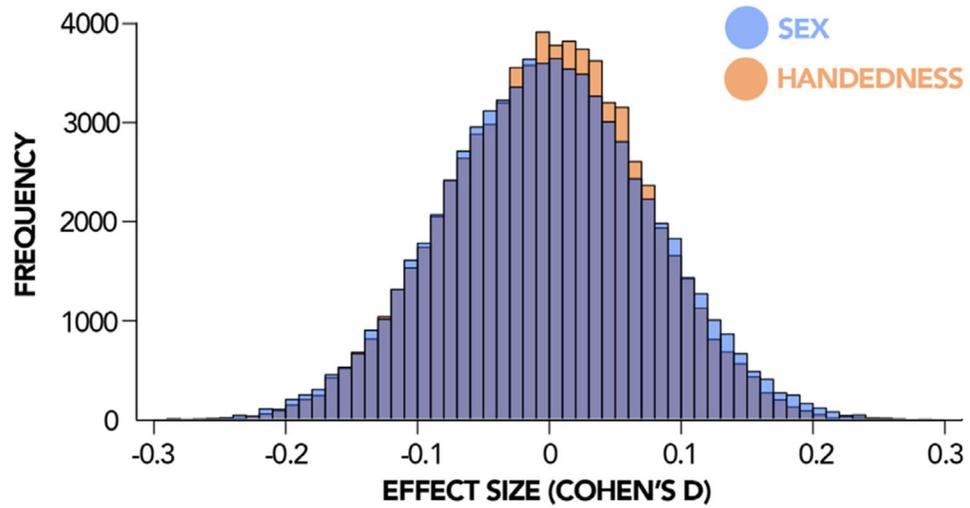
Fig. 3..

Comparison of effect sizes for each edge in a connectome (total 35,778 edges) plotted onto a histogram for handedness and sex. The large overlap between these distribtions suggest that handedness differences account for a similar amount of individual differences in the connectome as do sex differences.
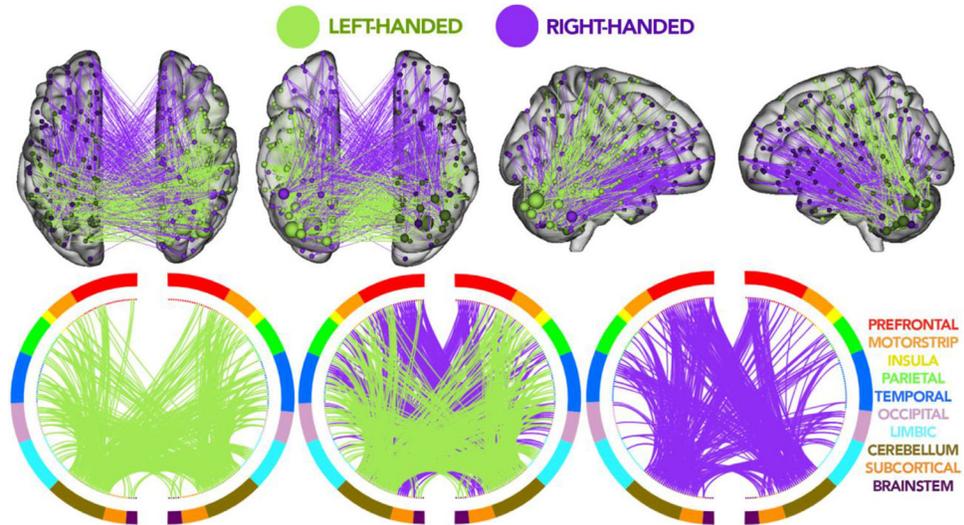
Fig. 4..

Brain and circle plots for all nodes in the cerebellum (p-val = 0.031). Edges of greater connectivity for left-handed individuals are shown in green while edges of greater connectivity for right-handed individuals are shown in purple. Top row shows significant edges drawn on an anatomical brain with nodes sized based on the number of significant edges identified. Bottom row shows circle plots where the left and right hemispheres are depicted as left and right semi-circles, respectively. The middle circle plot shows an overlay between left- and right-handed individuals. Nodes are color-coded by data-driven networks constructed based on the Shen atlas, each line depicts a significant edge identified through NBS.

Analysis	Datasets	EHQ or Binarized	Summary
Network of Interest: Motor	HBN	EHQ	• **Left-Handed:** Edges between right prefrontal and ipsilateral cerebellum. • **Right-Handed:** More between hemisphere edges.
Network of Interest: Somatosensory	HBN	EHQ	• **Left-Handed:** More within hemisphere edges in both hemispheres. • **Right-Handed:** More between hemisphere edges.
Network of Interest: Language	HBN	EHQ	• **Left-Handed:** Hub of significant nodes located on right hemisphere analogous of Broca's and Wernicke's areas. • **Right-Handed:** Hubs of significant nodes located in Broca's and Wernicke's as well as being more widespread through parietal cortex.
Whole Brain	HBN + PNC	Binarized	• **Left-Handed:** Significant edges are within and between the cerebellum. • **Right-Handed:** Bundles of significant edges between left prefrontal and right cerebellum.
Cerebellum	HBN + PNC	Binarized	• **Left-Handed:** Significant edges are within and between the cerebellum. • **Right-Handed:** Significant edges are between cerebellum and prefrontal regions.

Fig. 5.
Summary of handedness results across all analyses. Green text represents key observations for edges of greater connectivity in left-handed individuals. Purple text represents key observations for edges of greater connectivity in right-handed individuals.

Table 1

Allocation of nodes for each of the three networks of interest: motor, somatosensory, language. Node definitions for both left and right hemispheres are based on Brodmann Areas as reported from previous literature of differences in pure activation patterns.

Network	Brodmann Areas	Shen atlas nodes	
		Left	**Right**
Motor	• Premotor/ Supp. motor: BA6 (Longcamp et al., 2005) • Primary Motor: BA4 (K Amunts et al., 2000.)	• BA4: Node 158 • BA6: Node 157, 159–166, 218	• BA4: Node 23 • BA6: Node 24, 26, 27, 29–32
Somatosensory	• Primary Sensory: BA1 (Gorrie et al., 2008)	• BA1: Node 167, 171–173	• BA1: Node 33, 38–40
Language: Broca's, Wernicke's	• BA 44, BA9, BA 40 (Jörgens et al., 2007) • Wernicke's: BA22 (Meguerditchian et al., 2012), BA39 (Falk 1980) • Broca's: BA44, BA45 (Foundas et al., 1998)	• BA9: Node 145–147 • BA22: Node 197 • BA39: Node 182–184 • BA40: Node 179–181 • BA44: Node 156 • BA45: Node 155	• BA9: Node 10, 11 • BA22: Node 63, 64 • BA39: Node 48, 49 • BA40: Node 45–47 • BA44: Node 21, 22 • BA45: Node 20