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Brain functional connectivity in individuals with callosotomy and agenesis of the corpus callosum: a systematic review

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Abstract

In the absence of the corpus callosum due to either surgical transection or congenital agenesis, the interhemispheric exchange of information is disrupted, as emphasized by several clinical studies. In such cases, a reduction of interhemispheric functional connectivity, that is, an increased independence of the functional signals of the two disconnected hemispheres, is expected to occur. A growing literature has investigated this hypothesis, and a number of studies were able to confirm it. However, this increased independence is not always observed, especially in congenital agenesis, in which the functional signals of the two hemispheres are often found to be characterized by synchronization or correlation. The extent of these counterintuitive findings and possible explanations are discussed. Overall, these findings highlight both methodological and theoretical considerations that emphasize the importance of subcortical structures, the preservation of which may underlie alternative pathways of functional connectivity and interhemispheric communication.

Keywords: Split-brain; Corpus callosum agenesis; Commissures; Anterior commissure; Functional connectivity; Interhemispheric connectivity; Homotopic connectivity.

1.1 Introduction

In recent years a growing interest in interhemispheric functional connectivity (ihFC) in acallosal patients has emerged in the scientific community. First investigated during the 1990s by means of coherence in electroencephalography (EEG) signals, from the first decade of the new millennium several functional magnetic resonance imaging (fMRI) studies have attempted to shed light on this topic. However, discordant results have emerged from this literature.

The corpus callosum (CC) is the major white matter pathway of communication between the cerebral hemispheres. As such, studying the cases of its absence might be very useful for understanding the interhemispheric organization of the brain. While many behavioural studies have been conducted on interhemispheric transfer (IHT) of information in patients without a CC, the study of connectivity of acallosal brains can provide useful insights into how the two hemispheres communicate with each other and coordinate their functions. Brain connectivity can be studied by analyzing its structure (structural connectivity) or the statistical dependence between functional imaging signals (functional connectivity, FC). FC techniques are reliable tools that allow specification of brain networks (Buckner et al., 2013; Fox and Raichle, 2007; Greicius et al., 2003) and provide complementary findings to studies of structural connectivity. For instance, although functional networks are typically similar to the ones reconstructed by observing white matter tracts, they often exceed structural connectivity patterns (Adachi et al., 2012; Damoiseaux and Greicius, 2009). Furthermore, FC can be positive as well as negative (Fox et al., 2005), thus producing additional information about brain connectivity.

Given the importance of the CC in connecting the hemispheres, one might expect an impairment of ihFC in its absence, but this is not always the case, especially when the lack of a CC is congenital. In fact, congenital agenesis of the CC permits developmental adaptive reorganizations (Paul, 2011; Paul et al., 2007); therefore, it is not surprising that individuals without a CC from birth frequently exhibit less severe symptoms of disconnection syndrome compared with patients that underwent surgical transection of the CC during life (Brown et al., 2001; Chiarello, 1980; Jeeves et al., 1988). In spite of this, however, reports of these cases produce a picture characterized by inconsistencies, as they describe clear examples of FC asymmetries as well as no sign of functional disruption in patients with congenital agenesis (Paul and Tyszka, 2012).

The interplay of functional lateralization and hemispheric interaction, based on the interhemispheric segregation/integration dynamics (Gotts et al., 2013; Ringo at al., 1994), is a relevant feature of the human cerebral organization, and is likely to be implemented by the CC. Thus, understanding the impact of the absence of this structure over the architecture of the central nervous system is of great importance, and in this regard FC studies could provide significant insights. In particular, the discordant findings of ihFC research on the acallosal brain open an interesting scientific question. What degree of FC can be maintained across hemispheres when the major commissural path of the brain is absent? Does the extent of the functional disruption reflect the proportions of the anatomical impairment? Can the extant commissures compensate in part for the absence of the CC? Thus far, studies have given mixed answers to these questions.

This review aims to present the literature on ihFC in the absence of the CC, reconciling conflicting results in light of methodological considerations and theoretical models of subcortical connectivity. Specifically, the question of whether or not the absence of the CC should produce ihFC deficits will be addressed. It is worth noting that a clear dichotomy between reduced and intact ihFC could oversimplify the matter, as a certain degree of regional variability in ihFC impairments is often observed, especially in cases of callosal agenesis. First, we discuss commissural and callosal structural connectivity in the human brain and summarize cases of surgical and congenital acallosal brains. Subsequently, we examine the nature of the FC, its relationship with structural connectivity, and its symmetry. We then review studies investigating ihFC in the acallosal brain and, eventually, put forward an interpretation of the current literature, highlighting the role of alternative anatomical pathways of interhemispheric communication. In order to do so, a systematic review of the literature was made according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocol (PRISMA-P, Moher et al., 2015; Shamseer et al., 2015).

1.2 Methods

We conducted a search on PubMed database in order to identify the studies to be reviewed. We used the two following queries:

i) ((*split-brain*) OR *callosotomy*) AND *functional connectivity*

ii) (*agenesis*) AND (*corpus callosum*) AND (*functional connectivity*)

The first query produced 58 results, and the second retrieved 47 studies. Those papers were examined by the authors to ensure that they were original studies published in English n peer-reviewed journals, and that they were relevant for the topic. Pathologic lesion to the CC, or its surgical resection due to the removal of a tumour or other pathologies were used as exclusion criteria for the first query. Similarly, studies about pathologies associated with callosal agenesis or dysgenesis were excluded from the results of the second query. However, as it is very rare that callosal agenesis occurs without comorbidities, we did not excluded those studies in which the main focus was the callosal agenesis even if the patient had another primary diagnosis. Considered the scarcity of studies about acallosal patients, both group and single-subject studies were included. Following this stage of selection, 45 papers were excluded from the first query, and 36 from the second. A paper was found by both the queries. Consequently, 23 studies, of which 5 were on animal models, were maintained and discussed. Furthermore, an independent search was conducted by another author. Starting from a pool of studies known to the authors, a cross-citation strategy produced a second group of retrieved papers, which were selected with the same rules of exclusion of the PubMed search. Moreover, the reference list of all the retrieved papers was examined to include those researches that were not found with the PubMed queries. This resulted in 31 studies, of which 6 were on animals. The systematic and the cross-citation searches were highly overlapping, with the exception of some earlier EEG studies that were not retrieved by the PubMed query, and just a recent fMRI study.

The result of this selection constitutes the bibliographical basis for the section 3 of the present review. Section 2, which serves a general an introduction, is not based on the procedure previously exposed. Of note, all the studies conducted on non-human animals were discussed in section 2 (for more details on the selection procedure, see Fig. 1).

PLEASE INSERT FIGURE 1 HERE

2.1. The corpus callosum

The CC consists of approximately 200 million fibres (Aboitiz et al., 1992; Tomasch, 1954), making it the major bundle of white mater fibres connecting one hemisphere with the other and, consequently, the most important interhemispheric commissure of the human brain. Although it principally connects cortical areas, it also interconnects subcortical nuclei to the cortex (Huang et al., 2005). The CC is only present in placental mammals, which suggests that its phylogenetic appearance may be the result of a relatively sudden evolutionary jump (Aboitiz and Montiel, 2003). The other telencephalic commissures are the anterior commissure (AC) and the hippocampal commissure (Raybaud, 2010). Minor subcortical commissures are the habenular, the tectal, the collicular, and the posterior commissure (PC) (Aralasmak et al., 2006). Figure 2 shows the anatomy of the cerebral commissures.

PLEASE INSERT FIGURE 2 HERE

Commissural connections are more likely homotopic than heterotopic, that is, they have more projections connecting bilateral homologous areas rather than non-homologous regions (Raybaud, 2010). This is particularly evident in the CC (Hedreen and Yin, 1981; Jarbo et al., 2012), which can be segmented into different portions serving as commissural pathways for the cortical lobes (Fig. 2) (Abe et al., 2004; Hofer et al., 2008; Hofer and Frahm, 2006). Heterotopic connections link a specific brain region with different areas of the opposite hemisphere, which are a subset of the contralateral counterpart of ipsilateral associative connections of that region (Hedreen and Yin, 1981). In other words, if an area such as the left dorsolateral prefrontal cortex is connected with the left parietal cortex, it might also be connected with the right parietal cortex (for an illustration of this concept, see Fig. 2, top panel).

The fibres of the CC are known to have diverse diameters in different sites. Anterior regions connecting prefrontal areas and mid-posterior regions connecting temporal and parietal cortices are characterized by thinner fibres. Larger fibres are instead found in the central section, which is comprised of axons of motor and somatosensory areas, and in the most posterior portion, which is comprised of occipital fibres (Aboitiz et al., 1992; Caminiti et al., 2013; Hofer et al., 2015; Horowitz et al., 2015). It is well established that there is a relationship between axonal diameter and fibres' conduction time, with bigger fibres having faster conduction times (Gasser and Grundfest, 1939; Hursh, 1939; Ritchie, 1982). IHT times, therefore, can vary according to callosal fibres' diameter (Horowitz et al., 2015), such that the interhemispheric connections of sensory and motor areas are thought to be faster than those of associative regions. This might have functional implications, as fast IHT is thought to be necessary for the fusion of the two sensory and motor spatial hemirepresentations. Transfer delays produced by slow fibres of integrative cortices are thought to promote interhemispheric computational independence and, consequently, functional lateralization (Aboitiz et al., 2003; Aboitiz and Montiel, 2003; Ringo et al., 1994).

The exact function of the CC has long been debated. The excitatory model, proposed by Sperry in 1962 (Bloom and Hynd, 2005), posits that the CC plays an excitatory role by implementing the transfer of information between hemispheres. Many observations have supported this model: for instance, the evidence that most callosal fibres are glutamatergic (glutamate is an excitatory neurotransmitter) (Conti and Manzoni, 1994) and that callosotomy is effective in preventing the propagation of seizures across hemispheres (Devinsky and Laff, 2003). However, callosotomy can prevent not only the propagation of seizures, but also their inhibition (Roberts, 1999). This provides support for the theory of homotopic inhibition, first outlined by Cook (1984), according to which the CC allows one hemisphere to inhibit the activity of the other through the activation of inhibitory interneurons (Kawaguchi, 1992; Toyama et al., 1969). This mechanism is also thought to underlie functional lateralization.

Evidence for inhibitory function comes from the right ear advantage (REA) observed in dichotic listening, where a subject who is simultaneously exposed to different stimuli in each ear is more likely to report the stimulus presented to the right ear. The REA is reduced in patients with congenital agenesis of CC (AgCC) (Fischer et al., 1992; Lassonde et al., 1981) and with other CC alterations (Westerhausen and Hugdahl, 2008). A possible explanation for this phenomenon is that the CC may convey inhibitory signals for the activity of the right auditory cortex, so that this cannot interfere with the activity of the left auditory cortex. When the CC is damaged, this inhibitory effect would be absent and the REA diminished.

Surprisingly, however, the REA is reported by some authors to be enhanced in callosotomized patients (Clarke et al., 1993; Westerhausen and Hugdahl, 2008). As a consequence, Yazgan and colleagues (1995) interpreted the REA, pseudo-neglect, and turning bias as signs of hemispheric lateralization. They considered the inverse correlation of these phenomena with the dimension of the CC to support the excitatory model, which considers lateralization as a reduction of interhemispheric communication (Yazgan et al., 1995). Furthermore, right ear accuracy during dichotic listening is reported to be reduced in normal individuals with enlarged CC, possibly as a consequence of an increased interference (excitatory model) or inhibition (inhibitory model) of the right hemisphere over the activity of the left hemisphere (Clarke et al., 1993).

As both the excitatory and inhibitory models are supported by empirical observations, it is likely that the CC can carry out both functions of integration and segregation through excitatory and inhibitory synapses, depending on the actual task and cognitive load (Bloom and Hynd, 2005). Indeed, Bloom and Hynd (2005) have suggested that the CC could be seen not as a passive channel of information, but as a structure engaged actively in the execution of tasks.

The cases in which the CC is absent (i.e., surgical callosotomy and AgCC) have undoubtedly contributed to providing insights into its functions. It should be noted, however, that both callosotomized patients and individuals with AgCC cannot be simply considered as "normal" subjects without CC, as callosotomy is performed only on patients with severe forms of epilepsy, and commissural agenesis may be accompanied by many additional anatomical brain alterations, such as cysts, lipomas, and colpocephaly (i.e., an abnormal enlargement of the occipital horns of the lateral ventricles) (Hetts et al., 2006; Paul et al., 2007). Thus, even though these conditions provide useful insights into the role of CC in interhemispheric connectivity, considerations based on comparisons between these patients and normal controls should be taken with caution.

2.2. Callosotomy

The surgical transection of the CC is a procedure used in pharmacologically untreatable cases of epilepsy. The procedure consists of the total or partial incision of the CC with the purpose of isolating the two hemispheres to reduce the frequency of generalized seizures (Devinsky and Laff, 2003; Tanriverdi et al., 2009). When the transection is partial, the operation typically involves the anterior one-half or the anterior two-thirds of the CC (Tanriverdi et al., 2009). Sometimes, posterior sections are also performed (Paglioli et al., 2016). When all the major commissures (including the CC, AC and hippocampal commissure) are severed, the surgery is known as commissurotomy.

The first human callosotomies were performed by van Wagenen and Herren (1940). However, this procedure became popular only after Bogen and Vogel reintroduced it in the 1960s (Gazzaniga, 2005). In the so-called "split-brain" patients, the propagation of seizures was confined to the hemisphere of their inception, thus alleviating epileptic symptoms without producing severe neurological deficits (Sperry, 1984). Especially in the post-surgical phase, signs of functional disconnection of the hemispheres were detected (Gazzaniga, 2005, 1995; van Wagenen, 1940), as it was already highlighted by the early experiments with cats (Myers, 1956; Myers and Sperry, 1958). For instance, words presented to the left of the point of fixation could not be named after complete callosotomy (Gazzaniga et al., 1962; Sidtis et al., 1981). This impairment is explained by a lack of interhemispheric transfer. Information presented only to the left perceptual hemifield is processed initially by the right hemisphere and, without the transfer through the CC, is unavailable to the left hemisphere, which is the one capable of speech in most individuals. Moreover, split-brain patients claim that they have no knowledge of the test performed correctly by the right hemisphere, supporting the hypothesis that the speech areas of the left hemisphere do not have access to the activity of the other hemisphere (Gazzaniga et al., 1962; Sperry, 1982, 1968).

In general, visual and somatosensory perception of the two hemifields and control of the distal limbs in split-brain patients appear to be segregated in each contralateral hemisphere, with few signs of cross-integration (Gazzaniga et al., 1963, 1962, Sperry, 1984, 1968). Therefore, disconnection syndrome has allowed the study of the functions and abilities of each hemisphere independently of the other, providing further evidence for the left brain dominance for language and the right brain dominance for visuo-spatial skills (Gazzaniga, 1995). Split-brain patients also exhibit abnormally long IHT times (Aglioti et al., 1993; Clarke and Zaidel, 1989; Forster and Corballis, 1998; Sergent and Myers, 1985), a finding that is consistent with the idea that the CC is the major interhemispheric route of information transmission.

2.3. Agenesis of the corpus callosum

Cases of AgCC are frequently associated with the agenesis or dysgenesis of the other forebrain commissures and with generalized white matter alterations (Raybaud, 2010). In classical commissural agenesis, the commissural fibres are usually not entirely agenetic; in fact, most of the axons are generated but unable to cross the midline and form aberrant ipsilateral antero-posterior bundles called 'bundles of Probst' (Chiarello, 1980; Hetts et al., 2006; Rakic and Yakovlevi, 1968; Raybaud, 2010; Tovar-Moll et al., 2007). Interestingly, AgCC is often associated with various nervous and non-nervous anomalies (ranging from malformations of cortical development to cranio-facial abnormalities), as well as with a large variability in the performance of cognitive functions (Badeschi et al., 2006). The aetiology of AgCC likely involves a combination of different genetic, and possibly environmental, mechanisms, which differentially impair specific phases of callosal ontogenesis (Paul, 2011; Paul et al., 2007). Genetic factors related to AgCC seem to involve complex and variable mixtures of sporadic mutations. However, a genetic cause cannot always be identified. Between the environmental factors, data indicate that alcohol exposure of the foetus could produce malformations during the development of the CC (for an extensive review on this matter, see Paul, 2011). The severity of the pathology is likely to reflect the embryonic developmental stage at which the impairment occurs. Before the 10th week of gestation, the agenesis affects all forebrain commissures. Between the 10th and the 11th weeks, the AC may be spared but the other commissures may not. This is the most commonly observed type of AgCC. Right after the 11th week, both the AC and hippocampal commissure can be preserved but not the CC. This is, however, a rare form of AgCC. If lesions occur much later, only a partial agenesis of CC is produced (Chiarello, 1980). Figure 3 illustrates a case of callosal agenesis accompanied by an estimate of the frequency of the associated anomalies.

PLEASE INSERT FIGURE 3 HERE

The IHT times are found to be slower in individuals with AgCC than in normal controls, but faster than in split-brain patients (Aglioti et al., 1993; Forster and Corballis, 1998). Interestingly, even a complete AgCC does not result in the classic disconnection syndrome characterized by the same severity as that observed in split-brain patients (Brown et al., 2001, 1999; Chiarello, 1980; Jeeves and Silver, 1988; Sauerwein and Lassonde, 1983). Rather, social impairments (Badaruddin et al., 2007; Brown and Paul, 2000; Lábadi and Beke, 2017; Lau et al., 2013; Paul, 2004), deficits in pragmatic linguistic functions (Brown et al., 2005; Brown and Paul, 2000; Paul et al., 2003) and problem solving (Brown and Paul, 2000) are frequently observed in individuals whose primary condition is AgCC. These impairments are shared by patients with autism and schizophrenia, who sometimes are also affected by callosal agenesis (Paul et al., 2007).

The relative integration between hemispheres exhibited by individuals with AgCC compared with split-brain patients appears to reflect some form of neuronal plasticity that is likely to take place during development (Paul, 2011; Paul et al., 2007; Tovar-Moll et al., 2014, 2007). Indeed, visual cortices of individuals with AgCC reveal normal IHT measured with visual evoked potentials (Rugg et al., 1985). Moreover, IHT in individuals with AgCC measured with behavioural tests was found to show more subtle deficits than what has been observed in split-brain patients, though IHT was impaired with respect to healthy control subjects (Lassonde, 1995). Correct but slowed visual (Lassonde et al., 1981; Sauerwein and Lassonde, 1983) motor (Jeeves, 1969) and executive (Marco et al., 2012) processing, abnormal left ear advantage in dichotic presentation (Fischer et al., 1992; Lassonde et al., 1981), and overall performance drop in more difficult tasks (Brown et al., 1999) have been observed in AgCC. These results have been interpreted by some authors as an incapability of an alternative path of IHT to support complex patterns of cross-integration (Brown et al., 1999; Paul et al., 2003, Symington et al., 2010). This may account for impairments in processing higher-order computations required by novelty and demanding cognitive tasks, or social and pragmatic interpretations of language and behaviour in individuals for whom AgCC is the primary neuroanatomic finding and cognitive functioning is not globally impaired (Brown et al., 1999; Paul, 2011; Paul et al., 2007; Symington et al., 2010).

2.4. Functional connectivity and interhemispheric networks

Studies of white matter tracts are valuable investigations for assessing structural connectivity, which describes how brain regions are physically connected by axons at a macroscopic scale (Honey et al., 2010). However, as stated by Friston (2011): "structural connectivity per se is neither a sufficient nor a complete description of connectivity". Thus, the study of split-brain patients and individuals with AgCC should not focus only on their anatomical features. A complementary measure is FC, which is defined as a statistical dependence, often measured as temporal correlation, between neurophysiological signals extracted from different areas (Friston, 2011; Friston et al., 1993). The FC provides a measure of synchronization of signals recorded from distant parts of the brain. Early measures of FC were computed on direct electrical recordings (Gerstein and Perkel, 1969), but the same principle can be applied to EEG or to other neuroimaging techniques.

Biswal and colleagues (Biswal et al., 1995) were the first to apply this concept to fMRI data with a voxel-by-voxel comparison, showing that correlations between low frequency fluctuations in BOLD signals detected in motor cortex could be used to highlight a set of areas similar to that activated during a motor task. The quantitative symmetry of this network was also explicitly assessed by observing that in each hemisphere the number of voxels connected to a unilateral seed was statistically non-different. Since this pioneering work, connectivity in fMRI has often been measured during the so-called resting state (resting state FC, rsFC) (Buckner and Vincent, 2007; Gusnard and Raichle, 2001; Kelly et al., 2012). Covariance or statistical dependence of BOLD oscillation can reveal the intrinsic organization of the human brain in a set of networks that are relatively stable in time, similar across subjects and not so different from rest to task (Bolt et al., 2018; Cole et al., 2014; Fox et al., 2005; Fox and Raichle, 2007; Smith et al., 2009; Yeo et al., 2011). The FC is often considered an efficient method for studying how the functional connectome is organized. These studies allowed the examination of the functional architecture of networks related to both spontaneous and evoked brain activity (Buckner et al., 2013; Di et al., 2014; Goparaju et al., 2014; Sepulcre et al., 2010).

If we consider the pervasive relationship between structure and function that is found in any biological system, according to which the structure contemporarily constrains and defines function, it would be reasonable to expect that structural connectivity would shape FC. However, the latter is not entirely predictable on the basis of the former (Honey et al., 2010; Uddin, 2013). Although rsFC is known to largely reflect patterns of structural connectivity (Garcés et al., 2016; Greicius et al., 2009; Honey et al., 2009; Meier et al., 2016; Skudlarski et al., 2008; van den Heuvel et al., 2009), it is also usually found to exceed it (Damoiseaux and Greicius, 2009; Honey et al., 2009; Koch et al., 2002). In other words, the presence of a structural link is predictive of FC, but strong FC could still be detected between what appear to be structurally unconnected regions. Therefore, both structural and functional connectivity should be considered as complementary approaches to investigate the human connectome at a large-scale level. For instance, while structural connectivity between two regions could be either present or absent, FC too could be present but with a negative value (Fox et al., 2005). Although the effect of negative correlation is significantly influenced by the pre-processing choice for global signal regression (Murphy et al., 2009) – which is still a matter of debate (Chai et al., 2012; Chang and Glover, 2009; Fox et al., 2009; Liu et al., 2017; Saad et al., 2012; Van Dijk et al., 2010; Weissenbacher et al., 2009), casting doubts about its validity (Anderson et al., 2011) –, this negative correlation has been proposed to be associated with an intrinsic brain organization in which networks with opposite functions reveal anti-correlated signals (Fox et al., 2005; Hampson et al., 2010; Uddin et al., 2009). Gee and colleagues (2011) observed that, after comparing intrahemispheric associative connections with their corresponding heterotopic interhemispheric connections, the intrahemispheric FC had more positive correlation values than heterotopic ihFC, while the heterotopic ihFC was more characterized by negative correlations than analogous associative pathways. These findings lead to interesting speculations about the function of anatomical connections, such as possible differential functions of associative and callosal homotopic and heterotopic axonal pathways with respect to integration and segregation (Gee et al., 2011). Investigations of FC, therefore, provide useful insights into the organization of brain networks that cannot be obtained from studies of structural connectivity alone.

A remarkable feature of rsFC is that it reveals strong correlations between homotopic areas (Lowe et al., 1998; Mancuso et al., 2019; Medvedev, 2014; Salvador et al., 2005b, 2005a;

Stark et al., 2008), as well as symmetry in somatotopic organization (Cauda et al., 2011). The values of functional homotopic connectivity (HC) (i.e., the connectivity between mirror voxels) vary from region to region, with a distribution that is similar to that of the diameter of the CC fibres. Primary sensorimotor cortices, which are associated with large and fast callosal fibres, present higher HC, while associative cortices, which are characterized by small and slow axons, have relatively low HC (Stark et al., 2008). This reflects the relationship between FC and anatomical features of white matter tracts: faster conduction fibres are likely to produce tighter synchronization of neurophysiological signals (Aboitiz and Montiel, 2003). Nonetheless, every region of the brain exhibits the strongest FC with its homotopic area (Stark et al., 2008). Furthermore, HC has been observed to be stable in time and between rest and task conditions (Shen et al., 2015), suggesting that this kind of connectivity might have a central role in brain organization.

Functional networks, assessed with the technique of independent component analysis (ICA), are usually bilateral and symmetric (Beckmann et al., 2005; Damoiseaux et al., 2006; Doucet et al., 2011; Van De Ven et al., 2004). This symmetry is likely mediated by brain commissures, and especially by the CC, which is the major one. It has been observed in patients suffering from migraine that the structural fractional anisotropy (FA) of the anterior sections of the CC is correlated with the FC between the bilateral anterior cingulate cortices (Yuan et al., 2012). Split-brain patients and individuals with AgCC were studied in order to observe rsFC changes in the most typical cases of absence of the CC using EEG, magneto-encephalography (MEG) and fMRI. Despite the fact that the deficits of individuals with acallosal brains were observed during task, the relative similarity of FC between rest and task and the stability of HC between these conditions justified the choice of studying their intrinsic functional organization at rest. The hypothesis was that, in absence of a direct structural link, interhemispheric FC would be impaired. However, although most of these studies report reduced ihFC in split-brain patients and in individuals with AgCC, results have not been completely consistent.

Reductions of IhFC can be observed as the decrease in the indices of temporal coherence between electrodes placed in the two hemispheres, or the diminution of the number of the voxels found to be connected to a contralateral seed, or in the asymmetry of some independent components assessed with ICA. Animal studies have suggested the presence of such reductions in the split-brain and AgCC. In the cat, callosotomy was observed to abolish synchrony in the neuronal discharge between bilateral visual cortices (Engel et al., 1991). Global reduction of ihFC after complete callosotomy was reported in rats by two studies that used fMRI and EEG techniques (Magnuson et al., 2013; Zhou et al., 2014). In rats, the negative effect of partial callosotomy on ihFC was shown to be less intense and, after 28 days, completely recovered using fMRI ICA, but, interestingly, still partly impaired with EEG in delta band (Zhou et al., 2014). Increases of ipsilateral FC were also found in rats (Zhou et al., 2014) and monkeys (O'Reilly et al., 2013), suggesting that intra- and interhemispheric connectivity are not entirely independent of each other. O'Reilly and colleagues (2013) also showed that sparing the AC from the commissurotomy allows preserved IhFC. Electrophysiological evidence of impairment of ihFC in callosal agenesis was provided by a study conducted on B1 mice, a strain with high incidence of callosal dysgenesis. These mice showed a reduction of interhemispheric coherence (ICoh) that was dependent on the degree of callosal malformation: synchrony was weaker in total agenesis than in partial agenesis, in which, in turn, it was lower than in control mice (Vyazovskiy et al., 2004). A BTBR T+Itpr3tf/J mice study (Sforazzini et al., 2016) reported reduced frontal ihFC, along with a genetically induced absence of the CC. The same group (Vega-Pons et al., 2017) also showed that the IhFC impairments of this strain are less intense than those of the structural interhemispheric connectivity, pointing out that the FC seems to be somehow partly resilient to structural anomalies, and confirming that the two measures are related but also disjointed (Uddin, 2013). However, as BTBR mice are a socially impaired line considered to be an idiopathic model of autism spectrum disorder, we cannot be certain whether or not the observed FC alterations were only correlated with the lack of a CC. Although these studies suggest that the absence of CC might induce ihFC impairments, some human research has confirmed this prediction, but other investigations produced more discrepant findings.

3.1. Reduction of interhemispheric functional connectivity in split-brain patients

Early research on ihFC in humans (i.e., callosotomized patients) was conducted with EEG (Montplaisir et al., 1990). Two subjects were polygraphically recorded two weeks before and one week and six months after surgery, revealing a reduction in EEG ICoh in most frequency bands after the operation. One patient, who underwent a partial posterior callosotomy showed decreased ICoh only in the posterior portion of the brain, while the other, whose CC anterior section was much larger, presented a wider disruption of correlation across the brain. Subsequent EEG studies confirmed this generalized drop of ICoh after callosotomy (Brázdil et al., 1997; Matsuzaka et al., 1993). The importance of the extent of the transection has been highlighted in a study by Okumura and colleagues (2013). These authors compared EEG recordings associated with different steps of multi-stage total callosotomy and found a significantly lower ICoh in theta and alpha bands in all subjects after the final stage was executed; however, in some patients the first stages of partial anterior callosotomy produced little or no effects on the signal. A further confirmation of the reduction of reduced synchrony between hemispheres comes from an intracranial electrocorticography (ECoG) study (Rojas-Ramos at al., 2013), that observed diminished positive and negative connectivity in three individuals subjected to anterior callosotomy. In summary, all the electrophysiological studies presented above reported a severe drop of ihFC after callosotomy, strongly confirming the hypothesis of a major role of the CC in sustaining interhemispheric synchronization of neuronal activity. Unfortunately, these findings provided few details regarding the spatial variability of ihFC deficits, as they were limited by the poor spatial resolution of EEG.

With regard to fMRI research, Johnston and colleagues (2008) compared rsFC of a boy before and directly after a complete callosotomy, observing a marked reduction of ihFC after the operation. As fMRI is characterized by higher spatial resolution than EEG, the authors used predefined regions-of-interest (ROIs) corresponding to different network nodes and reported a strong reduction of both positive and negative correlations between the seeds and contralateral areas (for a graphical representation of their map of sensorimotor seeds, see Fig. 4). Although ihFC was generally reduced throughout the cortex, it also displayed regional variance. The seed placed in the motor area of the hand revealed a relative conservation of contralateral FC, probably because this region is more connected via thalamocortical connections than through the CC, as suggested by comparative anatomy (Killackey et al., 1983; Pappas and Strick, 1981) and by a study of human infants (Toulmin et al., 2015). In fact, Johnston and colleagues reported that the ihFC reduction between left and right thalamus was less severe compared with that of the cortices. Similar results of preserved connectivity were seen for seeds in the medial temporal lobe, and are probably explained by the known role of the AC in temporal connectivity (Di Virgilio et al., 1999; Patel et al., 2010). This first study of resting state fMRI data collected from a split-brain patient highlighted the importance of the CC for sustaining ihFC, but also suggested that other neuronal pathways could to some extent preserve FC. By using several seeds centred in the nodes of canonical functional networks, the same group (Pizoli et al., 2011) studied another patient who, after a partial callosotomy, showed a recognizable lack of interhemispheric and homotopic FC (Fig. 4). However, it should be noted that in this case comparisons with pre-surgical recordings could not lead to clear conclusions because of the extremely abnormal pre-operation connectivity of that individual.

PLEASE INSERT FIGURE 4 HERE

Further evidence of IhFC reduction derives from two patients subjected to anterior callosotomy and investigated with fMRI, ECoG and corticocortical evoked potentials (Lehner et al., 2018). Unfortunately, the focus of this study was not IhFC but the validation of an innovative procedure of laser callosotomy; a more detailed analysis of their FC data is still to be published.

Roland and colleagues (2017) analyzed the rsFC of 7 canonical networks in 22 callosotomy pediatric patients using voxel-wise and ROI-to-ROI techniques, before and one day after complete or partial callosotomy (16 complete, 6 partial). Similar to what was observed in rats and monkeys (O'Reilly et al., 2013; Zhou et al., 2014), the operation produced a significant global reduction in ihFC and a significant increase of intrahemispheric FC. Moreover, 3 patients were further examined: 2 in a two-year follow-up and 1 in a seven-year follow-up; none of them showed any sign of recovery of FC. These results presented some degree of regional variability, as HC appeared to be completely lost in multimodal frontal and parietal areas in patients with complete callosotomy, while it was reduced, albeit not absent, in visual and motor cortices. This supports the aforementioned observations made by Johnston et al. (2008) on the preserved ihFC of the motor area of the hand. Roland and colleagues observed that partial transection of the CC seemed to produce lesser impairment of ihFC. In particular, patients whose posterior CC was spared preserved their connectivity between bilateral visual cortices. Intriguingly, in individuals that underwent a partial transection, HC was also present in regions that were expected to be affected by the operation. This phenomenon, possibly due to preserved heterotopic callosal connections, emphasizes the complexity of structural interhemispheric connectivity, which goes beyond simple callosal homotopic connections to include heterotopic, ipsilateral, subcortical pathways and minor commissures as well (for a list of all the studies discussed in this section, see Table 1).

PLEASE INSERT TABLE 1 HERE

3.2. Maintained interhemispheric functional connectivity in split-brain patients

The previous considerations demonstrating the reduction of ihFC following transection of the CC have been questioned by other studies. In an EEG investigation by Corsi-Cabrera and colleagues (1995), ICoh was found to be intact in a woman one year after the transection of the two anterior thirds of the CC and complete transection of the AC. However, it should be noted that the post-surgical recordings were compared to those of normal individuals and not to the pre-surgical values, making it impossible to exclude the possibility that ICoh was abnormally high before the operation, as was observed, for instance, in a study by Matsuzaka et al. (1993). This and other methodological concerns were raised by Nielsen and Montplaisir (1996). Furthermore, another study by Corsi-Cabrera and colleagues (2006) reported an attenuation of ICoh from pre- to post-surgical recordings.

Other findings contradicting the thesis of a major role for the CC in ihFC have been published in a recent study examining a partial callosotomy case (Casimo et al., 2018). A patient underwent a two-stage partial callosotomy, and during the first stage a set of ECoG electrodes were implanted. This investigation compared the intracranial recordings of anterior regions (disconnected by the operation) to those that were considered spared on the basis of diffusion tensor imaging (DTI). No differences were found between preserved and spared electrodes. However, these results are to be taken with caution. Due to the clinical context surrounding the data collection, no pre-surgical recordings were performed, no comparison with healthy controls was made, and no electrode was implanted in the posterior cortices.

Uddin and colleagues (2008) studied a woman (N.G.) who underwent a complete telencephalic commissurotomy in 1963. The ICA conducted on resting state fMRI data identified two canonical bilateral networks, a visual network and the posterior portion of the default mode network (DMN) (Buckner et al., 2008; Greicius et al., 2003; Raichle et al., 2001). The FC maps produced by placing several seeds inside those networks revealed that they were substantially symmetrical (for a graphical representation of N.G.'s DMN, see Fig. 4). This finding is consistent with the known preserved transfer of visual information of this patient (Eviatar and Zaidel, 1994; Pollmann and Zaidel, 1998) and with her ability, just six months after the operation, to use indifferently one or the other hand in order to respond to unilateral stimulations (Gazzaniga et al., 2000). As the complete one-stage transection of telencephalic commissures normally implies that the IHT is to be supported by subcortical structures (Bogen et al., 1965), the preserved ihFC and visual transfer ability of this patient is surprising. Although this case should be regarded as unique, it undoubtedly draws attention to the capacity of subcortical commissures to provide alternative means of connectivity.

A recent diffusion weighted imaging study of N.G. observed increased FA compared with controls in the middle and superior cerebellar peduncles that give rise to the pontine decussations, which are part of the dentate-rubro-thalamic tract and the cortico-ponto-cerebellar loop connecting the cortices to the cerebellum (Nomi et al., 2019). These findings suggest that alternate subcortical paths might be involved in the preservation of ihFC exhibited by this patient. Still, in absence of pre-surgical measurement of brain diffusivity, it is impossible to know whether these abnormal connections were already present before surgery or represented the effects of a post-callosotomy reorganization. It is possible that some form of long-term plasticity occurred in N.G. over the course of her life. However, if we consider the uniqueness of the case of N.G., as observed in her fast post-operative recovery (Bogen et al., 1965), it seems likely that any reorganization should be favoured to some extent by congenital features of the patient's brain. In fact, during the post-surgical phase she was already able to correctly localize both verbally and with the indication of the hands tactile stimuli presented on either side of the body (Gazzaniga et al., 2000). This performance may imply a pre-surgical bilateral representation of each somatosensory hemifield of the patient, suggesting an anomalous congenital brain organization. In any case, the finding of increased FA in the pontine decussation of N.G. with intact ihFC indicates that FC may rearrange itself over different structural connections (Uddin, 2013), and that callosal function might also be sustained, at least in part, by subcortical pathways.

This case emphasizes the importance of human brain plasticity for the reorganization of information pathways after a severe lesion such as the transection of the CC. As reported above, Roland and colleagues (2017) did not observe signs of recovery in a patient after a seven-year follow up, but other two recent works challenge this view. Liang and colleagues (2018) obtained EEG recordings in 30 split-brain patients (12 complete and 18 partial) three months, one year and two years after the operation, observing that the topological measures of their cerebral networks suggest a reorganization of the interhemispheric paths. Strong IhFC connections shifted from the areas closer to the midline to the more lateral parts of the brain. Moreover, there was an increase of the number of regions placed on the shortest path between many nodes. This suggests that, after callosotomy, the regions that were previously able to bridge the two hemispheres needed to be substituted by a larger number of new hubs, as also testified by diminished clustering and increased long-distance communication. Hung and colleagues (2019) studied with fMRI 8 pediatric patients one year after total callosotomy. They replicated the results with humans (Roland et al., 2017) and animals (O'Reilly et al., 2013; Zhou et al., 2014) about decreased inter- and increased intrahemispheric FC, but they also observed preserved IhFC and HC in several frontal and temporal regions that are under the anatomic domain of the AC. This was interpreted as the ability of AC to mediate the recovery of IhFC, as suggested by the study conducted on monkeys by O'Reilly and colleagues (2013). Unfortunately, no scan right after the operation was performed, so it cannot be evaluated how much of this preserved IhFC was an effect of long-term plasticity and how much derived from the mere presence of spared commissures.

In sum, although almost all the studies of ihFC of split-brain patients reported a strong post-surgery reduction of FC between hemispheres, this finding has been questioned by Uddin et al. (2008), who studied a patient known to be atypical in her preservation of IHT (Eviatar and Zaidel, 1994). Notably, the neuroimaging data obtained from this patient were collected 40 years after surgery, a long period during which compensatory functional connectivity patterns may have emerged. Furthermore, other recent studies (Hung et al., 2019; Liang et al., 2018) indicate that such recovery might take place in a span of time shorter than it was previously thought. Nevertheless, local preservations of ihFC were also reported in the post-operative phase by other studies (Johnston et al., 2008; Roland et al., 2017). These findings are in line with the fact that communication between hemispheres does not exclusively rely on an intact CC. Moreover, possible mechanisms of intrahemispheric increase of FC have been proposed by other investigations (Hung et al., 2019; O'Reilly et al., 2013; Roland et al., 2017; Zhou et al., 2014), thus suggesting some form of interplay between inter- and intrahemispheric connectivity. A list of all the studies discussed in this section can be found in Table 2.

PLEASE INSERT TABLE 2 HERE

3.3. Interhemispheric functional connectivity in commissural agenesis: a presentation of current results

The first studies to assess ihFC in humans with AgCC were EGG investigations that found a diminished ICoh compared with controls; however, these studies were conducted on few subjects (Koeda et al., 1995; Kuks et al., 1987; Nagase et al., 1994; Nielsen et al., 1993). Nielsen et al. (1993) observed globally reduced ICoh but also a relatively maintained interhemispheric occipital connectivity in 4 subjects during sleep, a result explained by the authors with the preservation of the posterior commissure. Koeda et al. (1995) reported spared connectivity between the temporal lobes in a group of 5 subjects (2 adults and 3 juveniles). Observing a younger group of 5 subjects (comprised of 2 children and the same 3 juveniles of the previous group), ICoh between the temporal lobes appeared to be *increased* compared with controls. Since the temporal lobes are connected through the AC and the posterior part of the CC, (Abe et al., 2004; Di Virgilio et al., 1999; Hofer and Frahm, 2006; Huang et al., 2005; Park et al., 2008; Patel et al., 2010), any preservation of HC in the temporal lobes should depend on the presence or absence of these commissures. However, this was not observed by Koeda et al. (1995), as individual ICoh of temporal lobes was not clearly associated with preservation of the AC and anterior CC. A closer inspection of the subjects' anatomy led these authors to propose that regional ICoh was associated with an interaction between the spared commissures. In fact, 3 patients, one (patient A in Fig. 5) with total AgCC and no AC, another (patient E in Fig. 5) with partial AgCC and no AC, and a third (patient B in Fig. 5) with partial AgCC, intact AC but no PC, did not differed in their temporal ICoh. This suggests that the presence or absence of each commissure does not affect FC independently of the status of the others, but rather that they form a complex interplay of structural connections. At the same time, the absence of a PC produced a more impaired parietal and occipital ICoh in the subject who otherwise showed the lesser anatomical disconnection compared with the others. This might also imply that the effect of each commissure on ihFC is topographically specific. However, it should be observed that the sample of this research was rather heterogeneous, as 3 of the subjects had complete AgCC, 1 was deprived of 90% of the CC, and the remaining 3 lacked 75% of their CC. Furthermore, 2 were also affected by non-brain conditions (i.e., Poland syndrome and spina bifida).

PLEASE INSERT FIGURE 5 HERE

The findings of reduced general ICoh but preserved temporal ICoh in the 5 young subjects of the study by Koeda et al. (1995) were also observed during a finger tapping task (Knyazeva et al., 1997), which revealed decreased intrahemispherical coherence compared with controls in all brain areas except for temporal regions, where it was found to be increased. In summary, these EEG studies suggest that individuals with AgCC exhibit reduced ihFC compared with normal subjects, even though significant local preservations of ICoh were often detected.

An MEG study (Hinkley et al., 2012) on a sample of 18 individuals (9 with complete and 9 with partial AgCC) reported decreased interhemispheric and intrahemispheric coherence in the alpha band in three associative regions (dorsolateral prefrontal cortex, posterior parietal cortex, and parieto-occipital sulcus) that was related with the cognitive impairments of these individuals (for a graphical representation, see Fig. 5). Furthermore, reductions of connectivity of specific areas were found to be correlated with the speed of verbal processing as well as executive performance. No differences were found between individuals with partial or complete agenesis. Like the previous investigations, this study did not find a global reduction of ihFC, but only local deficits in associative regions. Of note, impairments were not exclusively interhemispheric, as the same regions showed reduced intrahemispheric FC. Nonetheless, as this study was conducted on the largest sample of subjects, the fact that it reported rsFC reduction in associative regions appears particularly convincing. However, it should be noted that many patients of this study also suffered from other neurological or psychiatric disorders, a fact that could have affected the results.

With regard to fMRI investigations, a study (Quigley et al., 2001) on a patient with complete AgCC and midline cysts observed absence of ihFC for seeds in the sensorimotor cortex and in the Broca’s area, but partially preserved ihFC for a seed in the auditory cortex. Conversely, a subsequent seed-based study (Quigley et al., 2003) found a lack of ihFC in both sensorimotor and auditory cortices of 3 individuals with complete AgCC (Fig. 5). Two of these subjects suffered from other neurological conditions (i.e., seizures and hydrocephalus). This study supports the idea that callosal agenesis induces asymmetries in rsFC, as the seeds obtained from the activation loci elicited by text listening and finger tapping tasks produced asymmetrical maps; however, its scope was partly limited by the small number of subjects and by the fact that only two networks were inspected.

A subsequent ICA study conducted on 11 subjects, 7 with complete and 4 with partial AgCC (Owen et al., 2013a) found altered connectivity in 5 associative regions, namely the left and right frontoparietal components, the bilateral precuneus component, the bilateral posteromedial parietal component (a central node of the DMN), and the bilateral insula component (an essential part of the salience network) (Seeley et al., 2007; Uddin, 2015). Although these components showed anomalous spatial distributions compared with controls, they still appeared symmetric (Fig. 5). However, the post-hoc seed-based analysis performed by Owen and colleagues revealed that ihFC was significantly decreased within the bilateral components and between the left and right frontoparietal components. On the other hand, the authors observed a globally preserved HC, even in the absence of the CC, as illustrated by the correlation matrices of patients and the control group, as well as by a similar functional connectome organization between patients and controls. Although this study highlights a global similarity between the connectome of normal subjects and individuals with AgCC, it confirms that callosal agenesis can induce some ihFC impairments, albeit subtle ones that are mainly localized to associative regions. It also emphasises the difference among results obtainable with ICA and with seed-based correlation.

Genç and colleagues (2015) observed that a group of 5 AgCC patients (4 complete and 1 partial) showed no positive or negative interactions in the BOLD signals of the bilateral hand motor areas during a unimanual motor task. On the contrary, controls exhibited a negative influence between ipsilateral and contralateral hand, which is positively correlated with the FA of the isthmus, providing evidence that the CC can exert cross-inhibitory functions over the motor cortices.

Further evidence for reduction of ihFC was observed with a seed-voxel correlation in a man with schizophrenia, complete AgCC and highly disrupted DMN and visual network IhFC (Rane et al., 2013). Although this result should be interpreted with caution, as schizophrenia has been associated with several FC alterations (Chang et al., 2015; Guo et al., 2014b, 2014a; Zhou et al., 2007), it is reasonable to consider it an additional proof of ihFC impairments in the congenital absence of CC.

A recent study conducted on individuals with AgCC (6 complete and 4 partial) (Zuo et al., 2017) found several brain sites of altered regional homogeneity (ReHo). ReHo measures the similarity of the time course of a voxel with those of its neighbours (Zang et al., 2004); it therefore provides a measure of local synchronization. Each altered area was used as a ROI for a seed-based correlation. Regions characterized by higher ReHo in AgCC patients compared with controls showed normal FC, but areas characterized by diminished ReHo revealed lower FC, providing evidence of reduced short- and long-range connectivity when AgCC occurs. However, several areas of reduced FC were bilateral, and absence of HC was reported only for two of the three ROIs taken into consideration (for a graphical representation of the reduced HC in the cuneus, see Fig. 5). As the focus of this study was not ihFC, but rather the intra- and interregional synchronization of BOLD signal, only regions of altered ReHo were chosen as ROIs for the seed-based analysis. It is therefore possible that other ROIs would have produced clearer results. Nonetheless, the reported absence of HC within the cuneus and lingual gyrus is an interesting finding that corroborates the hypothesis of some form of ihFC deficit caused by AgCC.

Though the studies discussed so far reported at least some regional decrease of ihFC in individuals with AgCC, others failed to detect significant differences from normal subjects, complicating the picture. For instance, Tovar-Moll and colleagues (2014) performed both an ICA and a ROI-to-ROI analysis between the DMN nodes and did not find asymmetries in the spatial distribution of ihFC in 6 individuals with AgCC (2 complete, 2 partial and 2 with CC hypoplasia) (Fig. 5). However, it should be noted that, even though analyses were performed on the whole group of individuals, only two had a complete AgCC. Khanna and colleagues (2012) used seed-voxel correlation with the same foci of the study by Johnston and colleagues (2008) and found strong ihFC in a patient with nearly complete callosal agenesis. It must be observed, however, that the AC, the PC and what remains of the CC showed preserved FA and long-distance structural connectivity, which might partly explain the ihFC preservation. Tyszka and colleagues (2011) used ICA and seed-based techniques to investigate 8 adults with complete AgCC but intact AC and PC, and reported no evidence of reduction in ihFC (Fig. 5). The only abnormalities found with ICA were that both the DMN and the dorsal frontoparietal network were split in an anterior and a posterior bilateral component; no asymmetries in their spatial distribution were detected. Interestingly, the antero-posterior division of the frontoparietal component was reminiscent of the intrahemispheric under-connectivity of dorsolateral cortices found by Hinkley and colleagues (2012). With regard to the seed-based analysis, the intracalcarine cortex, precuneus and cuneus revealed decreased HC, though those findings did not survive multiple comparison correction.

Another study (Hearne et al., 2018) investigated the ROI-to-ROI functional connectivity of the frontoparietal and salience networks during a cognitive task of increasing difficulty in 7 patients with callosal dysgenesis. The authors observed that intra- and interhemispheric FC of the frontoparietal network showed a reduction as the difficulty of the task increased, but it was normal in the low cognitive load condition. However, just 3 subjects had complete agenesis.

An interesting study examined a unique case of complete AgCC with alien hand syndrome (Ridley et al., 2016). Significantly reduced intra- and interhemispheric FC compared to controls was found in concomitance with alien hand manifestations, but FC was largely normalized after the remission of the symptoms. This is additional evidence of normal IhFC in AgCC, which, in particular, emphasizes that FC deficits might be related to the severity of symptoms. This is extremely relevant, as Tovar-Moll and colleagues (2014) found no evidence of IhFC reduction in their patients, as well as no signs of impaired IHT regarding tactile information. Furthermore, the study by Hinkley and colleagues (2012) reported a correlation between global FC of AgCC subjects and scores on cognitive tests. These observations raise the interesting hypothesis that both reduction and preservation of IhFC may be related to the gravity of the cognitive deficits.

As illustrated, the effects of callosal agenesis on ihFC are not as clear-cut as they appear to be after callosotomy. Most of the studies found ihFC deficits, but they were always localized.

On the other hand, the paper by Tyszka and colleagues (2011) provides evidence of ihFC preservation in AgCC, with some hints of local ihFC reductions that are in line with the findings from Owen et al. (2013) of FC deficits in the precuneus. It seems, therefore, that callosal agenesis is such a complex condition that it is difficult to find consistent evidence regarding rsFC impairments (for a list of all the studies discussed in this section, see Table 3).

PLEASE INSERT TABLE 3 HERE

3.4. Interhemispheric functional connectivity in commissural agenesis: a discussion of the presented studies

Research on individuals with AgCC did not report global ihFC decreases, which were observed in most of the studies of split-brain patients. In contrast to split-brain studies, if reductions of ihFC are present in cases of AgCC, they are usually found only in certain regions rather than occurring uniformly throughout the brain. Moreover, these reductions are more easily detected by targeted seed-based analyses rather than by whole brain techniques such as ICA or functional connectomics. This may imply that impairments of ihFC in individuals with AgCC are less severe than in split-brain patients. This is consistent with the fact that individuals with AgCC have milder symptoms of disconnection syndrome, probably due to structural reorganizations (Paul, 2011; Paul et al., 2007; Tovar-Moll et al., 2014, 2007).

Each of the studies reviewed in the previous section found different regions of reduced FC, however they were usually located in associative areas. This consideration suggests that rearrangement of white matter tracts is insufficient to fully support interhemispheric coordination between brain areas with higher-order functions. It also possibly explains the deficits showed by individuals with AgCC in executing novel and demanding cognitive tasks (Brown et al., 1999; Paul, 2011; Paul et al., 2007; Symington et al., 2010). As noted above, the associative areas of split-brain patients seem to be more functionally disconnected than primary areas (Roland et al., 2017). This aspect, which is probably related to the different speeds of information transfer between high and low hierarchy cortices, emphasizes the similarity of the two conditions of AgCC and split-brain. If alternative pathways are not able to sustain the correct balance between synchronization and independence that is supposed to be mediated by the action of slow callosal fibres (Aboitiz and Montiel, 2003), then the interhemispheric conduction between associative areas might be strongly impaired when the CC is absent.

The inconsistencies reported by studies of individuals with AgCC about the exact locations of ihFC reductions could possibly be due to the higher structural inter-subject variability of these patients compared with normal subjects, as noted by Owen and colleagues (2013b). Many studies were conducted on few subjects, and this could have caused other discrepancies. Studies with larger samples, for instance those by Owen et al. (2013a) and Hinkley et al. (2012), included individuals with both complete and partial AgCC. In both cases this could have been a possible confound, even though such variables were statistically controlled. Furthermore, most of the subjects studied by Owen and colleagues had additional brain malformations commonly associated with AgCC, and most of the subjects studied by Hinkley and colleagues also had neurological or psychiatric diseases. Hopefully, future studies will be able to examine individuals without significant comorbidities in order to better estimate the effect of callosal agenesis on ihFC.

Another potential confounding factor is the subjects' age. Some studies were conducted on children and infants, while others examined adults. However, the fact that impairments of ihFC were found both in adults and children supports the idea that results were substantially independent of age. This might also suggest that white matter reorganization may take place in the very first period of life or even in utero.

Another factor of variability derives from the imaging modality utilized in each study. EEG and MEG studies detected more evident reductions of ihFC than fMRI studies, thus suggesting that the resolution of the data could bring about different results. The fact that the techniques with lower spatial resolution were more sensitive seems to imply that these reductions are broadly spread. At the same time, the higher spatial resolution of fMRI might be useful for the observation of patterns of locally preserved ihFC, but such investigations should be appraised with caution, as the anatomical anomalies of individuals with AgCC could produce biased comparisons with control subjects, as various anatomical anomalies might make it difficult to register the individual brains to a common template. This might have biased the results, especially in medial regions and in posterior areas proximal to enlarged ventricles. Moreover, even if a precise co-registration were obtained, the midline anatomy of patients with AgCC would still be significantly irregular, complicating the interindividual matching of structure-function. Finally, the fact that fluctuations of ihFC were more clearly observed with imaging modalities of high temporal resolution might imply that they could more easily be detectable by modalities capable of discriminating different bands of the frequency spectrum. Of note, rats showed completely recovered IhFC 28 days after callosotomy when investigated with fMRI ICA, but not with EEG (Zhou et al., 2014).

4 . Alternative pathways of connectivity

As rsFC is usually mediated by more than just monosynaptic structural connectivity, it can reflect both direct and indirect anatomical connections (Honey et al., 2009; Koch et al., 2002). This is emphasized by the cases in which the CC is absent or transected and ihFC is maintained. In fact, regions that are no longer directly connected with the other hemisphere via the CC could find indirect pathways to maintain IHT. This reorganization testifies to the ability of FC to reconfigure itself after an alteration of the anatomical connections, as well as the dynamic relationship between functional and structural connectivity (Uddin, 2013). As suggested by Koeda et al. (1995), a possible interaction between the remaining commissural pathways could account for the different results found in patients with apparently similar cases of agenesis. The most likely candidate as a substitute for the CC is the AC. In fact, this commissure is often present and sometimes enlarged in cases of AgCC (Barr and Corballis, 2002), and even though its size is significantly smaller than the size of CC (Raybaud, 2010), it can nonetheless allow good IHT of information (Aralasmak et al., 2006; Barr and Corballis, 2002; Fischer et al., 1992). Furthermore, the capability of the AC to maintain ihFC after callosotomy has been experimentally demonstrated in macaques (O'Reilly et al., 2013) and proposed in humans (Hung et al., 2019).

Since patients of both Khanna et al. (2012) and Tyszka et al. (2011) had preserved ihFC and an intact AC and PC, these structures could have differentiated the patterns of connectivity. With regard to the AC, Owen et al. (2013a) omitted to report its presence or absence. However, its absence is unlikely, because, as already noted, the most common form of commissural agenesis spares the AC (Chiarello, 1980). Furthermore, data on AgCC patients with intact or enlarged AC but regionally impaired ihFC (Hinkley et al., 2012), as well as data on IHT time courses in AgCC or callosotomized patients with the AC (Aglioti et al., 1993), suggest that the AC cannot on its own fully support ihFC. In contrast, the PC develops independently of the forebrain commissures and appears neither atrophic nor hypertrophic in AgCC (Chiarello, 1980). The patient of the aforementioned study by Koeda et al. (1995), with a partial agenesis without a PC, should be considered an exception. Conversely, the study of a patient with a complete commissurotomy but with good IHT and preserved ihFC (Uddin et al., 2008) provides strong evidence that subcortical structures are able to play a fundamental role in the functional reconfiguration of the brain. For instance, in split-brain patients the commissure of the superior colliculus was found to be involved in visual information transfer (Savazzi et al., 2007), and the role of pontine decussations for maintaining ihFC in the callosotomized patient N.G. was highlighted by Nomi et al. (2019).

These models of subcortical connectivity seem to reflect the Y-shaped structure of consciousness proposed by Sperry (1984). According to this theory, the functional organization of the two hemispheres, which have become independent because of the absence of the CC, appears to bifurcate from a unified root of subcortical structures. As reported by Adachi and colleagues (2012), when two functionally connected areas are not directly linked by anatomical pathways, their functional connectivity can be better explained by common inputs or outputs than by an indirect flow of information through a mediating area. This model highlights the importance of subcortical structures in maintaining ihFC when the CC is absent, not only because their interhemispheric connections are preserved, but also because they can synchronize the activity of the two hemispheres by means of shared inputs and outputs. Moreover, this Y-shaped model based on common input and output seems to relate to the preserved ihFC of motor areas observed by Johnston et al. (2008), which relies on thalamocortical connectivity. Indeed, the capacity of the thalamus to synchronize cortical activity has been repeatedly observed (Goldman-Rakic, 1988; Herrero et al., 2002; Llinas et al., 1999; Mantini et al., 2007). In line with this model, a reduction of long-range symmetric FC was reported in a minimally conscious patient who suffered from brainstem ischaemia, possibly due to the absence of the ascending connections that maintain interhemispheric synchrony (Salvador et al., 2005a).

5. Future directions

The Y-shaped model discussed in the previous section might further explain why ICA fails to find asymmetrical components in individuals with AgCC. It is also worth noting that, while a suitable higher-order solution for normal subjects is considered to produce 70 components (Abou-Elseoud et al., 2010; Ray et al., 2013), the reviewed studies opted for relatively lower-order solutions: 25 components for the study by Owen et al. (2013a) and 44 for the study by Tyszka et al. (2011). It is therefore reasonable to speculate that, when a lower-order solution is adopted, the ICA algorithm is forced to aggregate split components into single networks. So, if common inputs and outputs drive the networks of the two hemispheres to have relatively similar patterns without being directly connected, it is plausible for the fMRI signals to be coupled in the same component by the ICA algorithms of maximization of independence, especially when the dimensional order of the model is low. Higher-order solutions may therefore guarantee more degrees of freedom to uncouple the hemispheres, thus retrieving more lateralized and asymmetrical components than in normal subjects. However, further studies are needed to verify this hypothesis. Finally, future research might consider the assessment of the spatial symmetry of several seed-based maps (Biswal et al., 1995), rather than using ICA or ROI-to-ROI correlations, a method that may be more precise for detecting subtle quantitative changes in ihFC.

Most of the reviewed studies were conducted during the resting state, under the hypothesis that rsFC is able to highlight the intrinsic connectivity of the brain, but FC acquired during task performance can show subtle but meaningful differences from rest (Bolt et al., 2017; Cole et al., 2014; Goparaju et al., 2014; Laird et al., 2011; Mennes et al., 2013; Sepulcre et al., 2010; Smith at al., 2009; Torta et al., 2013). Additional studies of ihFC in acallosal individuals during task performance might be useful in order to better understand the neurological basis of their deficits and to shed light on the role of the CC on information transfer and processing during cognitive activity.

A more accurate anatomical evaluation of patients with callosal agenesis would be beneficial. The hypothesis that some of the more severe malformations associated with AgCC may affect the IhFC could be investigated. In general, the high interindividual variability of this condition needs to be taken into consideration, for example by modelling the extent of the dysgenesis or the associated anomalies in the statistical analysis, or by using techniques that take in account the individual's connectivity fingerprint (Bijsterbosch et al., 2018; Finn at al., 2015) rather than group level analyses that discard inter-subject variability. Furthermore, the state of all the other commissures was not always reported by previous studies. Future research should investigate accurately the state of the forebrain commissures, if the AC is present or even enlarged, and ensure that subcortical commissures such as the PC are present, as expected. Tovar-Moll and colleagues (2014) already proved the existence in AgCC of reorganized axonal bundles that connect the hemispheres through AC and PC in concomitance with preserved IhFC, but further studies evaluating at the same time structural and functional connectivity might provide new useful insights into this fascinating condition and on brain connectivity in general. Also, future research could test the hypothesis that the severity of IhFC impairment might be correlated with that of cognitive deficits. Addressing this issue would shed further light on structure/function relationships in the human brain.

With regard to split-brain patients, it would be useful to study whether the findings regarding the structural connectivity of N.G. could be replicated in other subjects, especially in those that do not exhibit her good performance on cross-integration. Furthermore, as the extent of the possible plastic reconfiguration after the operation is still unclear, future longitudinal studies could investigate the post-operative changes of both functional and structural connectivity with more follow-ups along the years.

Finally, it would be interesting if acallosal individuals might be studied with both fMRI and EEG or MEG so as to compare the results of different research modalities, as the latter techniques seem to be more sensitive to IhFC impairments than the former.

6. Conclusions

The reduction of ihFC observed after callosotomy and in many studies of AgCC implies that the CC is the main structure dedicated to supporting interhemispheric connectivity. The preservation of ihFC between areas virtually disconnected in cases of partial callosotomy (Roland et al., 2017) highlights the importance of heterotopic connectivity of the CC, as well as of ipsilateral associative pathways that could help distribute information within each hemisphere. Both disconnection symptoms and ihFC impairments, if present, are less severe in individuals with AgCC than in patients that have undergone callosotomy; this suggests that structural and functional reorganization can more easily take place to partially normalize ihFC in these individuals. Possibly due to the high variability among individuals with AgCC (Owen et al., 2013b), studies have showed different results. A complete understanding of ihFC in AgCC is still lacking, as certain investigations found clear evidence of impairments while others did not. However, since behavioural studies reported several minor deficits in individuals affected by AgCC, it is reasonable to suppose that reorganization might not always be sufficient and that, consequently, some sort of connectivity alteration may occur. At the same time, recent studies (Hung et al., 2019; Liang et al., 2018) suggest that adaptive changes in the split-brain might have been underestimated.

With regard to the excitatory and inhibitory functions of the CC, we can observe that callosotomy disrupts not only positive but also negative FC in many ROIs (Johnston et al. 2008), a finding that is consistent with the idea that the CC supports both excitation and inhibition. Furthermore, while the generally reported reduction of ihFC in the absence of the CC seems to be associated with the excitatory function, the increased cortical intrahemispheric FC observed in both humans and monkeys with split-brain conditions (O'Reilly et al., 2013; Roland et al., 2017) could be considered as evidence of a lack of interhemispheric inhibition, thus supporting the hypothesis that the CC serves both these modes of interaction (Bloom and Hynd, 2005). As the increase of intrahemispheric FC appears just the day after the operation (Roland et al., 2017), it should not be taken as a sign of structural reorganization. Nonetheless, if we examine the correlation matrices of the three patients' follow-ups of the study by Roland et al. (2017), it seems that, at least in one patient, this intrahemispheric increase strongly intensified seven years after the surgery. This suggests that a sort of functional reorganization is still possible even years after the operation, and may be considered as a mark of ipsilateral connectivity enhancement. It should be noted that patient N.G. did not present increased FA in the uncinate fasciculus, the arcuate fasciculus and the cingulum bundle (Nomi et al., 2019). However, N.G. is an exceptional case, so her apparently normal interhemispheric structural connectivity may not be generalizable to other split-brain patients.

To conclude, the CC is a fundamental structure of the brain and is involved in important cognitive processes, such as lateralization of functions and informational integration between the hemispheres (Aboitiz and Montiel, 2003; Gazzaniga, 2000; Nowicka and Tacikowski, 2011; Ringo et al., 1994). A better understanding of its role is essential in order to achieve a deeper understanding of how the human brain works. The analysis of rsFC provides complementary information to that acquired with structural and activation studies; its investigation in acallosal brain has revealed and highlighted the importance of subcortical structures to interhemispherical communication, as well as the difference between ICA and seed-based correlation results when functional asymmetries are evaluated. Future research on these interesting patients will allow us to gain further comprehension of the human brain, its organization, and its function.

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Tables

Table 1. Summary of studies presented in section 3.1, in alphabetical order. CCEP: cortico-cortical evoked potentias; ECoG: electrocorticography; EEG: electroencephalography; fMRI: functional magnetic resonance imaging; Icoh: interhemispheric coherence; IhFC: interhemispheric functional connectivity.

Authors	Year of publication	Number of subjects	Imaging modality	FC measure	Results
Brázdil et al.	1997	3 (partial)	EEG	Coherence	Reduced ICoh in most of frequency bands
Johnston et al.	2008	1 (complete)	fMRI	Seed-voxel correlation	Reduced positive and negative IhFC, except for the hand motor area and the medial temporal lobe
Lehner et al.	2018	2 (partial)	fMRI, ECoG	Seed-voxel correlation, CCEP	Reduced IhFC with all the techniques
Matsuzaka et al.	1993	7 (partial)	EEG	Cross-correlation	Reduced interhemispheric correlations, especially in frontal lobe
Montplaisir et al.	1990	2 (partial)	EEG	Coherence	Reduced ICoh in most of frequency bands
Okumura et al.	2013	6 (complete)	EEG	Coherence	Reduced Icoh in all the subjects after the final step of a dual-stage callosotomy, but not necessarily after the first one
Pizoli et al.	2011	1 (partial)	fMRI	Seed-voxel correlation, ECoG cross-correlation, evoked potentials	Lack of interhemispheric and homotopic FC
Rojas-Ramos at al.	2013	3 (partial)	ECoG	Cross-correlation	Reduced positive and negative IhFC
Roland et al.	2017	22 (16 complete)	fMRI	ROI-to-ROI correlation	Reduced IhFC and increased intrahemispheric FC, no recovery in follow-up, partial preservation of motor and

					visual areas

Table 2. Summary of studies presented in section 3.2, in alphabetical order. ECoG: electrocorticography; EEG: electroencephalography; FC: functional connectivity; fMRI: functional magnetic resonance imaging; ICA: independent component analysis; Icoh: interhemispheric coherence; IhFC: interhemispheric functional connectivity; VMHC: voxel mirrored homotopic connectivity..

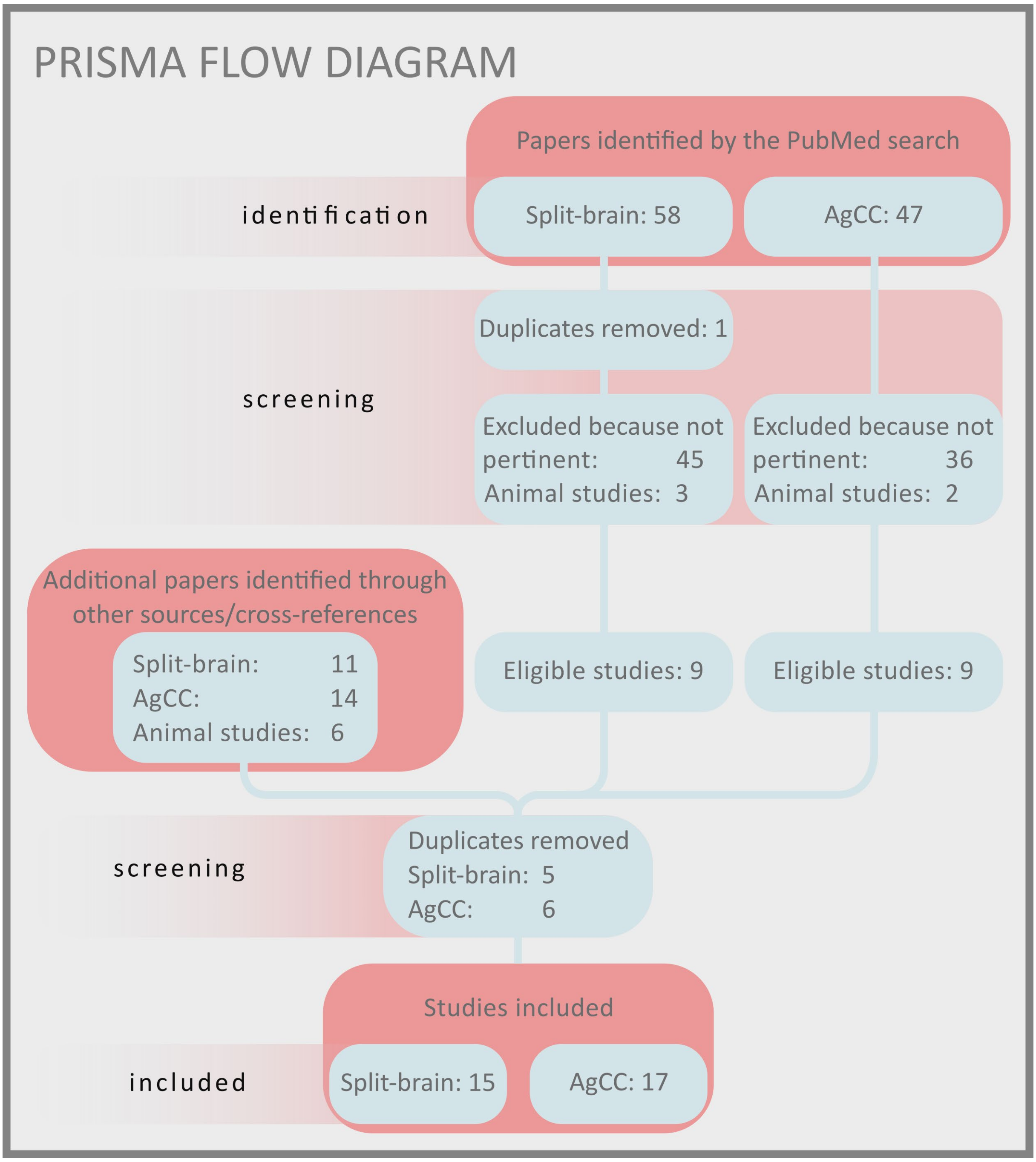
Authors	Year of publication	Number of subjects	Imaging modality	FC measure	Results
Casimo et al.	2018	1 (partial)	ECoG	Phase-locking	No difference between disconnected and spared electrodes
Corsi-Cabrera et al.	1995	1 (partial)	EEG	Coherence	Preserved ICoh
Corsi-Cabrera et al.	2006	2 (1 complete)	EEG	Cross-correlation	Reduced IhFC
Hung et al.	2019	8 (complete)	fMRI	Network analysis, VMHC	Reduced global IhFC but preserved IhFC in frontal and temporal lobe, increased intrahemispheric FC
Liang et al.	2018	30 (12 complete)	EEG	Mutual information, network analysis	Reorganization of FC over time
Uddin et al.	2008	1 (complete)	fMRI	ICA and seed-voxel correlation	Preserved IhFC

Table 3. Summary of studies presented in section 3.3, in alphabetical order. DMN: default mode network; EEG: electroencephalography; fMRI: functional magnetic resonance imaging; HC: homotopic connectivity; ICA: independent component analysis; Icoh: interhemispheric coherence; IhFC: interhemispheric functional connectivity; MEG: magnetoencephalography; ReHo: regional homogeneity; ROI: region of interest..

Authors	Year of publication	Number of subjects	Imaging modality	FC measure	Results
Genç et al.	2015	5 (4 complete)	fMRI	Psychophysiological interactions	Lack of interactions between the motor hand areas during an unimanual task
Hearne et al.	2018	7 (3 complete)	fMRI	ROI-to-ROI correlation	Preserved FC during an easy task but reduced intra- and IhFC in the frontoparietal network during a complex task
Hinkley et al.	2012	18 (9 complete)	MEG	Coherence	Globally preserved but reduced intra- and ICoh in the alpha band in prefrontal, parietal and parieto-occipital areas in the alpha band
Khanna et al.	2012	1 (partial)	fMRI	Seed-voxel correlation	Preserved IhFC
Knyazeva et al.	1997	5 (2 complete)	EEG	Coherence	Reduced global ICoh during finger tapping but increased in the temporal lobe
Koeda et al.	1995	7 (3 complete)	EEG	Coherence	Reduced global ICoh but spared or increased in the temporal lobe
Kuks et al.	1987	3 (complete)	EEG	Coherence	Decreased ICoh at low frequencies
Nagase et al.	1994	1 (complete)	EEG	Coherence	Decreased ICoh
Nielsen et al.	1993	4 (complete)	EEG	Coherence	Decreased ICoh but spared in the occipital lobe
Owen et al.	2013	11 (7 complete)	fMRI	ICA and seed-voxel correlation	Globally preserved HC but reduced IhFC in the posteromedial cortex,

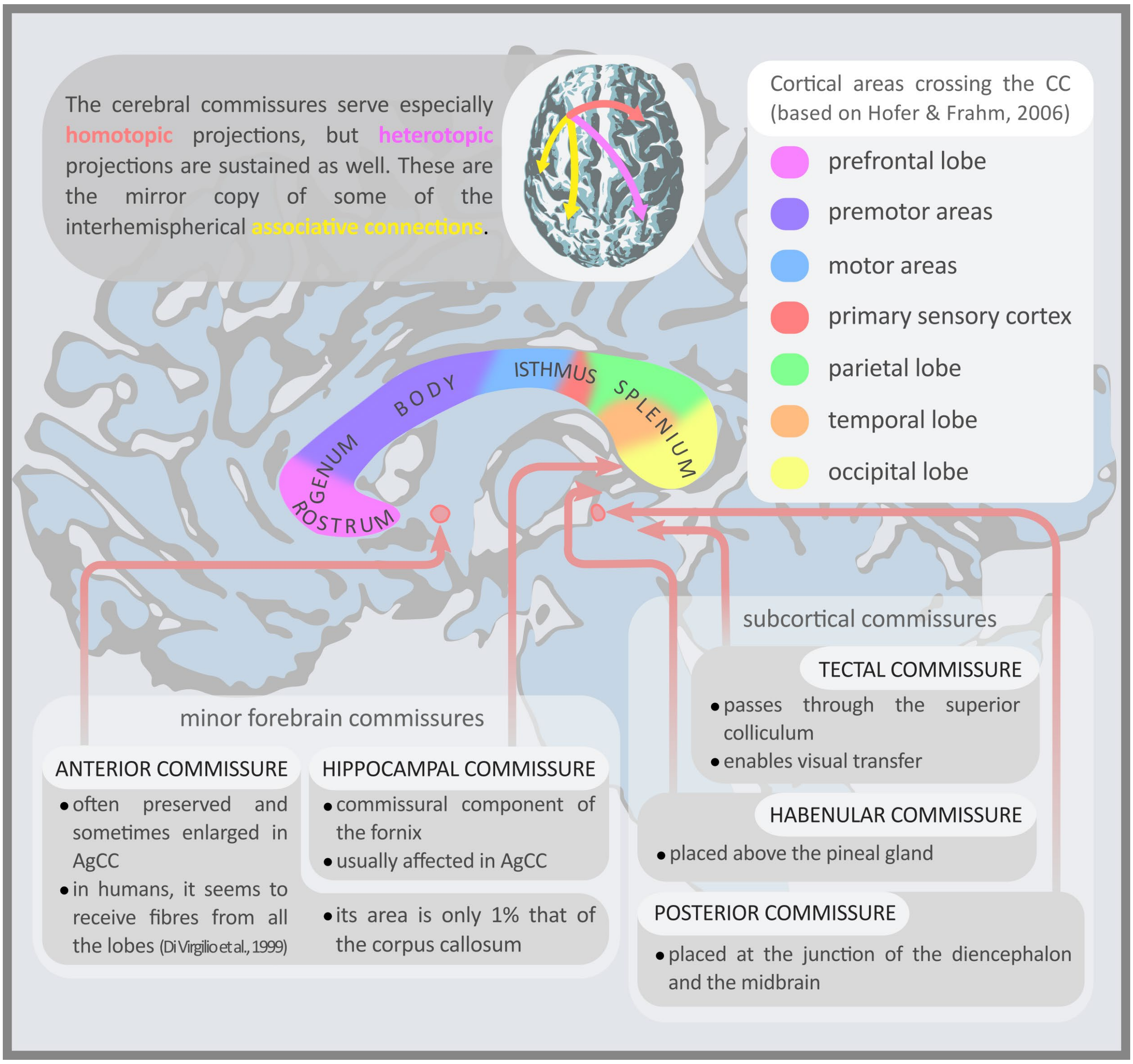
					the insula and the frontoparietal network
Quigley et al.	2001	1 (complete)	fMRI	Seed-voxel correlation	Reduced IhFC for sensorimotor and Broca's but not auditory seed
Quigley et al.	2003	3 (complete)	fMRI	Seed-voxel correlation	Reduced IhFC for sensorimotor and auditory seeds
Rane et al.	2013	1 (complete, schizophrenia)	fMRI	ICA, seed-voxel correlation	Reduced IhFC in the DMN and visual cortex
Ridely et al.	2016	1 (complete, alien hand)	fMRI	Wavelet transform, network analysis	Reduced intra- and IhFC only during alien hand symptoms
Tovar-Moll et al.	2014	6 (2 complete)	fMRI	ICA, ROI-to-ROI correlation	Normal DMN connectivity
Tyszka et al.	2011	8 (complete)	fMRI	ICA, ROI-to-ROI correlation	Preserved IhFC
Zuo et al.	2017	10 (6 complete)	fMRI	ReHo, seed-voxel correlation	Reduced IhFC in the occipital cortex

Figure 1. PRISMA flow diagram illustrating the selection of studies. AgCC: agenesis of the



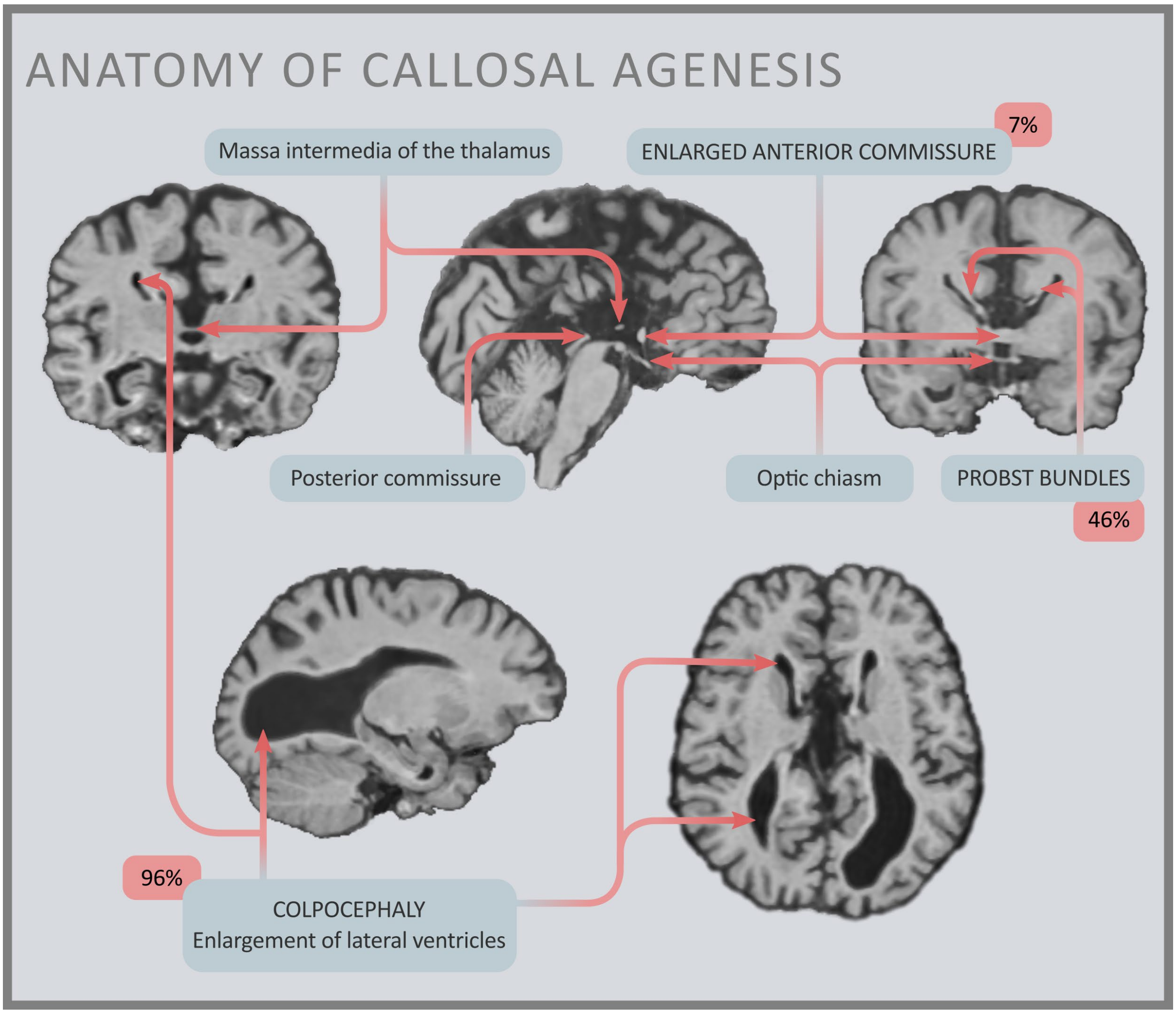
corpus callosum.

Figure 2. Anatomy of the corpus callosum and brain commissures. *Top:* homotopic, heterotopic and associative connectivity. *Middle:* different cortices connect to the other



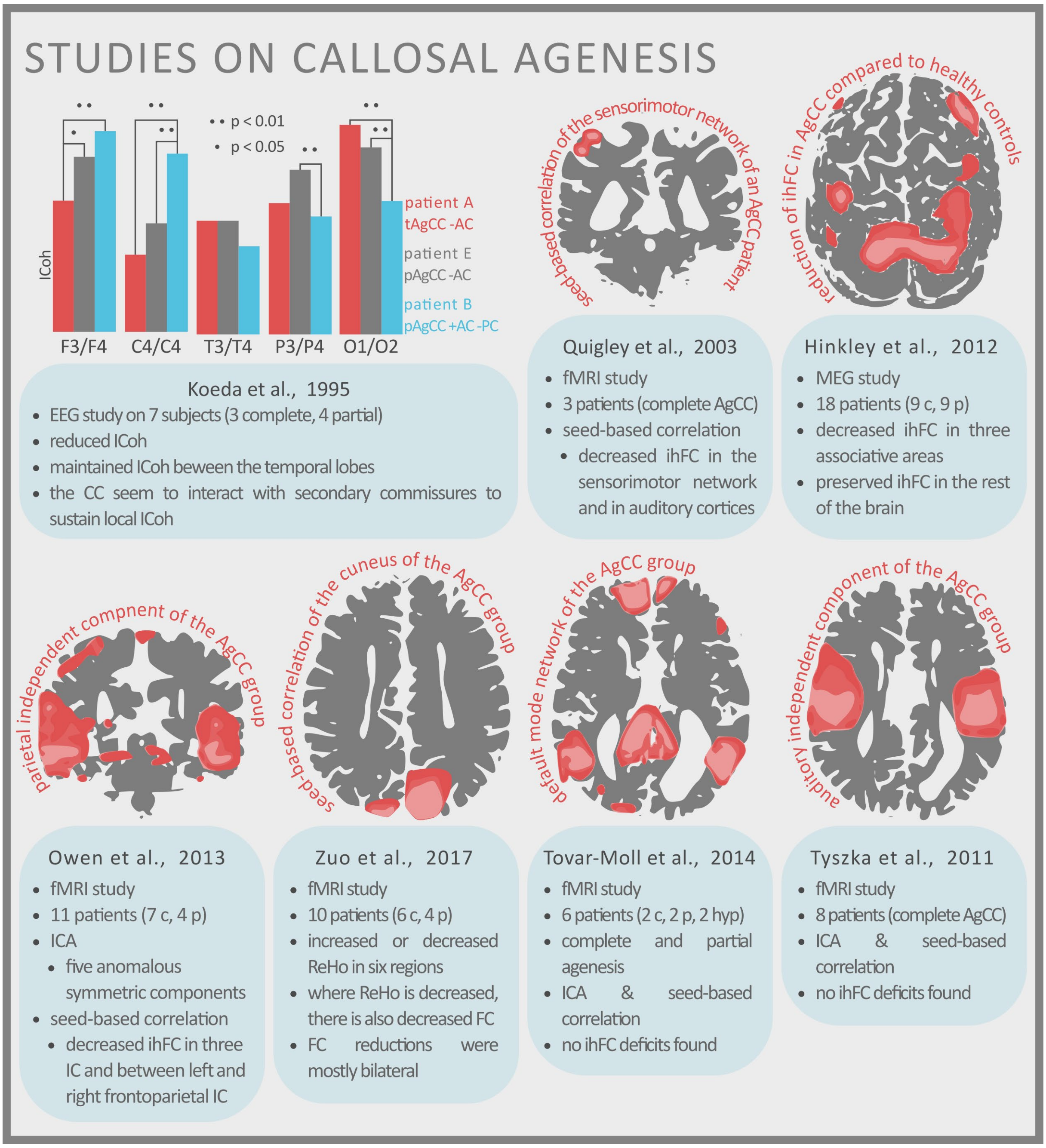
hemisphere through different parts of the corpus callosum. *Bottom:* secondary brain commissures.

Figure 3. Anatomy in callosal agenesis. Structures crossing the midline and enlarged occipital horns of lateral ventricles are highlighted. Pathological abnormalities are written in uppercase letters, and an estimated percentage of their prevalence in callosal dysgenesis is given, as



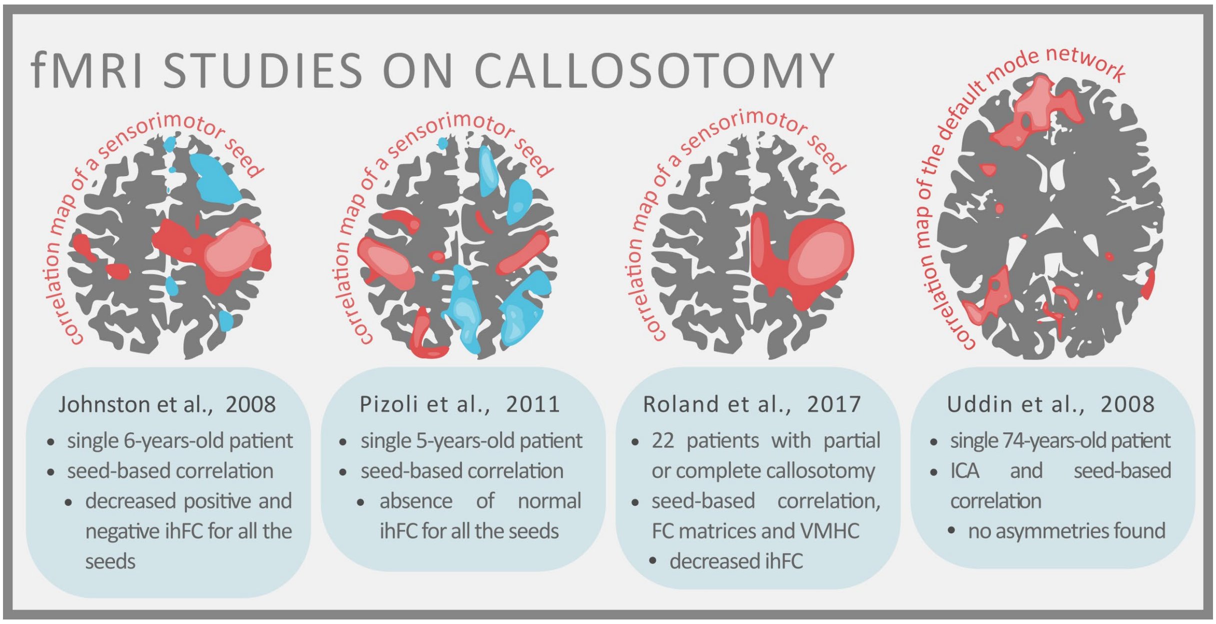
reported by Hetts et al. (2006) (25% of cases reported a reduced anterior commissure, while 33% reported the absence of the anterior commissure).

Figure 4. Summary of the most important fMRI studies on interhemispheric functional



connectivity in callosotomy.

Figure 5. Summary of the most important studies of ihFC in agenesis of the corpus callosum. *Top:* studies showing clear impairments of ihFC. *Bottom:* studies showing subtle or no



impairments of ihFC.