How does the corpus callosum mediate interhemispheric transfer? A review

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ABSTRACT

The corpus callosum is the largest white matter structure in the human brain, connecting cortical regions of both hemispheres. Complete and partial callosotomies or callosal lesion studies have granted more insight into the function of the corpus callosum, namely the facilitation of communication between the cerebral hemispheres. How the corpus callosum mediates this information transfer is still a topic of debate. Some pose that the corpus callosum maintains independent processing between the two hemispheres, whereas others say that the corpus callosum shares information between hemispheres. These theories of inhibition and excitation are further explored by reviewing recent behavioural studies and morphological findings to gain more information about callosal function. Additional information regarding callosal function in relation to altered morphology and dysfunction in disorders is reviewed to add to the discussion of callosal involvement in interhemispheric transfer. Both the excitatory and inhibitory theories seem likely candidates to describe callosal function, however evidence also exists for both functions within the same corpus callosum. For future research it would be beneficial to investigate the functional role of the callosal sub regions to get a better understanding of function and use more appropriate experimental methods to determine functional connectivity when looking at interhemispheric transfer.

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Contents

1. Introduction ................................................................. 00
2. Callosal anatomy .......................................................... 00
   2.1. Brain commissures ................................................. 00
   2.2. Functional organization ........................................... 00
3. Corpus callosum function: relation to behaviour ........... 00
   3.1. Animal disconnection studies ................................. 00
   3.2. Studies in humans ................................................... 00
      3.2.1. Lesion studies .................................................. 00
      3.2.2. Agenesis of the corpus callosum ....................... 00
4. Hemispheric interaction ............................................... 00
   4.1. The inhibitory model .............................................. 00
      4.1.1. Hemisphere dominance and metacontrol .......... 00
      4.1.2. The aging corpus callosum ............................. 00
   4.2. The excitatory model ............................................. 00
   4.3. Comparison of the two models ............................... 00
5. Pathologies ................................................................. 00
   5.1. Schizophrenia ...................................................... 00
   5.2. Autism ............................................................... 00
   5.3. Alien hand syndrome .......................................... 00
   5.4. ADHD ............................................................. 00
   5.5. Bipolar disorder and borderline personality disorder ... 00
1. Introduction

The corpus callosum is a brain structure in placental mammals that connects the left and right cerebral hemispheres. Containing numerous intra- and interhemispheric myelinated axonal projections it is considered to be the largest white matter structure in the brain. Patients undergoing complete or partial corpus callosotomy and callosal lesion studies have provided more insight into its function over the years. These callosotomies served as a treatment for intractable epilepsy, preventing seizures from spreading over the entire brain. The first callosotomy was performed by van Wagenen and Herren [1], and on first sight did not appear to induce any large cognitive or functional deficits. However, more elaborate behavioural studies have shown symptoms specific to callosotomies, now known as the callosal disconnection syndrome. Complete sectioning of the corpus callosum blocked the transfer of information to the opposing hemisphere, resulting in dissociation between left and right and difficulties in transferring learned information.

The unique cognitive state of callosotomized patients has led to more elaborate research regarding hemispheric transfer and communication between different cortical areas and the functional specialization of the corpus callosum. This review will address and investigate recent literature concerning callosal morphology, function and dysfunction in order to investigate the involvement and function of the corpus callosum in brain hemisphere communication.

2. Callosal anatomy

2.1. Brain commissures

Communication between cortical areas of the brain can occur both intra-, as well as interhemispherically. Intrahemispheric communication occurs by means of axonal projections connecting cortices of the frontal, parietal, occipital and temporal lobes, by means of cortico-cortical and cortico-subcortical pathways. This information is also available for interhemispheric processing [2,3]. Interhemispheric processing occurs through brain commissures; bundles of nerve fibers that connect the two cerebral hemispheres. The human brain contains three major commissures; the anterior commissure interconnecting the olfactory system and a part of the limbic system, the hippocampal (or posterior) commissure interconnecting a part of the limbic system, and the corpus callosum, largest in size and interconnecting a large number of cortical areas [4]. Although the hippocampal and anterior commissures are present in all vertebrates, the corpus callosum is limited to placental mammals, suggesting a sudden evolutionary origin as there are no ancestral structures of the corpus callosum present in nonplacental animals [5].

Because of its involvement in information processing of cortical areas the corpus callosum is thought to have contributed to the lateralization of brain function (dividing information processing in either the left or right cerebral hemisphere) by means of selection pressure demanding cortical space. The corpus callosum could have played a large role in enabling this lateralization by exchanging information between the hemispheres, thus saving cortical space allowing for specialized brain functions in the left and right hemispheres [6]. The corpus callosum might therefore also play a large role in the exchange of information between cortical areas with unilateral representations (e.g. language/speech in the left hemisphere).

2.2. Functional organization

The corpus callosum consists of around 200 million fibers connecting the two hemispheres [7] that are fixed at birth [8]. However, fiber myelination continues throughout puberty, which accounts for developmental morphological changes [8,9]. Although there are no clear anatomical landmarks or boundaries, the corpus callosum can be subdivided into several functionally and morphologically distinct sub regions, which are arranged according to the topographical organization of cortical areas (from anterior to posterior): the genu, truncus or midbody, and splenium [10]. Callosal size and width have been shown to vary between individuals and between sex [8,11–14], however these findings are often controversial. It has been posed that individual and sex differences are dependent on the developmental trajectory, with a longer callosal development period for females, possibly influenced by hormonal balance [15]. Differences between studies can be caused by variations in patient groups, lack of brain size corrections or technological variations such as the type of measurements.

Partial callosotomies and lesion studies have contributed greatly to the knowledge of callosal functional specificity [16]; studying how transfer of different sensory modalities is affected in patients with different types of callosal lesions provides information about the function of the specific sub regions.

Fiber size and composition along the corpus callosum differs according to the topographical organization of the cortex. The anterior part of the corpus callosum or genu contains the highest density of thin myelinated axons which connect the prefrontal cortex and higher order sensory areas. The density of fibers decreases from genu to the truncus or midbody of the corpus callosum. This midbody contains axons running to the parietal and temporal lobes. The posterior midbody of the corpus callosum contains thick axons involved in the transfer of information from primary and secondary auditory areas, whereas the middle portion of the truncus connects primary and secondary somatosensory and motor areas. Fiber density increases again in the splenium, the posterior part of the corpus callosum which connects visual areas in the occipital lobe. The area between the body and splenium is thinned and therefore known as the isthmus, connecting fibers of motor, somatosensory and primary auditory areas [3–5,7,17,18].

Axonal connections between cortical areas of opposing hemispheres do not have to be symmetrical, but can also provide asymmetrical connections to different regions of the brain [2,13]. The size of the axonal projections is representative for the interhemispheric transfer time. Thick myelinated fibers with large diameters provide a faster transmission of sensory-motor information, whereas the thin myelinated fibers with a small diameter provide a slower transmission between association areas [19]. However, transfer across hemispheres requires time and energy to coordinate and integrate information and is therefore not always beneficial. Some interhemispheric interactions through small diameter thin myelinated fibers can take as long as 100–300 ms [20].

Information can be processed in a single hemisphere without the need to integrate information from the other hemisphere.
If interhemispheric transfer is disadvantageous compared to intrahemispheric transfer, then why and when do we use interhemispheric transfer? To understand the importance and role of the corpus callosum in this process its function and relation to behaviour are now critically reviewed.

3. Corpus callosum function: relation to behaviour

3.1. Animal disconnection studies

Some early studies concerning callosal function were performed in animals, in which functional and behavioural changes were examined after sectioning of the corpus callosum. Bykov used Pavlovian conditioning in dogs to determine behavioural changes before and after sectioning of the corpus callosum (for translation see: [21]). Firstly, they identified that a conditioned response concerning one side of the body is automatically elicited when the opposite side is stimulated. Later Bykov investigated if sectioning the corpus callosum would block this generalized response. Although there was some difficulty with the surgical procedures, the surviving dogs showed that transfer of the learned response to the opposing side was inhibited.

Similar results have emerged from studies regarding inhibited transfer of somatosensory information between the two sides of the cerebral cortex in callosotomized cats and monkeys [22–25]. However, these experiments do not necessarily prove that interhemispheric transfer is inhibited, as it remains unclear if the lack of transfer is simply an effect of the induced lesion, affecting learning processes and performance. Glickstein and Sperry [23] therefore performed a more elaborate behavioural study on normal monkeys and callosum-sectioned monkeys. They trained healthy and callosotomized monkeys on a simple discrimination task using one arm. After several training sessions the value of the stimuli became reversed and the monkey was forced to use the untrained, contralateral hand, inducing a clear drop in performance after which performance steadily increased over time in a similar fashion as the initial training sessions. In a final test the original hand and stimulus values are used again. This is where the difference between normal and callosotomized monkeys became clear; whereas healthy controls went through the learning process again, starting with a score of 0% correct, the callosotomized monkeys readily showed an increased performance [25]. This indicates that the learning process in both hemispheres is still intact and unaffected by the callosal lesions. Both healthy and callosotomized monkeys received conflicting information in the left and right hemisphere, which resulted in interference in the second reversal in healthy monkeys, whereas this interference was absent in callosum-sectioned monkeys.

One observation made by Sperry and Glickstein during this experiment was that there was transfer of information regarding the act itself: when the reversal started monkeys knew what to do with their contralateral hand, even though they did not know which stimulus was the correct one. Monkeys with severed optic chiasm and corpus callosum sometimes also showed transfer of visual information such as colour. This is likely to be transferred through the anterior commissure which links the inferotemporal cortex of the left and right hemisphere, and this area is known to be involved in visual discrimination learning in monkeys [25]. Conversely, there are cases without corpus callosum or anterior commissure showing interhemispheric transfer of information, suggesting an alternative pathway linking vision and motor control. This pathway is likely to involve the cerebellum, affecting transfer of visual information on one side of the cerebral hemisphere and motor performance on the contralateral hemisphere [25,26].

3.2. Studies in humans

The studies performed on non–human animals served as a functional comparison to the human condition. Although, there are some differences between non–human animals and humans when it comes to callosal sectioning, e.g. monkeys that have undergone a callosotomy can still transfer visual information through the anterior commissure. Callosotomized humans with intact anterior commissure are not capable of transferring visual information interhemispherically, thus remaining lateralized [27]. Animal studies have contributed to the investigation of callosal function, but the higher cognitive functioning in humans and their ability to solve complex tasks and communicate by means of language underlines the importance of human behavioural studies when investigating the involvement and function of the corpus callosum.

Studies involving human callosotomies have provided insight into brain lateralization and interhemispheric interaction by blocking transfer and thus allowing the two hemispheres to be investigated independently (for review see [6]). Many studies investigating callosal function use visual stimuli. Visual information is crossed between hemispheres by means of the optic chiasm in both healthy and callosotomized subjects. This allows all visual information present in the left visual field to enter the right hemisphere, while information entering the right visual field is projected to the left side of the brain. The stimuli represented in each side of the brain cannot be shared or integrated in split brain patients, due to the lack of callosal fibers, allowing information to remain lateralized. Apart from visual information, stereognostic and somatosensory information also remain largely lateralized [28].

With regard to movement and motor control, callosal disconnection does not cause a complete lateralization of motor control. Motor pathways can originate from both the ipsilateral and contralateral hemisphere. Sectioning of the corpus callosum impairs only ipsilateral sensory-motor controls. These ipsilateral projections are involved in proximal responses and are not very strong, whereas contralateral projections are very strong and are involved in both proximal and distal responses [6,29]. Coordinated hand movements require proximal and distal movements for reaching and grabbing respectively, thus requiring interaction between ipsilateral and contralateral hemispheres and an intact (posterior) corpus callosum [30]. Callosotomized patients can consequently show antagonistic activity of the hands, which can result in intermanual conflict. This is however a more direct effect of the surgery and decreases with time [29].

Callosotomized patients receiving different conflicting stimuli in each isolated hemisphere can show different spatial movements in each contralateral arm, whereas the temporal coordination of bimanual movement remains intact [6,31]. Another feature investigated during split brain research is the lateralization of language and speech. Language processing is restricted to the left hemisphere, and information projected to the right hemisphere cannot be transferred to the left hemisphere in callosotomized patients. Thus information isolated in the right hemisphere is not accessible by speech areas located in the right hemisphere, causing problems such as naming objects held in the left hand and thus projected to the right hemisphere [17].

The lack of hemispheric integration of lateralized cues in callosotomized patients reflects a system consisting of two separate units, which can memorize information separately. Similar to the experiment by Glickstein and Sperry [23], callosotomized humans can also memorize stimuli per hemisphere without being affected by the integration of confounding information from the opposing hemisphere. Presenting different types of stimuli in each visual half field and thus each isolated hemisphere provides information about different processing strategies between hemispheres.
The studies that have been described in this section highlight the importance of the corpus callosum during transfer of information between isolated hemispheres. Especially lateralized processes that require interhemispheric cooperation, such as combining tactile information entering the right hemisphere with the speech process present in the left hemisphere became impossible by the complete removal of the corpus callosum, underlining its importance. Lateralization is thought to be an advantageous feature in evolution, allowing each hemisphere to process a specific type of information without being affected by contralateral interference (see e.g. [37]). Lateralization is also a very important feature when investigating callosal function; lateralization of specialized areas can require cooperation between hemispheres to produce a fitting response on a variety of tasks/stimuli. This interhemispheric transfer and cooperation can also be affected in healthy individuals, e.g. when working load increases in complex tasks and more interhemispheric cooperation is required, while simple tasks can be processed in a single hemisphere [38,39,41]. This transfer can require more time and energy, but can prove advantageous over single hemisphere activity when task difficulty increases, when bilateral processing outweighs the costs of transfer [38]. This is strengthened by fMRI studies, which have also shown a greater bilateral activity in complex tasks versus simple tasks and thus a decrease in lateralization [38–41].

The degree of connectivity between hemispheres is thought to be an important factor in interhemispheric transfer and cooperation, with fiber size and density accounting for the regulation of transfer. Fiber size and density measurements are no longer restricted to post-mortem studies. A relatively new imaging technique that gained territory over the years is diffusion tensor imaging (DTI), which allows for multidimensional scans of axon networks. It measures the magnitude and direction of water diffusion (fractional anisotropy, FA), which provides information about axon size, myelination, axonal connections and orientation due to the hindered diffusion of water molecules because of the axonal membrane and myelin sheet [42]. Another feature of DTI is fiber tractography, connecting fibers to their corresponding cortical regions and investigating which areas of the brain are connected.

Another often used method to study functional connectivity is transcranial magnetic stimulation (TMS). This is a non-invasive technique using a magnetic field to cause depolarisation of axons in selected brain regions, allowing researchers to study interactions between cortical areas within and between hemispheres. Several studies have been published regarding TMS and inter-, and intra-hemispheric interactions (for review see: [43]), and its potential use as a therapeutic agent (repetitive TMS) for stroke victims has also been reported [44–46], although additional research is needed to allow for long-lasting efficacy [47]. TMS has also been used to determine conduction through callosal fibers and interhemispheric interactions [48]. The excitability of one motor cortex can be affected by applying a TMS pulse to the contralateral motor cortex; a TMS induced inhibition of activity can then be seen in the untreated contralateral hemisphere. Several different TMS techniques are distinguished; the repetitive TMS which allows for a longer duration-effect, single pulse TMS which are non-repetitive and the double or paired pulse providing two stimuli at different intervals and possibly with different intensities.
It is however still uncertain how the corpus callosum regulates transfer and communication between hemispheres, as studies investigating the role of the corpus callosum have conflicting statements. Some studies suggest that the corpus callosum could play an inhibitory role, whereas others say that the corpus callosum serves an excitatory function [13,19], these statements have to be distinguished from the neurochemical properties of the callosal fibers itself. When we look at the callosal axons they mostly depend on glutamate as a neurotransmitter and are therefore thought to be excitatory [19,49,50]. However, due to the presence of inhibitory interneurons, callosal signals have also been found to be inhibitory [13,49,51] and concluding evidence for an excitatory or inhibitory callosal function is lacking. The relationship between the degree of callosal connectivity and lateralization therefore remains ambiguous, splitting views in two models; an inhibitory model, and an excitatory model. The inhibitory model poses that the corpus callosum is maintaining independent processing between the two hemispheres, hindering activity in the opposing hemisphere and causing greater connectivity to increase laterality effects (positively correlated). The excitatory model poses that the corpus callosum shares and integrates information between hemispheres, causing greater connectivity to decrease laterality effects by masking underlying hemispheric differences in tasks that require interhemispheric exchange (negatively correlated) [13,19]. The degree of connectivity between hemispheres can be reflected by the size of the corpus callosum area [7,11,13].

Anatomical and functional lateralization can be explained by either of the two theories. Lateralization could have originated from an inhibitory function of the corpus callosum by inhibiting the opposing hemisphere, thereby hindering development and allowing for asymmetrical hemisphere development. The excitatory model could have allowed unilateral mutations, by some regarded as the origin of lateralization, to exist by allowing hemispheres to integrate information.

The right ear advantage seen in dichotic listening can be explained in the inhibitory model point of view. The dichotic listening technique is a much used behavioural test to study laterality and hemispheric asymmetry by presenting auditory stimuli to the left and right ear simultaneously. When the stimuli involve words it is often found that the right ear has an increased performance over the left ear, known as the right ear advantage (REA). This has often been deduced from the dominance of the left hemisphere for language and speech related subjects [49]. The corpus callosum could be involved in blocking the signal from the right hemisphere, reducing noise and allowing a better performance of the hemisphere specialized in the task, in the case of verbal stimuli this is the left hemisphere and thus the right ear [19,52]. Yazgan et al. [52] also performed dichotic listening tasks and found a negative correlation between the size of the corpus callosum and behavioural laterality. This outcome is in accordance with the excitatory model of callosal function [52]. Split brain patients show a complete right ear advantage, which is also in accordance with the excitatory theory, loss of callosal fibers increases laterality [49,53].

4.1. The inhibitory model

The inhibitory model presumes that greater connectivity, seen as a larger corpus callosum size could prove to be more inhibitory compared to a smaller corpus callosum, thereby increasing lateralization by inhibiting the opposing hemisphere. Callosal inhibition can allow for intrahemispheric processing which can be more efficient during simple tasks. When this inhibition becomes mutually exclusive it allows a single hemisphere to take control and dominate processing. This phenomenon is known as metacontrol and is based on the idea that transferring and integrating information between both hemispheres requires time and energy, and it can therefore be more efficient to use one hemisphere and inhibit the other in simple tasks [41,54–56].

4.1.1. Hemisphere dominance and metacontrol

Metacontrol is the choice mechanism which determines which hemisphere will become dominant during a given sensorimotor or cognitive task, when each hemisphere has access to the relevant stimuli. This does not necessarily imply that the non-dominant hemisphere is not involved, or that the dominant hemisphere is functionally most advantageous or specialized to complete the task [54–56]. This phenomenon would fit best with the inhibitory model, by inhibiting activity of the opposing hemisphere the other hemisphere can become dominant for the processing of the stimulus information. It remains unknown which hemisphere will become dominant during a given task, but there are some factors influencing metacontrol, such as hemispheric stimulation time, task instructions/knowledge of features, input processing strategy and computational complexity [41,54,55]. Asynchronic stimulation can also cause a shift in cerebral dominance due to functional specialization, e.g. neural responses in right hemisphere during face matching tasks [55].

Tasks involving a single hemisphere, such as lateralized tasks projecting stimuli in one visual hemi-field can provide information about the functional specificity of that hemisphere. Bilateral representations involve both hemispheres and comparing unilateral information with bilateral information in conditions with conflicting stimuli can provide information about hemispheric dominance and its relation with functional specialization [55]. Urgesi et al. [55] have indeed found an indication of right hemisphere dominance for face processing tasks using chimeric faces. However, the functional dominance of the right hemisphere can be overruled when the stimulus is presented sequentially, indicating that dominance does not always rely on functional specificity.

The first dissociation between hemisphere dominance and hemisphere specialization was found in split brain patients [57,58]. These patients also received brief exposures to chimeric faces. When the patients were asked to point out which face they saw, they chose the face that corresponded with the left half of the stimulus, projected to the right hemisphere specialized in face processing. When patients had to verbally describe the stimulus, they described the face corresponding to the right half of the stimulus, projected to the left hemisphere. This suggests a modality related hemisphere dominance. Whereas the left hemisphere does not have a functional specificity for recognizing faces, it did prove dominant over the right hemisphere by describing the stimulus in the right visual half field, showing that dominance and specialization are not always associated, but this also resulted in a poor performance [57,58].

In the case of the split brain patients the request to verbally describe the stimulus required activation of the left hemisphere to access the speech areas, while the left hemisphere only contained information from the right visual half field. Activating the speech process in the left hemisphere appeared to be dominant over activation of the right hemisphere which was associated with a good performance due to its face recognition specialization. Still the line between dominance and specialization remains thin, as each specialized hemisphere is accessed based on different task instructions, and this makes it dominant over the other hemisphere. Dominance thus seems determined by the specialization for the given task instructions, it depends on which hemisphere needs to be activated in order to comply with the instructions. So in a way dominance could be guided by specialization to fulfill task requirements.

These studies of metacontrol were thought to reflect the theories of the inhibitory model. Though, no measures have been done concerning callosal size or callosal connectivity, which could have
provided insight into the function of the corpus callosum during metacontrol, strengthening the inhibitory theory. Though, according to the studies by Levy et al. [57,58] metacontrol is also possible in split brain patients, thereby questioning the functional importance of the corpus callosum during metacontrol.

Adam and Güntürkün [54] have investigated metacontrol in pigeons, seeing that bird eyes are placed more laterally allowing for a small binocular overlap. Also in birds the optic nerves cross almost completely allowing almost all information in one visual half field to be transferred to the contralateral hemisphere. Another important feature of birds is the lack of a corpus callosum. The pigeons showed an indication of hemispheric dominance or metacontrol in a color discrimination task with conflicting stimuli [54].

The fact that metacontrol is present in birds thus suggests that the corpus callosum is not necessary to develop metacontrol. It could thus be that metacontrol can also be established by structures other than the corpus callosum.

4.1.2. The aging corpus callosum

Age related changes in morphology or connectivity of the corpus callosum can have an impact on behaviour. Microstructural changes that occur in normal aging can have an effect on interhemispheric processing [59] and can provide evidence for the theories of function.

The corpus callosum has a relatively long developmental trajectory and fully develops during puberty. Callosal fibers are not completely myelinated until the age of 10–13 years [9,60]. This has an effect on the connectivity between hemispheres and can result in mirror movements or motor overflow in young children; involuntary movements of the ipsilateral and contralateral hand [61,62]. There is a developmental trend with motor overflow decreasing significantly until 6–8 years of age [62]. However, with old age mirror movements can sometimes be seen again as a result of callosal demyelination or atrophy [63]. Recent studies have shown a decrease in lateralization with age, tasks strongly lateralized for young adults can become bilateral in older brains. A possible explanation could be that the neuronal processing in one hemisphere is diminished, requiring the two hemispheres to work together in order to solve the task. This also seems to correlate with task difficulty in the brains of young adults [16]. This tells us something about the balancing properties of the corpus callosum in processing recourses between hemispheres.

Age related thinning of the corpus callosum is often reported, though still controversial. Studies involving older adults show age related atrophy in the anterior and middle sections of the corpus callosum, the posterior part does not appear to be susceptible to age related atrophy [12,54,64,65]. Sex effects have also been found, possibly guided by changes in hormonal balance [15].

DTI studies of white matter integrity and decreased callosal density with old age appear robust and are correlated with slower reaction times in an interhemispheric transfer time task. Reduced callosal integrity can affect the speed of interhemispheric transfer time, which can occur during the natural aging process and affects both motor and sensory processes [66].

Langan et al. [67] investigated if age related degeneration of the CC could alter inhibition between hemispheres. Age related differences in CC morphology were seen, with a smaller CC area in older subjects. Over-recruitment of the ipsilateral motor cortex was only seen in older participants and appeared to be associated with longer reaction times, reflecting interhemispheric transfer and negatively influenced performance. A decreased resting connectivity between hemispheres in older adults appeared to be associated with increased ipsilateral motor cortex recruitment, possibly due to a failed inhibition of the ipsilateral motor cortex. Recruitment of bilateral motor areas during unimanual tasks could thus be disadvantageous [67]. Bilateral recruitment does not always prove to be disadvantageous; in complex cognitive tasks or difficult speech perception tasks bilateral activation results in better performance of older adults [68,69].

According to Langan et al. [67] age related thinning causes a failed inhibition of the opposing hemisphere during a simple motor task. Decreased connectivity results in a decreased lateralization and thus mirror movements in older people. These findings provide evidence for the theory of inhibition.

Another recent study by Putnam et al. [70] investigated if individual differences in callosal organization of healthy individuals are associated with the activity in the non-dominant hemisphere when performing a lateralized task, combining DTI and fMRI data. They suggest that the fractional anisotropy (FA), as measured by means of DTI, is a reliable predictor for the cortical activity in the non-dominant hemisphere during performance of a lateralized task. Increased FA was associated with a decrease in activity of the non-dominant hemisphere, which is consistent with the inhibitory theory; greater FA indicates an increased connectivity, thus allowing for more inhibition causing increased lateralization, which is seen as a decrease in non-dominant hemisphere activity [70].

Using a paired TMS pulse interhemispheric inhibitory and excitatory effects have also been found in the motor cortex upon stimulation of the contralateral motor cortex [71,72], although most findings involve predominantly interhemispheric inhibition [43]. Excitatory effects are only elicited when interstimulus intervals (ISIs) are very short, whereas inhibitory effects are seen over short as well as longer ISIs [43,71] and are thought to be mediated by different mechanisms [43,73].

4.2. The excitatory model

The main theory behind the excitatory model is the reinforcement of information transfer and integration between hemispheres, activating the unstimulated hemisphere. Supporting evidence comes from early callosotomies used as a treatment for intractable epilepsy: sectioning the corpus callosum stops the spread of discharge to the other hemisphere, blocking the signal which activates the other hemisphere, which supports the evidence for excitatory function [19]. This is also strengthened by the disconnection syndrome as a result of callosotomies; these patients are unable to integrate information from each hemisphere, showing that the communication between hemispheres, and the sharing of information, is necessary for normal behaviour [19]. The recruitment of bilateral brain regions during tasks with a high level of complexity also provides evidence for the excitatory function of the corpus callosum and the ability to integrate information between hemispheres.

Yazgan et al. [52] and Clarke and Zaidel [13] have also found supporting evidence for the excitatory model by subjecting healthy right-handed participants to a series of psychological tests measuring behavioural laterality and MRI scans and found a significantly negative correlation between performance on the behavioural laterality tests and corpus callosum size [13,52]. This is in accordance with the excitatory model, a smaller corpus callosum and thus a lesser connectivity causes increased laterality effects. This also means that a lack of excitatory connections due to a smaller corpus callosum increases asymmetry in the brain.

Another simpler and much used measure of lateralization is handedness, as most right-handed people have a language representation in the left hemisphere. Handedness and callosal size have been subject of many MRI studies but are also found to have conflicting relations; some found that handedness affects callosal size whereas others did not find any association.

Although poorly reproducible, interhemispheric facilitation has also been found with TMS using short ISIs (3–5 ms) during a paired pulse over the motor cortex [71].
4.3. Comparison of the two models

Division of activity between hemispheres in simple or complex tasks can be attributed by the inhibitory function of the corpus callosum, allowing for intrahemispheric processing in simple tasks and thereby increasing efficiency compared to interhemispheric processing. Also callosal thinning with age and its association with a decreased laterality provides evidence for the inhibitory model. FA as measured by DTI in healthy individuals has also been shown to have an inverse relation with activity in the non-dominant hemisphere, indicating an inhibitory function of the corpus callosum. Metacontrol was initially thought to represent mutual inhibition of hemispheres, but its presence in individuals without corpus callosum suggests that the corpus callosum might not play a major role in this process.

Recruitment of bilateral brain regions can also be seen as an excitatory function of the corpus callosum, by allowing integration between hemispheres. This sharing of information is crucial to normal behaviour as seen by the split brain patients and the effectiveness of callosotomies is also attributed to the excitatory function of the corpus callosum. Other findings concerning callosal size and performance in behavioural laterality tasks also provide support for the excitatory model.

Activation of bilateral brain regions can also be seen from the inhibitory perspective; the unilateral processing during simple tasks can be caused by increased callosal inhibition, whereas bilateral processing during complex tasks can be attributed to increased callosal excitation. The models that have been described are tested best when callosal size is associated with functional lateralization. However, callosal size is not always measured and as mentioned earlier the differences between studies can also result in varying outcomes. Differences in patient groups, classifications (e.g. handedness), stimuli used and materials used to determine callosal morphology all have their influence on outcomes resulting in conflicting statements [13]. For example handedness does not always provide a good measure of brain lateralization, as left-handed individuals are sometimes found to have a bilateral language representation in the brain, and 1–5% of the right handers can have a right hemisphere language representation [19,74]. Another factor that needs to be taken into account is the individual differences in brain asymmetry, i.e. some individuals are equipped with a bilateral language representation which can affect performance in the dichotic listening task [13].

5. Pathologies

The studies mentioned so far have investigated callosal function by means of its absence (the split brain studies and lesion studies) or its function in healthy individuals. However, looking at associations between altered morphology and disorders can also improve understanding of function. Altered corpus callosum morphology and function has been related to several (psychiatric) pathologies, such as schizophrenia, autism, ADHD, alien hand syndrome, personality disorders and bipolar affective disorder. Some of these pathologies have no direct cause and show symptoms that are comparable to split brain patients with the post-operative disconnection syndrome. Other symptoms concern mood changes, which are thought to be related to altered activity in one hemisphere (for review see: [75]) and represent a disrupted balance between hemispheres. Investigating these disorders can help us look into altered behaviour patterns and their relation with altered CC morphology, allowing researchers to identify changes in morphology (of the whole corpus callosum as well as its sub regions) to similar behavioural alterations and their effects on interhemispheric transfer.

5.1. Schizophrenia

Schizophrenia literally means split-mind, it is a severe psychiatric illness characterized by hallucinations (mostly auditory) and delusions, thought alienation, deterioration of social functioning, abnormal speech production and motor disturbances [76]. The behavioural abnormalities seen in schizophrenics reflect problems in the connection between cortical areas, which ultimately points towards the corpus callosum. Schizophrenia has already been linked with disturbances in all kinds of brain regions, mainly in the frontal and temporal regions. The corpus callosum can be linked to schizophrenia through dysfunction of any brain region that transfers information through the corpus callosum. Another possibility is callosal dysfunction and its effects on processing and integration of information between cortical structures.

The effects regarding callosal dysfunction in schizophrenia can result in abnormal transfer. One theory that has been posed to be involved in schizophrenia is an excess of callosal connectivity resulting in (possibly unfiltered) overload of interhemispheric transfer. David [77] indeed found supporting evidence for hyperconnectivity in schizophrenics compared to controls using a variation of the STROOP task. This hyperconnectivity effect has also been seen in MRI, where patients show a much higher activation while at rest [78].

Cases with abnormalities in callosal morphology have been related to psychiatric disturbances; e.g. an increased prevalence of callosal dysgenesis is found in patients with schizophrenia [79]. The first MRI studies investigating callosal morphology in schizophrenics were subjected to high individual variability and have found conflicting results concerning callosal dimensions compared to healthy individuals, but in general these studies point towards a reduction in size in schizophrenics. This reduction in size is clearer in first-episode schizophrenics than chronic patients, possibly due to the antipsychotic medication [80].

Walterfang et al. [81] have compared callosal morphology and regional callosal thickness in first-episode and chronic schizophrenics by means of MRI and found a significant reduction in anterior genu in first-episode schizophrenics and extending to the posterior genu and isthmus in chronic schizophrenics [81,82]. Bersani et al. [83] have found a smaller splenium width in schizophrenics involved in transfer of visual information. Patients with schizophrenia have been found to have deficits in the perception of visual motion and could thus be related to the abnormal size of the splenium. They also found a smaller anterior midbody in the age group 26–35, this region is known to increase in size (by means of increased myelination or increase in axonal size) until the late twenties, which correlates with the time of onset of schizophrenia, suggesting reduced myelination in schizophrenics [83].

Findings regarding abnormal callosal dimensions suggest a reduction in size for schizophrenics. Also the hyperconnectivity theory seems likely to be involved in schizophrenia and can cause a disturbed integration of information concerning self and environment, resulting in symptoms characteristic to schizophrenia.

5.2. Autism

Autism is a developmental disorder characterized by impaired social interaction and communication and patients often show repetitive behaviours and have fixed interests and behaviour. As the major pathway integrating sensory, motor and cognitive information between hemispheres, callosal abnormalities have been linked with autism. Hardan et al. [84] have found a significantly smaller anterior area in autism patients compared to controls [84,85]. Using a different method (3D maps of MRI images) they found a significant smaller genu and splenium in patients with autism [85]. He et al. [86] used a shape comparison of the corpus callosum by means
of MRI in healthy participants and patients suffering from autism to define anatomical landmarks. They found differences in global shape caused by different bending degrees of the callosal body and shape differences in the anterior bottom of the corpus callosum between autism patients and controls [86].

A recent study by Just et al. [87] investigated brain synchronization as a measure of functional connectivity by means of fMRI in relation to callosal size in autism patients and controls. To investigate the degree of synchronization participants were asked to perform a task known as the Tower of London (TOL), which provides information about executive processing. In healthy individuals the TOL task evokes bilateral activation in the prefrontal and parietal areas. If autism causes a decreased connectivity, as has been posed by a new theory [88], this could result in a measurable effect during the task. Indeed they found three indications of underconnectivity; both groups showed activation in similar brain regions, but the autism group showed lower activation in the frontal and parietal regions, likely to relate to differences in structural connections. Also the genu and the splenium have been found to be reliably smaller in the autism group and this correlated with frontal-parietal activity in the autism group [87]. Other MRI and fMRI studies have shown thinning of the corpus callosum and underconnectivity, especially in the frontal areas of the brain and the fusiform face area. This could explain the preference of objects over people in children with autism [89].

5.3. Alien hand syndrome

Behavioural symptoms of alien hand syndrome (AHS) closely resemble the behavioural changes that are associated with the disconnection syndrome; dissociation of left and right and difficulties with bimanual activities. Patients suffering from alien hand syndrome report that one of their hands performs involuntary movements, resulting in intermanual conflict. Dysfunction of the corpus callosum was therefore thought to be a prime suspect in this syndrome. However, not all patients with alien hand syndrome suffered from callosal dysfunction. Some cases were caused by tumours which did not involve the corpus callosum, mainly involving frontal lobe areas [90]. Faber et al. [91] have investigated a case of alien hand syndrome and found the patient had a slit-like left paracallosal lesion extending from the genu towards the splenium, thus indicating the involvement of the corpus callosum in some cases of AHS.

Lesions involving the corpus callosum or the frontal lobe in patients suffering from alien hand syndrome do appear to have a different effect on behaviour of the autonomous hand. Where frontal AHS shows signs of compulsive manipulation of tools, callosal AHS is primarily characterized by intermanual conflict [90]. This underlines the importance of distinguishing symptoms when investigating morphological differences. Also alien hand syndrome is very rare, with relatively few cases that exists, making it a difficult case to study intensively.

5.4. ADHD

Attention deficit-hyperactivity disorder, or ADHD is characterized by high degree of impulsivity, hyperactivity and attentional problems. Although ADHD does not show similar behavioural changes as split brain patients, the corpus callosum has been shown to be involved in attentional processes and has therefore been pointed as a possible candidate in the development of ADHD. Hutchinson et al. [92] have done a meta-analytic review combining data from 13 studies. The results indicated that children and adolescents with ADHD indeed have a smaller splenium compared to controls with an additionally smaller anterior corpus callosum for boys. The areas connected by the splenium involve the parietal cortex, which supports functions as sustained and divided attention [92]. Cao et al. [93] have found a significant size difference between ADHD patients and controls with an overall decrease in size for ADHD patients and a decrease in size of the isthmus and posterior midbody with MRI. In addition they investigated microstructural differences with DTI and found a reduced FA in the isthmus, which also connects posterior brain regions which are known to be involved in attentional control [93], an important behavioural characteristic of ADHD.

5.5. Bipolar disorder and borderline personality disorder

Bipolar disorder is a mood disorder characterized by manic and depressive periods. Borderline personality disorder (BPD) shares a common feature with bipolar disorder, namely the mood instability but is regarded as an unrelated disorder mainly differing in the length of the mood change. It is thought that impaired information transfer plays a role in developing mood dysregulation in bipolar disorder and borderline personality disorder and could thus be caused by callosal dysfunction. Reductions in size of anterior and posterior callosal regions and a global thinning of the corpus callosum have been reported in patients with bipolar disorder [94,95]. These results have been compared with first-degree relatives to restrict callosal abnormalities with the disorder, and indeed these relatives did not differ with controls [95].

Walterfang et al. [96] have also investigated callosal morphology in teenagers with first-presentation borderline personality disorder, but did not find significant differences between BPD patients and controls in total size, length or curvature. This lack of morphological evidence could be related to the duration of the disorder, as Walterfang et al. [95] have found an association between illness duration and callosal shape in patients with bipolar disorder.

5.6. Multiple sclerosis

Multiple sclerosis (MS) is an inflammatory disease affecting myelinated axons, leading to neurological and cognitive impairments. The corpus callosum is the largest white matter structure in the brain and is therefore considered a target for inflammation. Corpus callosum degeneration and axonal loss is repeatedly described (e.g. [97–100]) and can result in impaired interhemispheric communication [99], such as an impaired motor inhibition in the contralateral motor regions [98]. Also an enhanced right ear advantage is seen in dichotic listening techniques with MS patients [100], which could relate to both inhibitory as well as excitatory function based on the correlations found in that particular study.

5.7. Callosal involvement in disorders

The exact function or dysfunction of the corpus callosum in above (psychiatric) disorders remains uncertain. The behavioural abnormalities seen in above mentioned disorders can be ascribed as being a primary effect of the corpus callosum, but can also be attributed to be a secondary effect of dysfunctional cortical regions. However, some of the above mentioned disorders do show evidence of callosal involvement, exhibiting signs of altered morphology, underconnectivity or hyperconnectivity which results in behavioural abnormalities as seen in these disorders. Callosal thinning by defective myelination or decreased fiber density, as seen in MS, alters interhemispheric communication resulting in behavioural deficits corresponding with the cortical regions connected to the corpus callosum that can manifest itself in pathology specific symptoms. Altered development of posterior regions can result in difficulties with attentional processes as seen in patients with ADHD, or visual processing as seen in some schizophrenics. Morphological alterations in anterior callosal regions affects frontal
lobe function as seen in patients with autism, creating difficulties with face recognition. These pathologies thus result from disturbed communication between hemispheres due to these callosal abnormalities. Significant morphological alterations in the corpus callosum can therefore inform us about function, and can consequently be responsible for dysregulation of interhemispheric transfer, i.e. underconnectivity, hyperconnectivity, possibly caused by differences in fiber density or defective myelination.

6. Discussion

The corpus callosum has proven to be an important structure in the human brain. Although it is possible to live without this white matter structure, it is required for a functional integration of cognitive and sensory information from one cerebral hemisphere to the other. How it regulates this transfer of information between cortical areas seems uncertain. In absence of this hemispheric communication behavioural abnormalities can occur, mainly due to the lateralization of brain function. Such lateralization is thought to be mediated by the corpus callosum. This allows for more cortical space, but requires integration of cortical areas in the opposing hemisphere to function properly in some situations. This is observed in patients with a sectioned corpus callosum and is known as the disconnection syndrome: left and right become dissociated and performance of ipsilateral body parts becomes poor when involving lateralized functional processes, such as language or spatial navigation. Partial callosotomies or callosal lesions have provided information about the functional specificity of the callosal sub regions. The sub-regions connect to different cortical regions, and vary in fiber size and density. They do not have clear anatomical landmarks or boundaries that separate them from each other and this complicates resolving the exact function of callosal segments. General morphology studies are subjected to a high degree of variation. This variation can be attributed to a number of factors, such as type of measurements, MRI, post-mortem studies, corrections for brain volume have not always been performed (males often have larger brains compared to females, also ADHD patients have been reported to have smaller brain volumes), faulty head positioning and head tilt can also attribute to incorrect measurements. Most early studies involve gross callosal size, there was no identification of callosal sub regions. This is incorporated in recent studies, but remains difficult due to the not well defined sub regions. The original classification by Witelson [10] dates from 1989 and is widely accepted, however recent studies by Hofer and Frahm [101] have proposed some modifications concerning fibers that project beyond the boundaries set by Witelson [10], based on DTI studies [101,102]. These concern projections to the motor areas of the brain, and are found more posteriorly than the original scheme.

The corpus callosum is an important mediator of interhemispheric transfer, but the nature of this mediation is a topic of discussion. According to some the corpus callosum acts as dam preventing information from reaching the opposing hemisphere and thereby increasing lateralization. Better callosal connectivity would then account for a higher degree of lateralization due to its inhibitory qualities, and this is known as the inhibitory theory. The excitatory theory poses that the corpus callosum actively integrates information between hemispheres. When the connectivity between hemispheres is increased this would decrease lateralization due to the excitatory qualities of the corpus callosum. Both theories are backed up with evidence from a number of different studies, and can both account for the origin of lateralization when looking from an evolutionary perspective. Still some confounding factors remain when investigating callosal function. The most used method to measure connectivity is callosal size, yet there is a lot of conflicting information between individuals of different age and sex and studies, relating to subject groups and methods used. Also, callosal size has been associated with small diameter fiber density but not with large diameter fibers, which allow for a much faster transmission of signals and involve mainly sensory information [7,11]. Clarke and Zaidel [13] have attributed the lack of significant associations between callosal morphology and behavioural laterality or interhemispheric transfer to the unreliability of size as a measure of connectivity. They proposed that callosal size is only a reliable measure when it comes to higher order associative functions, but not sensory functions [13,70]. There are other neuroimaging techniques to measure connectivity, such as the resting state functional MRI (fcMRI) used in the study by Lancaster et al. [67], tracking chances in blood flow in different regions of the brain and measuring temporally correlated BOLD signal oscillations. Diffusion tensor imaging also allows for in vivo studies and is an important technique for studies involving callosal organization, due to its poorly defined anatomical boundaries.

The possibility that the corpus callosum does not purely have an excitatory or inhibitory function exists; this may be dependent on a subcortico-cortical network that balances hemispheric activation according to the task demands [2,19]. The improvements in imaging techniques has provided more insight into callosal morphology, and the specific role of the different callosal sub regions in integrating cognitive and sensory information interhemispherically. Schulte and Müller-Oerling [2] have reviewed recent findings concerning callosal function in interhemispheric processing and imply that the different callosal areas can exhibit a different function. They suggest a different function for separate callosal regions for local-global processing [103,104], as well as semantic competition [2]. This difference in function of sub regions has been described before, combining fMRI and DTI to provide a relation between cortical activity during behavioural tasks and white matter integrity in specific callosal regions [105,106].

Another possibility to investigate callosal function is looking at alterations in morphology in disorders. However, when investigating psychiatric disorders there are a number of factors that can influence the outcome of an investigation. Many of these disorders have comorbidities, which in some cases have been controlled for, that can complicate any associations that have been found. Also, a lot of variation is seen in patient groups, such as age, sex and type of symptoms. Some psychiatric illnesses can have distinct symptoms in different individuals, this can again be attributed to different abnormalities in the corpus callosum. The stage of illness can also affect morphology as seen in the schizophrenia research, differences between first-onset schizophrenics were more pronounced compared to chronic patients, possibly due to the medical treatment. Differences in methods used determining callosal morphology (MRI, DTI and post-mortem) as well as differences in classification can also provide variation between patient groups.

In conclusion it remains difficult to investigate the true function of the corpus callosum. Although its function as mediator of interhemispheric transfer is established, its role regarding recruitment of brain regions in the opposing hemisphere by means of excitatory or inhibitory signals still is a topic of debate. The examples that have been discussed comply with both theories. However it seems likely that there is a possibility of both inhibitory and excitatory function within the same corpus callosum. Instead of looking at the corpus callosum as a single structure it would be crucial for future research to investigate the functional role of the callosal sub regions, and use better methods to determine functional connectivity such as fiber characteristics (e.g. DTI in combination with fMRI) when looking at interhemispheric transfer during behavioural laterality tasks.

References


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