Progress in Neurobiology 208 (2022) 102186

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Review article

The functional characterization of callosal connections

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ARTICLE INFO

This paper is dedicated to our friend Giorgio M. Innocenti, who passed away unexpectedly on January 12, 2021. He ideated and generously shared this work with us. We regret he is not able to see the final picture of the intricate mosaic he had imagined and first shaped. This paper is also *in memoriam* of Tullio Manzoni for introducing some of us (GMI, RC, MF) to the study of the Corpus Callosum.

Keywords:
Corpus callosum
Callosal axon diameter
Callosal conduction velocity
Callosal interhemispheric transfer

ABSTRACT

The brain operates through the synaptic interaction of distant neurons within flexible, often heterogeneous, distributed systems. Histological studies have detailed the connections between distant neurons, but their functional characterization deserves further exploration. Studies performed on the corpus callosum in animals and humans are unique in that they capitalize on results obtained from several neuroscience disciplines. Such data inspire a new interpretation of the function of callosal connections and delineate a novel road map, thus paving the way toward a general theory of cortico-cortical connectivity. Here we suggest that callosal axons can drive their post-synaptic targets preferentially when coupled to other inputs endowing the cortical network with a high degree of conditionality. This might depend on several factors, such as their pattern of convergence-divergence, the excitatory and inhibitory operation mode, the range of conduction velocities, the variety of homotopic and heterotopic projections and, finally, the state-dependency of their firing. We propose that, in addition to direct stimulation of post-synaptic targets, callosal axons often play a conditional driving or modulatory role, which depends on task contingencies, as documented by several recent studies.

Abbreviations: A1, primary auditory cortex; AAF, anterior auditory field; BDA, biotinylated dextran amine; BOLD, blood oxygen level dependent; CC, corpus callosum; CPN, callosal projection neuron; DCM, dynamic causal modeling; DW-MRI, diffusion-weighted magnetic resonance imaging tractography; EEG, electro-encephalogram; EM, electron microscopy; EP, evoked potential; EPSP, excitatory post-synaptic potential; GI, primary gustatory area; ICoh, interhemispheric EEG coherence; LFPs, local field potentials; M1, primary motor cortex; RF, receptive field; SC, split-chiasm; SCC, split corpus callosum; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; TMS, transcranial magnetic stimulation; V1, (primary visual cortex, area 17); V2, (secondary visual cortex, area 18); VM, vertical meridian of the visual field.

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https://doi.org/10.1016/j.pneurobio.2021.102186
Received 6 June 2021; Received in revised form 5 November 2021; Accepted 11 November 2021
Available online 12 November 2021

1. Introduction

Brain states, hence states of mind, are implemented by interactions among neurons engaging connections of different types within distributed systems (Mountcastle, 1978). To date, the functions of long-distance cortical pathways remain poorly characterized but for a few exceptions such as the fibers of the corpus callosum (CC). The CC is of particular interest because it is an ancient mammalian structure that may have originated together with long ipsilateral cortico-cortical projections. It is the largest commissure of the brain in all placental mammals and emerged about 150 millions years ago (Aboitiz and Montiel, 2003; Suárez et al., 2018, 2014b). It includes millions of interhemispheric fibers which link extensive portions of the cerebral cortex reciprocally, including the occipital, parietal, temporal, and frontal lobes. Therefore, it is implicated in higher-order brain functions. It has also been repeatedly suggested that callosal connections implement the same operations across the hemispheres as intra-hemispheric connections, including intrinsic and long inter-areal connections (Hubel and Wiesel, 1967; Innocenti, 1986; Kennedy and Dehay, 1988; Schmidt, 2016).

Countless anatomical and functional data concerning the CC fibers are available, obtained in different cortical systems and through various complementary approaches. In the present review, we compile these studies and propose that they provide a roadmap for future work as well as a reference frame for a general theory of cortico-cortical connections.

Contrary to classical models that consider the callosum essentially involved in transferring information across the hemispheres in an obligatory fashion to allow the unity of the perceptual world, we propose that callosal connections can preferentially drive their post-synaptic targets when acting with other inputs, therefore in a flexible fashion. In addition to direct stimulation of their targets they can play a conditional driving or modulatory role, which depends on task contingencies, and which emerges clearly also from the study of the callosal connectivity of higher-order association areas, which occupy most of the cortical mantle.

2. Hints from anatomy

In this section we will briefly highlight the essential features of the CC anatomy, and how this constrains the physiology of interhemispheric communication.

2.1. Microscopic

In general, the morphology of axons in many fiber tracts of the brain is not known although some data exist in humans (Liewald et al., 2014). In the CC, electron (EM) and light microscopy studies in both monkey (Lamantia and Rakic, 1990) and human (Aboitiz et al., 1992) reported antero-posterior differences in the diameter of callosal axons, with thicker axons in the midbody and splenium, thinner in the genu and anterior body. These gradients were confirmed with tract tracing and with advanced diffusion weighted MRI tractography (DW-MRI) which both provide an estimate of axon diameters, although at different scales.

Tracers transported retrogradely from the site of axonal termination to the cell bodies have defined in detail the topographical origin of specific pathways. For several cortical areas (Jones and Wise, 1977), the size of the cell bodies at the origin of different pathways is related to axon diameter (Tomasi et al., 2012), and hence conduction velocities, but less precisely to activation threshold (Fromm and Evarts, 1981). The morphology of the callosal projection neurons (CPNs) was obtained by bulk filling the cell bodies. With a few exceptions (Innocenti and Fiore, 1976; Buhl and Singer, 1989; Peters et al., 1990; Fabri and Manzoni, 2004) CPNs are pyramidal cells, that use glutamate or aspartate as neurotransmitter (Conti and Manzoni, 1994), while only some GABAergic neurons with long axons have been reported (Buhl and Singer, 1989; Peters et al., 1990; Fabri and Manzoni, 2004; Rock et al., 2018).

The fluorescent retrograde tracers introduced by Kuypers and collaborators enabled the detection of neurons with bifurcating axons (Bentivoglio and Kuypers, 1982) for the first time. Interestingly, it turned out that in monkeys less than 1% CPNs bifurcate and project also to ipsilateral areas, as found in prefrontal (Schwartz and Goldman-Rakic, 1984), superior (Johnson et al., 1989) and inferior parietal (Andersen et al., 1985) cortex, as well as in M1 (Johnson et al., 1989) and V1 (Meissirel et al., 1991). However, in rodents, callosal neurons projecting also to ipsilateral areas are more common (Economo et al., 2016; MacDonald et al., 2018; Zhang et al., 2019), suggesting the existence of species-specific differences on this aspect of long-distance cortical connectivity. However, new analyses with more advanced techniques in monkeys might temper this conclusion.

The question of which neuron is targeted by a given projection can now be answered by retrograde or anterograde trans-synaptic labeling (Wall et al., 2010; Beier et al., 2016), eliminating one of the most important obstacles in connectional neuroanatomy and providing insights into the function of neural circuits. The morphology of single axonal arbors filled by anterograde transport of biocytin, or biotinylated dextran amine (BDA) revealed several important features. When mouse somatosensory thalamo-cortical axons and cat visual callosal axons were compared, the terminal arbors of the two axonal systems were found to respect similar geometrical principles (Tettoni et al., 1998). However, thalamo-cortical axons had longer terminal branches each carrying numerous synaptic boutons, while the proximal bouton-free sector of the axon predominated in callosal fibers. This suggested that the axonal arbor could be subdivided into two compartments with different function: a *conduction compartment* devoid of boutons and transporting action potential from the cell body, and a *transmission compartment*, carrying synaptic boutons and hence delivering neurotransmitter to targets (Fig. 1**).** Such a sharp separation may not be found in all axons; for example, the cortico-striatal ones show very long branches delivering *en passant* boutons which might perform both transmission and conduction functions (Innocenti et al., 2017).

2.2. Axonal computation

Based on their morphology it was suggested that CC axons perform the following computational operations (Innocenti, 1995; Innocenti et al., 2016):

i) Mapping. Across all neurons, the position of the cell body is mapped into the position of the synaptic boutons within its terminal arbor which can have multiple components. Concerning callosal axons, any given cortical area projects fibers both homotopically and heterotopically, thus influencing terminal territories larger than the zones from which they originate. This is reflected in the topographical organization of the CC, as shown in Figs. 2**A-B** and 3 . Other aspects of mapping, such as receptive field size and properties will be treated in other parts of the manuscript.

ii) Differential amplification. Cortical axons differ in the density of synaptic boutons, which they distribute to their targets. But also, individual axons do not distribute the same number and type of boutons to all their targets (Houzel et al., 1994; Innocenti et al., 1994; Rockland and Knutson, 2000; Rochefort et al., 2009; Mukherjee et al., 2020). In other words, an action potential traveling down the axon impacts certain

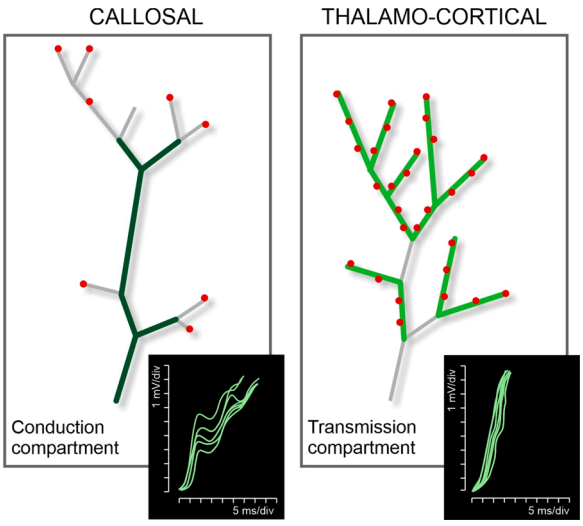

Fig. 1. Schematic summary of two sets of axons anterogradely filled with biocytin and reconstructed from serial sections. Maximal order of branching, branching angles, topological distribution of branches and boutons were similar for the two types of axons. However, thalamo-cortical axons had longer terminal branches carrying numerous synaptic boutons (the 'transmission compartment') while, in callosal axons, the proximal, bouton-free sector of the axon predominated (the 'conduction compartment'). Redrawn with modification from Tettoni et al., 1992. Insets show the steeper raising of EPSPs elicited by peripheral cutaneous stimuli than those elicited by callosal input from the contralateral S1 stimulation in the cat. The transcallosal input was also weaker and less secure than the peripheral input. Redrawn with modifications from Innocenti et al., 1972.

targets more strongly than others. The amplification of outputs positively relates also to the size of synaptic boutons. In many cortico-thalamic systems, some axons, usually originating in large layer V neurons, terminate with larger synaptic boutons than those originating in layer VI (Rouiller and Welker, 2000). The differences in the bouton size and other properties led to the classification of thalamo-cortical axons into "drivers and modulators", and in 'class 1' and 'class 2' for cortico-cortical axons (Sherman and Guillery, 2011). However, recent EM (Bickford, 2015; Rodriguez-Moreno et al., 2020) and functional studies of thalamic circuits (Mukherjee et al., 2020), as well as the study of terminal axonal arbors of cortical cells (Holler et al., 2021) rather indicate a multiplicity and heterogeneity of connectivity profiles and neurotransmitter release modes, a richness believed to expand the computation flexibility of synaptic circuits. In addition to the number of axons connecting two neural sites, the topological distribution of synaptic boutons, their size and packing density must be considered when interpreting the strength of axonal connections. Axons with dispersed cortical arbors but carrying small boutons, as it is the case for callosal ones, cannot expect to robustly activate their targets unless the summation of inputs of several converging fibers occurs, as predicted by the synfire chain hypothesis (Abeles, 1982), among others. Furthermore, the area of postsynaptic density and the spine volume (Arellano et al., 2007; Bopp et al., 2017) play a crucial role in determining the strength of synapses. Unfortunately, this information is not yet fully available for callosal recipient cells.

iii) Temporal transformations. In all projections studied so far, axons of CPNs display a broad range of diameters. As a rule, small, myelinated axons in the range of 0.5–1.5 μm predominate but a few, thicker axons are added to some pathways and also characterize species differences (Olivares et al., 2001; Aboitiz and Montiel, 2003; Caminiti et al., 2009, 2013; Tomasi et al., 2012; Innocenti et al., 2014). Axon diameter is directly proportional to conduction velocity (Hursh, 1939), therefore different pathways conduct at different speeds and, within the same pathway, temporal information is dispersed in time. In the CC of monkey, the thinnest axons (0.7 μm on average) originate in prefrontal areas 9 and 46, the thickest axons (mean 1.0 μm) from areas 4 (M1) and 2 (S1) but also from visual areas 17 (V1) and 18 (V2) **(**Fig. 2A). Also, in the human CC the thinnest axons (mean 1.0 μm) originate from prefrontal cortex and the thickest ones (mean 1.4 μm) from motor and visual cortex **(**Fig. 2B**).** Across species (macaque, chimpanzee and human) and areas, this provided a temporal hierarchy with mean conduction velocities between 4.9 and 11.4 m/s (Caminiti et al., 2009, 2013; Tomasi et al., 2012). Considering conduction distances, in the monkey shortest delays were predicted in the order of 4−5 ms between premotor, motor and somatosensory areas, the longest delays (10−12 ms) between the temporal areas (Tomasi et al., 2012). Since axon diameters remain constant from chimpanzees to humans, in spite of increasing brain volume, conduction of information between the hemispheres becomes slower and more dispersed in time (Ringo et al., 1994; Caminiti et al., 2009, 2013) (Fig. 2C). As expected, the longer axonal trajectories in larger brains amplified the consequences of the increased range of axon diameters and conduction velocities, and this multiplied the conduction delays between macaque and humans 3-fold **(**Fig. 2C**).** Based on these results, a network model (Caminiti et al., 2009) has shown how the interplay of excitatory and inhibitory delays between the hemispheres might modulate the cycle of cortical oscillators and might expand the number of assemblies that cortical connectivity can generate, by contrasting synchronous vs asynchronous neural pools.

Concerning conduction delays, some axonal arbors with long tangential trajectories behave as delay lines, activating targets at different times. A textbook example is the parallel fibers in the cerebellum, but this seems to apply to cortico-striatal axons as well (Innocenti et al., 2017). Other axons will, by their geometry, simultaneously activate spatially separate targets even when the geometry seems to violate Cajal' s principle of conservation of the "protoplasme nerveux transmetteur" (Ramón y Cajal, 1909; Innocenti et al., 1994). Today, DW-MRI tractography can estimate cortico-cortical connectivity non-invasively in animals and humans, albeit with coarser resolution than microscopy (De Benedictis et al., 2016; Maier-Hein et al., 2017; Schilling et al., 2019). Local water diffusion tensors are connected to each other with various algorithms generating "streamlines". How streamlines correspond to axons is unknown and the relationship between the two is not very tight (Aydogan and Shi, 2018). However, the connections traced by DW-MRI and axonal transport methods match in about 60 %–80 % of cases (Seehaus et al., 2013; Girard et al., 2020; Caminiti et al., 2021), with a good correlation between connectivity weights and the number of labelled cells obtained through tracing experiments (Caminiti et al., 2021; Donahue et al., 2016). Estimates in the conduction compartment of axons can be obtained with DW-MRI albeit for diameters above 2–2.5 μm (Fig. 3; Assaf et al., 2008; Barazany et al., 2009; Nilsson et al., 2017; Barakovic, 2021; Veraart et al., 2020). Future work might improve the resolution of the estimates, which is essential for the study of the temporal dynamics of distributed systems.

iv) Convergence and divergence of axons. Information processing in the cortex depends on axonal convergence, whereby neurons acquire progressively more complex properties along a processing stream. Nevertheless, axonal convergence is somewhat undocumented at the single axon level. Rather the opposite has been stressed, i.e., the divergence of axonal terminations in separate territories. Data obtained from callosal axons in the cat at the border between areas 17/18, where most callosal fiber originate and terminate in visual cortex, show that segregation and convergence can coexist (Fig. 4; Innocenti et al., 1994). Axonal divergence is puzzling although well documented (Bressoud and Innocenti, 1999; Cheng et al., 1997; Ding et al., 2000; Zhong and Rockland, 2003; Rockland, 2020). Why should a neuron send presumably the same message to widely separate targets? The answer might be found in cortico-cortical connectivity, whereby a long oligosynaptic cortical axon might not be able to drive the postsynaptic target in isolation, but rather must cooperate with other inputs. In some bifurcations, the ratio of diameters in the parent and daughter branches might cause action

potentials to skip one or the other branch thus acting as a filter (Segev and Schneidman, 1999). In other words, an axon might drive and/or modulate very different responses at widely separate brain sites in a conditional way, i.e., depending both on the nature of the inputs it co-operates with and on task contingencies. In the coming years, the intricate spatial configuration and the striking morphological diversity of individual axons within the same distributed system (see Rockland, 2020) will confront us with an unprecedented level of complexity. Therefore, functional interpretations will remain a major challenge for future studies on callosal connectivity.

In synthesis, the predominant glutamatergic, therefore excitatory nature of callosal axons, the mapping, and computations they seem to perform, their pattern of converge and divergence, make them well suited to drive assemblies of post-synaptic cells. At the same time, the variety of callosal diameters, hence of conduction velocities and delays, are a potential substrate that enables both homotopic and heterotopic connections to exert a conditional driving or modulatory role.

3. Lesions and inactivations

In this section we will illustrate and contrast the results obtained in the study of the role of callosal connections from different methodological approaches, namely neuropsychological studies on split-brain patients, electrophysiology and imaging, and reversible inactivation in animals and humans. This will help evaluating the contribution of each of the above methods and the apparent conflicting results they have sometimes generated.

3.1. Neuropsychological studies

The notion that certain connections between brain sites are fundamentally important for specific brain functions became popular in the 19th century due to the influential work of Meynert, Wernicke, Lichtheim, Dejerine and others, and was based on the analysis of the consequences of brain lesions, in particular aphasia (see Catani, 2010; Battaglia-Mayer and Caminiti, 2019). The paralysis resulting from lesions of corticospinal tract in man has been known for a long time, although the tract consists of projections of different origins (Lemon and Griffiths, 2005; Innocenti et al., 2019; Strick et al., 2021) whose functions remain debated (Krakauer and Carmichael, 2017). Symptoms caused by lesions of other tracts became known before they could be ascribed to individual systems of connections within the tracts, and they could not be dissociated from the consequences of lesioning the adjacent gray matter. The situation was not very different when Geschwind

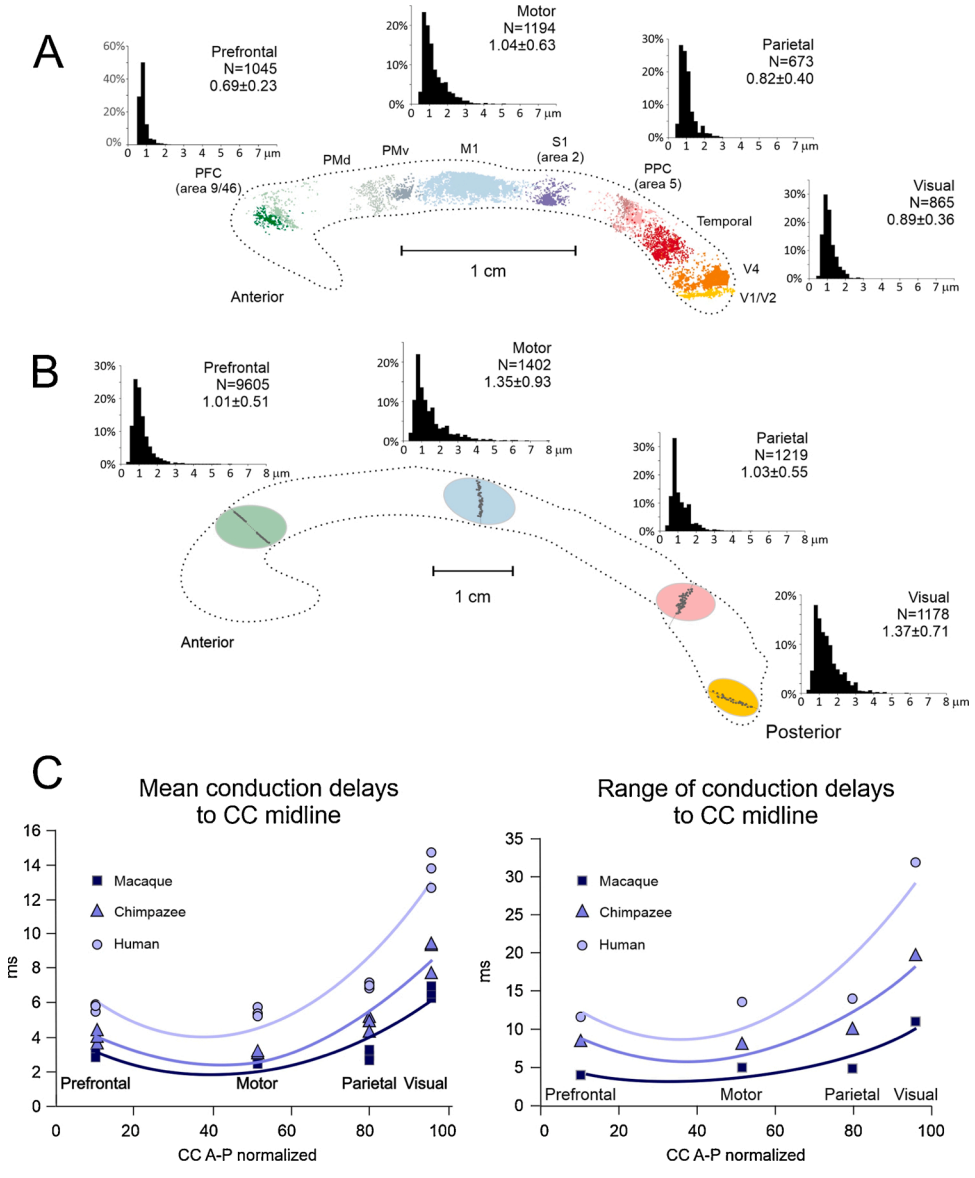

Fig. 2. A. Topographic organization of the CC of the macaque monkey after injections of anterograde BDA in different cortical areas, obtained by superposition of the outlines of the clusters of axon labeling from six different animals. Color gradients indicate axon labeling from prefrontal (9, 46), premotor (dorsal, PMd F2/F7; ventral, PMv, F4), motor (M1), somatosensory (S1, area 2), posterior parietal (area 5, PEc, PEip), temporal, extrastriate (V4), primary visual (V1/V2) cortex. The histograms indicate the distribution of axon diameters (n. of counts, mean ± SD) in selected prefrontal, motor, parietal, and visual sectors of the CC. Redrawn from Caminiti et al., 2009 and 2013. **B.** Distribution of axon diameters sampled from discrete dorsoventrally oriented probes in different anteroposterior sectors of the CC, in humans, where fibers from prefrontal, motor, posterior parietal, and visual cortex cross the midline. Convention and symbols as in A. **C.** Mean conduction delays (left panel) and range of conduction delays (right panel) to the CC midline in monkeys, chimpanzees, and humans plotted against normalized antero-posterior CC dimension and fitted with a polynomial function. Adapted from Caminiti et al., 2009.

published his influential "Disconnexion syndromes in animals and man", focusing on the role of association areas and on the little connectional anatomy known at that time (Geschwind, 1965a, 1965b). Nevertheless, from the literature, he reported symptoms caused by the interruption of callosal connections in two patients with left visual field alexia, and one patient he examined with tactile anomia i.e., impairment of naming objects presented to the left hand. There had been attempts to test the function of specific axonal tracts (namely the CC) that, however, initially led to negative findings (Dandy, 1936; Akelaitis, 1941; see also Glickstein and Berlucchi, 2008a). Although the role of the CC in transferring information between the hemispheres had been already anticipated by Bykov and Speranskii (1924) (see also Glickstein and Berlucchi, 2008b), the concept became well established only after the work of Sperry and collaborators (reviewed in Sperry, 1982; Gazzaniga, 2005; Glickstein and Berlucchi, 2008a; Berlucchi, 2012, 2014).

There is now a vast literature describing the multiple functions of the CC, ranging from interhemispheric transfer of sensory and motor information to the shaping of the lateralization of cognitive functions in a large series of studies in animal and human models of split-brain and callosal agenesis (Lassonde and Jeeves, 1994; Lepore et al., 1986; see also Roland et al., 2017).

The picture obtained from split-brain studies is however incomplete since the CC consists of different pathways originating in different areas and each terminating at both homotopic and heterotopic locations in the other hemisphere. More detailed information comes from studies on partial callosotomy (reviewed in Gates et al., 1993; Berlucchi, 2012, 2014), as also discussed in another section of this manuscript.

3.2. Electrophysiological and imaging studies

The dramatic results of human split-brain studies inspired decades of electrophysiological work in both animals and humans to identify the functions of callosal connections of different areas by blockade or section of the CC or by inactivating the contralateral cortex.

In the somatosensory cortex of the cat (SI and SII), the cathodal blockade of CC transmission or CC section decreased the responses to ipsilateral stimulation in neurons with bilateral receptive fields, by eliminating the earliest and largest components of the response (Innocenti et al., 1973; Robinson, 1973). The residual ipsilateral response

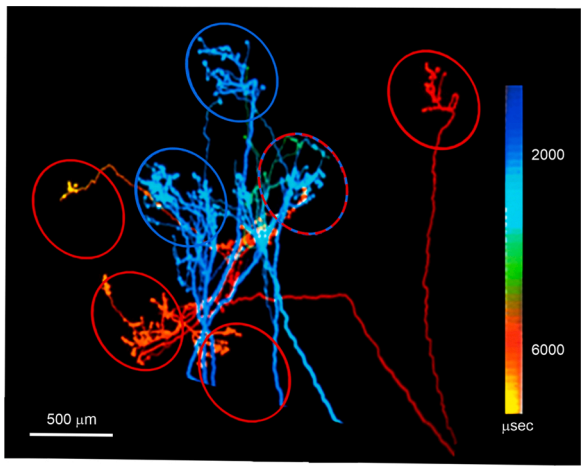

Fig. 4. Spatial and temporal divergence/convergence of callosal axons from cat area 17/18 border terminating onto the homotopic site, color coded according to the simulated delay (ms) from the CC midline. Notice that most axons terminate in separate territories (ovals), probably corresponding to orientation columns, and at different delays. The termination of two axons overlap spatially (inside blue-red contour) while being still temporally segregated. Adapted from Innocenti et al., 1994.

apparently originated in the posterior thalamic nuclei and was eliminated by damaging them (Robinson, 1973). A decrease in the proportion of ipsilateral receptive fields and in the interaction between stimuli applied bilaterally was also reported in SII of CC split-brain cats (Petit et al., 1990; Picard et al., 1990). Lesion of the contralateral cortex decreased the spontaneous activity by 80 % and the responses to whisker stimulation by 50 % in the barrel field of rats (Rema and Ebner, 2003). Although the influence of anesthesia might explain the different results across studies (Picard et al., 1990), the above data set suggests that callosal fibers exert a facilitatory influence on their target neurons. This is confirmed by the loss of ipsilateral responses to tactile hand stimulation in the somatosensory areas of CC transected humans reported with fMRI (Fabri et al., 1999), although bilateral responses remained to noxious stimuli (Fabri et al., 2002). Bilateral responses, independent of

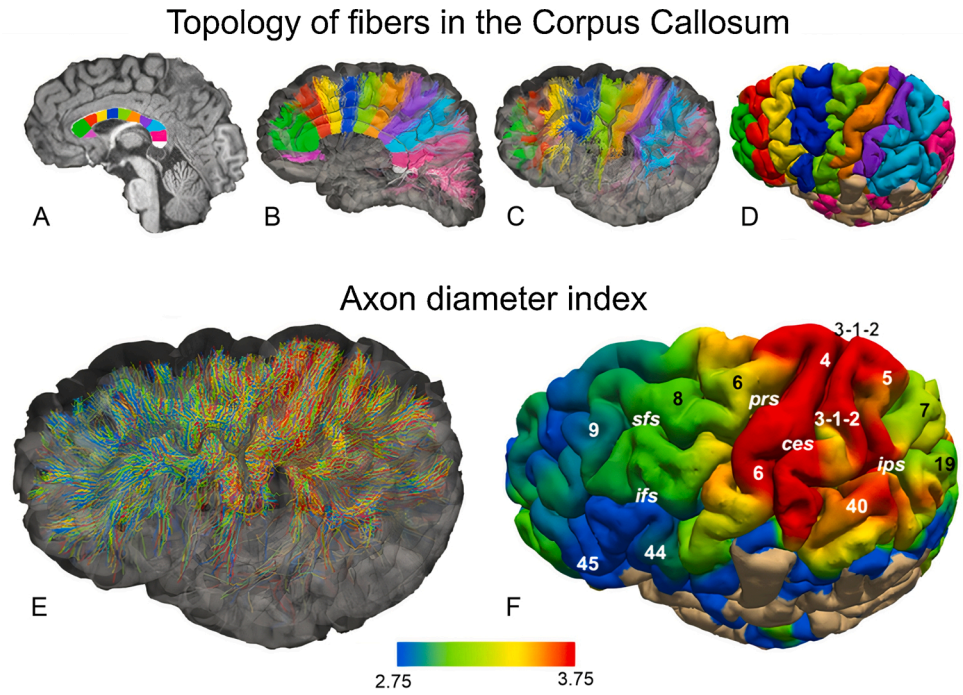

Fig. 3. A-D, Topology of fibers in the Corpus Callosum (CC) reconstructed by DW-MRI. **A.** Subdivision of the mid-sagittal section of the CC in 11 sectors (corresponding to ROIs). **B,C.** Streamlines colored according to ROIs projected on medial and lateral views of the hemisphere. **D.** Projection of the streamlines onto the pial surface. **E,F.** Axon diameter indexes of streamlines passing through the CC (**E**), colored according to their axon diameter index, and (**F**) projected onto the cortical surface. Colors correspond to the axon diameter index averaged across streamlines. Notice larger diameter indexes in the precentral and postcentral gyri, corresponding to motor (a 4) and somatosensory areas (3-1-2), the smaller indexes elsewhere as expected from histological work (Aboitiz et al., 1992) although skewed to larger estimates. Abbreviations: *ces*, central sulcus; *ifs*, inferior frontal sulcus; *ips*, intraparietal sulcus; *prs*, precentral sulcus; *sfs*, superior frontal sulcus. Numbers correspond to Brodmann areas. Adapted from Barakovic, 2021.

the CC, were recorded with fMRI after tactile stimulation of the body midline (Fig. 5; Fabri et al., 2006). An inhibitory role of the CC has been found, for example in flying fox and monkey, where cooling the contralateral areas increased receptive field size in somatosensory area 3b, suggesting the loss of an inhibitory callosal input; the effects disappeared with time (Clarey et al., 1996). Trans-callosal inhibition of the early component of the evoked potential (EP) to median nerve stimulation was also reported in the human somatosensory cortex (Ragert et al., 2011).

The visual areas of different species have been the most common experimental model of callosal functions. Studies were performed on cats, ferrets, rabbits, rats, mice, monkeys, and humans.

Of special interest is the role of callosal connections in generating binocular responses in early visual cortex, an issue which remained controversial for a long time. Whereas binocularity in lateral-eyed mammals, such as rodents, clearly depends on the integrity of the CC (Pietrasanta et al., 2012; Andelin et al., 2020; Laing et al., 2015), there is evidence that global binocularity in the cat does not (e.g. Minciacchi and Antonini, 1984; Gardner and Cynader, 1987; Conde-Ocazionez et al., 2018a,b). However, other studies showed the contrary (e.g. Payne et al., 1980, 1984), and the contribution of the CC to binocularity has been accepted for suprasylvian visual areas in Siamese cats which lack binocular neurons in V1 and V2 (Marzi et al., 1980, 1982). Taking advantage of the fact that stereovision and binocularity of neurons are tightly linked properties (for a review see Poggio and Poggio, 1984), the question was solved in the nineties (Ptito et al., 1991; Lepore et al., 1992) by investigating stereopsis behaviorally and electrophysiologically in adult cats trained on a Julesz's stereogram task before and after section of either the optic chiasm or the CC or both. Whereas normal ("intact") animals were able to perform the crossed disparity task, split-chiasm (SC) animals were largely perturbed but could nonetheless resolve the stereograms; cats with split callosum (SCC) were still able to carry on the task and at a significantly better pace than the SC group. Furthermore, in SC cats, the number of disparity sensitive cells was reduced but not abolished. Thus, both the retino-geniculo-cortical pathways and the CC contribute to generate stereopsis in normal adult cats, although with a bigger impact of the former.

The contribution of CC to depth perception is supported by various other studies on both animals and humans. For example, binocular activities in adult normal cats were recorded directly within the CC's splenium where callosal connections between the early visual areas of each hemisphere cross the midline; pairs of receptive fields mapped from these activities overlapped but also displayed some position disparities (Berlucchi et al., 1967; Hubel and Wiesel, 1967). Overall, binocular cells remain at the V1/V2 transition zone also after SC (e.g. Berlucchi and Rizzolatti, 1968; see Section 6.1 for further details). Similarly, in one human case of SC, stereopsis was still possible, supporting the contribution of the CC to binocularity (Blakemore, 1970). On the other hand, stereopsis turned out to be defective along the visual midline in many split-brain subjects (Mitchell and Blakemore, 1970; Lassonde, 1986; Jeeves, 1991).

Taking animal and human evidence together, the CC at the level of the primary visual cortex is implicated in rather "coarse" depth perception along the visual midline. The callosal terminals and the retino-geniculo-cortical pathways (likely mostly the ipsilateral ones; see Payne, 1990) thus interact in each hemisphere to elaborate binocular vision and depth perception along the visual midline. This mechanism complements the interactions between crossed and uncrossed retino-geniculo-cortical pathways that subtend binocular and stereovision along but also beyond the visual midline, in the whole binocular visual field (Hubel and Wiesel, 1967; Poggio and Poggio, 1984). This reasoning also applies when considering other attributes of the visual scene such as orientation, direction or spatial frequency encoded by the interconnected neurons (Berardi et al., 1987; Rochefort et al., 2007; Ribot et al., 2013; Conde-Ocazionez et al., 2018a,b).

3.3. Reversible inactivation studies

Direct drug application onto the cortex or reversible inactivation by cooling of CPNs in areas V1 and V2 of one hemisphere, further supports the conclusion that the CC can exert excitatory, inhibitory, and modulatory functions on spontaneous and evoked activity of neurons in the opposite hemisphere.

For example, application of GABA to visual cortex led mostly to a decrease in the contralateral hemisphere, and more rarely to an increase, of both the spontaneous and visually evoked neural activity (Sun et al., 1994), suggesting that the visual callosal fibers in cat are mainly facilitatory. However, reversible inactivation by cooling of CPNs in V1 and V2 of cat in one hemisphere brought about more complex activity changes of neurons in the opposite hemisphere (Payne et al., 1991).

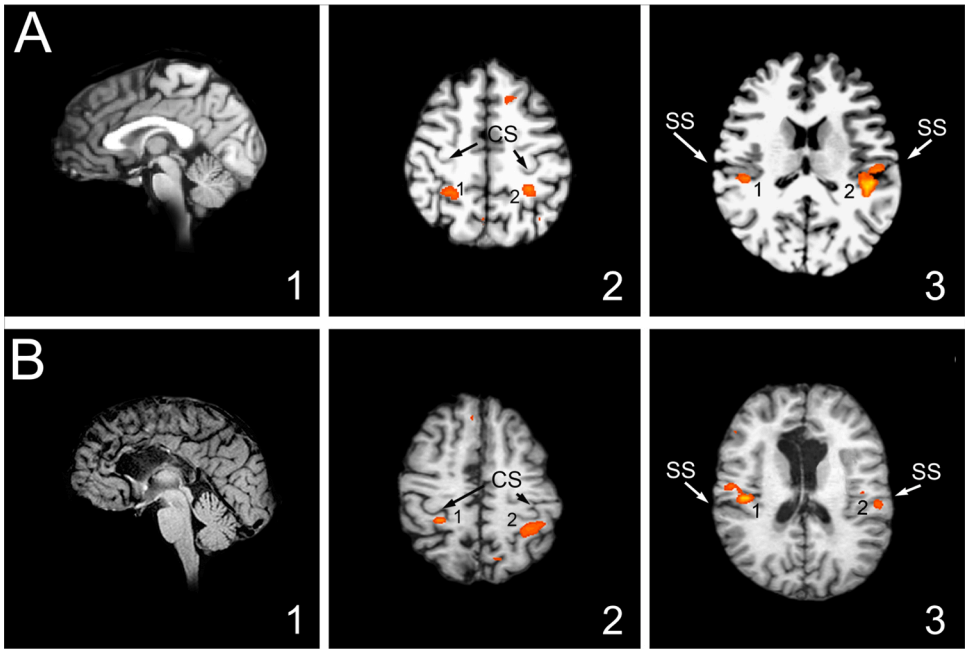

Fig. 5. Cortical activation evoked by tactile stimulation of the left medial trunk surface in a control subject with intact CC (A) and in a patient with complete callosal resection (B). A1 and B1, images through the midsagittal plane showing the integrity of the CC in the control subject and the total callosal resection in the patient. Unilateral tactile stimulation of the left ventral trunk midline evoked cortical activation foci in contralateral (A2,3 and B2,3, foci 1) and ipsilateral SI and SII (A2,3 and B2,3, foci 2), both in control subject (A2 and 3) and complete callosotomized patient (B2 and 3). Left hemisphere on the right. CS, central sulcus, SS, sylvian sulcus. Sagittal images are obtained from spin echo T1-weighted sequence (440 / 14 / 2 TR/ TE / excitations; matrix 256 × 224; scan time 3 min 20 s). Axial images (A2,3 and B2,3) are obtained from a T1 FLAIR sequence on which the regions activated during stimulation [obtained from a GE T2* single-shot echo planar image sequence; (3000 / 60 / 1) have been overlain]. Adapted from Fabri et al., 2006.

These included layer-dependent increases and decreases in spontaneous and evoked activity. The complexity of the changes was greatest in layers II and III, which are the major callosal recipient layers. Here, cooling evenly decreased the visually driven activity of 41 % of the neurons, suggesting the removal of an excitatory input. In addition, the visually driven activity of other neurons was increased reflecting a removal of inhibition. These results indicate that under normal physiological conditions transcallosal fibers largely contribute to both excitatory and inhibitory circuits. This is also supported by existence of GABAergic interhemispheric circuits in mice, as revealed by optogenetic tools (Rock et al., 2018).

The complexity of the interaction was confirmed through another study by recording local field potentials (LFPs) and the responses of single neurons at the V1/V2 border of the ferret after cooling in the opposite hemisphere (Makarov et al., 2008). While no changes in the responses to flashing spots were observed, changes in grating responses depended on whether identical or different orientations were displayed in the two hemifields. Responses mainly increased at short latency after stimulus presentation (25−50 ms), suggesting that cooling had eliminated an early inhibitory interaction. The responses mainly decreased after 50−100 ms, suggesting that an excitatory connection had been silenced. These results indicate that callosal connections to inhibitory interneurons are activated, at least in part, by axons faster than those of excitatory connections. Later, it became increasingly clear that the ratio between release from inhibition and decrease of excitation when deactivating the CC depends critically on the presented visual stimulus (Wunderle et al., 2013) and thus on all the different inputs a target neuron receives (Wunderle et al., 2015). Multiplication of excitatory gain by callosal input was especially clear with less salient stimuli involving contextual integration such as dot textures (Wunderle et al., 2013) or natural scenes (Conde-Ocazionez et al., 2018a,b) whereas potent inhibitory effects could be observed when using high contrast gratings (Wunderle et al., 2015). Thus, reversible deactivation studies were able to shed light onto the complex stimulus-driven dynamics between visual callosal and geniculo-cortical circuits, but they also revealed that the CC most likely provides an anticipatory signal for stimuli crossing the vertical meridian (VM; Fig. 6.; Peiker et al., 2013). Finally, combinations of voltage-sensitive dye imaging and electrophysiology both confirmed the feature selective nature of visual callosal connections (Schmidt et al., 2010) and revealed a similar selectivity in the ongoing activity waves between the hemispheres. Significantly, ongoing orientation maps preferring cardinal orientations were impacted by the absence of CC input (Fig. 7; Altavini et al., 2017**).**

Further evidence consistent with the inhibitory actions comes from manipulation of the visual callosal connections in human studies. Bocci et al. (2011) reported an increase of visually EP to high contrast stimuli after depression of activity by contralateral, low-frequency transcranial magnetic stimulation (TMS).

In area A1 of the cat, Carrasco et al. (2013) found that thermal inactivation of contralateral A1 and /or of the anterior auditory field (AAF) decreased the amplitude of single unit responses to noise, frequency-modulated sweeps and pure tones, without changing the receptive field properties. In contrast, Kitzes and Doherty (1994) have shown inhibitory as well as excitatory and mixed excitatory-inhibitory effects after stimulation of the contralateral A1 in the ferret.

In the human somatosensory cortex, trans-callosal inhibition of the early component of the EP to median nerve stimulation (Ragert et al., 2011) resembled what was shown by Makarov et al. (2008) in the ferret's visual cortex. In the human motor cortex, inhibitory interactions through the CC were reported after TMS inactivation of the contralateral motor cortex (Boroojerdi et al., 1999; Plewnia et al., 2003). Nevertheless, a conditional and task-dependent driving role of callosal connections is expected to operate during tasks requiring bimanual actions consisting of object manipulations, which depend on a fast and continuously refreshing sensory-motor input from the moving hands.

In conclusion, lesions, and inactivation of connections between cortical areas of the two hemispheres produce complex results pointing to both inhibitory and excitatory actions of CC connections. One common theme is that callosal axons seem to have often a "conditional driving" power on their targets thus cooperating with responses elicited by thalamic or other inputs. This agrees with the morphology of callosal connections described above and provides grounds for reinterpreting the classical account of interhemispheric transfer of complex information derived from the split-brain studies. It must be stressed that reversible pharmacological or thermic inactivation does not affect only callosal cells, but also different classes of intracortical interneurons influencing local circuits, which then project transcallosally, indirectly or directly (e.g., Rock et al., 2018).

Thus, the effects described in this section cannot be considered as the exclusive result of selective silencing of callosal neurons. On the other hand, there is a striking difference between the consequences of transient inactivation and those of permanent cortical lesions (Otchy et al.,

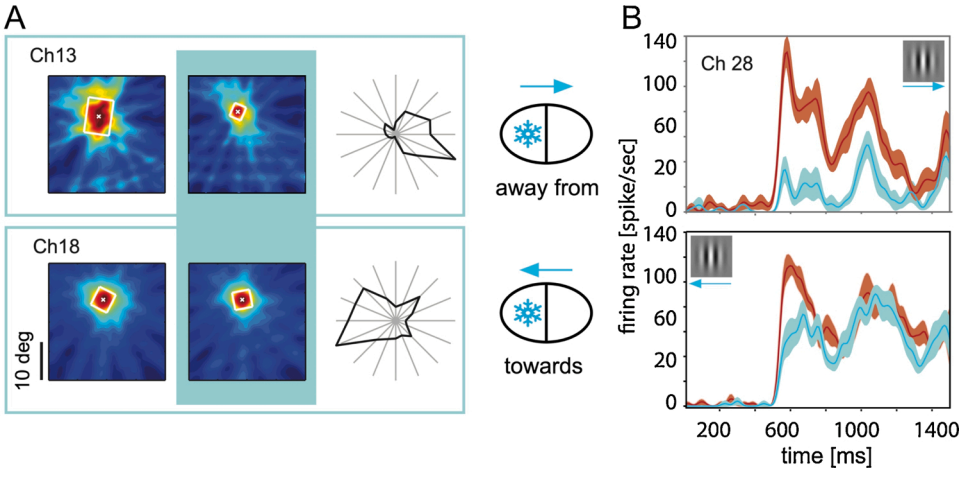

Fig. 6. Anticipation of horizontal movement across the VM of the visual field in cats revealed by removal of callosal input (CC). Examples of receptive fields **(A)** and spiking activity **(B)** in area 17 (ch18, ch28) and area 18 (ch13) during reversible thermal deactivation of the left 17/18 transition zone. A: Receptive fields in the right hemifield and preferring movement '*away from*' (ch13) or '*towards*' (ch18) the deactivated left hemifield during baseline (left) and CC deactivation (light blue box). Normalized polar plots (right) indicate the preferred direction of movement. Note that the neuron (Ch13) preferring the '*away from*' the deactivated hemifield movement is particularly affected although its RF is confined to the right hemifield. **B:** Peri-stimulus time histogram of a neuron preferring both horizontal movements (ch28) during visual stimulation with a RF tailored Gabor grating moving '*away from*' (upper) or '*towards*' (lower) the deactivated hemifield. Although stimulation does neither cross the VM nor enter the stripe of overlapping representation in the two hemispheres, baseline spiking activity (red) is decreased by deactivating CC (light blue) for the '*away from*' but not the '*towards*' movement suggesting a lack of ongoing and direction specific excitatory input. Adapted from original data published in Conde-Ocazionez et al., 2018a,b **(A)** and Peiker et al., 2013 **(B)**.

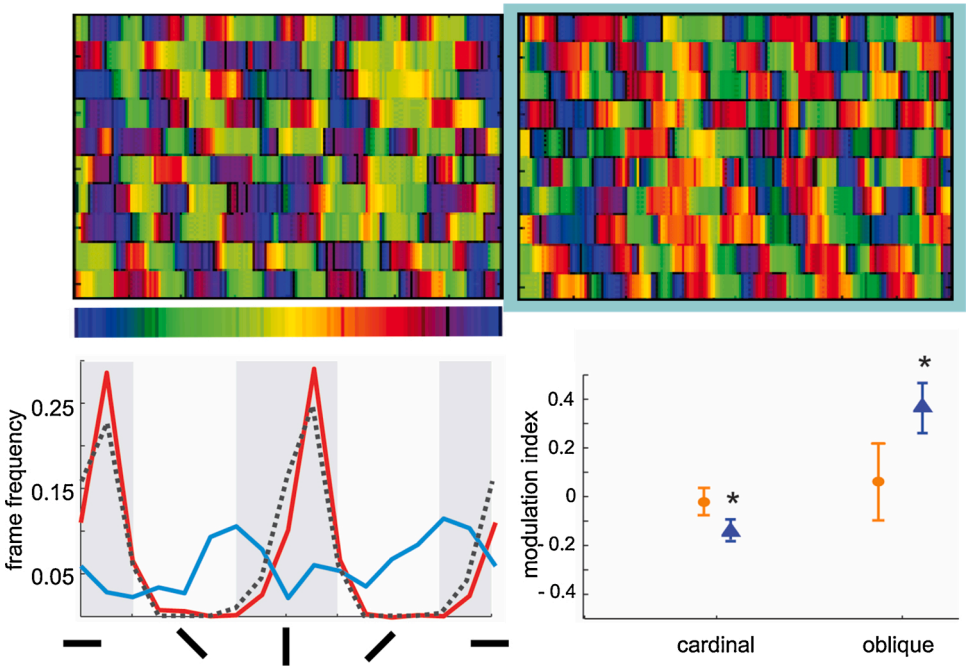

Fig. 7. Reversible thermal deactivation of CC removes the natural cardinal bias in ongoing maps recorded with voltage-sensitive dye imaging (VSDI) in cat area 18. Upper: Sequences of camera frames (6.25 ms each) during ongoing activity in 10 trials color-coded by preference angle (color bar below). Frame-wise preference angle obtained by vectorial sum of single correlation coefficients with eight reference orientation preference maps evoked by gratings. During CC deactivation (blue box), phases of yellow-green and blue (cardinal orientations) decrease at the expense of green and red (oblique orientations). Lower, left: Frequency of VSDI frames of ongoing activity significantly correlated with grating evoked maps of a certain preference angle (red line, baseline; blue line, deactivation; black dotted line, recovery), as quantified from the example data set above. Lower, right: Median modulation index (MI) for the probability of the sum vector to fall in one of three angle compartments for evoked (orange dots) and ongoing activity (blue dots) in 12 data sets. The MI is a measure of change in frequency (F) between baseline and CC deactivation states. $MI_F = (F_{baseline}-F_{deactivation})/(F_{baseline}+F_{deactivation})$, ranging from -1 to 1. Accordingly, negative MI indicates decreased excitation, positive MI indicates release from inhibition in the absence of CC. Dispersions are median absolute deviations.

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2015), probably due to diaschisis (Carrera and Tononi, 2014) and to the homeostatic regulation of neural activity in cortical circuits (for discussion Battaglia-Mayer and Caminiti, 2019 and the reference therein), which often allow a gradual recovery of functions (Keck et al., 2013; Marder and Goaillard, 2006; Turrigiano, 1999).

In synthesis, while the effects described in this section cannot be considered as the result of selective silencing of CPNs, at the same time caution is needed when interpreting the function of callosal connections solely from split-brain patients or from animal models with fiber tract lesions, because each of these methods suffer from limitations. With some differences, this might also hold true for the effects of electrical, magnetic and optogenetic stimulation as discussed in the following section.

4. Electrical, magnetic and optogenetic stimulations

In this section we will offer a "historical" perspective of these different methods, on their specificity and progressive refinement, and contrast their results on the role of the CC.

4.1. Electrical stimulation

Electrical stimulation has been important in the history of neuroscience. It provided the first evidence of cortico-spinal control with the work of Fristch and Hitzig, Ferrier, Sherrington and many others (reviewed in Ferrier, 1874; Hitzig, 1900; Sherrington and Grünbaum, 1901) and established functional maps in the human brain with Penfield and collaborators (Penfield and Boldrey, 1937).

Stimulation of one hemisphere and recording of evoked potentials (EPs) in the contralateral one provided the evidence of pathways between the hemispheres in monkey and cat (Curtis, 1940). Electrical stimulation was paralleled by strychnine neuronography introduced by De Barenne and Sherrington who, in 1924, published a somatotopic map of the primary sensory cortex in the macaque which inspired McCulloch and others to provide maps of callosal connections in macaque (McCulloch and Garol, 1941) and chimpanzee (Bailey et al., 1941).

Electrical stimulation of the CC established the motor function and topographic representation of the body of the CC in the monkey long before anatomy: "When the electrodes are applied over and just behind the genu, head and eye movements are produced; further back movements of the arms and shoulder and of the upper part of the trunk; then movements of the forearms and general movements of the hands and fingers; then of the lower part of the trunk and tail, and lastly, movements of the lower limbs" (Mott and Schaefer, 1890). Schaltenbrand et al. (1970) reported the results of CC stimulation in 9 patients. Depending on the stimulated site they obtained movements, paresthesia, as well as interference with speech and thinking. A coarse antero-posterior and dorso-ventral topography of the effects was observed.

The interpretation of the effects of electrical stimulation of the gray matter was discussed over 50 years (Ranck, 1975; Tehovnik et al., 2006). The current consensus is that axons are activated, in particular the axon hillock that has the lowest threshold for spike generation. With a series of *in vitro* and *in vivo* experiments, Nowak and Bullier (1998a, 1998b) concluded that mainly local axonal branches, rather than the cell bodies near the site of stimulation, were activated. This raises difficulties with the interpretation of results since the activation of neurons located at some distance from the site of stimulation might occur. Also, depending on neuronal geometry, cell bodies may be excited with different requirements (Encke et al., 2013; Komarov et al., 2019), as also discussed in Section 2.2. *ii)*.

The cellular origin of the various components of the EPs following electrical stimulation through the CC remained unclear since the components due to antidromic activation of CPNs and to the incoming callosal afferents could not be dissociated (Curtis, 1940; Chang, 1953). Despite these uncertainties, several types of information were obtained. One is whether a given pathway is excitatory or inhibitory to its target. Innocenti et al. (1972) found 31.6 % excitatory and 18.9 % inhibitory contralateral responses in the segmental division of SI and SII of the cat after stimulation of contralateral SI and SII. In the trigeminal subdivision

a majority of excitatory responses and only 8.5 % of inhibitory responses were found (Fadiga et al., 1972). Innocenti (1980) found 17.3 % antidromic responses (some followed by trans-synaptic activation), 32 % activations and 13.78 % inhibitions after electrical stimulation of the V1/V2 border region in the cat.

In the three studies mentioned above the callosal input was quoted as weak and less secure than the thalamo-cortical one, as judged from the amplitude of excitatory postsynaptic potentials (EPSPs) **(**Fig. 1 **inset)**. Also, the response required repetitive electrical stimuli or application of glutamate at the recording site to enhance the excitability of the recorded neurons. Electrical stimulation provided information about velocity, and other conduction properties of axons (Waxman and Swadlow, 1977; Swadlow et al., 1978; Innocenti, 1980; Swadlow, 1985; Firmin et al., 2014). Conduction in the visual areas revealed differences between species, with antidromic delays in cats in the order of 2–2.9 ms, longer delays in monkeys (2.6–18.0 ms), mice (8.3 ms) and rabbits (2.4–39.8 ms) (reviewed in Innocenti et al., 1994). In general, these results are in agreement with the anatomical predictions (Caminiti et al., 2009; Tomasi et al., 2012).

Electrical stimulation also revealed the response properties of the postsynaptic neurons. In the cat somatosensory cortex it was found that neurons activated by stimulation of the contralateral hemisphere via the CC had wide, “extra-lemniscal" receptive fields (Innocenti et al., 1972). At the border between areas V1/V2, the CPNs had simple or complex or hypercomplex receptive fields, while the majority of callosal recipient neurons had complex receptive fields near the VM (Innocenti, 1980; McCourt et al., 1990), in some conflict with the results obtained by identifying callosal neurons with antidromic stimulation (see Section 5.2). Finally, modulation of callosal connectivity has been shown by using bi-hemispheric transcranial alternating current stimulation, which in human subjects yields an interhemispheric oscillatory synchronization related to acoustic feature binding (Preisig et al., 2021).

4.2. Transcranial magnetic stimulation (TMS)

Contemporary studies in humans use TMS and EPs in the analysis of cortical connections. What exactly is stimulated is again unclear. Presumably the same excitable elements are activated, as with intracortical electrical stimulation, but in larger numbers since bigger volumes are reached by the stimulus. The response likely corresponds to the summed post-synaptic depolarization of dendrites and cell bodies. As by intracortical stimulation, the properties of the connections can be probed, albeit non-invasively, in humans (Bortoletto et al., 2015).

In pioneering studies (Cracco et al., 1989) the TMS stimulation of M1 elicited a positive/negative deflection with onset latency at about 8.8−12 ms in the contralateral hemisphere. This latency is close to the median values of interhemispheric delays between motor areas calculated from the diameter and length of CC axons in humans (10−11 ms; Caminiti et al., 2009, 2013). Ilmoniemi et al. (1997), controlled the artefact generated by the TMS with a special amplifier and found latencies of contralateral M1 responses at 22 ms on average, longer than what predicted by the anatomy and estimated by Ferbert et al. (1992), and Boroojerdi et al. (1999). A common observation with TMS is the spread of activation to multiple ipsi- and contralateral areas. These widespread activations resemble those obtained with micro-stimulation in animals (Tehovnik et al., 2006) and might be sub-threshold for spike generation. Interestingly, the spread of activity decreases during non–rapid eye movement sleep (Massimini et al., 2005) indicating that the activation induced by TMS is modulated by the state of cortical activity.

4.3. Optogenetic stimulation

The introduction of light-sensitive molecules (opsins) into neurons has paved the way for a new field, named “optogenetics”, whereby pathways can be reversibly activated (or inhibited) by light (Boyden, 2011, 2015; Deisseroth, 2011, 2015). Combinations of retrograde, trans-synaptic transport methods with the insertion of opsins in neurons at the origin of a projection have allowed specific pathways at the electrophysiological and behavioral levels to be functionally identified, such as the aversive component of projections to the lateral habenula from the lateral hypothalamus (Lazaridis et al., 2019). The method is applicable in a large spectrum of animal models including primates (Han et al., 2009; O’Shea et al., 2018). Compared to electrical stimulation optogenetics has the advantage of a higher specificity since only the infected neurons are activated at the site of stimulation. Nevertheless, the effects observed are not necessarily due to monosynaptic activation of the targets and, as for electrical stimulation, indirect effects mediated by circuits activated via axon collaterals cannot be excluded. *Invitro* studies using optogenetic techniques further dissected the circuits engaged by CC connections in mice. In the mouse somatosensory cortex, interhemispheric inputs contact interneurons in layer I, which evoke GABA-B-mediated inhibition in the distal dendrites of layer V pyramidal neurons (Palmer et al., 2012). Other studies have shown that that callosal axons synapse onto pyramidal neurons and interneurons across cortical layers II/III, V, and VI (Petreanu et al., 2007), under balanced interhemispheric cortical activity (Suárez et al., 2014a). In the auditory cortex of mice, neurons with cortico-cortical axons are inhibited while those with cortico-collicular axons are excited by callosal input (Rock and Apicella, 2015). This reaffirms older conclusions regarding the existence of a callosal input to cortico-collicular projections in the cat (Antonini et al., 1979). By combining retrograde fluorescent labelling and slice recordings *in vitro*, the authors further showed that CPNs were preferentially connected to CPNs, demonstrating the existence of projection target-dependent fine-scale subnetworks.

In synthesis, more than a century has passed since Fritz and Hitzig reported the effects of electrical stimulation in activating cortical neurons in the cortex. Today’s optogenetics, associated with other methods, offers a powerful tool for the identification of the sources and sinks of specific neural circuits, including the CC, whose cells of origin and termination have been shown with unprecedented precision and details, specifically the laminar origin of CPNs in both supra- and infra-granular layers, as well as their axonal multilayers terminations. CC axons can be either excitatory or inhibitory, as those releasing GABA-B at synapses on the apical dendrites of layer V pyramidal neurons arriving in layer I. In between, TMS remains a privileged tool for the study and manipulation of functional connectivity in humans, with the demonstration of the state dependency of effective cortico-connectivity, which most probably affects also interhemispheric transfer.

5. Functional properties of callosal projecting neurons

Here, we will describe the functional properties of CPNs since they mostly determine the nature of interhemispheric messages, at least in primary sensory areas. To this goal, different methods have been used, each providing a unique set of information. In V1 and V2, as well as in SI and SII, callosal connections preferentially link cortical zones representing the functional sensory midlines, while a more complex organization is found in A1.

5.1. Anatomo-physiological studies

The question of which kind of information is carried by a pathway is crucial to understand its function but relatively rarely addressed. A combined neuroanatomy and electrophysiology approach, taking advantage of orderly somatotopy, provided the first contribution to the identification of CPNs with receptive fields located on the forepaw in SI and SII of the cat (Caminiti et al., 1979), as well as in the thumb, index and middle fingers in monkey (Manzoni et al., 1984). This evidence ended a long discussion over the absence of callosal connections in the hand representations of SI and SII. These results can be reconciled with the “midline rule”, according to which callosal connections preferentially link “midline” sensory representations (Berlucchi et al., 1967;

Hubel and Wiesel, 1967; see also Section 5.2), if one only considers that skilled bimanual actions, such as object manipulations, mostly occur thanks to the simultaneous use of the thumb, index and middle fingers of each hand under foveal control and generally close to the body midline. The convergence of callosal axons at the SI/SII borders observed in rodents (Fenlon et al., 2017; Suárez et al., 2014b; Zhou et al., 2021) is related to the underlying somatotopy (Olavarria and Van Sluyters, 1995), and conforms to the "midline rule": the somatosensory maps in SI and SII are very similar in rat, mouse, hamster, and in agouti, evidencing that body regions close to the midline (head, upper vibrissae, trunk and proximal limbs) are represented in the lateralmost region of SI and in the bordering medialmost region of SII, in a mirror-like fashion (Krubitzer et al., 2011; Santiago et al., 2019). In both somatosensory and visual areas of mice, bilateral correlations, as measured with calcium imaging tend to be strongest close to the midline representations (Shimaoka et al., 2019).

Also, in agreement with the "midline rule", CPNs in the primary visual areas of the cat were found to be restricted to the V1/V2 border representing the VM of the visual field, although in greater numbers at the representation of the area centralis, i.e. central vision (Innocenti and Fiore, 1976). However, it is worth noticing that additional CPNs are present in both areas V1 and V2, leading to the conclusion of "non--mirror-symmetric patterns of callosal linkages between the hemispheres", not only in cats but also in rats and mice (Laing et al., 2015; Lewis and Olavarria, 1995; Olavarria, 1996; Olavarria and Hiroi, 2003). Thus, CPNs located in areas V1 and V2 project to the contralateral V1/V2 border, while those at the V1/V2 border project contralaterally in portions of V1 and V2 neighboring the border. Such organization explains how the CC contributes to the "fusion" of both hemifields along the visual midline while each hemifield is represented separately in each hemisphere.

More recently, Hagihara et al. (2021) investigated the relationships between the response properties of callosal projection neurons (CPNs) and the local connection pattern in layer II/III of the binocular zone of the mouse visual cortex. By combined retrograde fluorescent labeling and *in vivo* two-photon calcium imaging, CPNs were identified as having distinct functional properties compared to non-CPNs, namely ocular dominance. The former were indeed more strongly activated through the ipsilateral eye, while the latter were more strongly activated by the contralateral eye. By combining retrograde fluorescent labeling and slice recordings *in vitro*, the authors further showed that CPNs were preferentially connected to CPNs. It was concluded that in visual cortex CPNs show biased response properties and fine-scale local subnetworks. Furthermore, in both cats and rats, CPNs receive quite strong inputs from the ipsilateral eye in areas V1 and V2, while at the V1/V2 border are mainly activated through the contralateral eye, suggesting a common organization across mammals (Laing et al., 2015; Olavarria, 2001).

In V1, callosal-recipient spines cluster more frequently with non-callosal recipient ones with common orientation preference (Lee et al., 2019), thus favoring the integration of information from different networks. On the same lines, a recent study (Liang et al., 2021) has shown that a specific layer VI population of excitatory callosal neurons of mice monocular V1, characterized by higher spontaneous activity than that of thalamo-cortical neurons, participates in a distributed cortical system with complex relationships to different brain states and events.

Unlike the visual and somatosensory areas, where interhemispheric inputs are addressed to the boundaries between areas and vicinities (see above), callosal connections are widespread across the tonotopically-organized representation of A1 (Code and Winer, 1986, 1985; Hackett and Phillips, 2011) and connect tonotopic regions with corresponding frequency domains across the hemispheres (Diamond et al., 1968; Imig and Brugge, 1978; Lee and Winer, 2008; Rouiller et al., 1991). Homotopic interactions have also been established anatomically in rats (Cipolloni and Peters, 1983; Rüttgers et al., 1990). In cats, combined anatomical and electrophysiological experiments revealed a complex pattern of interhemispheric connections, since CPNs and terminals were preferentially distributed over regions exhibiting binaural summation or ipsilateral dominance and suppression, rather than in regions of monaural contralateral responses or contralateral dominance and suppression (Imig and Brugge, 1978).

Although callosal inputs arise from the axons of pyramidal cells, this pathway may not simply lead to cortical excitation in the contralateral hemisphere. Indeed, by using translaminar single-unit recordings and optogenetics to probe how the callosal input modulates spontaneous and tone-evoked activities in A1 of awake mice, it has been shown that callosal projections sharpen the frequency tuning and enforce the response fidelity in A1 through both increase and decrease in the firing of individual neurons (Slater and Isaacson, 2020).

5.2. Antidromic activation and recording from callosal fibers

A more direct approach is to study the activation properties of CPNs by antidromic invasion. This method allowed (e.g. Fromm and Evarts, 1981) to determine the activation properties of motor cortex neurons projecting into the pyramidal tract in the monkey. Also, CPNs antidromically activated near the V1/V2 border showed receptive fields of the simple, complex or hypercomplex type near the vertical meridian of the visual field (Innocenti, 1980). McCourt et al. (1990) confirmed that antidromically activated callosal neurons exhibited all receptive field types. Interestingly, neurons with the simple-type receptive field had faster conduction velocity (17 m/s) than those with complex receptive fields (10−11 m/s).

A second way is to record directly from the axons in each pathway. As mentioned above, Hubel and Wiesel (1967) recorded axons responsive to visual stimuli from the splenium of the CC of the cat. All axons had binocular receptive fields located along the VM, a finding shared by Berlucchi et al. (1967). In the somatosensory system, multiunit and single fiber responses could be obtained in the rostral part of the CC of the cat by stimulating the whiskers, forepaw and hind paw (Innocenti et al., 1974). These responses were abolished by ablation of the somatosensory areas. Guillemot et al. (1988) also recorded somatosensory responses from the CC of the cat, mapping both the peripheral receptive fields and the adaptation properties of the responses. Recordings were extended to the monkey (Guillemot et al., 1987) and the raccoon (Guillemot et al., 1992). All these studies identified callosal axons with receptive fields on the hands although the majority was on the face and trunk.

5.3. Recording fMRI signals from the CC

A further possibility of identifying the activation of axonal pathways was introduced by the finding that a fMRI/BOLD signal could be recorded from the CC during the Poffenberger paradigm, a task which requires information transfer between the hemispheres (Tettamanti et al., 2002). Since historically it was assumed that the fMRI/BOLD signal is only obtainable from the gray matter, the finding seemed to be controversial. Nonetheless, it was replicated (Courtemanche et al., 2018; Mazerolle et al., 2010), although the mechanisms are still discussed (Fabri et al., 2014).

Activation foci were consistently detected in discrete CC regions: anterior (taste stimuli), central (motor tasks), central and posterior (tactile stimuli), and splenium (visual stimuli). Using this approach, a functional map of the CC was established (Fabri et al., 2011 reviewed in Fabri et al., 2014). One would expect that the activated CC sites should be connected to activated cortical areas. This is indeed the case sometimes (Mazerolle et al., 2010; Fabri et al., 2014; Courtemanche et al., 2018) but not always. The possible causes for discrepancies are discussed in Mazerolle et al. (2010). With the refinement of fMRI techniques, the activation of white matter may become another powerful non-invasive tool in the functional characterization of axonal pathways.

In synthesis, CPNs in primary sensory areas display a variety of receptive field properties, such as simple, complex or hypercomplex

types along the VM representation of visual cortex. In the somatosensory cortex, CPNs have receptive fields located in the territories of innervation of the median and radial nerves of the hand, that is thumb, index, and middle fingers, that is the digits mostly used for manipulating small objects under foveal control, as well as along the body (trunk) midline. A more complex organization is shown in A1, where callosal cells and terminals occupy most of the tonotopic representation and seem to be involved in sharpening the frequency tuning and fidelity of auditory neurons. Contrary to previous expectations, functional representations have emerged in the CC from fMRI BOLD signals, largely thanks to studies in split-brain patients.

6. Matching pre- and post-synaptic response properties

6.1. Studies in visual cortex

This section concerns the type of information which is transferred through the CC. It focuses on the post-synaptic targets of the callosal axons and on how their properties are related to those of CPNs in the other hemisphere, that is on "interhemispheric integration". The question of the relationship with the ascending inputs from periphery is also addressed.

One of the most elegant experiments performed in animals to study the pre- and post-synaptic response properties of callosal neurons was to record neuronal activity in the primary visual cortex of the cat after section of the optic chiasm, i.e. the section of the crossing retino-geniculo-cortical pathways (Berlucchi and Rizzolatti, 1968; Lepore and Guillemot, 1982; Antonini et al., 1983; Milleret et al., 1994, 2005; Tardif et al., 1997; Milleret and Houzel, 2001; Watroba et al., 2001; Rochefort et al., 2007; Bui Quoc et al., 2011; Ribot et al., 2013). In this preparation, visual stimulation of one eye first activates the cell bodies of callosal neurons, among others, through the uncrossed retino-geniculo-cortical pathway in the ipsilateral hemisphere and subsequently their target neurons in the contralateral hemisphere, which are trans-synaptically activated through their axons. This directly determines which visual information is transferred between the hemispheres through the CC. In addition, visually stimulating the companion eye activates the retino-geniculo-cortical pathway converging onto these transcallosal activated neurons, which facilitates the comparison of their respective functional properties in the *same* hemisphere.

This approach established that near the VM of the visual field the responses generated via each pathway are similar for receptive field location but also for stimulus preference of orientation and motion direction, spatial frequency tuning and spatial resolution. However, spatial disparities between pairs of receptive fields are present and increase with eccentricity (Milleret et al., 1994, 2005; Bui Quoc et al., 2011). Using optical imaging from one given visual cortex in cats with section of the optic chiasm, Rochefort et al. (2007) demonstrated that the layout of orientation columns activated via the callosal pathway is similar to the one evoked by geniculo-cortical projections in the same hemisphere (Fig. 8). The same was observed with respect to spatial frequency maps (Ribot et al., 2013). Since intrinsic signals reflect both supra- and subthreshold activation, these findings do not imply that callosal axons drive their targets in the callosal terminal territory

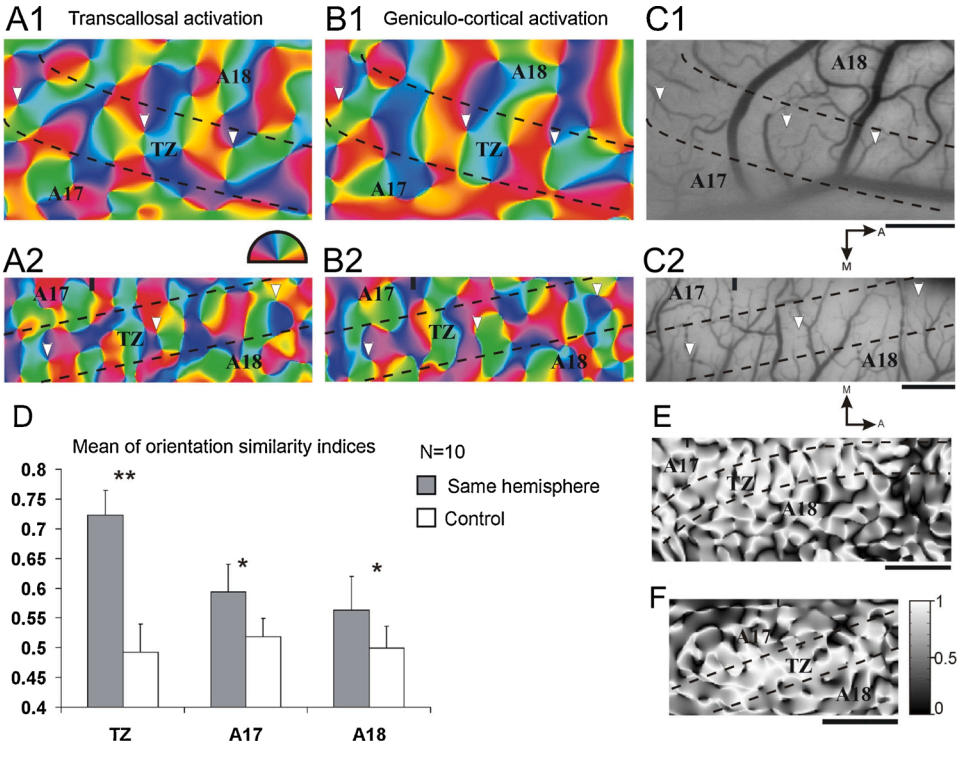

Fig. 8. Correspondence between the transcallosal and the geniculo-cortical orientation angle maps "overlapping" in the primary visual cortex (Area17 and Area 18 and transition zone, TZ) of individual adult cats in the same hemisphere. **A, B.** Optical imaging of intrinsic signals was used to visualize and quantify preferred orientations within these maps in split-chiasm preparations. The callosal and the geniculo-cortical pathways could be activated separately in the same cortical region by visually stimulating each eye in succession. Both maps were compared for their spatial organization; orientation angle maps were also compared quantitatively. Transcallosal (A1-2) and geniculo-cortical (B1 and B2) angle maps from the same hemisphere (1, cat Ca10, left hemisphere; 2, cat Ca01, right hemisphere). White arrowheads were placed on pinwheel centers of the transcallosal angle map and were copied onto the geniculo-cortical map. Thick dashed lines show the location of the 17/18 transition zone (TZ). **C1-2.** blood vessel patterns of the imaged regions in A1,2 and B1,2. Scale bar = 1 mm. **D.** Mean orientation similarity index (OSI) calculated in 10 hemispheres (from 7 cats), for the 1-mm-wide TZ between Area 17 and Area 18 as well as for the regions of Area 17 and Area 18 visible on the maps (excluding the TZ). Gray bars represent the mean of the orientation similarity indexes calculated with the transcallosal and geniculo-cortical maps of the same hemisphere of the same animal. The white bars represent the controls where the transcallosal map from one animal was compared with the geniculo-cortical map from another animal. Both groups (same hemisphere vs. control) appeared significantly different for each region (Mann–Whitney test; $^{**}p < 0.0001$; $^{*}p < 0.01$). The strongest difference appeared in the TZ, with a better score when both maps are of both the same hemisphere and the same animal. The difference between the TZ and Area 17 was also significant, as well as the one between the TZ and Area 18 (Mann–Whitney test; $p < 0.0001$). The difference between Area 17 and Area 18 was not significant. Error bars indicate the standard deviation. **E, F.** OSI maps. The OSI was calculated for each pixel from the angle maps of cats Ca16 and Ca12, respectively. The TZ appears clearly whiter than the other regions indicating that the similarity between transcallosal and geniculo-cortical angle maps decreased progressively with increasing distance from the TZ toward Area 17 and Area 18. Scale bar = 2 mm. Reproduced from Rochefort et al., 2007, with permission.

equally powerfully but rather they may exert a driving or a modulatory effect. In accordance, (Rochefort et al., 2007) showed that the geniculo-cortical pathway is, on average, twice as powerful than the transcallosal pathway in evoking an optical response. It should be further noted that transcallosal responses are state-dependent since they were obtained only when the animal's EEG was desynchronized. In anesthetized preparations, responses decreased or even disappeared (Yinon and Hammer, 1985), indicating that alertness is of importance to allow interhemispheric transfer of information through the CC and further supporting the notion of a conditional driving role of the CC input under special circumstances.

The functional specificity of callosal connections linking both hemispheres was also investigated by combining anatomy and optical imaging of intrinsic signals from visual cortex. The anatomical substrate for iso-orientation connectivity of callosal connections in the cat was first observed after optical imaging guided injections of latex microspheres by Schmidt et al. (1997) who found that retrogradely labelled CPNs were mainly localized in columns of the same orientation preference as in the contralateral injection site. This selectivity was then analyzed in detail by Rochefort et al. (2009) who found that the distribution of boutons by callosal axons in the orientation columns of one hemisphere did not only match that of the neurons of origin in the other hemisphere but was also coaxially aligned. This finding provides one paradigmatic example of the mapping function of axonal arbors mentioned above in Section 2.2. *i)*.

6.2. Studies in somatosensory and gustatory areas

In the representation zone of the trunk midlines of monkeys' S1, Conti et al. (1986) found neurons with bilateral receptive fields crossing the midline and neurons projecting to contralateral homologous regions in SI. Since in cats bilateral receptive fields were already recorded in the ventro-posterior lateral thalamic nucleus (Barbaresi et al., 1984; see also Robinson, 1973) it can be hypothesized that the CC is, in this case, not solely responsible for the bilateral responses.

A similar conclusion can be drawn for callosal fibers connecting primary gustatory areas (GI) from functional studies in healthy control subjects (Mascioli et al., 2015) and neuropsychological investigations in split-brain patients (Aglioti et al., 2001), both showing that unilateral taste stimuli to the tongue are transmitted to GI of both hemispheres.

In synthesis, the study of which information is transferred between the hemispheres through the CC has been undertaken by using different methods, such as neurophysiological recording and optical imaging in SC animals, combination of anatomy with optical imaging of intrinsic signals, fMRI, and others. The results have shown that there exists a very good match between the functional properties of peripheral and transcallosal signals influencing neural activity of callosal neurons in the same hemisphere, as elegantly shown in V1. However, peripheral influences are much stronger than those of callosal fibers and the callosal transfer of information is state-dependent, suggesting a modulatory or conditional driving role of callosal axons.

7. Correlations, imaging and electrophysiology

Since the introduction of fMRI in neuroscience, new methods and models have been developed for the study of cortical connectivity by using resting state activity. The achievements and limitations of these methods and their results are briefly discussed in this section, together with the results obtained from the study of the velocity of information transfer, electrophysiology, and task dependency.

7.1. Problems with inferring structural anatomy from fMRI

The attempt to infer anatomical connectivity from physiological or neuropsychological assessments predates the development of MRI-based anatomical methods to trace connections. Physiological measurements can be obtained with single unit recordings and cross-correlation of spike activity, LFPs, EEG and fMRI. Friston et al. (1993; 1994) introduced concepts of functional and effective connectivity and later of Dynamic Causal Modeling (DCM; see Friston et al., 2019) in the EEG-fMRI field as a way to bridge the gap between structure and function of cortical connections. However, as discussed by Honey et al. (2009) and Sokolov et al. (2019) a simple relationship between structural connectivity and effective or functional connectivity cannot be expected. Effective connectivity describes the causal influence that the activity of a group of neurons can have on another neuronal group. This influence can be polysynaptic and therefore not adequate to reveal the activity of an axonal pathway. Functional connectivity can be even more remote from structural connectivity since it might involve the activation of diverging structural architectures and recurrent loops. Even the simple correlation of spiking activity between two neurons is difficult to interpret as evidence for direct connections since it might be generated by a common input.

The difficulty in inferring structural anatomical connectivity from the study of functional connectivity in humans is well illustrated by the attempts to correlate resting activity between areas of the two hemispheres to CC connections. The question seems to be straightforward. If the symmetry of resting state BOLD signal in the two hemispheres is due to the CC connections between them, it should be abolished by CC transection. Unfortunately, the results turned out to be less clear, since in the monkey the functional connectivity between the two hemispheres is affected if both the CC and the anterior commissure are sectioned (O'Reilly et al., 2013), thus showing a contribution of the latter. These results unequivocally demonstrate, as they stated, that "there is not a one-to-one mapping between the existence of pairwise structural connections and functional connectivity patterns". Therefore, the role of structural connectivity cannot be inferred from functional connectivity even in the simplest possible situations. Roland et al. (2017) studied the functional connectivity between the two hemispheres before and after CC section. The results were obtained by partial or complete CC section in 22 human cases. Large part of the interhemispheric functional connectivity was affected after complete callosotomy. All cortical regions showed a dramatic decrease in interhemispheric connectivity, affecting more higher-order frontal and parietal association areas than primary somatosensory, motor, and visual areas.

Concerning inter-regional low frequency spontaneous fluctuations, more robust correlated activity was found between homotopic than heterotopic callosal regions, with highest correlations across primary sensory-motor, than across multimodal association areas, where lateralized functions are mostly represented (Stark et al., 2008). The correlations across areas connected by heterotopic axons were further characterized and compared with ipsilateral cortical connections in another study (Gee et al., 2011), to which the reader is referred to for details.

As an interim conclusion, available evidence indicates that both direct CC connections between the hemispheres as well as polysynaptic extra-callosal connections, and the anterior commissure play a role in the maintenance of interhemispheric functional connectivity. These human findings, obtained in brains probably modified by years of abnormal electrical activity due to epilepsy, as well as by the CC section, concur with the monkey findings mentioned above in discouraging the attempts of inferring the role of structural connectivity from functional imaging data in humans.

7.2. Studying the speed of interhemispheric information transfer

Another approach to the functional characterization of CC connections has been to test the speed of information transfer between the hemispheres by measuring reaction times in the so-called Poffenberger paradigm. In short, the reaction time to a visual stimulus presented to the right or left hemifield (i.e., hemisphere) is measured when the same hemisphere (uncrossed condition) or the contralateral hemisphere

(crossed condition) generated the motor response with the hand. The attempts to identify which sector of the CC mediates the response have generated different hypotheses (Tettamanti et al., 2002; Iacoboni and Zaidel, 2003; Peru et al., 2003; Weber et al., 2005; Tamè and Longo, 2015; Innocenti et al., 2017) but no firm conclusions. Consistent across studies, and unexpected, was that in fMRI studies, the crossed condition engaged many more areas than the uncrossed one. This can be interpreted as evidence that the interhemispheric transfer occurs over several CC sectors (Weber et al., 2005) possibly by convergence onto the same targets via heterotopic connections. Still, it should be kept in mind that the fMRI signal does not necessarily demonstrate increased spiking but also, or mainly, subthreshold postsynaptic activations.

Several of the areas activated in the crossed condition project via the CC to the contralateral striatum (Innocenti et al., 2017) and these connections are expected to generate transmission delays compatible with longer reaction times observed in the crossed condition (Innocenti, 2017). Dal Molin et al. (2013) reported faster interhemispheric transfer for visuospatial than for semantic information but it is unclear how these effects relate to conduction along different compartments of the CC.

In summary, the analysis of the speed of information transfer has provided intriguing results.

Behavioral response can be generated by the hemisphere that receives the information through peripheral or transcallosal inputs. In the latter case, the longer temporal delays of such responses are more compatible with transcallosal transfer addressed to subcortical structures, such as contralateral striatum, rather than to contralateral areas.

7.3. Electrophysiology

The reverse approach, namely that of inferring the function of specific anatomical connections through electrophysiological investigations might be more promising. Engel et al. (1991) and Munk et al. (1995) reported that CC section abolished the synchronization of activity of single neurons in primary visual areas of the cat. Using fast optical imaging in the cat, O'Hashi et al. (2018) reported interhemispheric synchrony of spontaneous cortical states at the level of the cortical column but the role of CC connections in the inter-columnar synchronization remained hypothetical, given that intra-cortically the same spontaneous states continue to be generated in the absence of callosal input (Altavini et al., 2017).

In a series of EEG and imaging studies in animals and humans, Kiper et al. (1999) and Knyazeva et al. (1999, 2006) exploited the fact that previous work had shown CC connections between neurons responding to iso-oriented stimuli in the two hemispheres in the primary and secondary visual areas. To that end iso-oriented or orthogonally oriented gratings were presented simultaneously to the two hemifields (i.e., hemispheres) of the ferret, and the responses were compared to those obtained with stimuli presented separately to each hemifield or to an un-patterned whole screen (Kiper et al., 1999). Electrophysiological responses were recorded with epidural electrodes and analyzed with EEG coherence, which measures the phase synchronization of neural activity in the frequency domain. In contrast to fMRI-based functional connectivity, dominated by low-frequency (< 0.1 Hz) oscillations of BOLD signal (see 7.1), EEG coherence reflects synchronized fluctuations of excitability in distributed neuronal ensembles on a millisecond time scale. It was found that interhemispheric EEG coherence (ICoh) increased in the beta-gamma band only with bilateral iso-oriented stimuli and decreased by cutting the CC. In humans, ICoh between EEG signals from occipital electrodes increased with iso-oriented stimulus covering the two hemifields (Knyazeva et al., 1999). The same stimuli also increased the BOLD response proportionally to the increased ICoh (Fig. 9; Knyazeva et al., 2006). No acallosal patients were available for further studies, but the ICoh response was absent or decreased in patients with early lesions of the visual areas (Knyazeva and Innocenti,

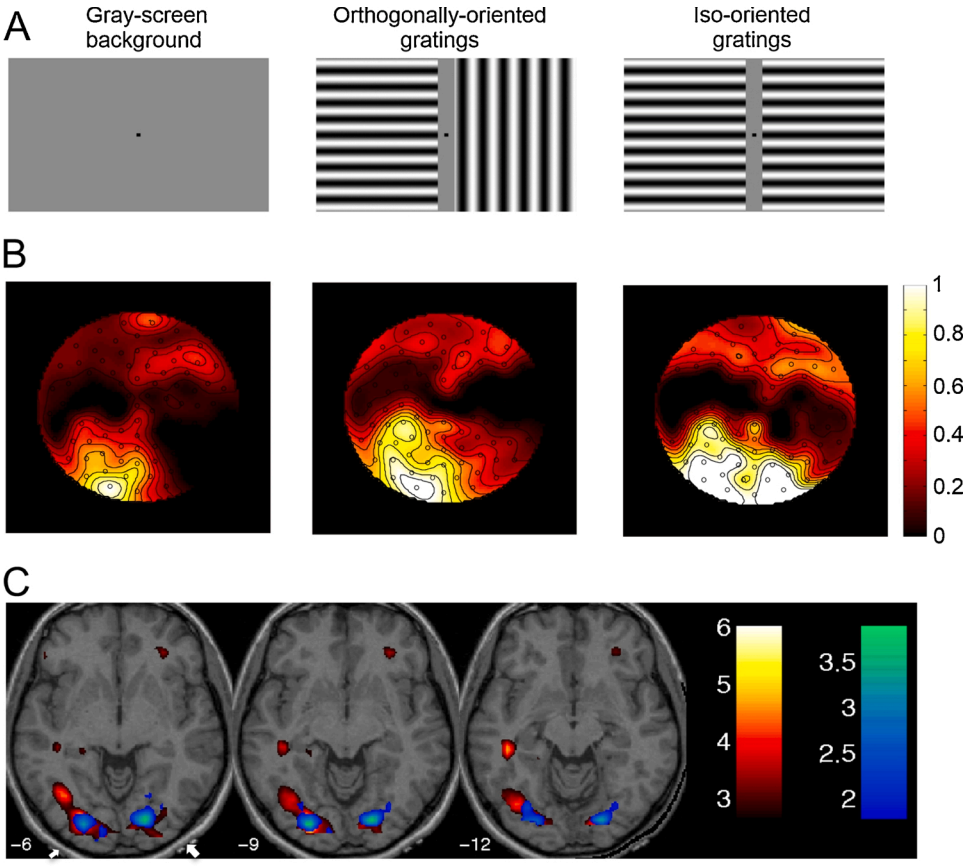

Fig. 9. Interhemispherically coherent neuronal assembly is formed in the human visual areas in response to collinear stimulus. A: Bilateral stimuli presented to subjects during EEG and fMRI recording sessions. B: Individual topographic maps of ICoh for peak response frequency in the EEG beta band under background condition (left) and stimulation with collinear (right) and orthogonal (middle) gratings. The color bar on the right shows the values of potential coherence. C: Correlation map (blue) between ICoh and BOLD responses to collinear gratings vs. background is co-localized with the BOLD contrast (red) as shown in transverse brain slices. The white arrows point to the EEG electrodes that showed increased ICoh. Color bars show T values for BOLD (hot scale) and for correlation (cold scale). Adapted from Knyazeva et al., 2006.

2001). In agreement with these results, Mima et al. (2001) observed a transient ICoh increase in the alpha band when familiar stimuli crossing the midline were recognized. Bland et al. (2020) reported increased gamma coherence between the hemispheres when moving stimuli were detected to cross the visual midline.

In synthesis, these results suggest that it might be possible to test specific cortico-cortical connections when appropriate stimuli are designed to activate the connected areas. Signals should be recorded preferentially with high temporal resolutions, for example using EEG. With this method, synchronization of activity could be identified not only with EEG coherence but also with other measurements (reviewed in Barzegaran and Knyazeva, 2017).

7.4. Behavioral effects on callosal architecture and communication

Perhaps the most exciting results from studies of interhemispheric interactions in humans are those suggesting that the engagement of callosal connections is conditional, depending on the difficulty and type of task adopted, age and other factors. Often these studies have used combined approaches, by linking the quantitative analysis of behavior to the structural and functional aspects of callosal transfer.

Höller-Wallscheid et al. (2017) and Belger and Banich (1992) found a reaction time advantage when complex stimuli were presented to both hemispheres but a disadvantage using simple stimuli. In the authors' interpretation, these results suggest that callosal transfer was uniform, automatic, and obligatory. When the task is easy, only one hemisphere can be involved to minimize the time costs of interhemispheric transfer. In contrast, when the task is difficult, sharing the load across hemispheres offers an advantage that outweighs the cost of callosal transmission. However, a different interpretation of these results is that different callosal connections, or their effects, are engaged with the two sets of stimuli.

Along a similar line, Stephan et al. (2007) used DCM and Bayesian model selections to show that the fusiform and lingual gyri of the two hemispheres, and presumably CC connections therefrom, were engaged in linguistic tasks in a lateralized manner, while parietal areas were symmetrically engaged in a spatial task.

Another study addressed the consequences of aging in the so-called "contralateral recruitment", that is the ability to activate cortical areas contralateral to the most active ones (Davis et al., 2012), while focusing on prefrontal cortex. The performance of older and younger adults was contrasted in a unilateral vs. bilateral lateralized word matching task. Interhemispheric communication was quantified in terms of greater accuracy for bilateral vs unilateral trials, an effect referred to as bilateral processing advantage (BPA). The results showed that older adults can distribute the neural processing necessary to meet the task demands across the hemispheres as a function of their white matter integrity. Furthermore, the recruitment of additional areas to face aging occurred thanks to the existing structural organization.

In a subsequent study, however, the additional recruitment of contralateral areas by interhemispheric transfer has been shown to be a general, rather than an age-dependent, strategy to face cognitive demands (Höller-Wallscheid et al., 2017). In this study, young and old subjects were brought to the limit of their verbal, spatial and object working memory (WM) capacity during fMRI scanning and the maintenance of WM signals across the hemispheres was compared to that of various lateralized task-relevant cortical regions. The results showed a bilateral processing in dorsolateral and anterior prefrontal areas on all working memory domains and age groups, while language-related areas of the cerebral cortex maintained a lateralized pattern of activation. Interestingly, this phenomenon was typical of prefrontal cortex, a region of the brain characterized by the flexibility, multiplicity and heterogeneity of functions encoded.

Finally, the way the two hemispheres interact to address increasing task difficulty was studied when subjects were requested to match the meaning of words, or the visual features of faces presented to the same (unilateral) or to different (bilateral) visual fields (Davis and Cabeza, 2015). Bilateral trials become faster as task difficulty increased, for both perceptual and semantic matching, showing a BPA. Whereas fractional anisotropy correlated with word-matching BPA in the genu of the CC, it correlated with face-matching BPA in the splenium-occipital sector of the commissure. The increase of task difficulty was also paralleled by increased interhemispheric functional connectivity in the frontopolar cortex, for both word and face matching, and by a decrease in temporal pole areas and in the fusiform gyrus for word matching and face matching, respectively. This study opens a window also on the processes underlying collaboration and segregation of neural operations between hemispheres.

In synthesis, these studies of the influence of task-dependency on the functional and structural architecture of the CC support a conditional and non-obligatory nature of callosal transfer, opening the avenue for the analysis of the callosal connections of higher-order association areas, where neural processes are typically conditional, context- and state-dependent (Mountcastle, 1978; Mountcastle et al., 1975).

8. Callosal connections of higher-order areas

Both callosal connections stemming from high-order association areas, such as prefrontal, posterior parietal and temporal cortex, as well as callosal connections from primary sensory areas project homo- and heterotopically. In association areas, however, callosal neurons are distributed over most of the tangential extent of the cortex and project to their target territories in a more diffuse fashion. Prototypical examples in macaque monkeys are the CC connections from superior (Caminiti et al., 1985; Caminiti and Sbriccoli, 1985; Johnson et al., 1989) and inferior (Andersen et al., 1985) parietal areas, as well as from prefrontal (Schwartz and Goldman-Rakic, 1984) and premotor (Marconi et al., 2003) cortex.

In humans, novel approaches combining microdissection and diffusion tractography have revealed a very complex 3-D structure of the frontal sector of the CC, where callosal fibers from higher-order frontal areas cross the midline, by clarifying its dorso-ventral organization, homotopic, heterotopic, and subcortical projections (De Benedictis et al., 2016). This study opens a new window for future detailed analysis of structural and functional aspects of the CC in humans. Despite this, the functional characterization of callosal connections of association areas is still at its birth, and their potential role can at the present moment only be predicted by imaging and spilt-brain studies and from the functional properties of callosal neurons in their areas of origin and termination. In the following paragraphs we provide some examples.

Very little is known about the function of prefrontal callosal connections, which form the rostral part of the rostrum of the CC. Surprisingly, patients with anterior callosotomy do not suffer of any deficit and do not show the symptoms typical of patients with complete commissurotomy (reviewed in Berlucchi, 2012) or with lesion of prefrontal areas. Patients with sections of the trunk of the CC show impaired inter-manual transfer of sensorimotor habits, a certain degree of inter-manual conflict (Wilson et al., 1977; Bogen, 1979), as well as an inability to perform complex bimanual tasks requiring independent sequencing of hand movements (Preilowski, 1975; Zaidel and Sperry, 1977).

The learning of new motor skills and their interhemispheric transfer depends on a distributed transcallosal network including dorsal premotor, motor, cingulate motor, somatosensory, and posterior parietal areas, as shown by an EEG study (Andres and Gerloff, 1999). While EEG ICoh is high when learning new sequences of finger movements, it decreases with practice, thus reflecting a time-dependent conditional driving role of the CC, necessary to face the high computational load required when learning novel tasks. Gerloff and Andres (2002) reported transient ICoh increases in the alpha and low beta bands during the acquisition of a bimanual task, which recruited different areas subserving the inter-manual coordination both before and after callosal

transection. Interestingly, split-brain patients are facilitated in performing tasks requiring simultaneous hand movements with conflicting directional information (Eliassen et al., 2000), suggesting that the CC participates in the interhemispheric transfer of hand movement direction. In both split-brain and callosal agenesis patients, difficulties have been observed in the absence of overt motor output, namely when coupling bimanual isometric forces (Diedrichsen et al., 2003). Split-brain patients also suffer from both temporal and spatial disorders during continuous bimanual movement (Kennerley et al., 2002). They are also unable to mimic with one hand, postures assumed or imposed to the other hand (Gazzaniga et al., 1967), suggesting that the CC might contribute to the unified representation of higher-order mental constructs, such as the body scheme (Battaglia-Mayer and Caminiti, 2019). For comprehensive reviews on the role of the CC in cognitive-motor behavior and its disorders in split-brain patients see Swinnen (2002) and Berlucchi (2012).

It must be stressed that caution is needed when comparing the results obtained from spilt-brain vs callosal agenesis studies. In the latter condition the absence of the CC from birth can promote the formation of anomalous white-matter pathways, such as those connecting the homotopic regions of the inferior parietal lobules (Brodmnann areas 39), via the anterior and posterior commissures (Tovar-Moll et al., 2014). This form of long-distance plasticity is probably responsible for the preservation of the interhemispheric transfer of tactile object recognition found in this study.

Neurophysiological studies in behaving monkeys (Kermadi et al., 2000) have suggested that intermanual coordination could be subserved by a distributed network based on neurons active during bimanual tasks in premotor, cingulate motor, primary motor, supplementary motor, and intraparietal areas. It is therefore plausible that CC connections from these areas play a role in such tasks, alone or in association with ipsilateral cortico-spinal projections. Future studies will have to address the functional properties of CPNs from these areas, to evaluate their role in bimanual coordination.

Concerning higher-order vision, reading evidently requires interhemispheric transfer of information. A fascinating example for a driving role of the CC comes from studies on the recognition of written words, showing that the interhemispheric integration of hemifield split words into a coherent orthographic representation occurs in the so-called "visual word form area" (VWFA; Strother et al., 2016, 2017) in the fusiform gyrus. This area is activated by string letters, equally, in both the right and left visual hemifields. Disruption of such integration leads to dyslexia (Henderson et al., 2007). The right-left responsiveness of the VWFA depends on callosal connections, since activation by stimuli presented in the left hemifield does not occur anymore in humans after posterior CC section (Dehaene and Cohen, 2011).

Another higher-order cognitive function requiring the CC is linguistic prosody, which is crucial for sentence comprehension (Sammler et al., 2010; Friederici, 2011), especially when facing ambiguous syntactic constructs, such as:

> *"the man said # the woman is stupid"* vs "*the man # said the woman # is stupid"*

The interpretation of this sentence (see Friederici, 2011) depends on the position of the prosodic boundary (#), indicating that intonational (pitch) prosodic information, mostly represented in the right hemisphere (Humphries et al., 2005), is necessary to disambiguate syntax, which is instead represented in the left dominant hemisphere. A dissociation of syntax from prosody occurs after lesion of the isthmus of the CC (Sammler et al., 2010; Friederici, 2011), where callosal fibers between areas related to language processing cross the midline (Innocenti et al., 2017). As a result, such patients cannot disambiguate the above sentence. Interestingly, lateralization of prosodic information to the right hemisphere is task-dependent (Perkins et al., 1996; Gandour et al., 2004), which also assigns a context-dependent conditional driving role to the CC.

In synthesis, callosal connections of association areas remain poorly understood, especially those between prefrontal areas. Available evidence indicates that those originating from fronto-parietal areas, therefore crossing the midline in the body, trunk, presplenial and part of the splenium of the CC, play an important role at least in the acquisition and transfer of sensory-motor habits, inter-manual coordination and linguistic functions. Split-brain studies in humans suggest that higher-order processing of visual information related to orthographic representations and to other aspects of language processing, such as prosodic information, are probably transferred through the isthmus and splenium of the CC. Overall, the above studies suggest that the callosal systems of association areas can have both driving and/or modulatory roles, depending on the task and brain state.

9. Conclusions and perspectives

Callosal connections between primary sensory areas do not appear to be functionally robust, for example when compared to thalamo-cortical axons (Tettoni et al., 1998), whose synaptic efficacy appears to be stronger. In addition to a conditional driving role, as described above, this observation also points to a modulatory and task-dependent role of callosal connections. Furthermore, the view of a complete separation of sensory information between the hemispheres has been modified. Both hemispheres in normal subjects receive visual and somatosensory input from the contralateral, as well as from the ipsilateral sensory periphery, although to a lesser extent. However, split-brain patients cannot integrate the sensory information across the hemispheres. They indeed fail to identify the same or different stimuli in opposite visual hemifields (Pinto et al., 2017; Corballis et al., 2018; de Haan et al., 2020) or tactile stimuli in opposite distal (Fabri et al., 2005, 2001) or proximal (de Haan et al., 2020) body parts.

These new findings seem compatible with an essentially modulatory or conditional driving role of callosal connections anticipated by Bianki and Shramm (1985) on evidence of a bilateral representation of body parts in cats.

Thus, the cortico-cortical axons, of which the callosal are one example, might be "conditional drivers" or "coactivators" i.e., they drive the targets conditionally on whether their input is coupled with some other input, notably from thalamus or other cortical areas. In support of this notion, a recent study in mice combining 3D calcium imaging in one hemisphere with optogenetic stimulation in the other, shows that spines receiving callosal input are closely co-localized with callosal neurons of the same orientation preference (Lee et al., 2019), directly demonstrating the intermingling of different circuits.

In this view, callosal axons can endow the whole circuitry with a high degree of flexibility. Axonal convergence and divergence, discussed in the section on axonal computation (Section 2.2. *iv*), are especially important in this respect. The role of callosal axons has both inhibitory and excitatory components. Together they seem to achieve selective signal enhancement (Wunderle et al., 2015). This may be akin to excitation with surrounding inhibition along sensory and motor pathways (Carson, 2020) and could be implemented by circuits with fast feed-forward inhibition coupled to convergent excitation.

These tentative conclusions prompt further considerations. First, the study of callosal connections between the primary sensory areas in animals and humans may not have provided information applicable to general callosal connectivity. Further studies will be necessary, targeting anatomical and functional connections of other areas, particularly higher-order association areas in behaving primates and possibly in humans. Moreover "conditional drivers" might become "drivers" or "modulators" under different circumstances, e.g., when the general excitability of the network changes. Second, callosal input might show variability and be stronger to some cortical neurons than to others. In the visual system, for example, neurons preferring midline crossing orientation or movement (i.e. preferring cardinal orientations) seem to

receive stronger influence (Schmidt et al., 2010; Peiker et al., 2013; Altavini et al., 2017, Fig. 7). The role of local callosal axon collaterals also needs to be fully evaluated. Inhibitory interneurons seem to be robustly activated by the CC input (e.g. Clarey et al., 1996; Makarov et al., 2008). As in preceding sections, available evidence suggests that cortico-descending pathways (to colliculus, thalamus, and possibly striatum) may be driven by CC input more strongly.

The notion that CC axons might have manifold roles is supported by the finding that during postnatal development juvenile CC fibers depend on thalamo-cortical input for their maintenance and stabilization (Innocenti, 1995; Innocenti and Price, 2005). Intra-areal axons also rely on thalamo-cortical input (Callaway and Katz, 1991; Zufferey et al., 1999), further stressing the generality of CC axons (Schmidt, 2016). Indeed, the CC is vulnerable to alterations in sensory inputs.

In rodents S1/S2, the disruption of callosal neurons associated to whisker ablation alters the normal formation of callosal connections (Suárez et al., 2014a), which require a balanced activity for correct fibers targeting, as also suggested by (Wang et al., 2007). Similar results were obtained after early partial lesions of somatosensory callosal recipient areas, such as S2, performed in kittens (Caminiti and Innocenti, 1981). Manipulations of visual inputs lead to re-arrangement of callosal projections in animals (Fig. 10; Innocenti et al., 1985; Schmidt et al., 1997; Milleret and Houzel, 2001; Ptito, 2003; Bui Quoc et al., 2011) and in humans (Ten Tusscher et al., 2018).

In humans, congenital blindness has proven to be an efficient model to study plasticity with MRI. In this condition, the splenium of the CC (Fig. 11**)** is altered or volumetrically reduced (Ptito et al., 2008; Bridge et al., 2009; Leporé et al., 2010; Tomaiuolo et al., 2014). More recently, Cavaliere et al. (2020) reported that in blind individuals, the reduction in volume of the splenium is accompanied by an increase in the volume of the posterior portion of the anterior commissure **(**Fig. 11**)**. This result is in agreement with older behavioral studies showing that if the CC is sectioned at birth in split-chiasm (SC) cats, interhemispheric transfer of visual information is still preserved and probably due to the enlargement of the anterior commissure (Ptito and Lepore, 1983). By the same token, Berlucchi et al. (1978) have shown a certain degree of plasticity in learning interocular transfer of visual discriminations in SC cats before callosal sections. In agreement with these data, interhemispheric connections between the primary visual cortical areas via the anterior commissure have been shown in humans with callosal agenesis while they are absent in normal conditions (van Meer et al., 2016; Torvar-Moll et al., 2014). Further progress on these issues should involve the characterization of the targets of cortico-cortical axons, the interplay between the various long projections and between long projections and the neuronal modules of intrinsic processing, as suggested by Liang et al. (2021).

Finally, the use of DW-MRI in evaluating connectivity should, in principle, provide functional information on specific cortical tracts, by pointing to deficits associated with white matter alterations. Possibly because of the distributed nature of cortical networks, it has proven difficult to relate specific deficits in physiological or neuropsychological functions to the white matter disturbances identified, although the latter seem to be, in a general way, involved in the deficits (Griffis et al., 2019; Meijer et al., 2020). Tighter connections between neuropsychiatric symptoms and the disruption of specific pathways might be found in the future, thanks to promising, inspiring results (Lyksborg et al., 2014; Huang et al., 2016; De Paepe et al., 2019). These questions need answering in order to model the function of brain circuitry in real time (e.g., Deslauriers-Gauthier et al., 2019; Stevner et al., 2019), one major goal of brain sciences.

Authors' contribution

Conception and design of the manuscript: GMI, RC.
Drafting of the paper: all authors.
Organization of the paper: GMI produced the first draft of the ms; RC and ABM made the final layout of into its different sections, based on all authors input.

Figures: Figs. 1, 2, 10, 11 have been redrawn and/or rearranged from their originals by ABM

Revising paper critically for important intellectual content: all authors

Final approval of the submitted version: all authors

We have reproduced with modifications and/or redrawn figures from:

Cerebral Cortex (Oxford University Press): Fig. 1 from Tettoni et al. (1998)

The European Journal of Neuroscience (Wiley): Fig. 4 from Innocenti et al. (1994), Fig. 5 from Fabri et al. (2006) and Fig. 10B from Innocenti et al. (1999).

Frontiers in Neuroscience: Fig. 3 from Barakovic et al. (2021).

Frontiers in System Neuroscience: Fig. 6A from Conde-Ocazionez et al. (2018a, b).

NeuroImage (Elsevier): Fig. 7 from Altavini et al. (2017), Fig. 8 from Rochefort et al. (2007), Fig. 9 from Knyazeva et al. (2006), Fig. 11B from

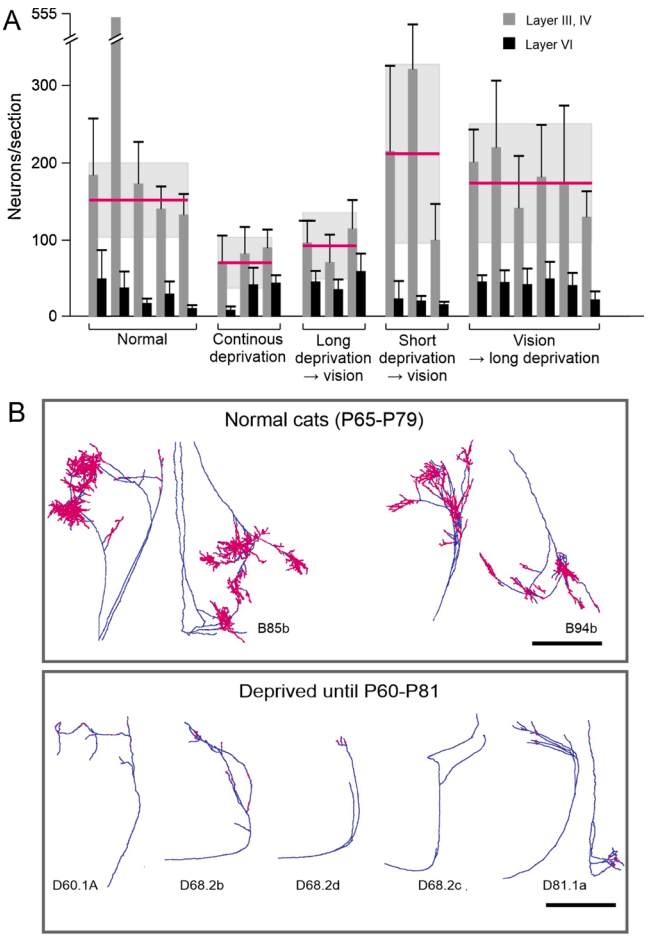

Fig. 10. Consequences of visual deprivation on the development of callosal connections. **A:** Histograms showing the mean number of HRP retrogradely-labeled callosal cells in areas 17 and 18 of individual cats grouped along the horizontal axis according to the rearing paradigm. The vertical bars indicate the number of labeled neurons per section; gray columns refer to supragranular- and back columns to infragranular neurons. Vertical lines represent 1SD per cat. Horizontal red lines indicate the mean number of labeled neurons and the grey areas the region of average 1SD across cats with the same rearing. Redrawn with modifications from Innocenti et al., 1985. **B.** Terminal arbors of callosal axons originating in areas 17 and 18 in normal cats (left) and in cats binocularly deprived of vision (right) until postnatal days P60 and P81. Redrawn with modifications from from Zufferey et al., 1999.

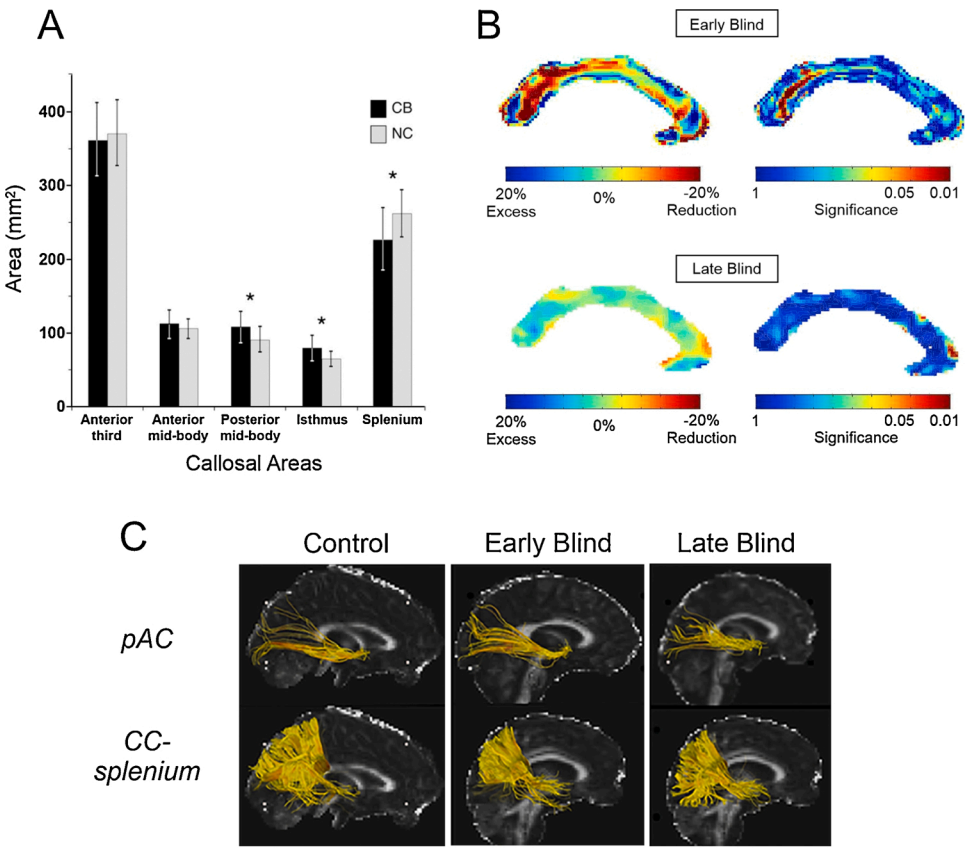

Fig. 11. A: Callosal sub-region areas in congenitally blind (CB) and normal sighted control (NC) human subjects. CB had a significant decrease in surface area of the splenium but a significant increase in the caudal part of the body and the isthmus. Reproduced with permission from Tomaiuolo et al., 2014. **B:** Percent reduction and excesses in cross-sectional area (left panels), and their significance (right panels), for the corpus callosum in the Early Blind (top), and Late Blind (bottom) groups. Human subjects with early-onset blindness show mean deficits (in cross-sectional area) of up to 20 percent, relative to controls, in the isthmus and splenium (A). Regional differences in the late-onset blind subjects, however, are not significant (**B** lower right panel) after multiple comparison correction: the global p-value, corrected, for the EB group difference is $p = 0.027$, while that for the LB is $p = 0.215$ (not significant): Reproduced with permission from Leporé et al., 2010. **C:** Tractography reconstructions for the posterior portion of the anterior commissure (pAC) and the splenium of the corpus callosum for a normal sighted control subject, an early blind, and a late blind subject. Note the significant increase in the number of streamlines in pAC for the early blind compared to control and late blind subject. Also note the significant reduction in the number of streamlines in the splenium of CC for EB and LB compared to SC. In both **B** and **C** rostral is to the right, caudal to the left. Reproduced with permission from Cavaliere et al., 2020.

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Leporé et al. (2010), and Fig. 11C from Cavaliere et al. (2020).

The Journal of Neuroscience (Society for Neuroscience): Fig. 2A-B from Caminiti et al. (2013), Fig. 6B from Peiker et al. (2013) and Fig. 10A from Innocenti et al. (1985).

PNAS (The National Academy of Sciences of the USA): Fig. 2C from Caminiti et al. (2009)

PLoS One: Fig. 11A from Tomaiuolo et al. (2014)

Declaration of Competing Interest

The authors declare no competing financial interests

Acknowledgments

We acknowledge the support of the Istituto Italiano di Tecnologia (to R Caminiti), FONDECYT project Nº1210659, Chilean fund for science and technology (to FX Aboitiz), Max Planck Society (to KE Schmidt), Natural Science and Engineering Research Council of Canada (to M Ptito), Ministry of the University and Research of Italy (PRIN 201794KEER_002 to A Battaglia-Mayer), Collège de France, CNRS and LUZ Optique & Audio (to C Milleret), European Research Council (Grant. n. 339939 to CA Marzi), the CaRiPaRo Foundation (to M Caleo), Canada Research Chair in Cognitive Neuroscience and Natural Sciences and Engineering Research Council of Canada (to F Lepore).

We are grateful to G. Berlucchi whose studies on callosal connections in animals and humans have powerfully motivated our own work, to K. Rockland for vigorous discussion on the manuscript, to R. Bufacchi, A. Koul, R. Somerveil, and A. M. Fitzpatrick (young researchers at the Neuroscience and Bahavior Laboratory, IIT, Rome) for their thoughtful comments to the final version of the ms. A special thanks to the many collaborators for their shared authorship in our papers. GMI was especially grateful to Jean-Philippe Thiran in whose laboratory at EPFL he enjoyed a late post-doctoral work supported by the grant SNF205320_175974.

Appendix A. The Peer Review Overview and Supplementary data

The Peer Review Overview and Supplementary data associated with this article can be found in the online version, at doi:https://doi.org/10.1016/j.pneurobio.2021.102186.

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