UNIVERSITÀ DEGLI STUDI DI PADOVA

Dipartimento di Psicologia dello Sviluppo e della Socializzazione

Corso di laurea Triennale in Scienze Psicologiche dello Sviluppo, della Personalità e delle Differenze Interpersonali

Tesi di laurea Triennale

Disconnected cerebral hemispheres after callosotomy: A disconnected mind?

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Anno Accademico 2022/2023

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1. General overview

The term 'split-brain' patient (or simply, split-brain) typically refers to a patient whose brain has been surgically treated in order to resect one or more major commissures interconnecting homologous cortical regions of the two cerebral hemispheres. The aim of the present thesis is to describe the reasons this surgery is carried out and, more importantly, the cognitive consequences of isolating the two cortical hemispheres in an adult brain. I will start by describing a neurological disease, termed epilepsy, whose treatment, when epilepsy is resistant to pharmacological treatment, contemplates the resection of the brain commissures, also known as commissurotomy. I will then provide a general overview of the cerebral anatomy of the adult brain, placing a particular emphasis on the most important interhemispheric commissure, termed corpus callosum. Lastly, I will conclude by focusing on the research question of whether a split-brain ends up as two minds (i.e., two conscious agents) in one single head, illustrating a subset of answers that populated the literature in the recent past.

2. Basic notions on epilepsy

Epilepsy denotes a neurological disorder predominantly characterized by recurrent and unpredictable interruptions of normal brain function, called epileptic seizures. Epilepsy manifests itself in a wide variety of clinical forms. This makes it difficult to attain a unitary and unequivocal medical classification for epilepsy. Among these attempts, the type of seizures and the degree of control of the symptoms before and after medication are of particular interest in the present context. In epilepsy, seizures are transient occurrence of signs and/or symptoms due to discharges of abnormally intense synchronous neuronal activity in the brain (Fisher et al., 2005). Given the electrical nature of the cause of epilepsy, it is not surprising that electroencephalography (EEG) is an important diagnostic tool for detection and possible epilepsy classification. The EEG is a test that measures appropriately amplified electrical activity of the brain using electrodes placed on the scalp. At first, EEG is recorded from the scalp with a non-invasive approach (i.e., surface EEG) (Noachtar & Rémi, 2009). Research shows that despite being less sensitive and precise, surface EEG is able to represent the epileptic activity in most of the patients, helping as well with the localization of its onset. The results consist of traces representing the electrical activity of individual the regions of the brain, each read by a single sensor. With this fundamental instrument is possible to detect and distinguish the epileptic brain activity from the standard one, locate the starting point of a seizure and inspect particular electrical activity related to epilepsy that do not necessarily result in overt seizures. There are indeed some patterns of EEG activity, termed figures, known to be predictive of the onset of so-called epileptiform discharges causing epileptic seizures. An example illustrating an epileptiform discharge detected through surface EEG is graphically reported in Figure 1.

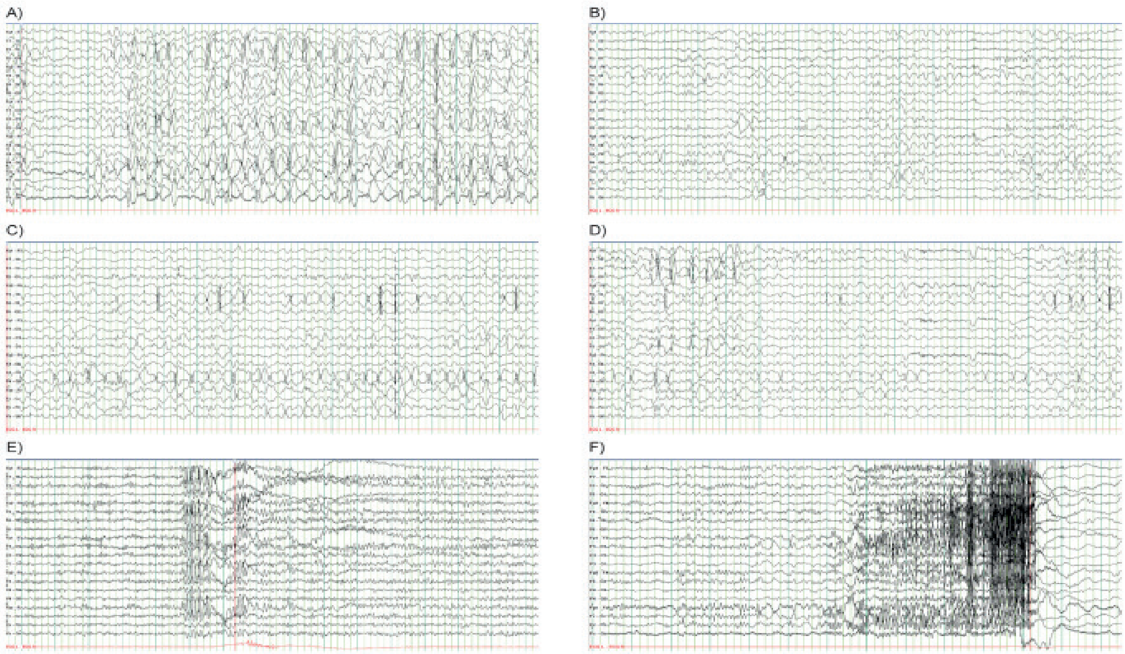

Figure 1: EEGs demonstrating activities associated with LGS in adult patients, including (A) generalized slow spike and wave discharge, (B) diffuse bilateral background slowing, (C) focal spike and wave discharge, (E) generalized polyspike and wave discharges, and (F) generalized paroxysmal fast discharges during tonic seizures. (Montouris et al., 2020)

These patterns are often composed of spikes and sharp waves that are related to seizure susceptibility and can be recognized in the first EEG in the 50% of the patients. Even with further tests there are, however, a 10% to 40% of patients that do not present these usual abnormalities, such that surface EEG alone cannot disprove a diagnosis of epilepsy (Louis et al., 2016). Only when the standard EEG and other non-invasive methods fail to detect abnormal EEG patterns, the possibility of using invasive electrodes is then considered. The test is more accurate but also more focused on a single part of the brain and the placement of the sensors requires anesthetics and an invasive intervention. Therefore, invasive EEG is generally used only when strictly necessary and, as a rule, only intraoperatively.

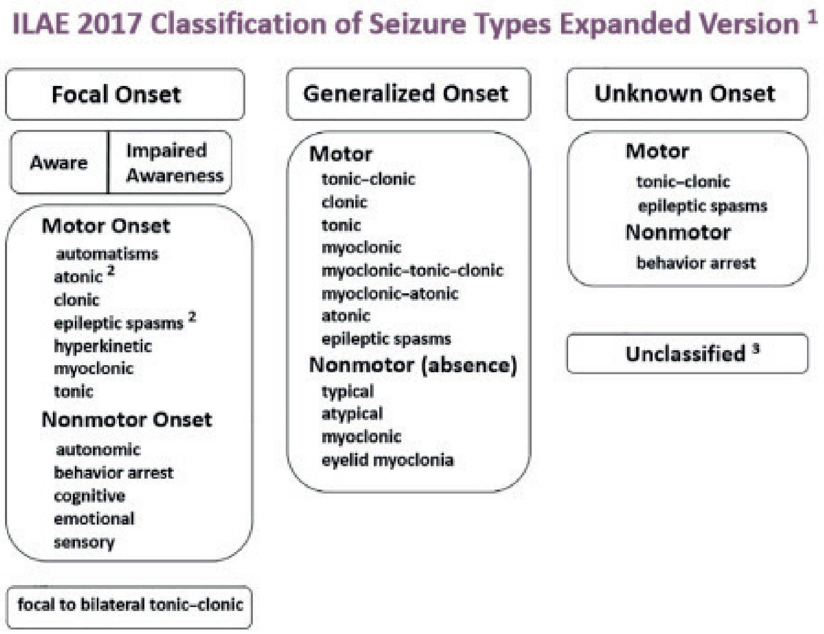

Figure 2: The expanded ILAE 2017 operational classification of seizure types (Fisher, Cross, D'Souza, et al., 2017)

As summarized in Figure 2, seizures can be classified according to whether the origin of the abnormal electrical discharge. This origin can be either localized in a limited region of the cortex or extends to the essentially the entire cortex. Therefore, they are organised in two types: those with the onset limited to a part of the hemisphere are called focal seizures. The effect of this kind of seizures is defined each time by the regions of the cortex that are involved and so do the symptoms that are caused. The range of these symptoms is rather wide but can in some cases involve the loss of control and tone of muscles leading to falls and self-injury. Seizures that involve the whole cortex from the beginning are called generalized seizures. Some seizures which onset cannot be found or defined and are classified as unknown onset. A specific and peculiar type of seizures are focal to bilateral tonic-clonic: this type of seizures seems to evolve during the course, in fact the seizure is produced by a cortical neurons discharge that originates in a point and spread in queue of discharges. The 2017 International League Against Epilepsy (Fisher, Cross, French, et al., 2017) seizure classification specifies three main categories of focal seizures: focal aware (nonmotor or motor), focal unaware (nonmotor or motor), and focal to bilateral tonic–clonic seizures. Generalized seizures of non-focal origin produces these classes of seizures: absence seizures, myoclonic seizures, tonic-clonic seizures, tonic seizures and atonic seizures (Louis et al., 2016; Steriade et al., 2022). Most of these appear at a young age and are caused by an actual brain damage that almost invariably makes the patient resistant to drugs or other type of medication. Drug-resistant epilepsies are very invasive in the life of the patient and deeply affect their life quality and freedom. Therefore, the possibility to control and regulate the impact of the disease (e.g., via a substantial decrement in the rate and/or intensity of seizures) is a great benefit experienced by the patient. Fortunately, there are many classes of drugs that are effective in the treatment of epilepsy and the research in this field improves continuously. ILAE denotes epilepsy as drug resistant when “two well-tolerated, appropriately selected drugs (used singly or in combination) fail to achieve sustained freedom from seizures” (Consales et al., 2021). Nevertheless, the medications involved in these therapies may have important side effects that continue to burden these patients. The pharmacological approach proves to be effective in most of the patients, yet there is a great incidence of refractory epilepsy that requires a surgical intervention to be mitigated. In 2016 the American Academy of Neurology reported that drug-resistant epilepsies represent 40% of total epilepsies and consist in 80% of the cost of epilepsy. When referred to the US population, this percentage amounts to 1 million people with active epilepsy that continue to have seizures despite appropriate trials of 2 antiepileptic drugs. Although the greatness in number less than 2000 patients with drug resistant epilepsy are treated surgically every, year, leaving the clue that many of these patients do not get the best evaluation and treatment for their disease (Engel, 2016).

The surgical approach to epilepsy generally involves the removal of a portion of the cortex or gray matter that is identified as the starting point (i.e., epileptic focus) for the seizures and is generally reserved to specific brain injury, malformation and/or tumors (resective surgery). In recent years, researchers have studied the possibility to perform Laser Interstitial Thermotherapy (LITT) instead of the normal resective surgery, but there are not enough data yet to understand if this leads to a significal improvement, when compared with previous surgical methods (Hoppe et al., 2017). These interventions are frequently needed to treat a congenital brain malfunction or malformation enabling an early intervention, which leads to a greater amount of time for the brain to recover and partially overcome the tissue loss. This aspect gains even more importance in cases where the part of the cortex that causes the malfunction is very large, but lateralized in a single hemisphere. In these cases, the most effective surgery that can be performed is a hemispherectomy, namely, the removal of an entire (or a large portion) of a hemisphere or the disconnection of it from the rest of the brain. If the hemisphere is removed, the approach is referred to as anatomic hemispherectomy. If instead it is disconnected but left in place the approach referred to as functional hemispherectomy. The functional approach, when possible, is always to be preferred since the presence of both hemispheres even if only one is connected to the rest of the brain prevents some major complications following the intervention — such as hydrocephalus or the need of blood transfusions — without reducing the effectiveness (Kim et al., 2018). Since these surgeries are very invasive and may produce important side-effects, new interventions have been created, focusing on the possibility to control the electric activity via nerve stimulation or deep brain stimulation (DBS). The stimulation is provided by electrodes connected to devices that stimulate subcortical portions, most often thalamic or para-thalamic, of the brain or connected to specific nerves (e.g., the vagal nerve) that can effectively contrast the abnormal seizure-inducing activity. When a refractory epilepsy produces falls (i.e., drop attacks), in a variety of generalized or multifocal seizures, in Lennox-Gastaux Syndrome or in rapidly spreading focal seizures difficult to lateralize, the best surgery could be the corpus callosotomy (Markosian et al., 2022). In Table 1, can be found a summary of indications of Corpus Callosotomy

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Summary of Indications of Corpus Callosotomy	
Indications (by seizure type)	Absence; atypical absence; epileptic spasms; atonic, tonic, or myoclonic leading to disabling falls; complex partial (focal) (with or without secondary generalization); tonic-clonic
Indications (by epileptic disorder)	Lennox-Gastaut syndrome; Sturge-Weber syndrome; tuberous sclerosis; West syndrome (infantile spasms)

Table 1: Indication of corpus callosotomy from (Markosian et al., 2022)

This surgical intervention consists in the resection of all or some parts of the corpus callosum. The corpus callosum is an internal part of the brain that connects the cortex of the two hemispheres. Since the generalized seizures are caused by the nature of the electric discharge that spreads on the cortex from one to the other hemisphere, the separation of these two causes a physical barrier in the diffusion of the impulse, resulting in the mitigation of seizures in number other than in symptoms. As predictable this procedure is proven not to be effective in the treatment of focal seizures. The positive results shown by this surgery have, by the years, gathered more attention and research, fostering the development of new techniques aiming to minimize the invasiveness and improve the precision of this procedure.(Vaddiparti et al., 2021).

3. **Why split a brain?**

The original hypothesis for the role of the corpus callosum in epilepsy dates back to the beginning of the 20th century, when one of the pioneers in the field, Sir Victor Horseley (1857-1916), begun to resect the corpus callosum in dogs. He then studied the effect caused by the excitation of a single hemisphere finding that the contralateral part of the body was presenting a full tonic-clonic activity whereas the ipsilateral was limited to none to a mild tonic activity. This made Horseley think about the role of the corpus callosum in epilepsy, which is yet to be completely discovered and understood. Surely EEG gives us a great view of the epileptic activity and represents a fundamental instrument for the study of this disease, with the possibility of this instrument to detect onset and intensity of the discharge in the cortex and track the path of the epileptic activity. EEG permitted to clearly see the diffuse activation involved in generalized seizures leading to the conclusion that in these cases the onset is near the center of the brain and spreads from a hemisphere to the other (Steriade et al., 2022). In Figure 3 refers to the EEG of a 25-years-old patient with childhood absence, typical epileptic spike-wave complexes can be clearly identified.

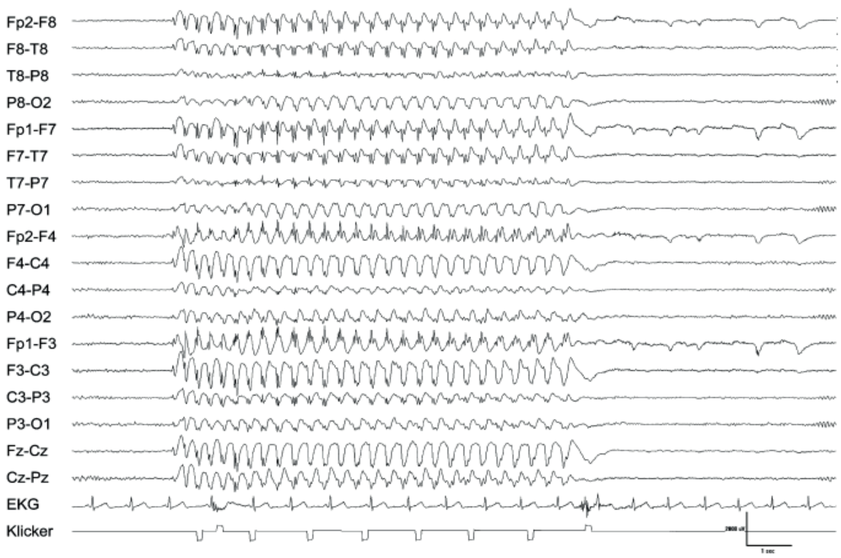

Figure 3: Generalized spike–wave complexes in a 25-year-old patient with childhood absence epilepsy who had a seizure relapse after being seizure free off medication for 8 years. This bipolar longitudinal recording demonstrates that the patient is able to respond to an auditory stimulus to push a button at the onset of the discharge, but fails to respond to later stimuli. At the end of the discharge a delayed response was recorded (Noachtar & Rémi, 2009).

Therefore, the possibility to disconnect these two parts avoiding the inter-hemispheric spread of the epileptic discharge by resecting the corpus callosum seemed very promising. For this purpose, EEG has been pivotal to understand the importance of the corpus callosum in effectively connecting the cortex of the two hemispheres, transferring both complex and precise information in a very effective and fast way.

The patients were monitored post-surgery, and this allowed us to comprehend even better which information the corpus callosum transfers. For humans, in contrast with monkeys, one of the clearest effects of the disconnection is related to the functional division of the visual field by blocking the passage of complex optical information through the corpus callosum. This makes each hemisphere able to visualize only what is in the contralateral field of view (due to the crossing of the optic nerve departing from the nasal retinae at the level of the chiasm) by reducing to nil the chance of a bilateral integration of visual information. In addition to visual information, even stereo-gnostic and somatosensory information appear to be transferred through the corpus callosum, based on the observation that these abilities remain typically lateralized in patients with a resected or injured corpus callosum (van der Knaap & van der Ham, 2011). The motor function instead does not need the corpus callosum to allow the passage of the signal. However, if the movement is fine and complex, then it appears to need a much more complex interaction between hemispheres, with a likely contribution of the corpus callosum for motor execution. Even if the surgery itself is very invasive, the burden of the intervention is justified by the fact that most studies report a decrease of drop attack by 50-80%, more than other surgical approaches (Vaddiparti et al., 2021). Moreover, this kind of intervention, while being palliative, can prevent the onset of generalized seizures resulting in a great reduction on the severity of the epilepsy, already proved to be drug-resistant. Refractory or drug-resistant epilepsy is often diagnosed in childhood and for this reason epilepsy is considered the disease that causes the greatest disability compared with any other neurological disease. It is also proved that it can coexist with an intellectual disability in 30-40% of the children (Janson & Bainbridge, 2021). The research in the drug industry is continuing uninterruptedly and some encouraging results seem to be gathered, but the possibility to obtain such a good result with a surgery can't be ignored. One complication that can occur with epilepsy especially in children drug-resistant epilepsy is the status epilepticus.

According to ILAE last definition (2015), as schematized in Table 2: "Status Epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1). It is a condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures" (Trinka et al., 2015).

Type of SE	Operational dimension 1 Time (t1) when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10-15 min[1]	Unknown
[1] Evidence for the time frame is currently limited and future data may lead to modifications.		

Table 2: Operational dimensions with t1 indicating the time that emergency treatment of SE should be started and t2 indicating the time at which long-term consequences may be expected (Trinka et al., 2015).

Normally, in hospitals the status epilepticus is treated with benzodiazepine (Lorazepam, Diazepam, Midazolam). If the status persists over 10 minutes anti-epileptic drugs such as Phenytoin, Valproic Acid, Levetiracetam, Lacosamide, Phenobarbital are administered (Minicucci et al., 2020). But here are still approximately 30% of patients who suffer from a refractory status epilepticus that are not responsive to drug treatment (Louis et al., 2016). In these cases, Propofol, Midazolam, Propofol or Thiopentone are used but even these drugs can fail to control the disease. A case report from 2021 in pediatric patients with non- lesional epileptic encephalopathy and with electrical status epilepticus during sleep, shows some good results using callosotomy to alleviate or even stop status epilepticus (Yokosako et al., 2021).

Another great risk correlated with generalized seizures (especially tonic-clonic seizures) and refractory epilepsy is the sudden unexpected death in epilepsy (SUDEP) that occurs in 1.4/1000 epileptic patients every year, with a peak in adolescence and under-45 (Costagliola et al., 2021). SUDEP seems to be caused by an interaction between cardiac orrespiratory regulation and epileptic activity involved in generalized seizures. Being able to control or halt generalized seizures is a great chance to prevent SUDEP, decreasing the number of deaths and alleviating the burden for the patient who no longer experience the drama subtended to the chance of death at every seizure occurrence.

4. **Anatomy of a cut**

Following Horseley's work, the role of the corpus callosum in epilepsy was investigated by William P. van Wagenen in the 40s, who observed the effect of the impairment of corpus callosum caused by brain disease other than epilepsy in an epileptic patient. In Figure 4 is shown the direction of the entry to the corpus callosum for surgical intervention, this permit a clearer visualization of this structure located in the middle of the brain.

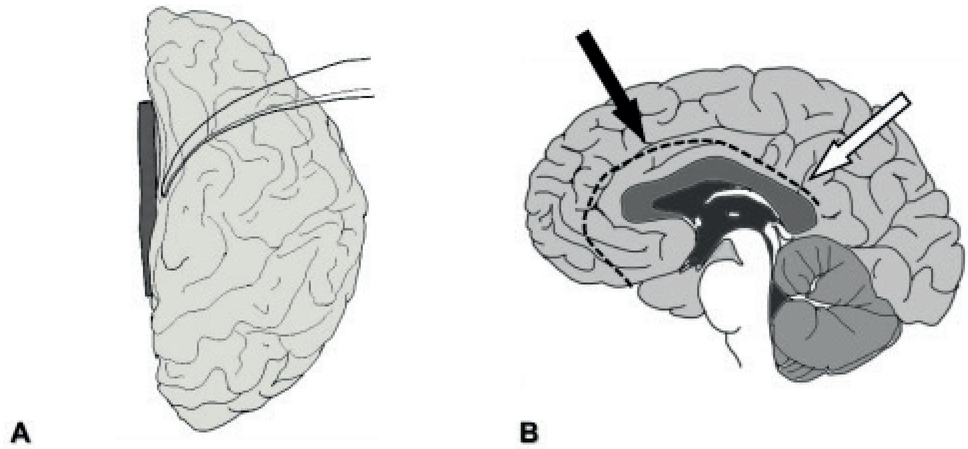

Figure 4: The direction of the entry to the corpus callosum. (A): After dural incision, the frontal lobe is retracted laterally with the spatula. (B): Black arrow indicates the direction toward the corpus callosum in anterior corpus callosotomy and total corpus callosotomy. White arrow indicates the direction toward the corpus callosum in posterior corpus callosotomy. Dotted line indicates the inferior edge of the falx cerebry.(Uda et al., 2021)

Starting from these observations, van Wagenen performed the first callosotomy in 1940 were the fibers of body, genu, and splenium of the corpus callosum were cut. By the end of 1943, van Wagenen had performed 9 more callosotomies with partial or near-complete resection of the corpus callosum. In the same year, he indicated the callosotomy as a safe and efficient intervention for the treatment of generalized seizures in drug-resistant epilepsy (Vaddiparti et al., 2021; Van Wagenen & Herren, 1940). The evidence is clear as the corpus callosum is one of the main connections between the cortices of the two hemispheres and its resection can stop the spreading of discharges involved in generalized seizures. Therefore, the callosotomy is considered a sharp tool in the hand of a doctor facing a drug-resistant epilepsy and, in particular, it demonstrates itself to be very effective in the reduction of falls that are also a great risk of harm to the patient due to self-injury related to the seizure. Due to this, the decrease or stop of drop attack represent the main purpose to choose this surgery (Uda et al., 2021). The surgery itself is rather delicate, the main steps are shown and exemplified in Figure 5. It starts with the patient on the bed facing up or on the side, by the preferences of the surgeon or for having a greater reach to the portion that had to be operated. The intervention can be performed with a craniotomy of about 6 cm and the coronal suture could be taken as posterior margin for the craniotomy. The choice of the location for craniotomy is fundamental due to the presence of big veins under the surface of the skullcap. When the brain is exposed, the surgeon retracts laterally the frontal lobe to reach to the corpus callosum itself between the two hemispheres inside the longitudinal fissure that divides the hemispheres. At this point, the corpus callosum is exposed and the surgeon has to dissect the inside of the fissure, saving as many veins as he can, and place attention on not damaging the near and fragile cerebral parenchyma. Then the cut is performed with microscissors exposing the cavum of the septum pellucidum that functions as a landmark for the disconnection of the callosal fiber. At first, the genu and the body of the corpus callosum are dissected, then the microscope is readjusted, and the dissection continued to the back of the corpus callosum this procedure varies with the portions of the corpus callosum that have to be resected. However there are some doctors who prefer to perform a partial callosotomy instead of a complete callosotomy with a regard to the risk of disconnection symptoms.(Uda et al., 2021). On the other hand, a meta-analysis for the results of this interventions, based on the PubMed, Scopus and Web of Science, that takes in account 57 articles on the outcome of this surgery finds out that there is no clear correlation between the complete resection of the corpus callosum and the disconnection symptoms. Instead there is a great reduction in the seizures-free goal and also on the reduction of drop attacks (Chan et al., 2018). Other than the anatomical perspective, another great tool that allows the best 3D representation of the corpus callosum comes from Diffusion tensor imaging (DTI) tractography.

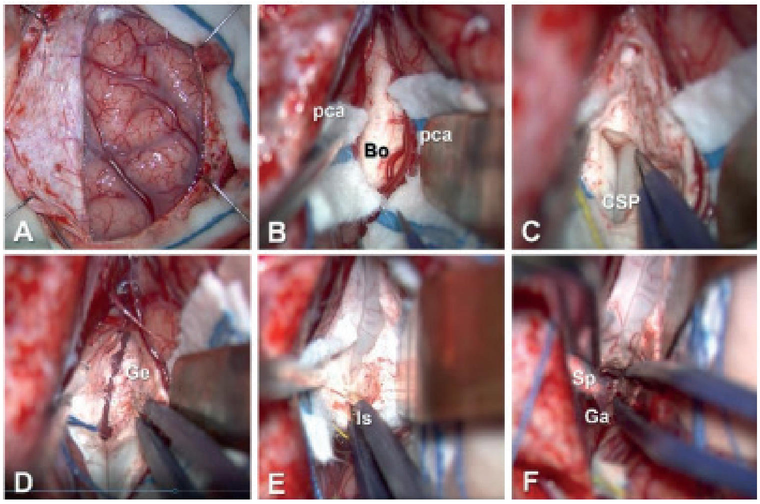

Figure 5: Intraoperative microsurgical total corpus callosotomy. (A): Brain surface after dural incision. (B): After opening the interhemispheric fissure, the body of the corpus callosum is seen between bilateral pericallosal arteries. (C): The cavum of the septum pellucidum is an anatomical landmark for severing the corpus callosum. (D): Callosal section of the genu and rostrum of the corpus callosum. (E): Isthmus of the corpus callosum. (F): Sectioning of the splenium of the corpus callosum. The vein of Galen is seen through the arachnoid membrane. (Bo: body of the corpus callosum; CSP: cavum of the septum pellucidum; Ga: vein of Galen; Ge: genu of the corpus callosum; Is: isthmus of the corpus callosum; pca: pericallosal artery; Sp: splenium of the corpus callosum (Uda et al., 2021)

Figure 6 consist of four representations of the corpus callosum from the Catani & Thiebaut de Schotten atlas of human brain connections obtained with this new method for imaging. This technique allows the virtual dissection of white matter tracts and visualization of the pathways in the living human brain. This technique assesses neural tracts using data collected by the analysis of a specific type of MRI that is sensitive to the diffusion of water molecules. The diffusion of water molecules in white matter follows along the functional pathway, this leads to clusters of data that contain the various diffusion of the molecules in the brain that are then analyzed and interpreted with mathematical models to obtain a synthesis that represent the 3D models of the areas activated and detected by the test. The significance of this instrument for both imaging and in diagnostic purposes was evident

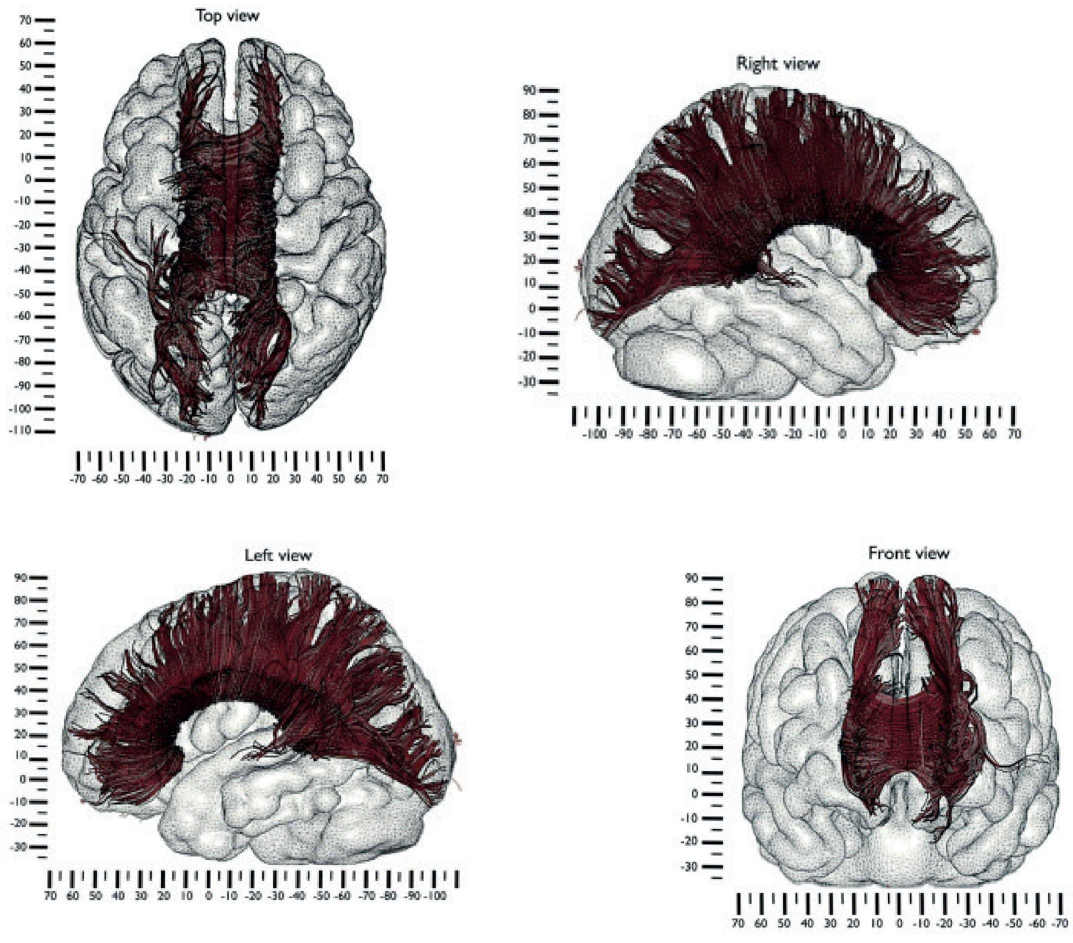

Figure 6 All the DTI images are taken from Catani & Thiebautdeschotten, 2008

from its initial version, which were used to detect and locate brain tumors using DTI tractography finding the interruption or deviation of the neural pathway caused by the tumor (Henderson et al., 2020; Jeurissen et al., 2019). The images of the white matter given by DTI are very evocative and allows a great visualization of the real shape and position of each pathways in the internal part of the brain. These (in figure 6) are DTI tractography images of the corpus callosum from the Atlas of Human Brain Connection (Catani & Thiebaut de Schotten, 2012). The position of the corpus callosum reflects itself its main feature of connecting the cortices of the hemispheres. In particular, the corpus callosum is involved in the transmission of signals regarding motion, perceptual and cognitive activity. It is conventionally divided into an anterior portion (rostrum, genu) connecting the prefrontal and orbitofrontal regions, a central part (body) connecting precentral frontal regions and parietal lobes, and a posterior portion connecting the occipital lobes (splenium) and temporal lobes (tapetum). The fibers of the genu and the rostrum arch anteriorly to form the anterior forceps (or forceps minor), whereas those of the splenium form the posterior forceps (or forceps major) (Catani & Thiebautdeschotten, 2008).

5. **Understanding the split**

Once the corpus callosum has been resected, the capability of the two hemispheres to communicate is quite compromised, causing distinctive symptoms whose systematic observation generated the empirical bases for interpretations of high-level expressions of the human mind, like consciousness. The idea of the symmetry of the brain as a form of divine perfection in creation has been surpassed many years ago, facing the evidence that the two hemispheres of the brain perform different tasks and possess different abilities which are then called lateralized. Brain and mind are divided in units or modules that assess different functions, meaning that the brain is not generally capable to assess all the tasks. These units are considerable as devices that assist the mind's information-processing demands (Gazzaniga, 1998).

In this organization the left hemisphere is quite dominant in problem-solving activities and has the possibility to maintain this ability even in patients with a silent right hemisphere (right hemisphere divided from the left one): proving that the left hemisphere does not need the support of the other half of the brain to assess these activities. The right hemisphere proves instead to be deficient in difficult problem-solving activities. To study the difference between the individual responses of the two hemispheres, the two halves must be assessed with different tasks to ensure and test the independence of each solving procedures. As each visual hemifield is connected to the contralateral hemisphere, the left hemisphere communicates with the right part of the visual field and the right hemisphere with the left one. Hand control and organization is also contralateral following the visual field and leading to the hand and visual field of the same side connected and controlled by the same structure to grant coordination (Mutha et al., 2012). This organization is easily revealed testing crossing answer in a recognition test. A recognition test is conducted with a computer or other type of screen with a cross in the middle. The patient is asked to look straight to the cross, focalizing attention and leaving the lateral part of the screen to be seen with lateral view. As lateral view is performed with the same hemiretina for each eye and contralateral to the side of the stimulus presented on the screen, it is perceived only by the contralateral hemisphere of the brain. Then the patient is asked to match the stimulus on the screen (e.g. a word) to the corresponding card shown in front of him. This ability is shown to be maintained in split-brain patient if the answer is conveyed with the ipsilateral hand of the visual hemifield that catches the stimulus: the stimulus, the matching and the hand motion are perceived and controlled by the same hemisphere. If instead the patient is asked to respond with the opposite hand, he is not able to match stimulus and answer, exposing the disconnection of the two hemispheres. To test furthermore the capability of the two hemispheres to share information, a test for synthesis can be performed: two stimuli are presented one to each hemisphere and the patient is asked to draw what he saw. Even if the patient is able to draw both the stimuli, demonstrating that some connection between the two hemispheres is still intact, the ability to synthetize the two stimuli in one (as shown in the figure 7 with the sky-scraper example) is lost, in fact the patient still draws the two stimuli by themselves, being unable to synthetize them. To test that this ability is severed by the disconnection of the corpus callosum, the two stimuli are presented to the same hemisphere and the patient syntheti-ze them in one (as shown with the fire-arm example that led to the drawing of a rifle) (Gazzaniga, 1998).

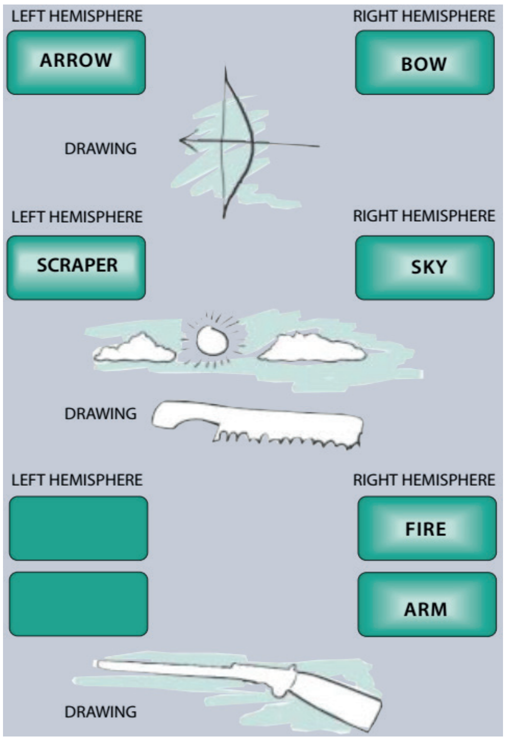

Figure 7: Some graphical examples of stimuli and answers showing the inability to synthetize infor-mations across the midline. (Gazzaniga, 1998)

In the 1990s evolution of brain imaging permitted a greater exploration of the portions of the brain involved in various activities and one of this is certainly language production and speaking. In an experiment of Lehericy at al. in 2000, he inspected the brain activity during three different language-related activities: word production, passive listening of stories and silent repetition of phrases (Bear et al., 2020). The resulting images show the dominance of left hemispheres in language-associated tasks, but also that all the different tasks were assessed by different parts of the brain, not only in the left hemisphere, leading to the conclusion that the complexity of language comprehension and production does not permit this ability to be completely lateralized. This theory is represented by the HOLISTIC model, reviewed by Skipper (2022). This model considers the speech and language production as the results of the composite work of various part of the brain in both hemispheres. In this view the historical areas for language production and the newer discovered ones are considered cores for the whole language system that spreads through the brain. The patterns of activation in the brain are shown in Figure 8 involving: language, autobiographical memories, self-knowledge, and unconscious (Skipper, 2022). Yet if a split-brain patient is asked to respond to a matching test speaking, he can only speak about the right stimulus being presented. Similarly, if the answer is conveyed with both hands upon two different stimuli and the patient is asked to explain why his left hand (or right hemisphere) answered that way, he cannot explain because the left hemisphere that is dominant in language production does not get that information from the right one. Interestingly, however, the patient does not stay silent. Instead, he generates logically a response that was interpreted as a false memory, since both the hemispheres appear to have the ability to generate false memories, but the dominance of it is on the left hemisphere as in language. Due to this, the answer was given with simplicity but does not match the reality of the association that led to the response indicated by the left hand (Gazzaniga, 1998).

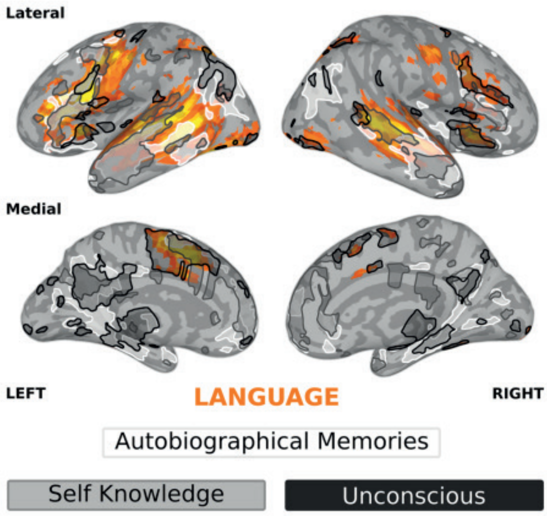

Figure 8: Neuroimaging meta-analyses of "language" (hot colors), "autobiographical memories" (white outline); "self-knowledge" (gray outline), and unconscious (black outline). Results are thresholded at 97% with a cluster size of 100 voxels. (Skipper, 2022)

Recently, tactile detection and localization has been tested in patient with resected corpus callosum. This study was done following the idea that tactile perception can be divided, as sight or arms control. To test these abilities a patient is asked to close eyes and often some body part can be covered with a cardboard to ensure that there is not help from the eyes. Then some tactile stimuli are produced based on the specific task to test. If the test is on threshold, the tester uses a gradient of stimuli which intensity decreases with every right answer, going from 300g to 0.16g. The stimulus correctly perceived before three errors represents the threshold tested and the result of the test. For localization instead, the arm or the leg of the patient is touched in different points, asking the patient to localize where he feels the touch with one or the other hand (as shown in Figures 9 and 10). In this test the resection of corpus callosum does not seems to heavily impact on the results, the patient performed well above chance level in all the variation of the exercise. Moreover, is interesting to notice that the ability to convey the answer is not impacted by the cross-answering condition. Although there is a difference between the ability to perceive the stimuli located on one side or the other, this has been related to the fact that there is a partial lateralization of somatosensory way and it is not cut in callosotomy. The greater result supporting

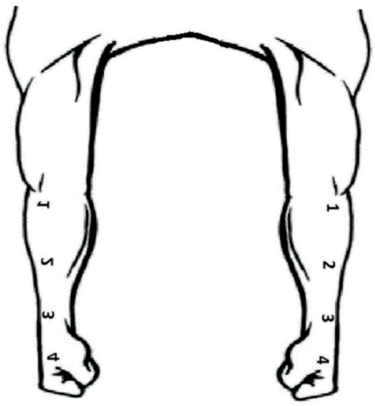

Figure 9: Graphic representation of the stimulationsites on his two arms. (de Haan et al., 2020)

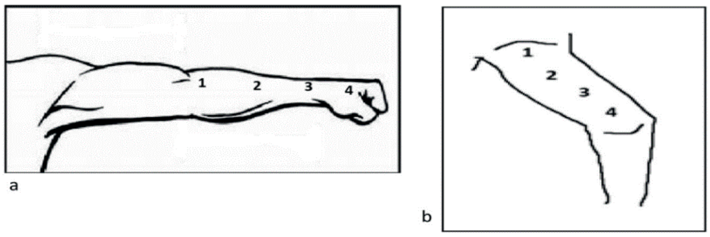

Figure 10: The response sheets on which DDc had to indicate where he thought he had been touched on the arm (1a) and the leg (1b). (de Haan et al., 2020)

this statement is the capability to convey the responses with both hands without decreasing the probability to get the right answer showing that the perceptual signal arrives in both hemispheres. The last situation tested is with simultaneous touches in both arms. In this case only the arms are touched but the patient has to indicate the positioning of two simultaneous touches. During the test, it appeared quite confident about its answers. Instead, the results disproved its confidence: it scored below, but not significantly different from a randomized guess (de Haan et al., 2020). However, this evidence is not related to the capability of controlling an arm with the contralateral hemisphere that was already been studied analyzing the results to Wada test for language dominance in preparation to brain surgery. In this test one hemisphere is anesthetized with drugs to evaluate the abilities of a single hemisphere per time. In this situation the contralateral arm appears paralyzed after the drugs take effect. However, if a test on the localization of the touch on a hand is performed just after the surgery the results related to answers conveyed with the other hand are degraded to the randomized level, where the results related to answer given with the same hand that perceived the stimulus remain unchanged after the surgery. This can suggest that the subcortical connections between hemispheres are able to overcome the split-brain condition but not with the same precision obtained with an intact corpus callosum (M. C. Corballis et al., 2018)

6. **Two halves or two units?**

Analyzing the behavior of a split-brain patient is fundamental to understand how this surgery can negatively impact on the patient's life but is also a great chance to understand more deeply the general functioning of the brain. The interest in studying damaged brains to understand healthy ones became a central theme in neurological and psychiatric thinking in the late 19th century, with the studies on disconnection syndrome. Disconnection Syndrome is the name given to a cerebral malfunctioning caused indirectly from brain damage, due to severed brain portion or connections. This idea is based on the view of the brain as an integration of different parts with different abilities highly connected to each other, where the malfunctioning, or disconnection, of a single part can compromise the parts that rely on the severed one. One historical example is Dejerine's "pure alexia" or "word-blindness": the patient was still able to see words and copy them but not read them. Furthermore, the patient has no aphasia as shown by the intact ability to understand speech and write (Catani & Mesulam, 2008). In the 1960s, Sperry and Gazzaniga reported and analyzed that the lateralization of word expression and comprehension were predominantly located in the left hemisphere but not absent in the right hemisphere. Initially, the right hemisphere was considered word-deaf and word-blind, mute and agraphic, and generally lacking in higher cognitive functions. To further understand or prove this picture Sperry and Gazzaniga studied some of the first split brain patients to investigate the abilities of each hemisphere independently. This brought to a great reconsideration of the classical picture, by showing the abilities of the right hemisphere in language comprehension both written and spoken (Pearce, 2019). The results of their studies indicate the corpus callosum as the most important way of interhemispheric communication, and the differences in linguistic abilities between the two hemispheres were considered and analyzed giving more independence to the right hemisphere. This also led Sperry to evaluate the idea that the two different views of the world perceived by the two hemispheres may lead to two different consciousnesses in the same brain. Despite the fact that some abilities are lateralized, most of them are performed by regions located in both hemispheres and this permits the theoretical autonomous existence of a hemisphere separated by the other, with an autonomous, yet limited, control on behavior. Another theory places the consciousness completely on the left hemisphere viewing the right one as a support in perception and other functions. The right hemisphere may prime the left one, but only after the consciousness is molded and interpreted by the left hemisphere. However, with the spreading of the data on the abilities of the two hemispheres, this second theory has been discarded as the two hemispheres appear to be capable to interact with the environment in different but still noticeable way, strengthening the two consciousness argument. This has been argued by Sperry himself who describes the split brain as "two separate conscious entities or minds running in parallel in the same cranium, each other with its own sensations, perceptions, cognitive processes" (Sperry, 1966).

The main arguments those sustain this theory are five hallmarks (that are summarized in figure :arguments those sustain this theory are 5 hallmarks (that are summarized in figure 10 - p. 23):

1) Response X visual field interaction,
2) Hemispheric specialization,
3) Post hoc confabulation,
4) Split attention
5) Inability to compare stimuli across the midline

These tasks are constructed to assess the ability of the hemispheres to share information between the middle of the brain through the corpus callosum (Pinto, de Haan, et al., 2017). The first hallmark is the "Response x visual field interaction". In this task is demonstrated the inability for the patient to verbally communicate a stimulus caught with the right hemisphere that has not the ability to produce a verbal output (Hagoort, 2005). In these situations, the patient says that it has saw nothing since the stimulus reached the "mute hemisphere". However, controlling the left hand, the left hemisphere is able to indicate what it saw in a questionnaire. This is the traditional view but even though it seems defined, this phenomenon is yet to be understood. More studies show how this situation cannot discriminate between a split consciousness or a partial consciousness model, because the response given by the right hemisphere is yet to be defined as conscious or automatic. (Pinto, Neville, et al., 2017) The second hallmark is considered the "Hemispheric specialization". Studies demonstrated that: the right hemisphere performs better in visual, casual inference, temporal discrimination, object-recognition based on fragments and detecting statistical regularities in visual scenes. The left hemisphere, instead, is considered more proficient in language production and verbal labelling of images, solving mathematical problems, recognizing of local details and self-recognition (Turk et al., 2002). These results, however, are descriptive of all the healthy brains and the distinctions found in the different areas has to be considered as standard. Moreover, as the different areas work together in parallel performing different tasks to function properly, it is reasonable to think that they continue to function concomitantly even if separated from the other hemisphere maintaining their specific role in whole brain activity. The third hallmark is "Post hoc confabulation": the behavior observed where the patients confabulate when asked to explain their own choices made. Corballis reported an example where a bell was shown to the left visual hemifield of patient J.W.. Then he was asked to indicate what was being shown and he correctly responded with his left hand. However, when J.W. was asked for explanation, he proposed that the choice he made was motivated by the sound of a bell he had heard coming to the laboratory (P. M. Corballis, 2003). From these studies comes the idea of "The left hemisphere interpreter", also confirmed in the study on the role of left hemisphere in hypothesis formation in healthy brains (Wolford et al., 2000). This is the idea that the role of interpreter of our actions belongs to the left hemisphere, even when disconnected from the other, as it is during the general activity, when no separation is present. Due to its ability to form hypothesis, when disconnected, the left hemisphere toghether with the majority of language production areas is able to create congruent and credible explanations to the otherwise inexplicable actions prompted by the right hemisphere. The fourth hallmark regards "Split attention", which is one of the most disputed points. The dispute is related to the conception that attention and consciousness are strictly interconnected. This comes from the observation that that is left unattended cannot be considered consciously. Therefore, the split attention observed in split-brain patients made the brain half unconscious leading to the idea that the split attention creates split consciousness or two separated consciousnesses. Nonetheless the studies and theories on this problem and on the definition of "consciousness" and "attention" are yet to come to an agreement or to an undisputable finding (Cohen et al., 2012). If consciousness is used to investigate itself, it seems to be clear and the power and extension of consciousness and attention are greatly magnified. A further proof of this comes from the psychological approach to the problem, that allows to detect some significant flaws in this view. Attention is considered to be the ability, partially out of one's control, to gather sets of information from one's surroundings and maintain those in iconic memory, where they can be stored and elaborated. This kind of memory has a quite volatile existence lasting up to 4 seconds and can be overwritten easily by any changes in the scene the eyes are perceiving. This memorization appears to be unconscious, and the objects perceived, at this level cannot be reported consciously. To be consciously perceived an object or scene must enter the working memory, allowing the personal report of the perceived image. This kind of elaboration takes time and comes after an object enters the iconic memory, after being formerly chosen and acquired through attention.

In Table 3 are schematized the major differences between Iconic and Working memory.

	Iconic Memory	**Working Memory**
Capacity	Large: scales with number of objects in scene, up to 16 documented	Limited: typically 4 or less, depending on complexity
Duration	Short: up to 4 seconds	Medium: minutes to hour
Stability	Fragile: overwritten by any new scene containing objects at approximately the same location. Probably also erased by eye movements	Stable: resistant to new visual information, eye movements. Interference from other working memory load
Frame of reference	Mostly retinotopic	Mostly spatiotopic
Quality	Some feature binding, high visual accuracy. Capacity drops with complexity of objects	Feature binding, "object file", … Capacity drops with complexity of objects
Cognitive value	Limited	Extensive

Table 3: A comparison between Iconic and Working memory.

The fifth hallmark concerns "Inability to compare stimuli across the midline" . Since the transmission of complex and high-resolution information take place via cortical connection, the interruption created afflict the ability to compare this kind of signals across the midline, producing the inability to compare an object presented in the left visual field with one presented in the right visual field. This makes it impossible to answer a question such as: "Are the two object the same?". This effect, seen not only in visual tasks, is one of the most significant. It consists of the brain maintaining the access to the information gathered by the two hemispheres, even when the two halves seen to be independent and not communicant. This can lead to the conclusion that there are two separate entities in the same brain. Further analysis of these cases allows us to arrive at an unexpected result, as the lost ability to communicate across the midline is partially, but significantly, regained, leaving researchers with the challenge to understand why. Moreover, this condition does not manifest in every split-brain patient forming a set of patients that maintain their ability to compare across the midline.

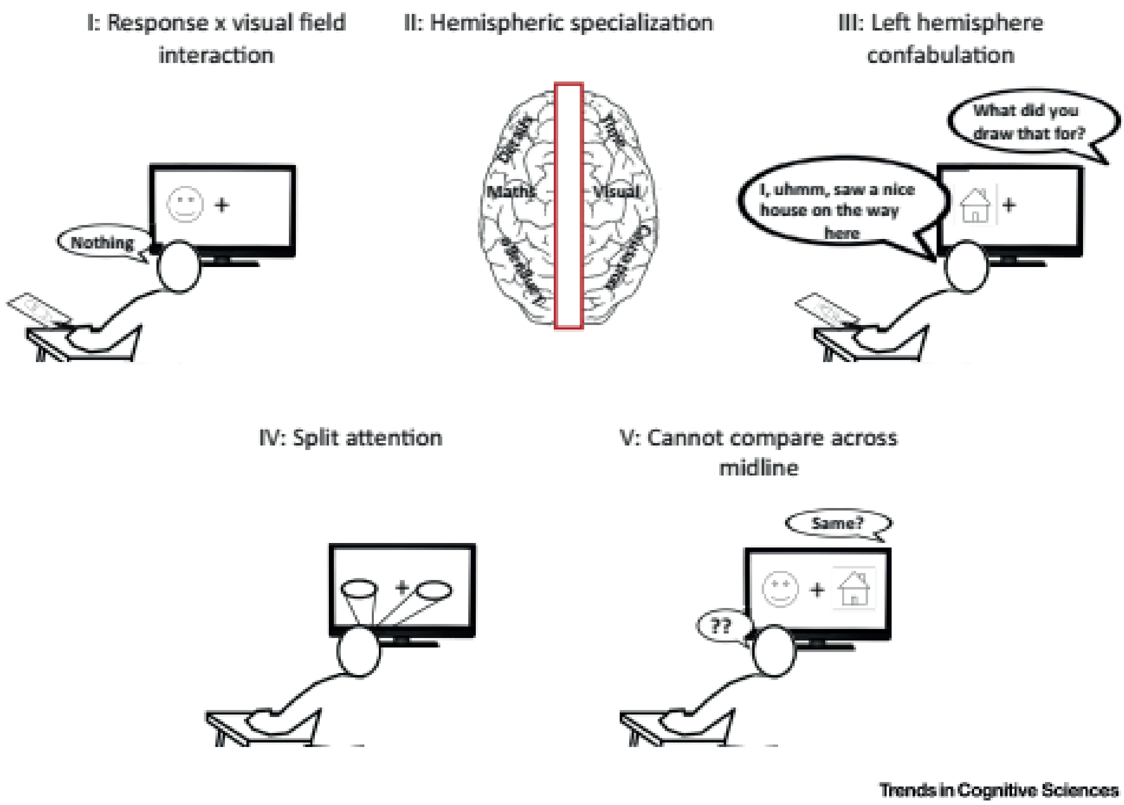

Figure 10: The classical view of split-brain patients asserts that conscious unity is disrupted in this syndrome. The evidence for this view comes from five hallmarks. First, a marked response type visual field interaction occurs in split-brain patients. They can only respond accurately to stimuli in the right visual field with the right hand or verbally, and to stimuli in the left visual field with the left hand. Therefore, when a stimulus appears in the left visual field, the patient verbally reports that he/she saw nothing, yet draws the image with his/her left hand. This supports the notion that each hemisphere controls half the body, and consciously perceives half the visual field. The second hallmark is extreme hemispheric specialization. The left hemisphere is, among other things, better at language, math, and detailed processing. The right hemisphere is better at visuospatial tasks, time perception, and causal inferencing. This again suggests that each hemisphere operates independently of the other, and thereby creates consciousness autonomously. The third striking phenomenon is that split-brain patients confabulate wildly when asked to explain actions of their left hand (controlled by the mute right hemisphere). The notion here is that the left hemisphere creates an independent conscious agent, who is unaware of why the right hemisphere chooses its actions. Therefore, this agent resorts to ad hoc confabulations. Fourth, in split-brain patients, each hemisphere seems to have its own focus of attention. Since attention and consciousness are thought to be tightly linked [64–67], this again supports the classical notion that consciou ness is not unified in split-brain patients. Fifth, split-brain patients cannot compare stimuli across the midline. This makes sense if two independent conscious agents each view half of the visual field, and cannot communicate their perceptions to each other. (Pinto, de Haan, et al., 2017)

7. **Conclusions**

A complete understanding of the implications of callosotomy is yet to be achieved. The resection of the corpus callosum overall does not seem to impair the abilities of both single hemispheres, but to impose substantial limitation in the band-width of inter- hemispheric information transfer determining their inability to interact in the fastest and most detailed way. Despite the clear repercussions described in the foregoing sections of the present thesis, callosotomy does not seem to impact the ability of patients to cope with daily living. Clinically, patients report less seizures and minimal perceived countereffects. Overall, from the clinical point of view this is a great improvement in patients' condition.

With regards to the psychological studies revolving around the split-brain condition evaluation is more complex. First of all, there is no clear understanding of the set of abilities that each hemisphere has on its own. In fact, studies on this condition led to the realization that the activation of the brain due to a specific function or stimulus generally does not involve a single part of the brain in a specific hemisphere. This caused the formation of opposing theories on whether or not each hemisphere can experience the world as a single unit creating its own consciousness. Theoretically the lateralization of perceptive stimuli can be the base for the creation of two separate ambient systems, that can produce two separate consciousnesses based upon the two different conceptions of reality. This point is further reinforced by the evaluation of the abilities of the patients after the surgery, that appear to be consistent with the idea that there are two conscious agents in the brain, working in parallel but partially blinded one to each other. Scientific discussion has promoted further studies on the ambient system, which is yet to be fully understood. However, the importance of this system to the unity of the consciousness appears clear, and the evidence suggests that the information needed in the creation of this view are transmitted through subcortical connections, as opposed to more complex data from conscious perception that travel on the cortex. These differences are fundamental and underline the possibility of a deeper connection linking the two hemisphere even when a cortical disconnection occurs. Moreover, the existence of a deep unified ambient system paved the road to a possible explanation on the recovery seen in split-brain patients. Given the severity of the damage, the capability of the brain to regain some interhemispheric connections, and abilities, appears inexplicable and has led to multiple explanatory theories. One of these sees the subcortical connections as a possible secondary lane for the information to flow from one hemisphere to the other and, with enough time, this secondary lane, normally not used for this purpose, can be trained and amplified to manage the needs of a higher networkif severed. Unfortunately the definition of a specific study on these amplified connections is difficult, especially because the pool of patients to be studied is very narrow, but also because the techniques necessary are pretty new and difficult to be managed. Hopefully DTI will play a key role in the further understanding and discovery of these paths, thanks to its ability to follow and draw back the individual electrical impulses, involved in a specific kind of activation, DTI could be able to catch the differences between normal and amplified connections. Even though DTI needs the use of premade masks to focus the visualization of one specific activated section, and silence the noise produced by all the other activities of the brain. This specific need could be a limit in the use of this instrument for studying new and undiscovered sections of the brain.

Other alternative explanations for the regained abilities are based on the possibility that the two halves, now independent one to each other, could find, with enough time provided, a way to hint the missing information to the other half. These ways can be internally transmitted, through some impulses shared by the two hemispheres, or externally as a gesture or a movement that can be physically seen from the other hemisphere. Regardless of the fact that these theories consider the existence of two conscious agents as certain, there are some flaws that can be tested to provide evidence to these ideas. For example, the activity of hinting for each useful information to share between the two hemispheres should result in a significantly longer time in response production, which does not seem to occur. Moreover, even if the internal hints could diminish the time needed and produce responses in similar time as the internal connection, the quantity of information and their quality should be determined by the surrounding area. These limits should impact in the quality of the responses and this effect should be visible in tests results, which has not been the case for now.

The importance of understanding the physical functioning of the brain is taking more and more space in the research and in the psychological debate. Howeveer, its subtle bond with the conscious experience and psychological products however is yet to be grasped. From this point of view, the possibilities given by this condition are astonishing. Creating this impediment in the normal harmonic functioning of the brain lets us take a picture of a middle stage of the brain activity, allowing a closer study of the functioning of the single hemisphere which would normally be extremely challenging. As this work has tried to highlight, there still exist widespread debate on the abilities of the different parts of the brain, it will be of great interest to observe the impact of the recent studies on Broca's area for language production or the contribution of both hemisphere in hypothesis formation and how these results will counter the canonical view. This kind of research could shed some light on some of the greatest psychological and philosophical problems involving consciousness and intelligence, allowing a better comprehension of our own functioning. Furthermore, with the new interest in the production of artificial intelligence, which aims to get closer and closer to the capability of the human brain, deeper understanding of consciousness and its relation to the neurological mechanisms of the brain, could play an important role in providing new perspectives and driving innovation in this fast growing and exciting new field of research.

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