UNIVERSITÀ POLITECNICA DELLE MARCHE
FACOLTÀ DI INGEGNERIA
CORSO DI LAUREA MAGISTRALE IN BIOMEDICAL ENGINEERING

HUMAN WORK-RELATED STRESS CLASSIFICATION USING A CONSUMER-GRADE ELECTROENCEPHALOGRAPHIC DEVICE AND MACHINE LEARNING MODELS

Candidate:

Gina Primavera

Supervisor:

Prof. Lorenzo Palma

Cosupervisor:

Dott. Ilaria Marcantoni

Dott. Luisiana Sabbatini

Academic Year 2020/2021

ABSTRACT

Work-related stress manifests itself among workers when the demands made on them exceed their ability to cope, with damaging consequences for their health and mental equilibrium. It is therefore essential to constantly monitor their pathophysiological mechanisms.

Stress is a common experience in everyday life. In biological terms, it represents the set of physiological responses that have evolved over millennia to enable us to react quickly in emergency situations and to keep us safe. It is therefore a natural, normally positive, and useful phenomenon. However, the incessant action of stressful factors can undermine physical and mental health, so the aim of this project is to carry out a binary classification of mental workload (MWL) using a particular app able to train models to classify data and monitor stress.

From a scientific point of view, however, it is something different: stress is defined as the reaction of an organism to a stressful agent, or stressor. In fact, therefore, it is possible to say that stress is an entirely natural and fundamental phenomenon for organisms, because it puts them in a position to react to a potentially dangerous situation. The brain is an organ divided into two hemispheres joined by the corpus callosum, which communicates with the spinal cord through the brainstem. Its outermost layer is the cortex, while at its center are the basal ganglia and at its base, posteriorly, the cerebellum. Each hemisphere is divided into several lobes: frontal, parietal, occipital and temporal. Two types of cells are sufficient to form all these structures: neurons and glia. The brain is surrounded by membranes, the meninges, which form a triple protective layer. The brain controls thoughts, memory and language, the movements of the arms and legs and the functioning of all the body's organs. Finally, by regulating breathing and heartbeat, it determines reactions to stressful events that may occur in daily life. The central nervous system plays a key role in processing stressors and eliciting and controlling the stress response. Indeed, all types of stressful stimuli converge on the central nervous system where they are processed, and stress responses are triggered. Recently, considerable progress has been made in discovering the nervous and neuroendocrine correlates that mediate the cascade of reactions triggered by stress.

The non-invasive recording of electrical activity in the brain using external electrodes is called an electroencephalogram (EEG). The electrical activity detected is represented by a series of waves reproduced on a screen and then printed on paper or transferred to an electronic medium. Nowadays, most companies in the industry use devices that use EEG electrodes that are placed on the scalp, where the patterns of electrical activity generated when millions of brain cells are actually acting are detected. Different types of brain waves have been associated with different mental states, such as relaxation or other actions. One device to help monitor and assess stress in order to prevent unpleasant situations is to consider the Emotiv Epoc wearable helmet, which is able to record the individual's eeg signal and assess their stress level. The learner classification app was applied to five different features extracted from the whole stew dataset, containing a collection of EEG signals, acquired through wearable sensors by the subjects in two experiments, namely "NO TASK" and "SIMKAP-based multitasking activity". From the analysis of the results obtained, it can be seen that for the classification of workload levels the ensemble boosted trees model achieves 92.0% and 93.1% classification accuracy for the training and test results respectively. Consequently, it can be stated that this type of model provides good results, the remaining percentage is a good starting point for future studies, where more attention will be paid to finding more accurate methods to analyze even very noisy signals.

INTRODUCTION

According to the European Agreement on Work-Related Stress of 2004 [1] , stress is "a condition that may be accompanied by disorders or dysfunctions of a physical, psychological or social nature and is a consequence of the fact that some individuals do not feel able to respond to the demands or expectations placed in them". Work-related stress can therefore potentially affect every workplace and every worker as it is caused by different aspects closely connected with the organization and work environment. In Italy, the current regulatory framework, consisting of d.lgs. 81/2008 obliges employers to assess and manage the risk of work-related stress like all other risks, in transposition of the contents of the European Agreement. In this regard, in November 2010 [2] the Permanent Advisory Commission on Health and Safety at Work developed the necessary indications for the assessment of the risk of work-related stress, identifying a methodological path that represents the minimum level of implementation of the obligation.

First of all, it must be taken into account that at work, as in life, stimuli represent fundamental elements for the development and growth of the individual. Selye himself argued that "complete freedom from stress is death." Contrary to what is usually thought, one should not, and in fact, one cannot avoid stress, but one can deal with it effectively and take advantage of it by learning more about its mechanisms and adapting the philosophy of existence to it.

Specifically, in 2021 43% of the population said they had experienced stress due to work, while this percentage was 38% in 2019 [3] .

This approach to work stress tends, therefore, to attach great importance to subjective characteristics and individual responsibility for the protection of one's health by mitigating it from potentially harmful stimuli coming from the work environment with consequent loss of centrality of the role of those forms of primary prevention that aim to eliminate their presence.

Because of these observations, it is therefore considered preferable to take as a reference an approach that places greater emphasis on elements potentially harmful to the well-being of the individual at work rather than on subjective perception and individual cognitive assessments.

Work-related stress is one of the biggest problems affecting the European labor market, at all levels of all economic enterprises. No role is exempt from it and can affect anyone during their working life. What makes it important to investigate this disorder is that any workplace can potentially be a source of this type of stress. It is therefore important to understand this type of disorder that can affect all of us to deal with it in the best possible way. Stress can be caused by the way work is organized and/or the tasks you have to perform. Occupational medicine refers to work-related stress as the feeling of imbalance that workers experience at work if the demands placed on them are greater than their ability to cope. When the European Agreement defined stress, this condition stems from the fact that people do not feel able to meet the expectations and demands that are placed on them as professionals. By transferring this general concept to the workplace, it is therefore possible to define work-related stress as a perception of imbalance: the worker experiences this feeling when the needs of the organization and the work environment are excessive. That is, they exceed his individual abilities, because he does not feel able to cope with these demands. Working under some positive pressure can lead to better performance and be a source of satisfaction when the individual and team achieve important goals. On the contrary, when the demands, expectations and pressure become excessive and out of control, it causes stress. Importantly, work-related stress is not a disease in itself, but a condition in the human organism that responds to external stress and involves a series of adaptations that, if prolonged over time, can become pathological. If it occurs with prolonged intensity, it can cause mental and physical health problems in the worker.

Work-related stress monitoring is very important in order to prevent unpleasant consequences and thus protect the subject during the course of work. In particular, quantifying stress through biological signals, through the use of well-defined and proven methods, allows to arrive at objective results. In this regard, there is an excellent preliminary work to evaluate and classify the different types of stress. Several studies were conducted using the STEW dataset for the MWL multitasking task induced by a simultaneous single-session skill experiment with forty-eight subjects. In this regard, the aim of the present project is to go to carry out a binary classification of MWL using the Classification Learner app, able to train models to classify data. Using this app, it is possible to explore supervised machine learning using various classifiers. Regardless of

the results, this project is a good starting point for future studies, where more attention can be paid to finding more accurate methods.

CHAPTER 1.

STRESS: Definition and Health Consequences

1.1 DEFINITION OF STRESS

The construct of "stress" is one of the most complex and arises today, in an increasingly evident way, as one of the most relevant social problems, which must be given a timely response at the level of both treatment and prevention.
Notwithstanding that in general stress involves a state of "pressure", as the etymological origin of the term confirms, it is important to make a first distinction between the words stressor and stress properly said:

- ***Stressor*** is a stimulus-situation here, that is, anything that happens to us; this can be both positive and negative.

- ***Stress*** (an English term that means "effort") is the generic response of body to the stressful stimulus.

The adaptive response to stress depends on a highly interconnected neuroendocrine, cellular, and molecular infrastructure, namely the stress system. The key components of the stress system are the hypothalamic-pituitary-adrenal axis (HPA) and the autonomic nervous system (ANS), which interact with other vital centers in the central nervous system (CNS) and with tissues/organs in the periphery to mobilize a successful adaptive response against the imposed stressor(s).
All vital physiological systems of the body are intrinsically programmed, through rigorous fine-tuning achieved during evolution, to preserve a predefined steady state called homeostasis or eustasis, which is essential for life and well-being [3-5] . This optimal balance is constantly challenged by adverse forces that are intrinsic or extrinsic, real or even perceived, and are described as stressors [3] . Thus, stress is defined as a state of disharmony, cacostasis or allostasis, and it is countered by an intricate repertoire of physiological and behavioral responses that aim to maintain/re-establish threatened homeostasis [3]. This adaptive response to stress is mediated by a complex and interconnected neuroendocrine, cellular and molecular infrastructure that makes up the stress system and is located both in the CNS and in the periphery [3-4] . Everyone's adaptive response to stress is determined by a multiplicity of genetic, environmental and

developmental factors. Changes in the ability to respond effectively to stressors, such as inadequate, excessive and/or prolonged reactions, can lead to illness. In addition, highly potent and/or chronic stressors can have detrimental effects on a variety of physiological functions, including growth, metabolism, reproduction, and immune competence, as well as on personality behavior and development. It should be noted that prenatal life, childhood, and adolescence are critical periods in the process of forming the matrix of the adaptive response to stress, characterized by a high plasticity of the stress system and greater vulnerability to stressors.

The stress system receives and integrates a great diversity of visual, auditory, somatosensory, nociceptive, and visceral, blood and limbic neurosensory signals that reach the various centers/stations of the stress system through distinct pathways. Acute activation of the stress system triggers a group of time-limited changes, both behavioral and physical, that are quite consistent in their qualitative presentation and are collectively defined as the stress syndrome [3-6] . Under normal conditions these changes are adaptive and improve the chances of survival. Initially, the stimulation of the components of the stress system follows a specific mode for the stressor; however, as the potency of the stressor(s) increases, the specificity of the adaptive response decreases to eventually present the phenomenology of relatively nonspecific stress syndrome that follows exposure to potent stressors.

Behavioral adaptation includes an increase in arousal, alertness, cognition, focused attention, and analgesia, while there is a concomitant inhibition of vegetative functions, such as feeding and reproduction. In parallel, physical adaptation mediates an adaptive redirection of the body's energy and resources. As such, increases in cardiovascular tone, respiratory rate and intermediate metabolism, gluconeogenesis and lipolysis, work in concert to promote this redirection of vital substrates, while energy-consuming functions for example, digestion, reproduction, growth, and immunity are temporarily suppressed. Thus, oxygen and nutrients are mainly shifted to the CNS and to the sites of the body subjected to stress, where they are most needed.

In addition to the adaptive response to stress, containment forces are also activated during stress to prevent a potential excessive response of the various components of the stress system [3-6] . The ability to develop containment forces in a timely and precise manner is equally essential for a positive outcome against the imposed stressor(s), as prolonging the

mobilized adaptive stress response can become maladaptive and contribute to the development of the disease.

Interestingly, the mobilization of the stress system is often of a magnitude and nature that allows the perception of control by the individual. In such conditions, stress can be rewarding and pleasurable, or even exciting, providing positive stimuli to the individual for growth and emotional and intellectual development [7] . So, it is not surprising that the activation of the stress system during nutrition and sexual activity, is mainly related to pleasure.

It is also important to understand, starting from Selye's theories to the most recent psychophysiological studies, how to move from an acute type of stress, for which the organism puts itself in a position to react to external events that must be faced and resolved, to a chronic type in which stress remains beyond the real external needs and produces extremely harmful effects of attrition and imbalance of the normally physiological functions of the organism.

The stress response is crucial for every organism to adapt plastically to the environment and its demands. An optimal response is characterized by conditions that produce rapid activation and deactivation of biological systems, synchrony in biological and behavioral responses, and variable intensity in relation to the individual response.

Deviations from the ideal characteristics of this optimal stress response can be manifold.

However, some common characteristics can be described and organized as follows:

- ***Acute stress of high intensity***: it is possible that in the first phase of the general adaptation response some manifestations of stress reactions in acute and particularly intense conditions may be the basis of amplified reactions up to pathological.

- ***Prolonged chronic stress***: exposure to stress continues over time beyond the possibilities of reaction of the organism. It corresponds to the phase of exhaustion described by Selye: the final stage of the reaction of the general adaptation syndrome.

- ***Acute and/or chronic stress in a condition of blockage of action***: a state of biological activation is present in the absence of an effective possibility of behavioral reaction towards the stressor. Blocking the ability to act and inactivate the stressor, in both acute and chronic conditions, is generally associated with hyperactivation of the response of various physiological functions.

- ***Acute stress in a system with chronic inhibition of the stress reaction***: it is based on the hypothesis that an acute stress condition in an organism with chronic inhibition of the stress reaction can produce effects, much more powerful and deleterious, than the biological effects it would produce in an organism "trained" to stress.

Experimental studies carried out on animals have in fact shown that by "protecting" an organism for a long time and artificially from normal stressful stimulations, the response to normal stressors even of moderate magnitude is abnormal and excessive. On the neurophysiological level, there is an over-response of the pituitary-adrenal axis, while on the behavioral level there is a greater disorganization and inability to set up an inadequate fight/flight reaction. In humans, similar conditions can be produced by personality structures or emotional-cognitive factors, so the subject organizes a lifestyle that avoids stressors as much as possible or that, in any case, filters and minimizes the emotional impact. Therefore, a systematic avoidance of the activation of the normal stress reaction produces a state of chronic inhibition of stress, if in the face of an unavoidable and serious event the body undergoes an excess stress reaction, with a greater risk of developing stress-dependent problems.

1.2 HISTORY AND EVOLUTION

The scientific study of stress has historically evolved through a variety of phases that initially emphasized the role of the external environment as a determining factor in the

experience of stress [8]; subsequently the focus shifted to the factors internal to the individual in influencing stress responses; up to consider the interaction between the person and the environment.

Selye proposes a physiological model of stress called the theory of the general adaptation syndrome which can be seen in the figure 1.1. According to the author, "stress is the strategic response of the organism in adapting to any need, both physiological and psychological, to which it is subjected. In other words, it is the body's nonspecific response to every request made about it" [8] . Selye insists a lot on the non-specific nature of the body's response: the adaptation response aimed at restoring homeostasis will be the same, regardless of the nature of the stressor, and takes place in three phases: in the first phase there is the appearance of a stressor that causes an alarm reaction in the organism; this is followed by a mobilization to deal with the threat, and the activation of coping strategies. However, Selye, considers mainly the chemical-physical effects, neglecting the psychological ones. In fact, all the studies following his have shown that stress, at any level, is induced by determinants of an emotional nature.

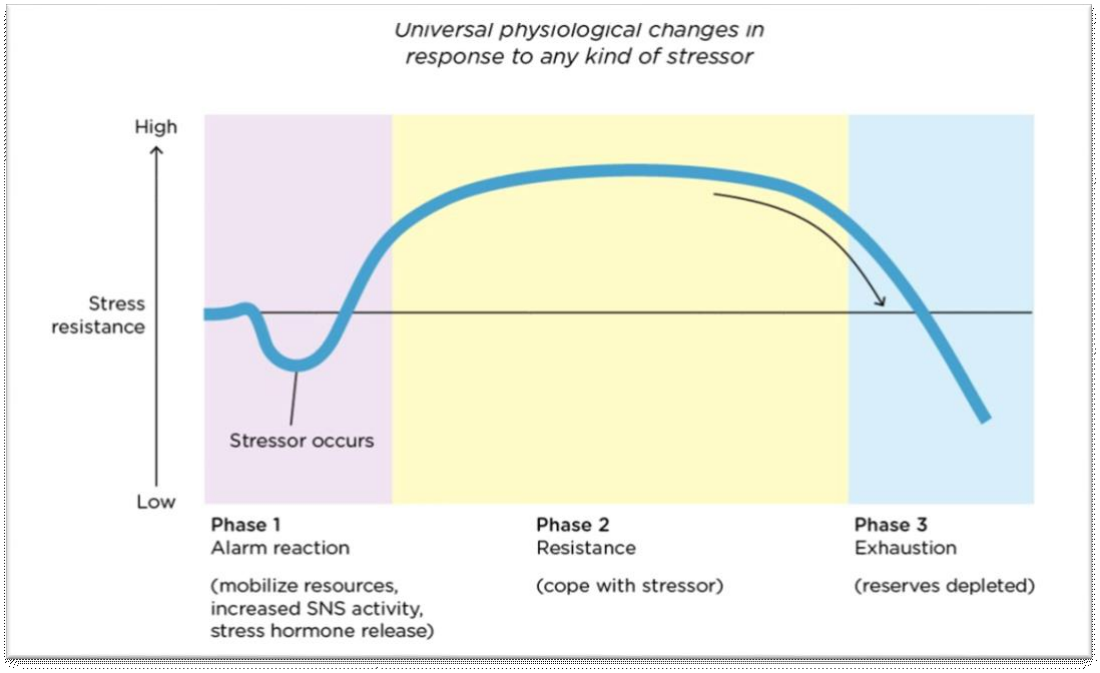


Figure 1.1: Seyle's general adaption syndrome

One of these studies was that of Mason on the "first mediator" [9] , a concept already postulated by Selye but never proven, which according to the author is represented by the anatomical-functional structures responsible for emotional activation at the physiological level and by the psychological apparatus involved in the emotional response.

According to Mason [9] , the intensity of emotional activation can influence the quantity, duration and quality of the stress reaction, including its level of 'non-specificity', which can vary from a minimum to a maximum depending on stress conditions. So, the more important the event is for the individual, the more intense the emotional response will be, decisive in the manifestation of the stress reaction.

According to Levi [10] , the emotionality of an individual is influenced by various stressors, which could be: an unhappy marriage, economic insecurity, few social contacts and work difficulties.

The emotional structure concerned is the "emotional brain", that is, the limbic system, which exercises behavioral and endocrine control of the stress reaction, improving the ability to adapt and defend against life-threatening stressors.

The importance of emotions has led some authors to propose the concept of psychological stress. According to Lazarus and Folkman [11], stress consists of a transaction between the person and the environment in which the situation is evaluated by the individual in excess of his own resources and such as to endanger his well-being. The authors describe stress as a process that includes stressors and the responses put in place by the subject, but add the relationship between the person and the environment, between the demands and personal resources to cope with them as they come perceived by the individual.

What differentiates this approach from the previous ones is the introduction of the concept of coping[11], defined by the authors as "the efforts of the person to manage the internal and external requests posed by those person-environment interrelationships that are evaluated as exceeding the resources possessed".

The model of stress and coping of Lazarus and Folkman is still the undisputed starting point of all theories on stress and coping. However, there are new theoretical perspectives in the literature that give more attention to changing situational/contextual factors in influencing the experience of stress and coping efforts; they shift the emphasis from vulnerability factors to adaptability forces and the resilience capacity of subjects, which means that from highly stressful situations it is possible to get

out with positive and constructive outcomes and place the subject within the social context of life, where the process of stress and coping are seen not as the property of individuals, but of social units.

1.3 HOW TO MEASURE STRESS: INSTRUMENTAL ANALYSIS AND PHYSIOLOGICAL MEASUREMENT

To make the assessment of the stress level as objective as possible, it is studied in terms of the physiological changes associated with it, which are mainly attributable, at the level of the ANS, to a sympathetic hyperactivation and an inhibition of the parasympathetic, mainly concerning cardiac effectors.
There may be several techniques to be used for the measurement of these alterations:

1. ***Microneurography***

Microneurography is a unique neurophysiological technique, shown in the figure 1.2, that allows the direct recording of related and postganglionic non-myelinated nociceptive fibers by means of tungsten needles inserted into the peripheral nerve fasciculus. In recent years, microneurography has been used to ascertain neurological disabilities in central neurological disorders such as sleep disorders, Parkinson's disease, amyotrophic lateral sclerosis, or vasovagal syncope. In these disorders, abnormal abdominal muscle sympathetic nerve (MSNA) activity and cutaneous sympathetic nerve activity (SSNA) or abnormal sympathetic response to arousal have been described. [12]

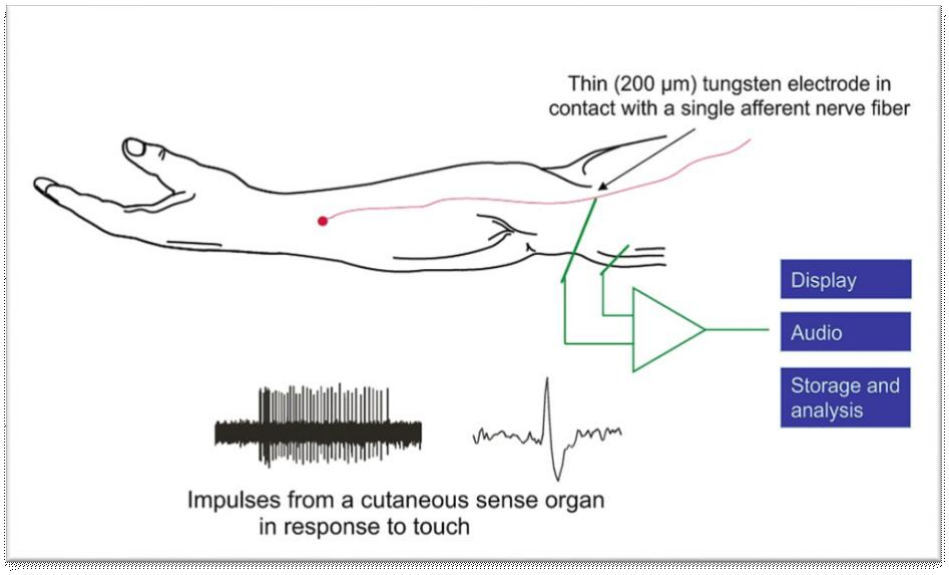


Figure 1.2 : The microneurographic technique

2. ***Adrenal evaluation***

Another dimension of the stress response is hormonal (figure 1.3). The most well-known stress hormones are adrenaline and cortisol. Adrenaline is known to create a burst of energy that helps people cope with stress (it's part of the "fight-or-flight"). Cortisol does something similar, but has a longer action, for example, it raises blood sugar so that the cells have more fuel available. When cortisol is chronically high it causes problems such as brain damage, and the symptoms tend to be anxiety and hyperarousal, feeling of tension and hypervigilance. Cortisol can also drop too low; this tends to be seen in exhaustion and burn-out. Cortisol has, or should have, a daily rhythm: it should be high in the morning when people get up (giving energy) and go down later in the day so that it is low at bedtime. Often this rhythm is lost in chronic stress. To assess adrenal function, a laboratory test is required: the most common uses dried urine samples, which are easy to collect and transport. Ideally at least four or more samples of a day are needed, so that the daily rhythm can be seen. Adrenal laboratory tests typically also look at another adrenal hormone, DHEA but not adrenaline that has a life too short to be tested significantly.

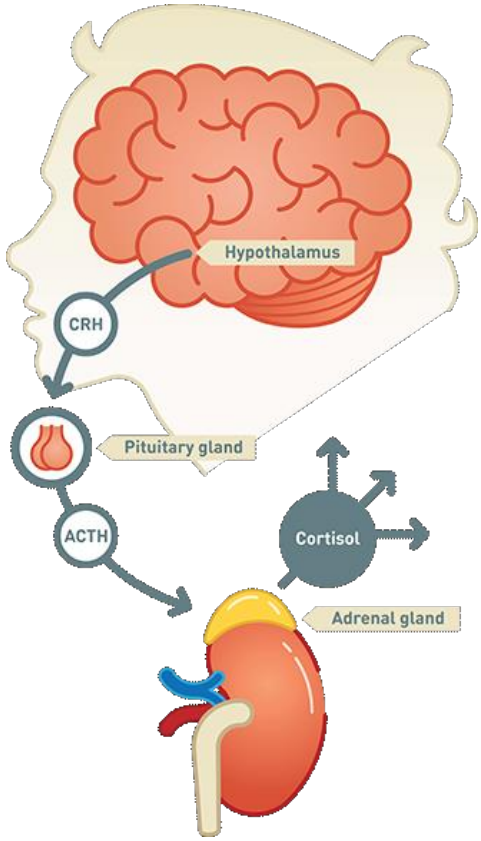


Figure 1.3: Neuroendocrine system

3. *Heart rate variability analysis*

Heart rate variability (HRV) is probably the most used method for stress assessment analysis, and it consists of observing the patterns of change in heart rate over time, and in particular the rhythms of change, on different time scales. The heart rate is modulated by the ANS, which has two branches: the sympathetic that drives the fight or flight and increases the heart rate, and the parasympathetic that drives the relaxation response and slows the heart rate. So, HRV can tell something about how ANS works and the balance between sympathetic and parasympathetic. The latter is a bit of a controversial issue - it seems that HRV is a good biomarker for the parasympathetic but not really for the sympathetic [13] . A potential pitfall of HRV as a stress biomarker

is that the results are strongly influenced by respiratory rate. Of course, breathing rate is influenced by stress, but it is possible to easily change breathing rate during the assessment and thus end up with a distorted image.

4. *Electroencephalogram*

EEG, visible in the figure 1.4, is a tension measured by the scalp, and the rhythms within the EEG are known as brain waves. Frequency bands have names such as alpha and theta, and the relative amounts of activity in each band are correlated with mental and emotional state, to some extent. The theta-beta ratio in the back of the head, when this is low suggests a busy, agitated mind, running thoughts and that are difficult to turn off. It is probably the most found marker of stress, although many people show it and do not necessarily experience it as anxiety. Right-left balance in the front of the head, the imbalance tends to show mood problems. The use of this relatively simple EEG system is that it seems quite accurate in the sense that it agrees with the person's experience: it is more stable than an HRV, if one does one's best to relax throughout the duration of the evaluation, it probably wouldn't make much difference to the results.

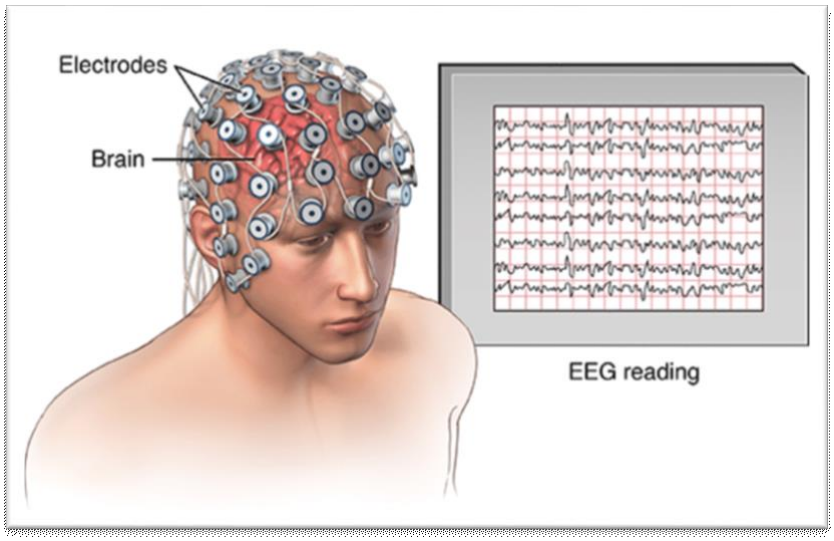


Figure 1.4: Electroencephalogram

5. *Capnometry*

A common facet of the stress response is the transition to faster breathing, based on the chest and overthinking. Overthin breathing is a matter of degree, and mild cases are largely unrecognized. A capnometer can assess the degree of underbreathing by measuring carbon dioxide in the exhaled air [14] . The capnometer is a powerful biofeedback device for optimal breathing training that can make significant changes with relative ease.

6. *Skin conductance and skin temperature*

These two measures have the advantage that they can be easily measured by the skin. The changes are driven by the sympathetic nervous system, the engine of the fight-or-flight response. Both are short-term reactive, especially skin conductance, which makes them useful for demonstrating and learning the stress response. Skin conductance, which is linked to the skin's galvanic response (GSR) and electrodermal response, is used in the famous polygraph or "truth machine" test. It can't really detect lies, but it can detect the immediate spike in sympathetic activity that is expected from an emotionally significant event [15] . Their disadvantage is that they are affected by several other factors besides stress. This means that while relative changes are useful, absolute measurements are less clear: it cannot be said that a reading of X means a stress level of Y. For example, both conductance and skin temperature are affected by ambient temperature.

7. *Sleep Monitoring*

The ideal would be to use a high-level EEG-based sleep monitoring system to track sleep and sleep quality. Optimal sleep means the right amount of sleep but also the right proportions of deep sleep, light sleep, and REM sleep (the latter is related to dreams and emotional stress). Nowadays it is possible buy numerous consumer

devices at relatively low cost, which claim to track sleep, including at least one or two devices based on EEG. Most of the others are based on heart rate analysis and HRV. Some claim to differentiate light sleep, deep sleep, and REM sleep.

With these simple examinations it is possible to evaluate the state of stress of a subject with particular focus on his mental and physical condition having in this way a predictive examination for the protection of health.

1.4 HEALTH CONSEQUENCES

Stress is a natural physical and mental reaction to life's experiences. Everyone expresses stress from time to time. Anything from everyday responsibilities like work and family to serious life events like a new diagnosis, a war, or the death of a loved one, can trigger stress.

For immediate and short-term situations, stress can be beneficial to health. It can help to cope with potentially serious situations. The body responds to stress by releasing hormones that increase heart and respiratory rate and prepare muscles to respond. However, if the stress response doesn't stop shooting, and these stress levels stay elevated much longer than is necessary for survival, it can take a toll on health.

Chronic stress can cause a variety of symptoms and affect overall well-being. Symptoms of chronic stress include irritability anxiety depression headache insomnia.

The CNS is responsible for the "fight or flight" response. In the brain, the hypothalamus kicks off the dances, telling the adrenal glands to release the stress hormones adrenaline and cortisol. These hormones speed up the heartbeat and cause blood to flow into the areas that need it most in an emergency, such as the muscles, heart, and other important organs.

When the perceived fear is gone, the hypothalamus should tell all systems to return to normal. If the CNS fails to return to normal, or if the stressor does not go away, the response will continue.

Chronic stress is also a factor in behaviors such as eating too much or not eating enough, alcohol or drug abuse, and social withdrawal.

The attack and flight response together with the cortico-adrenal system, generates several changes within the body (figure 1.5), in particular:

- In the ***heart***: under stress, the heart pumps faster. Stress hormones cause blood vessels to constrict and divert more oxygen to the muscles so one has more strength to act. But this also increases blood pressure. As a result, frequent or chronic stress will cause the heart to work too hard for too long. When blood pressure rises, the risk of having a stroke or heart attack also increases.

- In the ***circulatory system***: the organism reacts as if it were facing a physical threat, so it prepares to be attacked and injured. For these reasons, the blood vessels narrow, and the blood becomes denser and coagulates, avoiding bleeding in the case of a wound.

- In the ***digestive system***: the increased influx of blood to the limbs and heart, slows down all those activities not strictly related to survival. Therefore, digestion is slowed down. It can be deduced that a constantly stressed person, even if he eats correctly and does adequate physical activity, will not be able to correctly assimilate the nutrients necessary for him precisely because digestion is slowed down and inhibited by stress. Under stress, the liver produces extra blood sugar (glucose) to give an energy boost. Under chronic stress, the body may not be able to keep up with this extra increase in glucose. Chronic stress can increase the risk of developing type 2 diabetes. The surge of hormones, rapid breathing and increased heart rate can also upset the digestive system. The sensation of heartburn or acid reflux is more likely due to the increase in stomach acids. Stress does not cause the ulcer (often a bacterium called H. pylori does), but it can increase its risk and cause the appearance of already existing ulcers.
  Stress can also affect the way food moves in the body, leading to diarrhea or constipation. Or even experience nausea, vomiting or stomach pain.

- In the ***immune system***: it is another system of the organism that is disabled when the organism is under stress.

  A person who must defend himself and/or escape cannot waste resources on other vital functions but not necessary now, such as fighting bacteria, viruses, and diseases in general. Stress stimulates the immune system, which can be an advantage for immediate situations. This stimulation can help avoid infections and heal wounds. But over time, stress hormones weaken the immune system and reduce the body's response to foreign invaders. People under chronic stress are more susceptible to viral diseases such as the flu and the common cold, as well as other infections.

  Stress can also increase the time it takes to recover from an illness or injury.

- In ***breathing***: an organism in danger needs more oxygen to flow to its muscles (limbs). For this reason, breathing should be faster, more labored, and superficial. This can, in some cases, lead to hyperventilation, as occurs in panic attacks.

- In ***sweating***: a body that requires greater blood flow, greater energy, and greater muscle activation, will turn out to be an overheated body: the greater sweating allows to keep it fresh. That is why people under stress, as well as those anxious people who share with them the response of attack and flight, sweat conspicuously.

- In ***muscles***: muscles stretch to protect themselves from injury when under stress. They tend to relax again once relaxation occurs, but if one is constantly under stress, the muscles may not have a chance to relax. Tense muscles cause headaches, back and shoulder pain, and body aches. Over time, this can trigger an unhealthy cycle when people stop exercising and resort to painkillers.

- In the ***endocrine and hormonal system***: a person under stress has a higher blood glucose level (blood sugar) precisely because this is required by the muscles. In the long run this state can lead to health problems such as diabetes (insulin resistance). The production of growth hormone (GH hormone) is also slowed

down with effects on the ability and speed of turnover of aged cells.

- In the ***reproductive and sexual system***: in the same way as other systems not strictly necessary for immediate survival, the reproductive system is also disabled during the fight and flight response. This involves, in practice, a lower concentration of sex hormones resulting in a decrease in libido. If stress continues for a long time, a man's testosterone levels may begin to drop. This can interfere with sperm production and cause erectile dysfunction or impotence. Chronic stress can also increase the risk of infections to the male reproductive organs such as the prostate and testicles. For women, stress can affect the menstrual cycle. It can lead to irregular, heavier or more painful periods. Chronic stress can also amplify the physical symptoms of menopause.

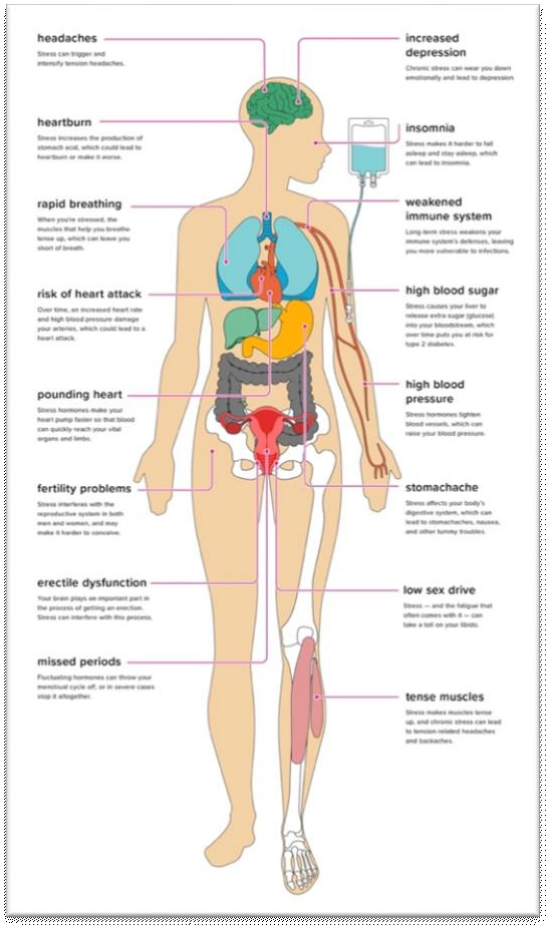


Figure 1.5: Health consequences of stress

CHAPTER 2.

THE BRAIN AND ITS ROLE IN STRESS

2.1 THE BRAIN

The brain (figure 2.1) is the vital organ of the CNS, it takes place in the skull, superior to other nerve structures, always of the brain and always very important for life, such as the diencephalon, the brainstem, and the cerebellum. The brain consists of two almost symmetrical elements, called cerebral hemispheres. Each cerebral hemisphere has a distinct superficial cell layer, called the cerebral cortex, and a deeper cellular component, generically called the subcortical component. The brain presides over the control of emotions and voluntary functions, the control of sensory functions such as hearing, smell, sight, touch and taste, the ability to language and understand language, the faculty of memory, learning and processing memories.

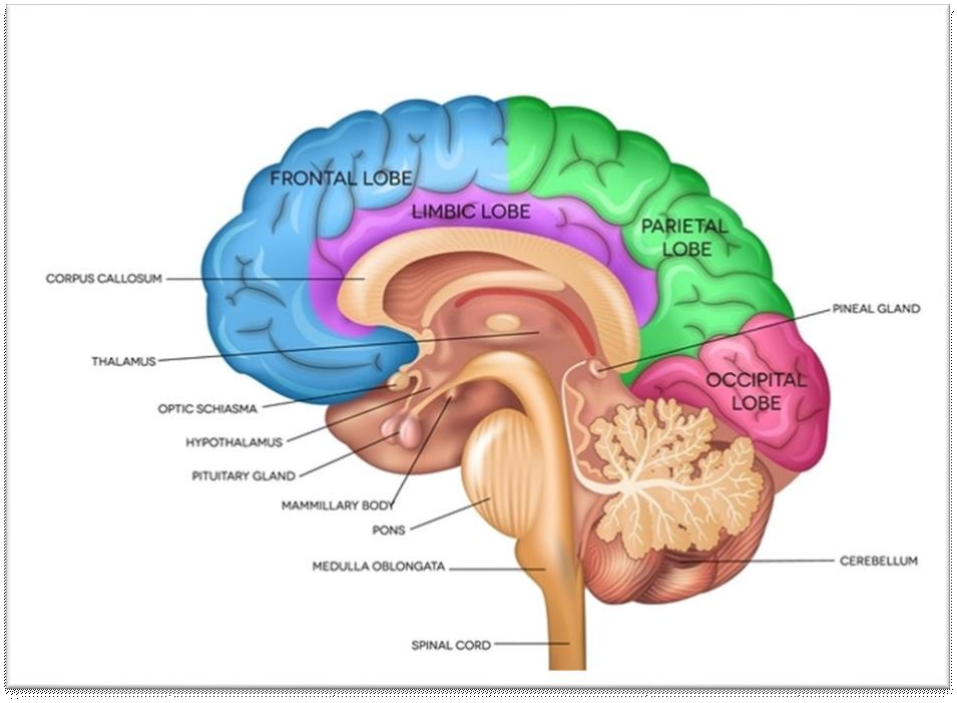


Figure 2.1: The anatomy of human brain

The brain is the largest and most specialized portion of the encephalon. Enclosed within the braincase, the brain is a vital organ, which belongs to the CNS. In anatomy, the brain is also known as the telencephalon or brain proper; these alternative names serve to not confuse it with the encephalon, of which it is, as stated just before, a portion.
The brain is, together with the spinal cord, one of the two fundamental components of the CNS. [16]
Weighing about 1.4Kg and containing 100 billion neurons in the adult human being, the brain is a very complex structure, divided into four large regions, which are the brain or telencephalon, the cerebellum, the diencephalon and the brainstem.
The brain is the largest and most specialized portion of the encephalon. Tending to develop in the ventrodorsal, or anteroposterior sense, the brain consists of two almost symmetrical structures, separated by a deep longitudinal fissure, which are called the right cerebral hemisphere and the left cerebral hemisphere.

In each cerebral hemisphere, the brain has a distinct surface layer, called the cerebral cortex, and a deeper component, generically called the subcortical component [16] . The cerebral cortex is pure gray matter, while the subcortical component comprises both gray matter-based structures and white matter-based structures (figure 2.2).
Gray matter and white matter are the two tissues that make up the CNS. Gray matter consists of neurons without myelin; white matter, on the other hand, consists of neurons with a layer of myelin.

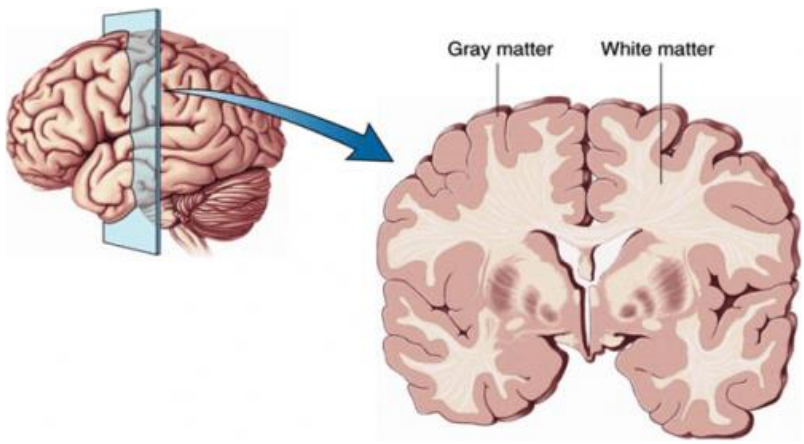


Figure 2.2: Difference between gray and white matter

The brain resides in the upper part of the skull, protected by: the frontal bone, anteriorly; the two parietal bones, superiorly; the two temporal bones, laterally; the occipital bone, posteriorly.

Inside the braincase, the brain borders on:

- The ***meninges***, above.
  They are the 3 thin membranes of connective tissue that interpose between the organs of the CNS and the bone structures within which these organs are contained;

- The ***brainstem***, hellish-posteriorly.
  It consists of midbrain, Varolio's bridge and medulla oblongata, the brainstem is the important nerve structure that connects, both physically and functionally, the brain to the spinal cord;

- The ***diencephalon***, inferiorly and medially.
  The diencephalon includes structures such as the hypothalamus, the neurohypophysis, the epiphysis, the thalamus and the epithalamus;

- The ***cerebellum***, hellish-posteriorly.
  Located below the occipital lobe, the cerebellum is involved in the coordination of voluntary muscles, the regulation of balance and posture and motor learning; in addition, it also plays a role in attention span and language.

The cerebral hemispheres are the two almost symmetrical portions that make up the brain. To distinguish the cerebral hemispheres from each other is a deep longitudinal fissure, the name of which is median longitudinal fissure. [16]
Each cerebral hemisphere has a superficial mantle, called the cerebral cortex, and a more internal component, referred to as the subcortical component.

To facilitate its description, anatomists identify on each cerebral hemisphere three poles: the frontal pole, anteriorly, the occipital pole, posteriorly, and the temporal pole, on both sides.

It is interesting to highlight two aspects of the cerebral hemispheres:

1. The right cerebral hemisphere controls the motor functions of the left half of the body, while the left cerebral hemisphere controls the motor functions of the right half of the body; the same applies to sensory information related to the sense of hearing and touch. This functional feature of the cerebral hemispheres is what experts call ***contralateral organization*** *of the brain.*

2. The control centers of different cognitive abilities reside on a specific cerebral hemisphere; for example, language control centers take place on the left cerebral hemisphere, while cognitive faculties related to orientation in space belong to the right cerebral hemisphere. This functional peculiarity of the cerebral hemispheres is what experts define with the term ***cerebral lateralization***.

Extremely important from a functional point of view, the cerebral cortex is the layer of gray matter about 2.5mm thick, which covers the surface of both cerebral hemispheres. The cerebral cortex includes over 20 million neurons and more than 300 trillion nerve synapses; such high numbers, despite a limited thickness, are possible thanks to the particular architecture of the cerebral cortex itself: the latter, in fact, presents an alternation of grooves, better known as ruts and ridges, better known as convolutions , which significantly increases its extent.

The cerebral cortex of each hemisphere of the brain is ideally divided into four areas that have brain lobes: the frontal lobe, the temporal lobe, the parietal lobe and the occipital lobe.

The ***frontal lobe*** (figure 2.3) represents the anterior portion of the cerebral cortex; it adjoins the temporal lobe, posteroinferiorly, and with the parietal lobe, posterosuperiorly, and enjoys the protection of the frontal bone. On the frontal lobe, there are important functional areas of the brain, including: the primary motor cortex, the premotor cortex, the supplementary motor area, the Broca's area, and the prefrontal cortex; in addition, always on the frontal lobe, resides a large number of neurons responsible for the production of dopamine. The frontal lobe is important for the control of voluntary movements, long-term memory, the production of spoken and written language.

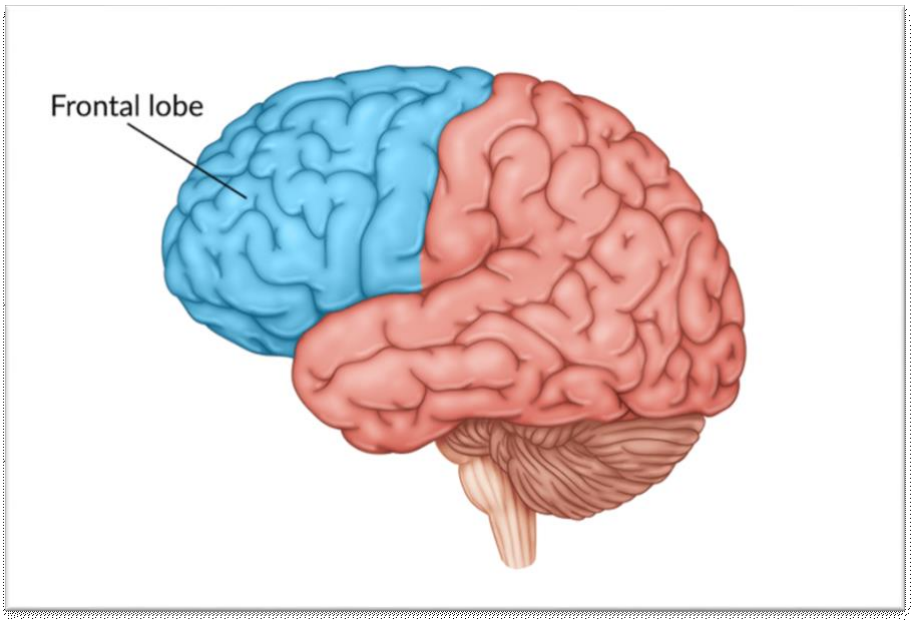


Figure 2.3: Frontal lobe visualization

The ***temporal lobe*** (figure 2.4) represents the lateroinferior portion of the cerebral cortex; it adjoins the frontal lobe, superoanteriorly, the parietal lobe, superiorly, and the occipital lobe, posteriorly, and enjoys the protection of the temporal bone. On the temporal lobe, there is an important functional region of the brain, known as the Wernicke's area. The temporal lobe is the lobe of the brain that presides over the perception of sounds, the

interpretation of visual stimuli and the recognition of objects, the understanding of spoken and written language.

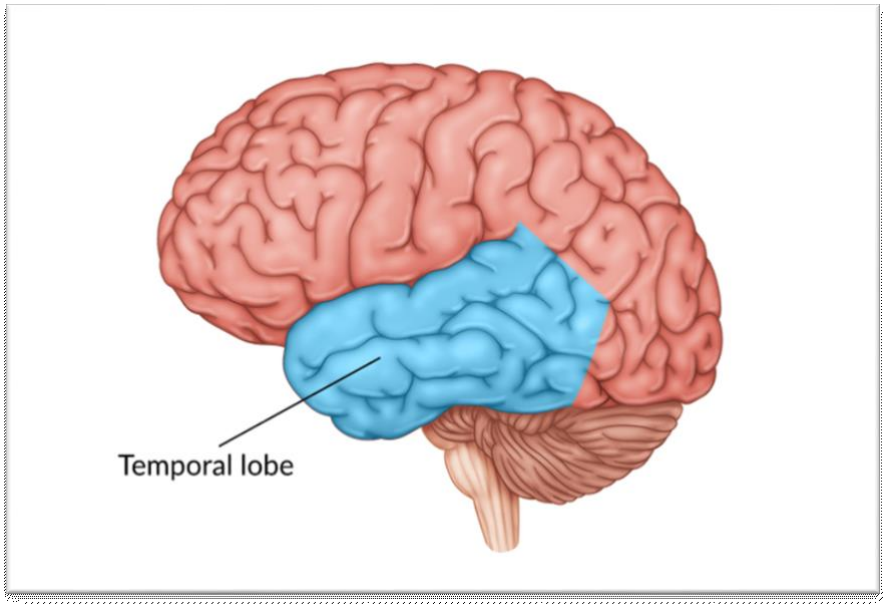


Figure 2.4: Temporal lobe visualization

The ***parietal lobe*** (figure 2.5) represents the portion of the cerebral cortex between the anterior frontal lobe, the temporal lobe, inferiorly, and the occipital lobe, posteriorly. Protected by parietal bone, the parietal lobe includes two important functional areas of the brain: the primary somatosensory cortex, or primary somesthesis area, and the posterior cortical cortex. The parietal lobe has a key role in ensuring the sense of position and space, and in the processing of sensitive information such as pain, sense of heat or cold, touch coming from the skin. In addition, it contributes to memory capacity, computing skills and the ability to interpret language.

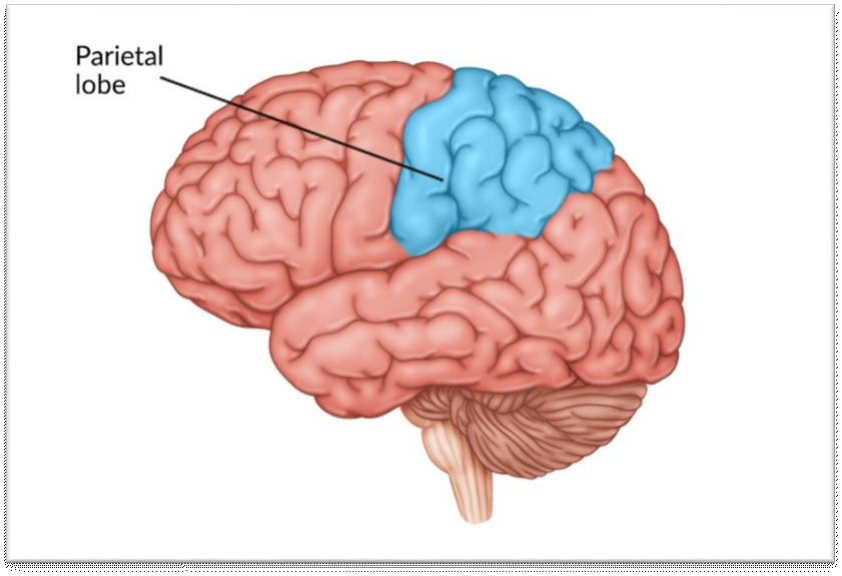


Figure 2.5: Parietal lobe visualization

The ***occipital lobe*** (figure 2.6) represents the posterior portion of the cerebral cortex; it adjoins the parietal lobe, anterosuperiorly, the temporal lobe, anteroinferiorly, and the tentorium of the cerebellum, inferiorly, and enjoys the protection of the occipital bone. On the occipital lobe there are two important functional areas of the brain: the primary visual cortex and the secondary visual cortex providing it with the ability to interpret visual stimuli.

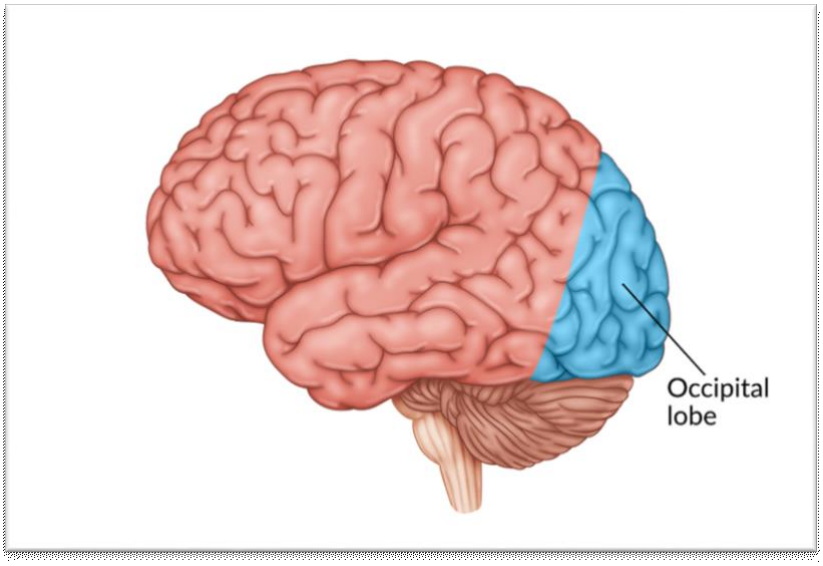


Figure 2.6: Occipital lobe visualization

The subcortical component of the brain includes all those nerve structures, composed of white matter or gray matter, which take place below the cerebral cortex.

2.1.1 Grey matter structures

Subcortical structures of the brain composed of gray matter include:

- The ***amygdala***:
  morphologically similar to an almond, the amygdala is a particular agglomeration of nerve nuclei, which resides in the subcortical region corresponding to the temporal lobe and which belongs to the so-called limbic system.

- The ***hippocampus***:
  morphologically like the seahorse, the hippocampus is a formation based on grey matter, which, just like the amygdala, resides in the subcortical region of the temporal lobe and takes part in the constitution of the limbic system.

- The ***basal ganglia***:
  closely connected to the cerebral cortex, thalamus and brain stem, the nuclei of the base are distinguished into various components, which are called: dorsal striatum, ventral striatum, pale globe, ventral pale globe, substantia nigra and subthalamic nucleus. The cores of the base are associated with various functions, including: the control of voluntary movements, eye movement, procedural learning, learning habits; moreover, they also seem to be involved in emotion, decision-making, and motivational states.

- The ***olfactory bulb***:
  located below the frontal lobe, the olfactory bulb plays a pivotal role in the process of smell perception. It should be noted that the olfactory bulb communicates with other structures and regions of the brain, including the amygdala, hippocampus, substantia nigra and orbitofrontal cortex and the hippocampus.

2.1.2 White matter structure

Among the subcortical structures of the brain composed of white matter, there are:

- The ***capsules***:
  they are the thick bands of white matter that interpose between the nuclei of the base. In the human brain, there are three types of capsules: the inner capsules, the outer capsules, and the extreme capsules.

- The ***cerebral interhemispheric commissures***:
  they are the white matter formations that serve to connect the two cerebral hemispheres or homologous areas of the two cerebral hemispheres. The category of interhemispheric commissures includes the corpus callosum, the commissure of the fornix and the anterior commissure. The corpus callosum is located between the two hemispheres and allows the exchange

of information; the commissure of the fornix connects the hippocampus of the right hemisphere with the hippocampus of the left hemisphere; the anterior commissure is concerned with creating a communication between the temporal lobes of the two cerebral hemispheres.

2.1.3 Pathologies

Among the main conditions that can affect the brain, head trauma, stroke, brain tumor and forms of dementia deserve a mention. All these conditions are potentially deadly and have disabling effects; what makes them so is the fact that they damage a vital organ and on which fundamental functions such as the motor skills of the body, language, language comprehension, hearing, etc. depend. [17]

Brain tumor is a neoplasm, benign or malignant, that originates from the uncontrolled proliferation of a cell of brain tissue. More frequent among the elderly and in people suffering from particular congenital diseases (ex: neurofibromatosis), brain tumor is a treatable condition with results that vary according to factors such as the type, location and size of the neoplasm, and the patient's state of health.

Dementias are neurodegenerative diseases of the brain and brain more generally. Among the various known forms of dementia, the most important are Alzheimer's disease, vascular dementia, Lewy body dementia, and frontotemporal dementia that affects the frontal and temporal lobes of the brain.

2.2 THE CENTRAL ROLE OF THE BRAIN IN STRESS RESPONSE

The CNS plays a key role in the processing of stressors and in eliciting and controlling the stress response. In fact, all kinds of stressful stimuli converge towards the CNS where they are processed and from which the stress responses start. Considerable progress has recently been made in the discovery of the nerve and neuroendocrine correlates that mediate the cascade of reactions triggered by stress.
When Selye introduced the concept of stress, he described it as a non-specific response of the organism to any aggression towards itself [18] . To date, the conceptualization of Selye has been revised and some criteria for classifying stressful stimuli have been introduced [19] . The most important criteria for classifying stressors are the type of stress, the duration of the stimulus, the nerve pathways involved in both processing and response to the stimulus.
As a result, stress can be classified primarily as physical stress and psychological stress. In addition, according to their duration, stressors can also be classified as acute or chronic stressors, while in terms of the nerve pathways involved, stressors can be divided into systemic stressors, involving "short" paucisynaptic nerve circuits (ex: spinal reflexes) or involving "long", polysynaptic nerve circuits and the complex integration of different brain areas, including higher brain centers such as the limbic system and cerebral cortex [20] [21] .
The concept of physical stress implies that the organism is directly exposed to a physical, systemic, threat. Pain, heat/cold, vibration, noise, hypoglycemia, bleeding, inflammation, and changes in cardiovascular tone are defined as physical stressors. Physical stressful stimuli activate mechanical, chemical, and nociceptive receptors and reach the brain through the somatoviscerosensory pathways. Central nerve processing and the response to physical stressors mainly involve the brainstem nuclei, the midbrain, the locus coeruleus (LC) and the raphe nuclei (RN) [19] [20][22] . These "short" nerve circuits allow for a rapid but raw physical stress response, aimed at quickly restoring homeostasis. On the other hand, the concept of psychological stress implies the absence of a concrete physical threat to homeostasis. Problematic relationships with parental figures, isolation,

unemployment, and many other conditions of daily life, are classified as psychological stressors. Limbic "high" regions such as the amygdala, hippocampus (HC), cingulate cortex (CC) and prefrontal cortex (PFC) are strongly involved in the nervous processing of psychological stressors and represent the complex circuits involved in the interpretation of these stimuli [19] [20] [23] .

Of course, the schematic description just proposed does not consider different overlaps between the nerve pathways described. In fact, even physical stimuli, after a few minutes, can involve the cortical, cognitive, and limbic, emotional, nerve centers and naturally take on an emotional and cognitive coloring. On the other hand, stressful stimuli of a psychological nature can quickly provoke systemic physical reactions (ex: tachycardia) mediated by reflex nerve pathways. Ultimately it is plausible to think that the heterogeneity of stressful stimuli may result in the presence of specific nerve circuits aimed at responding efficiently to different stressors. In fact, although various evidence indicates that the activation of the hypothalamus pituitary adrenal axis and that of the adrenal medulla sympathetic axis (SMA) are the common denominators of the stress response of any type of stress, there is evidence to confirm a certain heterogeneity in the neuroendocrine response to different stressors. In fact, using five different types of stressors (immobilization, cold, hypoglycemia, hemorrhage, pain), Pacak and Palkovits [19] found a marked heterogeneity of neuroendocrine response. Their results, obtained from animal studies, reinforced the concept that each stressor can have its own neurochemical "brand" with associated distinct central processing mechanisms.

In humans, the development of functional neuroimaging methods has greatly enriched our knowledge of the role of the CNS in regulating stress axes. Recent functional neuroimaging studies have in fact confirmed the direct involvement of different nerve centers in the stress response, confirming the decisive contribution of the amygdala, hippocampus, prefrontal cortex [24] [25] . The advanced functional magnetic resonance imaging (fMRI) neuroimaging technique has allowed researchers to study directly in humans the effects of stressful tasks on brain structures. Thanks to this technique, the knowledge of the nerve circuits involved in the processing and response to psychological stress in humans has been greatly expanded.

2.2.1 Amygdala

"Amygdala" in medicine and anatomy is a part of the brain that manages emotions, especially fear and terror. At the anatomical level it is also defined as a group of interconnected structures of gray matter that is part of the limbic system, placed above the brainstem, in the rostromedial region of the temporal lobe, below the hooked gyrus and anterior to the formation of the hippocampus. It has an ovoid structure located at the lowest point of the upper wall of the lower horn of each lateral ventricle (figure 2.7). It is in continuity with the putamen, behind the tail of the caudate nucleus.

Within it, at least ten or twelve areas are distinguished, with their own internal subdivisions and with different functions. The individual nuclei that are part of the amygdala complex do not have a specific name, therefore they are referred to as "basolateral nuclei" and "corticomedial nuclei".

The amygdala sends impulses to the hypothalamus for the activation of the sympathetic nervous system, to the thalamic reticular nucleus to increase reflexes, to the nuclei of the trigeminal nerve, the facial nerve, the ventral tegmental area, the locus ceruleus and the tegmental laterodorsal nuclei.
The amygdala is believed to be the center of integration of higher neurological processes such as emotions, also involved in emotional memory systems. It is active in the system of comparison of stimuli received with past experiences and in the processing of olfactory stimuli. The signals coming from the sense organs first reach the thalamus, then using a monosynaptic circuit, reach the amygdala; a second signal is sent from the thalamus to the neocortex. This branching allows the amygdala to begin to respond to stimuli before the neocortex. In this way the amygdala can analyze every experience, probing the situations and every perception. When evaluating a stimulus as dangerous, for example, the amygdala snaps like a kind of neural trigger and reacts by sending emergency signals to all major parts of the brain; stimulates the release of hormones that trigger the fight-or-flight reaction, (adrenaline, dopamine, norepinephrine), mobilizes the centers of movement, activates the cardiovascular system, muscles, and intestines. At the same time,

the mnemonic systems are "browsed" with absolute priority to recall any useful information in the situation of fear. While the hippocampus "remembers" the facts, the amygdala judges their emotional value. The amygdala, therefore, provides each stimulus with the right level of attention, enriches it with emotions and, finally, initiates its storage in the form of a memory. The amygdala is therefore the archive of emotional memory, so it analyzes the current experience, with what has already happened in the past: when the present and past situation have a similar key element, the amygdala identifies it as an association and acts, sometimes, before having a full confirmation. So, it can react before the cortex knows what is happening, and this is because the raw emotion is unleashed independently of conscious thought, and generally before it.

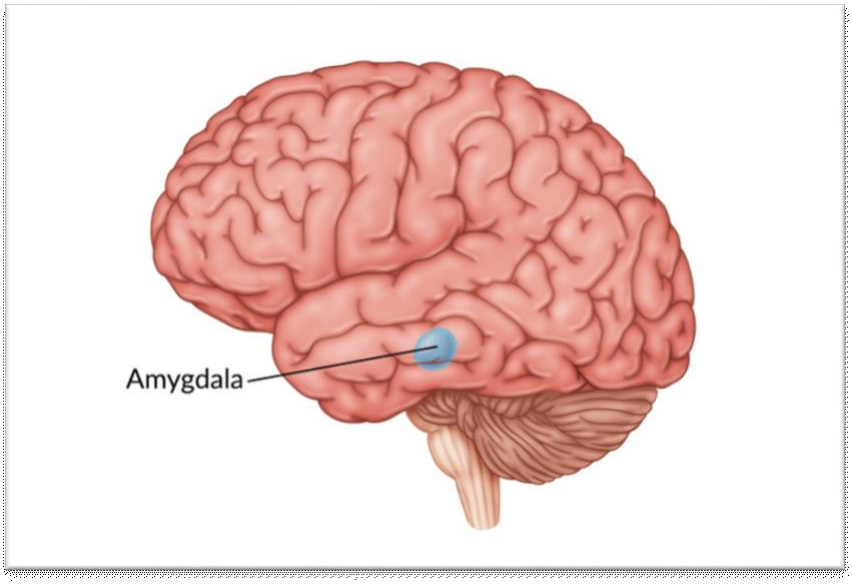


Figure 2.7: Amygdala localization

2.2.1.1 Role of the amygdala in stress

The amygdala may play the role of a key structure in the mechanism linking stress to the occurrence of cardiovascular disorders.
The presence of hyperactivation in the amygdala seems to be associated with an increased risk of heart disease and stroke, according to a recently published study which clarifies the mechanism by which exposure to high levels of stress over prolonged periods of time can lead to cardiovascular disorders [26] .
Although some cardiovascular disorders are a secondary consequence of the implementation of non-adaptive coping strategies, there also seems to be a direct connection between high levels of stress and heart disease.
Animal studies had already found that stress increased the production of white blood cells in the bone marrow, which in turn increased levels of inflammation.
The authors, Tawakol, of Massachusetts General Hospital in Boston, and his colleagues, of the Icahn School of Medicine at Mount Sinai in New York [27] , were thus able to ascertain the existence of an association between the probability of developing a cardiac event and amygdala activity, suggesting that the presence of hyperactivation in the amygdala, as shown by the scans carried out at the start of the study, is associated with a higher risk of developing cardiac disease in subsequent years [28] .
Moreover, the relationship between amygdala activity and cardiovascular disorders seems to be so strong that it is possible to predict the timing of the development of the cardiac event. In fact, it has been found that higher levels of amygdala activation at the initial scan seem to be associated with an earlier onset of cardiac events.
Increased amygdala activation would also appear to be associated, in humans, with increased levels of metabolism in areas responsible for generating new blood cells (e.g., marrow and spleen) and also with increased levels of arterial inflammation. The second study further supported the findings of the first study. Participants' perceived stress levels were again significantly associated with amygdala activation and levels of arterial inflammation and levels of amygdala activation and levels of inflammation in the arteries.
All in all, what emerged would make it possible to demonstrate empirically the existence of a real connection between cardiovascular disorders and stress. There is a very strong

link between resting amygdala activity and the subsequent occurrence of cardiac events, independently of known cardiovascular risk factors. Furthermore, amygdala activity is also linked to higher levels of perceived stress, as well as higher levels of hemopoiesis and vascular inflammation [29] .

The amygdala, therefore, may play the role of a key structure within the mechanism linking stress to the onset of cardiovascular disorders, also involving mechanisms such as increased blood cell production and increased inflammation in the arteries.

2.2.2 Hippocampus

The hippocampus is part of the brain, located in the temporal lobe and plays an important role in long-term memory and spatial navigation (figure 2.8). Humans and other mammals have two hippocampi, one in each hemisphere of the brain. In rodents, animals in which the hippocampus has been studied extensively, the hippocampus is roughly the shape of a banana. In the human being, it has a curved and convoluted shape, which inspired the first anatomists the image of a seahorse.
In Alzheimer's disease, the hippocampus is one of the first regions of the brain to suffer damage; Memory deficits and disorientation are the first symptoms that appear. Injuries to the hippocampus may also occur because of lack of oxygen (anoxia), encephalitis or epilepsy of the medial temporal lobe. People who have extensive damage to hippocampal tissue may show amnesia, that is, an inability to form or maintain new memories.

Over the years, three dominant ideas have emerged about the function of the hippocampus: inhibition, memory, and space. The theory of behavioral inhibition [30] , popular until the 60s, originated from two observations: first, animals whose hippocampus was damaged tended to be hyperactive; the second, that animals with damage to hippocampal tissue often showed difficulty learning to inhibit answers that had been taught to them before. Jeffrey Gray [31] developed this line of thought into a real theory on the role of the hippocampus in states of anxiety. The theory of inhibition is not much considered today,

since this and other functions are currently attributed to the amygdala, a structure anatomically close to the hippocampus.

The second important line of thinking associates hippocampal function with memory. The most important is contained in the famous treatise by Scoville and Milner [32] on the consequences of the surgical destruction of the hippocampus in an attempt to eliminate the seizures of epilepsy. The patient had severe amnesia and did not remember what had happened to him after the operation or events that happened earlier, even in a period of years. This aroused such interest that it was the most studied medical case in history. In the following years, other patients who had similar mnemonic dysfunctions related to hippocampal lesions (due to accidents or congenital malformations) were studied with the same intensity, and thousands of experiments were carried out concerning the physiology of neural plasticity in the hippocampus. Today there are almost no more differences on the importance of the hippocampus, universally considered as the seat of memory. However, the specific role it plays in relation to this psychic function remains the subject of debate.

Anatomically, the hippocampus is an elaboration of the edge of the cortex. It can be distinguished as an area where the cortex tapers into a single layer of densely organized neurons, which bends to form a very narrow S. The structure that aligns with the edge of the cortex forms the so-called limbic system: this includes the hippocampus, the bark of the girdle, the olfactory cortex, and the amygdala.
The hippocampus shows two main "modes" of activity, each of which is associated with a distinct pattern of EEG waves and neural population activity. These modes are named after the EEG patterns associated with them: theta and large irregular activity (LIA). The hippocampus can be considered as a "memory space" in which the multisensory information connected to a declarative memory would integrate for a short time. Subsequently, they will be sent to parahippocampal regions that dissociate them will make them a more lasting memory.

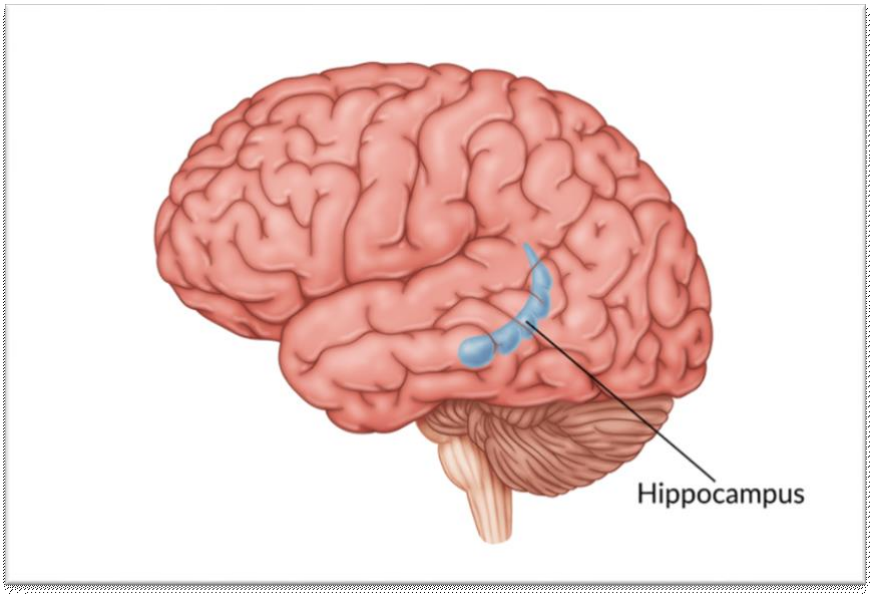


Figure 2.8: Hippocampus localization

2.2.2.1 Role of the hippocampus in stress

Stress starts in what is called the hypothalamic-pituitary-adrenal axis. When the brain detects a stressful situation, the hypothalamic-pituitary-adrenal axis is immediately activated and releases a hormone called cortisol, which triggers an immediate reaction in the body.
But high cortisol levels over long periods of time can damage the brain. When they rise, electrical signals in the hippocampus, the part of the brain associated with learning, memory, and stress control, deteriorate.
The hippocampus also inhibits the activity of the hypothalamic-pituitary-adrenal axis, so when the latter is weakened by the inhibition of its activity, the ability to control stress is also reduced. [33]
Cortisol can literally cause the brain to shrink in size, in particular the loss of synaptic connections between neurons and the shrinking of the prefrontal cortex. Increased cortisol also causes a reduction in the production of new brain cells in the hippocampus. This means that chronic stress can make it harder to learn new concepts and remember things, and set the stage for more serious mental distress, such as

depression and possibly Alzheimer's disease.
There are many ways to reverse the changes that cortisol makes on the stressed brain. The most powerful weapons are exercise and meditation, which involves breathing deeply, being aware of yourself and focusing on your surroundings. Both activities decrease stress and increase the size of the hippocampus, thus improving memory [34].

2.2.3 Prefrontal cortex

The prefrontal cortex indicates the anterior part of the frontal lobe, localized on the precentral, superior frontal and middle frontal convolutions (figure 2.9). It is also recalled that, in addition to the prefrontal cortex, the frontal lobe of the brain contains other areas: the primary motor cortex, the supplementary motor area, the Broca area, the prefrontal cortex.

The prefrontal cortex occupies the most rostral part of the frontal lobes and connects to the motor, perceptual and limbic areas of the brain. The prefrontal cortex is in front of the primary motor cortex and the premotor cortex.
The prefrontal cortex connects through a series of fascicles to the basal ganglia and thalamus. It is divided into two regions: dorsolateral and orbitofrontal or ventromedial prefrontal cortex.
The prefrontal region of cortex is implicated in many higher and complex brain functions, including planning complex cognitive behaviors, personality expression, decision making, moderation of social conduct, control of antisocial impulses, adaptation of behavior to the situation.

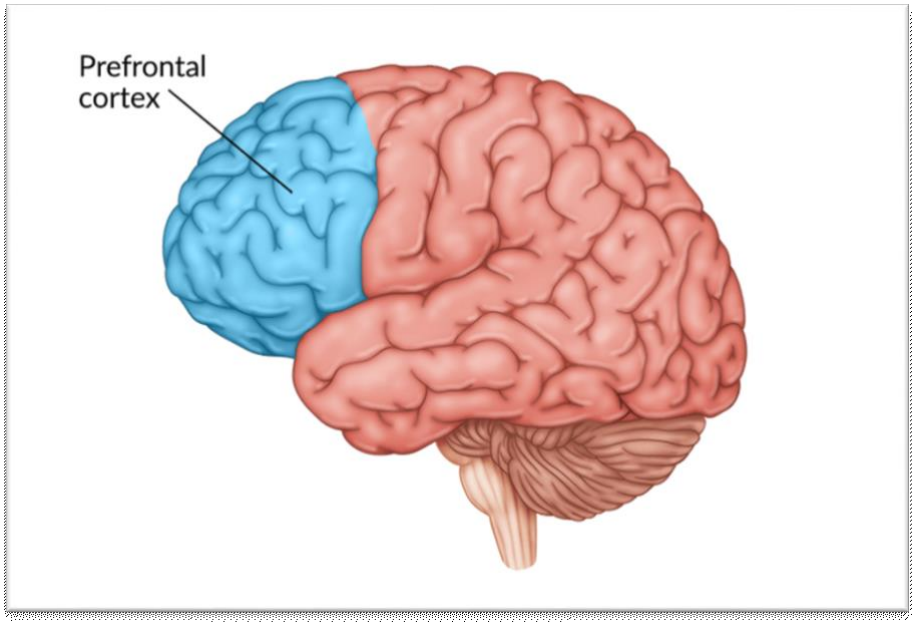


Figure 2.9: Prefrontal cortex visualization

The basic activity of this region is the guide of thoughts and actions according to one's goals. The typical psychological term for the set of functions assigned to the prefrontal cortex is that of executive system. Executive functions are involved in skills such as distinguishing conflicting thoughts, determining good and evil, equal, and different, determining the consequences of current activities, working towards a certain goal, predicting outcomes, making expectations based on actions, and social "control", i.e., the ability to suppress stimuli that could lead to unacceptable social behaviors. The prefrontal cortex can be divided functionally, into two portions right portion, seat of negative emotions and left side related to positive emotions. These parts are activated in a different and asymmetrical way in response to different emotions and states in different social situations.

Damage to the prefrontal lobe can be determined by various causes: trauma, tumors, ischemia, hemorrhages, and cerebral strokes. It would seem that even many addictions such as drugs, gambling and other obsessive compulsive behaviors, can chronically determine an irreversible damage to these areas, contributing to the already reduced judgment that these subjects have, leading to what is called "frontal syndrome" or

"hypofrontality". Damage to the prefrontal lobe leads to different consequences depending on the portion of the prefrontal cortex involved.

2.2.3.1 Role of the prefrontal cortex in stress

In a study published in 2001 [35], 80 patients with epilepsy were pharmacologically blocked the prefrontal cortex. The prefrontal cortex inhibits what is the excitatory sympathetic circuit and therefore, by deactivating it, should increase the heart rate while the variability of the heart rate linked to the vague should decrease. This is what has been proven.
A drug with hypnotic-sedative properties has been injected into the carotids that manages to inactivate the anterior portion of the cortex and it has been observed that when the prefrontal cortex is inactivated, the heart rate rises as when the heart rate increases in response to stress but, in this case, there is an increase in heart rate without there being a stressor. Therefore, if the action of the prefrontal cortex is blocked, there is a stress response.

In another study [36] , patients with damage to the prefrontal cortex were examined and in whom a correlation with an increase in heart rate had already been verified. They were given an orthostatic challenge and a stress test that involved giving a speech in front of an audience. It was observed that women and men had different responses; women showed higher cortisolemia, while men demonstrated a higher response regarding heart rate. Both men and women who have damage to the prefrontal cortex have had an exaggerated response to the tests, and it is therefore evident that this part of the brain is important in regulating the stress response.

In a very recent paper, it was shown that the thickness of the brain, and in particular a part of the brain, is associated with HRV. The most important correlation is in the anterior cingulate area: the thicker this part of the brain is, the higher the HRV will be.

In another study, a meta-analysis was carried out in which, looking at the correlations of HRV, it was shown that, through different modalities and different challenges, there were

three significant brain activations: the cingulate front on the right side, the subgenual cingulate anterior cortex on the right side and the left part of the amygdala.

In other subsequent studies it has been shown that the level of correlation between these regions and the amygdala is closely linked to HRV, that is, the stronger this connection is, the higher the HRV will be. This shows that this prefrontal region regulates the amygdala.

These parts of the brain are associated with different functions: the most dorsal part is associated with the cognitive aspect and the control of actions, the rostral part with emotions and social cognition and the third part concerns the reward for how the control of actions took place. HRV is associated with all three regions and all these functions.

2.3 HYPOTHALAMUS PITUITARY AXIS

The hypothalamic-pituitary-adrenal axis (figure 2.10) is the main hormonal mediator of the stress response; in stressful situations, in fact, the cortical and subcortical centers modulate the activation of the paraventricular nucleus of the hypothalamus, which stimulates a neuroendocrine reaction vital for the maintenance of homeostasis. The activation of the paraventricular nucleus induces the release of corticotropin (Corticotropin Releasing Hormone, CRH) in the pituitary portal circulation, the CRH reaches the anterior pituitary and stimulates in a pulsatile way the cells that produce proopiomelanocortin, from whose cleavage beta lipotropins, beta endorphins and adrenocorticotropic hormone (ACTH) are released. ACTH is released from the pituitary gland into the systemic circulation and reaches the adrenal cortex where it induces the production and secretion of cortisol.
Cortisol has a circadian rhythm that follows that of ACTH, and in turn controls the secretion of the hormones that determined its stimulus. In particular, the CRH and the locus ceruleus/norepinephrine system (LC/NA) stimulate the attention and the general "activation" of the organism, the mesocorticolimbic dopaminergic pathway is involved in the phenomena of anticipation and reward, while the hypothalamic beta-endorphin

system modulates painful sensations by increasing analgesia. Overall, the stress response promotes adaptive processes that include increased appetite, immune function, and event memory.

Cortisol therefore plays a dual action: on the one hand it supports the homeostasis of the organism in the face of the threat, as it stimulates the catabolic pathways, acting on the metabolism of proteins, lipids and carbohydrates, and also promotes the synthesis of liver glycogen and glycogenesis, stimulates the synthesis of liver enzymes and regulates, in part, the excretion and distribution of body water, thus increasing the availability of energy, it also increases blood pressure to support any physical exertion and promotes immunoreactivity; on the other hand, it closes a negative feedback circuit by inhibiting further activation of hypothalamic-pituitary-adrenal; exerts, that is, a negative feedback on ACTH, on LC with inhibition of the noradrenergic component, on hypothalamic CRH and at the suprahypotalamic level, in the hippocampus [37] . To this end, cortisol interacts with glucocorticoid receptors in the hippocampus, hypothalamus, and pituitary gland. The internal contradiction of such a system lies in the difference between the short- and long-term effects of glucocorticoids. In fact, glucocorticoids, when secreted transiently, help survival since they mobilize energy, increase cardiovascular tone and enhance immune activity, but the excessive number of glucocorticoids can increase the risk of hypertension, diabetes mellitus II, gastro-duodenal ulcer and immune suppression. CRH acts not only as an endocrine agent for the release of ACTH but is also endowed with modulatory and neuroprotective functions. In fact, it is present in the cerebral cortex, in the limbic system (amygdala), in the brainstem (locus ceruleus and raphe nuclei) and in the adrenal cortical with an ultrashort CRH-ACTH-cortisol axis that would allow peripheral activation of the system [38] . Therefore, the secretion of CRH modifies, at the cortical level, cognitive and behavioral responses, in the limbic system emotional reactions and, through the brain stem, autonomic responses. In addition, CRH is endowed with anxiogenic actions, inhibits appetite and activates thermogenesis through the catecholaminergic system; by means of glucocorticoids and catecholamines inhibits inflammatory processes, while when CRH is secreted peripherally it stimulates inflammation locally [39] . CRH through somatostatin inhibits somatotropic hormone (GH), thyrotropin (TRH) and thyroid-stimulating hormone (TSH) secretion; in addition, it blocks gonadotropin-releasing hormone (GnRH), while CRH2-type receptors have been detected on anterior pituitary

gonadotropic cells where they likely regulate gonadal function under stressful conditions [40]. In turn, glucocorticoids counter regulate the CRH, the LC/NA system, the beta-endorphin system and stimulate the mesocorticolimbic dopaminergic system and the central peptidergic CRH nucleus of the amygdala. They also stimulate biphasic immune function, inhibit pituitary secretion of gonadotropins, GH [41] ,TSH and the conversion of thyroid hormone T4 to T3, further contributing to the suppression of reproductive, growth and thyroid functions.

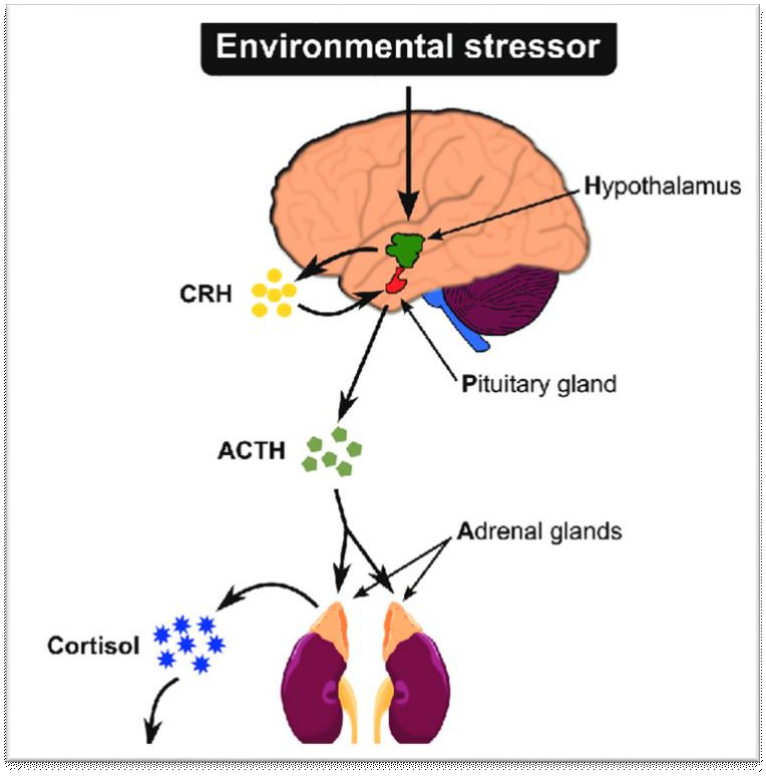


Figure 2.10: Hypothalamus pituitary axis

CHAPTER 3.

ELECTROENCEPHALOGRAPHIC SIGNAL AND WEARABLE DEVICES

3.1 NEUROPHYSIOLOGICAL ORIGINS OF ELECTROENCEPHALOGRAM SIGNALS AND RHYTHMS

EEG is a bioelectric potential related to brain activity that is recorded on the scalp with electrodes and appropriate instrumentation.
In 1870 the English physicist Richard Caton [44] was the first to discover that the brain generated electricity with the use of a galvanometer.
In the years that followed, numerous studies were started on the human brain particularly aimed at the study of brain cells and their functioning.
In 1924 Hans Berger [43] recorded, thanks to the invention of a rudimentary electroencephalograph, the signals coming from his son's head, observing the first temporal patterns of brain electric waves.
From 1924 to 1938 he laid the foundation for many of the present applications of electroencephalography and coined the term EEG, commonly used today to describe the recording of brain electrical potentials.
Despite all the research done on the brain, no one is exactly sure what functions electrical activity represents.
It is important to underline that the EEG trace does not reflect brain activity in the strict sense, but rather it represents a useful indicator of certain aspects of brain functioning; waveforms, in fact, can be good detectors of pathologies or injuries or simply of the state of relaxation of the subject.

3.1.1 Dipole sources and postsynaptic potentials

Although the EEG signal is recorded by the scalp, it is known to be produced by the pyramidal cells that reside in the upper layers of the cortex [45] . The normal activity of these cells is mediated by small electrical potentials that are managed across cell membranes. These potentials are typically in the range of tens of millivolts but can also reach hundreds of millivolts or more. Each cell produces an extremely small current flow

in the immediate vicinity, but due to a phenomenon known as "conduction volume", this flow propagates throughout the brain.
The conduction volume is due to the passive circulation of electric current in the tissues; the whole body, including the head, consists of more than 80% water and thus acts as a good conductor of electrical potentials. For this reason, other electrical signals, concerning eye movement, muscle, and heart activity, can spread through the head by volume of conduction.
When an EEG signal is recorded, it will inevitably include small amounts of other signals from non-neuronal physiological sources. The mathematical law that describes the conduction of the electrical potential from the cells of the brain to the surface of the head is known as the "Poisson equation" (1):

$$\nabla^2 \varphi = -\frac{\rho^2}{\varepsilon} \qquad (1)$$

where φ is the electrical potential, measured in volts, ρ is the charge density, measured in coulombs per cubic meter, and ε is the dielectric constant, in farads per metre.
This law relates the surface distribution of potential to the underlying charge and permissibility of the tissue mass.
The pyramidal cells therefore behave as dipole sources that produce the so-called "dipolar fields"; the total field generated will be given by the linear combination of potential fields that each source would produce individually.

The presence of such a dipole (figure 3.1) requires a significant population of neurons to depolarize in unison to produce the external potential. This phenomenon is referred to as local synchrony.

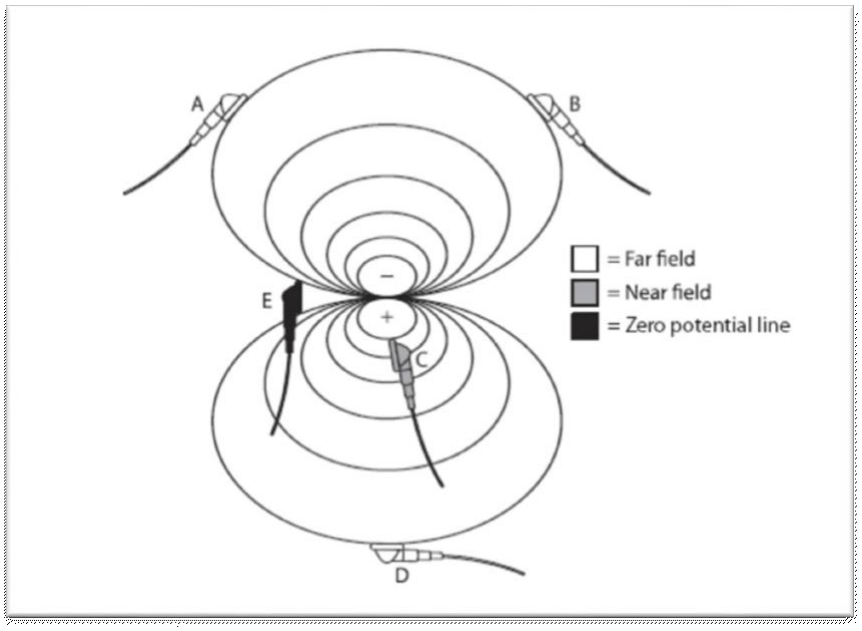


Figure 3.2: Dipole field and possible sensor positions for field recording

The role of local synchrony in the generation of EEG rhythms is so intense that less than 5% of pyramidal cells in the brain may be responsible for more than 90% of the EEG signal energy [46] . Most pyramidal cells operate asynchronously, so that their external potentials cancel each other out, but, if only a small number of pyramidal cells begin to polarize in unison, this will be visible in the EEG. Because of the "conduction volume" brain activity, even localized, can appear largely dispersed on the scalp, and each brain event can be reflected in more than one site on the scalp.
As a rule, 50% of the signal recorded by a sensor placed on the leather comes from the brain tissue immediately below that sensor, while the remaining signal is received from other locations, primarily from adjacent sites.
One might think that the cortical dipoles are all oriented vertically (perpendicular to the cortical surface), so that, if the sensor is located directly above the active site, then it will record the greatest response (figure 3.2). However, this is often not true. A considerable amount of cortical surface resides in the folds and produces dipoles that are oriented differently. If a dipole has a completely horizontal orientation, a sensor directly above it will in fact register zero potential, because it will "see" the positive and negative poles in the same way. This phenomenon is known as "paradoxical lateralization" and means that,

in cases of central motor cortex, the potentials generated on one side of the brain can produce the greatest potential entirely on the other side of the leather.

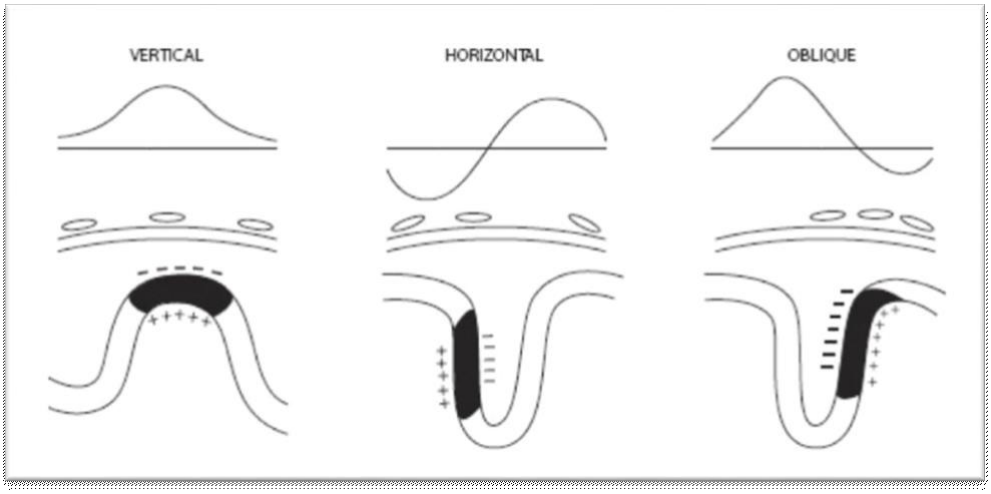


Figure 3.3: Surface potentials due to a vertical, horizontal, and oblique cortical dipole

3.1.2 Fundamentals of neuronal dynamics

Given how groups of neurons can produce measurable potentials in the form of EEG signals, it is useful to examine how these signals are generated from a systems and networks perspective.

The cortex of the brain contains tens of billions of neurons, organized into functional groups; these groups are interconnected through a complex series of links between cortical regions, as well as with underlying brain structures. During normal brain functioning, these networks are subjected to rhythmic activity that occurs at frequencies ranging from 1 to 100 Hz and more [47] . The underlying neuronal activity proceeds at a frequency of thousands of hertz but the measurable external potentials are all in the EEG range. These groups of cortical neurons undergo cycles of activity in which they are sequentially recruited, engaged in processing tasks, and then released. The coordinated activity of the different regions is highlighted by rhythmic waves that are distinguished positions. This cyclical pattern of activity produces an identifiable growing and falling

rhythms, which has a temporal trend of the order of seconds and shows great variability. As a result, when examining the EEG from a particular position, it is possible to identify the dominant rhythms present, each indicating the general state of activation or relaxation of that region. A specific mechanism found throughout the cortex is that of repetitive cyclic patterns of activation involving the thalamus and associated cortical regions. Most cortical areas can undergo reverberation activity with the thalamus, referred to as thalamus-cortical reverberation. This is the mechanism that gives rise to the alpha rhythm and the slow beta rhythm. Through a similar, but slightly different, mechanism, low-frequency theta waves are produced by reverberation between the cortex and subthalamic nuclei. Faster waves, beta waves, are mediated mainly by cortico-cortical reverberations and are produced by short-range connections between cortical sites.
All this cyclical-repetitive activity is evident in the EEG, whose characteristic trend reveals the general state of activation and deactivation of the areas at the origin of the surface potentials that can be measured. Neuronal subgroups as well as operating on a collective basis also can isolate themselves from their neighbors; this property is referred to as lateral inhibition and it is an essential mechanism by which the brain is able to self-regulate and process meaningful information [48] . If all brain connections were excitatory, there would be little opportunity to process complex signals.
Lateral inhibition between adjacent areas is an essential mechanism for providing acuity and precision in sensory processing and it plays a key role in thalamo-cortical regulation. The thalamus contains lateral nuclei that project into the nuclei from the outer regions of the thalamus, which in turn project into the cortical regions. These are the laminar nuclei that provide key regulatory functions in the inhibitory process. For example, when the sensorimotor rhythm appears in the motor cortex, it must be accompanied by a relaxation of the inhibitory influence of the laminar thalamic nuclei. Therefore, the expression of this rhythm is also an expression of the relaxed inhibition of these positions. The cycle of activation and inhibition is a fundamental aspect of a healthy cerebral neuronal network. When excitatory neurons are activated, they begin to stimulate their associated inhibitory cells, these then become active, and in turn begin to inhibit excitatory neurons, whose activity decreases [49] . As the drive for inhibitory neurons decreases, inhibitory activity decreases, allowing excitatory activity to resume its cycle in a period. Based on this cycle, it is possible to define a continuum of activity for any part of the brain. A healthy brain

will be able to perform cycles flexibly between an extreme of relaxation, which corresponds to a low-frequency, high-amplitude EEG state characterized by highly synchronous neuronal populations, and an extreme associated with greater work done by the brain, which corresponds to a high-frequency, low-amplitude, and less synchronous EEG state.

The importance of cyclic activation was brought to light by research by Sterman et al. [50] conducted on fifteen men undergoing a test. The research team was able to distinguish professional men from amateurs on the basis of their EEG tracing. The activity of the top performers during the task was characterized by shorter response times, greater accuracy and less fatigue than that of their peers. By examining the EEG recordings acquired during the tasks, Sterman and Kaiser [50] were able to identify a specific pattern of activation and relaxation that characterized those who were better prepared. During the preparation period of the task, professionals were typically in a state of readiness, characterized by low-amplitude, high-frequency beta waves. When the test was completed and the individual received feedback, a high-amplitude alpha state was observed in the EEG. Sterman referred to this state as post-reinforcement synchronization (PRS) and associated it with information consolidation and relaxation. Less trained men did not exhibit this natural cycle. In the moments of preparation for the test, they were indifferently in an alpha or beta state. If the task appeared while in alpha, the men had to enter a beta state to perform the task. Having to change state caused delays in their response time, and they were less accurate in general. In addition, they were more fatigued at the end of the test because they were unable to exercise the PRS phase. Sterman concluded that the trained men possessed an innate control of the brain's natural cycle that enabled them to perform repeated tasks promptly and accurately. Ultimately, the brain can be imagined as a huge set of neuronal complexes, all connected in various ways. Each neuronal complex functions as a unit but is also hyperconnected with itself and with other parts of the brain. Each group has the potential to produce a measurable potential if its constituent pyramidal cells are activated in unison and has control properties that have to do with the realization and maintenance of states and transitions between these states. In the broadest sense, control systems maintain certain states in the face of changed conditions or inputs (homeostasis) or facilitate goal-directed changes (allostasis). Given these considerations, neurofeedback can be thought of as a

mechanism that sets additional goals so that the brain learns to self-regulate in new ways, facilitating change.

3.2 THE COMPONENTS OF THE EEG SIGNAL AND THEIR PROPERTIES

EEG is a stochastic and stationary signal, in particular it is a complex waveform that includes multiple components in frequency.
However, two reasons lead to the identification of specific components.
The first is that often a particular type of wave dominates, and it is predominant at sight, the second is that, when using filters, it is possible to isolate a frequency band even in the presence of other components. Therefore, regardless of what the dominant rhythms are, it is possible to isolate a band via computer processing. It is preferable to define these EEG components as component bands rather than frequencies or bandwidths. This is because what distinguishes them more properly is the physiological meaning and the visual aspect rather than the use of specific frequencies, which is often ambiguous and artificial. A particular component could in fact appear outside the usual frequency range without necessarily having to conform to the usual definition of that band. It should also be emphasized that the components are often not really sinusoidal but have a distinctive morphology. Frequency analysis, by Fourier transform, assumes that the waves are purely sinusoidal. Any deviation from a pure sinusoid leads to the appearance of higher harmonics, thereby complicating mathematical analysis. Therefore, a visual inspection of the EEG track is always important to avoid these problems. The main EEG rhythms were identified through clinical and research experience, and the associated frequency ranges were identified later. The frequency bands, therefore, describe the complete series but do not define it. It is important not to arbitrarily identify any EEG rhythm based solely on its apparent frequency; other factors that must be considered are the location and behavior of the component as well as the state of the patient.
The ***delta***, visible in the figure 3.3, is the slowest of the EEG rhythms and generally has a frequency of 1-3 Hz; it is associated with non-REM sleep or states of unconsciousness.

It tends to have a characteristic irregular pattern. A small amount of delta is normal. Concentrated delta rhythm is associated with localized injury or trauma, while excess global delta indicates toxicity, generalized pathology, ageing or other systemic problems. Because it generally reflects injury or dysfunction, excess concentrated delta rhythms are often associated with failure of the affected areas.

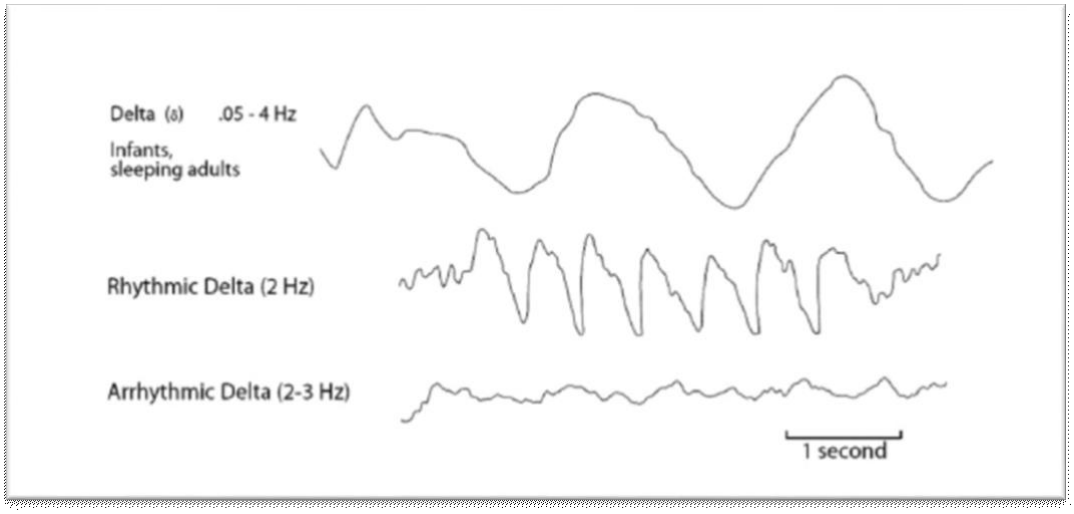


Figure 4.3: Examples of delta waves

The ***theta***, shown in the figure 3.4, rhythm, typically 4-7 Hz, is a rhythm mediated by subthalamic mechanisms, and, like delta, tends to have a characteristic non-sinusoidal appearance. A certain amount of theta is normal, particularly in frontal areas, where it can be associated with will and movement. However, excess theta is among the most common deviations associated with brain dysregulation.

Despite theta's association with inattention and internalized thinking, it must be recognized that this rhythm is also associated with creative thoughts and memory retrieval. Therefore, since it can occur at moderate levels even in an alert brain, it should not be considered as an inherently "bad" rhythm that must always be minimized.

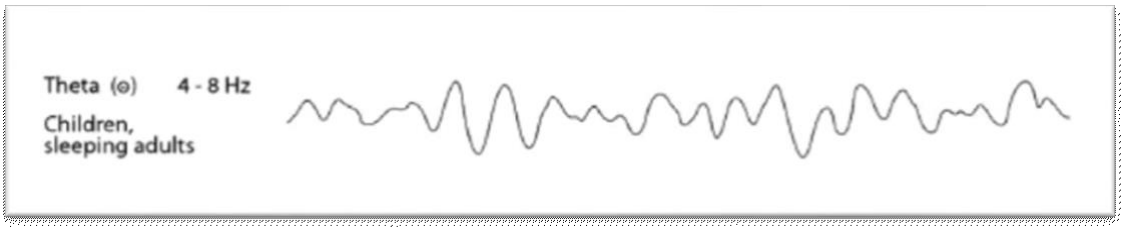


Figure 3.4: Examples of theta waves

The ***alpha*** wave (figure 3.5) is sometimes referred to as the 8-12 Hz rhythm. The alpha rhythm is a rhythm of rest of the visual system, maximum posteriorly, which increases when the eyes close, and which has a typical increasing and decreasing trend. All these features derive from the fact that alpha is a thalamo-cortical reverberation involving the optic pathways and the primary visual cortex, which represents the relaxation of the visual system, and which also performs some types of memory scanning. An individual is typically aware, but relaxed, during alpha intervals. The actual alpha frequency may vary outside the 8-12 Hz range, and other components may occur in this range. Therefore, a signal whose frequency is in the range of 8-12 Hz is not necessarily an alpha wave. What is certain is that, if it is detected a sinusoidal and symmetrical signal, maximum posteriorly and that increases when the eyes are closed, then it is an alpha wave. A rhythm that can occupy the alpha band but that is not the alpha rhythm is the "***mu***" rhythm. This wave has an arched appearance distinguishable by eye and is clearly not sinusoidal. The mu rhythm does not have a characteristic growth and degrowth, and it is maximum centrally, not occipitally. Its meaning is unclear, and some controversy remains as to whether it is an abnormal rhythm or not, and what clinical decisions can be made in its presence.

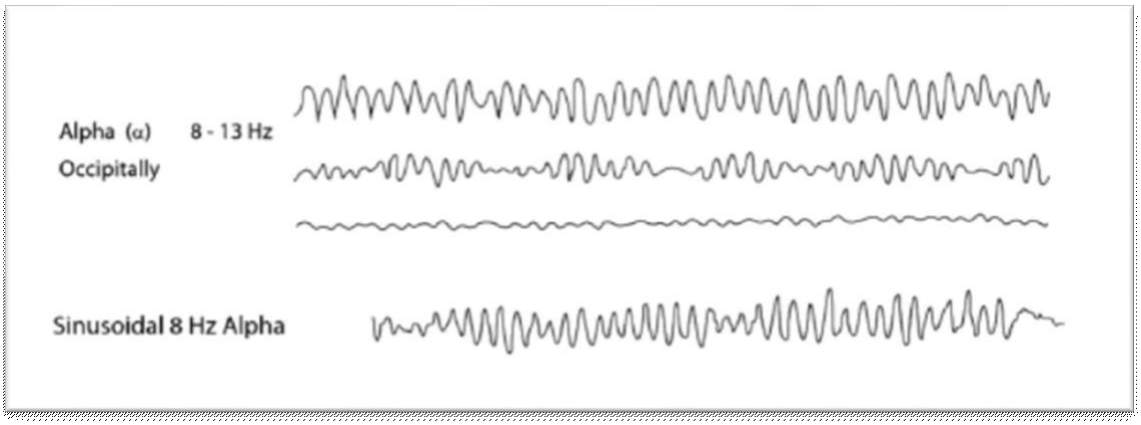


Figure 3.5: Examples of alpha waves

An important distinction must be made between alpha activity and brain activity in a brain region. Alpha activity is associated with reduced brain activation, so when alpha waves are present, this region is in a state of inactivity, and therefore is less active. Therefore, when we detect an increase in alpha waves, the brain is less active. In healthy individuals, the left frontal alpha is typically between 10 and 15 percent lower than the right frontal alpha, and this asymmetry is important for normal mood control. Baehr et al., 2001 [51] has been reported that depression is associated with a higher alpha rhythm in the left frontal area, and that training that restores asymmetry by reducing the alpha rhythm in this area produces an improvement in mood. Such an approach is justified by the fact that the left frontal area is responsible for positive thoughts, while the right frontal area mediates negative judgments. To ensure a normal mood, the negative area (right side) should be a little less active than the positive zone (left side). Therefore, a slightly lower alpha on the left corresponds to a greater activation of this zone. An important aspect regarding alpha, is the presence of two fundamentally different intervals. The range of fast alpha waves, between 10 and 12 Hz, represents the typical occipital rhythm at rest, which reflects the processing of the background memory and an inactive, but not inattentive, state. Slow alpha waves, typically between 8-10 Hz, appear more frontally and are more associated with emotional processing. When depictions of the EEG spectrum are displayed in real time, the independent rising and falling of these two alpha waves is evident. Interestingly, alpha rhythm may slow down with age; while a significant slowdown in alpha rhythms is associated with degradation of mental processing, a general

slowdown with age may indicate that increased processing occurs at the ends of the thalamo-cortical circuit. The slow beta rhythm is one of the most interesting rhythms of the brain, partly because it includes the sensorimotor rhythm, when produced by the sensorimotor cortex; this rhythm is actually an alpha wave if we consider the fact that it is a thalamo-cortical reverberation, and that it represents a state of inactivity. The slow beta rhythm (or SMR) is characterized by frequencies of 12-15 Hz, and is associated with states of alertness, concentration, and the intention to remain still (figure 3.6). Overall, it was found that sensorimotor rhythm (SMR) training has significant benefits in a wide range of situations, particularly for seizures and for the treatment of insomnia. It seems that SMR training is a central mechanism associated with the stability of the brain, body, and resistance to stress.

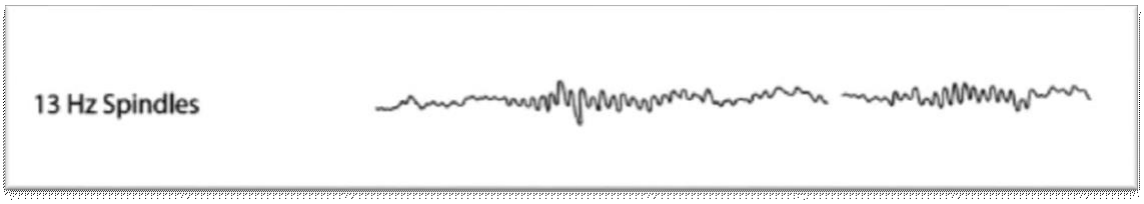


Figure 3.6: Examples of slow beta rhythm or sensorimotor rhythm at 13Hz

Beta waves (15-20 Hz) are those most associated with conscious and intentional thinking. When present, they indicate brain activation and cortico-cortical communication. Because cortico-cortical connections that mediate beta tend to be between neighboring sites ("short-range connections"), beta tends to be more localized than lower frequency rhythms. The beta wave is one of the most trained components in neurofeedback and it is used to stimulate the activation of specific areas. When beta rhythm deficits are evident, and clinical signs see them associated with under-activation, beta rhythm training can be an effective way to activate affected regions and to normalize thoughts and behaviors. The neural feedback of the beta rhythm is also used on subjects not suffering from clinical disorders but who wish to increase and improve their cognitive performance. High beta waves (typically 20-30 Hz) are typical of anxious states and agitation. ***Gamma*** waves are fast waves (35-45 Hz), identified in more recent times than the others and therefore

known in less depth; they are not easy to record because of their very small amplitude [52] . They can be found in moments of maximum physical and mental performance and deep concentration. Gamma bursts can appear as single waves that occur at low frequency and that are relatively short. The brevity of gamma bursts justifies the need to use a high-bandwidth filter to track these events.

3.2.1 Direct current potentials and slow cortical potentials

The direct current potential (DCP) (0-0.1 Hz) is the potential that includes sensor offset, drift, skin potential and all electrical sources, its value is therefore typically non-zero and technically does not vary over time.
In and of itself it is of limited use since it includes many sources of voltage, and it is difficult to acquire through stable recordings.
More useful is the slow cortical potential (SCP) (0.01-2 Hz) which has glial origin, and it is associated with the general activation of the brain [53] . Glial cells are known to be related to general cortical excitation and they are particularly relevant in epilepsy and other abnormal processes.
SCPs consist of signals that vary with long time constants, moving above and below the baseline for periods of seconds. An SCP shift can occur in an interval of one to five seconds, reflecting a change in cortical excitability.
DC/SCP training is generally monopolar; in this way the system measures the levels of brain potential relative to a reference standard.
Unlike regular EEG rhythms, the polarity of the training is important, as it determines whether brain potentials will be trained to activate or deactivate. Generally, the SCP is exploited in the formation of epilepsy as it undergoes considerable variations in the moments preceding the seizures.
A more recent development [54] has been the use of feedback with filters set at very low frequencies. Such filters are fixed so low that it no longer makes sense to think of the underlying signals as rhythms, but rather transient changes from the DC baseline. The emerging use of feedback using very low frequencies has been called potential work of "infra-low frequency" (ILF) or "infra-slow fluctuation" (ISF).

The work of ILFs is generally done with the addition of inhibitors on most, if not all, of the conventional EEG frequency bands.
Ultimately, it is important to emphasize that EEG consists of a set of surface potential measurements that reflect the underlying brain activity, and that therefore standard rhythms, SCP, DCP and ISF are all derived from the same basic signal through the use of special filters.

3.3 EEG SIGNAL ACQUISITION AND MANIPULATION

The system for measuring brain bioelectric potentials has the function of taking the weak electrical signal on the scalp, increasing its amplitude, processing it and, finally, recording or visualizing it.
This system, to operate correctly, must meet precise requirements, including, first, the specifications of the amplifier relating to input impedance, common mode rejection and gain.
In addition, in modern neurofeedback systems the signal is digitized and processed in such a way as to return adequate feedback to the patient.

3.3.1 Electrodes for electroencephalogram

Conventionally, cerebral electrical activity is recorded via biopotential electrodes placed on the head or in the ears. Since the outermost layers of the scalp are typically bad conductors, it is necessary to prepare the skin before applying the electrodes; this preparation consists of a first phase of cleaning the region of interest through a special abrasive paste, followed by the application of the electrode by gel or electrolyte solution. This has the dual purpose of creating an optimal electrode-skin contact, favoring the conduction of the signal, and to maintain a constant adhesion between electrode and skin, reducing motion artifacts [55] . The presence of an electrolyte is extremely important, as electric charges are not able to move directly from a biological tissue to a metal; the pair

of electrodes then acts as a transducer of electrical signals between an ion conduction medium (the electrolyte solution) and an electronic conduction medium (the metal conductor).
The interface between the electrode contact point and the area from which the EEG is derived is a critical point for the entire electroencephalographic recording process and has relatively complex functional characteristics.
An ideal electrode should have the characteristics of a circuit equivalent to a metal cable that allows the free passage of all the currents generated by the brain present at the interface without frequency and direction limitations.
In practice the equivalent circuit is much more complex, and the values of the components depend mainly on three factors: the electrolyte, the material of construction of the electrode and the density of current passing through the junction.

In leads on the cranial surface, the electrolyte used must not cause irritation and must be compatible with the chemical substrate of the skin. The active part in most electrolytes is a chloride, usually sodium (Na) or calcium (Ca).
There is a wide variety of materials used for the construction of electrodes; among the metals the most used are silver, stainless steel, gold, and tin. Sensor materials should never be combined in an EEG application, and only one type of metal should be used for the electrode and active cables. The presence of different metals can cause an electrolytic reaction causing a DC offset potential superimposed on the signal.
All sensor materials, except silver chloride (AgCl), provide a metal connection in contact with the electrolyte solution, and are said to be non-polarizable. Because ions cannot physically enter or exit the sensor material, they accumulate at the interface, forming a capacitive layer that blocks direct current and low frequencies. Therefore, while various metal sensors are acceptable and commonly used for clinical EEG, none of them are sufficient for work at low frequencies (0.01 Hz or lower) except for AgCl.
The latter is an ideal sensor material, not polarizable, as it is the only material capable of exchanging ions continuously; in theory it has an infinite time constant, thus also allowing the recording of potential lenses without signal distortion.

The voltage-current relationship that describes the phenomena at the electrode-electrolyte interface is a function of the frequency and is independent of the current density, as long

as it remains below a threshold value *(0.5* mA/cm^2 for stainless steel electrodes). The voltage-current relationship can be described, through the following equation (2), by means of an electrode impedance of the type:

$$Z(jw) = A\,\frac{1+jw\tau_2}{1+jw\tau_1} \qquad (2)$$

which can be interpreted as the series between the resistance R_S of the electrolyte and the parallel between the capacitance R_d and the resistance C_d of the electrode-electrolyte interface (figure 3.7). The process of measuring the EEG signal via a pair of surface electrodes can therefore be represented by the equivalent circuit:

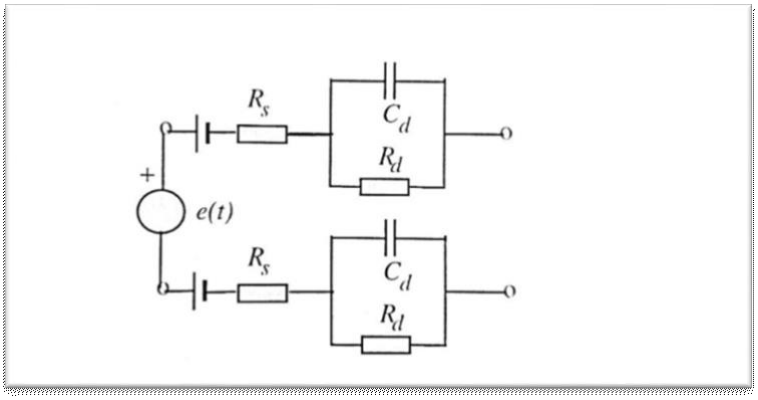


Figure 3.7: Electrical analogue of the surface measurement of a brain biopotential

Typically the electrode impedance should be less than 10 KΩ per pair of electrodes.

3.3.2 Standard positioning system 10/20

The exact arrangement of the electrodes on the scalp is regulated by the international 10/20 system, a standardized method developed in the late 40s [56] . The 10-20 system provides, shown in the figure 3.8, for the positioning of the electrodes according to ideal lines: anteroposterior, medial and lateral sagittal line; frontal, central and parietal coronal line, traced starting from fixed landmarks: the inion, external protuberance of the occipital bone, the nasion, small depression immediately above the nose and preauricular points. The distance between one electrode and another is always 10% or 20% of the total length of the line, hence the name of the system.
Each position of the electrode is named using a letter and a number (or a second letter). The letter refers to the region of the underlying cortex: Fp = frontopolar, F = frontal, C = central, T = temporal, P = parietal and O = occipital, the numbers indicate lateralization: the evens on the right hemisphere, the odd on the left while the letter z identifies the position on the midline.
Overall, therefore, the 10-20 system includes 19 sites, 8 on the left side, 8 on the right side and 3 central.

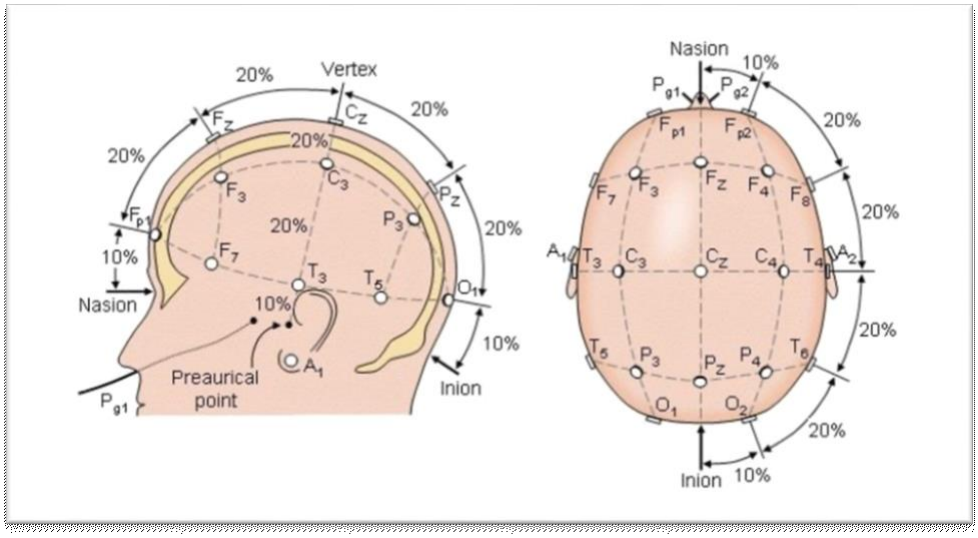


Figure 3.8: EEG electrode positions on the scalp defined by the system 10-20

The brain signals taken from the scalp are sent via the differential amplifier electrodes, each of which has an inverting and a non-inverting input; therefore, electrodes are always used in pairs. A pair of electrodes can be positioned according to monopolar or bipolar derivations depending on the specific experimental requirements (figure 3.9).
In monopolar derivation, one electrode is placed on the electrically active area, while the other is placed on the reference electrode at an electrically neutral site (e.g. the earlobe). Monopolar recording highlights the absolute level of electrical activity underlying the active site and is mainly used to pick up signals from deeper areas of the brain.[65]
In bipolar derivation, on the other hand, both electrodes are placed on active sites of the area of interest and the detected signal corresponds to the difference that emerges between the activities of the two sites. The signal thus measured represents the activity coming from the outer layers of the cortex, as the potentials generated by deeper sources are considered commonly by the differential amplifier.
In addition to the two inputs, an amplifier also requires a ground connection, which allows current to flow between it and the active or reference conductor, thus allowing the amplifier to operate. Therefore, for single-channel work (an active, a reference, mass), three sensors are needed. For two-channel work, an additional active and reference is generally used, for a total of five sensors.

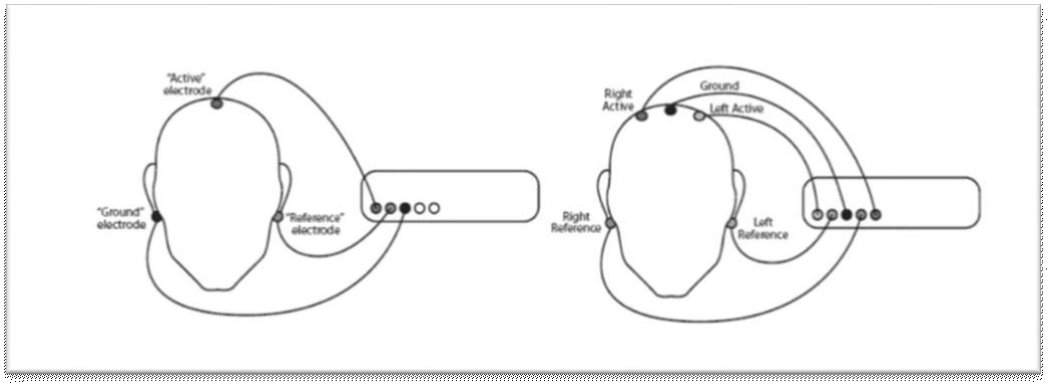


Figure 3.9: Example of single and two-channel monopole shunt

3.4 AMPLIFICATION

When using surface electrodes, the electrical signal output from the sensor is weak, typically varies between 25 and 100 μV, and it is therefore necessary to amplify it before it can be transmitted, processed, and visualized.[66]
An EEG amplifier must therefore have characteristics such as to collect electrical signals of very low amplitude from a high impedance source and amplify them even more than 1000 times without introducing distortions into the signal within variable frequency bands from 0 Hz to 100 Hz and even more.
The fundamental property of an adequate biological amplifier is that it is a differential amplifier, that is, a type of electronic amplifier that amplifies the difference between two sites and generates the difference signal as an output. As mentioned above, it has two input signals to its terminals in addition to a ground connection; the two input signals are defined respectively as active and reference signals and the recording between the two sites represents a single EEG channel.
The use of differential amplifiers is necessary to separate the useful EEG signal from the noise sources that generally appear in phase on both inputs, and which include offset, drift, and interference.
A key feature of electroencephalographic amplifiers lies in the input impedance value, which must be 100 to 1000 times greater than the electrode output impedance. The high input impedance allows the signal to be collected without significant attenuation due to the interconnection error. Typically, EEG amplifiers have input impedances of at least 1GΩ that provide accurate recordings when the equivalent electrode impedance remains below 10 KΩ.

To measure the activity of a specific region, the differential amplifier must be able to collect the difference from the sites by limiting the effects on the output of disturbances commonly present at the input.[59]
When interpreting EEG signals, it is important to keep in mind the fact that the amplifier measures the difference between two sites, thus losing a certain amount of information. There is more than one way to get the same output; the amplifier, for example, can measure a null or very small EEG signal both when the two inputs are small and when

they are equal.
Conceptually this is a "many to one" problem as multiple combinations of input signals can produce a given output. For this reason, when observing an EEG signal, it is not possible to determine exactly what the underlying activity is, unless additional channels are acquired that make it possible to carefully analyze all combinations of inputs. Overall, in the process of acquiring the EEG signal, no electrical energy is taken or transferred to the patient's head. Internationally, the ISO (International Standards Organization) and the IEC (International Electrotechnical Committee) have established the highest acceptable levels of each electronic interference, and the technical specifications that must meet the EEG acquisition systems. The application of these standards guarantees a non-invasive and noise-free EEG instrumentation.

3.5 ANALOG-TO-DIGITAL CONVERSION AND SIGNAL PROCESSING

The architecture of an EEG signal measurement system not only includes the analog part necessary for the amplifier, but also includes additional processing capabilities, made by means of digital circuits or, increasingly, with microcomputers.
In most modern neurofeedback systems, the analog signal is first digitized and then processed through digital techniques. When working with digital EEG it is important to keep some considerations clear: the first is that every abstraction of the wave involves compromises, the second is that there is no "correct" way to treat the quantization of the EEG. There are many ways to reduce EEG waveforms to digital signals, and it is essential to be accurate about what is being monitored, evaluated, or trained.
The basic properties of a periodic signal are amplitude and frequency, which represent respectively the maximum variation of the wave from the equilibrium position and the number of times the signal repeats in the unit of time.[60]
The peak-to-peak amplitude (P-P) and the mean quadratic value (or effective value, RMS) are two ways to measure the amplitude of a periodic signal. The P-P derives from the physiological world, and it is a measure of the excursion of the signal from its minimum point to its maximum point; effective value, on the other hand, comes from the world of

telecommunications engineering, and is a measure of signal energy. No real signal consists of a single frequency, but it is possible to identify the predominant frequency and express it in cycles per second, reflecting how fast the signal is oscillating.

3.5.1 Sampling

To be reduced to a digital form, the signal must be sampled, i.e., converted into a discrete signal. Sampling accuracy, or resolution, is described in terms of the number of digital bits used to sample the signal. Typically, a minimum of 8 or 10 bits is used in the cheapest systems, 12 to 16 bits in the most common systems and up to 24 bits in the highest resolution systems. A significant advantage of 24 bit sampling is that it is possible to sample the entire signal field, including the DC component, and save it accurately. Systems with less than 24 bits must be coupled in alternating current (AC) to avoid extremely high offset voltages that would take the signal out of the digitizer range. The second important factor in sampling is the frequency, expressed in samples per second, at which the signal is sampled.
In order to not lose information, the signal must be sampled with a sampling rate equal to at least twice the maximum frequency of interest of the signal, according to the Nyquist-Shannon theorem [61] (3):

$$f_c > 2 * f_m \qquad (3)$$

Where f_c represents the sampling rate and f_m the highest frequency. However, this frequency does not ensure an adequate visual representation of the signal, as it only guarantees two samples per cycle of the fastest frequency. Therefore, much higher sampling rates are used in neurofeedback, which ensure that the signal is not contaminated by power line noise harmonics, which in turn can extend to hundreds of hertz.

3.5.2 Frequency analysis

The fast Fourier transform (FFT) [62] is the most common method of frequency analysis of sampled signals and forms the basis of many advanced methods (figure 3.10). It is an efficient computational algorithm designed to quickly transform the signal and display it in real time.
Mathematically the Fourier transform, of which the FFT is an implementation, is an operator that allows to decompose a generic signal into an infinite sum of sinusoids of different frequencies, amplitudes, and phases in such a way as to see how much of each frequency is present in the signal. The set of values as a function of frequency (frequency components), continuous or discrete, is called the amplitude spectrum.
When performing an FFT analysis the sampled signal is further divided into epochs called time windows of a certain fixed duration, typically one or two seconds. The size of the window is an important factor as it determines the lowest frequency that can be detected by mathematical analysis.
The frequency of FFT is equal to the inverse from the epoch size.
Note that the sampling rate is not the same as the frequency of FFT; the sampling rate is the frequency with which the data is collected while the frequency of the FFT is an indicator of how often the mathematical operation is performed on the sampled points.
The limits of the sampling rate and the length of the time window are absolute, and they are based on mathematical principles.

One method that overcomes some limitations of the FFT era and provides rapid estimates of changes in EEG is that of joint time-frequency analysis (JTFA). This method is like FFT but does not use a fixed size of the time.

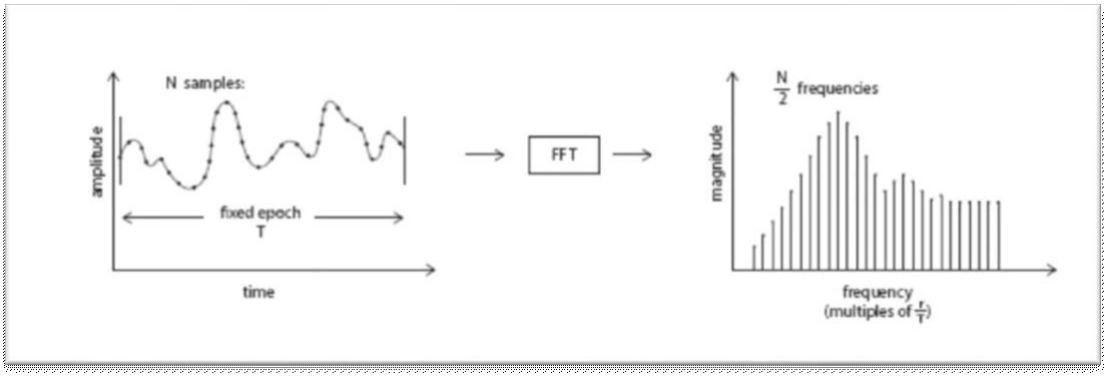


Figure 3.10: Using the Fourier transform to convert a time domain signal into its frequency components

3.5.3 Digital filtering and time parameters

Digital filtering is a process that allows to retrieve frequency-dependent EEG information in real time, as illustrated in the figure 3.11. There are different approaches to designing and implementing digital filters, and they all share weaknesses and strengths. An important factor of digital filters is that bandwidth and frequency must be specified in advance. In typical neurofeedback systems, a minimum of three digital filters are generally provided, although more than eight filters are usually used. It is common to allow the user to select the filter type (Butterworth, Chebycheff, elliptical), the lower and upper cut frequencies, and the order (one, two, three up to 1011 or 1012). Order is a measure of the sharpness of the cutting region in what is called the stop band of the filter and it is reflected in how sharply out-of-band frequencies are reduced. No realistic filter can completely cut all out-of-band signals due to mathematical limitations. The more sharply a filter cuts out unwanted frequencies, the longer it will take to respond to a change in input, in addition, the response time of the filter is inversely proportional to the bandwidth of the filter. The choice of such parameters depends on the type of application and the personal preferences of the therapist. Some trainers tend to favor lower-order filters because they offer a faster response time; such filters provide less selectivity, but therapists who prefer them claim that the patient's brain can sort out

useful information by rejecting what it does not consider relevant. Lower-order digital filters are typically used in high-frequency training (beta) with inexperienced customers or with children [63] . Those who prefer higher-order filters emphasize selectivity, and the ability to repel signals that are outside the desired bandwidth. Higher-order filters require slightly longer response times (a sixth-order filter may require three cycles of the input signal) but the benefits in terms of out-of-band signal rejection are considerable. High-order filters (usually 5, 6) are normally used in low-frequency training (theta, alpha) in adult or trained subjects. The dynamics of the filter play an important role in the choice of cutting frequencies. Low-frequency rhythms, such as alpha or theta, rise and fall much more slowly than higher-frequency rhythms. Alpha bursts typically last 100 to 500 milliseconds, and the central frequency of the alpha wave is usually in the range of 9-11 Hz; To respond adequately to the rise and fall of the alpha wave, a bandwidth of about 4 Hz is required (which is the main reason why frequent cutting frequencies are generally fixed at 8 and 12 Hz). If, on the other hand, the filter must show a short beta burst, then it must have a wider bandwidth, up to 10 Hz, in order to respond quickly enough. The gamma rhythm typically consists of very short bursts, 20 to 50 ms, which are harder to see with a narrowband filter. To respond adequately to such bursts a filter must have a bandwidth of about 10 Hz (with cutting frequencies commonly set to 35 and 45 Hz).

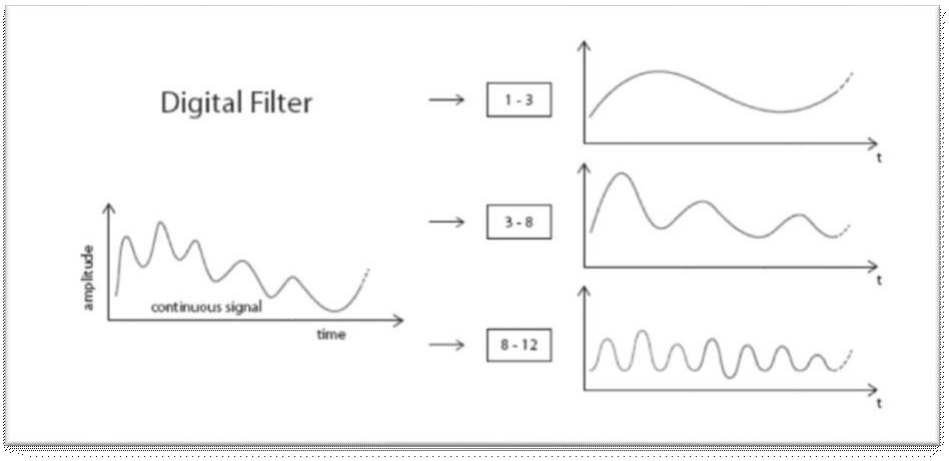


Figure 3.11: A digitally filtered signal using various bandwidths

Another important aspect of signal processing is the use of tuning parameters such as sustained reward criterion, refractory period, and damping factors. All these factors allow to adjust the response of the system over time in a functional way to guarantee a pleasant and informative feedback. In fact, the brain requires that the information of the training be properly organized and timed, to respond adequately to stimuli and satisfy the mechanism of operating conditioning [64] .

3.6 VISUALIZATION AND STORAGE

In order to monitor the distribution of specific amplitude or power bands, computerized visualization programs have been developed. Such software uses graphical techniques called compressed spectral arrays (CSAs) to display in real time the signal acquired by a single channel. The CSA technique uses frequency analysis to provide a three-dimensional representation of the EEG signal, depicting the amplitude on the vertical axis, frequenting it on the horizontal axis and the time on the "z" axis.
This representation of the signal is mainly used by the therapist to identify abnormalities in the EEG signal and to manage the session but can also be exploited by the patient during the training phase. The feedback signal can be made available to the patient in multiple forms (visual, tactile, acoustic) at the choice of the therapist.
Typically, an option software makes it possible to visually present the return signal via amplitude or power bands, animations and diagrams and allows to analyze the results and record the data.
To evaluate the effectiveness of the training or to plan future sessions, it is useful to be able to review the results obtained by the patient.
Software developed for neurofeedback is equipped with the tools needed to export session data to Excel, Matlab, or other software packages for offline data analysis.

3.7 WEARABLE DEVICES

By wearable devices, it is meant any type of machine with computational capacity that can be used by the user by making it interact directly with his body, with which it must be in contact.
It can be a garment such as a jacket or shoes or an accessory such as a bracelet, a watch or a pair of glasses and offer the user who uses them practical functions in a compact design to the point of being wearable [58] . In their collected designs they contain a considerable number of sensors that allow them to monitor the user's movements or to provide the user with additional information about what they are observing.

3.7.1 History and evolution

The history of wearable technology has evolved over time thanks to the use of new materials, but above all thanks to the transition from analog to digital and its use, thanks to the miniaturization of components, increasingly smaller, powerful, and reliable processors, more efficient and durable batteries. The concept of wearable electronics is not new, indeed the first real wearable device dates back to the 60s of the last centuries. It was Claude E. Shannon, one of the greatest mathematical geniuses of all time, together with Edward O. Thorp, a professor of mathematics fascinated by mathematical theories related to gambling, who developed the first device [67] .
The two buy a roulette and begin their experiments. Equipped with cameras and sensors they study the physics of roulette, curves and trajectories of the ball, times, and speed of rotation of the pot. They thus create a complex algorithm capable of increasing the probability of winning at the table by 40%. They design and build a microcomputer the size of a pack of cigarettes placed inside a shoe and connected with a very thin wire to a hearing aid. At each turn of the wheel the microcomputer was controlled through the big toe so that it memorized the times of passage of the ball on certain reference points. With this data the device returned, in the form of a musical note, the sector of the wheel in which the sphere would stop. The experiment turned out to be a crazy effort, for the

tension and for the bets, but above all for technical problems, first the very thin wire that connected the headset that continued to break. However, it seemed to work so well that Nevada outlawed it in 1985. Since the last twenty years, the components used to create devices with computing capabilities have developed exponentially to the point of favoring an important growth in the production of increasingly smaller, powerful, and interconnected devices. With the development of the Internet the trend is to have more and more devices connected to the network to have everything under control, even at a distance, from our body weight to everyday appliances, such as the washing machine. With the introduction of Bluetooth technology, which allows to connect two devices through a secure and short-range WPAN (Wireless Personal Area Network) for data exchange via radio waves, the first Bluetooth earphones were introduced in 2002, which allow, when connected to a phone, to answer a call like any other headset, then pressing the answer button placed on the device itself, but without it being physically connected to the phone with an audio jack.

3.7.2 Future prospects for wearable devices

Thanks to the development of technology that facilitates the miniaturization of components and the consequent lowering of costs, wearable devices are becoming increasingly affordable for everyone. In the future, operating systems for wearable devices will be developed by manufacturers to such an extent that they will make it increasingly easy to use even for less experienced users. With the evolution of the Internet of things, which provides as many interconnected systems as possible in order to create an ecosystem of different devices connected to each other, to exchange information of any kind, it will be possible to manage what is around the individual also through wearable devices.

3.7.3 Main applications of wearable devices in various real-life contexts

Wearable devices are increasingly sinking their roots in the technology market by always offering a larger number of users the opportunity to transmit information by interacting with technology in a way they had never done before. In fact, in just a few short years, there has been a shift from the use of bulky computers with little computing power to the use of powerful hand-held devices. With wearable devices one has the possibility to monitor everyday reality and get information about what is around one. The areas of application of this modern technology are many and can vary from fitness and well-being to video-recreational or health. The most well-known technology companies are developing increasingly innovative and affordable technologies to expand the market. But the wearable sector can also be an opportunity for companies born from crowdfunding.

One of the main applications of wearable devices is undoubtedly related to the care of the user's well-being and the monitoring of the body during sports activities. The miniaturization of electronic components has allowed technology to be used more and more easily in the field of sport and control of the body's response during the performance of a physical activity. Thanks to the use of wearable technologies equipped with reliable sensors for the detection of a varied number of information, athletes at a competitive and non-competitive level can independently monitor their performance and thanks to the synchronization with the smartphone they can have a constantly updated report of their physical activities. Wearable devices are able to monitor the body, not only during sports, but also throughout the day and can report, in a fairly precise way, how many calories have been burned, how many steps have been taken or even mark the sleep cycles, in order to make a history of the latter in order to give advice to improve habits and to start waking up at the most appropriate time through a vibration directly on the wrist, in case an alarm has been set. Almost all smartwatches on the market are equipped with a sensor for detecting heartbeats, but often turn out to be inaccurate, because during the measurement they need to be as attached to the wrist as possible and stationary, so it is preferred to use elastic chest straps or sensors inserted into a garment such as a t-shirt.

Wearable devices have also found wide use in the health sector, they are also used in the medical field for post-operative monitoring of the patient. In this way it can be checked in real time by the doctor who is automatically updated on his state of health. An example can be the use of GSR (Galvanic skin resistance), a technique that is used to monitor the change in electrical resistance of the patient's skin caused by emotional stimuli (figure 3.12). This variation results from the amount of moisture produced by the sweat glands of the fingers.
There are two types of activities that can be measured through GSR feedback:

- ***tonic activity***, which expresses an index of activation of the body's nervous system; if the value is high, the individual is in a situation of relaxation while if it subsides, sweating increases and the patient becomes agitated and nervous.

- ***phasic activity***, i.e. the rapid responses provoked by emotions that the patient experiences during the rehabilitation phase.

This tool therefore allows to reduce the response in patients suffering from phobias following the evaluation of the nervous system of the subject under observation.

Figure 3.12: A device to measure the galvanic skin response

However, the effectiveness of the use of monitoring tools in the post-operative phase does not derive only from the accuracy of the sensors. Patients can now wear devices that can measure heartbeat, blood pressure or respiratory rate, but the reliability of these devices largely stems from the patient's attention to follow the instructions dictated by the doctor. With a correct and constant use by the patient of these monitoring devices, the doctor's work in reading the data can be facilitated, in order to be able to identify a better treatment procedure [68] .

3.7.4 Advantages and disadvantages in the daily use of wearable devices

The use of wearable devices certainly has several advantages for those who use them thanks to their compact size, ease of use and information always at hand, however, the use of these tools also involves disadvantages, always for users. Specifically, one of the biggest advantages of wearable devices is immediacy; often when the user is using a smartphone, he has in front of him a set of applications and no immediate information, while a wearable device such as a smartwatch or smart glasses gives the user information without delays, relevant to what he is looking for [69] . For example, a user can monitor in real time the progress of his training directly on the lens of the smart glasses or on the display of the smartwatch without having to resort to the use of the smartphone. So, the use of wearable devices involves an increase in efficiency as these tools allow to take a quick look at a message, an email and wanting to respond using voice, even before picking up the smartphone to unlock it, search for the application, and find the information that the user is looking for. Another advantage is the user's involvement with the surrounding environment. During the use of smartphones or tablets, in fact, the user is induced to focus on what happens on the screen, effectively excluding himself from what surrounds him. In addition, these tools can give useful information to the user who wears them, remaining discreet. In addition, the data collected by wearable devices in general, can be exploited for medical research and therefore benefit the entire world population that, in a certain sense self-monitoring, involuntarily helps researchers from all over the planet to fight diseases that have always afflicted

people all over the world, such as cardiovascular disorders. Despite the many advantages of using wearables, there are also disadvantages. One of these is certainly the technical limit deriving from the technological development of batteries. The dimensions collected to make them wearable oblige manufacturers to use batteries with a small number of amperes that turn into a not too high autonomy. In the presence of a screen, in fact, if one takes smartwatches as a sample, the average duration is one and a half days [70]. Wearable devices contain personal choices regarding lifestyle and habits. Losing such a device could lead to a major problem for the user's privacy. Many devices use GPS and camera, two technologies that track every moment of life, from where ever a person is, to what one does, and if someone violates security systems can have access to detailed information about users; the problem of privacy is therefore one of the biggest problems for wearable devices, therefore companies that use sensitive data for scientific or other purposes must make their privacy policies very clear [71] .

3.8 WEARABLE DEVICES FOR ELECTROENCEPHALOGRAPHIC MONITORING

The most suitable techniques for the realization of a BCI (Brain-Computer Interface) are electroencephalography and techniques based on optical images, both for good results and for reduced costs, based on non-invasive biosensors that capture the electrical waves generated by brain activity and eye movement and translate the information into digital signals for BCI. This wearable technology encompasses new applications in electronics, medical applications, wellness, safety, education and much more. Communication with machines has always been limited to conscious and direct forms that is a simple operation such as turning on the lights with a switch or complex such as robotic programming, one has always had to give a command to the machine, or a series of commands so that it did something for a particular purpose. Communication between people, among other things, is more complex and much more interesting as it is taken into account much more than is explicitly expressed. By observing facial expressions, body language, one can intuit

emotions and feelings by dialoguing with another human being and this plays a very important role in the process of making decisions.
What they want to do is to introduce this complex world of human interaction into the interaction between the computer and the human being, so that computers can understand not only what they are being commanded to do but can also react to facial expressions and emotional experiences. One way to do this is to interpret the signals produced by the brain, which is the control and experience center. The task is not the easiest, mainly for two reasons. The first is that of the detection algorithms. The brain is composed of billions of active neurons. The total length of the axons amounts to a total of about 170,000 km. When these neurons interact, the chemical reaction emits a measurable electrical impulse. Most mental abilities are distributed on the outer surface layer of the brain. In addition, to increase the surface area available to mental capacity, the surface layer of the brain has countless folds. Such cortical folds represent a complex challenge to the interpretation of the electrical impulses of the surface layer. The cerebral cortex of everyone has different folds, much like a fingerprint. Through this technology it is possible to allow facial expressions to be linked to commands for movement.

3.8.1 The Emotiv Epoc helmet

In recent years, being able to have an EEG device has become affordable for everyone, in fact economic devices have entered the market that are easily usable and available: this allows to carry out the most disparate scientific experiments both at an academic level and in the amateur/independent field of software development.
In the field of hardware peripherals, the Epoc helmet, available on the market since 2009, released by Emotiv Systems, an Australian-born electronic company founded in 2004 by four scientists: Allan Snyder, Nell Weste, Tan Le and Nam Do, which develops BCIs based on the acquisition of EEG signals, allows to record and analyze the signals of an EEG in a simple and immediate way, making the software available to explore its features and to integrate its functionality into third-party programs.
Emotiv Epoc is a high-resolution, multi-channel and wireless neuro-device that uses 14 sensors that require initial preparation before use based on international positioning 10-

20 (AF3, F7, F3, FC5, T7, P7, O1, O2, P8, T8, FC6, F4, F8, AF4) plus 2 references (CMS/DRL) to tune in with the electrical signal produced by the brain to detect thoughts, feelings and expressions in real time, as reported in the figure 3.13.

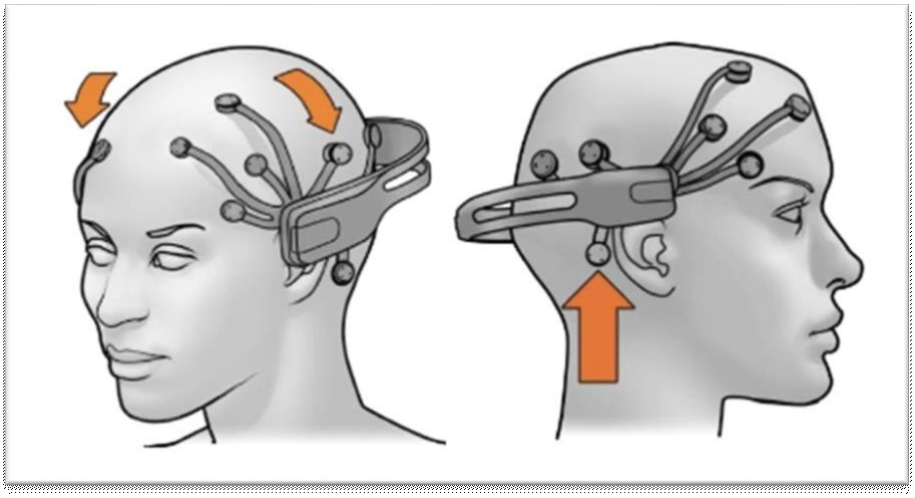


Figure 3.13: Emotiv helmet positioning scheme

The sensors inserted at the ends of each arm are removable and are fixed and disassembled with a simple "screw" rotation in their compartment clockwise (attachment) or counterclockwise (detachment) (figure 3.14); each sensor has a metal contact in the attachment part and spongy material at the outer end and is always interchangeable with the others.

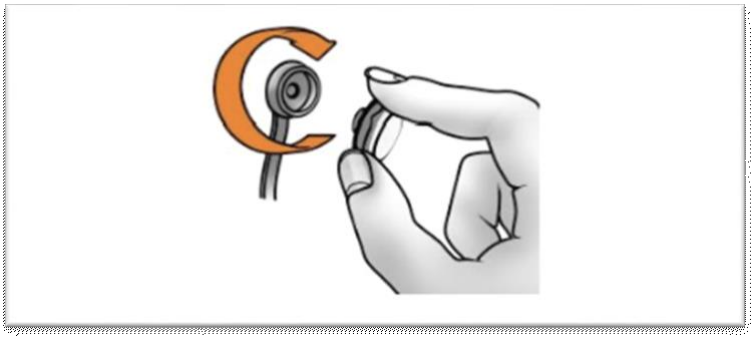


Figure 3.14: Mounting a sensor in the helmet arm

A fundamental operation for correct operation is to hydrate each sensor with a saline solution that must completely wet the absorbent sponge part (figure 3.15): if this operation is not done well, it will be impossible for the helmet to correctly detect the EEG signals.

Figure 3.15: The part of the sensor in contact with the scalp must be moistened with saline solution

Communication with the computer software takes place via a USB wireless transmitter, without any driver installation (figure 3.16 left), while in the part of the helmet behind the nape of the neck there is an ignition switch and socket for the charger (figure 3.16 right).

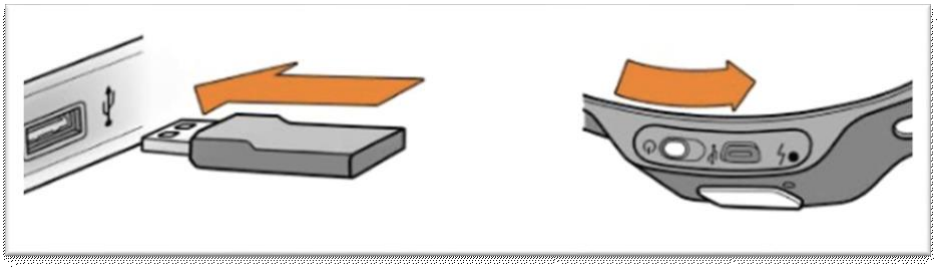


Figure 3.16: USB wireless transmitter and helmet switch

To establish a good signal, it is necessary to press for 5/10s the reference sensors which are located just above and behind the ears and then slowly all the others until in the control panel software all the dots referred to the sensors go from pink to green, as shown in the figure 3.17.

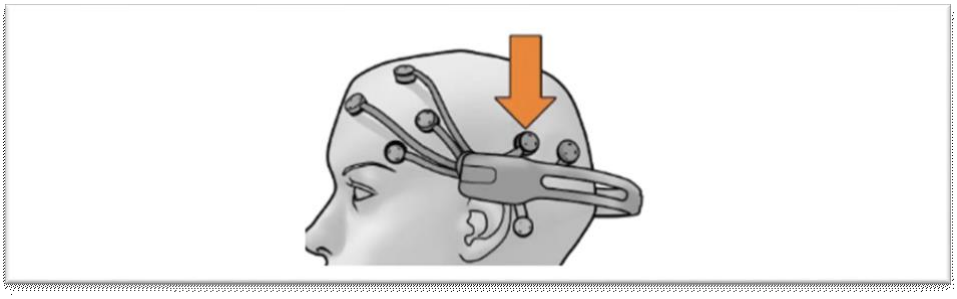


Figure 3.17: The control sensor must be held down at the start of configuration

3.8.1.1 Emotiv software to use the helmet

The control panel [72] (figure 3.18) is the Emotiv software that allows to interface graphically with the helmet in real-time.

The upper part of the screen is called EmoEngine status panel with the User status section on the right and the Engine status section on the left where the "System Status" and "Wireless Signal" items inform about the quality of the wireless connection and data transmission.

In the lower part it is possible to select the Headset Setup tab dedicated to the signal quality of the sensors: a visual representation allows to evaluate the connection and transmission status of each active sensor (the values range from black to green, passing through red, orange and yellow).

Figure 3.18: The control panel here divided into status panel (above) and sensor signal quality section (below)

The Control Panel has other tabs of panels with peculiar functionality and applications:

- ***Expressiv suite***: shows the functionality of facial expressions and non-verbal communications; an avatar will mimic the facial expressions that the user assumes highlighting closing and opening of the eyes, right / left eye movements, smiles, eyebrow movements and grinding teeth.

- ***Affectiv suite***: detects the different levels of subjective emotions such as interest, excitement and involvement, the measurements of which are then translated into real-time graphs.

- ***Cognitiv suite***: evaluates the user's brain waves to determine what action he

consciously wants to perform on a physical or virtual object: the possible actions are varied such as pressing, pulling and rotating the object in every direction, as well as making it disappear from the monitor; it is possible train the system to recognize up to four actions at the same time.

The Affectiv data, shown in the figure 3.19, are interesting for experiments because they allow to monitor in real time the emotional state of the user. The control panel shows in two graphs (short term and long term) the pre-processed values of emotions such as Engagement, Excitement, Long Term Excitement, Meditation and Frustration:

1. ***Engagement*** is associated with states of interest, attention, stimulus, and alert with an increase in beta waves and attenuation of alpha waves.

2. ***Instantaneous Excitement*** is a positive indication of a conscious physiological excitement and is characterized by the activation of the sympathetic nervous system with dilation of the pupils, opening of the eyes, muscle tension and increased sweating and heartbeat; the associated emotions in the short term (in terms of seconds) are stimulation, nervousness, agitation.

3. ***Long-Term Excitement*** is very similar to the previous one but is measured more accurately over a longer period (i.e. in minutes).

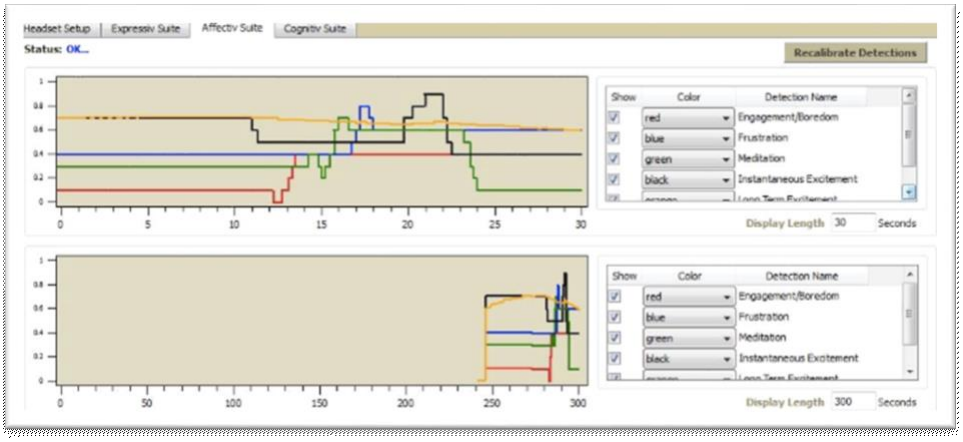


Figure 3.19: Affectiv data panel with real-time graphs of emotional values

CHAPTER 4.

DATASET

4.1 STEW DATASET DESCRIPTION

As mentioned earlier the aim of BCI research is to provide an alternative route for users to communicate with devices. Specifically, for an EEG-based BCI, this is achieved by receiving EEG signals from the user's brain, which should elicit a particular response from the device. To obtain the desired response, the processing algorithm must be able to correctly identify and classify the incoming brain signal from the user. This dataset, called STEW, aims to provide single-session EEG data of forty-eight subjects performing multitasking mental workload (MWL) tasks.

MWL is defined as the amount of mental or cognitive resources required to meet the demands of the current task [73] . A high MWL would mean that most or all cognitive resources have been used to perform the given task.
The assessment of MWL is an important consideration in the area of operator performance in order to avoid task errors due to high workload or "overload" condition [74] . Being able to correctly recognize an operator's MWL can improve safety with practical BCI applications.
The MWL is traditionally assessed with questionnaires such as the NASA Task Load Index (NASA-TLX) [75] or the Subjective Workload Assessment Technique (SWAT) [76] . As these methods only provide a subjective assessment of an operator's workload, the current trend is to supplement these assessments with physiological measurements using devices that measure biosignals such as EEG or fMRI.
In order to correctly assess MWL with such devices, it is necessary to be able to recognize the workload level of the incoming signal, and this can be achieved with the use of various machine learning techniques [77][78] .

Fifty male subjects from the university's undergraduate population participated in this study. All recruited subjects stated that they did not have any neurological, psychiatric, or brain-related diseases. They also stated that they had not taken part in any previous EEG experiments. Participants were informed about the experimental procedure and consent was obtained. This study was conducted according to the Declaration of Helsinki and was approved by the Institutional Review Board of Nanyang Technological University.

Subjects are asked to perform the Simultaneous Capacity (SIMKAP) test module of the Vienna Test System [79]. The SIMKAP is a commercial psychological test created by Schuh- fried GmbH for the purpose of assessing an individual's multitasking and stress tolerance.

While the test was designed as an assessment tool to examine personnel for their ability to multitask in heavy multitasking occupations such as air traffic management, the test has also been applied in a variety of research scenarios involving multitasking [80][81]. The SIMKAP multitasking test requires subjects to tick identical items by comparing two separate boxes while answering auditory questions that may be arithmetic, comparative, or data search in nature. Some instances of auditory questions require subjects to respond later, requiring them to monitor a clock in the upper right-hand corner. This multitasking component lasts 18 min. The order of questions and tasks in this task is fixed for all subjects, as designed by the developers of the Vienna Test System. A screenshot of the interface of SIMKAP can be viewed in Figure 4.1.

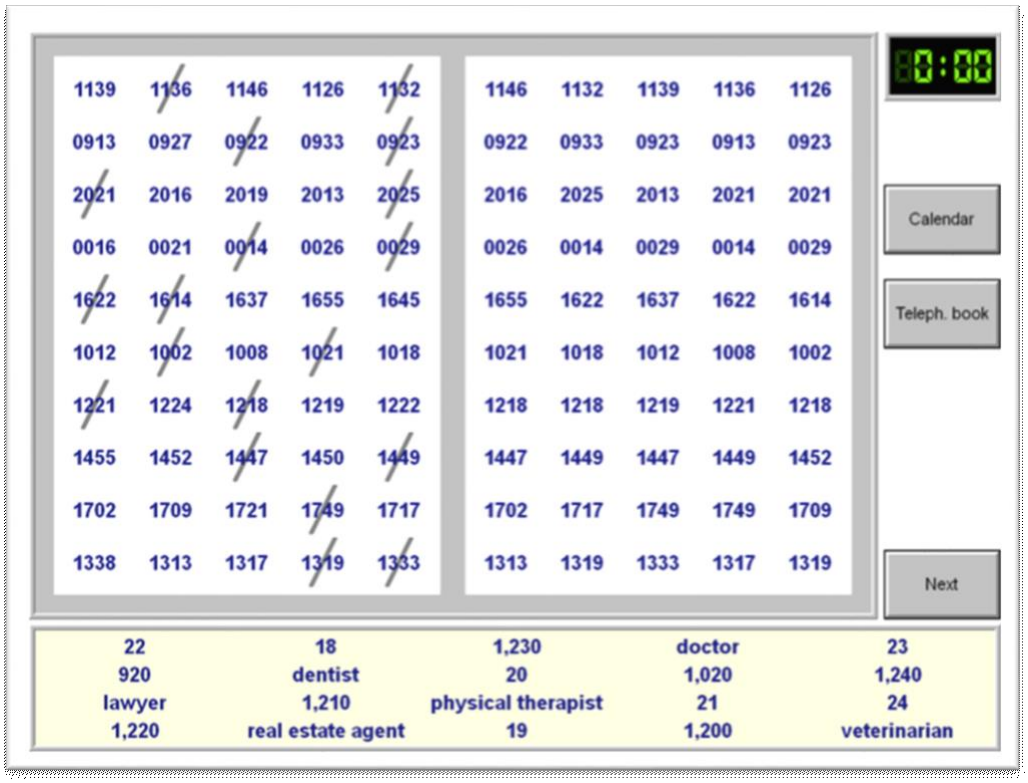
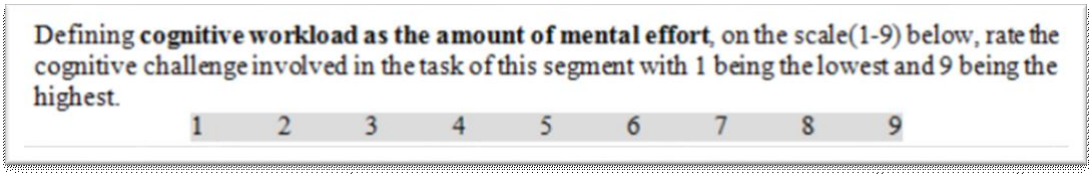


Figure 4.1: Screenshot of the SIMKAP multitask test

Since the test uses the task battery format and involves some form of arithmetic problems in addition to other auditory questions, the test follows the formats established in previous studies [82] and thus is a valid stimulus to induce MWL.
Subjects were seated comfortably; about 60 cm in front of a 24-inch LED display and were told not to make any unnecessary movements other than responding to stimuli during the experiment.
There are two parts to the experiment. First, the subjects were asked to maintain a comfortable position with their eyes open and not to perform any task for 3min. Their EEG was recorded, and these 3 minutes of recording were used as a resting condition. Subsequently, subjects were asked to perform the SIMKAP test with EEG recording and the last 3 minutes of recording were used as the workload condition. The first and last 15 seconds of data of each recording were excluded to reduce the effects of any activity between tasks, resulting in recordings of 2.5min. Subjects were asked to rate their perceived MWL after each segment of the experiment on a rating scale of 1 to 9. This was performed as a form of subjective validation that the subject experienced an increase in workload during the performance of the test compared to the resting condition. A rating of 1-3 can be perceived as low (lo) workload, 4-6 as moderate (mi) workload and 7-9 as high (hi) workload. The 9-point rating scale [83] used is analogous to the NASA-TLX 1-21 scale and is the most frequently used measure in cognitive load studies according to the review in [76].
A screenshot of the questionnaire used can be viewed in Figure 4.2.


Defining **cognitive workload as the amount of mental effort**, on the scale(1-9) below, rate the cognitive challenge involved in the task of this segment with 1 being the lowest and 9 being the highest.

1 2 3 4 5 6 7 8 9

Figure 4.2: Questionnaire on a 1-9 scale for rating of mental workload

EEG data were collected using the Emotiv Epoc EEG headset with a sampling rate of 128Hz and 16-bit A/D resolution. The device comprises fourteen electrodes located at

AF3, F7, F3, FC5, T7, P7, O1, O2, P8, T8, FC6, F4, F8, AF4, shown in Figure 4.3, according to the international 10-20 system [84] . The data are transmitted to a paired desktop PC via wireless Bluetooth and the raw data are recorded using the Emotiv software.

The Emotiv device was used because it can be easily mounted and provides signal quality comparable to a BioSemi or G-TEC device [85] [86] .

Figure 4.3: The Emotiv EEG device used and electrode positions based on the 10-20 system.

Only forty-eight of the data from the fifty subjects were used to form the database, as the data from two subjects were incomplete.

All data processing was done using MATLAB with EEGLAB, a popular and well documented tool for EEG signal processing [87] . A pre-processing of the raw EEG data was performed on the dataset itself: it is important to pre-process the raw EEG data to remove artifacts from muscle movement and to clean the noise from the data before proceeding with any analysis.

The general steps are high-pass filter on the raw data at 1Hz, remove line noise, perform subspace artefact reconstruction (ASR) and finally return the data to the mean.

The key pre-processing step is ASR which is a non-stationary method to remove large amplitude artefacts [88][89] . Figure 4.4 shows the sample data before and after the pre-processing steps. It is possible to observe that the ASR algorithm removed the large amplitude artefact in the F3 channel and reconstructed the channel data successfully.

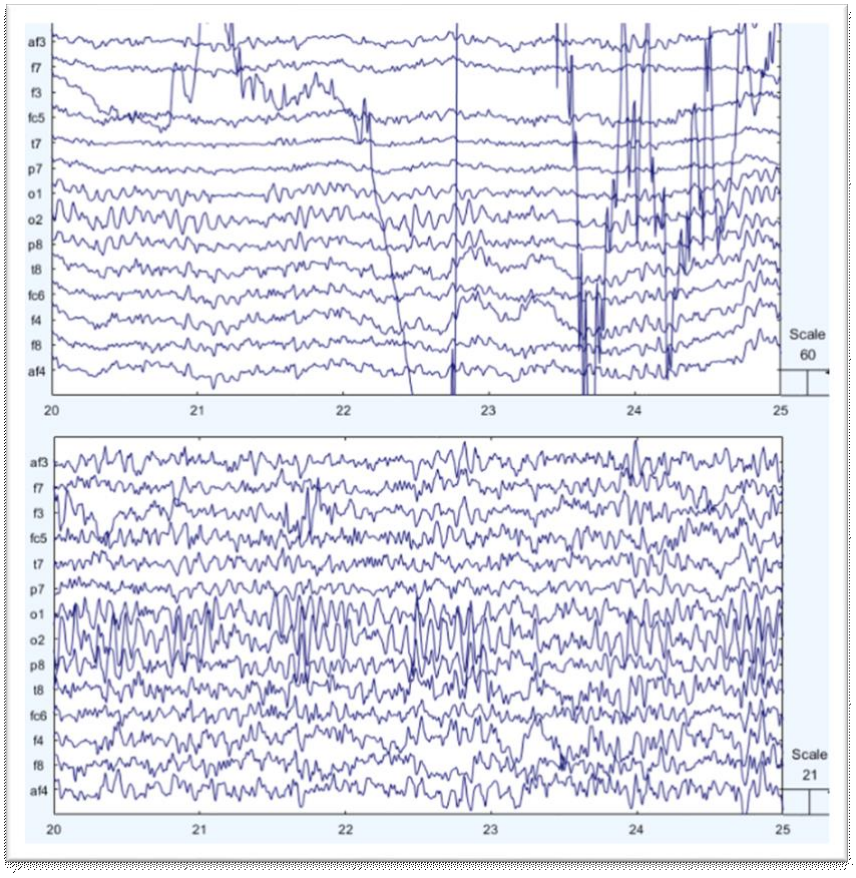


Figure 4.4: Sample continuous time EEG channel data before (top) and after preprocessing steps (bottom).

4.2 PRE-PROCESSING AND ANALYSIS OF STEW DATASET

To recapitulate, the STEW dataset consists of raw EEG data from forty-eight subjects who participated in a multitasking workload experiment using the SIMKAP multitasking test.

The brain activity of resting subjects was also recorded before the test and is also included.

The Emotiv Epoc device, with 128Hz sampling rate and 14 channels was used to obtain the data, with 2.5 min of EEG recording for each case. Subjects were also asked to rate their perceived MWL after each phase on a rating scale of 1 to 9.

The data for each subject followed the naming convention: subno_task.txt. For example, sub01_lo.txt would be raw EEG data for subject 1 at rest, while sub02_hi.txt would be raw EEG data for subject 2 during the multitasking test. The rows of each data file correspond to the samples in the recording and the columns correspond to the 14 channels of the EEG device: AF3, F7, F3, FC5, T7, P7, O1, O2, P8, T8, FC6, F4, F8, AF4, respectively.

Before starting, each .txt data was converted into a .mat. Once the conversion was done, all .mat data for the forty-eight individuals were loaded into the MATLAB® 2022a program. The sampling rate was kept at 128 Hz. Since EEG data are subject to noise, artifacts were removed from the EEG further with a second mild preprocessing using bandpass filters. The permissible frequency range of the band-pass filter was set between 0.5 and 40 Hz.

After filtering, feature extraction was performed: in particular, the features considered were extracted considering time windows of 10s.

EEG features can be broadly classified into four categories: frequency, time, linear and non-linear. More attention was paid to the power spectral density of the different EEG bands that can be treated as frequency domain features and statistical features such as mean, standard deviation, skewness and kurtosis that can be represented as time domain features. In particular:

- ***Power spectral density***:

Power spectral density refers to the distribution of spectral energy over time. Since the total energy/power of such a signal over time would be infinite, the total power can be calculated by integration or summation of the spectral components over time. The PSD is calculated by the pwelch function in the alpha, beta, delta, theta ranges [8 12]Hz, [12-30]Hz, [0-4]Hz and [4-7]Hz respectively.

- ***Mean***:

The mean is calculated by averaging the amplitude value of all EEG data samples for each channel, using the mean function.

- ***Standard deviation***:

The standard deviation calculates the deviation of each sample from the mean value for each channel. It is calculated for each channel of the EEG signal using the std function.

- ***Skewness***:

Skewness defines the degree of skewness in the distribution. It is calculated using the skewness function.

- ***Kurtosis***:

Kurtosis defines the degree of spiking in the distribution. It refers to the fact that the channel data has a heavy or light tail compared to the average of the normal distribution. A channel value with high tail/high kurtosis refers to the presence of noise in the data. It is calculated using the kurtosis function.

By using Excel, the different features extracted in the different time intervals in the respective channels are schematized into a large matrix. The matrix is reloaded into MATLAB® and the randomization is performed on it before starting the training and testing of the models in the classification learner app. Then, after randomizing the matrix, we move on to using the classification learner app.

The Classification Learner app trains models to classify data. Using this app, supervised machine learning can be explored using various classifiers. Input data can be explored, features selected, validation schemes specified, models trained, and results evaluated. Machine training can also be performed to find the best type of classification model, including decision trees, discriminant analysis, support vector machines, logistic regression, nearest neighbors, naive Bayes, kernel approximation, ensemble, and neural network classification.

It is possible to perform supervised machine learning by supplying a known set of input data (observations or examples) and known responses to the data (e.g., labels or classes).

CHAPTER 5.

RESULTS AND DISCUSSION

5.1 RESULTS

Through the classification learner app, different classification models are obtained: Ensemble boosted tree, Ensemble bagged trees, RUSBoosted trees, Medium tree, Fine tree, Subspace KNN, Coarse tree, Linear discriminant, Wide neural network, Quadratic SVM, Medium neural network, Subspace discriminant, Narrow neural network, Bilayered neural network, Fine gaussian SVM, Logistic regression, Trilayered neural network, Kernel naïve bayes, Linear SVM, Weighted KNN, Medium gaussian SVM, Fine KNN, Cosine SVM, Medium KNN, Cubic KNN, Cubic SVM, Coarse KNN, Quadratic discriminant, Coarse gaussian SVM, Gaussian naïve bayes.

All these obtained models are classified based on the accuracy percentages reported in the training and testing results.

Classification accuracy is a metric that summarizes the performance of a classification model as the number of correct predictions divided by the total number of predictions (4). It is easy to calculate and intuitive to understand, making it the most widely used metric for evaluating classification models.

In other words, training accuracy is usually the accuracy obtained by applying the model to the training data, while test accuracy is the accuracy for the test data.

$$Accuracy = \frac{True\ Positives + True\ Negatives}{All\ Samples} \qquad (4)$$

The performance analysis of each model was performed using the confusion matrix.

The confusion matrix shows the total number of observations in each cell. The rows of the confusion matrix correspond to the true class, and the columns correspond to the predicted class. Diagonal and off-diagonal cells correspond to correctly and incorrectly classified observations, respectively.

All the observations obtained from the different matrices of confusion are schematized in the tables 5.1 which collect the results of the phase of training and testing of the various trained models.

The table in the specific contains the accuracy training and testing, the true positive (TP), true negative (TN), false positive (FP), false negative (FN), sensitivity and specificity. Sensitivity and specificity mathematically describe the accuracy of a test that reports the presence or absence of a condition.

Sensitivity (true positive rate) refers to the probability of a positive test (5), conditional on actually having the condition.

$$Sensitivity = \frac{True\ Positives}{True\ Positives + False\ Negatives} \tag{5}$$

Specificity (true negative rate) refers to the probability of a negative test (6), conditional on one not having the condition.

$$Specificity = \frac{True\ Negatives}{True\ Negatives + False\ Positives} \tag{6}$$

By analyzing the entire STEW dataset, the following results are obtained:

MODEL	ACCURACY TRAINING	TRUE POSITIVES	FALSE POSITIVES	TRUE NEGATIVES	FALSE NEGATIVES	ACCURACY TESTING	SENSITIVITY	SPECIFICITY
ENSEMBLE BOOSTED TREE	92.0%	521	38	550	55	93.1%	0.90	0.94
ENSEMBLE BAGGED TREES	86.9%	511	88	500	65	87.6%	0.89	0.85
RUSBOOSTED TREES	82.4%	462	91	497	114	79.4%	0.80	0.85
MEDIUM TREE	81.4%	458	98	490	118	78.0%	0.80	0.83
FINE TREE	80.5%	468	119	469	108	80.1%	0.81	0.80
SUBSPACE KNN	79.8%	457	116	472	119	81.4%	0.79	0.80
COARSE TREE	76.3%	486	186	402	90	71.5%	0.84	0.68
LINEAR DISCRIMINANT	76.3%	451	151	437	125	75.9%	0.78	0.74
WIDE NEURAL NETWORK	76.0%	429	132	456	147	73.2%	0.74	0.78
QUADRATIC SVM	75.9%	459	164	424	117	77.7%	0.80	0.72
MEDIUM NEURAL NETWORK	74.6%	425	145	443	151	73.9%	0.74	0.75
SUBSPACE DISCRIMINANT	74.4%	436	158	430	140	77.0%	0.76	0.73
NARROW NEURAL NETWORK	73.5%	410	142	446	166	71.5%	0.71	0.76
BILAYERED NEURAL NETWORK	73.2%	417	153	435	159	67.0%	0.72	0.74
FINE GAUSSIAN SVM	71.2%	365	124	464	211	71.1%	0.63	0.79
LOGISTIC REGRESSION	71.0%	381	142	446	195	68.7%	0.66	0.76
TRILAYERED NEURAL NETWORK	70.8%	393	157	431	183	70.8%	0.68	0.73
KERNEL NAIVE BAYES	69.9%	329	103	485	247	64.3%	0.57	0.82
LINEAR SVM	68.9%	444	230	358	132	74.2%	0.77	0.61
WEIGHTED KNN	67.4%	384	186	400	192	67.4%	0.67	0.68
MEDIUM GAUSSIAN SVM	65.0%	463	294	294	113	69.4%	0.80	0.50
FINE KNN	65.0%	368	199	389	208	63.6%	0.64	0.66
COSINE SVM	64.9%	423	255	333	153	65.3%	0.73	0.57
MEDIUM KNN	64.3%	399	239	349	177	67.0%	0.69	0.59
CUBIC KNN	61.3%	381	255	333	195	63.6%	0.66	0.57
CUBIC SVM	60.9%	528	407	181	48	49.5%	0.92	0.31
CORSE KNN	60.5%	418	302	286	158	59.8%	0.73	0.49
QUADRATIC DISCRIMINANT	60.3%	507	393	195	69	62.9%	0.88	0.33
COARSE GAUSSIAN SVM	55.8%	527	465	123	49	56.4%	0.91	0.21
GAUSSIAN NAIVE BAYES	53.4%	541	507	81	35	54.3%	0.94	0.14

Table 5.1: Results obtained from the analysis of the entire STEW dataset

From the analysis of the 48 subjects of the STEW dataset, the highest level of accuracy was achieved by the trees model, in particular the Ensemble Boosted, which has a training result accuracy of 92.0% and a test result accuracy of 93.1%.

As can be seen from the above results, the performance analysis of each model was carried out using the confusion matrix.

It can be noted that, comparing the different models, among the *decision trees* the model that prevails is the medium tree with an accuracy of 81.4% in the training results and 78.0% in the test results;

in the *discriminant analysis* the model that is dominant is the linear discriminant with an accuracy of 76.3% and 75.9% in the training and test results respectively;

with regard to the *naive bayes classifiers* the kernel model predominates with an accuracy of 69.9% in training and 64.3% in testing; continuing in the group of *support vector machines* the highest accuracy is reported by the quadratic SVM with the respective percentages of 75.9% and 77.7%; for the group of *nearest neighbor* classifiers we have the weighted KNN with an accuracy in training of 67.4% and in tests equal to 67.4%; in the *neural network classifiers* the model that prevails is the wide neural network with the respective percentages of accuracy in training and testing of 76.0% and 73. 2%; finally, in the group of *ensemble classifiers* the best model appears to be, as already seen at the beginning of the paragraph, the ensemble boosted trees, but the latter is followed by two other models that were able to report good results: ensemble bagged trees and ensemble RUSBoosted trees with respective levels of accuracy in training and testing of 86.9% and 87.6% for the first and 82.4% and 79.4% for the second model.

5.2 DISCUSSION

In summary, five types of features were extracted from the EEG signals of the forty-eight subjects in the dataset. In particular, power spectral density, in the respective alpha, beta, delta and theta ranges, mean, standard deviation, skewness and kurtosis were extracted for each subject, relative to the 14 channels in different 10sec time windows.

From these results it is evident that the best performance is reported by the ensemble boosted trees model with an accuracy in the training results equal to 92.0% and in the test results equal to 93.1%.

The comparative study of these models based on the classification learner app is shown in the previous results.

This section discusses the comparative analysis between the different proposed models.

Discussing the different types of models, it is possible to say that the decision tree is a classifier with a tree structure (decision trees), in which each node can be either a leaf or an internal node: if leaf, it indicates the value of the class assigned to the instance; if internal node, it specifies the test performed on an attribute. For each value assumed by an attribute in a test, the algorithm creates a branch and its sub-tree. The main focus of the decision tree growth algorithm is how to choose the attributes to be tested in each internal node of the tree.

The goal is to select the most useful attributes to classify the training instances through a top-down strategy, which consists of a greedy search for attributes without going back to reconsider previous choices.

Discriminant analysis is a classification method assuming that different classes generate data based on different Gaussian distributions.

To train (create) a classifier, the fitting function estimates the parameters of a Gaussian distribution for each class.

To predict the classes of the new data, the trained classifier finds the class with the lowest classification error cost.

Linear discriminant analysis is also known as Fisher's discriminant, named after its inventor, Sir R. A. Fisher.

In statistics, naive Bayes classifiers are a family of simple "probabilistic classifiers" based on the application of Bayes' theorem with strong assumptions of independence between

features. They are among the simplest Bayesian network models, but coupled with kernel density estimation, they can achieve higher levels of accuracy. Naïve Bayes classifiers are highly scalable, requiring a linear number of parameters in the number of variables (features/predictors) in a learning problem. More formally, a support vector machine constructs a hyperplane or set of hyperplanes in a high or infinite dimensional space, which can be used for classification, regression, or other tasks such as outlier detection. Intuitively, a good separation is obtained by the hyperplane that has the largest distance from the closest point to the training data of any class (the so-called functional margin), since in general the larger the margin, the lower the generalization error of the classifier. Nearest neighbor classification is a machine learning method that aims to label previously unseen query objects by distinguishing two or more target classes. Like any classifier, it generally requires some training data with given labels and is therefore an instance of supervised learning.

Neural networks as classifiers, consist of units (neurons), arranged in layers, which convert a vector of input into some output. Each unit takes an input, applies a function (often non-linear) to it and then passes the output to the next layer. Generally, the networks are defined as feed-forward: a unit passes its output to all the units of the next layer, but there is no feedback to the previous layer. Weightings are applied to the signals that pass from one unit to another, and it is these weightings that are tuned in the training phase to adapt a neural network to the particular problem in question. This is the learning phase. Neural networks have found application in a wide variety of problems. These range from function representation to pattern recognition.

In statistics and machine learning, ensemble methods use several learning algorithms to achieve a better predictive performance than could be achieved by any one of the constituent learning algorithms alone. Unlike a statistical ensemble in statistical mechanics, which is usually infinite, a machine learning ensemble consists only of a concrete and finite set of alternative models, but typically allows a much more flexible structure between these alternatives.

Several studies have been conducted using the STEW dataset [90] for the multitasking mental workload task induced by a single-session simultaneous ability experiment with 48 subjects.

This work [91] estimates mental workload by monitoring different mental states from neural activity. EEG spectral power and Event-Related Potentials (ERPs) are the two means to monitor mental states. The workload during multitasking mental activities of human subjects is estimated. Different workload levels of two tasks were estimated using the composite framework consisting of Grey Wolf Optimizer (GWO) and deep neural network. GWO was used to select optimized features related to mental tasks. Other optimization techniques such as Genetic Algorithm (GA), Particle Swarm Optimization (PSO) are generally slower than the convergence rate of GWO. A deep hybrid model based on Bidirectional Long Short-Term Memory (BLSTM) and Long Short-Term Memory (LSTM) has been proposed for the classification of workload levels. The proposed deep model achieves 86.33% and 82.57% classification accuracy for "No task" and "SIMKAP-based multitasking task", respectively. In the future, the model can be extended with the classification of more challenging tasks related to mental workload. Furthermore, the patterns of each brain region during different tasks can be identified using brain connectivity analysis.

Another kind of research [92] tries to use graphical methods, which analyze the relationship between each point and other points in the EEG signals, may provide a more accurate identification of mental load. To investigate this hypothesis, it was proposed to identify optimal graph features from 14-channel EEG recordings in order to detect the high cognitive load associated with multitasking. Each experimental subject performs two tasks: no task and a simultaneous ability task, respectively. After the completion of the experiment, the subject sensation with cognitive load tags in three types: low load, medium load, and heavy load. The optimal features of these three levels of the subject's sensation and two types of cognitive load in different tasks are selected based on the statistical analysis. Then all graph features are forwarded into a support vector machine and a decision tree to conduct an objective score classification and a classification of three subjective ratings, respectively. Based on the current results, the accuracy of identifying two types of mental load is 89.6%.

A further paper [93] presents a comparative study of machine learning algorithms used to estimate workload using EEG data. The paper presents an implementation of various classification models using EEG data to predict workload. In this paper, the implementation of KNN classifier (57.3%), Random Forest classifier (57.19%), MLP

network classifier (58.2%), CNN+LSTM network classifier (58.68%) and LSTM network classifier (61.08%) has been reported. The paper can be further extended to study the real-time operator workload using a BCI paradigm for any type of task in a real-world application. The workload classification can be further used in human-machine tasks to decide the allocation of tasks among the system for optimal performance in a complex critical system.

An additional comparison of existing methodologies for EEG signal analysis using deep learning models is proposed in the following article [94] : the study showed that combining traditional analysis approaches with deep learning results in effective estimation of mental workload, sleepiness detection and fatigue assessment. Among the following models LSTM-BLSTM, LSTM building blocks, DSCAEN and CNN, CNN achieves a better accuracy of 97.37%. The purpose of this study is to help research in BCI applications by considering deep learning methodologies. Further experiments should be conducted for multi-modal architecture.

In further research, this study is helpful to improve the system by using advanced neural networks and deep learning frameworks. The study also encourages a combination of deep learning techniques to overcome the disadvantage of a single model.

CONCLUSIONS

The aim of this project is to implement a binary classification of MWL using the Classification Learner app, which is able to train models to classify data. In fact, by means of this app, it is possible to explore supervised machine learning using various classifiers using brain signals, in particular the EEG signal.

The EEG signals of 48 participants were acquired using a commercially available Emotiv Epoc helmet with 14 channels for EEG detection. The framework was tested on a known STEW dataset. The MWL was estimated through two experiments, namely "No task" and "Multitasking activity based on SIMKAP".

The recorded data were analyzed based on five features, which include power spectral density, mean, standard deviation, skewness, and kurtosis. These features were extracted from the incoming EEG signal, considering 10sec time windows, helping to improve the accuracy of the classification and the accuracy of the results. After feature extraction, different classification models were obtained using the classification learner application, which is able to train models to classify data. Using this application, it is possible to explore supervised machine learning using various classifiers and finally compare the results obtained.

The ensemble boosted trees model, belonging to the class of decision trees, was the best in terms of accuracy as it was able to achieve 92.0% in the training results and 93.1% in the training results for the experiments "No task" and "Multitasking task based on SIMKAP".

With the passage of time and the advent of new technologies, future studies may place special emphasis on signal detection, so that highly dirty and noisy signals are discarded a priori to automatically provide clean and easily analyzed signals, or even consideration could be given to integrating other biomedical signals to provide more information.

BIBLIOGRAPHY

[1]. Leka, S., Jain, A., Zwetsloot, G., & Cox, T. (2010). Policy-level interventions and work-related psychosocial risk management in the European Union. *Work & Stress*, *24*(3), 298-307.

[2]. Cardo, D., Dennehy, P. H., Halverson, P., Fishman, N., Kohn, M., Murphy, C. L., ... & HAI Elimination White Paper Writing Group. (2010). Moving toward elimination of healthcare-associated infections: a call to action. *Infection Control & Hospital Epidemiology*, *31*(11), 1101-1105.

[3]. Chrousos, G. P. (2009). Stress and disorders of the stress system. *Nature reviews endocrinology*, *5*(7), 374-381.

[4]. Chrousos, G. P., & Gold, P. W. (1992). The concepts of stress and stress system disorders: overview of physical and behavioral homeostasis. *Jama*, *267*(9), 1244-1252.

[5]. Chrousos, G. P. (1992). Regulation and dysregulation of the hypothalamic-pituitary-adrenal axis: The corticotropin-releasing hormone perspective. *Endocrinology and metabolism clinics of North America*, *21*(4), 833-858.

[6]. Tsigos, C., & Chrousos, G. P. (1994). Physiology of the hypothalamic-pituitary-adrenal axis in health and dysregulation in psychiatric and autoimmune disorders. *Endocrinology and metabolism clinics of North America*, *23*(3), 451-466.

[7]. Dorn, L. D., & Chrousos, G. P. (1993). The endocrinology of stress and stress system disorders in adolescence. *Endocrinology and metabolism clinics of North America*, *22*(3), 685-700.

[8]. Selye, H. (1956). *The stress of life*.

[9]. Mason, J. W. (1975). A historical view of the stress field. *Journal of human stress*, *1*(2), 22-36.

[10]. Blech, I. A., & Levi, A. A. (1981). Comments on Aleck's stress distribution in clamped plates.

[11]. Biggs, A., Brough, P., & Drummond, S. (2017). Lazarus and Folkman's psychological stress and coping theory. *The handbook of stress and health: A guide to research and practice*, 351-364.

[12]. Vallbo, A. B., Hagbarth, K. E., & Wallin, B. G. (2004). Microneurography: how the technique developed and its role in the investigation of the sympathetic nervous system. *Journal of applied physiology*, *96*(4), 1262-1269.

[13]. Electrophysiology, T. F. O. T. E. S. O. C. T. N. A. S. O. P. (1996). Heart rate variability: standards of measurement, physiological interpretation, and clinical use. *Circulation*, *93*(5), 1043-1065.

[14]. Grassi, G., Bolla, G., Seravalle, G., Cattaneo, B. M., Lanfranchi, A., Gennari, A., & Mancia, G. (1993). Short-and long-term reproducibility of techniques employed to assess sympathetic tone in humans: a preliminary report. *Journal of Hypertension*, *11*, S166-S167.

[15]. Grassi, G., Seravalle, G., Colombo, M., Bolla, G., Cattaneo, B. M., Cavagnini, F., & Mancia, G. (1998). Body weight reduction, sympathetic nerve traffic, and arterial baroreflex in obese normotensive humans. *Circulation*, *97*(20), 2037-2042.

[16]. Brown, R. E., Stevens, D. R., & Haas, H. L. (2001). The physiology of brain histamine. *Progress in neurobiology*, *63*(6), 637-672.

[17]. Kovacs, G. G., Alafuzoff, I., Al-Sarraj, S., Arzberger, T., Bogdanovic, N., Capellari, S., ... & Budka, H. (2008). Mixed brain pathologies in dementia: the BrainNet Europe consortium experience. *Dementia and geriatric cognitive disorders*, *26*(4), 343-350.

[18]. Selye, H. (1936). A syndrome produced by diverse nocuous agents. *Nature*, *138*(3479), 32-32.

[19]. Pacak, K., & Palkovits, M. (2001). Stressor specificity of central neuroendocrine responses: implications for stress-related disorders. *Endocrine reviews*, *22*(4), 502-548.

[20]. Herman, J. P., & Cullinan, W. E. (1997). Neurocircuitry of stress: central control of the hypothalamo–pituitary–adrenocortical axis. *Trends in neurosciences*, *20*(2), 78-84.

[21]. Herman, J. P., Figueiredo, H., Mueller, N. K., Ulrich-Lai, Y., Ostrander, M. M., Choi, D. C., & Cullinan, W. E. (2003). Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo–pituitary–adrenocortical responsiveness. *Frontiers in neuroendocrinology*, *24*(3), 151-180.

[22]. Herman, J. P., Ostrander, M. M., Mueller, N. K., & Figueiredo, H. (2005). Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *29*(8), 1201-1213.

[23]. Pruessner JC, Dedovic K, Pruessner M et al. Stress regulation in the central nervous system: Evidence from structural and functional neuroimaging studies in human populations. Psychoneuroendocrinology. In press (2009).

[24]. Dedovic, K., Duchesne, A., Andrews, J., Engert, V., & Pruessner, J. C. (2009). The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. *Neuroimage*, *47*(3), 864-871.

[25]. Griffiths, T. D., Uppenkamp, S., Johnsrude, I., Josephs, O., & Patterson, R. D. (2001). Encoding of the temporal regularity of sound in the human brainstem. *Nature neuroscience*, *4*(6), 633-637.

[26]. Blumenthal, J. A., Sherwood, A., Smith, P. J., Watkins, L., Mabe, S., Kraus, W. E., ... & Hinderliter, A. (2016). Enhancing cardiac rehabilitation with stress management training: a randomized, clinical efficacy trial. *Circulation*, *133*(14), 1341-1350.

[27]. Tawakol, A., Ishai, A., Takx, R. A., Figueroa, A. L., Ali, A., Kaiser, Y., ... & Pitman, R. K. (2017). Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. *The Lancet*, *389*(10071), 834-845.

[28]. Bot, I., & Kuiper, J. (2017). Stressed brain, stressed heart?. *The Lancet*, *389*(10071), 770-771.

[29]. Pessoa, L., & Adolphs, R. (2010). Emotion processing and the amygdala: from a'low road'to'many roads' of evaluating biological significance. *Nature reviews neuroscience*, *11*(11), 773-782.

[30]. O'keefe, J., & Nadel, L. (1979). Précis of O'Keefe & Nadel's The hippocampus as a cognitive map. *Behavioral and Brain Sciences*, *2*(4), 487-494.

[31]. Gray, J. A., & Hinde, R. (1987). *The psychology of fear and stress* (Vol. 5). CUP Archive.

[32]. Scoville, W. B., & Milner, B. (2000). Loss of recent memory after bilateral hippocampal lesions. *The Journal of neuropsychiatry and clinical neurosciences*, *12*(1), 103-a.

[33]. Kim, E. J., Pellman, B., & Kim, J. J. (2015). Stress effects on the hippocampus: a critical review. *Learning & memory*, *22*(9), 411-416.

[34]. Jarrard, L. E. (1993). On the role of the hippocampus in learning and memory in the rat. *Behavioral and neural biology*, *60*(1), 9-26.

[35]. McEwen, B. S., Nasca, C., & Gray, J. D. (2016). Stress effects on neuronal structure: hippocampus, amygdala, and prefrontal cortex. *Neuropsychopharmacology*, *41*(1), 3-23.

[36]. Golby, A. J., Poldrack, R. A., Brewer, J. B., Spencer, D., Desmond, J. E., Aron, A. P., & Gabrieli, J. D. (2001). Material-specific lateralization in the medial temporal lobe and prefrontal cortex during memory encoding. *Brain*, *124*(9), 1841-1854.

[37]. Wager, T. D., Waugh, C. E., Lindquist, M., Noll, D. C., Fredrickson, B. L., & Taylor, S. F. (2009). Brain mediators of cardiovascular responses to social threat: part I: reciprocal dorsal and ventral sub-regions of the medial prefrontal cortex and heart-rate reactivity. *Neuroimage*, *47*(3), 821-835.

[38]. Sapolsky, R. M., Romero, L. M., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine reviews*, *21*(1), 55-89.

[39]. Stefanski, V., & Engler, H. (1999). Social stress, dominance and blood cellular immunity. *Journal of neuroimmunology*, *94*(1-2), 144-152.

[40]. Patchev, V. K., Hassan, A. H. S., Holsboer, F., & Almeida, O. F. X. (1996). The neurosteroid tetrahydroprogesterone attenuates the endocrine response to stress and exerts glucocorticoid-like effects on vasopressin gene transcription in the rat hypothalamus. *Neuropsychopharmacology*, *15*(6), 533-540.

[41]. Kageyama, K., Li, C., & Vale, W. W. (2003). Corticotropin-releasing factor receptor type 2 messenger ribonucleic acid in rat pituitary: localization and regulation by immune challenge, restraint stress, and glucocorticoids. *Endocrinology*, *144*(4), 1524-1532.

[42]. Hamanaka, K., Soya, H., Yoshizato, H., Nakase, S., Ono, J., Inui, K., ... & Nomura, J. (1998). Enhanced Response of Growth Hormone to Growth Hormone-Releasing Hormone and a Decreased Content of Hypothalamic Somatostatin in a Stress-Induced Rat Model of Depression. *Journal of neuroendocrinology*, *10*(4), 259-265.

[43]. Sterman, M. B. (1977). Sensorimotor EEG operant conditioning: experimental and clinical effects. *The Pavlovian Journal of Biological Science: Official Journal of the Pavlovian*, *12*(2), 63-92.

[44]. Barnhofer, T., Chittka, T., Nightingale, H., Visser, C., & Crane, C. (2010). State effects of two forms of meditation on prefrontal EEG asymmetry in previously depressed individuals. *Mindfulness*, *1*(1), 21-27.

[45]. Kirschstein, T., & Köhling, R. (2009). What is the source of the EEG?. *Clinical EEG and neuroscience*, *40*(3), 146-149.

[46]. Ahmed, O. J., & Cash, S. S. (2013). Finding synchrony in the desynchronized EEG: the history and interpretation of gamma rhythms. *Frontiers in integrative neuroscience*, *7*, 58.

[47]. Andalman, A. S., Burns, V. M., Lovett-Barron, M., Broxton, M., Poole, B., Yang, S. J., ... & Deisseroth, K. (2019). Neuronal dynamics regulating brain and behavioral state transitions. *Cell*, *177*(4), 970-985.

[48]. Caton, R. (1875). Electrical currents of the brain. *The Journal of Nervous and Mental Disease*, *2*(4), 610.

[49]. Tudor, M., Tudor, L., & Tudor, K. I. (2005). Hans Berger (1873-1941)--the history of electroencephalography. *Acta medica Croatica: casopis Hravatske akademije medicinskih znanosti*, *59*(4), 307-313.

[50]. Sterman, J. D. (1994). Learning in and about complex systems. *System dynamics review*, *10*(2-3), 291-330.

[51]. McBee, J. K., Palczewski, K., Baehr, W., & Pepperberg, D. R. (2001). Confronting complexity: the interlink of phototransduction and retinoid metabolism in the vertebrate retina. *Progress in retinal and eye research*, *20*(4), 469-529.

[52]. Beatty, J. (1971). Effects of initial alpha wave abundance and operant training procedures on occipital alpha and beta wave activity. *Psychonomic Science*, *23*(3), 197-199.

[53]. Antal, A., & Paulus, W. (2008). Transcranial direct current stimulation and visual perception. *Perception*, *37*(3), 367-374.

[54]. Sallen, R. P., & Key, E. L. (1955). A practical method of designing RC active filters. *IRE Transactions on Circuit Theory*, *2*(1), 74-85.

[55]. Lopez-Gordo, M. A., Sanchez-Morillo, D., & Valle, F. P. (2014). Dry EEG electrodes. *Sensors*, *14*(7), 12847-12870.

[56]. Homan, R. W., Herman, J., & Purdy, P. (1987). Cerebral location of international 10–20 system electrode placement. *Electroencephalography and clinical neurophysiology*, *66*(4), 376-382.

[57]. Evans J. R., Abarbanel A., *Introduction to quantitative EEG and neurofeedback*, Academic Press, San Diego, c1999.

[58]. Teplan, M. (2002). Fundamentals of EEG measurement. *Measurement science review*, *2*(2), 1-11.

[59]. Sanei, S., & Chambers, J. A. (2013). *EEG signal processing*. John Wiley & Sons.

[60]. Farrow, C. L., Shaw, M., Kim, H., Juhás, P., & Billinge, S. J. (2011). Nyquist-Shannon sampling theorem applied to refinements of the atomic pair distribution function. *Physical Review B*, *84*(13), 134105.

[61]. Nussbaumer, H. J. (1981). The fast Fourier transform. In *Fast Fourier Transform and Convolution Algorithms* (pp. 80-111). Springer, Berlin, Heidelberg.

[62]. Lemm, S., Blankertz, B., Curio, G., & Muller, K. R. (2005). Spatio-spectral filters for improving the classification of single trial EEG. *IEEE transactions on biomedical engineering*, *52*(9), 1541-1548.

[63]. Hjorth, B. (1970). EEG analysis based on time domain properties. *Electroencephalography and clinical neurophysiology*, *29*(3), 306-310.

[64]. Feinberg, I., Koresko, R. L., & Heller, N. (1967). EEG sleep patterns as a function of normal and pathological aging in man. *Journal of psychiatric research*, *5*(2), 107-144.

[65]. Ching, K. W., & Singh, M. M. (2016). Wearable technology devices security and privacy vulnerability analysis. *International Journal of Network Security & Its Applications*, *8*(3), 19-30.

[66]. Thorp, E. O. (1998, October). The invention of the first wearable computer. In *Digest of Papers. Second international symposium on wearable computers (Cat. No. 98EX215)* (pp. 4-8). IEEE.

[67]. Duggan, R. (2015). Wearable Tech Is Your Doctor's Newest Assistant (Op-Ed).

[68]. Castleman, M. (2014). The Advantages and Disadvantages of Wearable Tech.

[69]. Barett, J. T. (2015). The Disadvantages of Wearable Computers.

[70]. Vijayan, J. (2014). 7 Hidden dangers of wearable computers. *Computerworld*.

[71]. Taylor, G. S., & Schmidt, C. (2012, September). Empirical evaluation of the Emotiv EPOC BCI headset for the detection of mental actions. In *Proceedings of the Human Factors and Ergonomics Society Annual Meeting* (Vol. 56, No. 1, pp. 193-197). Sage CA: Los Angeles, CA: SAGE Publications.

[72]. Young, M. S., Brookhuis, K. A., Wickens, C. D., & Hancock, P. A. (2015). State of science: mental workload in ergonomics. *Ergonomics*, *58*(1), 1-17.

[73]. Reason, J. (2000). Human error: models and management. *Bmj*, *320*(7237), 768-770.

[74]. Hart, S. G., & Staveland, L. E. (1988). Development of NASA-TLX (Task Load Index): Results of empirical and theoretical research. In *Advances in psychology* (Vol. 52, pp. 139-183). North-Holland.

[75]. Reid, G. B., & Nygren, T. E. (1988). The subjective workload assessment technique: A scaling procedure for measuring mental workload. In *Advances in psychology* (Vol. 52, pp. 185-218). North-Holland.

[76]. Lotte, F., Congedo, M., Lécuyer, A., Lamarche, F., & Arnaldi, B. (2007). A review of classification algorithms for EEG-based brain–computer interfaces. *Journal of neural engineering*, *4*(2), R1.

[77]. Khorshidtalab, A., & Salami, M. J. E. (2011, May). EEG signal classification for real-time brain-computer interface applications: A review. In *2011 4th International Conference on Mechatronics (ICOM)* (pp. 1-7). IEEE.

[78]. Bratfisch, O., & Hagman, E. (2008). SIMKAP–Simultankapazität/Multi-Tasking. *Mödling: Schuhfried GmbH*.

[79]. Bühner, M., König, C. J., Pick, M., & Krumm, S. (2006). Working memory dimensions as differential predictors of the speed and error aspect of multitasking performance. *Human Performance*, *19*(3), 253-275.

[80]. Ahmad, A., Darmoul, S., Dabwan, A., Alkahtani, M., & Samman, S. (2016). Human error in multitasking environments. In *Proc. Int. Conf. Ind. Eng. Oper. Manage.* (pp. 1265-1272).

[81]. J. R. Comstock, Jr., and R. J. Arnegard, "The multi-attribute task battery for human operator workload and strategic behavior research," NASA Langley Res. Center, Hampton, VA, USA, Tech. Rep. NASA- TM-104174, 1992.

[82]. Paas, F. G. (1992). Training strategies for attaining transfer of problem-solving skill in statistics: a cognitive-load approach. *Journal of educational psychology*, *84*(4), 429.

[83]. De Jong, T. (2010). Cognitive load theory, educational research, and instructional design: Some food for thought. *Instructional science*, *38*(2), 105-134.

[84]. Homan, R. W., Herman, J., & Purdy, P. (1987). Cerebral location of international 10–20 system electrode placement. *Electroencephalography and clinical neurophysiology*, *66*(4), 376-382.

[85]. Ries, A. J., Touryan, J., Vettel, J., McDowell, K., & Hairston, W. D. (2014). A comparison of electroencephalography signals acquired from conventional and mobile systems. *Journal of Neuroscience and Neuroengineering*, *3*(1), 10-20.

[86]. K. Stytsenko, E. Jablonskis, and C. Prahm, “Evaluation of consumer EEG device Emotiv EPOC,” in *Proc. MEi, CogSci. Conf.*, Ljubljana, Slovenia, 2011.

[87]. Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of neuroscience methods*, *134*(1), 9-21.

[88]. Mullen, T. R., Kothe, C. A., Chi, Y. M., Ojeda, A., Kerth, T., Makeig, S., ... & Cauwenberghs, G. (2015). Real-time neuroimaging and cognitive monitoring using wearable dry EEG. *IEEE Transactions on Biomedical Engineering*, *62*(11), 2553-2567.

[89]. W. Yang, K. Wang, and W. Zuo, “Neighborhood component feature selection for high-dimensional data,” *J. Chem. Phys.*, vol. 7, no. 1, pp. 161–168, 2012.

[90]. Lim, W. L., Sourina, O., & Wang, L. P. (2018). STEW: simultaneous task EEG workload data set. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *26*(11), 2106-2114.

[91]. Chakladar, D. D., Dey, S., Roy, P. P., & Dogra, D. P. (2020). EEG-based mental workload estimation using deep BLSTM-LSTM network and evolutionary algorithm. *Biomedical Signal Processing and Control*, *60*, 101989.

[92]. Zhu, G., Zong, F., Zhang, H., Wei, B., & Liu, F. (2021). Cognitive Load During Multitasking Can Be Accurately Assessed Based on Single Channel Electroencephalography Using Graph Methods. *IEEE Access*, *9*, 33102-33109.

[93]. Pandey, V., Choudhary, D. K., Verma, V., Sharma, G., Singh, R., & Chandra, S. (2020, November). Mental Workload Estimation Using EEG. In *2020 Fifth International Conference on Research in Computational Intelligence and Communication Networks (ICRCICN)* (pp. 83-86). IEEE.

[94]. Belsare, S., Kale, M., Ghayal, P., Gogate, A., & Itkar, S. (2021, March). Performance Comparison of Different EEG Analysis Techniques Based on Deep Learning Approaches. In *2021 International Conference on Emerging Smart Computing and Informatics (ESCI)* (pp. 490-493). IEEE.