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Review

Cross-hemispheric communication: Insights on lateralized brain functions

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SUMMARY

On the surface, the two hemispheres of vertebrate brains look almost perfectly symmetrical, but several motor, sensory, and cognitive systems show a deeply lateralized organization. Importantly, the two hemispheres are connected by various commissures, white matter tracts that cross the brain's midline and enable cross-hemispheric communication. Cross-hemispheric communication has been suggested to play an important role in the emergence of lateralized brain functions. Here, we review current advances in understanding cross-hemispheric communication that have been made using modern neuroscientific tools in rodents and other model species, such as genetic labeling, large-scale recordings of neuronal activity, spatiotemporally precise perturbation, and quantitative behavior analyses. These findings suggest that the emergence of lateralized brain functions cannot be fully explained by largely static factors such as genetic variation and differences in structural brain asymmetries. In addition, learning-dependent asymmetric interactions between the left and right hemispheres shape lateralized brain functions.

INTRODUCTION

From the tiny brain of the freshwater fish *Danionella translucida*[1] to the human brain and much larger cetacean brains, all vertebrate brains have a striking organizational feature in common: they are organized in two halves, called hemispheres.[2] These two hemispheres are not isolated from each other but interconnected by several white matter tracts called commissures, with the corpus callosum as the major commissure in placental mammals (*Eutheria*).[3]

Functionally, the two hemispheres of the vertebrate brain are not equivalent, with several major neuronal networks showing functional lateralization, e.g., differences in accuracy or latency while generating behavioral output or reacting to the environment.[4] For example, lateralized brain functions in the vertebrate brain are common in the motor domain. In humans, 10.6% of people are left-handed for fine motor behavior like writing, while the remaining 89.4% are right-handed.[5] Although this strong population-level asymmetry seems to be typically human, side preferences for fine motor behavior such as manipulating food are common across vertebrate species.[6] For example, a recent meta-analysis in rodents showed that 81% of mice and 84% of rats showed a preference for one paw over the other.[7] Other examples of lateralized functions in the motor domain include turning bias,[8] head-turning asymmetries,[9] and left-right decisions in T-mazes or similar situations.[10] Besides the motor domain, approach/avoidance motivation[11] and emotion processing[12] are major research areas for lateralized functions in the vertebrate brain. Moreover, species-specific vocal communication is a strongly lateralized brain function.[13–15] In humans, a recent fMRI study across 45 languages and 12 language families found that left-lateralization is a key functional property of human language networks.[16] Neuroanatomically, Broca's area and Wernicke's area (the cortical centers for language production and perception) are located in the left hemisphere in most people.[13] In non-human vertebrates, evidence for lateralization of conspecific vocalization has been found in several mammalian species, mostly with the *Primates* order but also in several avian species.[17]

Importantly, the two hemispheres are not isolated from each other but exchange information with each other constantly.[18] As the visual, somatosensory, and auditory cortical areas preferentially process stimulus information from the contralateral space, and the motor cortex commands mostly contralateral body parts,[19,20] cross-hemispheric (CH) communication plays a key role in the coordination of sensory, cognitive, and motor functions across hemispheres.[21] Disruption of callosal function can severely affect sensory integration, motor coordination, and cognitive and emotional processing.[22,23] Research on split-brain patients, in whom the corpus callosum has been cut to treat intractable epilepsy, reveals that many cognitive and perceptual processes are functionally lateralized,[24] with

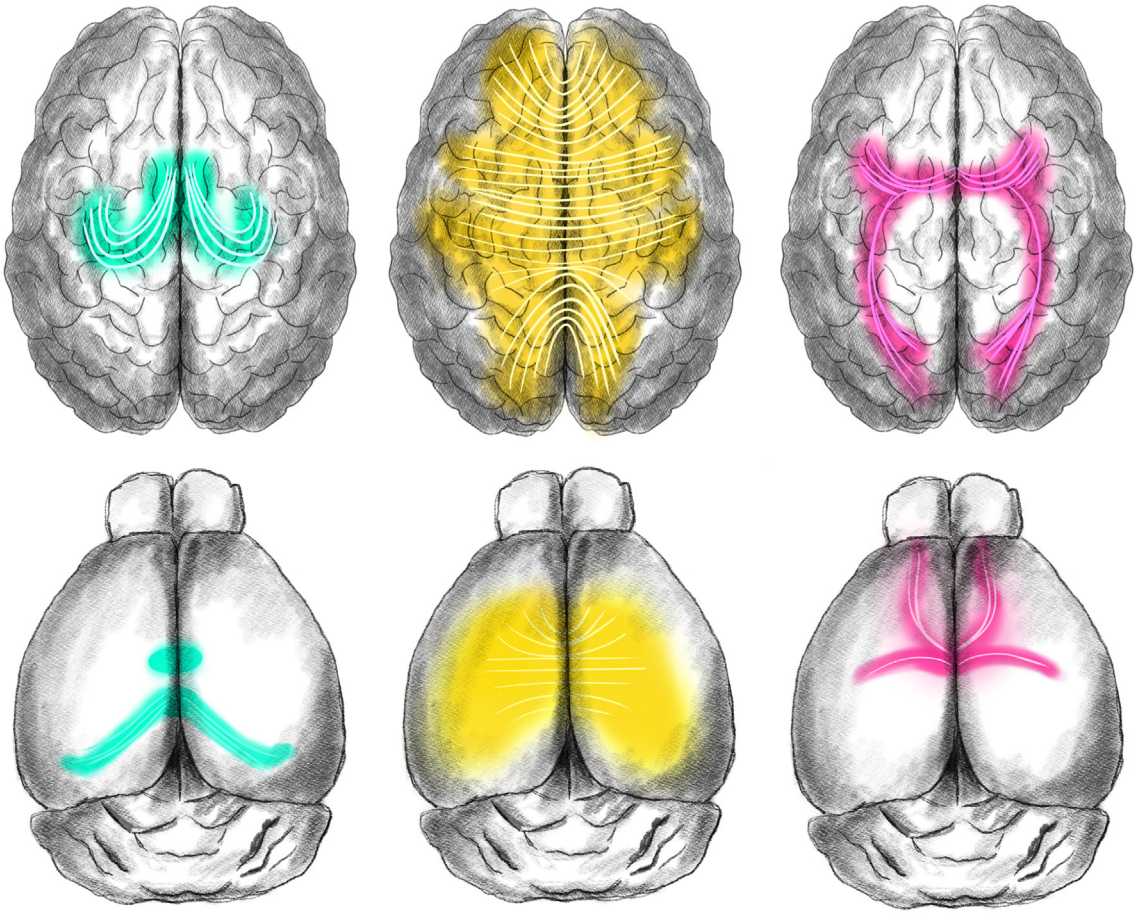


Figure 1. The three larger commissures in the vertebrate brain shown in the human brain (upper row) and the mouse brain (lower row): the hippocampal commissure of the fornix (green), the corpus callosum (yellow), and the anterior commissure (red)

the left hemisphere playing a larger role in verbal tasks and the right hemisphere dominant in nonverbal and spatial tasks.[22,25,26]

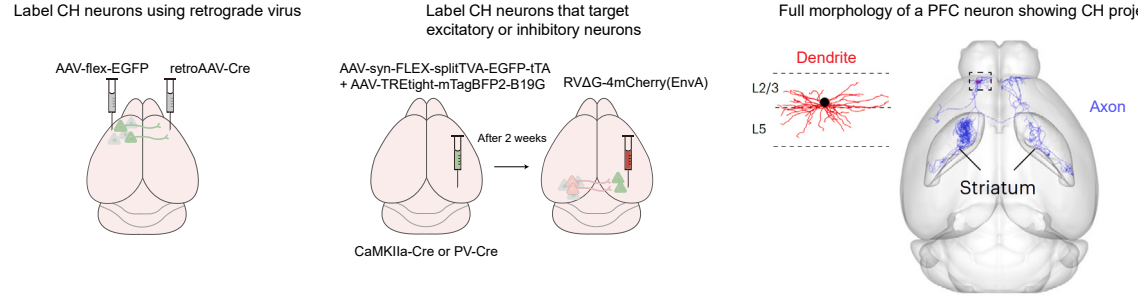
How does functional lateralization emerge on the neurophysiological level? One central idea is that CH communication gives rise to lateralized brain function. From behavioral experiments in split-brain patients in the 1960s[27] to modern neuroimaging studies,[28] many studies on CH communication have been conducted in human participants, with relatively few studies in rodents. However, recent advances in genetic targeting, cell-type-specific perturbation, large-scale electrophysiological recordings, and quantitative behavior assessment have made rodents a highly attractive model to study CH communication. Importantly, rodent models allow for mechanistic insights at the level of circuits that are amenable to manipulations to probe causal contributions of CH communication. This is typically not possible with neuroimaging and other techniques used in human participants. Therefore, the present review article aims to give an overview of CH communications, with a specific focus on how modern molecular techniques have advanced our understanding of CH communication and on how lateralized brain functions emerge from asymmetric CH communications.

COMMISSURES: THE ANATOMICAL BASIS OF CH COMMUNICATION

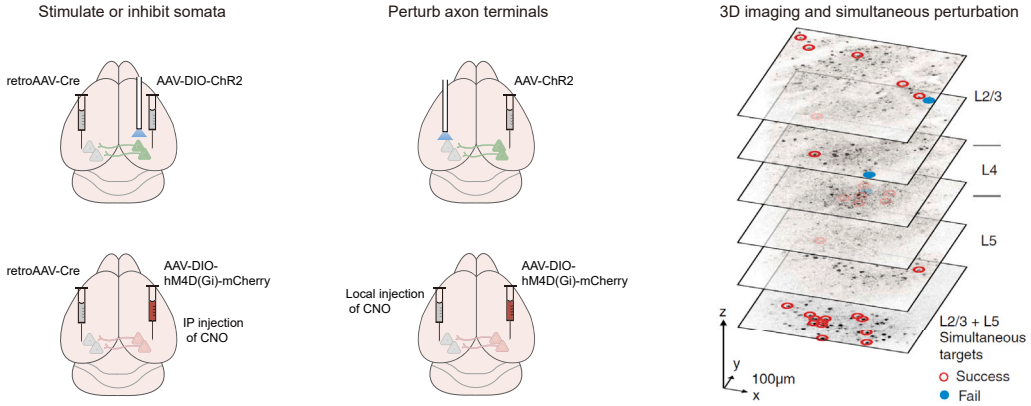
In the human brain, three larger and several additional smaller commissures (e.g., fibers that cross the brain's midline) have been described (see Figure 1).[29] The three larger commissures include the anterior commissure, the corpus callosum, and the hippocampal commissure of the fornix. The smaller commissures include the reticular commissure in the brainstem, the habenular commissure in the diencephalon, the tectal commissure, and the interthalamic adhesion connecting the two thalami.[29] The anterior commissure connects temporal cortical areas and is involved in olfaction, pain perception, and survival.[30] The hippocampal commissure of the fornix connects the two hippocampi via the fornix and is likely relevant to memory function.[31]

The largest commissure in the human brain is the corpus callosum, which connects large parts of the cortex and is involved in motor coordination,[32] interhemispheric integration of sensory information,[33] and interhemispheric integration of other forms of neuronal information such as memory traces.[34] The corpus callosum is the major commissure in all placental mammals (*Eutheria*) (Figure 1).[3] In *Metatheria* (marsupials and closely related species),

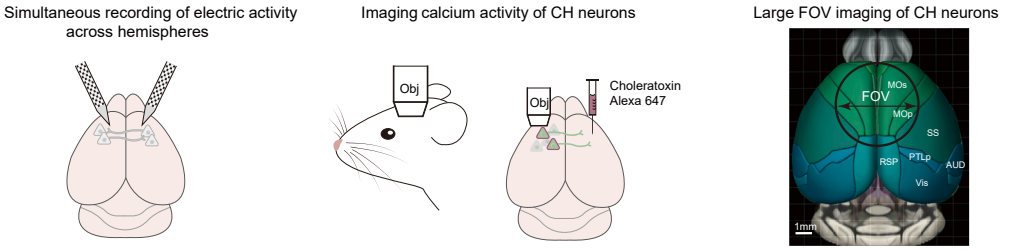
A Genetic targeting of CH neurons



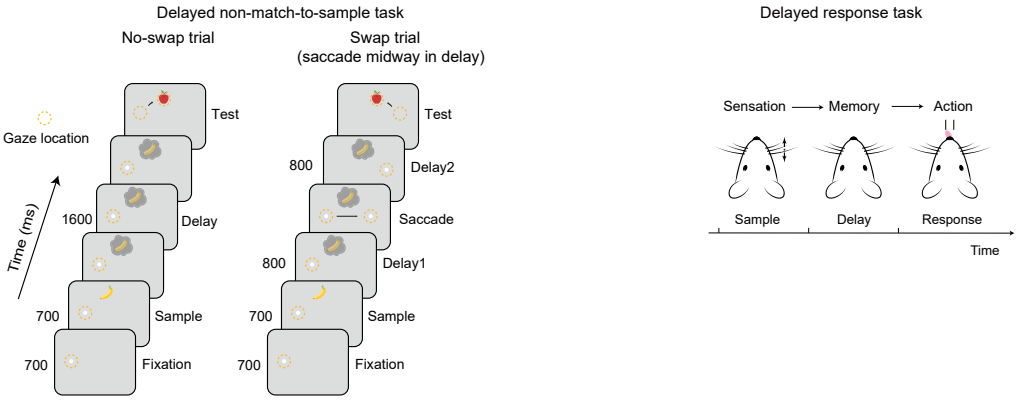
B Perturbation of CH neurons



C Large scale recording of neural activity



D Example behavioral tasks for probing CH communication



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which do not have a corpus callosum, the anterior commissure is the major pathway for cortico-cortical CH communication.[35] The anterior commissure shows similar organizational features as the corpus callosum in these species, suggesting a largely conserved pan-mammalian map of interhemispheric brain connections.[36] Birds also do not show a corpus callosum and the anterior commissure is the largest commissure in the avian telencephalon.[37] Similarly, the corpus callosum is absent in fishes, reptiles, and amphibians. Because brain lateralization is well documented in birds, fishes, reptiles, and amphibians,[38–40] and even in several invertebrate species,[41] understanding its emergence requires the integration of other factors than just CH communication over the corpus callosum.[42]

Neuroanatomically, the corpus callosum consists of contralateral axonal projections, with the human corpus callosum comprising about 200–250 million fibers.[43] It contains about 70% myelinated axons and about 30% unmyelinated axons and, additionally, cell bodies of oligodendrocytes, astrocytes, and neurons.[44] The ratio of myelinated to unmyelinated axons in the corpus callosum differs between mammalian species. One study found considerably fewer myelinated axons in the corpus callosum of mice (28%) compared with humans.[45] Most of the axons in the corpus callosum connect homotopic areas and show a roughly topographic organization in that the anterior part of the corpus callosum connects the anterior parts of the brain.[46] Consequently, most callosal axons allow for CH communication between homotopic areas (e.g., connecting the left and right primary visual cortex), with only a few heterotopic connections between different brain areas in the left and the right hemisphere.[46] Based on the connected brain areas, the corpus callosum has been divided into different segments: the anterior third connects prefrontal, premotor, and supplementary motor areas; the anterior midbody connects motor areas; the posterior midbody connects somesthetic and posterior parietal areas; the isthmus connects superior temporal and posterior parietal cortices; and the splenium connects the inferior temporal and occipital cortices.[47]

INVESTIGATING CH COMMUNICATION AT THE CELLULAR LEVEL

How can the function of the corpus callosum and other commissures in the vertebrate brain be assessed experimentally? In principle, CH communication is a special case of inter-areal interaction[48] in which the interacting brain areas are located in different hemispheres. Thus, tools used in research on inter-areal interactions can be readily adapted to study CH communication. The extra benefits here are that the interaction route is known, i.e., through the commissures, and that the homotopic areas are well separated into two hemispheres. Here, we review the current knowledge on methodologies that can be used to map CH anatomical connections, to perturb CH communication, and to monitor neural activity underlying CH communication, with a focus on modern techniques that provide cell-type-specific labeling and manipulation, as well as high-throughput monitoring of neural activity.

Labeling of neurons involved in CH communication

Specific imaging of CH neurons requires genetic targeting of fluorescent proteins to this particular type of cells. CH neurons comprise mainly intratelencephalic (IT) neurons that are spatially intermixed with the other two major types of cortical projection neurons: pyramidal tract (PT) and corticothalamic (CT) neurons.[49] Specific targeting of CH neurons can be conveniently achieved by injecting Cre-dependent virus in IT-specific transgenic lines[50] or using a dual viral strategy, with an injection of retrograde adeno-associated virus (retro-AAV) infecting CH axons to express Cre recombinase and a contralateral injection of Cre-dependent AAV to drive expression of green fluorescent protein (GFP) (Figure 2A). Combining sparse labeling and light microscopy for fast whole-brain imaging, researchers have reconstructed the complete morphology of individual CH neurons, revealing their intricate dendritic and axonal processes and the diverse ipsilateral and contralateral projection patterns (Figure 2A).[49,51–54]

Specific targeting of CH neurons combined with trans-synaptic tracing can delineate one central question concerning CH communication, i.e., whether CH neurons target excitatory, inhibitory, or both types of neurons in the contralateral hemisphere. Callaway and colleagues developed a rabies-virus-mediated monosynaptic tracing method that allows mapping of brain-wide inputs to molecularly defined types of neurons.[60] Cortical excitatory and inhibitory neurons can be targeted using transgenic Cre-driver mouse lines,[61] for example, with CaMKIIα-Cre (calcium/calmodulin dependent protein kinase II alpha, CaMKIIα) for excitatory neurons and PV-Cre (parvalbumin, PV) for fast-spiking interneurons. To

Figure 2. Strategy to genetically label CH neurons for spatiotemporally precise perturbation and recording of neural activity in behaving animals

(A) Genetic labeling of CH neurons (left) or their CH targets (middle). CH neurons typically target many ipsilateral and contralateral brain areas. The right panel shows the full morphology of an example CH neuron from layer 3 of the prefrontal cortex.

(B) Strategy to specifically perturb CH neurons using optogenetic and chemogenetic tools (left). With local light or drug delivery, perturbation can be limited to CH pathways (middle). By combining optogenetic and two-photon imaging, it is possible to simultaneously perturb ensembles of neurons during three-dimensional (3D) imaging (right).

(C) Large-scale, multi-regional recording enables high-throughput monitoring of neural activity underlying CH communication (left, simultaneous recording of extracellular electric signals from the left and right hemispheres using multiple Neuropixel probes; middle, imaging of calcium transients using two-photon microscopy; right, large field-of-view imaging to cover CH-connected brain areas).

(D) Quantitative behaviors for probing CH communication. The left panel illustrates a non-match-to-sample visual working memory task performed by body-restraint monkeys. Monkeys were required to make a saccadic eye movement to the test object if it did not match the remembered object in either location or identity. In swap trials, monkeys were instructed to saccade to the opposite side midway during the delay, which shifts the remembered object's retinotopic position to the opposite visual hemifield (relative to the gaze). The right panel shows a delayed response task in a head-fixed mouse. Mice discriminate whisker stimuli during the sample epoch, maintain a prospective short-term memory (motor planning) during the delay epoch, and lick a water spout as instructed by sensory input.

(A, middle) Modified from Adaikkan et al.[55] with permission. (A, right) Reproduced from Gao et al.[49] with permission. (B, right) Reproduced from Marshel et al.[56] with permission. (C, right) Schematic made from the Allen Brain Atlas.[57] (D left) Reproduced from Brincat et al.[58] with permission. (D, right) Modified from Wang et al.[59] with permission.

map inputs to excitatory neurons, helper AAV particles are delivered to CaMKIIα-positive neurons to induce expression of tumor virus A (TVA), a specific receptor for the avian sarcoma and leucosis virus envelope protein (EnvA) (Figure 2A). Rabies viral particles, pseudotyped with the glycoprotein EnvA, bind TVA to initiate the endocytosis and delivery of viral cargo to the infected neurons. The viral genome, with the gene encoding the rabies glycoprotein (G) deleted, complements the rabies G protein expressed by helper AAVs and then spreads to presynaptic CH neurons (and many other neurons ipsilaterally). The rabies virus will not retrograde further from the directly connected CH neurons as the genome lacks the glycoprotein gene. Using this strategy, Adaikkan et al. demonstrated that CH neurons are mainly excitatory and that they target both excitatory and inhibitory neurons that are distributed across different cortical layers.[55]

Perturbing CH communication

To probe the causal consequences of CH communication on downstream neural dynamics and behavior, it is necessary to perturb the underlying neural activity. Transcranial magnetic stimulation (TMS) and electric stimulation are widely used to perturb neural activity in humans and non-human primates, and the findings have contributed substantially to our knowledge in both basic and applied research. However, these approaches inevitably affect multiple cell types in the stimulated brain area. To achieve cell-type-specific perturbation, it is necessary to combine the aforementioned CH-specific labeling with opto- or chemo-genetic actuators.[62,63]

Optogenetics is widely used in rodents to manipulate the activity of a specific type of neurons at milliseconds temporal resolution.[62] The specificity comes from the combination of precise spatiotemporal control of light delivery with genetic targeting of molecularly defined cell types (Figure 2B). Mapping functional CH projections can be achieved by expression of light-gated ion channel channelrhodopsin-2 (ChR2) in CH neurons, laser scanning of presynaptic terminals, and whole-cell recording of evoked synaptic currents in post-synaptic neurons.[64] Using this technique, Petreanu et al. revealed that callosal projections from layer (L) 2/3 of the mouse somatosensory cortex connect with L2/3, L5, and L6, but not L4, neurons in the contralateral cortex.[64] Compared with optogenetic stimulation, which typically induces synchronous activity, inhibition by removing neural activity is a milder perturbation. Optogenetic inhibition can be achieved by expressing light-driven ion pumps, such as halorhodopsin (NpHR), archaerhodopsin, or *Guillardia theta* anion-conducting channelrhodopsins (GtACRs), in excitatory neurons.[65] Alternatively, it can be achieved by employing the natural inhibition mechanisms of the brain, i.e., by stimulating GABAergic (gamma-aminobutyric acid, GABA) neurons expressing ChR2.[66] This strategy achieves efficient, localized silencing of millimeter-sized cortical tissue with low intensity of light.[67] After the removal of inhibition, typically a rebound excitation can be observed. This can be greatly reduced by tapering the light off gradually.[66] Using this optimized protocol, unilateral inhibition of the premotor cortex reveals that disruption of CH information affects lateralized planning of tongue-reaching movements in rodents.[68]

Chemogenetic tools possess the specificity to target genetically defined cell types while providing the convenience to manipulate neural activity for a whole session or to perturb the activity of widely dispersed neurons.[63] CH pathway-specific perturbation can be achieved by local infusion of small molecular ligands to activate chemogenetic receptors expressed on CH terminals (Figure 2B). Combining this specific inhibition with simultaneous activity recording, Adaikkan et al. have shown that synchronous oscillations between homotopic visual areas through CH communication are necessary for the detection of novel visual stimuli.[55]

Brain region or pathway-level perturbation is still a rather crude approach for investigating the causal contribution of CH activity to lateralized cognition. However, with improvements in optical methods for spatial targeting, it is feasible to stimulate spatially dispersed neurons with defined functional response properties.[56,69–71] In these experiments, two-photon microscopy is first used to monitor stimulus-, memory-, or action-selective neurons. Subsequently, physiological levels of activation can be elicited in dozens to hundreds of single neurons at behavior-relevant time scales (Figure 2B). These all-optical, read-and-write techniques will facilitate the perturbation of CH neurons with single-cell resolution and defined functional response properties.

Large-scale, multi-regional recording of neural activity underlying CH communication

To study which information is transferred across hemispheres, it is necessary to simultaneously monitor the activity of CH neurons bilaterally. Silicon-based microelectrode arrays (MEAs) contain high-count microelectrodes through which neural activity from hundreds of neurons can be simultaneously recorded.[72] The "Utah" MEAs are widely used in non-human primates and, when bilaterally implanted in the prefrontal cortex (PFC), can be used to study CH transfer of working memory (WM) information.[58] The "Michigan" MEAs are more versatile regarding the number, size, and spatial distribution of recording sites, providing a convenient way to record populations of neurons from rodent brains.[72] Recently, a new class of silicon probes has been developed: Neuropixel probes. Each probe features 384 dual-band, low-noise recording channels, thus enabling simultaneous recording of several hundred neurons in rodents, ferrets, and non-human primates.[73–75] As each probe has a 10-mm long shank that is attached to a small base, up to 8 probes can be inserted into rodent brains in one experiment, yielding more than two thousand neurons that cover the frontal, sensorimotor, visual, and retrosplenial cortex, as well as subcortical areas including the hippocampus, striatum, thalamus, and midbrain.[76] Implanting multiple Neuropixel probes bilaterally allows for analyses of task-related sensory, choice, and action signals between areas in both hemispheres that are connected over the commissures,[77] or CH coordination of brain states during sleep[78] (Figure 2C). The high temporal resolution of spiking activity facilitates the identification of functionally connected or even mono-synaptically connected neuron pairs using cross-correlogram analysis.[79,80] Simultaneous recording of hundreds of neurons greatly increases the chance of finding functionally connected pairs, providing a convenient way to probe information transmitted across hemispheres.

Electrophysiology does not directly specify the type of recorded neurons, and neither does it provide a cellular spatial resolution. Optical imaging techniques, which provide subcellular

spatial resolution and compatibility with cell-type-specific targeting, therefore can be used to complement electrophysiological recordings (Figure 2C). Simultaneous monitoring of CH neurons in both hemispheres requires large field-of-view imaging. One photon imaging through an intact mouse skull can achieve cortex-wide imaging at video frame rate over multiple days.[81] However, due to light scattering through the cortical tissue and the intact skull, this approach typically does not have a single-cell resolution, except under the condition of very sparse labeling of a subset of superficial cortical neurons.[82] Light scattering is greatly reduced in two-photon microscopy because of the nonlinear concurrent absorption of infrared photons, which can achieve high-definition and high-resolution recording of deep-layer cortical neurons.[83] Traditionally, this method has a limited field of view due to multiple factors, such as the relatively slow speed of scanning and the tradeoff between a high-resolution objective and a large field of view.[84] Recent optical engineering has enabled subcellular resolution imaging of a large field of view (LFOV) of ~20–25 mm^2, which is large enough to encompass (CH) cortical areas at a distance of up to 5–7 mm (Figure 2C).[84–86] Together with genetic labeling of CH neurons with activity sensors[87] and single-cell-resolution perturbation, large-scale imaging allows the investigation of CH communication with unprecedented precision.

Quantitative behavioral tasks for investigation of CH communication

Investigating CH communication requires behavioral studies in well-controlled environments. Body restraint paradigms in non-human primates and rodents enable precise stimulus control, behavioral monitoring, neural recording, and perturbation. We here review two example tasks with precise behavioral control in order to probe CH communications. Brincat et al. modified a delayed non-match-to-sample task to study the neural mechanism underlying the interhemispheric transfer of WM.[58] Monkeys were trained to remember the position and identity of a visual stimulus that only briefly appeared in the left or right hemifield (Figure 2D). Maintenance of WM shows functional lateralization, with spike rates and oscillatory power in the contralateral PFC enhanced compared with the ipsilateral PFC.[58] Visual WM storage largely reflects objects in the contralateral hemifields. Thus, when saccadic eye movements shift the remembered object's retinotopic location to the opposite hemifield, CH communication is necessary to form a seamless representation of object location. Following saccadic eye movements, neurons in the two hemispheres switched their firing patterns, indicating interhemispheric transfer of the WM trace.[58] Around the time of WM transfer, there was an increase in synchronous oscillations between the left and right PFC. These findings illustrate that CH communication stitches WM traces together to enable seamless mental perception of the external world.

Rodents are an increasingly prominent model for the analyses of mammalian neural circuits. In a memory-guided decision-making task, mice chose one of two waterspouts based on the strength of whisker stimulation to obtain rewards.[66] Notably, mice were trained to withhold licking during the delay epoch, creating a "clean" period to study the choice signal that links sensation and action. In one experiment, choice-related selectivity in the premotor cortex (the anterior lateral motor cortex [ALM]) was disrupted by a brief optogenetic inhibition.[88] Interestingly, after inhibition offset, ALM neurons accelerated their ramping so that the activity recovered to the same level as in the unperturbed condition. This phenomenon depended on the CH inputs from the contralateral ALM, as simultaneous inhibition of the contralateral ALM or physically severing the corpus callosum blocked the recovery of choice activity, highlighting the importance of CH communication to maintain robust activity that is resistant to transient perturbation.[88] The memory-guided task can also be varied to probe asymmetric CH communication (e.g., by changing the side of whiskers to stimulate or by switching the association contingency between tactile strength and licking direction).[68,89] In these tasks, unilateral inhibition produces different patterns of behavioral deficits, with perturbation of one side of the ALM causing a strong ipsilateral bias in respect of upcoming licking direction (i.e., the dominant side) and perturbation on the other side of the ALM having little effect (i.e., non-dominant).[68] This pattern of behavioral deficits is consistent within individual tasks and animals but is different across tasks. Interestingly, the pattern of behavioral effects depends on the asymmetric CH communication between the dominant and non-dominant hemispheres (see CH communication and functional lateralization—toward a dynamic view).[68,89]

THE ROLE OF CH COMMUNICATION FOR THE COORDINATION OF EXCITATION AND INHIBITION

On the most basic level, a white matter fiber that crosses between the two hemispheres can have either an excitatory or an inhibitory effect on neuronal circuits in the contralateral hemisphere. A traditional idea about the main reason for CH communication is that commissures transfer neural information to the other hemisphere by exciting neurons there to allow for a unitary sensory perception of the world. In general, the idea that callosal neurons serve an excitatory function on post-synaptic targets is supported by the fact that most neurons that are part of the corpus callosum either use glutamate or aspartate as neurotransmitters, both of which are excitatory neurotransmitters.[90] A recent meta-analysis using simple visual integration paradigms compared interhemispheric integration of neural information in patients that underwent complete commissurotomy, complete callosotomy, or partial callosotomy.[33] CH visuo-motor integration took significantly longer in patients that underwent complete callosotomy (43.5 ms) or full commissurotomy (60.6 ms) compared with patients that underwent partial callosotomy (8.8 ms) or healthy controls (2.86 ms). These findings strongly suggest that the corpus callosum is essential for transferring visual information to the hemisphere that controls the motor response, suggesting excitation of the visual areas in the targeted hemisphere.

An influential model on how excitatory information transfer over the corpus callosum may affect hemispheric asymmetries was proposed by Ringo et al.[91] This model focused on the potential negative impact of interhemispheric conduction delay during time-critical tasks. It assumed that larger brains have a bigger corpus callosum, which leads to a longer conduction delay when sensory information is transferred between the

hemispheres to make an adequate motor response. Because longer conduction delays may lead to slower responses in life-threatening situations, species with bigger brains should have a stronger evolutionary pressure to develop functional hemispheric asymmetries to be able to make quick decisions in one hemisphere and escape dangerous situations, such as facing a predator, on time. A diffusion tensor imaging (DTI) study in 138 small and large human brains found a relation between brain size and structural connectivity, largely in line with the Ringo model.[92] Overall, larger human brains showed stronger intrahemispheric connectivity, but only a small increase in interhemispheric connectivity. However, a recent cross-species meta-regression study, which used brain mass and neuron number data as predictors for limb preferences, found that the empirical evidence only partly supports the Ringo model.[93] The model predicts that larger-brained species show an increase in laterality and a decrease in ambilaterality. The study, however, found no effect of brain size on ambilaterality. Moreover, larger-brained species showed more rightward but less leftward functional lateralization. This suggests that further factors, such as the direction of laterality, need to be considered and that the Ringo model alone cannot explain the emergence of functional lateralization.

Although only a few callosal neurons use GABA as their neurotransmitter and thus are inhibitory,[94] many of the excitatory CH neurons have inhibitory interneurons as their post-synaptic targets in the contralateral hemisphere.[18,95] In contrast to the Ringo model, it has therefore also been suggested that the effect of CH communication on functional hemispheric asymmetries may be primarily inhibitory, e.g., that the dominant hemisphere caused functional lateralization by inhibiting neural activity in the non-dominant hemisphere.[96] In the motor domain,[97] TMS studies in humans and animal experiments suggest that CH communications inhibit pyramidal neurons in the contralateral hemisphere.[98] Typically, if a movement is generated in one limb, CH communication is used to inhibit motor neurons in the same limb on the contralateral side.

Taken together, empirical evidence suggests that CH projections can have both excitatory and inhibitory effects on contralateral brain networks.[99] Research in animal models based on experiments involving simultaneous perturbation and electrophysiological recordings further provide new evidence. First, unilateral cortical inhibition typically has little effect on the mean activity of the contralateral circuits.[55,88,100] In the delayed response task (Figure 2D), optogenetic inhibition of the mouse premotor cortex ALM only slightly affects contralateral membrane potentials and firing rates, in sharp contrast to the inhibition of the reciprocally connected motor thalamus.[88,101] In a visual novelty discrimination task, chemogenetic inhibition of CH neurons in the visual cortex did not affect the mean contralateral firing rate of neurons.[55] Mirroring findings in mammalian brains, pharmacological inhibition of the avian arcopallium, a visuo-motor area, also affected contralateral mean activity only to a small extent.[100] Little effect on mean activity does not mean that firing rates of individual neurons are not affected. Careful examination indicates that optogenetic inhibition both up-regulated and down-regulated a large fraction of neurons, which leads to little net effect on mean activity.[68] Thus, CH communication coordinates both excitation and inhibition to regulate contralateral activity during sensory perception and motor behaviors.

Second, CH projections modulate contralateral neural activity along behaviorally relevant directions in the activity space. Neurons in the premotor cortex ALM show trial-type-selective activity that emerges during the sample epoch, ramps up during the delay epoch, and reaches the peak during the early-response epoch.[66] Population activity during the delay epoch can be decomposed into choice-selective and non-selective ramping activity modes.[88] Optogenetic inhibition of ALM removes almost all activity and thus the selective and non-selective modes. Although this perturbation does not affect average contralateral activity much, it specifically affects selectivity along the choice-selective mode while leaving the non-selective ramping mode intact.[88] Interestingly, this effect is task dependent. In the different versions of the delayed response task, unilateral inhibition of ALM produces variable behavioral deficits across tasks and animals, ranging from near complete biasing to almost no effect.[68] The variability is predicted by how strongly the inhibition affects the contralateral choice-selective mode. The effect of unilateral inhibition on contralateral activity is also state-dependent.[89] The modulation is largest when there is asymmetric CH communication, with the dominant side providing strong functional drive to the contralateral hemisphere. The modulation is minimal if the other hemisphere can insulate its activity from perturbation.[89] Thus, CH communications coordinate excitation and inhibition in a task- and state-dependent manner to modulate contralateral activity preferentially along behaviorally relevant dimensions.

CH COMMUNICATION AND FUNCTIONAL LATERALIZATION: THE TRADITIONAL VIEW

The question of how functional lateralization is determined ontogenetically and physiologically and how it is shaped by CH communication has fascinated neuroscientists for decades. In general, how individual left- or right-hemispheric preferences for a given functional domain are established is far from being well understood. Different experimental approaches have been used to answer this core question of laterality research. Researchers typically link structural (e.g., related to gray or white matter volume) and genetic factors to a leftward or rightward behavioral preference. Indeed, human left-handers show alterations of thickness asymmetries in the postcentral gyrus relevant for motor functions and the inferior occipital cortex relevant for visual perception.[102] In rats, asymmetries of dopamine levels in the nucleus accumbens differ between left-pawed and right-pawed animals.[103] However, we here argue that these effect sizes are rather subtle (Cohen's d of less than 0.1 for the human handedness effect), suggesting that other factors, such as dynamic developmental process as well as plasticity in adults, play additional roles.

For human handedness, arguably the most widely investigated form of functional lateralization in vertebrates, evidence suggests that it is a complex phenotype determined by multiple genetic[104] and non-genetic factors.[105] The largest published genome-wide association study on human handedness identified 41 genetic loci associated with left-handedness as well as

7 genetic loci specifically associated with ambidexterity.[106] The identified loci were largely associated with the development of the central nervous system, the most prominent pathways being brain morphology and the regulation of microtubules. Importantly, additive genetic effects only explained an estimated 11.9% of the variance in handedness data in this study. The authors estimated that the remaining variance was explained by non-genetic effects (shared environmental effects: 4.6%; individual environmental effects: 83.6%). These findings suggest strong effects of environmental factors on handedness, but studies that experimentally assess environmental factors and associate them with handedness hardly find any effects. For example, a study assessing the impact of early life factors on handedness in the UK Biobank reported that handedness was significantly affected by birthweight, being part of a multiple birth, season of birth, breastfeeding, and sex, but that all of these factors only had minimal predictive values for handedness.[105] Moreover, a recent epigenome-wide association study linking whole-blood DNA methylation to handedness did not identify any differentially methylated sites between left- and right-handers.[107] As DNA methylation is one of the major processes in how environmental factors modulate gene expression in humans, these findings further suggest that environmental factors likely do not explain a substantial amount of variance in human handedness. Thus, the vast amount of variance in human handedness data presently cannot be explained by ontogenetic factors, leading to the recent suggestion that random processes during brain development may play a large role in how individual leftward or rightward preferences are determined.[108] How exactly developmental randomness affects handedness is not well understood. It has been suggested that an interaction between subtle genetic side bias in early development (e.g., a gene expression gradient that is lateralized to one hemisphere) and later developmental steps that reinforce the initial cue, result in a bimodal trait in adults.[105]

In rodent research, genetic knockout has been performed to identify genes relevant for functional motor lateralization.[109] The study focused on the transcription factor Lim domain only 4 (LMO4), which shows substantial expression asymmetries in the brains of both human fetuses and wild-type mice. In control mice, more than 80% of mice showed no clear functional motor lateralization. In contrast, unilateral knockout of LMO4 in the right hemisphere of the developing mouse brain led to an increase in rightward functional motor lateralization, with more than 50% of animals in this group showing right-pawedness. This suggests that altering LMO4 expression indeed affects functional motor lateralization but does not fully determine it.

Taken together, ontogenetic studies suggest that invariable genetic predispositions or structural brain asymmetries typically account for small amount of variance in individual preferences (see conclusion and outlook). This posits a pivotal role of dynamic developmental processes affecting asymmetries in brain structure and function. For example, research in birds has shown that the sensory environment during critical periods in early development is highly important for functional and structural lateralization.[110] Specifically, exposure to light during incubation alters both structural and functional asymmetries in birds, with dark incubation leading to a reduction of functional and structural asymmetries.[111] Light incubation affects the expression of immediate early genes[112] and embryonic retinal gene expression.[113] Importantly, a recent study in chicken also found evidence that gene-environment interplay affects interhemispheric communication.[114] In this study, embryonic light stimulation affected interhemispheric transfer and enhanced communication from the right to the left hemisphere.

These findings highlight the importance of developing a more dynamic view of how behavioral asymmetries emerge. In the following, we present a dynamic model of CH communication in complex interacting neuronal networks and how asymmetric CH communication induces functional lateralization in a sensorimotor system.

CH COMMUNICATION AND FUNCTIONAL LATERALIZATION—TOWARD A DYNAMIC VIEW

Existing excitatory or inhibitory models do not reflect the full complexity suggested by recent empirical studies. How exactly is the activation of seemingly symmetric brain networks influenced by CH communication to produce lateralized brain functions? Several behavioral paradigms have been developed to assess how different patterns of functional lateralization depend on the direction of CH communication.[68,89] In these behavioral tasks, animals learn to associate a tactile stimulus with directional licking to obtain a reward. Experimental and simulation results suggest that learning-induced plasticity during the processing of sensory stimuli, sensory-motor associations, and repeated motor actions can break the symmetry of CH communication to induce functional lateralization (Figure 3).

The primary sensory neocortical areas preferentially process information from the contralateral space.[19,20] As attention seems to only be directed to one principal item at a time,[115] the tendency to direct attention to the contralateral hemisphere enhances the detection of stimulus features required for behavior.[116] Enhanced sensory detection coupled with action-induced reward will further strengthen the sensory-motor transformation in the contralteral hemisphere, probably at a higher learning rate due to a stronger phasic activity of midbrain dopamine neurons that is induced by the more salient stimulus.[117] Recent findings obtained with a tactile-based decision-making task supports this view.[68,89] Stimulation of whiskers induced faster and stronger activation of sensory-selective neurons in the contralateral ALM, inhibition of which strongly affected decision-related activity in the other hemisphere. Decision activity in the contralateral ALM was more robust and resisted perturbation by the non-dominant ALM. Chen et al. further used recurrent neural networks (RNNs) to explore network conditions that support this robustness.[89] RNNs consistent with experimental findings revealed an asymmetry in CH communication, with information flowing from the dominant side to the non-dominant side. Thus, when a more salient sensory stimulus is repeatedly relayed to one hemisphere to induce a motor action, experience-dependent plasticity breaks symmetric CH communication to produce functional lateralization. How fast can this experience-dependent plasticity induce asymmetric CH communication? As mice were typically trained for over a month to learn the task, this process likely takes a few weeks in order for the long-term synaptic plasticity processes to consolidate.[118]

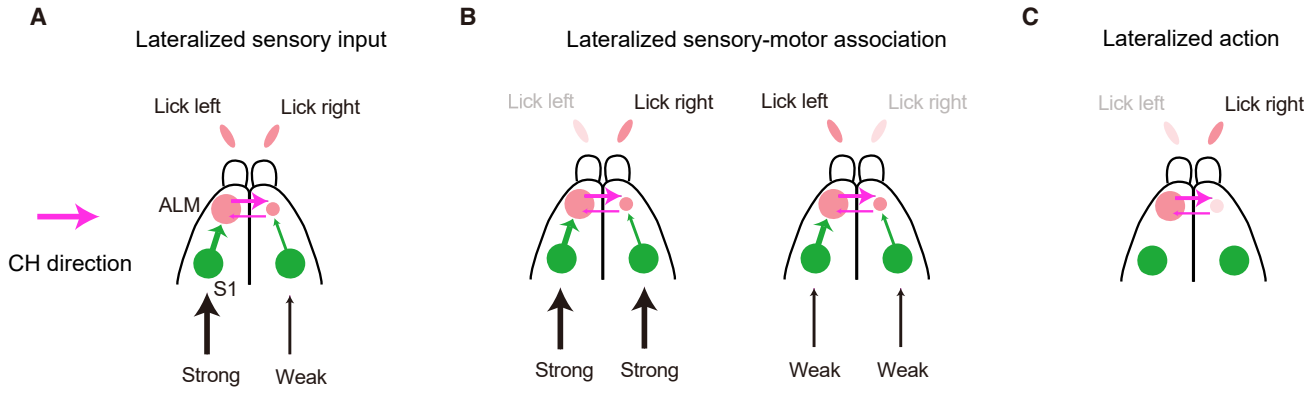

Figure 3. Scenarios to produce asymmetric CH communication in sensory and motor processing
(A) Asymmetric sensory inputs with the strong (weak) stimulus paired with the right (left) water spout licking.
(B) Symmetric sensory inputs with the strong (weak) stimulus paired with the right (left) water spout licking.
(C) Repeated licking of the right water spout.

Asymmetric sensory input is not the only factor to induce functional lateralization. Stimulation can be applied to both sides of whiskers at the same strength in the task and the left or right ALM still exhibits dominance.[68] The dominant ALM is always contralateral to the licking direction that is associated with the more salient stimulus, indicating that it is not the stimulus nor the licking direction (as sensory input and licking directions are symmetric) but the association of stimulus and licking direction that determines which side is dominant. As the strong stimulus can be easily detected while the less salient stimulus evokes activity with higher noise, an optimal strategy for mice is to preferentially reinforce the strong stimulus-induced action while choosing the alternative action when the stimulus is weak or undetected. As the strong stimulus-induced action is highly dependent on the contralateral premotor cortex, the strengthening of sensory-motor association circuits will make the contralateral ALM dominant. Movement and preparation-related activity are widespread across the dorsal cortex,[81] and broadcasting of this activity depends on the premotor cortex.[119] The other side of the ALM, which mostly follows task-related signals through CH communication, will gradually become non-dominant with training. Indeed, inhibition of the dominant ALM strongly affects decision activity in the other ALM, but not vice versa.[68,89] In summary, asymmetry in sensory input and sensory-motor association can induce asymmetric CH communication and functional lateralization.

Repeated practice of movements of a particular body part can render the corresponding somatosensory and motor cortices dominant by inducing reorganization of the underlying cortical circuits.[120] For example, studies in owl monkeys have shown that repeated touching of a rotating disk with the tips of the distal phalanges causes an expansion of the somatotopic sensory map for the used fingers.[121] In humans, repetition of rapid sequences of finger movements caused an extension of the activated motor cortex.[122] Interestingly, this expansion only occurs in the contralateral motor cortex. In the future, it will be important to verify whether CH communication shows asymmetric flow in these tasks.

Besides the sensory-motor domain, technical advances have begun to reveal the neural mechanisms that lead to hemispheric asymmetry during emotion processing. Empirical evidence suggests that for the processing of fear and avoidance, right-hemispheric brain areas play a major role within the complex interrelated networks that control these processes.[12,123] Causal manipulation in rodents indicate that the right anterior cingulate cortex (ACC) plays a dominant role in observational fear learning (a process to acquire fear by observing conspecifics being subjected to aversive stimuli).[124] ACC forms reciprocal connections with the basolateral amygdala (BLA), and neural oscillations at the theta range (5–7 Hz) are causally linked to observational fear learning.[125] Interestingly, optogenetic perturbation of the hippocampal theta rhythm bi-directionally modulates fear learning,[125] highlighting the dynamic nature of network interactions among the hippocampus, ACC and BLA.[126] The left and right ACC are reciprocally connected, and the left ACC is implicated to play a larger role in positive emotions.[21] Research on CH communication will shed light on how the right ACC becomes dominant during observational fear learning.

CONCLUSIONS AND OUTLOOK

Despite larger and larger sample sizes in genetic, epigenetic, and neuroimaging studies, individual variation in functional hemispheric asymmetries cannot be fully explained by ontogenetic factors and structural brain asymmetries. This supports the idea that dynamic CH communication between homotopic and heterotopic brain networks is crucial for lateralized brain functions. Although the link between CH communication and lateralized brain functions has been previously investigated in patient studies and neuroimaging and behavioral experiments in humans, the applied techniques typically had low resolution and did not allow for causal inference.

Recent studies in rodents and other model species using modern neuroscientific techniques support the idea that asymmetric CH communication plays an important role in the emergence of functional lateralization. However, the association seems to be more complex than previously proposed. Rather than CH being either excitatory or inhibitory in nature, CH communication coordinates excitation and inhibition to facilitate interhemispheric information transfer, maintenance, and updating of information in

a variety of sensory, memory, and motor behaviors. With this, CH communication does not have a major effect on the overall activity but rather drives activity along behaviorally relevant directions to support cognitive functions such as decision-making and WM. CH communication can be asymmetric and can be induced by many factors, including asymmetric sensory input, sensorymotor association, and motor actions. It is currently unknown how experience-dependent plasticity induces asymmetric CH communication. Donald Hebb's cell assembly theory hypothesized that "any two cells or systems of cells that are repeatedly active at the same time will tend to become 'associated' so that activity in one facilitates activity in the other."[127] In ALM, neurons with similar task-parameter preferences have a higher correlation in firing, and are indeed preferentially coupled, forming distinct cell groups.[69] The Hebb learning rule postulates how synaptic weights are modified by experience: if cell A repeatedly excites cell B or persistently takes part in firing together with cell B, the connection from cell A to B will be strengthened.[127] Symmetric CH communication could be broken if a unilateral sensory input frequently excites the contralateral frontal cortex a few milliseconds earlier than the ipsilateral cortex.[89] Directly testing this in behaving animals will be challenging as it requires long-term recording of large groups of neurons to monitor the relative timing of CH neurons and probing the connection strength between CH connected neurons. However, tools for the investigation of CH communication with high spatiotemporal resolution are constantly evolving with technological advances. Therefore, it is likely that it will be feasible to elucidate precisely how CH communication evolves to be asymmetric in the near future.

Besides technical challenges, there are also many unresolved questions regarding the role of CH communication in lateralized behaviors. For one, most research on the association between commissural structure and function and lateralized brain functions in humans and other placental mammals has focused on the corpus callosum, with only a few studies investigating the anterior commissure or any of the other commissures in the vertebrate brain. To get a complete picture, future studies on CH communication and lateralized behavior should integrate data on the structure and function of all commissures. Moreover, previous works have largely focused on homotopic connections between the hemispheres. The role of heterotopic CH communications for lateralized brain functions is largely unclear and needs further investigation.

Although we here emphasize the role of dynamic CH communication in functional lateralization, we want to caution readers that brain structure and genetic factors could play disproportional roles in functional consequences. It has been shown that in nervous system development, seemingly small differences in biological processes can have large functional consequences. For example, it has been shown that an increase of 5.8% in dopamine D2-receptor-binding capacity can account for a disproportionate increase of 50% in dopamine sensitivity.[128,129] Although similar associations have so far not been reported in the field of functional lateralization, this may be due to a lack of research targeted at such processes.

At the neurophysiological level, how does functional lateralization emerge? Answering this question would not only be highly relevant from a basic neuroscience perspective but also for several neighboring fields. For example, because so many fundamental cognitive systems in the human brain are organized asymmetrically,[130] psychological research does benefit from insights on hemispheric asymmetry. Moreover, several different neurodevelopmental conditions and psychiatric disorders are associated with an increase in atypical asymmetries,[131] making a better understanding of the emergence of hemispheric asymmetries highly relevant for psychiatry. Last, but not least, recent research shows that machine learning algorithms[132] and programming of artificial neural networks[133] benefit from asymmetric organization. Therefore, insights into how hemispheric asymmetries emerge may be relevant for various aspects of computer science, including research on artificial intelligence.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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