\section{The Brain}

\subsection{Brain Anatomy and Functions}

The nervous system can be subdivided into two main parts: the \ac{PNS} and the \ac{CNS}. The peripheral nervous system is composed of the \ac{SNS} and the \ac{ANS}, while the \ac{CNS} is composed of the brain and the spinal cord \cite{MaldonadoAlsayouri2023}

With about 100 billion neurons when mature, the human brain is arguably the most complex biological system. The brain is an organ made of nerve tissue that controls senses, emotions, movement, language, thought, memory and task-evoked reactions. The human brain is divided into the cerebellum, cerebrum and brainstem. \cite{StilesJernigan2010}

\begin{figure}[H]

\centering

\includegraphics[width=0.6\linewidth]{images/Chapter\_2/brain lobes anatomy.jpg}

\caption{Different regions of the brain (Extracted from \cite{JohnsHopkinsMedicine2023}).}

\label{fig: Brain Regions image}

\end{figure}

The cerebrum, the biggest part of the brain, governs a wide array of functions, including memory, motor and sensory perception, conscious and unconscious actions, emotions, and intelligence. It is divided into four distinct lobes: frontal, parietal, temporal, and occipital, each responsible for a unique set of functions. The cerebral cortex, an outer layer of gray matter, and the inner subcortical white matter, collectively span both hemispheres, forming the structural foundation of this intricate organ \cite{MaldonadoAlsayouri2023}.

The cerebellum, comprising the cerebellar cortex and deep cerebellar nuclei, establishes connectivity with the brainstem through the cerebellar peduncles. This crucial brain region contributes significantly to motor learning, governing motor movement and balance. While it lacks the capacity to initiate muscular contractions, the cerebellum excels in the coordination of locomotion, control of voluntary muscle activation, modulation of tone, and maintenance of posture \cite{JimsheleishviliDididze2023}.

The brainstem controls autonomic processes like breathing, heart rate, temperature regulation, respiration, coughing, sneezing, digestion, vomiting, and swallowing, its main role is being a conduit for all the nerve connections between the brain and the rest of the body. Both gray and white matter can be found in the brainstem. The white matter is made up of fiber tracts, or neural cell axons, that ascend from the spinal cord and peripheral nerves to reach the highest regions of the brain, carrying sensorial information \cite{FernandezGilEtAl2010}.

\subsection{Brain Regions Associated with Empathy}

%Falar do bottoms-up and top-down empathy, neste caso queremos o bottoms up pq e um stimuli.

Empathy can be described as a change in the emotional state or perspective, brought about by contemplating another person's emotional state and feeling an emotion (or combination of emotions) that bears a resemblance to the emotion felt by that other person. Previous neuroimaging data showed evidence suggesting that observing the suffering of others causes activations in certain parts of the brain \cite{Light2009} \cite{Eisenberg2000} \cite{Hoffman2006}.

Previous research indicates that there are at least two ways for empathy to process information: top-down and bottom-up modes \cite{JankowiakSiuda2011} \cite{MillerCohen2001}\cite{BurkettNaghavi}.

Bottom-up processing describes automatic, instinctive responses that are primarily determined by sensory stimuli and the established brain pathways connecting these stimuli to similar emotional reactions. This process, which enables us to automatically connect with the emotions of others, is mostly driven by our immediate sensory experience and natural emotional reactions \cite{MillerCohen2001} \cite{BurkettNaghavi}.

On the other hand, top-down processing involves the application of cognitive capacities to comprehend the emotions and situations of others. This includes abilities like empathetic perspective-taking and explicit situational assistance. It provides us with the cognitive tools to assess information that may not be directly observable, such as imagining or reasoning about the internal state of others. Top-down processes engage neural regions associated with working memory, executive function, emotion regulation, and visuospatial perception, which is the ability to identify and understand the physical location of objects in relation to one’s own body and to identify the physical relationship between different objects. This cognitive endeavor allows us to understand and respond to the emotions and situations of others in a nuanced and thoughtful manner\cite{MillerCohen2001} \cite{BurkettNaghavi} \cite{HohlerRasamoelRohrbach2021} .

The activation of top-down cognitive empathy can feed back into bottom-up emotional empathy, even in the absence of an observable other, leading to representations at the emotional level. In summary, bottom-up processing might involve an immediate emotional response to another person's distress, while top-down processing might involve a more cognitive understanding of the other person's perspective \cite{MillerCohen2001} \cite{BurkettNaghavi}.

\begin{figure}[H]

\centering

\includegraphics[width=0.9\linewidth]{images/Chapter\_2/Bottom\_Top.png}

\caption{Brain regions related to empathy are associated with two types of information processing: top-down (dark grey) and bottom-up (light grey) interoception. ACC - anterior cingulate cortex; AI - anterior insula; SII - somatosensory cortex; MPFC - medial prefrontal cortex; TPJ - temporo-parietal junction; STS - superior temporal sulcus; TP - temporal pole.(Extracted from \cite{JankowiakSiuda2011})}

\label{fig: Bottom\_Top}

\end{figure}

The main neural components involved in empathy are the \ac{AI} and the \ac{ACC}, these are part of the Pain Matrix, a network of brain areas involved in processing pain and feeling other people's pain. These regions play a crucial role in empathy for pain, contribute to our comprehension and experience of other people's suffering, and are essential for developing empathy for pain. The hippocampus, amygdala, parietal operculum, posterior insula, primary and secondary somatosensory cortices (S1 and S2), and several frontal cortical regions are among the other brain regions implicated in pain empathy \cite{Gu2012} \cite{Xiang2018}.

The anterior insula (\acs{AI}) is responsible for processing emotions and interpreting body states as affective feelings. It integrates subjective feelings, uncertainty, and empathy, especially in situations where external sensory information is lacking. The anterior cingulate cortex (\acs{ACC}) is involved in cognitive and emotional processes, including attention, decision-making, and emotion regulation. It is believed to be involved in the affective component of empathy, which involves sharing emotional experiences. It is also involved in pain processing, activated when individuals observe others experiencing pain \cite{KilroyAzizZadeh2023}.

A network of brain regions known as the \ac{MNS} reacts when a person performs an action and when they witness someone else completing an action that is similar. This network is made up of sensorimotor areas such as the rostral section of the inferior parietal lobule and the lower half of the precentral gyrus, as well as the inferior frontal gyrus (IFG). \cite{KilroyAzizZadeh2023}

It is thought that the \acs{MNS} secretly "mirrors" the actions we witness in others onto our own motor system, enabling us to comprehend their intentions and behaviors by imitating them as though we were carrying out the activity ourselves. This technique, which allows people to see things from another person's perspective and put themselves in their shoes, is believed to be a crucial part of cognitive empathy. Numerous facets of empathy have been associated with the \acs{MNS}, and variations in individual empathy features have been linked to the \acs{MNS}'s activity \cite{KilroyAzizZadeh2023}.

\begin{figure}[H]

\centering

\includegraphics[width=0.6\linewidth]{images/Chapter\_2/MirrorNeuron.png}

\caption{Lateral image of the brain showing the superior temporal sulcus, as well as the frontal and parietal labels of the mirror neuron system. STS is the superior temporal sulcus; IFG is the inferior frontal gyrus; and IPL is the inferior parietal lobule. (Extracted from \cite{KilroyAzizZadeh2023}).}

\label{fig: Brain Mirror Neuron}

\end{figure}

The intricate neurological underpinnings of empathy include several interacting brain areas, particular kinds of empathy (cognitive vs. emotional), as well as the characteristics and experiences of a individual might also affect the precise processes.

\subsection{Brain Responses to Fear}

Fear is the feeling that arises in response to imminent or immediate harm or threat, triggering a defensive mechanism essential for human survival. Fear can be elicited by visual and auditory stimuli, including predators, aggressive individuals, environmental disasters, dangerous situations, or social threats \cite{Bocchio2016} \cite{Tao2021}.

Fear-related stimuli can be processed in both explicit and implicit conditions. In explicit fear processing, the scary component of the stimuli can be easily recognized by those with conscious awareness. On the other hand, implicit fear processing happens when an individual is unaware of the type, content, or even existence of the stimuli that cause them to feel fear\cite{Tao2021}.

The brain processes fearful stimuli through a network of symmetrically distributed regions across both hemispheres. These include subcortical regions, such pulvinar and the amygdala, and front-occiptal regions, such as the inferior occipital gyrus, the inferior frontal gyrus and the fusiform gyrus \cite{Tao2021}.

Linked to the visual cortex and fronto-parietal attention network, the pulvinar is thought to play an important role in visual attention, with interactions between cortical areas and the ventrolateral pulvinar maintaining the cortex in an active state. The amygdala, located in the medial temporal lobe and divided into the corticomedial, basolateral, and central nuclei, serves as a central hub for highly processed sensory information \cite{AbuHasan2023} \cite{Pessoa2010}. Additionally, its extensive connections with regions of the cortex, such as the orbital, medial, and lateral prefrontal cortex, contribute to its integrative functions \cite{AbuHasan2023}. Regardless of the level of awareness, the amygdala plays a pivotal role in processing fear \cite{Tao2021}.

The fusiform gyrus and inferior occipital gyrus are the fronto-occipital areas noted to exhibit activation in the core fear network and are critical in processing visual emotional stimuli, particularly negative ones \cite{Tao2021}.

Different levels of awareness show distinct functional patterns for fear processing, indicating varied neural mechanisms underlying explicit and implicit fear processing. Increased activations in the pulvinar and parahippocampal gyrus during explicit fear processing indicate that visual attention/orientation and contextual association are important processes during explicit fear processing. On the other hand, the cerebellum-amygdala-cortical pathway exhibits more activations during implicit fear processing, suggesting the existence of a "alarm" system during implicit fear processing \cite{Tao2021}.

\subsection{Brain Mechanisms of Defensive Responses}

The fear-defense system is an innate mechanism present in every human, organizing hard-wired, species-specific defensive reactions to threats that promote survival. Without conscious awareness, an arousal response mediated by the amygdala precedes the activation of defensive behavior. The feeling of anxiety, such as tensing of neck muscles, elevated heart rate, perspiration, and hyperventilation, is the conscious perception of this reaction. Some defensive reactive patterns include the fight or flight response and freezing. Therefore, the type of threat faced, its proximity, and its imminence all influence the type of defensive response \cite{GhaemiKerahrodi2020} \cite{Livermore2021}.

Particular neurohumoral networks, including the amygdala, hypothalamus, periaqueductal gray, and the ventromedial prefrontal cortex , are involved in these defensive responses \cite{Rigoli2016} .

\section{The Central Visual System}

\subsection{Visual Pathways}

For humans to see the world as a unified picture with object properties such as shape, color, and spatial awareness, there must be certain neurons that are sensitive to these properties. This visual sensory information is extracted by the retina and analyzed by the Central Visual System \cite{BearConnorsParadiso2006}.

The lateral geniculate nucleus (LGN) of the thalamus and the primary visual cortex, also called the striate cortex, are responsible for the pathway serving conscious visual perception. It is possible to define visual perception as the ability to receive, interpret and react to visual stimuli. This information is fed through the geniculocortical pathway to neurons specialized in analyzing various stimulus attributes, where it is processed in parallel and then sent to different extrastriate cortical areas in the temporal and parietal lobes \cite{BearConnorsParadiso2006}.

The term retinofugal projection is often used to describe the neural pathway that exits the eye towards the brain stem, starting with the optic nerve. Before forming synapses in the brainstem, the ganglion cell axons that are "fleeing" the retina travel through three components of the retinofugal projection: the optic nerve, the optic chiasm, and the optic tract, in that sequence. Neurons in the lateral geniculate nucleus (LGN) extend axons that project to the primary visual cortex; this projection from the LGN to the cortex is known as optic radiation. Lesions in the retinofugal projection are associated with blindness in humans, therefore it is correct to assume that this pathway mediates conscious visual perception. However, the LGN also receives synaptic inputs from the brainstem, so it is also involved in processes related to attentiveness and alertness \cite{BearConnorsParadiso2006}.

The striate cortex is the starting point of two primary cortical streams of visual processing, which project in distinct directions: the dorsal stream, which projects dorsally into the parietal lobe, and the ventral stream, which projects ventrally towards the temporal lobe. Visual perception and object recognition are under the control of the ventral stream. The analysis of visual motion and the visual regulation of action are processes carried out by the dorsal stream \cite{BearConnorsParadiso2006}.

\begin{figure}[H]

\centering

\includegraphics[width=0.6\linewidth]{Dissertação de Mestrado - Eng. Biomédica/images/Chapter\_2/Visual System.png}

\caption{Schematic representation of the human visual system (Extracted from \cite{Baskin2021}).}

\label{fig: Visual System}

\end{figure}

\subsection{Human Visual Reaction Time}

The human reaction time can be described as the interval between the start of a stimulus and the moment at which a person starts to move in response to it, and has been used to study the duration it takes for an individual to perceive visual stimuli. This period spans the successive actions of the different visual areas that are involved, roughly ranging from 150 to 200 ms \cite{Amano2006}.

In studies conducted previously by Potter et. al and at MIT, an experiment was undertaken to investigate the time required for an observer to detect and comprehend visual stimuli. The study employed rapid serial visual presentation (RSVP) of a series of pictures at durations ranging from 13 to 80 milliseconds per picture. As the exposure time decreased gradually to values of 80 ms, 53 ms, 40 ms, 27 ms, and 13 ms, the results revealed that participants were able to detect and comprehend the visual stimuli even at the shortest duration of 13 milliseconds. To convert milliseconds to frames per second, the formula FPS = 1000 / milliseconds can be used. Therefore, at 13 milliseconds, it corresponds to 75 frames per second \cite{MITPotter}.

\section{Electroencephalography}

Electroencephalography, often referred to as EEG, is a non-invasive method used to record brain activity. This technique has prompt a lot of interest in the scientific community, due to its safety, sensitivity to dynamic changes in neural signal, and high temporal resolution. From a neurophysiology standpoint, the EEG represents the postsynaptic potential, which is generated when neurotransmitters attach to receptors on the postsynaptic membrane, creating electric fields around neurons \cite{Light2010}

Once a reasonable number of neurons are activated, the cumulative activity of large populations of cortical neurons can be captured through a voltage amplifier. However, because the electrical signals captured by EEG pass through the skull, they have poor spatial resolution and a low signal-to-noise ratio \cite{Zhang2023}. In addition, subcortical structures, which are deep within the brain and farther from the EEG sensors on the scalp than cortical structures, can produce weaker and smaller EEG signals. This is because certain neurons in subcortical structures can be arranged in a closed-field geometry, which means that their individual electrical fields cancel each other out \cite{Krishnaswamy2024} \cite{Zhang2023}.

Compared to other methods such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), electroencephalography (EEG) has poor spatial resolution. However, EEG excels in temporal resolution, measured in milliseconds, which is significantly superior to the second-scale resolution of fMRI and PET. Furthermore, due to its low equipment cost, EEG has become the most popular technology for functional brain imaging \cite{Zhang2023} \cite{Zaboski2021}. Therefore, despite its low spatial resolution, the excellent temporal resolution and cost-effectiveness of EEG have contributed to its widespread use in functional brain imaging and shown great results when analyzing emotions\cite{Jalilifar}.

\subsection{Brain Waves}

Brain waves consist in electrical voltages in the brain that are only a few millionths of a volt and can be measured with a EEG. EEG waveforms can be described based on their position, amplitude, frequency, shape, continuity (whether they are rhythmic, intermittent or continuous), synchrony, symmetry, and reactivity, with frequency being the most common method to classify EEG waveforms. These can be divided into five EEG rhythms: delta (0.5-4Hz) , theta (4 to 7 Hz), alpha (8 to 12 Hz), beta (13 to 30 Hz), and gamma(30 to 80 Hz) and are shown in the image bellow fig.(\ref{fig: Waveform\_Signal}) . Each rhythm is associated with different frequencies and corresponds to different states of behavior, pathology, consciousness, and cognitive processes \cite{Nayak2024} \cite{Abhang2016}.

It is important to note that not all regions of the brain emit the same brain wave frequency at the same time. When electrodes are placed on the scalp, the recorded EEG signal consists of many waves, each with different characteristics, that can change depending on what a person is doing \cite{Abhang2016}.

\begin{figure}[H]

\centering

\includegraphics[width=0.6\linewidth]{Dissertação de Mestrado - Eng. Biomédica/images/Chapter\_2/brain\_waves.png}

\caption{Brain wave samples for different waveforms (Extracted from\cite{Abhang2016})}

\label{fig: Waveform\_Signal}

\end{figure}

\subsection{EEG Electrode Placement}

In EEG, there are a few standard electrode placement systems on the scalp: 10-20, 10-10, and 10-5. This numbers refer to the distance of neighboring electrodes placed on the skull. This means that in the 10-20 standard, an electrode is either 10\% or 20\% of the distance from the corporal landmarks: inion, nasion, left and right preauricular points \cite{Oostenveld2001} \cite{Soufineyestani2020}.

Each electrode name begins with a letter, succeeded by either an even or odd number, as we can see in fig. \ref{fig: Electrode\_Placmt}. The initial letter represents the cortical area: "F" for frontal, "C" for central, "T" for temporal, "P" for posterior, and "O" for occipital. The subsequent number signifies the hemisphere of the brain, with even numbers indicating the right side and odd numbers denoting the left side \cite{Abhang2016}.

\begin{figure}[H]

\centering

\includegraphics[width=0.6\linewidth]{Dissertação de Mestrado - Eng. Biomédica/images/Chapter\_2/Electrode\_Placmt.png}

\caption{Placement of the electrodes in the 10-20 International System using 19 EEG channels (Extracted from \cite{Sanchis2024})}

\label{fig: Electrode\_Placmt}

\end{figure}

The main difference between the 10-20 and 10-10 EEG systems lies in the increased spatial resolution offered by the latter, due to the addition of electrodes between the positions defined in the 10-20 system. This implies that the 10-20 system is suitable for tasks such as transcranial brain mapping and recording evoked and event-related potentials1, while, the 10-10 system is more appropriate when a higher level of detail in EEG data is required, such as in presurgical evaluations \cite{Soufineyestani2020} \cite{Acharya2016}.

\subsection{Visual Evoked Potential}

Visual evoked pontentials (VEP) are electrical scalp potentials produced by the brain in response to visual stimuli \cite{Mohr2023}. By detecting neural pool activity responding to stimuli regardless of the patient's consciousness and attention state, these potentials offer a non-invasive approach to investigating the functioning of the human visual system. VEP can be measured by placing electrodes on the scalp in the occipital region and presenting visual stimuli to a patient with their eyes open. Pattern visual evoked potentials can reveal varied information about the integrity of the optical pathways and the functioning of the different sectors of the visual field, depending on the characteristics of the stimulus \cite{Baiano2023}.

In summary, VEP are a vital tool in electrophysiological work for investigating the mechanisms underlying visual-cognitive processes and how they differ across a range of clinical disorders \cite{Mohr2023}.

\subsection{EEG Artifacts}

In EEG, the term artifact refers to signals (noise) with no cerebral origin that can be linked to a particular source. These artifacts can be either patient-related, such as eye movements, eye blinks, cardiac activity, and muscle activity, or technical, like faulty electrodes, line noise, and high electrode impedance Since these artifacts might mimic pathological or cognitive activity, it is imperative to identify and eliminate them in order to avoid biasing visual perception and diagnosis in clinical research \cite{Abhang2016} \cite{Jiang2019}.

\subsubsection{Ocular Artifacts}

Ocular artifacts, which spread over the scalp and can be recorded by an EEG, are divided into two categories: eye blinks and eye movements. Eye blink artifacts are caused by eyelid movements and are usually about 10 times larger than the ongoing EEG. Since these artifacts originate from the eyes, they are most prominent in the forehead electrodes, specifically Fp1 and Fp2, while also having a minor influence on other frontal electrodes and showing symmetry between the two hemispheres \cite{Abhang2016} \cite{Jiang2019} \cite{NeuralDataScience}. These artifacts can be identified by a quick increase in electrical potential, followed by a rapid decrease, typically over a duration of approximately 250–300 ms and when analyzed in the frequency domain, they introduce components primarily into the delta and theta EEG bands \cite{Jiang2019} \cite{NeuralDataScience} \cite{BrainProducts2022}.

\begin{figure}[H]

\centering

\includegraphics[width=1\linewidth]{Dissertação de Mestrado - Eng. Biomédica/images/Chapter\_2/Eye\_Blink.png}

\caption{Blink artifacts over continuous data. The spectral profile of the eye blinks frequencies in a horizontal EOG (electrooculogram) channel. The normal distribution of blinks throughout the scalp is depicted in the topography. (Extracted from \cite{BrainProducts2022})}

\label{fig: Eye\_Blink}

\end{figure}

The highly oriented arrangement of the retina's neurons results in the formation of an electrical dipole (source with positive and negative poles). If the eye's position doesn't change, there is no effect on the EEG recording. However, as the eyes move to focus on different points in space, eye movement artifacts are picked up by the electrodes on the scalp because the retina and cornea dipole shifts position. When the eyes shift to the right or left, the electrical potential will increase at the frontal electrodes on one side of the head and decrease on the other. While looking at the electrodes Fp1 and Fp2, eye movement artifacts can appear similar to a blink. However, when examining the electrodes F7 and F8 (and, to a lesser degree, F3 and F4), we can observe a box-shaped deflection with opposite polarity on each side of the head, meaning it goes positive at F7/F3 and negative at F8/F4 \cite{Jiang2019} \cite{NeuralDataScience} \cite{BrainProducts2022}. When analyzed in the frequency domain, they introduce components primarily into the delta and theta EEG bands, but has effects up to 20 Hz \cite{BrainProducts2022}.

\begin{figure}[H]

\centering

\includegraphics[width=1\linewidth]{Dissertação de Mestrado - Eng. Biomédica/images/Chapter\_2/Eye\_Movmnt.png}

\caption{Artifacts caused by eye movements in continuous data. The spectral profile of the eye movement frequencies in a horizontal EOG (electrooculogram) channel. The normal distribution of eye movements across the scalp is depicted by the topography.(Extracted from \cite{BrainProducts2022})}

\label{fig: Eye\_Mvmt}

\end{figure}

\subsubsection{Non-ocular Muscular Activity}

Muscle activity, such as muscle contractions or stretches near signal recording sites, can cause artifacts. These artifacts can result from activities like talking, sniffing, swallowing, jaw or forehead movements, and shoulder or neck tension \cite{Uriguen2015}. In the time domain, the amplitude and waveform of these artifacts depend on the extent of muscle contraction, stretch and muscle groups involved \cite{Jiang2019}. In the frequency domain, these artifacts produces high-frequencies bands that overlap with the entire EEG spectrum, being more prominent above 20 Hz, and up to 300 Hz \cite{BrainProducts2022}.

\begin{figure}[H]

\centering

\includegraphics[width=0.5\linewidth]{Dissertação de Mestrado - Eng. Biomédica/images/Chapter\_2/Muscular Artifacts.png}

\caption{Example of muscle contraction artifact in EEG data.(Extracted from \cite{NeuralDataScience})}

\label{fig: Muscular Artifacts}

\end{figure}

\subsubsection{Cardiac Artifact}

When electrodes are placed near a blood vessel, the expansion and contraction of the vessel due to the heartbeat can cause rhythmic movement of the electrodes and introduce artifacts. These artifacts have frequencies around 1.2 Hz and are very hard to remove due to its similarity with the EEG waveform \cite{BrainProducts2022} \cite{Jiang2019}.

\begin{figure}[H]

\centering

\includegraphics[width=1\linewidth]{Dissertação de Mestrado - Eng. Biomédica/images/Chapter\_2/Cardiac Artifacts.png}

\caption{Spikes in the pulse artifact during an EEG recording. Observe how the pulsations sometimes blend in with the EEG data and e pulse artifact distribution that is most prevalent.(Extracted from \cite{BrainProducts2022})}

\label{fig: Cardiac Artifacts}

\end{figure}

\subsubsection{Extrinsic Artifacts}

Besides the physiological artifacts mentioned, there are also non-physiological or extrinsic artifacts that originate from external sources, such as the environment or equipment. Examples of equipment artifacts include electrode misplacement and cable movements. Poor contact between the electrodes and the scalp can result in an unstable signal with slow drifts \cite{Jiang2019} \cite{BrainProducts2022}.

Line noise and electromagnetic interference emitted from the surroundings are examples of environmental artifacts. Electromagnetic noise, or line noise, is produced by the alternating current flowing through the room's electrical wires and equipment. This noise is detected by the EEG cables at frequencies around 50 Hz or 60 Hz \cite{Jiang2019} \cite{BrainProducts2022}.

\section{Electrocardiography}

An electrocardiogram (ECG or EKG) is a non-invasive diagnostic tool utilized to record the electrical activity of the heart from the body's surface. This technique is critical in the medical field for assessing the presence of normal and pathological cardiac rhythms \cite{Pooyan2016}.

When analyzing an ECG graphic it's important to have some concepts in mind. If the electrical activity is towards the lead it will display an upward deflection, the opposite happens if its away from the lead, downward deflection. Re-polarization and depolarization deflections take place in opposite directions. This basic patterns have been described in three main waves shown in the figure bellow \cite{Ashley2004}.

\begin{figure}[H]

\centering

\includegraphics[width=0.6\linewidth]{Dissertação de Mestrado - Eng. Biomédica/images/Chapter\_2/ECG\_Singal.png}

\caption{Basic Pattern of an ECG signal with the most important waves (Extracted from \cite{Ashley2004}).}

\label{fig: ECG\_Signal}

\end{figure}

While the P wave (small deflection) represents atrial depolarization, the QRS complex is divided into three waves and depicts ventricular depolarization. The Q wave is the smaller of the three and it stands for the depolarization of the inter-ventricular septum and is related to breathing. The R wave, being the largest, is associated with the depolarization of the main mass of the ventricles and the S wave signifies the last depolarization of the ventricles. Finally, the T wave depicts ventricular re-polarization \cite{Ashley2004}.

\subsection{Heart Rate Variability}

To calculate the heart rate from an electrocardiogram (ECG), standard textbooks of physiology and medicine explain that it is calculated in seconds by dividing 60 by the interval (in seconds) between two successive R peaks. This is because the R-R interval represents the duration of one cardiac cycle \cite{Prakash2005}.

\begin{equation}

\text{Heart Rate (beats per minute)} = \frac{60}{\text{R-R interval (seconds)}}

\end{equation}

While heart rate is the number of heartbeats per minute, the variation in intervals between successive heartbeats is known as Heart Rate Variability (HRV). HRV measures neurocardiac function, reflecting the influence of the ANS on the heart, and is produced by the connection between the heart and the brain, as well as dynamic, non-linear ANS processes \cite{Shaffer2017}.

Ultra Low Frequencies, or ULF ($\leq $ 0.003 Hz) bands measure very slow fluctuations in intervals between heartbeats (IBIs) and range from 5 minutes to 24 hours. Very Low Frequencies, or VLF (0.0033-0.04 Hz) bands consist of rhythms with periods between 25 and 300 seconds. Low Frequencies, or LF (0.04-0.15 Hz) bands are composed of rhythms with periods between 7 and 25 seconds and are affected by breathing from approximately 3 to 9 bpm. Finally, High Frequencies (HF), or respiratory band (0.15-0.40 Hz), measure rhythms influenced by breathing from 9 to 24 bpm \cite{Shaffer2017}.

There are sympathetic and parasympathetic components to the ANS. Both these components influence the heart rate by modulating the intervals between heartbeats (RR-intervals) at different frequencies. Sympathetic activity is related with the low frequency (LF), whereas parasympathetic activity is associated with the higher frequency (HF) range. Therefore, the ratio of LF to HF is important as it estimates the ratio between sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) activity under controlled conditions \cite{Shaffer2017} \cite{Malarvili2006}.

\subsection{ECG Artifacts}

The presence of noise and artifacts can significantly impact or restrict the detection of ECG signal properties, including the QRS complex. These artifacts are frequent and usually identifiable, arising from both physiological and non-physiological sources. The most common types of artifacts in ECG signals include Motion Artifact (caused by patient movement), Baseline Wander (low-frequency signal due to subject motion or electrode issues), Muscle Noise (resulting from muscular contractions), and Power Line Interference (typically occurring at around 50 or 60 Hz) \cite{Fariha2020} \cite{PerezRiera2018}.

\section{Signal Processing Techniques}

Performing pre-processing on EEG and ECG signals mainly involves noise removal with the objective of getting closer to the true pure signals, as noise can contaminate the signals and influence subsequent classifications algorithms' performance \cite{Dhanaselvam}\cite{Sanchis2024} \cite{Torres2020}. Therefore, to increase the signal-to-noise ratio, we can clean the signal using the methods below.

\subsection{EEG Filtering}

Filters are a good way to clean the EEG signal by limiting or removing unwanted frequencies. However, it is important to choose the filter types and parameters carefully, so as to only filter out frequencies that are not relevant to the study, as removing them can also mean losing information of interest.

A human EEG contains mostly signal power within the frequency range of 1 to 30 Hz; however, clinical EEG scalp recordings are often analyzed in the broader range of 0.5 Hz to 70 Hz, as frequencies above 30 Hz can have clinical significance in certain studies. Low-pass filters preserve the frequencies below a certain threshold while cutting off frequencies above it. On the other hand, high-pass filters retain frequencies above a given threshold while cutting off frequencies below it. Sometimes, instead of using both high-pass and low-pass filters, a bandpass filter is used to cut frequencies below and above a specific frequency band, retaining only the frequencies within that band. Another kind of filter is the notch filter, which preserves frequencies higher and lower than the designated notch frequency while cutting off a very small range of frequencies. Notch filters are often used to suppress frequencies like the powerline noise frequency at 50 or 60 Hz \cite{Sanchis2024} \cite{Cheveigne2019} \cite{Dhanaselvam}.

The impulse response of filters can be classified as finite impulse response (FIR) and infinite impulse response (IIR). FIR filters lack feedback and have a finite impulse response, meaning their output is based only on a finite number of past input values. IIR filters, on the other hand, have feedback in their structure, enabling them to have an infinite impulse response. Their output is determined by considering the current input, past inputs, and past output values. FIR filters are non-recursive and generally more stable compared to IIR filters, which are recursive and can potentially be unstable \cite{Stavrou2021} \cite{AskAnyDifference}.

\subsection{Independent Component Analysis}

Independent Component Analysis (ICA) is a crucial blind source separation technique widely utilized in biomedical engineering for signal denoising, among other applications.

This method assumes that the signal source is a linear mixture of cerebral and artificial sources, and can decompose observed signals into independent components (ICs). Once the independent components containing artifacts are identified, a clean signal is reconstructed by removing these ICs \cite{Jiang2019} \cite{Chaddad2023}. ICA-based EEG signal denoising may be described as follows:

\begin{equation}

\text{X = AS}

\end{equation}

In the equation, X is a matrix containing EEG and ECG data, S is a matrix representing independent components, which include both brain sources and artifact sources, and A is a matrix representing the linear mixing of these sources, reflecting how these sources are mixed together to produce the observed EEG data \cite{Chaddad2023}.

The process of signal denoising using ICA begins with X as an input matrix containing EEG and ECG data and the specified number of independent components to estimate. After, the EEG data matrix X is centered and whitened. Following this, the matrix A is randomly initialized. The algorithm then iteratively updates A by exploiting the non-Gaussianity of the independent sources until convergence is achieved. Once A has converged, the matrix S is computed from A and X. Artifact components within S are identified and subsequently removed. The cleaned data is then reconstructed from the modified S. Finally, the matrices S and A are returned as the output \cite{Chaddad2023}.

\subsection{Short-Time Fourier Transform}

Short-Time Fourier Transform (STFT) is a series of Fourier transforms applied to windowed segments of a signals. When a signal's frequency components change over time, the STFT provides both the frequency and time information \cite{Kehtarnavaz2008}.

When performing STFT, a narrower window segment results in better resolution in the time domain but poorer resolution in the frequency domain, and vice versa. Which means that the time and frequency resolution depend on the window size \cite{Kehtarnavaz2008}.

\subsection{Wavelet Transform}

Wavelet transform is a time-frequency transform that is precisely localized within the time domain and takes into account the characteristics of the EEG signals within a frequency domain \cite{Saeidi2021}.

In contrast to the STFT, the wavelet transform adjusts the window size based on frequency. This helps overcome the time-frequency resolution limitation of the STFT algorithm. At high frequencies, fine resolution is achieved using smaller windows, while at low frequencies, longer windows are used to cover the frequency contents. Because EEG signals are transient, the wavelet transform can be more effective than SFTF \cite {Saeidi2021} \cite{Chaddad2023} \cite{Adeli2003} \cite{Alturki2020}.

\section{Feature Extraction}

EEG and ECG signals usually contain complex and large amounts of information. Therefore, one of the most important elements of any successful study is the capacity to extract the appropriate characteristics from the signals \cite{Saeidi2021}.

Features are descriptive values that characterize a signal from a specific perspective. Different signal features can be derived from an EEG signal, and these features should be as independent as possible to prevent redundancy. Features collected from EEG data can be divided into multiple classes, such as time domain features, frequency domain features, time-frequency domain features and nonlinear such as entropy \cite{Stancin2021} \cite{Boostani2017}.

\subsection{Time Domain Features}

Time domain features can represent the morphological characteristics of a signal and are easily interpreted. These features can be divided into statistical features, such as mean, standard deviation (dispersion of a dataset), skewness (degree of symmetry with respect to the mean), kurtosis (measure of tail heaviness), median (value that divides a dataset into upper and lower halves), and threshold percentile (proportion of samples falling below a threshold). Non-statistical features include the zero crossing rate, which represents the number of times a signal crosses the baseline, indicating the number of sign changes in a windowed signal \cite{Boostani2017}.

\subsection{Frequency Domain Features}

At the base of frequency domain features is the power spectral density (PSD) of the signal, this can be calculated with parametric and non-parametric methods. Non-parametric methods are more broadly used, as they don't need to select parameters, and include methods such as Fourier Transform (most commonly the Fast Fourier Transform), Welch's method, or Thompson multitaper method, while parametric include autoregressive (AR) models, or autoregressive-moving average (ARMA) models. Some statistical features used in the time domain are also used in the frequency domain, such as mean, median, variance, standard deviation, skewness, kurtosis \cite{Stancin2021}.

One of the most commonly used frequency-domain features is the power of certain frequency bands. When studying EEG, the most commonly used frequencies are delta ($\delta$, $0.5$--$4$ Hz), theta ($\theta$, $4$--$8$ Hz), alpha ($\alpha$, $8$--$12$ Hz), beta ($\beta$, $12$--$30$ Hz), and gamma ($\gamma$, $>30$ Hz). Many ratios between frequency bands are frequently employed as characteristics in the analysis of EEG signals, such as $\theta/\alpha$, $\beta/\alpha$, $(\theta + \alpha)/\beta$, $\theta/\beta$, $(\theta + \alpha)/(\alpha + \beta)$, $\gamma/\delta$, and $(\gamma + \beta)/(\delta + \alpha)$ \cite{Stancin2021}.

When examining the ECG, the distribution of absolute or relative power across four frequency bands is estimated using frequency-domain features. These bands include ultra-low-frequency (ULF) ($\leq 0.003$ Hz), very-low-frequency (VLF) (0.0033--0.04 Hz), low-frequency (LF) (0.04--0.15 Hz), and high-frequency (HF) (0.15--0.4 Hz) \cite{Shaffer2017}.

\subsection{Entropy}

Because EEG exhibits non-linear characteristics, non-linear measures can be an effective techniques for processing EEG signals. Methods based on entropy assess the irregularity and impurity of signals in the time domain. Consequently, the entropy value of a windowed signal decreases as the signal becomes more regular, and vice versa \cite{Boostani2017}.

\subsection{Functional Connectivity}

The goal of uncovering brain connectivity is to describe the patterns in which various brain regions interact with one another. This concept relies on the fundamental idea of functional integration, which involves the coordinated activation of neural ensembles across different cortical areas, as opposed to functional segregation, which refers to the activation of specific brain regions. In this context, functional connectivity (FC) describes which brain areas are related and how strongly they are connected over time by examining the statistical relationships between the activities of different brain regions \cite{Friston1994} \cite{Chiarion2023}.

FC metrics can be subdivided based on whether they quantify the direction of the interaction or not. Directed functional metrics are based on the principle that causes precede their effects; therefore, they aim to establish a statistical causal relationship from the data. In some cases, such as transfer entropy and Granger causality, causes predict their effects. On the other hand, non-directed metrics measure the interdependence between signals without considering the direction of effect \cite{Bastos2016}.

When analyzing EEG data, the most common methods used are coherence-based methods, phase-synchronization methods, and correlation-based methods. Coherence is the covariation in amplitude and phase between two signals, and measures the linear correlation between two time series in the frequency domain. The higher the coherence, the more synchronized and integrated the signals are. Coherence can detect changes in power and phase correlations but cannot directly provide the causal nature of the link between the two signals. Some examples of coherence metrics include the imaginary part of coherence, the coherence coefficient, and partial coherence \cite{Bastos2016} \cite{Gaudet2020}.

As an substitute to classic amplitude-based indices of coherence, phase synchronization metrics have been developed \cite{Bastos2016}. These methods measure the degree of synchronization or coherence in the phase relationships between oscillatory signals originating from remote brain regions \cite{Vindiola2014}. Some examples include phase-locking value (PLV) methods, phase lag index (PLI) and phase slope index (PSI) \cite{Bastos2016} \cite{Gaudet2020}.

Finally, correlation-based methods measure the linear relationship between two variables. These algorithms calculate how much one signal may predict the other based on their linear relationship \cite{Bastos2016}. Some examples of these methods are the Pearson correlation, Spearman correlation, and cross-correlation\cite{Bastos2016} \cite{Briels2020}.

\subsection{Pan-Tompkins Algorithm}

The Pan-Tompkins algorithm is typically utilized for ECG analysis as a QRS detection algorithm. To find the R-peaks in QRS complexes, this algorithm utilizes amplitude, slope, and width of an integrated window \cite{Pan1985}. This technique can be divided into two stages, pre-processing and decision.

Pre-processing has as an input the raw ECG and includes noise removal, signal smoothing, and width and QRS slope increasing. Next, on the decision step, thresholds are applied selectively identify signal peaks and filter out noise peaks \cite{Fariha2020} \cite{AlJabbar2023}.

This algorithm comprises several components including Low Pass Filter (LPF), High Pass Filter (HPF), derivatives, a squaring function, Moving Window Integration (MWI), thresholding, and decision making. A bandpass filter is also used to mitigate false detections that can result from noise and artifacts in the ECG. In the decision phase, the thresholds were automatically modified using the parameter to accommodate variations in QRS shape and heart rate. A quick summary of this process can be find in the diagram below \cite{Fariha2020} \cite{AlJabbar2023}.

\begin{figure}[H]

\centering

\includegraphics[width=1\linewidth]{Dissertação de Mestrado - Eng. Biomédica/images/Chapter\_2/Pan\_Tompkins.png}

\caption{Scheme summary of the Pan-Tompkins Algorithm.(Extracted from \cite{Fariha2020})}

\label{fig: Pan\_Tompkins}

\end{figure}

\section{Virtual Reality}

\subsection{Definition}

The concept of Virtual Reality (VR) has been around for nearly 50 years. It involves a display system that presents sensory information and images generated by a computer, while a tracker updates the images based on the user's position and orientation \cite{Freeman2017} \cite{Sokolowska2023}.

Recently, VR has become more common thanks to a new generation of head-mounted displays (HMDs) that have made VR more affordable and accessible. The HMD creates a stereo scene by displaying separate images for each eye. Each image is calculated and generated independently, using accurate perspective based on each eye's location in relation to a mathematical representation of a three-dimensional (3D) virtual environment. Typically, HMDs are tracked, allowing the user to turn or move their head to look around. As users move, the computer updates the image display at very high frame rates \cite{Freeman2017}.

One of the main advantages of virtual reality (VR) is that it offers a more realistic and immersive setting, which can improve the ecological validity of tests or therapies. Additionally, it seems to be able to get around some of the drawbacks of actual exercises, particularly for practical training \cite{Sokolowska2023}.

\subsection{VR Applications}

Virtual Reality (VR) has a wide range of applications across various fields, including virtual prototyping, architectural walkthroughs, visualization, training, and entertainment \cite{Sherman2003}.

Visualization and training are the two main areas in which medical applications of VR are categorized. Applications for visualization include data processing from CT and MRI scans, which can aid in surgical planning, and even visualization inside of the patient's body. On the other hand, medical training such as surgical suturing and minimally invasive surgery can be used to train medical staff \cite{Sherman2003}.

A clinician-controlled walkthrough of a VR visualization of a portion of the real environment can serve as psychological therapy for various conditions, including anxiety disorders, depression, psychosis, substance use disorders, and eating disorders. The manipulation of VR environments can enhance the understanding of these disorders, and simpler psychological treatments can be effectively administered using VR \cite{Sherman2003} \cite{Freeman2017}.