Review

Handedness and White Matter Networks

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Abstract

The development and persistence of laterality is a key feature of human motor behavior, with the asymmetry of hand use being the most prominent. The idea that asymmetrical functions of the hands reflect asymmetries in terms of structural and functional brain organization has been tested many times. However, despite advances in laterality research and increased understanding of this population-level bias, the neural basis of handedness remains elusive. Recent developments in diffusion magnetic resonance imaging enabled the exploration of lateralized motor behavior also in terms of white matter and connectional neuroanatomy. Despite incomplete and partly inconsistent evidence, structural connectivity of both intrahemispheric and interhemispheric white matter seems to differ between left and right-handers. Handedness was related to asymmetry of intrahemispheric pathways important for visuomotor and visuospatial processing (superior longitudinal fasciculus), but not to projection tracts supporting motor execution (corticospinal tract). Moreover, the interindividual variability of the main commissural pathway corpus callosum seems to be associated with handedness. The review highlights the importance of exploring new avenues for the study of handedness and presents the latest state of knowledge that can be used to guide future neuroscientific and genetic research.

Keywords

handedness, white matter, diffusion imaging, tractography, corpus callosum, corticospinal tract, superior longitudinal fasciculus

Introduction

Lateralized motor behavior represents the key feature of our daily life. In behavioral terms motor asymmetries are exemplified at the level of hand and feet as well as eye dominance. Among these the most researched and most prominent example of lateralization is the asymmetrical hand use, also known as handedness (McManus 2009, 2019). Handedness can be classified in terms of hand preference or hand performance, depending on the tests and measures used (Box 1). Regardless of taxonomy, studies tend to converge toward similar figures and frequencies. Thus, most adults (around 90%) prefer to use their right hand over the left for most types of hand movements (Papadatou-Pastou and others 2020; Porac and Coren 1981), with numbers varying according to the geographical location (Raymond and Pontier 2004). The remaining 10% consist of ambidextrous and left-handed individuals.

Although the two cerebral hemispheres, just like our two hands, seem identical at first, they show both functional and structural hemispheric asymmetries (Box 2). This phenomenon, termed hemispheric specialization (HS), has long been thought of as a division of labor (Vingerhoets 2019). Handedness is intimately linked to the notion of HS and the fact that one hemisphere seems dominant for hand control. However, the erroneous idea that left-handers have very different underlying neural asymmetries, which could increase the variance in data, led to their unfortunate exclusion from many research studies (Willems and others 2014). A majority of left-handed individuals have typical functional hemispheric lateralization, and only a small minority presents with a reversed or atypical hemispheric dominance for language, praxis, spatial attention, face recognition or prosody (for a review, see Vingerhoets 2019).

Handedness is thought to either result from or to induce asymmetries in the functional and structural organization of the human brain (Toga and Thompson 2003; Vingerhoets 2019). Whether it is handedness or HS that came first is a matter of debate, since a point-to-point mapping across developmental stages remains a challenge (Andersen and Siebner 2018; Buckingham and

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Box 1. Short Summary of Handedness Classification.

Hand preference denotes a tendency of one hand to play a leading, manipulative role (e.g., rubbing a matchstick on the side of the matchbox or opening a jar lid) while the other hand plays a supporting, stabilizing role (e.g., holding the matchbox or the jar firmly). Hand preference can vary along two dimensions: direction (right-handedness vs. left-handedness) and degree (pure/consistent handedness vs. mixed/inconsistent handedness). It is usually assessed via experimental manipulation tasks (for infants/children) or self-reported questionnaires made by items describing everyday habits, unimanual and bimanual (for adults). The Edinburgh Handedness Questionnaire (Oldfield 1971) is the most popular assessment tool, resulting in a laterality quotient expressing the strength of the bias toward right- or left-handedness.
Hand performance (also referred to as hand proficiency, manual dexterity, relative hand skill) can be assessed with motor performance tasks, such as the Annett pegboard (Annett 1970), rapid tapping (Peters 1980; Peters and Durding 1978), circle-marking (Tapley and Bryden 1985), and kinematical tasks (Begliomini and others 2008). Hand preference correlates reliably, but not perfectly, with hand performance (Todor and Doane 1977), highlighting the importance of using both measures when assessing asymmetrical hand use (Henkel and others 2001).

Carey 2015). Some insights emerged from fetal ultrasound and gene expression studies: the right-side handedness bias was observed as early as 10 weeks gestation, or as soon as fetus starts to independently move its arms (for a review, see Hepper 2013). This behavior was noted before the maturation of the main central motor pathway, the corticospinal tract (ten Donkelaar and others 2004), and the gene expression asymmetries in cerebral hemispheres (12 weeks of gestation; Sun and others 2005), but occured around the same time as differential gene expression in the left and right segments of the spinal cord (i.e., 10 weeks of gestation; Ocklenburg and others 2017). The prenatal asymmetry of hand use was found to be a precursor of postnatal handedness in terms of direction (Hepper and others 2005; Parma and others 2017) but not degree, which stabilizes only in mid-childhood (McManus and others 1988). The phenotypic plasticity supports the notion of bidirectional influence across ontogeny—the neural traits influencing handedness and vice versa. This reciprocity is supported by studies showing that handedness shifts can modulate brain asymmetries (Marcori and Okazaki 2020; Marcori and others 2019; Sun and others 2012) but also by studies reporting that lesions altering brain structure can produce shifts in hand selection (Howells and others 2020). It is in light of such bidirectionality that discussion on the brain asymmetries and handedness should be viewed.

Recent advances in neuroimaging methods allowed for the measurement and the visualization of both functional and structural asymmetries of the human brain (Box 2). Although anatomical factors are crucial in modulating brain's functional organization (Rockland 2020), the relationship between the functional and structural asymmetries is weak due to the absence of one-to-one mapping. When considering structural brain asymmetries, we can distinguish between the more traditional exploration of *gray matter* asymmetries using structural magnetic resonance imaging (sMRI; for a review, see Hervé and others 2013) and the study of *white matter* asymmetries using postmortem or diffusion MRI methods (Budisavljevic and others 2015; Thiebaut de Schotten

and others 2011b; Fig. 1). Literature on gray matter asymmetries and handedness reveals a plethora of equivocal findings, and these will be briefly mentioned in the relevant sections. In general, large-scale studies using automated parcellation methods reported that handedness had little to do with gray matter asymmetries in terms of cortical volume, cortical thickness, surface area, and sulcal depth (Kong and others 2018, Maingault and others 2016). However, associations with handedness did sometimes appear by lowering statistical thresholds (Guadalupe and others 2014; Maingault and others 2016) or by using the manual gray matter parcellation approach that takes into account the local brain morphology (Germann and others 2019).

The white matter and handedness exploration gained momentum when the invasive "gold standard" postmortem approach was complemented by diffusion MRI. This is a noninvasive, fast, repeatable, whole-brain technique that can be used across large samples and combined with other MRI modalities to produce blueprints of "structural connectivity." The importance of studying structural connectivity is highlighted by a networked nature of the brain and the importance of interacting brain regions for brain function (ffytche and Catani 2005). Up to date, both interhemispheric and intrahemispheric connections have been implicated as important factors in shaping HS (Ocklenburg and others 2016a; Stephan and others 2007; Tzourio-Mazoyer 2016), and hence potential neural substrates for lateralized motor behavior. As more and more articles using various neuroimaging methods are published on handedness and HS, the laterality research pendulum is swinging toward the need to integrate this different information. The present review aims to synthesize the current state of knowledge and to test the hypothesis that behavioral asymmetry of hand use reflects the structural asymmetries of our brain, focusing on white matter.

Exploring White Matter Networks

White matter networks act as a highway system—a substrate for information travel between different cortical

Box 2. Short Summary of Brain Asymmetries.

Hemispheric specialization (HS) or hemispheric dominance is a long-standing concept assuming structural and/or functional asymmetries of the human brain. With advances in neuroimaging, it became possible to investigate HS in terms of structure and function at voxel-wise, regional, and hemispheric levels. The correspondence between structural and functional brain asymmetries is not straightforward since there is no one-to-one mapping between structure and function, with the relationship exhibiting regional specificity (Baum and others 2020; Vázquez-Rodríguez and others 2019). The whole-brain structural connectivity (i.e., macrostructural organization) explains no more than 50% of the variance in functional connectivity (Suárez and others 2020), while the variation in the microstructural signature of white matter tracts predicts up to 13% of the cross-subject variance (Mollink and others 2019). Structural networks tend to be more spatially constrained and differences in developmental patterns and susceptibility to environmental factors further add to this divergence (Tzourio-Mazoyer 2016).

Structural gray matter asymmetries in humans can be observed as early as 23 weeks of gestation using in utero MRI (Habas and others 2012). Grey matter asymmetries can be characterized in terms of volume, shape, cortical thickness, surface, or microstructural features (Amunts 2010). Large-scale asymmetries commonly reported at the population level include the leftward asymmetry of the frontal regions and the rightward asymmetry of the occipital regions in cortical thickness (Fig. 1A; Kong and others 2018; Plessen and others 2014), likely related to the protrusion of the left occipital and right frontal petalia (i.e., Yakovlevian torque; Lyttelton and others 2009; Toga and Thompson 2003). Commonly observed focal gray matter asymmetries, instead, include the left asymmetry of the planum temporale (Geschwind and Levitsky 1968; Steinmetz 1996) and the Heschl's gyrus (Marie and others 2015). Large-scale structural MRI studies using automated methods report that handedness is not significantly associated with cortical brain asymmetries (Kong and others 2018), with a trend toward significance found at the precentral sulcus level (Guadalupe and others 2014; Maingault and others 2016; Fig. 1B) and several temporal regions (Guadalupe and others 2014; Kong and others 2018). Studies using manual parcellation approach suggest that local asymmetries in the primary motor cortex are related to handedness (Amunts and others 1996; Germann and others 2019).

Structural white matter asymmetries are commonly studied using in vivo diffusion MRI and quantified by indirect measures of macrostructure (i.e., volume, number of streamlines) and microstructure (i.e., fractional anisotropy, mean diffusivity etc.). Evidence suggests a whole-hemisphere right-greater-than-left interconnectivity and efficiency (Iturria-Medina and others 2011) as well as volume (Barrick and others 2005). Early leftward asymmetries (i.e., larger tracts and/or higher fiber organization in the left hemisphere compared to the right) in infants from 1 to 4 months are found for white matter tracts underlying language (i.e., arcuate fasciculus) and sensorimotor system (i.e., corticospinal tract; Dubois and others 2009), persisting into adolescence and adulthood (Budisavljevic and others 2015; Thiebaut de Schotten and others 2011b). Some white matter asymmetries change with age (Fig. 1C; Catani and Budisavljevic, 2014), reflecting nonuniform patterns of white matter development (Budisavljevic and others 2015; Lebel and others 2019). It should be noted that white matter asymmetries are only weakly related to gray matter asymmetries (Takao and others 2011).

In terms of *functional brain asymmetries* the literature suggests that the left hemisphere is dominant for language (Duffau and others 2008) and motor/hand control (Jung and others 2008), while the right hemisphere is specialized for nonverbal and visuospatial functions (Szaflarski and others 2006) in right-handed population. Besides this "typical" hemispheric functional segregation, the literature also shows the existence of other phenotypes, including complete (reversed typical) and partial (atypical) reversal of functional asymmetries (for a review, see Vingerhoets 2019). Compared to structural asymmetries, the development of functional brain asymmetries can be more protracted, shifting from predominant interhemispheric connectivity at birth to a largely intrahemispheric connectivity patterns in adults, at least for higher order language areas (Friederici and others 2011; Tzourio-Mazoyer 2016). The functional brain asymmetries seem to bear little relation to handedness. Similar patterns, in terms of direction, are observed in non–right-handers (Begliomini and others, 2018) with weaker left hemispheric dominance for speech and language-related functions (Carey and Johnstone 2014) and increased right lateralization of dorsal attention network (Petit and others 2015). It is suggested that frequent reports of less asymmetric brains in left-handers when taken as averages could be explained by left-handers exhibiting higher variability, that is, having a small group of individuals with reversed typical functional lateralization (i.e., mirrored activation patterns), a condition commonly absent in right-handed participants (for more details, see Carey and Karlsson 2019; Vingerhoets 2019).

and subcortical brain areas. Before the advent of diffusion MRI, white matter networks of the human brain could only be studied using postmortem dissection techniques. That meant that we could neither investigate them in a living human brain and simultaneously acquire behavioral data, nor we could gather large samples, which made the study of interindividual differences tenuous.

In the last two decades, in vivo tractography based on diffusion MRI enabled the study of the brain's anatomical connections and opened up new possibilities to explore structure-function relationship (Conturo and

others 1999; Jones and others 1999). By following the direction of the highest diffusivity of water molecules in the brain, one can extract orientational information and start to reconstruct white matter pathways (Jones 2008). However, due to the fact that tractography tracing of white matter connections occurs according to mathematical models, this technique does not necessarily imply true axonal pathways. To reach the best estimates of white matter pathways, many diffusion models and algorithms have been proposed, starting from the simple tensor model (Basser and others 1994) to more complex
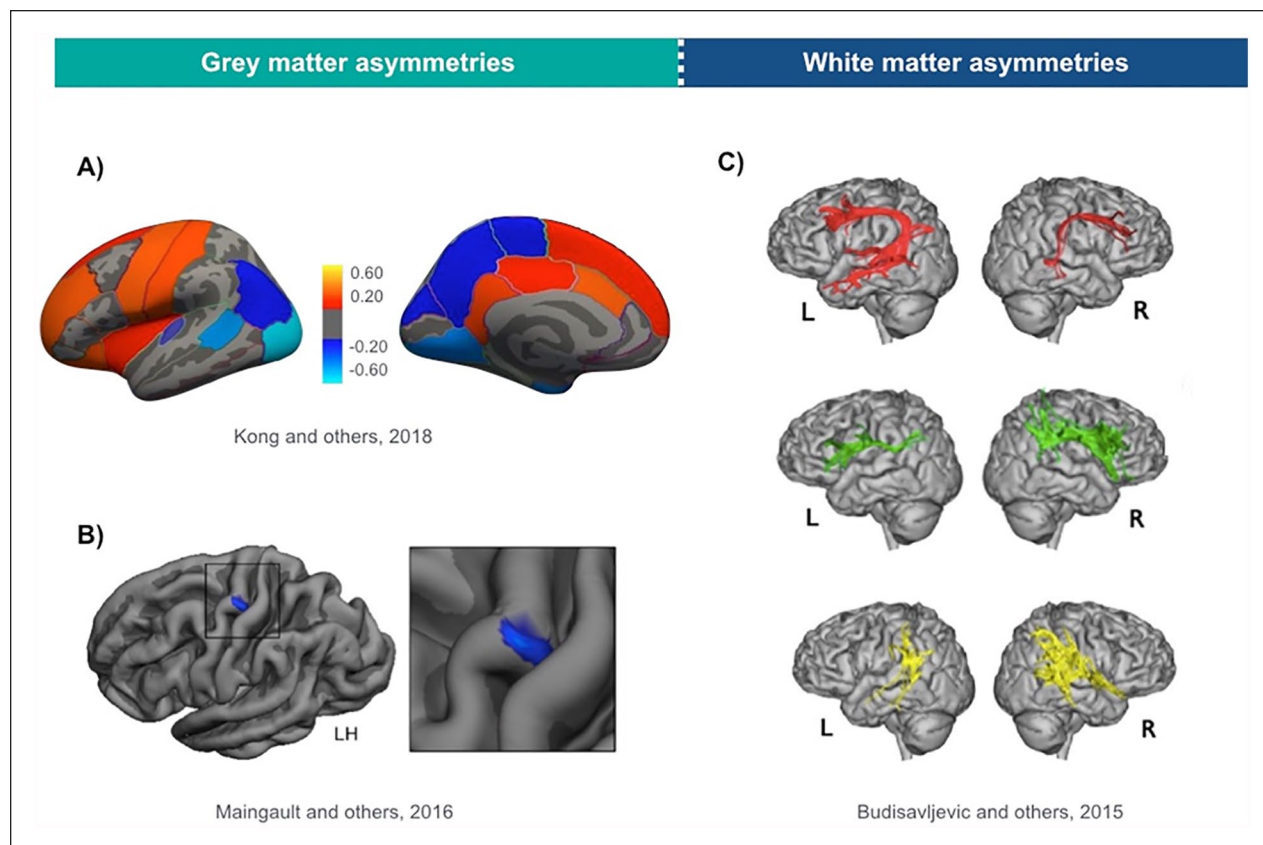
Figure 1. Structural brain asymmetries. (A) Regional asymmetries in cortical thickness showing a fronto-occipital pattern. Red-yellow gradient indicates leftward asymmetry (i.e., higher cortical thickness in the left compared to the right hemisphere) and a blue-light blue gradient indicates a rightward asymmetry, with the corresponding asymmetry score annotating the effect size of the interhemispheric difference. Based on data from 17,141 participants (reproduced with permission from Kong and others 2018). (B) A trend for a significant difference in the sulcal depth asymmetry at the level of the hand motor area, with deeper sulcus in the left compared to the right hemisphere in right-handers, and the opposite pattern in left-handers. Results are displayed on the left hemisphere pial surface of the symmetrical template, with the light gray corresponding to gyri (reproduced with permission from Maingault and others 2016). (C) Tractography dissections of the long (frontotemporal, in red), the anterior (frontoparietal, in green), and the posterior (temporoparietal, in yellow) segments of the arcuate fasciculus in the left (L) and right (R) hemispheres. The volume of the long segment is left lateralized, while the opposite pattern is found for the anterior indirect segment—more volume in the right hemisphere compared to the left. The posterior segment shows a right lateralization before adolescence (age 9–11), but bilateral lateralization pattern throughout adolescence and adulthood (reproduced with permission from Budisavljevic and others 2015).

approaches using high-angular-resolution diffusion imaging (HARDI; for a review, see Dell'Acqua and Tournier 2019) or diffusion spectrum imaging (Wedeen and others 2008).

Diffusion measures that can be extracted from tractography are sensitive to either macrostructural (the number of streamlines, volume − the number of voxels occupied by the streamlines) or microstructural properties of white matter such as myelination, axonal membrane integrity, axonal diameter, fiber density, and fiber organization (fractional anisotropy [FA], hindrance modulated orientational anisotropy [HMOA], mean diffusivity [MD]. etc.' Beaulieu 2002). Despite firmly established behavioral

relevance, the interpretation of diffusion measures is challenging, considering there is no one-to-one mapping with the underlying anatomy (for a review, see Johansen-Berg 2010). Best approaches combine several diffusion MRI measures, since it is not only the presence of a connection (volume/number of streamlines) but also the interindividual variation in the microstructural properties that modulate conduction velocity and thus brain function (Mollink and others 2019; Seidl 2014). For example, the mean FA, a measure of fiber coherence in a given white matter tract, was found to correlate positively with conduction velocity (Caminiti and others 2013) and the strength of functional connectivity (van den Huevel and
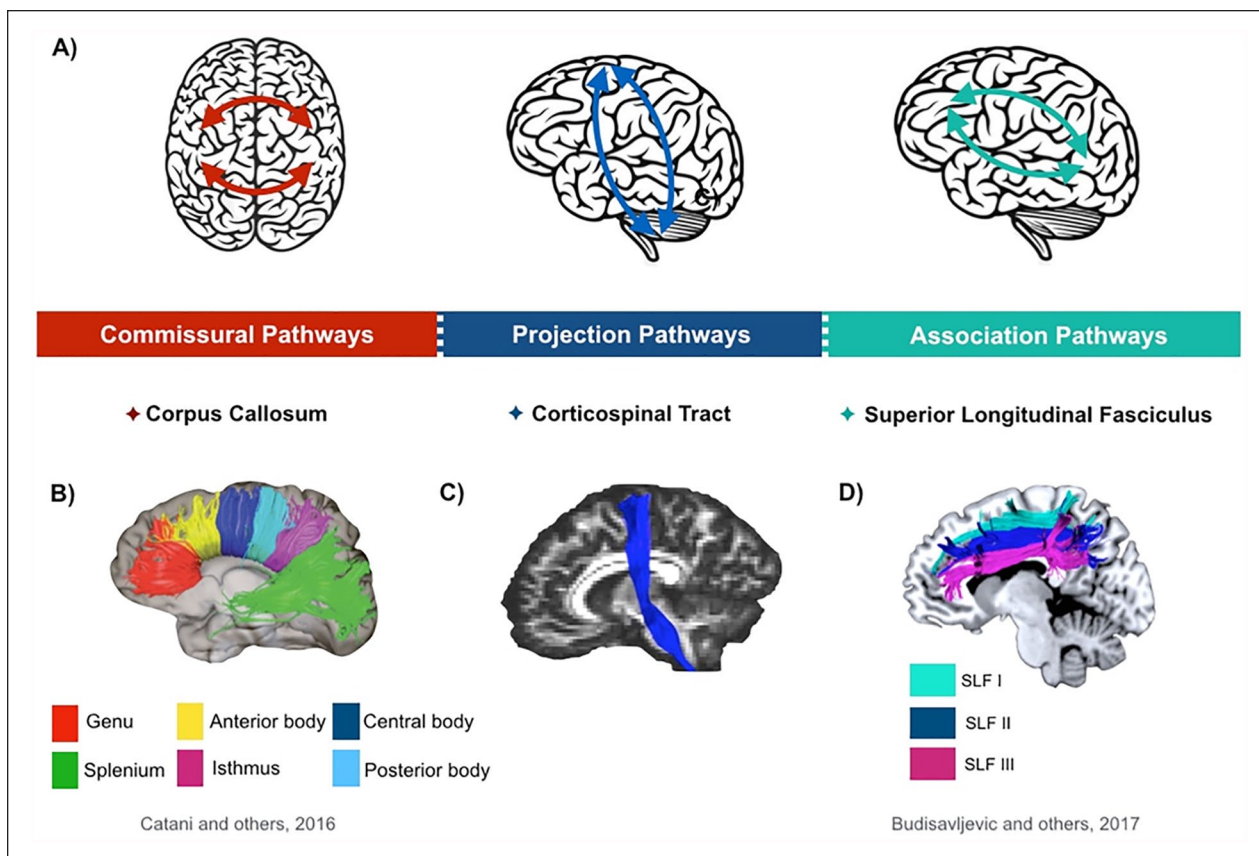
Figure 2. White matter connections, (A) classified into commissural, projection, and association pathways, with their corresponding tractography reconstructions representing (B) corpus callosum, (C) corticospinal tract, and (D) the three segments of the superior longitudinal fasciculus (SLF; superior SLF I, middle SLF II, and inferior SLF III). Reproduced with permission from Budisavljevic and others (2017). Tractography parcellation of the corpus callosum according to Witelson's (1989) criteria was reproduced with permission from Catani and others (2016).

others 2008; Wahl and others 2007). Most brain regions show a relationship between white matter microstructure derived from diffusion MRI and functional connectivity, with the microstructural measures explaining from 1 to 13% (Mollink and others 2019) and macrostructural up to 50% of cross-subject variance in brain function (Suárez and others 2020). Brain structural and functional connectivity are closely aligned in primary sensory and motor regions, but less so in association areas, possibly allowing for additional functional flexibility (Suárez and others 2020). This highlights an important aspect and advantage of diffusion MRI—its potential to study interindividual variation in white matter properties and relate anatomy to brain function and behavior.

Handedness-Related White Matter Connections

The widely accepted classification proposed by Meynert (1888) describes three main categories of white matter

fibers: (1) projection fibers—the ascending or descending pathways arising or terminating in the cortex; (2) commissural interhemispheric fibers—mainly connecting homologous regions in the two hemispheres; and (3) association intrahemispheric fibers—connecting different regions within the same hemisphere (Fig. 2A). The three white matter tracts that have been most frequently explored in relation to handedness include (1) corpus callosum (commissural tract), (2) corticospinal (projection) tract, and (3) superior longitudinal fasciculus (association tract; Fig. 2B). The corpus callosum in humans was found to be involved in bimanual coordination, bimanual finger opposition movements, and the speed of finger tapping movements (Bonzano and others 2008; Fling and others 2011; Muetzel and others 2008), the corticospinal tract in motor execution and manual dexterity (Rose and others 2012; Stinear and others 2007), and the superior longitudinal fasciculus in visuomotor processing during hand movements (Budisavljevic and others 2017; Koch and others 2010; Steele 2000) and visuospatial attention (Thiebaut de Schotten and others 2011a).

Another white matter tract frequently investigated in relation to handedness is the arcuate fasciculus, which supports language functions (Allendorfer and others 2016; Propper and others 2010; Vernooij and others 2007). The interest comes from a widely held belief that the lateralization of language is intricately linked with handedness (Corballis 2003). Neuroimaging data of healthy participants showed that the functional networks associated with handedness and language seem independent (Häberling and others 2016), and that any relation between handedness and language dominance could be explained by the existence of a small left-handed group of individuals with reversed right-hemispheric language dominance, a condition that seems absent in right-handers (Vingerhoets 2019). The cause of this relation remains uncertain. So far there has been little support for a genetic link between handedness and language functional lateralization. However, a recent study reported shared genetic roots between handedness and the arcuate fasciculus connectivity (Wiberg and others 2019).

Exploring the relationship between the arcuate fasciculus asymmetries and handedness is still at its infancy, and it is outside the scope of this review. We instead focus on assembling evidence, though incomplete and in parts inconsistent, on potential white matter markers of handedness outside the language domain. However, it should be noted that due to proximity and spatial overlap of the arcuate fasciculus and the superior longitudinal fasciculus fibers, the estimates derived from diffusion MRI could represent a mix of white matter properties from both tracts. This is a general confound in diffusion MRI measurements, which can often mix multiple white matter bundles. The extent of this confound depends on the choice of diffusion model and algorithm—with more advanced methods better able to reduce or exclude the "partial volume" effect, as well as the choice of tractography segmentation and delineation of regions of interest. Thus, the discourse on the inferior fibers of the superior longitudinal fasciculus (III) might inevitably overlap with the arcuate fasciculus narrative, and this should be taken into account.

Corpus Callosum and Handedness

The corpus callosum is the largest and most homogeneous fiber bundle in the human brain, consisting of between 200 and 300 millions of axons that connect the two hemispheres and allow for interhemispheric transfer of information (Fig. 2B; Aboitiz and others 1992). The corpus callosum and interhemispheric conduction delay have been implicated in the development of HS for decades (for reviews, see Aboitiz and Montiel 2003; Gazzaniga 2000; van der Knaap and van der Ham 2011). Research suggests that language left-hemisphere specialization develops first through callosal interactions, but it

is not clear if the same is true for other lateralized functions such as praxis (Tzourio-Mazoyer 2016).

How exactly interhemispheric communication influences the ontogenesis of functional hemispheric asymmetries is still a matter of debate. Most callosal axons rely on the excitatory neurotransmitter glutamate, but by exciting inhibitory interneurons they can also have an inhibitory effect on the contralateral hemisphere (for reviews, see Bloom and Hynd 2005; van der Knaap and van der Ham 2011). This has led to two models on the relation of corpus callosum structure and the emergence of HS: (1) the excitatory model (greater callosal connectivity—a decrease in asymmetry; Ringo and others 1994) and (2) the inhibitory model (greater callosal connectivity—greater asymmetry). Studies provide support for both excitatory (e.g., Karolis and others 2019) and inhibitory callosal effects on the HS (e.g., Josse and others 2008). Having in mind the variations in functional specializations, morphology, and axonal diameter of callosal fibers, it seems plausible that both functions exist within the same corpus callosum (Bloom and Hynd 2005; van der Knaap and van der Ham 2011). Different subregions of the corpus callosum can be differently linked to the HS, and the relationship can depend on the chosen indicator of anatomical asymmetries (Luders and others 2003). The studies imply that callosal structure might be a relevant factor for development of handedness, that is, the behavioral expression of motor HS.

Ever since the 1980s there has been a plethora of studies linking the variability in callosal structure and function with handedness. Functional MRI and paired-pulse transcranial magnetic stimulation (TMS) studies underlined the link between the corpus callosum and manual dominance. Namely, the strength of the interhemispheric inhibition, mainly mediated by transcallosal fibers, was found to modulate the ipsilateral deactivation of the primary motor cortex (M1) during hand movements in healthy participants (Hayashi and others 2008; Tazoe and Perez 2013; Tzourio-Mazoyer and others 2015). The importance of the ipsilateral deactivation as a potential marker of manual preference was highlighted by Tzourio-Mazoyer and others (2015) in a large study balanced for handedness (142 right-handers vs. 142 left-handers). They observed a handedness effect on between-hands difference in ipsilateral M1 deactivations, with left-handers having comparable activity decrease of ipsilateral M1 activity for the unimanual finger movements of both dominant and nondominant hands, while in right-handers the deactivation was larger for the dominant hand. This was explained by the lower between-hands asymmetry in manual ability in left-handers, induced by better nondominant hand skill. The authors suggested that difference in ipsilateral M1 deactivation, reflecting the strength of transcallosal inhibition, is a marker of difference in

manual ability asymmetry, with a larger difference in manual skills across hands corresponding to a larger difference in ipsilateral deactivation in both right- and left-handed participants (Tzourio-Mazoyer and others 2015). These studies did not investigate callosal structure per se, but several observations suggest that interhemispheric inhibition is mostly mediated by transcallosal fibers (Ferbert and others 1992) including studies of alien hand syndrome after callosotomy or callosal infarction (Della Sala and others 1994; Espinosa and others 2006; Gao and others 2016). Moreover, two studies using diffusion imaging combined with paired-pulse TMS (Wahl and others 2007) and TMS-induced ipsilateral silent period (Fling and others 2013) reported strong positive correlations between the strength of interhemispheric inhibition and the microstructure (FA) of callosal tracts connecting M1. Increased FA could reflect more coherent fiber organization, better axonal membrane integrity, and higher myelin content (Beaulieu 2002), leading to faster conduction velocity (Caminiti and others 2013) of interhemispheric information and increased ability to inhibit the contralateral hemisphere. Taken together, these results suggest that the corpus callosum, through inhibitory modulation of ipsilateral motor cortices, could lend support to manual preference.

Conversely, structural studies mostly focused on how the size of the corpus callosum relates to handedness. Early postmortem reports noted a larger midsagittal area of the corpus callosum in left-handed and ambidextrous people compared to consistent right-handers (Witelson 1985, Witelson and Goldsmith 1991). This effect was particularly evident in isthmus, known to contain callosal motor fibers (Wahl and others 2007). However, these studies were based on seriously ill cancer patients with different chronicity of illness and heterogeneity in symptom profiles, and are not comparable to the study of healthy controls. Nonetheless, the difference in callosal size was supported by other in vivo MRI studies of healthy participants showing a larger corpus callosum in both its anterior and posterior (isthmus) regions in left-handers and mixed right-handed participants (Cowell and Gurd 2018; Denenberg and others 1991; Habib and others 1991), though the opposite pattern was also observed (Hopper and others 1994; Westerhausen and others 2004). However, a large number of studies did not replicate these results and found no difference in callosal size between the handedness groups (Hines and others 1992; Jäncke and others 1997; Luders and others 2003; O'Kusky and others 1988; Reinarz and others 1988; Steinmetz and others 1992). A number of explanations might account for these discrepancies, including differences in sample sizes, handedness classification methods and cutoff scores, callosal parcellation schemes as well as confounding effects of age, sex, education, and total brain weight.

Denenberg and others (1991) made an important contribution in showing that different instruments for handedness classification produce different results—from no difference (Kertesz and others 1987) to a larger isthmal area in nonconsistent compared with consistent right-handers when the classification used by Witelson was adopted.

Overall, the idea that the direction of manual preference, left- versus right-handedness, can have a single relationship with callosal structure seems to be an oversimplification. The more likely scenario, which would explain the equivocal findings, is based on the idea that callosal size is related to a degree of handedness (Corballis 2009). Habib and others (1991) studied 53 healthy participants and reported that the greater the degree of hand lateralization, the larger the several areas of the corpus callosum. However, a more recent and larger morphology study, including 324 right-handers and 37 left-handers, reported the opposite: thicker callosal anterior and posterior midbody related to a weaker hand lateralization (Luders and others 2010). The authors suggested that commonly reported increase in callosal size in left-handers might be due to them being less strongly lateralized compared to right-handers. Unlike observations on callosal microstructure (Fling and others 2013), it is not clear if thicker callosal area indicates faster interhemispheric processing, or an increased extracellular space without functional consequence. Adding information from diffusion MRI would help disentangle the relevance of callosal size for interhemispheric facilitation and inhibition, as well as its relationship to asymmetry of ipsilateral deactivation as a marker of manual preference (Tzourio-Mazoyer and others 2015). It should be noted that these structural studies relied on the midsagittal surface area for callosal size calculations, and that mapping of callosal connections based on diffusion MRI tractography would draw a more comprehensive picture. It would also help to establish whether the putative difference in callosal size is driven directly by callosal motor pathways.

There has been no tractography study to date that investigated the size of the corpus callosum, as indexed by volume or the number of streamlines, in relation to handedness. To our knowledge, only four diffusion MRI studies investigated handedness effects on callosal microstructure, with three reports coming from the same group. None of these studies employed tractography to analyze callosal structural connectivity, but instead performed the region of interest (ROI) analysis on a midsagittal slice (Westerhausen and others 2003; Westerhausen and others 2004; Westerhausen and others 2006) or tract-based spatial statistics (TBSS) on the mean FA skeleton that represents the centers of all white matter tracts (McKay and others 2017). All four studies reported significant

associations between the microstructural organization of the corpus callosum and handedness, seen as an increase in FA in the total midsagittal region of the corpus callosum or across its subregions in the left-handed population. Higher callosal FA in left-handers compared to right-handers could represent an increased ability to inhibit the contralateral hemisphere (Fling and others 2013). This could be related to reports that left-handers have two dominant motor cortices and would thus need strong contralateral inhibition during the movement of either hand, unlike right-handers. It is worth noting that the link between the corpus callosum (or any other tract) and handedness, even if found significant might not reflect any causal relationship, but could instead underlie similar developmental mechanisms. Future studies of handedness should ideally combine genetic and functional brain analysis with diffusion MRI tractography that assesses both macrostructural and microstructural callosal properties.

Corticospinal Tract and Handedness

Manual dexterity is often linked to the primary motor cortex (M1) where most of the neurons of the corticospinal tract originate, making both structures plausible candidates for the anatomical substrate of handedness (Hammond 2002). The corticospinal tract (Fig. 2C) is the principal motor pathway for voluntary movements, whose axons travel in bundles from the sensorimotor cortex through the internal capsule, cerebral peduncles, pons, and medulla to synapse onto lower motor neurons of the spinal cord (Porter and Lemon 1993). A majority of axons cross the midline at the pyramidal decussation to form the lateral spinal cord, with a small number of axons remaining on the ipsilateral side to form the anterior corticospinal tract (Nathan 1990). This causes the corticospinal tract to be broadly left-lateralized, with this asymmetry also confirmed in diffusion imaging studies (Seizeur and others 2014; Thiebaut de Schotten and others 2011b) in both right- and left-handed individuals (Howells and others 2018). Similar to the M1 that is considered to be a dynamic motor control region exhibiting activity-dependent plasticity (Sanes and Donoghue 2000), the corticospinal tract continues to mature well into the second decade of life (Dubois and others 2009), which could reflect increasing hand proficiency with age.

In the last few decades a large number of structural MRI studies investigated the difference in the sensorimotor cortical areas between different handedness groups, albeit with inconsistent results. Large-scale studies of volumetric grey matter asymmetries (Kavaklioglu and others 2017; Ocklenburg and others 2016b; Watkins and others 2001) and asymmetries in the cortical thickness and surface area (Guadalupe and others 2014; Kong and

others 2018; Maingault and others 2016) failed to find strong association with handedness. However, trends toward significance were observed at the level of the precentral sulcus (Guadalupe and others 2014) and the hand motor area (Fig. 1B; Maingault and others 2016). Due to the large sample sizes, these studies used automated segmentation methods and systematic manual checking was not feasible. On the other hand, studies that used manual segmentation more often reported significant associations with handedness (both in terms of direction and degree), especially in the hand motor area, with pronounced left asymmetry in right-handers and weaker, absent (Hervé and others 2006; Germann and others 2019) or reversed (Amunts and others 1996; Amunts and others 2000) asymmetry in left-handers. Similar observation was noted in monkeys, with handedness found to correlate with the depth asymmetries of the contralateral central sulcus, within a mid-portion of M1 that could correspond to the motor hand area (Margiotoudi and others 2019). There is a need for improved automated parcellation methods that would take into account the local morphology, which might solve some of the inconsistencies in the findings.

In terms of white matter, exploratory analyses found neither global nor regional effect of hand preference on white matter volume (Good and others 2001) or microstructure (Jang and others 2017). This null result was replicated in a handful of diffusion MRI studies investigating the corticospinal tract. The asymmetries of the corticospinal tract (Ciccarelli and others 2003; Howells and others 2018; Westerhausen and others 2007; Seizeur and others 2014), the posterior (Westerhausen and others 2007) and the anterior limb of internal capsule (Peled and others 1998) were found to be unrelated to hand preference. However, some diffusion studies reported a link between the asymmetry of the corticospinal tract and manual dexterity (Angstmann and others 2016; Rüber and others 2015). In a sample of 52 right-handed participants, intra-individual asymmetry of manual dexterity was reflected in microstructural differences between the right and the left corticospinal tract (Angstmann and others 2016). Stronger hand lateralization in a circle-drawing task corresponded to a stronger left asymmetry of the corticospinal tract. The relationship might be task-dependent as others found no effect of corticospinal tract asymmetry on manual dexterity as assessed by Grooved Pegboard test or by the speed of unimanual finger dexterity (Howells and others 2018).

The idea coming from the structural MRI studies that asymmetries at the level of the precentral gyrus instead could be more relevant for handedness has been explored by several diffusion MRI studies. Büchel and others (2004) are the only ones that reported a significant effect of hand preference on the white matter of the precentral

gyrus. They found that the FA was higher in the left compared to the right hemisphere in right-handers and vice versa in left-handers. The authors used a voxel-based analysis of diffusion-weighted images, which did not allow for identification of possible tracts implicated, and a small sample size of 9 left-handed and 19 right-handed participants. Having in mind the problems that arise from spatially normalizing diffusion information (Greene and others 2018) performed routinely in voxel-based analysis, especially close to gray-white boundaries (Adluru and others 2016), these results merit replication in a bigger sample and in a native space.

Two studies used tractography to dissect and explore whether the short U-shaped fibers running beneath the central sulcus, first described by Catani and others (2012), relate to handedness. The findings point to an association between U-fibers connecting the hand region of the M1 and the somatosensory (S1) cortex and manual dexterity. Thompson and others (2017) showed that the microstructural measures (FA, MD) of the left-hemisphere M1-S1 hand-region tract correlated with both left and right hand performance on the Purdue Pegboard dexterity test in right-handers. In the same study, a disruption of M1-S1 connections was associated with precision grasping impairments in a group of individuals with autism spectrum disorders. The authors did not investigate hand preference because they included only right-handers. However, Magro and others (2012) observed left asymmetry of these short M1-S1 U-fibers fibers, in terms of volume and the number of streamlines, presumably driven by left-handers. They also noted a correlation between asymmetry index and handedness scores in the left-handed group only. This is explained with the higher variability in left-handers (handedness scores were from 7 to 20) compared to right-handers (between 1 and 0). However, the study was small and included only 10 right-handed and 10 left-handed participants. It should be noted that these superficial white matter fibers that run close to the cortex pose challenges for identifying and measuring with diffusion MRI tractography (Reveley and others 2015), especially for the tensor model used by Magro and others (2012). It remains to be seen if future studies using larger samples and more advanced tractography algorithms will replicate the findings. Lastly, the idea that asymmetries at the lower level of the spinal cord might be relevant for handedness still remains to be tested (Nathan 1990; Ocklenburg and others 2017).

Superior Longitudinal Fasciculus and Handedness

Given the lack of association between handedness and white matter networks implicated in motor output (corticospinal tract), it is plausible to turn attention to connections of the nonprimary motor regions. The compelling candidate is the superior longitudinal fasciculus (SLF), a major bidirectional association tract that connects an extensive range of premotor and parietal areas. The SLF is subdivided into three branches on the basis of its course and cortical terminations (Fig. 2D). According to previous studies (Budisavljevic and others 2017; Thiebaut de Schotten and others 2011a) the most superior branch (SLF I) originates from the precuneus and the superior parietal lobule and projects to the superior frontal gyrus; the middle pathway (SLF II) connects the inferior parietal lobe (angular gyrus and intraparietal sulcus) and the posterior regions of the middle frontal gyrus; the inferior branch (SLF III) originates in the inferior parietal lobe and terminates in the pars opercularis, triangularis, and the inferior frontal gyrus. The exact functional correlates of the SLF are not entirely known, but it has been implicated in visuomotor planning (Budisavljevic and others 2017; Koch and others 2010), visuomotor learning (Bonzano and others 2008), and spatial attention (Thiebaut de Schotten and others 2011a) among others.

The relevance of the frontoparietal network for handedness was highlighted by a recent functional MRI study balanced for handedness (46 right-handed and 46 left-handed healthy participants) by Häberling and others (2016). They reported that the handedness-linked network relied strongly on the regions connected by the SLF: the parietal lobe (the inferior and superior parietal cortex and the intraparietal area) and the premotor cortex. Activation of this network showed a leftward bias in right-handed participants, but a lack of bias in left-handers. The parietal involvement in handedness could reflect a presumable link between attentional asymmetries and manual laterality (Buckingham and Carey 2015). The attentional bias hypothesis postulates that right-handedness stems from a rightward attentional bias, that is, the right hand being allocated more attentional resources during bimanual tasks (Peters 1981), which could, in turn, drive hand preference. The SLF tract is known to connect two important attention networks, the dorsal (SLF I and partly SLF II) and the ventral (SLF III and partly SLF II) (Corbetta and Shulman 2002), with its asymmetry modulating the speed of the visuospatial attention processes (Rhys Marshall and others 2015; Thiebaut de Schotten and others 2011a). Right-larger-than-left SLF II (volume) was associated with faster visuospatial processing (Thiebaut de Schotten and others 2011a). The right-hemisphere advantage was also observed for initial movement trajectory features, with right-larger-than-left SLF II corresponding to higher movement acceleration during right hand reaching in right-handed subjects (Budisavljevic and others 2017). The larger tract in the right hemisphere could reflect an increase in the number of axons, greater fiber myelination and larger axonal diameter that would

lead to faster conduction speed and faster performance. Stronger right-lateralization of the SLF II could facilitate visuospatial and visuomotor information transfer. This view is supported by a study on surgical patients where the resection of the SLF II induced postoperative declines in selective attention task (Howells and others 2020). The patients also presented with postoperative hand selection shifts during reach-to-grasp movements, using more often then before their nondominant hand. The study highlights a possible link between attentional processing and lateralized hand selection, that is, the strength of dominance over the other hand. The SLF II could play a role in the top-down monitoring of one hand over the other, and the strength of the M1 ipsilateral deactivation affecting intermanual asymmetry (Tzourio-Mazoyer and others 2015).

Up to date, the strongest effect of handedness was found for the superior branch, the SLF I. The SLF I asymmetry, in terms of volume, strongly correlated with hand preference: a left-asymmetry was observed in 29 right-handers, and a right-asymmetry in 20 left-handers, with significant difference between the two groups (Howells and others 2018). These results were supported by a subsequent study showing that the surgical resection of the SLF I was associated with changes in hand performance and hand selection shifts (Howells and others 2020). Furthermore, a lateralized hand performance on a unimanual peg placing visuomotor task was associated with the SLF I asymmetry in 31 participants (13 left-handed, 18 right-handed; Howells and others 2018). Results were driven by differences in the SLF I volume in the right hemisphere and the left hand performance: participants with a stronger right-asymmetry of the SLF I had faster performance with the left hand, and vice versa. This observation is in line with reports that manual asymmetry depends on the activity of both hemispheres and not only the dominant one (Tzourio-Mazoyer and others 2015).

There are several reports linking the inferior branch, the SLF III to hand preference. The association was first described by a repetitive TMS and diffusion tractography study by Cazzoli and Chechlacz (2017). They reported that the lateralization of the SLF III (in terms of HMOA) was related to a direction but not to a degree of self-reported handedness. Left-handers showed stronger right asymmetry of the SLF III due to a lower HMOA within the left SLF III compared to right-handers. However, the study sample was small and included only 7 left-handed and 17 right-handed participants. A subsequent study by Howells and others (2018) confirmed that asymmetry of the SLF III differs between self-reported right- and left-handers. Both groups exhibited a significant right-asymmetry of the SLF III volume, with stronger right lateralization in the left-handed group, in line with the previous study (Cazzoli and Chechlacz 2017). These results are consistent with the functional MRI results showing that left-handers are characterized by a stronger right lateralization of the frontoparietal attention network (Petit and others 2015). Nevertheless, the surgical resection of the SLF III was found not to affect lateralized motor behavior, that is, hand selection during reach-to-grasp movements (Howells and others 2020). This result is difficult to explain in light of the previous findings. Taken together, the SLF I may represent the most significant tract associated with handedness, with its asymmetry being a potential anatomical marker of hand lateralization. The SLF II and SLF III also modulate aspects of upper limb control, though their role in handedness is less clear.

Conclusions and Future Directions

In this review, we synthesized the existing evidence on the role of white matter networks in handedness. A general concern is a lack of standardized reporting, due to a variety of neuroimaging and behavioral methods, poor sample sizes, and underreporting of group tendency and variability (see Carey and Johnstone 2014 for problems of central tendency in handedness research). There are also inherent challenges associated with diffusion MRI, from tracing difficulties in the regions of crossing fibers or close to the cortex, to the specificity and interpretation of diffusion measures. However, diffusion MRI has been validated using different approaches and remains a viable tool in both research and clinical areas (Jbabdi and others 2013; Azabdakht and others 2015; for a review see Lawes and Clark 2010). In general, although a direct one-to-one relationship is unlikely, structural variability of both interhemispheric and intrahemispheric white matter pathways seem to modulate the asymmetry of hand use. Handedness, in terms of hand preference and performance, seems related to asymmetries of the frontoparietal association pathways (particularly the SLF I) important for visuomotor and visuospatial processing, but not to projection pathways (the corticospinal tract) involved in motor execution. The role of the SLF and the right hemisphere for handedness could reflect an intimate link between attentional and manual asymmetries. The findings highlight the important contribution of both hemispheres for hand laterality, as well as the importance of inter-hemispheric transfer supported by corpus callosum. Replication of these results is a crucial next step in order to further advance our understanding of the neural basis of handedness.

There are several areas of research that deserve an important place within the study of handedness and white matter, but were beyond the scope of the present review. Attention should be devoted to the relationship with anatomical asymmetries of the language pathways and

regions (Hervé and others 2006; Hervé and others 2013, Vingerhoets, 2014, 2019) as well as the cerebellar white matter networks (Powell and others 2012; Howells and others 2018; Polat 2019; Germann and other, 2019). Future studies should move away from direct correlation methods toward more advanced mapping of structure-function relationship taking into account information from different modalities, for example, transcriptomic, cytoarchitectonic, and neuromodulatory information (for a review, see Suárez and others 2020) as well as the effects of familiar sinistrality, sex, age, environment, and epigenetics (Schmitz and others 2017; Wiberg and others 2019). Although the overall picture drawn from the diffusion MRI studies is sometimes equivocal and not exhaustive, we hope this review highlights its incredibly valuable potential in understanding the neural basis of hemispheric specialization and handedness.

Declaration of Conflicting Interests

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