

Revisiting human hemispheric specialization with neuroimaging

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Hemispheric specialization (HS) is a hemisphere-dependent relationship between a cognitive, sensory, or motor function and a set of brain structures. It includes both the hosting by a given hemisphere of specialized networks that have unique functional properties and mechanisms that enable the inter-hemispheric coordination necessary for efficient processing. Long derived from neuropsychological and behavioral observations, knowledge of HS is currently being profoundly modified by cutting-edge neuroimaging research that focuses both on the neural implementation of HS for language, visuospatial functions, and motor control/handedness across development and on the analysis of interactions between brain regions within and across hemispheres. New findings reveal the fundamental role of lateralization in the large-scale architecture of the human brain, whose ontogenesis has begun to be investigated with genetic-heritability brain mapping.

Hemispheric specialization: a fundamental organizational trait of the human brain

Although its discovery is usually attributed to Paul Broca, HS, namely, the hosting of a cognitive function or behavior by a given brain hemisphere, was first discovered by Marc Dax in 1836 [1]. Soon thereafter, HS for both handedness and speech were linked, giving birth to the concept of a dominant hemisphere assumed to control hand preference and, if damaged, to result in aphasia.

HS is a property not unique to the human brain, anatomical and behavioral hemispheric asymmetries being observed not only in chimpanzees [2], but also in all vertebrate classes, which supports the conclusion that HS was, at least partly, inherited from our ancestors [3]. Against this conclusion, the dramatically high occurrence of right-handedness is specific to the human species and the co-lateralization in the left hemisphere of the control of hand preference (right for more than 90% of human beings) with language has nourished different theories that link HS specifically to the human condition. Some accounts are rooted in genetics, such as Crow's proposal that HS relates to the origins of speech and speciation [4]. Others defend a gestural origin of language [5,6] or the idea that HS has allowed the emergence of the integrated sense of self that humans have, thereby enabling the human condition [7].

As reviewed in the present article, recent advances in imaging techniques have enabled the *in vivo* macroscopic description of the physiological bases of neural asymmetries that result from genetic, developmental, hormonal, and/or adaptive influences [8]. Imaging techniques allow the fine-grained description of: (i) anatomical asymmetries across the lifespan; (ii) intra- and inter-hemispheric connectivity at rest (intrinsic connectivity; see [Glossary](#)) or during cognitive or sensorimotor tasks; (iii) the directionality of these connections (effective connectivity); and (iv) with diffusion tensor imaging (DTI), the white matter connectivity that supports the functional wiring. There is continuing methodological innovation in the field, as evidenced by recent developments in network analysis that allow the tracking of the time-course of inter-hemispheric connectivity during cognitive tasks [9]. Such developments can be viewed as the continuation of split-brain research in the understanding of each hemisphere's function and their coordination [10].

Hemispheric differences in anatomical and intrinsic connectivity

The functional lateralization of cognitive functions, such as language, and sensorimotor functions, such as motor control, was initially related to gray matter asymmetries ([Box 1](#)) and more recently to differences in white matter

Glossary

Familial aggregation: occurrence of a trait in more members of a family than can be readily accounted for by chance; presumptive but not cogent evidence of the operation of genetic factors.

Fractional anisotropy: measure used in diffusion imaging that reflects density, axonal diameter, and myelination of white matter fibers. It is a scalar value between 0 and 1 that describes the degree of anisotropy of a diffusion process. A value of 0 indicates that diffusion is isotropic, that is, it is unrestricted (or equally restricted) in all directions, as, for instance, in the cerebro-spinal fluid. A value close to 1 indicates that diffusion occurs almost along one axis and is fully restricted along all other directions, as, for instance, in the most central part of the corpus callosum.

Genetic variant: variation in the genome of a population or species resulting from new gene combinations (e.g., crossing over of chromosomes), genetic mutations, genetic drift, etc.; may refer to a single nucleotide polymorphism (SNP) or copy number variation (CNV).

Heritability: fraction of phenotype variability that can be attributed to genetic variation.

Intrinsic connectivity: correlations between functional signals recorded in distant brain regions during the resting state or a baseline condition.

Probabilistic tractography: using diffusion MR imaging, white matter tractography methods can infer *in vivo* the continuity of fibers from voxel to voxel and reconstruct an entire white matter pathway. Probabilistic fiber tracking methods provide an estimate of the confidence of fiber connectivity between cerebral regions.

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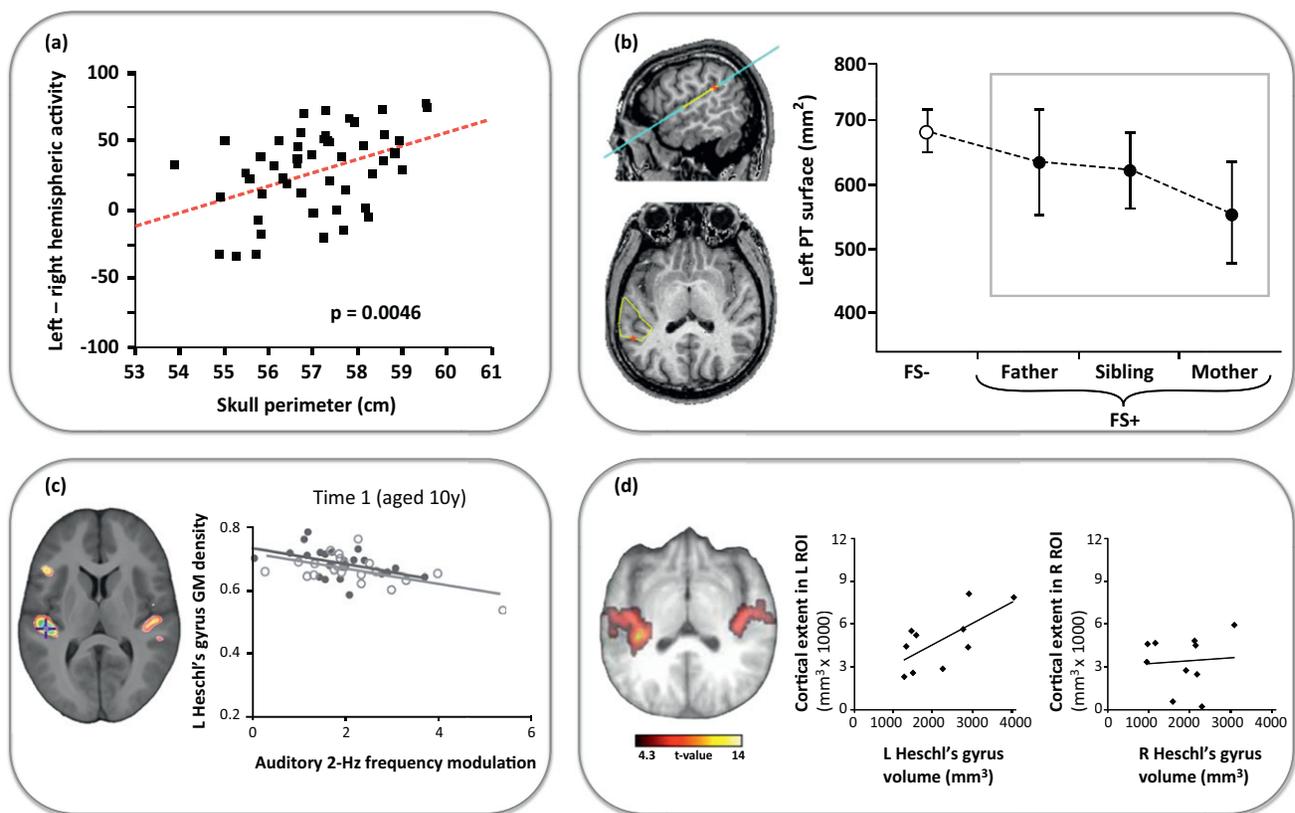
Box 1. Factors determining variability in HS

Handedness was identified early as a source of between-subject variability in language HS, which has nourished both evolutionary and genetic models of the origin of both HS and language, including the theory of a gestural origin of speech [6,82]. However, it must be underlined that more than 80% of left-handers exhibit typical left lateralization during language production [33], left-hander variability being mainly characterized by the existence of rightward asymmetrical individuals. Handedness appears to have no influence on the maturational increase of leftward asymmetries for language and the proportion of atypical left-handers is identical in children and adults [33]. In fact, familial sinistrality, rather than individual handedness, has been associated with a significant decrease in the surface area of the left planum temporale, a marker of HS for language, in individuals with a history of familial sinistrality, regardless of whether they are right- or left-handed [83] (Figure 1b). However, effective connectivity affords new perspectives on the understanding of the impact of handedness on language HS, as shown by a recent study where, during picture naming, left-handers exhibited stronger RH connectivity between fusiform and frontal areas as compared to right-handers [84].

Aside from handedness, anatomical factors partly explain HS variability. Brain volume, which increases inter-hemispheric distance and transfer time, constrains high-speed processes to

intra-hemispheric clustering. In fact, positive correlations between brain volume and both leftward functional asymmetry during speech perception [85] (Figure 1a) and leftward gray matter hemispheric asymmetry [83] demonstrate the ‘mechanical’ impact of brain volume on LH lateralization. Numerous observations regarding the anatomy of auditory areas are also in support of perceptual theories postulating that language HS arises from speed constraints on speech perception. For example, leftward asymmetry of temporal processing of speech sounds positively correlates with left Heschl’s gyrus volume [86] (Figure 1c), and so do phonological skills [87] or related parameters [88] (Figure 1d).

Notwithstanding this evidence, the recent discovery that insula volume asymmetry strongly correlates with language functional asymmetry [89] indicates that unexpected factors of HS variability are still to be sought. The picture is likely to be even more complex, given that factors can interact. For example, in right-handers, weaker manual lateralization decreases the leftward lateralization for language only in individuals with familial sinistrality [83]. Moreover, factors that influence variability in HS, such as gender and brain volume, may also be partially confounded [90]. Finally, it must be underlined that, although much is known about HS for language, the factors that might influence RH specialization remain to be discovered.



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Figure 1. Examples of anatomical factors explaining part of the inter-individual variability of the left HS for language. **(a)** Correlation between the functional hemispheric asymmetry index and head size indexed by skull perimeter during story listening compared to a story in a language unknown to the participants. The larger the brain of the right-handed participants, the stronger the leftward asymmetry. Reproduced, with permission, from [85]. **(b)** Familial sinistrality (FS) has a significant impact on the left planum temporale (LPT) surface area. Subjects with a left-handed first degree relative (FS+) have a smaller LPT surface area than subjects who do not, independent of their handedness. Note that subjects with left-handed mothers have the smallest LPT surface area. Reproduced, with permission, from [83]. **(c)** Correlation between gray-matter density in Heschl’s gyrus and 2-Hz frequency modulation detection threshold at age 10 overlaid on a T1-weighted average image template of participants at age 11.5. Colored areas represent the value of the *t* statistic for voxels where gray-matter density significantly correlates with auditory FM threshold score; the peak in the left Heschl’s gyrus is marked with a cross. Reproduced, with permission, from [88]. **(d)** Left: group average covariation map during temporal processing of sounds; middle: correlation between left Heschl’s gyrus volume and the extent of temporal-related activity within left Heschl gyrus; right: absence of correlation between activation and right Heschl’s gyrus volume. Reproduced, with permission, from [86].

structure between the two hemispheres [11]. In fact, asymmetries in gray and white matter structure reflect differences in the network structure of each hemisphere. White matter probabilistic tractography and graph theory ([12], Box 2) have shown that the right hemisphere (RH) is organized more efficiently, with greater regional interconnectivity than the left hemisphere (LH). In turn, the LH counts more crucial hub regions. According to Iturria-Medina [12], such differences reflect RH specialization for broader processes, such as visuospatial integration tasks, and the leading role of the LH for highly demanding specific processes, such as language and motor actions.

Anatomical hemispheric asymmetries are also observed with respect to the connections between homotopic (i.e., corresponding) areas of the two hemispheres. Strong inter-hemispheric connectivity corresponds to systematic co-activations of homotopic regions during cognitive tasks [13] and to strong homotopic correlations in functional intrinsic connectivity [14]. This strong component of intrinsic functional connectivity leaves an imprint on cortical anatomy during development: a longitudinal study in adolescents showed an increased correlation of observed changes in cortical thickness between pairs of homotopic cortical regions, compared with non-homotopic pairs [15]. The variation of the relative strength of homotopic correlations across the brain likely reflects differing degrees of HS. Intrinsic correlations are highest in primary areas due to synchronous thalamic inputs to these regions [16] and to bilateral sensory processes [14]. By contrast, heteromodal regions exhibit increased interactions with ipsilateral regions, rather than with other contralateral regions [17]. Callosal connections likely mediate most of the inter-hemispheric connectivity, because these correlations were shown to disappear following callosotomy [16]. In addition, a greater number of splenial callosal fibers originate from the right than the left visual cortex, which suggests directionality in inter-hemispheric connectivity with respect to HS [18].

Development of anatomo-functional support for HS

The most prominent anatomical asymmetries are established early in life (Figure 1), likely under the influence of genetic factors (Box 3). Imaging studies performed *in utero* [19,20] or in preterm [21] and term [22] newborns and infants [23] have reported a larger left planum temporale and a deeper right superior temporal sulcus (STS). During foetal development, sulcal pits, defined as the locally deepest points of sulcal fundi, are the earliest appearing parts of cortical sulci ([24]; Figure 1d). Their asymmetries are potentially relevant to HS for language: sulcal pits are more frequently detected in the LH than in the RH at both STS extremities [24]. The posterior left STS sulcal pit is also less variable than its right counterpart. In white matter, early LH asymmetries are also found in the corticospinal tract (CST) and arcuate fasciculus (AF) [25]. Accordingly, a LH asymmetry of the CST has been reported in adolescent right-handers [26], as well as in adults. A leftward AF asymmetry in newborns is also consistent with reports of leftward asymmetry of the long AF segment in adults (for a review, see [11]).

In contrast to anatomical asymmetries, functional lateralization is the result of maturational processes, as

developmental studies of language and visuo-spatial functions have revealed [27]. Intrinsic connectivity evolves from local before birth to inter-hemispheric homotopic connection at birth (for a review, see [28]; Figure 1c). In two-day-old infants, functional and white matter connectivity during language listening are characterized by inter-hemispheric connectivity, whereas the adult pattern is dominated by prominent connectivity within the LH ([29]; Figure 2b). The immature pattern of predominantly inter-hemispheric intrinsic connectivity is still present in 6-year-old children [30] and LH functional connectivity between the superior temporal gyrus and inferior frontal gyrus (IFG) increases between 5 and 18 years of age during story listening [31]. The development of progressive leftward asymmetry with age also reflects this trajectory from inter-hemispheric to predominantly LH intra-hemispheric connectivity [30]. This feature has been observed in children imaged while performing verb generation [27,32,33] and implicit word segmentation [34] tasks. Interestingly, between 6 and 24 years of age, increase in frontal asymmetry is present during articulation of words, but absent during story listening [32,35], which suggests partly different maturational mechanisms between language comprehension and production (Box 1). Although much less studied, the same phenomenon has been reported concerning the development of RH functions. Two studies have reported increased lateralization with age during visual search [27] and visuospatial memory [36] tasks, which suggests that the rise of functional asymmetries during childhood and adolescence could be a general phenomenon. In addition to the progressive functional maturation of early asymmetric cortical regions and related intra-hemispheric white matter pathways, the earliest development of the corpus callosum, which spans adolescence and beyond ([37]; Figure 1f), may explain developmental changes in the amplitude of functional asymmetry: its microstructure, as evaluated by fractional anisotropy, has been associated with inter-hemispheric inhibition capacities in the motor system ([38]; Figure 3). There is also evidence that fractional anisotropy in the corpus callosum is lower in those with 'typical' asymmetries, which suggests that hemispheric asymmetries arise through callosal pruning [39].

The maturation of HS is associated with improvement of both visuospatial and language abilities [27] and appears mandatory for the development of efficient cognitive processes. Between 7 and 15 years of age, better syntactic skills are associated with increased left IFG activation [40], whereas frontal and temporal asymmetries are positively correlated with both age and verbal IQ [27]. Note that this is also true for the leftward asymmetry of the AF, which is associated with better verbal performance in children [41]. Importantly, the restoration of left lateralization for language appears necessary for recovery after aphasia in children, which is in contrast to a limited RH contribution [42]. Indeed, the level of linguistic performance increases with leftward language lateralization during recovery from acquired aphasia [43] and pre- or peri-natal LH stroke [42]. Symmetrically, the lack of development of leftward lateralization for language is associated with dysphasia [44] and autism [45].

Box 2. New approaches for mapping brain asymmetries

In order to map the asymmetry of a quantitative functional or anatomical parameter across the brain, one must match the structures that are anatomically or functionally homologous in the two hemispheres. The average locations of these structures differ between the two hemispheres in a systematic way and, when relying on stereotaxic normalization, one risks comparing, for instance, gyral white matter in one hemisphere with sulcal gray matter in the other. Segmenting anatomical structures or functional areas, and matching them across hemispheres and subjects helps to circumvent this problem [91]. Alternatively, new automated surface-registration-based analytic strategies rely on the iterative construction of a symmetric, average model of the cortical surface (a hybrid of left and right hemispheres [92]) or on bringing left and right average surface models into correspondence [93,94]. This enables the separation of translocation and morphological asymmetries, and the computation of separate maps for positional, cortical surface area [92] (Figure 1a) or thickness asymmetries [93].

Graph theory allows the description of the organization of functional or anatomical networks within hemispheres [12,95] (Figure 1b). Distributed brain networks are modeled as graphs. The brain regions in the network constitute the graph nodes and the connections between regions constitute the edges. Such graphs can be built from different

modalities: edges can be defined according to the presence of white matter tracts or of significant functional correlations between regions. Many parameters can be obtained from these mathematical objects. Counting the edges at each node enables quantifying how highly connected the node is (degree centrality). Identifying the shortest paths between any pair of nodes, in terms of the number of steps required to go from one node to the other, is also valuable: nodes traversed by many shortest paths are important hubs (betweenness centrality); nodes connected by short paths to other nodes have high closeness centrality or nodal efficiency. If, on average, paths in the graph are short, the network is well integrated and globally efficient. Global efficiency is the opposite of modularity, whereby tightly interconnected nodes form mutually segregated cliques with high local efficiency. All these parameters that index global and local network properties can be compared across hemispheres.

Inter-hemispheric interactions can be addressed by DCM (Figure 1c), a method for estimating whether path coefficients from the LH to the RH and vice versa are positive (facilitatory) or negative (inhibitory) in nature [96]. New developments in magneto-encephalography permit probing these connections through correlations of low-frequency amplitude envelopes of the α -band activity between sensors placed over different hemispheres [9].

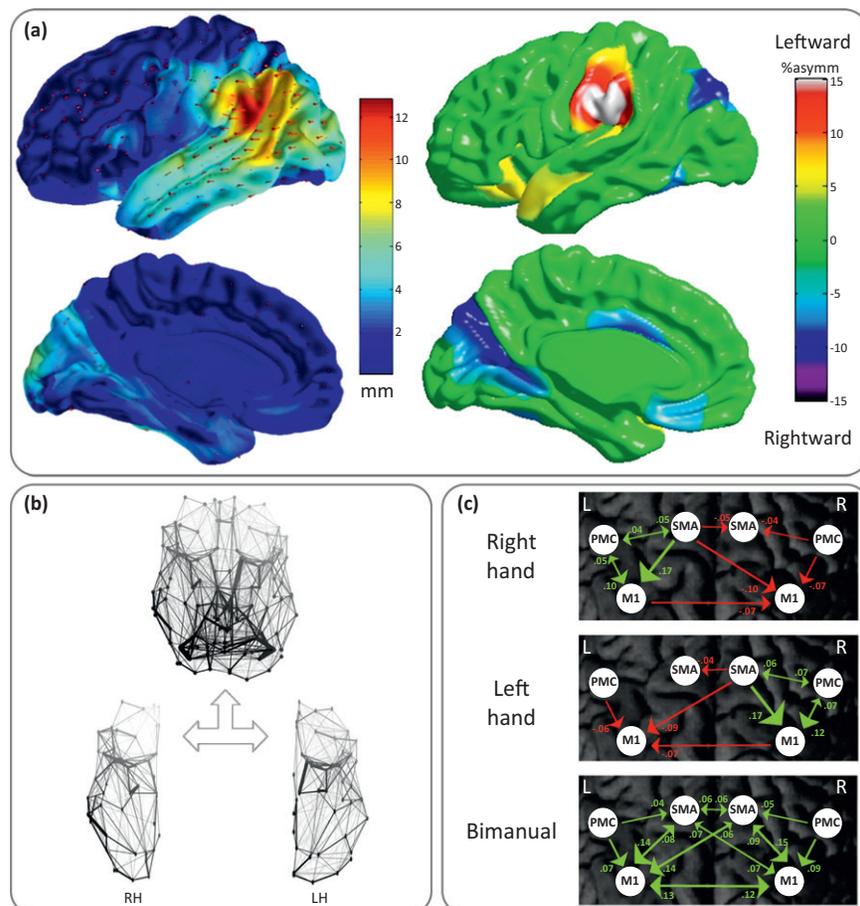


Figure 1. Anatomical asymmetry maps and analysis of intra- and inter-hemispheric networks. **(a)** Average maps of positional asymmetry (left) and cortical surface area asymmetry (right). The arrows on the positional asymmetry indicate the direction and the distance between LH points and equivalent points in the RH. Postero-inferior structures of the RH are shifted anteriorly and dorsally compared to the LH, with asymmetry culminating in the temporo-parietal junction. Cortical surface area asymmetry maps reveal increased surface in the left supramarginal gyrus and in the right parieto-occipital fissure. Reproduced, with permission, from [92]. **(b)** Hemispheric graphs of white matter connectivity. Reproduced, with permission, from [12]. **(c)** Dynamic causal modeling of the motor system: modulations of effective connectivity during movement of the right, left or, both hands. The inter-hemispheric interactions between primary motor areas are more negative during unimanual movements, but more positive during a bimanual condition.

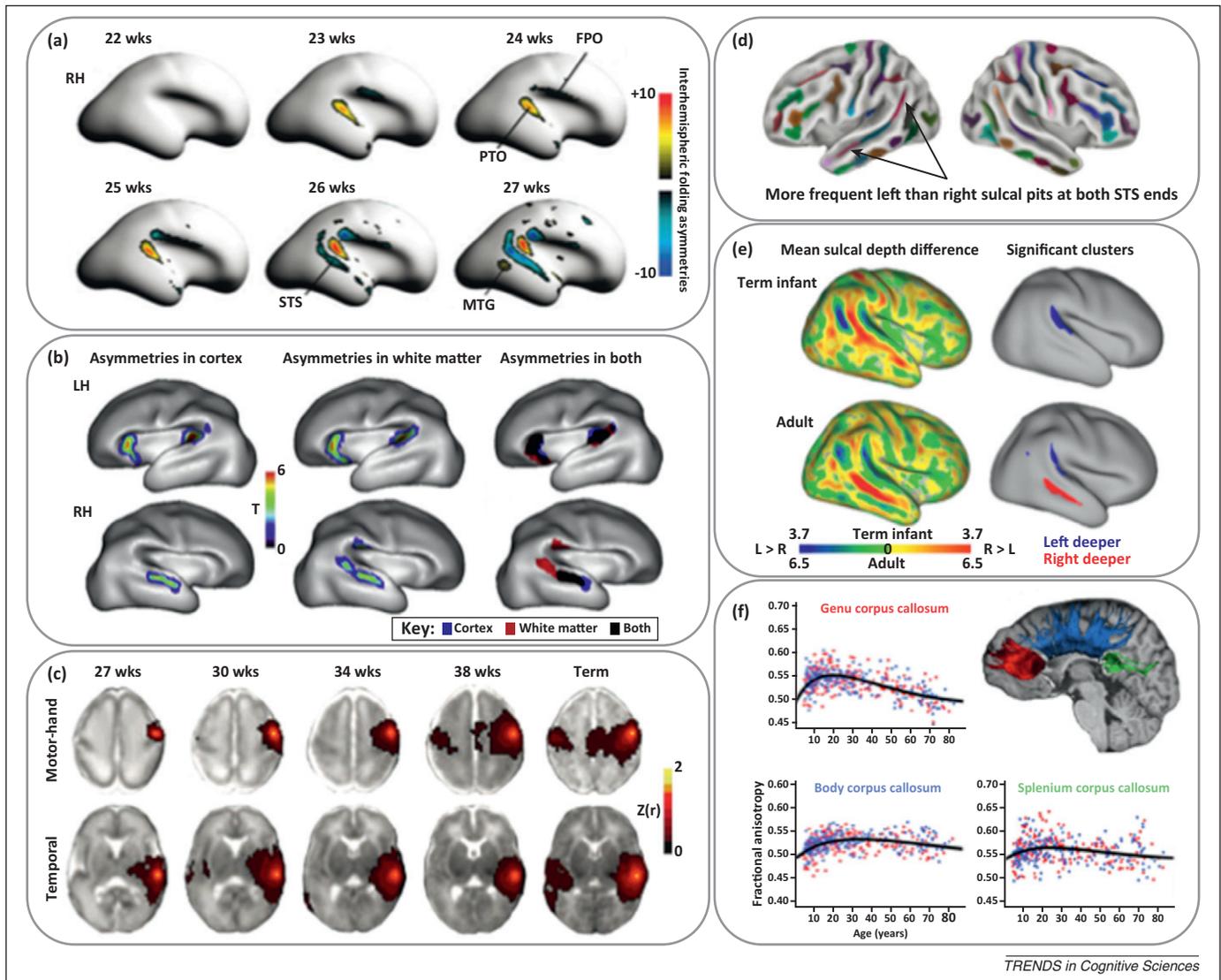


Figure 1. Development of anatomo-functional support for hemispheric specialization (HS). (a) Right hemisphere (RH) age-specific maps indicating regions of the fetal brain surface with significant interhemispheric folding asymmetries at different gestational ages. Hot colors represent regions that are significantly more concave in the RH. Cold colors represent regions that are significantly more convex in the RH. Abbreviations: FPO, fronto-parietal operculum; PTO, posterior temporal operculum; STS, superior temporal sulcus; MTG, middle temporal gyrus. Reproduced, with permission, from [20]. (b) Inter-hemispheric asymmetries in preterm infants. Statistical t-maps are superimposed onto the 3D averaged cortical surface for the significant clusters showing asymmetries in cortex (left) and white matter (middle) for left hemisphere (LH) and RH. On the right side, the clusters for cortex (blue) and white matter (red) are mainly overlapping (black). Reproduced, with permission, from [21]. (c) Longitudinal neural network development in preterm infants showing the evolution from intra-hemispheric connectivity limited to local surrounding areas to inter-hemispheric connectivity at term. Average functional connectivity correlation maps corresponding to seed locations in motor-hand (top row) and temporal (bottom row) regions are displayed at different post-menstrual ages. The illustrated quantity is the group mean Fisher z-transformed correlation coefficient (color threshold value = 0.3) overlaid on the gestational age specific atlas. Reproduced, with permission, from [28]. (d) Distribution of sulcal pits belonging to major sulci. Forty-eight and 47 clusters are shown in the left and right hemispheres, respectively. The number of the pits in LH was significantly larger than in RH at both STS ends. Reproduced, with permission, from [24]. (e) Analysis of hemispheric depth asymmetries for a population of 12 term infants and 12 adults. Left column, maps of mean sulcal depth difference between hemispheres. Blue and green regions are deeper on the left; red and yellow regions are deeper on the right. Right column, location of significant depth difference clusters. Reproduced, with permission, from [22]. (f) Plots of fractional anisotropy within callosal fibers across the lifespan. The age of peak fractional anisotropy for these tracts occurs at different ages, with the peak in the genu occurring at approximately 20 years, and that of the body not occurring until age 35 years (splenium peak age is 25 years). Males and females are shown separately as blue and red dots, respectively. Reproduced, with permission, from [37].

In adults, the relationship between functional lateralization of cognitive functions and performance seems limited to specific cognitive functions, such as phonological processing (Figure I, Box 1). However, functional asymmetries during post-lesional reorganization remain critical. During aphasia recovery, patients' verbal performance correlates with the amount of spared LH gray matter tissue [46] and with the strength of left intra-hemispheric connectivity ([47]; Figure 2e). By contrast, the role of the RH during recovery is possibly deleterious, as indicated by the positive effects on aphasia recovery of inhibitory

repetitive transcranial magnetic stimulation (rTMS) applied to RH frontal areas [48]. A comparable observation has been reported for RH lateralization in the visuospatial domain: inhibitory rTMS on LH parietal areas improves recovery from visual neglect [49].

From the identification of LH language areas to the mapping of language lateralized networks

The large LH network of language areas is now well characterized in adults ([50,51]; Figure 2c). In line with a meta-analysis of the relative contribution of the two

Box 3. The genetics of HS

The transcultural and overwhelming predominance of joint right-handedness and brain leftward lateralization for language suggest a strong genetic component at the origin of behavioral and brain asymmetries [6]. Currently, the most debated issues concern: (i) the degree of heritability of such asymmetries, (ii) whether they are governed by the same genetic variants, and (iii) the identification of these variants. Studies in monozygotic (MZ) and dizygotic (DZ) twins have demonstrated that handedness heritability is on the order of 25% [97], whereas structural brain phenotypes have much higher heritability – up to 80% for gray matter volume and cortical thickness [98–100]). However, discrepant results have been reported regarding a possible asymmetry in this genetic control of brain structure size, rightward for some [101], leftward for others [99]. Notably, a network of areas, including those involved in language processing, seems to exhibit significant heritability for leftward asymmetry ([100]; Figure 1). Genetics also has a significant influence on brain white matter phenotypes, namely its volume [100] and its asymmetry at the microstructure level of temporal and frontal white matter [102]. On the functional level, familial aggregation of strong left dominance for language has been reported [103], as well as higher concordance of language lateralization in MZ than DZ twins [65].

Handedness and language hemispheric dominance have been proposed to share a common single gene, exhibiting Mendelian transmission (for a review, see [82]). Several candidate genes have recently been proposed on the basis of evolutionary theoretical considerations (PCDH11X, [4]) or genetic studies of language-related disorders (FOXP2 and the KE family [104], DYX1C1 in dyslexia [105], DYX1C1 and PCSK6 in dyslexia [106,107], PYC19A1 [108]). However, the very few studies that have attempted to test directly the validity of the single gene model in normal subjects have yielded conflicting results [109,110]. In fact, several arguments point towards a multigene model, one being the difficulty for a single gene model to predict accurately the effect of sex on handedness distribution and to account for familial sinistrality

effects on brain asymmetry [97], the second being the evidence that some genetic variants, such as FOXP2 [111] or GRIN2B [109], are involved in language lateralization, but have no related involvement in handedness. Additionally, although very little is known about the molecular mechanisms at the origin of HS, recent findings have highlighted the potential role of epigenetic regulation (changes in the regulation of gene activity and expression that are not dependent on gene sequence) [112].

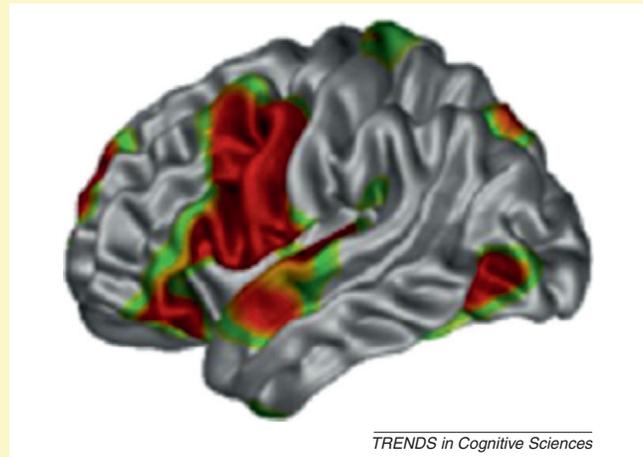


Figure 1. Brain regions that exhibit significant genetic effects on the leftward hemispheric asymmetry of their cortical thickness. These regions include the middle and inferior frontal gyri, lateral fronto-orbital and occipito-temporal junction, pars opercularis, planum temporal, and precentral gyrus. Reproduced, with permission, from [100].

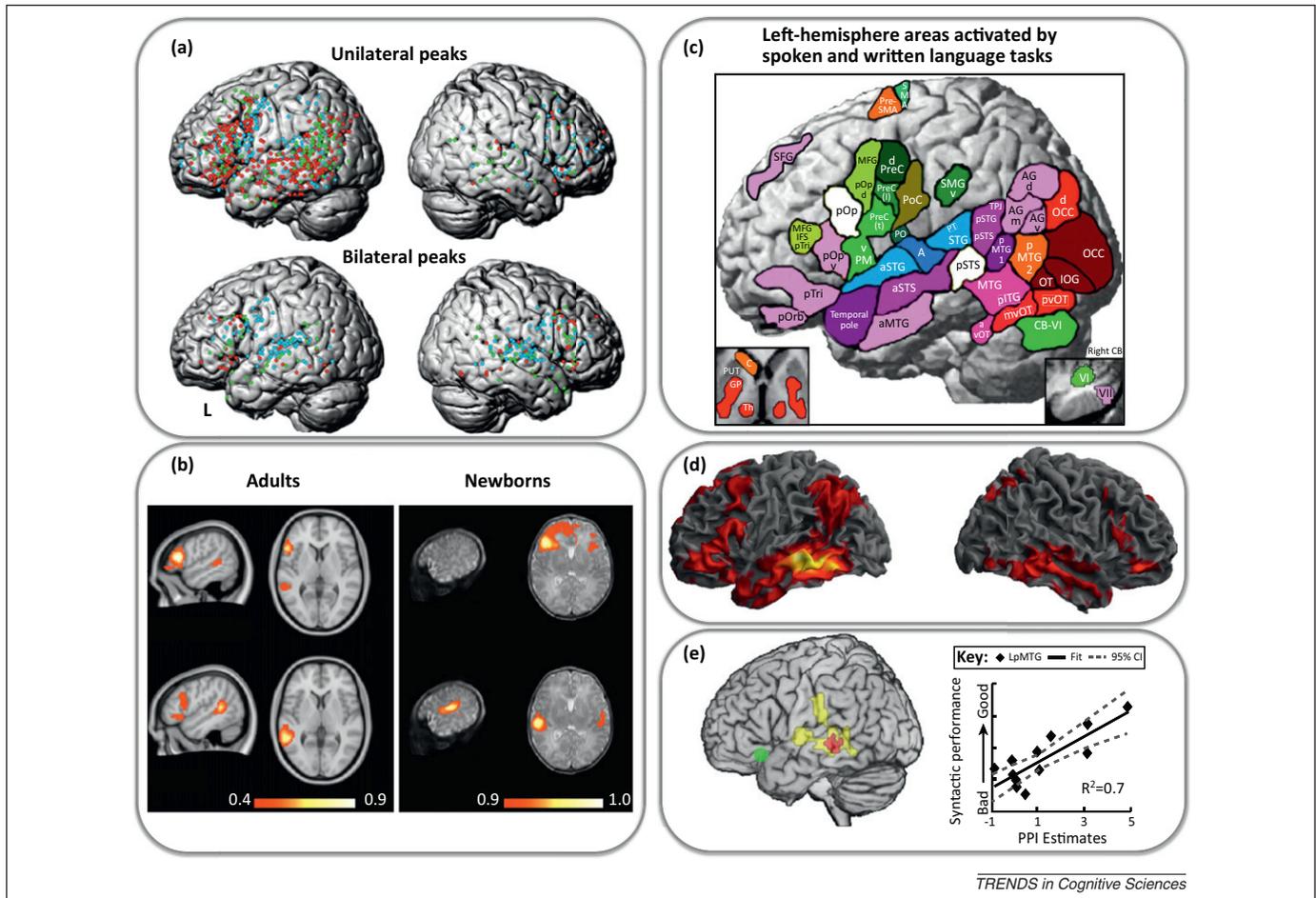
hemispheres during language tasks ([52]; Figure 2a), multimodal connectivity analyses have started to reveal the intra-hemispheric network organization of this remarkably consistent set of language areas. Converging evidence based on voxel-based lesion mapping, DTI, and intrinsic connectivity analyses has revealed a LH network critical for sentence comprehension that includes temporo-parietal and IFG areas connected by the inferior occipito-frontal, arcuate, and middle and inferior longitudinal fasciculi ([53]; Figure 2d). As mentioned earlier, aphasic patients' syntactic performance is positively correlated with the strength of functional activity ([47]; Figure 2e) and anatomical integrity of the fibers that connect the frontal and temporal areas of this comprehension network [46].

Important information on the HS of language networks has also been provided by measures of hemispheric asymmetries of intrinsic connectivity. Combining fMRI connectivity analyses and concurrent measures of EEG cortical rhythms, a core network has been identified, which is composed of auditory, somatosensory, motor and inferior parietal cortices, and which exhibits leftward asymmetries at specific frequencies [54]. Importantly, asymmetry of intrinsic connectivity of this network predicts asymmetry in higher-order language areas, which demonstrates the essential link between intrinsic perceptuomotor processing and higher-order language network lateralization [54].

RH specialization for visuospatial attention: a consequence of the LH specialization for language?

Compared to language, relatively little is known about the lateralization of visuospatial skills. Nevertheless, recent evidence from studies in healthy subjects and neglect patients converges in defining the neural basis of RH functional dominance for attentional reorienting. This RH specialization is supported by a ventral fronto-parietal attentional network composed of the temporo-parietal junction (TPJ), the inferior part of the middle frontal gyrus, the IFG, and the anterior insula (also called the ventral frontal cortex) [55–57]. RH dominance of the ventral attentional network is attested by the rightward asymmetry of both its intrinsic connectivity [58,59] and the white matter structural connectivity between the TPJ and anterior insula [60]. Note that visuospatial lateralization has also been associated with a rightward volumetric asymmetry in the most ventral part of the superior longitudinal fasciculus [61].

Although there has been progress on the understanding of the neural basis of RH dominance, there is still little evidence on its origin. The general view considers RH specialization as a side-effect of LH dominance for language. Two competing sets of theories have been proposed to account for the origin of LH-RH specialization: causal complementarity theories postulate that visuospatial functions are localized in the RH because the LH has already assumed responsibility for language, whereas independent



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Figure 2. Mapping hemispheric specialization (HS) for language. **(a)** Proportion of unilateral and bilateral homotopic activations in each hemisphere during phonological lexico-semantic and sentence tasks revealed in a meta-analysis of 209 functional imaging studies. Whereas the left hemisphere (LH) hosts a high proportion of unilateral peaks (80%), the right hemisphere (RH) aggregates principally co-activations of homotopic areas (66%) (colors correspond to 3 language components: blue represents phonological, red represents lexico-semantic, and green represents sentence and text processing). Reproduced, with permission, from [52]. **(b)** Correlation value during language experiments in adults and in 2-day-old infants with seeds in the left inferior frontal gyrus (IFG; top row) and in the superior temporal gyrus (bottom row). Strong connectivity only between the two hemispheres is observed in children, in contrast to the adult pattern of prevalent intra-hemispheric connectivity. Reproduced, with permission, from [29]. **(c)** Cortical areas of the LH activated by spoken and written language tasks reported in a meta-analysis of language mapping studies over 20 years. Reproduced, with permission, from [51]. **(d)** Intrinsic connectivity of the left posterior middle temporal region found to be critical for the core processes supporting sentence comprehension with a lesion approach (colors indicate t-values: dark red, lowest; yellow-white, highest). Reproduced, with permission, from [53]. **(e)** Left: psychophysiological interaction results for aphasic patients during a syntactic task using a seed located in the left IFG (green circle). The yellow color indicates results at voxel-level $p < 0.01$; red shows results at voxel-level $p < 0.001$. Right: regression line between performance and contrast estimates from the posterior part of the left middle temporal cluster (LpMTG) extracted from the regression model with performance in the patient group as the dependent variable: the stronger the connectivity between left IFG and LpMTG, the better the patients' syntactic performance. Reproduced, with permission, from [47].

theories consider that this division of labor between hemispheres is a reflection of independent, probabilistic biases, which may be genetic, biological, or environmental in origin (or a combination of these) [62]. To decide between these alternative theories, functional transcranial doppler studies attempted to identify negative correlations between RH visuospatial and LH language lateralization. In the absence of such correlations, these studies concluded that LH and RH specializations are independent [62–64]. One study used fMRI to investigate the correlations between regions specific for lateralized functions and found negative correlations between frontal lobe asymmetry for word generation and both temporal lobe asymmetry for face processing and parietal lobe asymmetry for visuospatial attentional processing, in favor of the causal complementarity theory [65]. However, the absence of impact of handedness on spatial lateralization constitutes disproof of a causal link for the complementary specialization of the two hemispheres.

Rather, it suggests some degree of independence, with different influences of handedness on language and visuospatial HS [65]. Behavioral lateralization of handedness and hemispheric lateralization for language are often confounded because their occurrence can be approximated with a single gene transmission model that assumes their co-lateralization in the LH (Box 3). Such confounding of handedness and language lateralization can lead to spurious conclusions, such as interpreting the absence of rightward lateralization of the fusiform face and extrastriate body areas in left-handers as a global effect of handedness on HS [66]. In fact, the LH is also dominant for praxis (i.e., the ability to perform learned gestures, that is, to generate, coordinate, and execute an acquired intentional motor program). The fact that the co-lateralization of language and praxis [67] is independent of handedness [68] shows how complex the issue of complementary specialization is, which certainly differs between pairs of cross-lateralized functions.

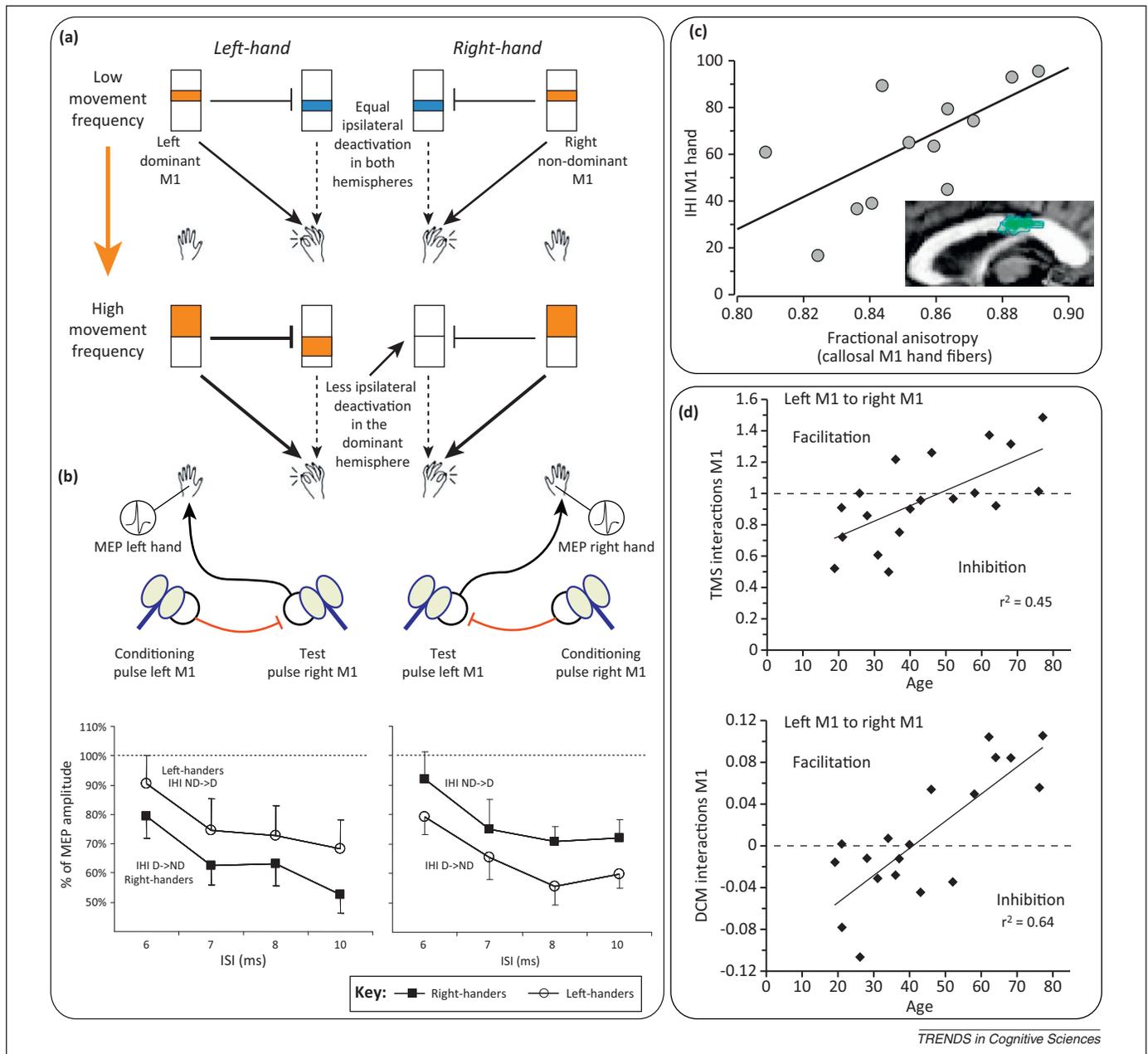


Figure 3. Hemispheric interactions between primary motor areas. **(a)** Ipsilateral activations of the left motor cortex during unimanual movements of the left hand can be explained by an asymmetry of inter-hemispheric inhibition and ipsilateral motor control capacities favoring the left dominant motor cortex. At low movement frequency with either hand, the left or right contralateral motor cortex is moderately activated, and the left or right ipsilateral motor cortex are similarly deactivated, due to inter-hemispheric inhibition from the active contralateral motor cortex. At high movement frequency, the left contralateral motor cortex exerts a stronger inhibitory influence over the right motor cortex than previously, resulting in increased right ipsilateral deactivation. Conversely, the dominant left motor cortex participates in ipsilateral motor control and becomes less deactivated as this activity counters the inter-hemispheric inhibition from the right M1. Reproduced, with permission, from [73]. **(b)** This proposed mechanism is compatible with TMS observations based on the paired-pulse paradigm. A test pulse over M1 causes a motor evoked potential (MEP) in hand muscles. When a conditioning pulse is applied over M1 in the other hemisphere shortly before the test pulse (inter stimulus interval between 6 and 10ms, abscissa), the MEP amplitude is reduced (ordinates), due to inter-hemispheric inhibition mediated by callosal fibers. The plots display inter-hemispheric inhibition from left-to-right (left) and right-to-left (right), in right-handers (filled squares) and left-handers (open circles). Inter-hemispheric inhibition is stronger from the dominant (D) than the non-dominant hemisphere (ND). Reproduced, with permission, from [77]. **(c)** Inter-hemispheric inhibition as recorded in hand muscles is positively correlated with fractional anisotropy in the isthmus of the corpus callosum, which contains fibers joining bilateral M1 hand areas. Reproduced, with permission, from [38]. **(d)** Both TMS measurements and estimates based on dynamic causal modeling (DCM) of motor fMRI data suggest that the influence of left M1 on right M1 changes with age, with inter-hemispheric inhibition in younger participants and facilitatory interactions in older participants. Reproduced, with permission, from [81].

Manual preference: a window into the anatomical and functional mechanisms underlying HS

In approximately 85–90% of the adult population, the right hand is preferred over the left hand for daily-life skilled manual activities. This variable and heritable (Box 3) behavioral asymmetry allows the investigation of how lateralized cortical specialization and inter-hemispheric

relationships contribute to behavior, and how, in turn, experience can influence the brain in an asymmetric way.

Asymmetric hand use is related to both innate and plastic anatomical phenomena in the central sulcus (CS) [69,70]: left-handers forced to switch to their right hand during childhood ('switched-handers') display a leftward asymmetry of the CS surface area, similarly to right-handers,

whereas left-handers show an opposite asymmetry [69]. This suggests that motor experience is the main determinant of CS surface area asymmetry in adults. Detailed automated analysis of the shape of this sulcus, however, revealed a different location of the left CS ‘hand knob’ between right-handers and either left- or switched-handers [70]. This subtle morphological trait of the left CS represents an innate anatomical bias in favor of left-lateralized specialization of motor cortical areas. Overall, manual skill may depend on both left HS for movement control and inter-hemispheric inhibition: in right-handed children, a leftward asymmetry of the functional connectivity of key motor regions (indicative of greater HS) is associated with better motor performance [71]. Conversely, the role of inter-hemispheric interactions between motor cortices is revealed by the observation in right-handed adolescents of a positive correlation between the performance of the dominant hand at the pegboard task (‘place as many pegs as possible onto the board within 30 s’) and a thicker isthmus of the corpus callosum [72].

Although during unimanual movement primary motor cortex (M1) activity occurs mainly in the contralateral hemisphere, activations are often detected on the same side as the performing hand, particularly during skilled or forceful movements. These ipsilateral motor activations could represent a marker of motor HS: they are more frequent in the motor dominant LH than the RH in right-handers (for reviews, see [73,74]). In the context of a unimanual motor-sequence task, online perturbations of the ipsilateral motor cortex with TMS impair hand motor performance. This indicates that the disrupted ipsilateral activity participates in unimanual motor control [74]. Yet, inhibitory rTMS applied to the ipsilateral M1 prior to execution of a learnt motor sequence is associated with improved execution times, regardless of the moving hand [75]. This suggests that the ipsilateral M1 interferes with the contralateral M1, consistent with a ‘hemispheric rivalry’ hypothesis that relies on mutual inter-hemispheric inhibition [75]. In right-handers performing a unimanual finger-opposition task (visually paced opposition of index and thumb at frequencies ranging from 0.25 Hz to 4 Hz), the left ipsilateral motor cortex becomes less deactivated as the pace increases, whereas the right ipsilateral motor cortex becomes more deactivated ([73]; Figure 3). Furthermore, a study that combined TMS and fMRI in right-handers found a correlation between lower right ipsilateral activation during hand grip and stronger inter-hemispheric inhibition in left-to-right M1 [76]. The HS associated with ipsilateral activation in right-handers may thus involve an asymmetry in inter-hemispheric inhibition capacity, favoring the dominant LH. Accordingly, inter-hemispheric interactions also appear to change with hand dominance: the inter-hemispheric inhibition asymmetry seen in right-handers is reversed [77] or absent [78] in left-handers as a group (Figure 3). Additionally, left-handers also display shorter inter-hemispheric transfer times, as assessed by response times, than right-handers [79]. In EEG studies, right-handers display shorter visual inter-hemispheric transfer times from the RH to the LH than vice versa, whereas no such asymmetry is found in left-handers [80].

As mentioned earlier, fractional anisotropy of callosal white matter fibers correlates with improved inter-hemispheric inhibition [38]. Both TMS and dynamic causal modeling (DCM; Box 2) assessments of inter-hemispheric interactions in M1 suggest that they become less inhibitory, and even facilitatory, during aging, possibly in order to maintain motor performance levels ([81]).

Concluding remarks

HS is supported by anatomical asymmetries in gray and white matter, some of which are in place at birth. These asymmetries are more heritable than handedness, which argues against a simple single gene model for HS transmission. Functional asymmetries that support HS emerge throughout development as the result of dynamic decrease in inter-hemispheric connectivity and increase of intra-hemispheric connectivity. Maturation increase in asymmetry, observed for both RH lateralization of visuospatial functions and LH lateralization for language, appears essential to the development of efficient cognitive networks; its failure is associated with developmental pathologies, such as dysphasia and autism. Inter-hemispheric inhibition appears to be a key component of the establishment of HS organization as revealed by DCM research on motor HS and the beneficial effect of suppressive rTMS over the minor (as opposed to the dominant) hemisphere on recovery of lesions of motor, language, and attentional networks. Recent developments in network-based connectivity

Box 4. Questions for future research

- Studies in monozygotic and dizygotic twins have shown that structural brain phenotypes have strong heritability. Genetics also has a significant influence on language lateralization. Does heritability of brain functional asymmetry differ between the different language components? Are asymmetries in intrinsic brain connectivity phenotypes for language more or less heritable than asymmetries in structural brain phenotypes?
- It has been shown that left-handers have a more variable lateralization of language, with a higher incidence of atypical individuals with rightward asymmetry. Does this mean that left-handers as a group have a different neural organization than right-handers? Do they exhibit variation in their intrinsic brain connectivity? How can structural and/or functional asymmetries be related to cognitive functioning in left-handers? How does lateralization vary with age or learning in left-handers? Considering the low occurrence of left-handedness in the general population, samples rich in left-handers will be needed in order to answer these questions.
- In adults, inter-hemispheric relationships between language and visuo-spatial functions seem to be under the influence of both independent and causal complementarity mechanisms. What is the weight of each of these mechanisms in the establishment of functional asymmetries? Does their respective contribution vary with different pairs of cross-lateralized functions, such as language – attention, or word – face processing? How does their respective influence evolve across development and the lifespan?
- How does the structural maturation and aging of the corpus callosum influence the emergence of functional asymmetries during childhood and their decline during aging?
- The relationships between macroanatomical and functional asymmetries in adults are subtle. Are such relationships clearer during development?
- Asymmetries of hub regions are apparent in both anatomical and functional hemispheric network graphs. How are these hubs related? How do they relate with the HS of different systems?

analysis show that HS of cognitive functions is supported by hard-wired networks of anatomical and intrinsic connectivity and by dynamic temporal changes in homotopic area connectivity.

Despite significant recent developments, a number of outstanding questions in this field remain. The most crucial ones are outlined in Box 4.

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