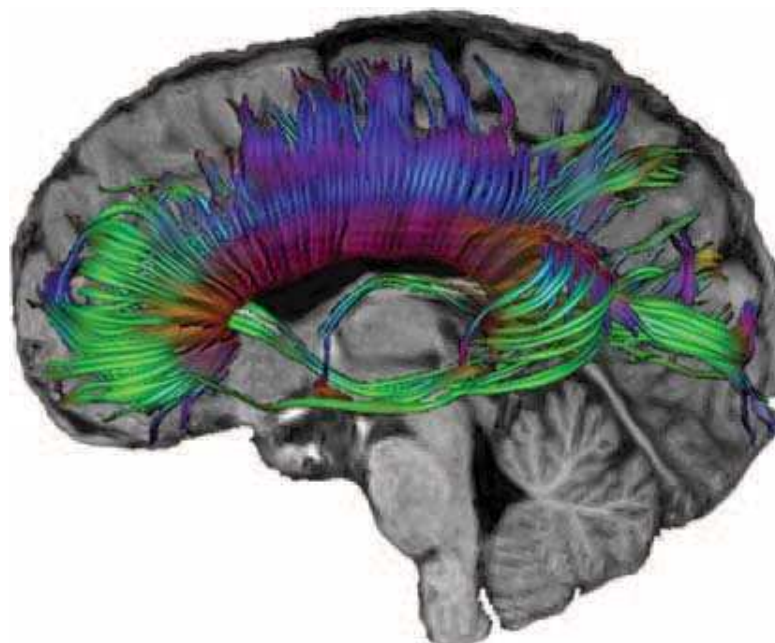# The Corpus Callosum and Brain Hemisphere Communication

How does the corpus callosum mediate interhemispheric transfer?

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Image on front page taken from Wilde et al., (2008).

Abstract

The corpus callosum is the largest white matter structure in the human brain, connecting symmetrical and asymmetrical cortical regions of the opposing cerebral hemispheres. Complete and partial callosotomies or callosal lesion studies have provided a great opportunity to further investigate the organization and connection of motor and sensory functions across hemispheres as well as cortical representations of cognitive functions and perceptual processes and the lateralization of function. It has also granted more insight into the function of the corpus callosum, namely the facilitation of communication between the cerebral hemispheres. The corpus callosum is thought to have attributed to the functional specialization of hemispheres by mediating information transfer between hemispheres, but how the corpus callosum mediates this transfer is still a topic of debate. Some pose that the corpus callosum maintains independent processing between the two hemispheres, causing a greater connectivity to increase laterality effects. Others say that the corpus callosum shares information between hemispheres and serves an excitatory function, causing greater connectivity to decrease laterality effects. These theories are further explored by reviewing recent behavioural studies and morphological findings to tell us more about callosal function. Additional information regarding callosal function in relation to altered morphology and dysfunction in disorders is also reviewed to supplement the knowledge of callosal involvement in interhemispheric transfer. Both the excitatory as well as the inhibitory theory seem likely candidates to describe callosal function, although evidence from recent studies favour the inhibitory model. However the corpus callosum is a complex structure consisting of distinct components which could allow for the possibility to have both an excitatory or inhibitory function that can alter according to task demands. Instead of focusing on the corpus callosum as a single structure it would be beneficial for future research to investigate the functional role of the callosal sub regions, and use better methods to determine functional connectivity when looking at interhemispheric transfer.

Keywords: *Corpus callosum, Interhemispheric transfer, Split brain, Lateralization, Connectivity, Morphology.*

History

The corpus callosum

The corpus callosum is a structure in the brain of all placental mammals that connects the left and right cerebral hemisphere. Containing numerous intra-, and interhemispheric axonal projections it is considered to be the largest white matter structure in the brain. In the past its function has been regarded as unimportant, however over the years more insight into its function has originated from callosal lesion studies and patients undergoing complete or partial corpus callosotomies. These callosotomies served as a treatment for intractable epilepsy, preventing seizures from spreading over the entire brain. The first callosotomy was performed by Dr. van Wagenen and Herren (1940), this treatment was found to be effective 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, showing that complete section 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. These patients are often named split brain patients, but originally the split brain refers to the sectioning of all commissures in the brain. In this thesis the term split brain will represent patients without corpus callosum, but with other intact brain commissures.

This unique cognitive state of callosotomized patients has led to more elaborate research regarding hemispheric transfer or communication between different cortical areas and the functional specialization of the corpus callosum. The questions that are posed in this thesis concern callosal function; when and how does the corpus callosum direct the communication between the cortical areas of each hemisphere? In order to investigate callosal function we first have a look at the gross anatomy and functional organization of the corpus callosum. Following anatomy, function is investigated by means of disconnection studies that have been performed in animals and humans. We will then have a look at how the corpus callosum regulates interhemispheric transfer and the different theories that have been posed concerning callosal function. Pathology is studied to further complement knowledge about the role of the corpus callosum, and the effects of callosal dysfunction and altered morphology on behaviour. Finally the theory described will be discussed and some concluding remarks are given concerning callosal function.

Corpus Callosum Anatomy and Functional Organization

Brain Commissures

Brain communication can occur within hemispheres (intrahemispheric) or between hemispheres (interhemispheric). Intrahemispheric communication occurs by means of white matter tracts that connect cortices of the frontal, parietal, occipital and temporal lobes, by means of cortico-cortical or cortico-subcortical pathways and its information is also available for interhemispheric processing. Interhemispheric processing occurs through brain commissures consisting of white matter connecting the two cerebral hemispheres (Schulte & Müller-Oehring, 2010). The human brain has 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 (Raybaud, 2010). 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 (Aboitiz & Montiel, 2003).

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 (Gazzaniga, 2000). 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 left hemisphere). In order to investigate how the corpus callosum mediates the transfer of information we first have to take a look at the functional organization of the corpus callosum.

Functional Organization

The corpus callosum consists of around 200 million fibers connecting the two hemispheres (Aboitiz, Scheibel, Fisher & Zaidel, 1992b) which are fixed at birth but fiber myelination continues through puberty and also accounts for morphological changes (Luders, Thompson & Toga, 2010a; Mayston et al., 1997). 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; (anterior-posterior) the genu, truncus or midbody and splenium (Witelson, 1989). Corpus callosum size and width have been shown to vary between individuals and possibly across gender (Aboitiz, Scheibel, Fisher & Zaidel, 1992a; Junle et al., 2008; Luders et al., 2010a; Clarke & Zaidel, 1994; Hasan et al., 2008), however these findings are often controversial, some saying that women have a larger corpus callosum compared to men, whereas others do not find any differences. It has been posed that individual and gender differences are dependent on the developmental trajectory, with a longer callosal development period for females, and possibly influenced by hormonal balance (Salat, Ward, Kaye & Janowsky, 1997). Differences between studies can be caused by variations in patient groups, corrections for brain size (males often have a larger brain), technological variations such as the type of measurements.

Partial callosotomies and lesion studies have contributed greatly to the knowledge of callosal functional specificity (Gazzaniga, 2005); 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. For example Fabri and colleagues (2005) have investigated the role of the different callosal sub regions in transferring tactile stimuli. Investigating performance in partial callosotomized patients (with intact splenium and possibly also the posterior callosal body), complete callosotomized patients and controls pointed out that transfer of tactile stimuli is most likely to travel through the posterior corpus callosum, as the partial

callosotomized patients performed significantly better compared to the complete callosotomized patients (Fabri et al., 2005).
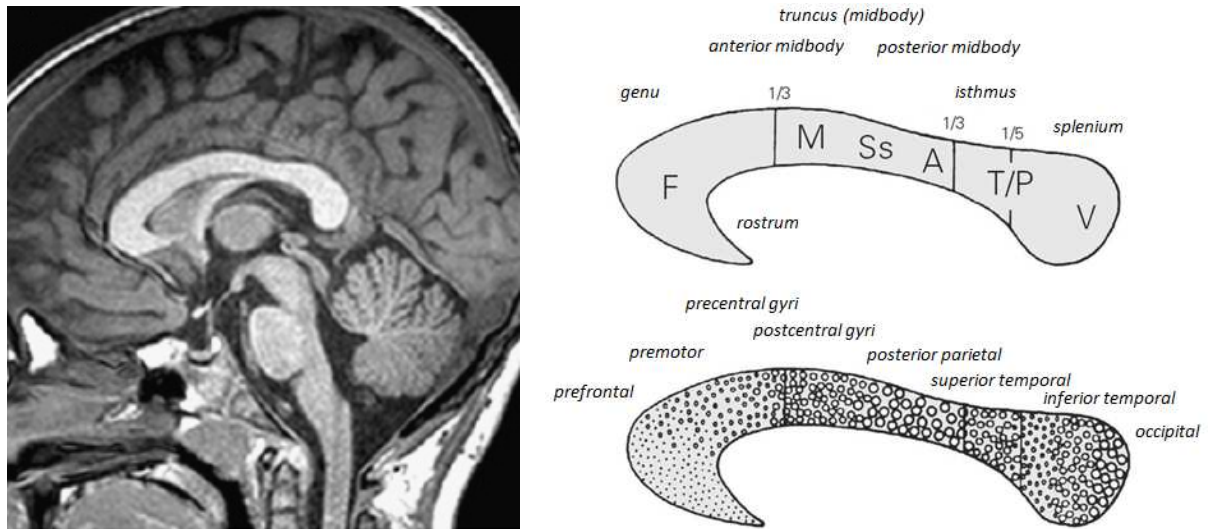

Figure 1. A) Midline saggital cross section of the human brain visualizing the corpus callosum. (Raybaud, 2010) B) The corpus callosum representing different cortical regions (top) and differences in fiber composition along the corpus callosum (circle size representing fiber diameter)(bottom). A, auditory fibers; F, frontal fibers; M, motor cortex fibers; Ss, somatosensory fibers; T/P, tempoparietal fibers; V, visual fibers. Adapted from Aboitiz & Montiel (2003)

Fiber size and composition along the corpus callosum differs according to the topographical organization of the cortex (see figure 1). The anterior part of the corpus callosum, also known as the genu contains the highest density of thin myelinated axons connecting the prefrontal cortex and higher order sensory areas. The density of fibers decreases from genu to the truncus or body of the corpus callosum. The midbody contains axons running to the parietal and temporal lobes. The posterior midbody of the corpus callosum contains thick axons involves 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 is therefore known as the isthmus, connecting fibers of motor, somatosensory and primary auditory areas. (Buklina, 2005; Aboitiz et al., 1992b; Aboitiz & Montiel 2003; Fabri et al., 2005; Raybaud, 2010; Aralasmak et al., 2006)

Not all axonal connections are directed at regions in the symmetrical plane (e.g. frontal lobe to frontal lobe) but can also be asymmetrical (e.g. frontal lobe to temporal lobe) (Schulte & Müller-Oehring, 2010; Clarke & Zaidel, 1994). Fiber size is representative for the interhemispheric transfer time. The thick myelinated fibers with large diameters will provide a faster transmission of sensory-motor information, whereas the thin myelinated fibers with a small diameter provide a slower transmission between association areas (Bloom & hynd, 2005). However, transfer of information or parallel processing requires time, energy, coordination and integration and is therefore not always beneficial; some interhemispheric interactions through small diameter thin myelinated fibers can take as long as 100-300ms (Liederman, 1998). Functional connectivity between cortical areas of opposing hemisphere can be investigated by means of behavioural measures and fMRI and DTI techniques and are subjected to individual variation (Baird, Colvin, VanHorn, Inati & Gazzaniga, 2005).

It is possible to process information in a single hemisphere without having 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 and how important is the corpus callosum in this process? To answer these questions we have to take a look at callosal function and its relation to behaviour.

Animal Disconnection Studies

Some of the first studies concerning callosal function were done in animals, in which functional and behavioural changes were examined after sectioning of the corpus callosum. In 1925 Bykov used Pavlovian conditioning in dogs to determine behavioural changes before and after sectioning of the corpus callosum (for translation see: Glickstein & Berlucchi, 2008a). Firstly one of his students identified that a conditioned response concerning one side of the body is automatically elicited when the opposite site 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 two surviving dogs did show 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 (Stamm & Sperry, 1957; Glickstein & Sperry, 1960; for review see: Glickstein & Berlucchi, 2008b; Glickstein, 2009). However, these experiments no 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 (1960) 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, creating one trained arm and one untrained 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. 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 becomes clear; where normal monkeys have to go through the learning process again, starting off with a score of 0% correct, the callosotomized monkeys readily show an increased performance (see figure 2) (for a review see: Glickstein, 2009). 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.
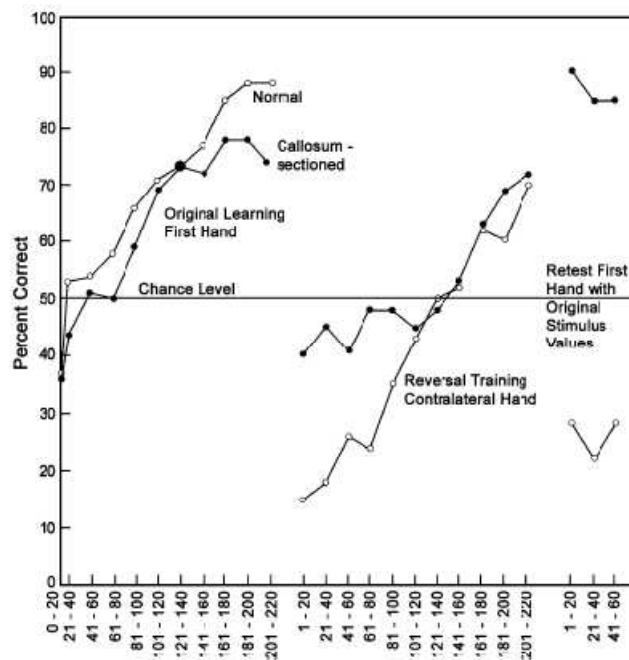

Figure 2. The performance of normal (n=3) and callosotomized (n=3) monkeys during a tactile discrimination task followed by two reversals. A clear difference can be seen between normal and callosotomized monkeys in the second reversal, returning to the original stimulus variables, ▣ = normal o = callosum sectioned. (Glickstein & Sperry, 1960)

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 readily 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 show 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 (Glickstein, 2009). 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 (Glickstein, Buchbinder & May, 1998; Glickstein, 2009).

Human Disconnection Studies

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 which have undergone a callosotomy can still transfer visual information through the anterior commissure, whereas callosotomized humans with intact anterior commissure are not capable of transferring visual information interhemispherically, thus remaining lateralized (Gazzaniga, 2005). Animal studies have provided a stepping stone for investigating callosal function. But the higher cognitive functioning in humans and their ability to solve complex tasks and communicate underlines the importance of human behavioural studies when investigating the involvement and function of the corpus callosum. The next section will explore some of the behavioural studies performed with callosotomized patients to investigate its function. 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. 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 all the information entering the right visual field enters 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. Besides visual information, stereognostic information also remains completely lateralized, two similar items held in the right and left hands are not recognized as being identical by touch (Gazzaniga, 2000). Somatosensory information also remains largely lateralized; studies involving heat stimuli did not provide an equal response in both hemispheres, the ipsilateral hemisphere often underperformed with the same stimulus (Gazzaniga, 2000).

When it comes 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. Ipsilateral projections are only involved in proximal responses and are not very strong, whereas contralateral projections are very strong and are involved in both proximal and distal responses (Gazzaniga, 2000). When the corpus callosum is sectioned ipsilateral sensory-motor controls are impaired (i.e. the left hemisphere will have impaired control over the left hand). During bilateral movements the corpus callosum is thought to be involved in three different ways; initiation of movement and transfer to the opposing hemisphere, informing each hemisphere of the output from the other and regulating feedback processes originated from sensory information to regulate movement (Hoy, Fitzgerald, Bradshaw, Armatas & Georgiou-Karistianis, 2004; Geffen, Jones & Geffen, 1994). Coordinated hand movements require proximal and distal movements for reaching and grabbing respectively, thus requiring interaction between ipsilateral and contralateral hemispheres and an intact corpus callosum. Callosotomized patients can thus 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 (Geffen et al., 1994).

Callosotomized patients receiving different conflicting stimuli in each isolated hemisphere can show different spatial movements in each contralateral arm. This has been investigated in an experiment where split brain patients and healthy controls were shown two figures in each visual field and asked to draw the images simultaneously, the images could be either identical, mirror images or conflicting images. The callosotomized patients did not have interference of the conflicting images, and could relate each image into unimanual spatial movement, whereas healthy participants showed a much poorer performance (see figure 3). The spatial information thus remains separate between arms, whereas the temporal coordination of bimanual movement remains intact (Franz, Eliassen, Ivry, & Gazzaniga, 1996; Gazzaniga, 2000). Eliassen, Baynes and Gazzaniga, (1999) discovered that the integration of direction information for bimanual movements takes place in the posterior corpus callosum.
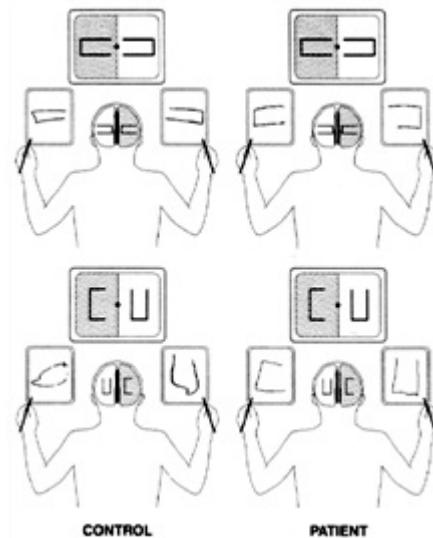

Figure 3. Sectioning of the corpus callosum allows for separate spatial movements directed by each isolated hemisphere. Interaction between hemispheres in controls interferes with spatial navigation between left and right hand. (Gazzaniga, 2000)

Another feature investigated during split brain research is the lateralization of language and speech. Callosotomized patients receiving different objects in the left or right hand could only name objects that were placed in the right hand. The tactile information is transferred to the contralateral hemisphere through the posterior corpus callosum, as partial callosotomized patients (with intact splenium and posterior callosal body) perform significantly better compared to patients who have undergone a total callosotomy with tactile stimuli tests (Fabri et al., 2005). Objects placed in the right hand thus project to the left hemisphere, allowing the patients to name the object. Objects placed in the left hand and projected to the right hemisphere could not be named, but could be recognized and selected from a list of objects. This was an indication that language processing is restricted to the left hemisphere and could not be transferred to the right hemisphere (Buklina, 2005).

The lack of hemispheric integration of lateralized cues in callosotomized patients reflects a system consisting of two separate systems, which can also be memorized separately (per hemisphere). Similar to the experiment by Glickstein & Sperry (1960) with the split brain macaques, split brain humans can also memorize stimuli per hemisphere without being affected by the integration of confounding information from the opposing hemisphere. The two images/stimuli entering each isolated hemisphere cannot be compared to one another in callosotomized patients, and transfer of information can only occur outside the body by sending information to the opposing hemisphere by presenting it to the other visual half field. Presenting different types of stimuli in each visual half field and thus each isolated hemisphere can provide information about differences in processing strategies between hemispheres. Kingstone, Friezen and Gazzaniga (2000) have discovered different processing strategies concerning attentional orientation between the left and right hemisphere. It appears that

the right hemisphere controls mainly reflexive joint attentional processes (following gaze direction of others), whereas the left hemisphere does not show a similar response (Kingstone et al., 2000; Gazzaniga, 2000).

Studies have shown right hemisphere superiority for many perceptual functions such as visuospatial processing, perceptual grouping, episodic memory, complex auditory processing, amodal completion of illusionary contours, part-whole relations, spatial relations, apparent motion detection, mental rotation, spatial matching and mirror image discrimination. The left hemisphere is specialized for cognitive function, intelligence, hypothesis formation (searching for patterns in events), semantic memory and many aspects of language and speech (Wolford, Miller & Gazzaniga, 2000; for reviews see: Gazzaniga, 2000; Gazzaniga, 2005; Aralasmak et al., 2006).

In rare cases language organization is bilateral. Sometimes this can also occur as long as 10 years following surgery in split brain patients (Gazzaniga, 2000). Low level visual processing does not require lateralized mechanisms but can be solved by either hemisphere (such as anorthoscopic shape perception, where shapes are moved behind a narrow slit so only parts of the shape are visible over time). Thus when it comes to visual tasks without spatial component both hemispheres show equal performances. (For a review see: Gazzaniga, 2000; Gazzaniga, 2005)

Lesion Studies

The studies mentioned so far involve complete sectioning of the corpus callosum. This split brain research has provided a lot of insight concerning hemisphere specialization and lateralization. However callosotomies do not provide information about the function of the different callosal sub regions. As mentioned earlier the callosal lesion studies have contributed greatly to investigating the function of the different callosal sub regions. However, partial callosal lesions can be very difficult to organize anatomically, as there are no clear-cut boundaries or anatomical landmarks and functionally intact fibers might still be present but not detectable by MRI (Fabri et al., 2005; Hofer & Frahm, 2006). Nonetheless several distinct modality-specific functions have been detected for different areas of the corpus callosum by means of MRI data of callosal lesions (Buklina, 2005; Raybaud, 2010; for review see: Gazzaniga, 2000).

Table 1. Anatomical organization of callosal sub regions. (Based on Raybaud, 2010)

Callosal sub region	Connecting areas
Rostrum	Fronto-basal cortex.
Genu	Prefrontal cortex and the anterior cingulate area.
Truncus (midbody)	Precentral cortex (premotor area, supplementary motor area), the adjacent portion of the insula and the overlying cingulate gyrus.
Isthmus	Pre- and post central gyri and primary auditory area.
Splenium	Posterior parietal cortex, occipital cortex, medial temporal cortex.

Agenesis of the Corpus Callosum

Another defect involving the corpus callosum is agenesis of the corpus callosum, ACC, patients suffering from ACC do not develop a callosal structure. Callosal agenesis is rarely limited to the callosal structure, it often also involves defects or absence of the hippocampal commissure and anterior commissure (Raybaud, 2010). It seems like a good subject to investigate callosal function and hemispheric transfer, however callosal agenesis does not show the same 'defects' as callosotomized patients. This because during development brain reorganization takes place (due to neural plasticity), allowing compensatory mechanisms such as bilingual representations (Glickstein, 2009). Callosal agenesis patients have also been shown to be capable of intra and interhemispheric transfer (although much slower), which has been attributed to extra callosal structures (Sauerwein & Lassonde, 1983).

Summary

The studies that have been described in this chapter highlight the importance of the corpus callosum in transfer and integration of sensory and cognitive information. Absence of a callosal structure results in disturbed behaviour caused by a lack of communication between hemispheres. As mentioned before, in order for split brain patients to have a form of communication between hemispheres it must occur outside their body. It would be interesting to investigate how the corpus callosum mediates normal communication between the cerebral hemispheres, now that the main function and importance of the callosal structure is highlighted. The fact that the corpus callosum is involved interhemispheric transfer is established, but how the corpus callosum mediates this transfer is the topic of the following chapter.

<center>**Hemispheric Interaction**</center>

Interhemispheric Transfer

Split brain research provided an understanding of the importance of the corpus callosum during transfer of information between each isolated hemisphere. 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 (Magat & Brown, 2009). 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, whereas simple tasks can be processed in a single hemisphere (Banich, 1998; Braver et al., 1997; Smith, Jonides & Koeppe, 1996). 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. 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. (Welcome & Chiarello, 2008; Banich, 1998; Braver et al., 1997; Smith et al., 1996).

A much used behavioural test to study laterality and hemispheric asymmetry is the dichotic listening technique. In dichotic listening techniques two auditory stimuli are presented simultaneously to the left and right ear, which are then sent to ipsilateral (through weaker and lower connections) and contralateral hemispheres (through strong and fast connections). Auditory information is transferred through the posterior truncus and isthmus region according to split brain studies, callosal lesion studies report the isthmus and anterior splenium to be involved in auditory transmission, but a high degree of individual variability exists (Westerhausen & Hugdahl, 2008). 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) and a left ear advantage for non-verbal sounds. This has often been deduced from the dominance of the left hemisphere for language and speech related subjects (Westerhausen & Hugdahl, 2008), and the function of the corpus callosum in this task has long been speculated.

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. It is however still uncertain how the corpus callosum regulates this 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 (Clarke & Zaidel., 1994; Bloom & Hynd, 2005), 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 (Westerhausen & Hugdahl, 2008; Conti & Manzoni, 1994), but due to the presence of inhibitory interneurons, callosal signals have also been found to be inhibitory (Kawaguchi, 1992; Westerhausen & Hugdahl, 2008) and does not provide concluding evidence for an excitatory or inhibitory callosal function. The relationship between the degree of callosal connectivity and lateralization therefore has two views, the inhibitory model and the 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) (Clarke & Zaidel., 1994; Bloom & Hynd., 2005). The degree of connectivity between hemispheres can be reflected by the size of the corpus callosum area, Aboitiz and colleagues (1992a, 1992b) have found a significant positive association between small diameter fiber density and midsaggital callosal area, but not with large diameter callosal fibers.

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 other by allowing hemispheres to integrate information.

The right ear advantage in dichotic listening tasks mentioned earlier can be explained in the inhibitory model point of view, 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. Yazgan, Wexler, Kinsbourne, Peterson and Leckman (1995) however also performed dichotic listening tasks and found a negative correlation between the size of the corpus callosum and behavioural laterality, they found that increased lateralization was associated with a smaller size of the corpus callosum. This outcome is in accordance with the excitatory model of callosal function (Yazgan et al., 1995). Split brain patients show a complete right ear advantage, which is also in accordance with the excitatory theory, loss of callosal fibers increases laterality. Patients suffering from callosal agenesis do not show a right ear advantage or left ear suppression, which is possibly explained by compensatory mechanisms during brain development, such as increased use of ipsilateral pathways, bilateral language representation or recruitment of commissures that are non-callosal for interhemispheric transmission (Westerhausen & Hugdahl, 2008; Lassonde, Sauerwein & Lepore, 1995; Hausmann, Corballis, Fabri, Paggi & Lewald, 2005).

Now that the inhibitory and excitatory model have been introduced and implemented in a study of lateralization, both theories will be further explored.

The Inhibitory Model
The idea behind this model is 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 (Adam & Güntürkün, 2009; Urgesi, Bricolo & Aglioti, 2005; Hellige, Taylor & Eng, 1989; Welcome & Chiarello, 2008).

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 mean that the non-dominant hemisphere is not involved, or that the dominant hemisphere is functionally most advantageous or specialized to complete the task (Adam & Güntürkün, 2009; Urgesi et al., 2005; Hellige et al., 1989). 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 timing, task instructions/knowledge of features, input processing strategy and computational complexity (Adam & Güntürkün, 2009; Urgesi et al., 2005; Welcome & Chiarello, 2008). 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 (Urgesi et al., 2005).

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 (Urgesi et al., 2005).

Urgesi and colleagues (2005) have investigated the role of timing of hemispheric stimulation on hemispheric Interaction and attempted to investigate the influence of asynchronous stimulation of hemispheres by presenting chimeric or entire faces separated by different time intervals and varying exposure times (ET). Brief exposure times hindered detection of chimeric faces, also matching chimeric faces required a longer reaction time and had lower accuracy compared to entire faces, suggesting that the conflicting information required additional processing. A strong preference was found for matching the probe stimulus with the left half of the chimeric face projecting to the right hemisphere, indicating dominance of the right hemisphere for face processing tasks during brief exposure times. In a second experiment two halves of a face (chimeric or entire) are briefly (below chimeric detection threshold as measured in previous experiment) presented sequentially with an interval of 20ms, ensuring that the participants have seen both sides of the face. This led to a more accurate matching for the chimeric half face seen last, independently of which hemisphere received the visual input. This suggests that functional dominance of the right hemisphere is overruled, indicating that dominance does not always rely on functional specificity (Urgesi et al., 2005).

The first dissociation between hemisphere dominance and hemisphere specialization was found in split brain patients (Levy, Trevarthen & Sperry, 1972; Levy & Trevarthen, 1976). These patients also received brief exposures to chimeric faces, two halves of a face joined at the vertical meridian of the visual field. This allowed each half of the face to be projected to the contralateral hemisphere. The split brain patients reported seeing complete images and did not notice that the stimuli were composed of two different 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. (Levy & Trevarthen, 1976; Levy et al 1972)

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 is thus 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 is guided by specialization to fulfil 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 study by Levy et al., metacontrol is also possible in split brain patients, thus questioning the functional importance of the corpus callosum during metacontrol.

Adam and Güntürkün (2009) 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 were trained monocularly (using eye caps) and binocularly to engage in a simple colour discrimination task. In the monocular task each hemisphere was trained with a different colour pair, whereas during the binocular task the pigeons were exposed to a different combination of colours; both the positive colour of one hemisphere and the negative colour of the other hemisphere and vice versa during a single trial, creating a conflicting situation. The pigeons with a biased response (towards one colour pair) show an indication of hemispheric dominance, or metacontrol (Adam & Güntürkün, 2009).

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, and if that is the case this would not eliminate metacontrol as evidence for the inhibitory model.

The aging corpus callosum

Age related changes in morphology or connectivity of the corpus callosum can have an impact on behaviour and can provide evidence for one of the theories of function. Microstructural changes that occur in normal aging can have an effect on interhemispheric processing (Schulte, Sullivan, Müller-Oehring, Adalsteinsson & Pfefferbaum, 2005).

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 (Mayston et al., 1997; Qiu, Li, Liu, Xie & Wang, 2010). This has an effect on the connectivity between hemispheres and can result in mirror movements in young children. These mirror movements are also called motor overflow: involuntary movements of the ipsilateral and contralateral hand (Hoy et al., 2004; Shim, Karol, Hsu, Alves de Oliveira, 2008). There is a developmental trend between motor overflow decreasing significantly between 6-8 years of age. However, with old age mirror movements can sometimes be seen again as a result of callosal demyelination or atrophy (Addamo, Farrow, Hoy, Bradshaw & Georgiou-Karistianis, 2007). 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 (Gazzaniga, 2005). 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 (Salat et al., 1997; Persson et al., 2006; Junle et al., 2008). Takeda and colleagues (2003) have found age related thinning of the rostrum, body, splenium and length and height on a midsaggital section of the corpus callosum. Salat and colleagues (1997) have also found a difference in CC atrophy between older males and females, possibly guided by changes in hormonal balance.

DTI studies of callosal thinning with old age appear robust and are correlated with slower reaction times in an interhemispheric information processing or transfer time task (ITT). The effects of old age involve a significant thinning of callosal volume, based on MRI and post-mortem studies. Reduced callosal integrity can affect the speed of interhemispheric transfer time, which can occur during the natural aging process, or as an effect of alcoholism and ITT both affects motor and sensory processes (Schulte, Pfefferbaum & Sullivan, 2004). One way to asses ITT is by looking at reaction time tasks where targets are presented in the same (uncrossed) or

opposite (crossed) visual field in relation to the responding hand hemisphere. The difference between the reaction times of each task (CUD, crossed-uncrossed difference) serves as a measure of ITT as callosal transfer to the other hemisphere results in a measurable loss of speed. In this study they did indeed find significant shorter CUDs for subjects below 50 years of age compared to those older than 50 years (Schulte et al., 2004). This suggests that callosal thinning has a negative effect on interhemispheric transfer time, causing longer reaction times.

Langan and colleagues (2010) investigated if age related degeneration of the CC could alter inhibition between hemispheres. They recruited young and older subjects to participate in a simple motor task. Age related differences in CC morphology were seen, with a smaller CC area in older subjects (diminished size in the genu, anterior and posterior intermediate truncus and the isthmus). Using fMRI it appeared that the older participants showed greater recruitment of the ipsilateral motor cortex during the motor task, whereas younger individuals did not show this recruitment. Over-recruitment of the ipsilateral motor cortex appeared to be associated with longer reaction times, reflecting the inter-hemispheric transfer, and negatively influenced performance. The additional activation of the ipsilateral motor cortex did not scale with task difficulty, indicating that it was not compensatory. In younger individuals activity of the ipsilateral motor cortex was inhibited by movement of the dominant hand, allowing for greater accuracy during unimanual movements. Also Langan and colleagues have found that a decreased resting connectivity between hemispheres in older adults is 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 (Langan et al., 2010). 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 (Obleser, Wise, Dresner & Scott, 2007; Wierenga et al., 2008).

Age related thinning of the corpus callosum (as measured by means of MRI, DTI or post-mortem studies) can affect interhemispheric transfer by increasing interhemispheric transfer time and can allow for motor overflow. According to Langan and colleagues the age related thinning also causes a failed inhibition of the opposing hemisphere during a simple motor task, causing decreased connectivity to result in a decreased lateralization mirror movements) in older people which is disadvantageous when it comes to unimanual tasks, but can also be advantageous in other tasks concerning cognitive functioning. These findings provide evidence for the theory of inhibition.

Another recent study by Putnam, Wig, Grafton, Kelley and Gazzaniga (2008) have 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 (Putnam et al., 2008). 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 (Putnam et al., 2008).

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 (Bloom & Hynd, 2005). 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. 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., 1995 and Clarke and Zaidel (1994) have also found supporting evidence for the excitatory model by subjecting healthy right-handed participants to a series of neuropsychological test measuring behavioural laterality and MRI scans and found a significantly negative correlation between performance on the behavioural laterality tests and corpus callosum size (Yazgan et al., 1995; Clarke & Zaidel, 1994). This is in accordance with the excitatory model, a smaller corpus callosum, thus a lesser connectivity causes increased laterality effects. This also means that a lack of excitatory connections because of a small corpus callosum increases asymmetry in the brain. For the dichotic listening task Yazgan and colleagues found that a larger corpus callosum was associated with a smaller right ear advantage (REA), this would indicate that a larger corpus callosum facilitates activation of the opposing (non-specialized) hemisphere which would cause confounding effects resulting in a smaller REA. For the line bisection task (indicating the midpoint in a horizontal line) a larger corpus callosum was associated with a smaller bias. The right hemisphere is thought to be necessary during this task, and when a larger callosal body would increase activation in the left hemisphere as well, performance would decrease. The turning bias test did not provide significant correlation, but did also show a strong inverse correlation between callosal size and performance (Yazgan et al., 1995).

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 callosum size whereas others did not find any association. Luders and colleagues (2010b) have therefore investigated a possible relationship between callosal size and the degree of handedness lateralization. They did find a negative correlation between callosal size and the degree of handedness lateralization relating to the excitatory model, but these results were not significant.

Summary
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.

Both models have thus far been investigated and there is no clear evidence pointing towards a single direction. Activation of bilateral brain regions can be seen from both the inhibitory as well as the excitatory 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. Crudely looking at neurochemical properties of callosal fibers would point towards an excitatory function, however when we take the different neurotransmitters and inhibitory interneurons into account, the possibility for inhibition also exists. The two models that have been described in this chapter 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 (Clarke & Zaidel, 1994). 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 (Bloom & Hynd, 2005). 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 (Clarke & Zaidel, 1994).

Disorders

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 several (neuropsychiatric) 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: Hecht, 2010) 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.

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 (David, 1994). 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, but 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. To investigate this theory of hyperconnection a variation of the stroop task has been presented to schizophrenics and controls. During the test the colour and colour word are either presented unilaterally (central) or bilaterally (left and right visual field). The difference between the reaction time of incongruent and congruent stroop stimuli in the bilateral condition is used as a measure of connectivity and known as the Combined Stroop Effect (CSE). Increased difference between reaction times represents hyperconnectivity caused by an overload of interfering information, whereas a reduced difference between reaction times slower reaction times is represented by inhibition or disconnection. The control group shows a decrease in CSE in the bilateral conditions, whereas the schizophrenics show an increase in CSE, which could be a reflection of hyperconnectivity (David, 1994). This hyperconnectivity effect has also been seen in MRI, where patients show a much higher activation while at rest (Withfield-Gabrieli et al., 2009).

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 (Swayze et al., 1990). 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 (Arnone, McIntosh, Tan & Ebmeier, 2008).

Walterfang and colleagues (2008) 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 (Walterfang et al., 2008; Walterfang et al., 2009c). Bersani and colleagues (2010) 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 (Bersani et al., 2010).

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.

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, Minshew and Keshavan (2000) have found a significantly smaller genu and rostrum in autism patients compared to controls (Hardan et al., 2000). Vidal and colleagues (2006) also found a decrease in the anterior third of the corpus callosum. Using a different method (3D maps of MRI images) they found a significant smaller genu and splenium in patients with autism (Vidal et al., 2006). He, Duan, Karsch and Miles (2010) 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 (He et al., 2010).

A recent study by Just, Cherkassky, Keller, Kana and Minshew (2007) 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 synchronisation 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 (Just, Cherkassky, Keller & Minshew, 2004), 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 (Just et al., 2007). 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 symptoms related to autism as children with autism prefer to concentrate on objects and not on people (Hughes, 2007).

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 having 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. It was found that 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 (Kim, Lee, Lee & Kim, 2010). Faber, Azad and Reinsvold (2010) 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 (Faber et al., 2010).

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 (Kim et al., 2010). This underlines how important dissociation of symptoms is in investigation of morphological differences. Also alien hand syndrome is very rare, with relatively a few cases that exists, making it a difficult case to study intensely.

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, Mathias and Banich (2008) 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 and boys additionally had a smaller anterior corpus callosum. The areas connected by the splenium involve the parietal cortex, which supports functions as sustained and divided attention (Hutchinson et al., 2008). Cao and colleagues (2010) 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 (Cao et al., 2010).

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 (Walterfang et al., 2009a; Walterfang et al., 2009b). 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 (Walterfang et al., 2009b).

Walterfang and colleagues (2010) 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., (2009b) have found an association between illness duration and callosal shape in patients with bipolar disorder.

Summary

The exact function or dysfunction of the corpus callosum in above (neuropsychiatric) 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 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 consequentially be responsible for dysregulation of interhemispheric transfer, i.e. underconnectivity, hyperconnectivity, possibly caused by differences in fiber density or defective myelination.

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 another. Without this hemispheric communication behavioural abnormalities occur, mainly due to the lateralization of brain function, thought to be mediated by the corpus callosum. This lateralization allows for more cortical space, but requires integration of cortical areas in the opposing hemisphere to function properly in some situations. This is seen in patients with a sectioned corpus callosum and is also 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 have also 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, whereas 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 corpus callosum is an important mediator of interhemispheric transfer, but how the corpus callosum intercedes this transfer 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. Although, evidence from recent studies in healthy and aged individuals do tend to bend towards the inhibitory model.

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. Clarke and Zaidel (1994) 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 (Clarke & Zaidel, 1994; Putnam et al., 2008). There are other neuroimaging techniques to measure connectivity, such as the resting state functional MRI (fcMRI) used in the study by Langan and colleagues (2010), which shows the health of brain networks by tracking changes in blood flow to different regions of the brain (Langan et al., 2010), this measures resting state connectivity as well as callosal size. Another relatively new imaging technique is Diffusion Tensor Imaging (DTI) that has gained territory over the years. DTI is based on 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 (Mooshagian, 2008).

To direct a complex structure such as the corpus callosum into a single direction, inhibition or excitation, more one-sided evidence is necessary. However, the corpus callosum is a complex body of information with distinct components that act separately, maybe there is more than just one method of hemispheric interaction (Bloom & Hynd, 2005). It could be that the corpus callosum does not purely have an excitatory or inhibitory function, but this may possibly be dependent on a subcortico-cortical network that balances hemispheric activation according to the task demands (Schulte & Müller-Oehring, 2010). Although new techniques have provided more insight into callosal morphology, still little is known about the specific role of the different callosal sub regions in integrating cognitive and sensory information interhemispherically. Schulte and Müller-Oehring (2010) have reviewed recent findings concerning callosal function in interhemispheric processing and suggest that the different callosal areas can exhibit a different function. They suggest a different function for separate callosal regions for local-global processing (anterior callosal integrity mediates inhibitory signals, whereas posterior callosal integrity mediates facilitation) (Müller-Oehring, Schulte, Raassi, Pfefferbaum & Sullivan, 2007; Müller-Oehring, Schulte, Fama, Pfefferbaum & Sullivan, 2009), as well as semantic competition.

Another possibility to investigate callosal function is looking at alterations in morphology in disorders. However, when investigating neuropsychiatric 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, gender and type of symptoms. Some neuropsychiatric 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 classifications 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 posed in this thesis comply with both theories, making them both likely candidates. 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 beneficial 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.

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