ORIGINAL ARTICLE

Hand preference and local asymmetry in cerebral cortex, basal ganglia, and cerebellar white matter

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Abstract

Hand preference is a striking example of functional lateralization, with 90% of the population preferentially using their right hand. However, the search for brain structural correlates of this lateralization has produced inconsistent results. While large-scale neuroimaging studies using automated methods have largely failed to find local anatomical asymmetries associated with hand preference, other studies identifying specific motor regions have been able to find local morphological and functional differences. The present study looked at brain asymmetries in the brain's motor system using established cortical landmarks to identify the somatomotor hand region and extracted regional volumes of subcortical and cerebellar regions. Our results showed a strong left–right asymmetry in the cortical hand region, with weaker asymmetries appearing in the striatum and cerebellar white matter. Such asymmetries were much more pronounced in right-handers, whereas much weaker or absent lateralizing effects were observed in left-handed subjects. This study demonstrates the importance of local landmarks in studying individual anatomical differences. More generally, establishing structural correlates of hand preference is important, as this could further establish the origins of cerebral lateralization.

Keywords Left–right asymmetry · Hand preference · Brain morphology · Motor system

Introduction

The majority of human subjects (90%) consistently prefer their right hand for tasks requiring dexterity (Gilbert and Wysxki 1992). Although hand preference is observed in some other primates, such a strong and consistent behavioural preference for one side is unique to humans (Lonsdorf and Hopkins 2005; Hopkins et al. 2011). That being said, examining the neuroanatomical correlates of this strong asymmetry has not been easy. Large-scale whole-brain studies using Voxel-Based Morphometry (VBM) have not found significant regional grey matter asymmetries in either the

cerebrum or cerebellum (Ocklenburg et al. 2016; Kavaklioglu et al. 2017), nor did large-scale studies examining brain surface area and cortical thickness (Guadalupe et al. 2014; Kong et al. 2018). In a recent opinion article, Andersen and Siebner concluded that there were no grey matter differences associated with handedness (Andersen and Siebner 2018). Yet, studies using other methods have reported asymmetries associated with hand preference. Measuring the depth of the central sulcus in axial Magnetic Resonance Imaging (MRI) sections, Amunts and colleagues (Amunts et al. 1996, 2000) found that, at least in men, the sulcal depth tends to be greater in the left hemisphere for right-handers, with similar findings apparent in the right hemisphere for a majority of the left-handers. Hand preference has also been related with asymmetries in fronto-parietal connectivity, as suggested with Diffusion Tensor Imaging (DTI) (Howells et al. 2018).

The primary aim of the present study is to examine the relationship between hand preference and anatomical asymmetries in the sulcal area along the central sulcus.

One specific anatomical landmark, the 'hand-knob', can readily be identified in serial MRI images demarcating the primary motor/sensory hand region along this central sulcus (Yousry et al. 1997; Boling et al. 1999) (Fig. 1). In

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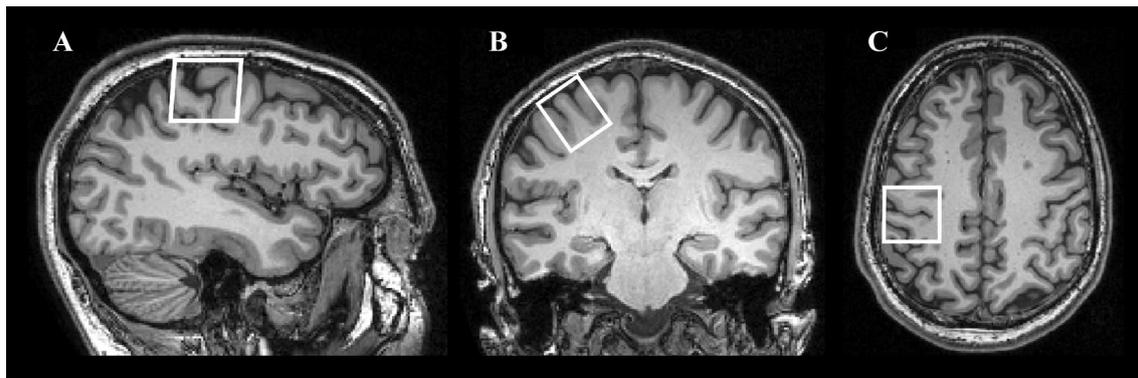
Fig. 1 Illustration of the hand-knob in the human brain in sagittal (**a**) coronal (**b**) and horizontal (**c**) view [as described in (Yousry et al. 1997)]. These three views permit a reliable delineation of the morphological feature

addition, since the basal ganglia and the thalamus are intimately involved in motor control, we also sought to examine potential asymmetries in these deep grey matter structures. Lastly, as the cerebellum is closely involved in fine motor control (Manto et al. 2012), possible cerebellar asymmetries were also investigated. Thus, in this manuscript, in addition to examining cortical morphology, we also examine subcortical (Chakravarty et al. 2013; Pipitone et al. 2014) and cerebellar white and grey matter (Park et al. 2014) using the MAGet Brain segmentation algorithm.

Method

For manual segmentation, the sample consisted of 35 participants from the International Consortium for Brain Mapping (ICBM) project (Mazziotta et al. 2001) and included 20 right-handers (7 female, average age 25.4 years (stdev 5 years) and 15 left-handers (6 female, average age 24.6 years (stdev 5.1 years). We used 1 mm³ T1 W anatomical MRI images aligned (lsq9) to MNI space (Collins et al. 1994). This approach allows for identification of corresponding anatomical structures as section orientations are comparable. Since the variable of interest for volume analysis is left/right volume ratio, linear registration would not affect the outcome. The segmenter (JG) was blind to the subject handedness when segmenting the brain to avoid any possible bias. All images were re-coded to that effect.

Volumetric analysis of basal ganglia, thalamus and cerebellum was conducted with 168 participants from the ICBM project [91 females, average age 43 years (stdev 15.4 years)]. We also used defaced 0.7 mm³ T1 W anatomical MRI images from a subsample of 511 individuals [302 females, average age 29 years (stdev 3.5 years)] from the Human Connectome Project (HCP) data (Van Essen et al. 2012; Milchenko and Marcus 2013). Both ICBM and HCP datasets provide a continuous measure of hand preference.

For the ICBM dataset, handedness is measured on a scale of 0–10 (0 being strongly left-handed and 10 strongly right-handed). The HCP dataset uses a scale from − 100 to 100, with − 100 being strongly left-handed and 100 being strongly right-handed. All images were non-uniformity corrected (Sled et al. 1998); excess data (shoulder/lower neck) were removed using the MNI headmask. Preprocessing was done using the minc-bpipe-library pre-processing pipeline (https://github.com/CobraLab/minc-bpipe-library).

To obtain volume measures of the thalamus, basal ganglia, and cerebellum, we used MAGeTbrain (Chakravarty et al. 2008, 2013). MAGeTbrain is a software tool that enables reliable, reproducible and fast automated segmentation of brain structures (https://github.com/CobraLab/MAGeTbrain). For the thalamus and basal ganglia, we used single atlas defined using a three-dimensional reconstruction of serial histological data warped to an MRI template (Chakravarty et al. 2008). For the cerebellum, five atlases defined by expert manual segmentation were used (Park et al. 2014). Figure 2 illustrates the segmentation of the basal ganglia and cerebellum. MAGeTbrain works by first customizing the atlases to a subset of each dataset (i.e., 21 randomly selected participants), using a non-linear transformation estimated in a region of interest defined around subcortical structures and cerebellum (Avants et al. 2011). This subset then acts as a set of templates, with subsequent participants' data warped to these templates. This provides 21 candidate segmentations for each subject's basal ganglia and thalamus, and 105 (21 × 5) for the cerebellum. Final segmentation is decided upon using a voxel-wise majority vote, that is, by retaining the label occurring most frequently at a specific location (Collins and Pruessner 2010). Using such a template library for atlas-to-subject registrations offers two advantages: (1) it reduces bias, and (2) it averages registration errors. MAGeT has proven to be highly reliable in comparisons against 'gold standard' manual definitions of the striatum and thalamus ($\kappa = 0.86$), as well as
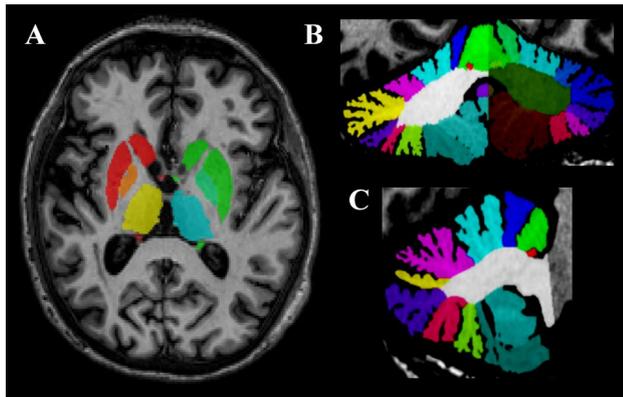
Fig. 2 MAGeT segmentation examples. **a** MAGeT segmentation of the subcortical structures: The striatum in red (left) and green (right), globus pallidus in orange (left) and turquoise (right), thalamus in yellow (left) and cyan (right). **b** and **c** MAGeT segmentation of the cerebellum

the cerebellum and it's lobules ($\kappa > 0.7$) (Chakravarty et al. 2013; Pipitone et al. 2014). We used a first order linear model to test for the relationship between hand preference (assessed by laterality index as a continuous measure) and left–right asymmetry (ratio of left/right individual structure volume).

As there are no anatomical landmarks delineating the rostral border of the cortical hand area, it is impossible to obtain a volume estimate. However, the morphological feature of the hand-knob, in the depth of the central sulcus, enables an estimation of two dimensions of the cortical hand area; this is provided by the surface area of the feature along the central sulcus. To calculate the surface area of the hand-knob, the sulcal ribbon that delineates it was manually segmented on the individual anatomical image. The sulcal segment was then identified and marked using DISPLAY, an interactive 3D imaging software package that is part of minc-toolkit (http://bic-mni.github.io/). DISPLAY allows

the MRI file to be viewed and marked simultaneously in all three planes. The hand-knob area of the central sulcus was examined in 1-mm steps and a continuous line of voxels was drawn through the centre of the sulcus from the fundus to the surface. Detailed inspection at each point using different sections and viewing angles is essential to allow the investigator to accurately identify the extent and depth of the sulcal morphology (Germann et al. 2005). Figure 3 demonstrates the manual segmentation with a red line of voxels delineating the hand-knob in the coronal, horizontal and axial view. In 3D, the labelled voxels form a sulcal ribbon that captures the whole depth and extent of the sulcal segment. After the sulcal ribbon was segmented in all subjects, ANTs (https://github.com/ANTsX/ANTs) were used to calculate the surface area of the hand-knob, allowing for a comparison between the size of the individual hand representation areas and left–right asymmetry (Avants et al. 2011).

Results

As can be seen in Table 1, the sulcal region of the hand-knob area showed a strong asymmetry. On average, this region is enlarged in the dominant hemisphere in both left- and right-handers, presumably related to enable increased fine motor control. There was a significant relationship ($p = 0.013$) between handedness and the ratio of left/right sulcal area (Fig. 4). On average, the ratio is 0.97 (stdev 0.22)

Table 1 Average surface area of hand-knob area separated by handedness and hemisphere

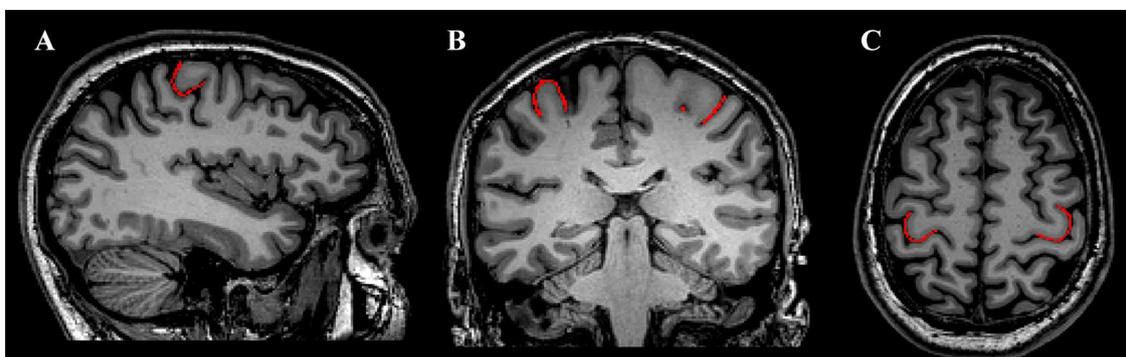| Surface area of hand-knob area	Left hemisphere [average (stdev)]	Right hemisphere [average (stdev)]
Left-handers	481 mm^2 (129 mm^2)	506 mm^2 (126 mm^2)
Right-handers	504 mm^2 (116 mm^2)	431 mm^2 (152 mm^2)

Fig. 3 Example illustrating the segmentation of the sulcal ribbon along the hand-knob of one subject in saggital (**a**), coronal (**b**) and axial (**c**) planes. Investigating the sulcus in sagittal, coronal, and horizontal planes enables a reliable delineation of the sulcal ribbon along this morphological feature
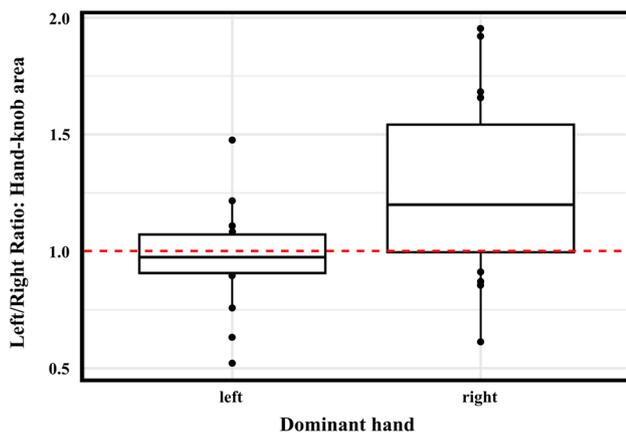
Fig. 4 Boxplot graphic showing the asymmetry of hand-knob area in left- vs right-handed subjects. The red line corresponds to symmetry (same surface area in both hemispheres). Note that on average a strong asymmetry is found in right-handed subjects

for left-handers, and 1.26 (stdev 0.37) for right-handers. Although 6 out of the 15 left-handers had a larger sulcal area on the left, the ratio was > 1.1 in only two cases. Five of 20 right-handers have a ratio < 1 (4 with a ratio < 0.9). Overall, the asymmetry is clearly stronger in right-handers. There was no effect of sex.

Volumetric analysis of the basal ganglia revealed a significant relationship between asymmetry of the striatum and hand preference in male subjects ($p < 0.01$ ICBM, $p < 0.05$ HCP, Fig. 5). While the ratio left/right is on average larger than 1 as indicated by the red dotted line (the left volume is larger), that asymmetry follows a linear trend: the more strongly right-handed the subject is as measured by the laterality index, the stronger the asymmetry. However, there is great interindividual variability even in subjects with similar hand preference.

In the ICBM data, there was also a significant relationship between hand preference and cerebellar white matter volumes, but again only in male participants ($p < 0.05$). Here, again the left/right ratio is always greater than 1 but the asymmetry now is larger the more left-handed the subject is. The linear trend shows that the asymmetry grows as we move along the laterality index towards more strongly left-handed subjects. In strong right-handers, the ratio is almost 1 (Fig. 6).

Discussion

The present study examined asymmetries associated with hand preference in several regions that are known to play a role in motor function: the primary motor cortex, the

basal ganglia and the cerebellum. Asymmetries in the basal ganglia and cerebellum were not prominent and were only observed in male participants when using large datasets and automated segmentations methods. The absence of strong asymmetry in the basal ganglia and the cerebellum might reflect the fact that, while important for hand motor function, both structures are involved in all motor functions and are also engaged in other cognitive functions outside of motor control. By contrast, asymmetries in the primary motor hand area—the hand-knob—were quite pronounced. The hand area in right-handers was, on average, 26% larger in the left hemisphere than in the right. This asymmetry is only apparent if one uses local morphology and manual segmentation. These findings are in accordance with other studies using individual anatomical measures (sulcal depth) as opposed to automated image registration methods (Amunts et al. 1996, 2000; Foundas et al. 1998). These results consistently showed cortical asymmetry in right-handers. Whereas Amunts and colleagues found a difference in length in the depth of the central sulcus (Amunts et al. 1996, 2000), this can likely be explained by the difference in the area of the hand-knob. As described in the present study, limiting the measure to the hand-knob region would emphasise the asymmetry (i.e., the depth of the central sulcus in axial sections would include many more motor representations). Of note, there was no effect of sex when using the hand-knob area asymmetry though a larger sample would be necessary to investigate a possible gender effect more thoroughly.

The limited observation of cortical asymmetry in previous large-scale studies may be due to the fact that individual measures are not specific to the relevant cortical region (Guadalupe et al. 2014). To our knowledge, no image registration algorithm is able to identify the local landmarks specifically associated with the somatomotor area of the hand area. Interestingly, a Magnetic Encephalography study fine-tuned to measure individual functional finger areas in detail was able to find a strong asymmetry associated with hand preference (Volkmann et al. 1998). This was done by quantifying individual asymmetry by estimating the volume of the hand area in each hemisphere. In fact, their findings included all left-handers with a right- and all right-handers with a left-hemispheric dominance without exception.

The observed asymmetries involving the basal ganglia and cerebellum were relatively small and only present in males. Though both the HCP and the ICBM include a significant number of females the number of strongly left-handed subjects is fairly low in both. Thus, a larger sample with a larger proportion of left-handed subjects will be necessary to make conclusive statements about gender
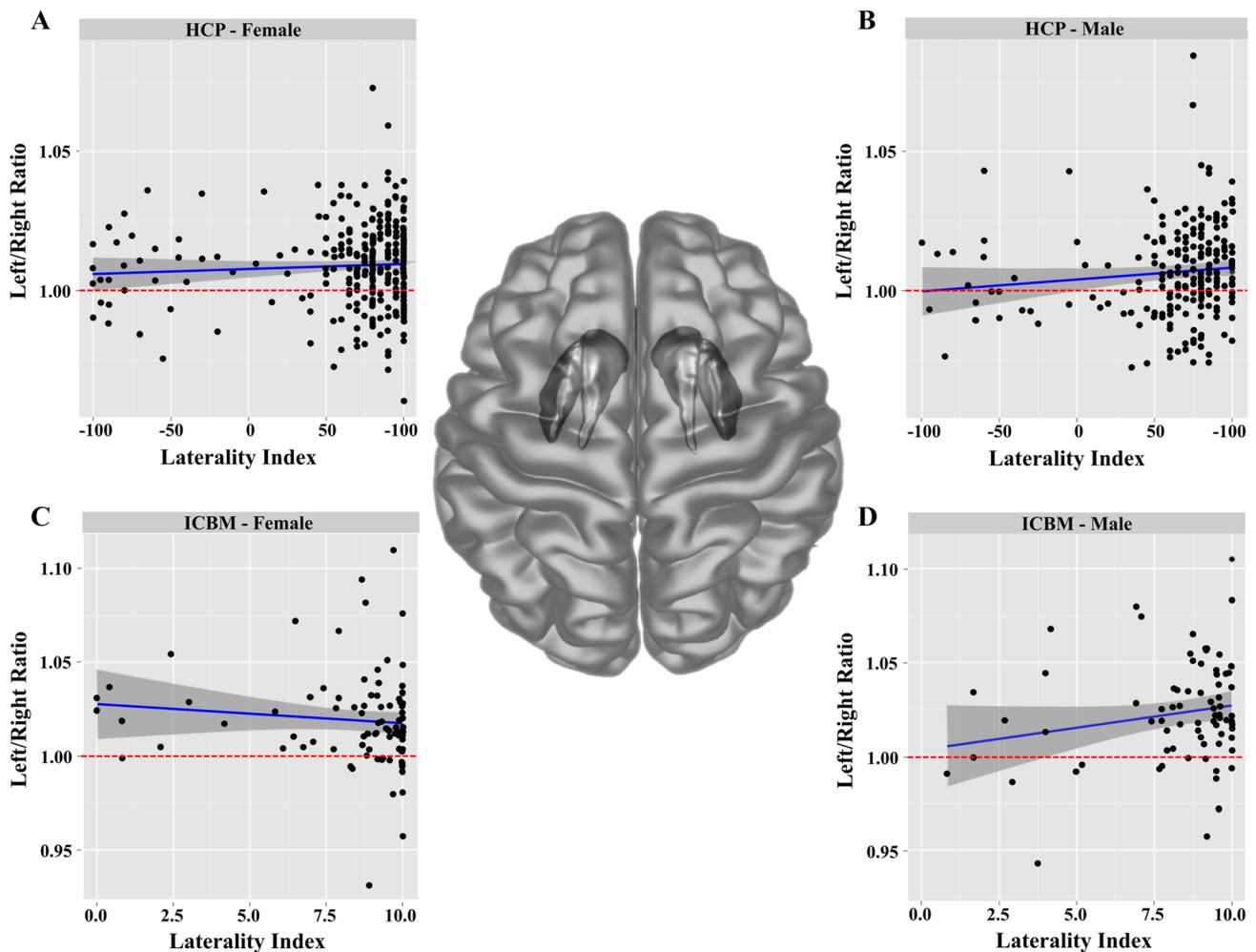
Fig. 5 Graphs describing the volume asymmetry is the striatum (illustrated in 3D in the centre). The laterality index on the *x*-axis (strongly left-handed on the left, strongly right-handed on the right), the left/right ratio of individual striatal volume on the *y*-axis. The red line corresponds to symmetry (same volume in both hemispheres). **a** and **c** Female subjects. **b** and **d** Male subjects. **a** and **b** HCP; **c** and **d** ICBM. A significant linear relationship between hand preference and left/right striatal volume ratio is found only in males (both subject pools): the asymmetry is significantly stronger the more right-handed they are

differences in brain asymmetry related to hand preference. A previous study looking at cerebellar grey matter did not find asymmetries associated with hand preference (Kavaklioglu et al. 2017). Similarly, we found no significant asymmetries in grey matter volume in this region. However, cerebellar white matter, in the present segmentation, is dominated by the middle cerebral peduncle (van Baarsen et al. 2016; Steele et al. 2017) and thus includes primarily afferent fibres from the pontine nuclei part of the cortico-pontocerebellar pathway. Along with the analogous asymmetry found in the striatum, this suggests that asymmetries

associated with hand preference may be observed in multiple regions of the motor system.

In summary, we found that hand preference was associated with clearly detectable anatomical asymmetries, not only in motor cortex, but also in the basal ganglia and the cerebellum. These asymmetries appear to be influenced by gender and are most prominent in right-handers, with left-handers exhibiting less pronounced asymmetries. The interesting question remains whether such asymmetry is the result of plastic changes associated with life-long
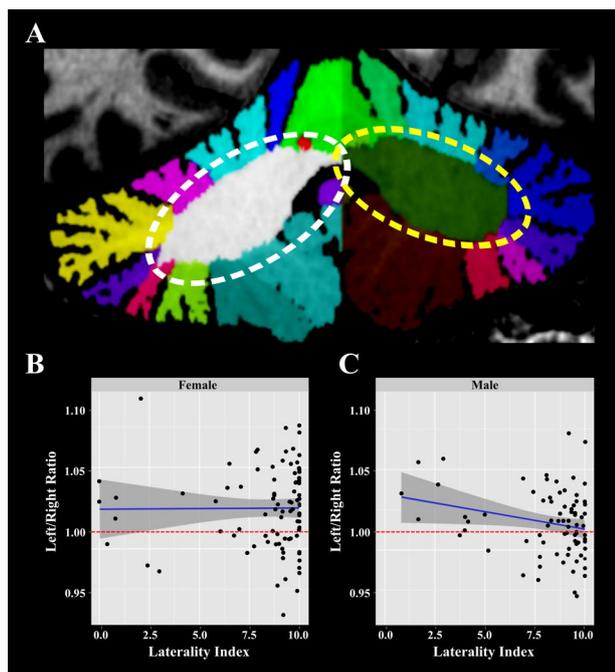
Fig. 6 Central cerebellar white matter. **a** Outlines the left and right cerebellar white matter. **b** and **c** Show the volume asymmetry in females (**b**) and males (**c**) of the ICBM dataset. The laterality index on the *x*-axis (strongly left-handed on the left, strongly right-handed on the right), the left/right ratio of individual central cerebellar white matter volume on the *y*-axis. The red line corresponds to symmetry (same volume in both hemispheres). A significant linear relationship is found in males only: the asymmetry is significantly stronger the more left-handed they are

practice or whether they are the result of early differences in neuronal development that—among others—give rise to hand preference.

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