PHYSICS DEPARTMENT – FACULTY OF SCIENCE AND TECHNOLOGY OF THE UNIVERSITY OF COIMBRA

Masters' Degree in Biomedical Engineering

Dissertation:

Decoding Neuronal Patterns Resulting from Visual Responses to Animations

'Oddball' Paradigms Based in Stimuli Animation

Carlos Manuel Pinheiro Pereira Amaral - 2006106130

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Advisor:

Professor Miguel Castelo-Branco

IBILI - Institute for Biomedical Research in Light and Image

“I’m taking my ride with destiny
Willing to play my part
Living with painful memories
Loving with all my heart...” (Mercury, Made in Heaven, 1984)
“...Don’t stop me now
I’m having such a good time
I’m having a ball
Don’t stop me now...” (Mercury, Don't Stop Me Now, 1978)

A ti Teresa, minha adorada Mãe,
e também a ti Francisco, meu Irmão favorito,
por me darem todas as razões que alguém possa precisar.

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Bem-haja a todos.

Resumo

As principais características das desordens do espectro autista incluem a ocorrência de défices de interacção social e de comunicação, assim como de um repertório de actividades, comportamentos e interesses marcadamente restritos e estereotipados.

Os objectivos desta tese passam pela criação e validação de um novo tipo de paradigmas de potenciais evocados de tipo 'oddball' (baseados em eventos raros imersos noutros mais frequentes) usando estímulos tridimensionais (3D) como forma de dissecar as redes cognitivas subjacentes à atenção a estímulos animados de complexidade e significado social crescente.

Esta dissertação apresenta cinco diferentes paradigmas 'oddball', tendo como estímulos base objectos simples ou modelos 3D de seres humanos. Três paradigmas são paradigmas do tipo clássico em que os estímulos “piscam”. Os outros dois estímulos baseiam-se na animação de modelos 3D de seres humanos como foco de atenção.

Os resultados comprovam que objectos ou modelos 3D conseguem gerar uma resposta P300, semelhante à observada em paradigmas clássicos, e que a animação de modelos visuais humanos pode ser usada do ponto de vista metodológico em estudos de foco de atenção.

Abstract

The essential features of autistic spectrum disorders (ASD) are the presence of deficits in social interaction and communication and a markedly restricted and stereotyped repertoire of activity, behaviour and interests.

The purposes of this thesis consisted in the creation and validation of new visual evoked potential oddball paradigms based on 3 dimensional (3D)/Virtual Reality stimuli, in order to dissect the cognitive networks underlying normal attention to animated stimuli of increasing complexity and social content.

This dissertation presents five 'oddball' paradigms (based on rare events immersed in more frequent ones) having as basic stimuli 3D objects/human models simulating basic movements or social interactions. Three paradigms are typical stimuli flashing paradigms, and the other two are based in the animations of 3D human models as focus of attention.

The results proved that 3D objects/models can elicit a P300 brain signal, and that the 3D human models animations can be used from the methodological point of view in studies of focus of attention.

Keywords:

Autism Spectrum Disorders, EEG, Event-Related Potentials, P300, 'Oddball' Paradigm, Movement Animation, Brain-Computer Interface.

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The thesis here presented was elaborated within the scope of the project discipline of the Biomedical Engineering Master's Degree at the Faculty of Science and Technology of the University of Coimbra. The project that will be considered was developed in the Institute of Biomedical Research on Light and Image (IBILI), throughout the course of a year, under the supervision of Professor Miguel De Sá e Sousa de Castelo-Branco from the Faculty of Medicine of the University of Coimbra.

Chapter 1

Introduction

1.1 Motivation

The essential features of autistic spectrum disorders (ASD) are the presence of deficits in social interaction and communication and a markedly restricted/stereotyped repertory of activity, behaviour and interests (American Psychiatric Association, 2000).

This group of disorders has a significant economic and social impact due to their high prevalence (reported rates estimated at 36.4 per 10.000 children (Fombonne, 2007)), morbidity and impacts on daily family life (Analysis of Social Interactions as Goal-Directed Behaviors in Children with Autism, 2001).

Although there is no cure to this disorder some forms of intervention are possible to help increase the quality of life of these individuals and their families.

It has been shown that computer interactions can increase some impaired functions in this individuals (Hetzroni, et al., 2004). Therefore, it will be interesting to explore the neural correlates involved in these interactions.

1.2 Problem Definition

The IBILI work group has recently developed neurofeedback approaches as a way to create rehabilitation tools for autistic social interactions impairment. These tools consist in the use of a Brain-Computer Interface (BCI) approach. It uses P300 oddball EEG signals to identify the focus of attention. By creating visual stimuli simulating social interactions it could be possible to train the attentional processes related to the social orienting of these individuals so that they can gain automatized routines in attending to social stimuli and then generalize the tasks proposed, in a way that can be used in real world situations.

The role of attention to stimuli of increasing structuring complexity, from simple physical motion of objects to motion of avatars in virtual reality environment, and social content from simple balls trough avatar identification, will be studied to understand the neural correlates of behavioral saliency in normal subjects and their potential application to autistic individuals.

This project consists in the creation and validation of new approaches to complex oddball paradigms.

1.3 Objectives

Although the invention of new clinical paradigms seems surprisingly to be somewhat discouraged by the International Federation of Clinical Neurophysiology (Duncan, et al., 2009), the desire to open the application boundaries of 'oddball' paradigms by introducing three-dimensional/virtual reality technologies makes this project a motivating challenge.

Objectively, it is intended to:

- Proof that structurally complex stimuli, based in three dimensional (3D)/Virtual Reality animated stimuli, can elicit a P300 signal.
- Introduce variable social meaning in these paradigms, directing this research simultaneously to the dissection of the cognitive networks underlying normal attention to stimuli of increasing complexity of social content.

The accomplishment of these points will open the perspectives for the use of P300 in BCIs.

Chapter 2

A State of The Art on Methodological Windows into the Brain

The human brain, the core of the human central nervous system, is one of the most complex, ordered and fascinating structure known. It is one of the most important organs in the human organism as it is responsible for the processing and integration of external information. It is indispensable for the correct adaptation of the organism to the surrounding environment.

The modern human brain, enclosed in the cranium, has an average weight of 1500 grams (The High North Alliance brochure, 1994) and an average volume of 1200 cm^3 to 1500 cm^3 (Stringer & Gamble, 1993). Despite this there are some differences amongst human individuals, depending on several factors such as age, environment, sex, and body size. These differences are not correlated in a simple manner to the cognitive performance of the individuals (Gur, et al., 1999).

The major cellular components of the brain are the neurons, responsible for communication; the astrocytes, which perform biochemical support; the oligodendrocytes, responsible for the formation of myelin fatty sheath around the nerve cells contributing for its insulation and protection; the microglia, which acts in reparation and protection of the central nervous system; and the ependyma, involved in the production of cerebrospinal fluid.

Neurons are generally constituted by the soma, the cell body, the dendrites, structures that receive other cell signals, and the axon from where the signals of the neurons are sent to other dendrites through synapses (Fig. 2.1).

A STATE OF THE ART ON METHODOLOGICAL WINDOWS INTO THE BRAIN

Neurons are cells capable of producing and conducting electrical impulses. They act like as little batteries with their own electromagnetic current. Similarly to a car's battery producing electricity with the reaction between the sulphuric acid and lead, the sodium (Na+), potassium (K+), chloride (Cl-) and calcium (Ca2+) ions migrate across the neuron's membranes via voltage-gated ion channels which generate electrical impulses that propagate across the axons.

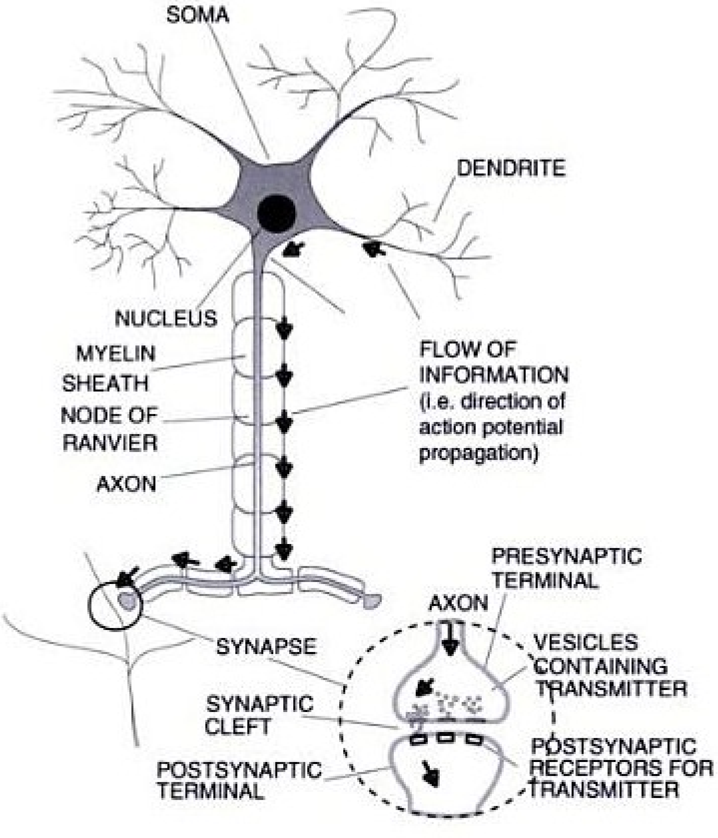


Fig. 2.1 – Illustration of neurone structure (Barker & Dunnett, 1999) *in* (Nunez & Srinivasan, 2006)

The higher inflow of positive charges into the cell membrane of the axon creates an increase in potential inside of the axons, creating a small electrical current and associated voltage change (action potential) that propagates across the membranes in a consistent trajectory.

After the action potential, the charges return to their normal concentration in both sides of the membrane, a process called re-polarization, making the potential of the membrane return to the resting potential.

The information flow in the brain is due to these action potentials that, reaching the end of axons (synapses), set off the release of chemical neurotransmitters that travels across the small gap (synaptic cleft) between the two neurons. The electrochemical transmission travels from the presynaptic terminal to the postsynaptic receptors of the other neuron, initiating another action potential in this neuron. Starting from the soma, the information can be transmitted this way.

It is estimated that each neuron establishes between five thousand and fifty thousand synaptic connections with neighbouring neurons, thus forming a neural network of more than one hundred billion connections. It is "estimated that an adult brain has around one hundred billion neurons and an even larger number of glial cells" (Salem Press, 1998) *in* (Elert, 2002).

There are two types of synaptic inputs to a neuron: the excitatory post synaptic potentials (EPSPs) producers, facilitating the action potential in the target neuron, and the inhibitory post synaptic potentials (IPSPs) producers, which act in the opposite manner on the output neuron.

There are two areas that can be distinguished in the brain. The cortex, the upper outer layer, is made of the cell bodies of the neurones and is referred as *grey matter* because of its darker colour. The axons, with their insulating white myelin sheath, give to the area beneath the cortex the characteristic white colour, hence its name - *white matter*. This myelin sheath is important in the conduction of the action potentials. The myelin insulates the axon, preventing the electrical current from leaving it. Therefore, the action potential propagates across the axon efficiently, passing only by the breaches between the myelin segments, and the nodes of Ranvier, the only places capable of generating electrical activity. This is called the "jumping" or saltatory propagation of action potentials.

The nearly symmetrical cortex, left and right hemispheres, can be divided into four 'lobes' (Fig. 2.2):

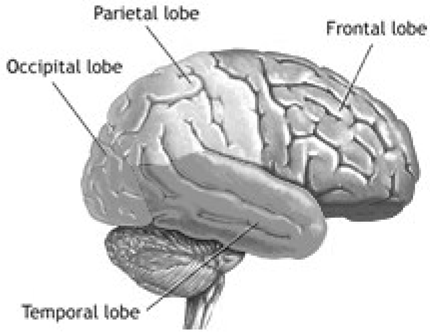


Fig. 2.2 – Lobes of the brain. Each lobe has a different function. Lesions in a specific lobe may determine the problems to be expected from this lesion (University of Maryland Medical Center (UMMC), 2008).

- **Frontal lobe**: in front of each hemisphere and positioned in front of the parietal lobe and superior to temporal lobes. Most of the dopamine-sensitive neurons of the cerebral cortex are found in the frontal lobe. The dopamine-system is related to the processing of the short-term memory tasks and attention. Among others functions, the frontal lobe is associated with reward, planning, driving and the processing of the actions of an individual.
- **Parietal lobe**: positioned above the occipital lobe and behind the frontal lobe. Among other functions the parietal lobe integrates the sensory information from various parts of the body, shaping the spatial sense and navigation of the organism.
- **Occipital lobe**: located at the back terminal part of the skull, the occipital lobe is specialized in visual tasks such visuospatial processing, colour discrimination, and motion perception.

- **Temporal lobe**: the temporal lobes are anterior to the occipital lobes, inferior to the frontal lobes and parietal lobes, and lateral to the lateral sulcus. The temporal lobe is specialized in the auditory perception and is also important in the processing of the speech and vision. This lobe incorporates the hippocampus playing an important role in the formation of long-term memory.

There are several techniques that allow the studying of the brain and understanding its intrinsic processes. The most popular techniques are electroencephalography (EEG), functional magnetic resonance imaging (fMRI), and Positron Emission Tomography (PET).

Comparing these techniques, EEG has best temporal resolution because samples are obtained in the order of milliseconds. Relatively to the fMRI and PET scans, the time frames are between seconds or even minutes. The analysis of event-related potentials is done in the scale of the hundreds of milliseconds (see section 2.2), which allows to perform decisions in real time, essential for brain-computer interfaces (see section 2.3). It outperforms the other techniques in this context.

2.1 Electroencephalography

In the brain, the flow of information takes place via the already discussed action potentials. The synchronized/desynchronized occurrence of multiple action potentials in the various regions of the brain can produce a considerable electrical activity. The placement of electrodes on the human scalp, associated with an appropriate recording system, enables the recording of brain electric potential oscillations. This process is called electroencephalography (EEG) and was firstly performed by Hans Berger in 1924. EEG is widely used in the diagnosis of epilepsy, coma, encephalopathies, and brain death diagnosis.

The typical recording system of an EEG includes the electrodes that capture the electrical signal on the scalp; differential amplifiers, sensitive to potential differences, but not to the spatially constant potentials over the scalp; analog filters, removing superfluous artifacts in the frequency domain; the signal amplifier that boosts the potential difference of the signals; analog to digital convertors (ADC), where the waveforms of the analog signals are sampled to the corresponding number of the calibration signals. After that, the EEG waveforms can be displayed on a screen or on a paper chart and stored digitally for posterior processing. See the schematic diagram in Fig. 2.3.

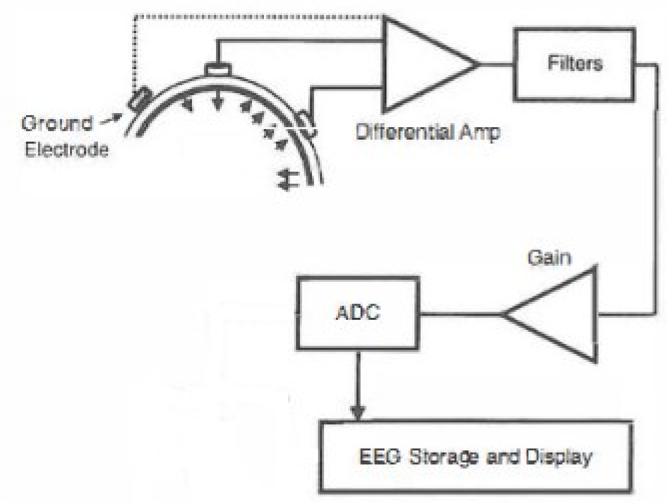


Fig. 2.3 – Schematic diagram of a generic EEG recording. The electrical signal is captured by the electrodes and the potential difference between the electrodes and the ground electrode is amplified. The signal is filtered and then amplified, before being converted to digital. The EEG can be displayed and stored. Adapted from (Nunez & Srinivasan, 2006).

The electrodes are placed in the scalp with a conductive paste or gel to decrease impedance, the resistance to electrical current. The used gels have conductivity similar to skin, and its gelatinous consistency helps improve the contact of electrodes with skin which diminish the loss of electrical power of the signal. Usually before the placement of the electrodes, the scalp of the individuals is prepared by abrasion to remove the dead skin cell reducing also the impedance.

2.1.1 The International 10-20 System

The position of the electrodes in the scalp is standardized by the International 10-20 system. This method ensures the standardized reproducibility of EEG so that all the studies can be compared.

According to this system, the position of the electrodes on the scalp is based on the distances between adjacent electrodes. As a reference, it uses two anatomical sites: the nasion, the point between the forehead and the nose; the inion, the prominent bump at the lowest point of the skull from the back of the head. The skull perimeters are measured from these points, in the transverse and median planes. The electrodes are placed into the 10% and 20% intervals of these perimeters and another three are placed on each side equidistant from the neighbouring points (Jasper, 1958; Cooper, Osselton, & Shaw, 1969) *in* (Garzon). The intermediate 10% electrode positions can be also used (Sharbrough, Chatrian, Lesser, Lüders, Nuwer, & Picton, 1991) *in* (Garzon). See Fig. 2.4.

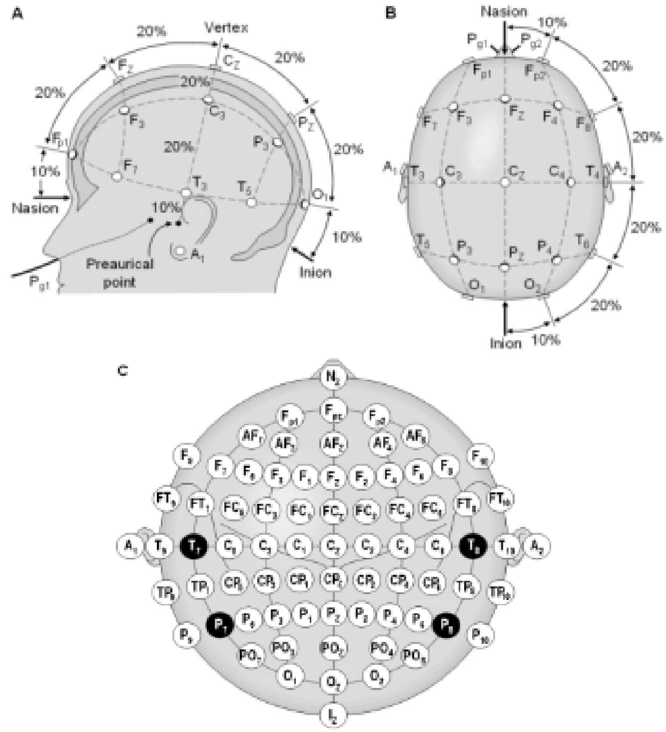


Fig. 2.4 – Left (A) and top (B) of the head views of the international 10-20 system. (C) Location and nomenclature of the intermediate 10% electrodes, as standardized by the American Electroencephalographic Society (Sharbrough, Chatrian, Lesser, Lüders, Nuwer, & Picton, 1991)

It is believed that the cortex is the structure that generates most of the electric potential measured on the scalp. The cortical neurons are strongly interconnected, which makes the scalp potential severely space-averaged by volume conduction between the brain and scalp. These facts hamper the researcher's intention to relate the potentials measured on the scalp, to brain current sources and their underlying physiological processes. A single electrode provides information of the electrical activity of tissue masses containing between roughly 100 million and 1 billion neurons. This is the big disadvantage of the EEG. The high correlation between the data from each electrode diminishes substantially the EEG spatial resolution.

The correct choice of the reference electrode's position in the scalp is important, but not very helpful in elimination of this problem. This is because "potential differences between pairs of locations on the head are measured and these differences depend on both electrode locations as well as all brain generator configurations and locations" (Nunez & Srinivasan, 2006).

2.2 Event-Related Potentials

Freeman and Ingber (Freeman, 1975; Ingber, 1982) *in* (Nunez & Srinivasan, 2006) suggested that processes of the brain involve the formation of cell assemblies in numerous spatial scales and Nunez (Nunez P. L., 1995) *in* (Nunez & Srinivasan, 2006) conjecture that these cell assemblies produce a wide range of local delays and characteristic frequencies. This dynamic electrical activity can be divided into two categories: spontaneous potentials, such as alpha and sleep rhythms, and evoked potential or event-related potential (ERP). Evoked potentials are the direct response to an external stimulus such as a light flash or an auditory tone. ERP also depends on multiple ongoing state-dependent brain processes of stimulus interpretation (Regan, 1989) *in* (Nunez & Srinivasan, 2006).

Recent studies have shown good potentialities of ERPs as a measure of injury severity and in predicting recovery from stroke and other brain trauma (Fischer, Morlet, & Giard, Mismatch negativity and N100 in comatose patients, 2000; Fischer, Morlet, Bouchet, Luaute, Jourdan, & Salord, 1999; Fischer, Luauté, Némoz, Morlet, Kirkorian, & Mauguière, 2006; Fischer, Luaute, Adeleine, & Morlet, 2004) *in* (Duncan, et al., 2009).

Transmission times for action potentials along corticocortical axons may range from roughly ten to thirty milliseconds between the most remote cortical regions. The ERPs are associated to endogenous brain states and these brain behaviours are the result of multiple interactions of neurons and assemblies of neurons (Freeman, 1975; Hart, 1993; Scott, 1995) *in* (Nunez & Srinivasan, 2006). Because of this, the ERPs may even last beyond stimulus duration.

The recording of ERP is done by time averaging the single-stimulus waveforms. By doing this, the influence of spontaneous potentials in the data is reduced (Nunez & Srinivasan, 2006).

An ERP consists of a wave form containing a series of characteristic peaks occurring after the presentation of each stimulus (see Fig. 2.5).

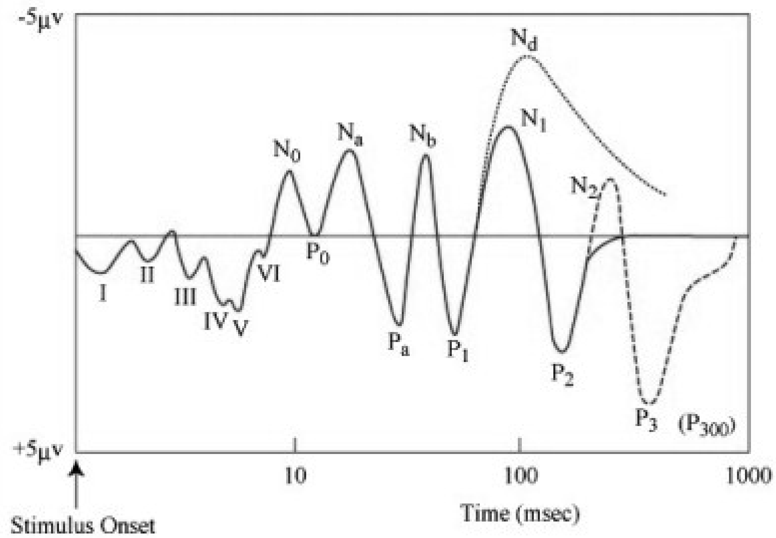


Fig. 2.5 – Idealized representation of ERPs components. Each component is dependent on stimulus context and subject attention. The name of the components is based in amplitude polarity and the latency of the peak. The vertical axis is the potential of the EEG record. Adapted from (MIT OpenCourseWare, 2006).

The parameters that define the ERPs are its positive or negative potential difference, its latency (time between the stimulus presentation and he wave peak), its scalp distribution and its relation to experimental variables. The latency informs about the processing activity time and the amplitude indicates the amount of allocation of neural resources interactions to specific cognitive processes. The bigger the latency of the ERP the more complex the brain structures and systems involved in the formation of those components.

The ERP components are sometimes referred to with acronyms (e.g., contingent negative variation - CNV, mismatch negativity – MMN). Most of the ERP components are referred to by a letter indicating polarity of the peak amplitude (P - positive; N - Negative), followed by a number indicating the latency in milliseconds or number indicating the ordinal position of the component in the waveform. For example, the first negative peak in the waveform that occurs about 100 milliseconds after a stimulus is presented, is called the N100 (negative and latency of 100 milliseconds) or N1 (first peak and is negative). The use of the number is sometimes preferred because component's latency may vary considerably across experiments.

2.2.1 The P300 Component

The positive deflection of the ERP waveform about 300 milliseconds after the presentation of the stimuli is called the P300 wave. It was first reported in 1965 by Sutton (Sutton, Braren, Zubin, & John, 1965).

The P300 component is defined by its amplitude and latency. The amplitude (usually in microvolts) is the difference between the average voltage of the pre-stimulus baseline and the largest positive peak of the ERP waveform within a defined time window. The time window can vary from approximately 250 to 1000 milliseconds (Kutas, McCarthy, & Donchin, Augmenting mental chronometry: the P300 as a measure of stimulus evaluation, 1977; Squires, Donchin, Squires, & Grossberg, 1977; Duncan-Johnson C. , 1981).

P300 has a scalp distribution over the midline electrodes (Fz, Cz, Pz), and its magnitude decreases from de parietal to frontal electrode sites (Johnson R. , 1993).

2.2.1.1 "Oddball" Paradigms

The stimulus that gives rise to the P300 component is often called an "oddball" paradigm. This paradigm consists of a random sequential presentation of visual or auditory stimuli (Fig. 2.6). For these tasks the individuals are instructed to respond to target stimuli (**Target**) with less frequent occurrences, among other more frequent stimuli (**Non-Target**). Typically, the instruction to the individual is to mentally count the occurrence of target stimuli, or to press a button in each target occurrence. The works of Donchin and Pritchard are some of the studies that clarified the roles of stimulus probability and task relevance in "oddball" paradigm (Donchin, Ritter, & McCallum, Cognitive psychophysiology: the endogenous components of the ERP, 1978; Pritchard, 1981).

Fig. 2.6 represents the **ISI** and **Flash Duration** intervals. They represent the time between two stimuli (**ISI** = Inter-Stimuli Interval), and the time duration of the stimulus presentation, respectively. This scheme originally designed in the presentation of visual stimuli. Hence the name Flash Duration. The visual stimuli are presentend in sucessive flashes.

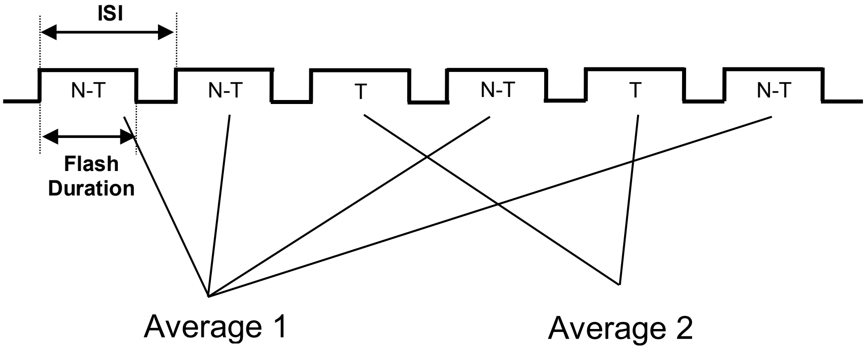


Fig. 2.6 – Schematic illustration of traditional oddball paradigm. Two different stimuli are presented in a random sequence, with the target stimulus occurring less frequently (Target = T) than the standard stimuli (Non-Target = N-T). Each stimulus is specifically classified and the signal is averaged accordingly to stimulus type.

Those parameters have an extreme importance in the structure of the oddball paradigms as it influences the modulation of P300: ISIs are positively correlated with P300 amplitude (Picton & Stuss; Woods & Courchesne, 1986) *in* (Duncan, et al., 2009).

The **Number of Events**, number of total stimuli flashes, is also important to the paradigm sctructure and the **Number of Target**, number of target stimulus, defines the probability of the target stimuli appearance. Duncan-Johnson and

Donchin (Duncan-Johnson & Donchin, 1977) reported that the lower the probability of an attended stimulus, the larger the amplitude of P300.

It is known that the expectancies generated by the sequence of stimuli also affets the P300 amplitude. Successive repetitions of stimuli decreases the P300 amplitude, and if the repetition pattern was broken the elicited P300 is larger (Squires K. , Wickens, Squires, & Donchin, 1976).

Usually the tasks are done in several blocks of stimuli presentation. The increasing of **Number of Blocks** creates more data to average giving beneficial effects in ERP averaging (because signal to noise ratio increases as a function of the square root of the number of repetitions).

Another type of paradigm, similar to oddball paradigm but including a task-irrelevant, infrequent and distinct stimulus among the series of stimuli, elicits a positive-going component having central/parietal maximum amplitude. This component is labeled the P3a (Snyder & Hillyard, 1976; Squires K. C., Wickens, Squires, & Donchin, 1976). P3a can be distinguished from P300 on the basis of an earlier peak latency of 250–300 milliseconds and a scalp distribution over the midline of the scalp and a central/parietal maximum. The relation between P3a and P300 is not consensual yet, and has been the focus of theoretical debate (Polich, Updating P300: an integrative theory of P3a and P3b., 2007).

2.2.1.2 Theoretical Models of Mental Oddball Paradigm Interpretation

There are some models that attempt to explain and describe the mental mechanisms of oddball processing. The P300 context-updating model (Polich, Overview of P3a and P3b, 2003) has had a major theoretical strength in the last twenty-five years because of its versatility. This model states that the stimuli, after an initial sensory processing, are evaluated by attention-driven comparison mechanisms (Heslenfeld, Kenemans, Kok, & Molenar, 2003; Kujala &

Näätänen, 2003). Those mechanisms ascertain whether the current stimulus is identical to the previous stimulus or not. If the new stimulus does not have any alteration, the mental model or "schema" of the stimulus is unchanged and normal sensory evoked potentials are obtained (e. g., N100, P200 N200). If the stimulus shows any difference, the subject allocates attentional processes to the target and the neural representation of the stimulus environment is updated, generating a P300 component in addition to the sensory evoked potentials (Fig. 2.7–a)).

The resource allocation model gives a general view of how the attentional resources can affect the P300 measures. This model asserts that the overall level of excitation of the stimulus determines the amount of cerebral resources allocated to processing on-going tasks. This theory is supported by several results: salience of the target stimulus and its reward value also influences the P300 amplitude (Kei, Bradley, Hauk, Rockstroh, Elbert, & Lang, 2002; Yeung & Sanfey, 2004); The "subjective probability and salience are modulated by the amount of attentional resources allocated to the stimulus" (Isreal, Wickens, Chesney, & Donchin, 1980; Kramer, Wickens, & Donchin, 1985; Johnson J. R., 1993; Johnson, Barnhardt, & Zhu, 2004) *in* (Polich, Updating P300: an integrative theory of P3a and P3b., 2007). That means that the P300 peak amplitude and latency is intrinsically linked to the attentional resource alocation, and therefore to the overal arousal level (Fig. 2.7-b)).

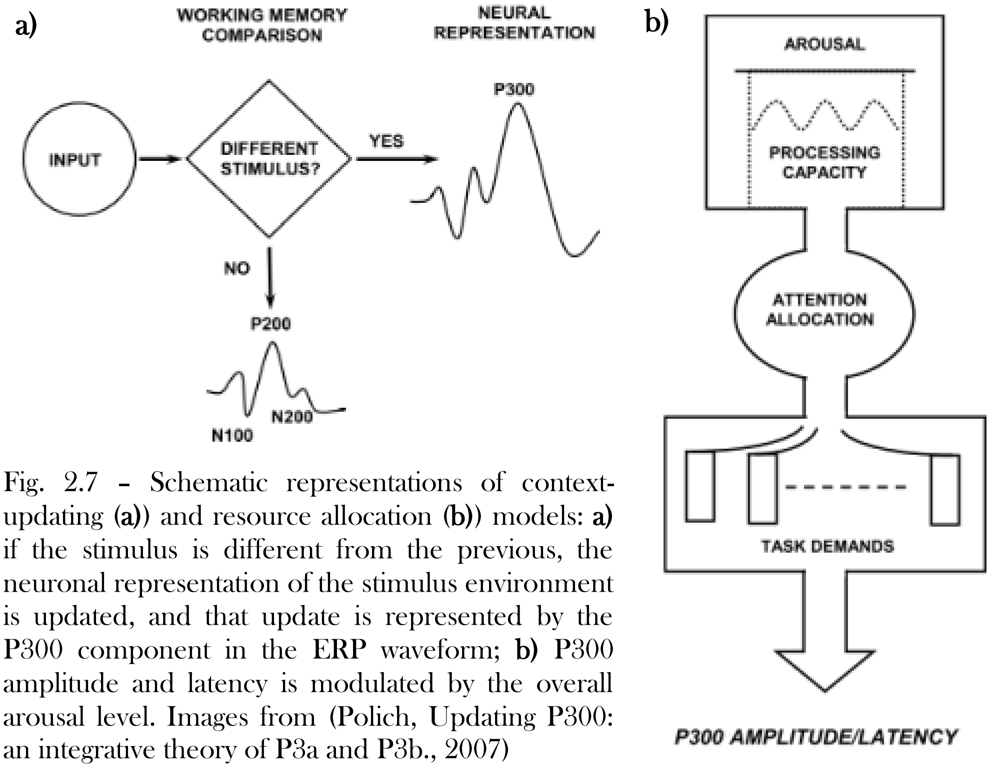


Fig. 2.7 – Schematic representations of context-updating (**a)**) and resource allocation (**b)**) models: **a)** if the stimulus is different from the previous, the neuronal representation of the stimulus environment is updated, and that update is represented by the P300 component in the ERP waveform; **b)** P300 amplitude and latency is modulated by the overall arousal level. Images from (Polich, Updating P300: an integrative theory of P3a and P3b., 2007)

The P300 latency is believed to be an index of classification speed. Neuropsychological tests correlated the P300 latency and subjects' cognitive capability to allocate attentional resources to the target stimulus (Houlihan, Stelmack, & Campbell, 1998; Pelosi, Holly, Slade, Hayward, Barrett, & Blumhardt, 1992; Reinvang, 1999) *in* (Polich, Updating P300: an integrative theory of P3a and P3b., 2007). The time required to detect and evaluate a target stimulus is proportional to the P300 latency (Kutas, McCarthy, & Donchin, Augmenting mental chronometry: P300 as a measure of stimulus evaluation time, 1977) *in* (Polich, Updating P300: an integrative theory of P3a and P3b., 2007). P300 component latency, as the amplitude, is smaller over frontal areas and bigger over parietal areas of the scalp (Mertens & Polich, 1997; Polich, et al., 1997). Therefore the overall level of stimulation influences the speed of subjects' discrimination capability.

In the last decades several experimental findings and neurophysiological results *in* (Polich, Updating P300: an integrative theory of P3a and P3b., 2007) have revealing arguments that support the hypothesis that P300 and its underlying subprocesses could be a result from a rapid neural inhibition of on-going activity to facilitate the transfer of incoming stimulus information from frontal to temporal–parietal areas to refine memory operations (Friedman, Cycowicz, & Gaeta, 2001; Birbaumer & Elbert, 1988; Nieuwenhuis, Aston-Jones, & Cohen, 2005). This theory is reviewed in (Polich, Updating P300: an integrative theory of P3a and P3b., 2007).

Some studies also indicate that P300 generation is affected by dopaminergic activity (Polich & Criado, Neuropsychology and neuropharmacology of P3a nad P3b, 2006) and is also related with the locus coeruleus-norepinephrine system (Nieuwenhuis, Aston-Jones, & Cohen, 2005; Aston-Jones & Cohen, 2005) suggesting a link with reward and arousal systems.

2.3 Brain-Computer-Interfaces

P300 is affected by various biological factors, environmental variables, and individual differences: circadian cycles (Deldin, Duncan, & Miller, 1994), exercise and fatigue (Yagi, Coburn, Estes, & Arruda, 1999), drugs, age, IQ, handedness, gender as well as personality variables (Polich & Kok, Cognitive and biological determinants of P300: an integrative review., 1995).

Nevertheless results clearly suggest that P300 is generated by oddball sequences in about every subject (Fabiani, Gratton, Karis, & Donchin, 1987). This consistency of P300 makes it a good corridor to assess to mental processes and its use in BCI applications (see definition below). Beyond P300, other cerebral features can be used also in BCI: induced changes of oscillatory activity, slow cortical potentials, and steady-state evoked potentials.

Using the definition proposed in (Wolpaw, Birbaumer, McFarland, Pfurtscheller, & Vaughan, 2002), a BCI is "a system for controlling a device e.g. computer, wheelchair or a neuroprothesis by human intention which does not depend on the brain's normal output pathways of peripheral nerves and muscles".

P300-based BCI's works using EEG electrodes placed outside (non-invasive) or inside (invasive) the scalp. The data acquired is then analysed online (real time) in order to detect the P300 features, and thus classify the focus of the attention allocation of the subjects. This way it is possible to know what the subject is "thinking" about at that exact moment.

The major objective of BCIs is to provide a way of having access to competences to individuals that lost or never had basic skills. For example enable patients with locked-in syndrome to communicate with the outside world again. Such people could use a BCI to efficiently use a computer or other devices.

There are three main visual paradigms used for this purpose. The most common paradigm is the <u>row/column paradigm</u> (RC) (Fig. 2.8) (Farwell & Donchin, 1988) where the rows and columns of a visual matrix are flashed in a random order while the user directs his attention to the desired selection within the matrix.

MESSAGE

BRAIN

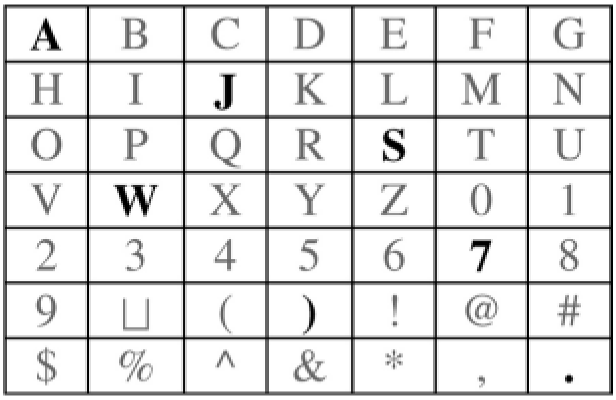
Choose one letter or command

A	G	M	S	Y	*
B	H	N	T	Z	*
C	I	O	U	*	TALK
D	J	P	V	FLN	SPAC
E	K	Q	W	*	BKSP
F	L	R	X	SPL	QUIT

Fig. 2.8 – Representation of the original row/column paradigm proposed by Farwell and Donchin. The rows and the columns of the matrix are flashed alternately and randomly. (Farwell & Donchin, 1988)

Another paradigm is the single cell paradigm (SC). In this paradigm the various stimulus are distributed on the screen and each of them simply flashes alternately. This paradigm elicits larger P300 components (Guan, Thulasidas, & Wu, 2004) but its accuracy and speed of communication tends to be lower (Guger, et al., 2009).

The other paradigm is the checkerboard paradigm (CB) (Townsend, et al., 2010), where "groups of matrix elements are flashed in a quasi-random pattern that controls for directly adjacent flashes and double flashes (i.e. two consecutive flashes of one single element within the matrix)." (Mak, et al., 2011). Studies with CB paradigm reported a better classification performance when compared with the RC presentation (Townsend, et al., 2010).



A	B	C	D	E	F	G
H	I	**J**	K	L	M	N
O	P	Q	R	**S**	T	U
V	**W**	X	Y	Z	0	1
2	3	4	5	6	**7**	8
9	⊔	(	**)**	!	@	#
$	%	^	&	*	,	**.**

Fig. 2.9 – Checkerboard paradigm example. Groups of elements flash instead of a row or a column. It diminishes the confusion and misclassification that may be created by the adjacency of elements of the rows or columns.

The integration of 3D stimuli in oddball paradigms is something poorly studied, because as it stands now, there has only been one known study that has integrated this kind of stimuli. See in References: (Donnerer & Steed, 2010). Michael and Anthony used a virtual reality environment with thirty-six spheres, and flashed them at a time in colour. The participants were asked to count the number of flashes on each sphere. Their results, although still using very simple environments, had been satisfactorily which encourages further study of this issue.

The real-time classification of P300 is a true challenge in BCIs. Several mathematical strategies are used: wavelet feature extraction (Salvaris & F., 2009; Donchin, Spencer, & Wijesinghe, The mental prosthesis: assessing the speed of a p300-based brain-computer interface, 2000); Principal Component Analysis (Lenhardt, Kaper, & Ritter, 2008); Step-Wise Linear Discriminant Analysis (SWLDA) (Selim, Wahed, & Kadah, 2009); Bayesian statistical classifiers (Pires, Castelo-Branco, & Urbano, Visual P300-based BCI to steer a Wheelchair: a Bayesian Approach, 2008); Neural Networks (Cecotti & Gräser, 2011), and Support Vector Machine (SVM) classifiers (Selim, Wahed, & Kadah, 2009).

Having, in the IBILI work group, an EEG-neurofeedback oddball paradigm already validated based on the real time classification of P300 EEG signals to identify the focus of attention of individuals (Pires, Castelo-Branco, & Urbano, Visual P300-based BCI to steer a Wheelchair: a Bayesian Approach, 2008; Pires, Nunes, & Castelo-Branco, Brain computer interface approaches to control mobile robotic devices, 2008), this can provide a solid basis to validate the paradigms that are intended to be created.

Chapter 3

Clinical Context

3.1 Autism Spectrum Disorders

Autism Spectrum Disorders (ASD): Autistic Disorder, Asperger's Syndrome, and Pervasive Developmental Disorder – Not Otherwise Specified, are a permanent heterogeneous group of neurodevelopmental syndromes. ASD are characterized by deficits in social interaction, deficits in communication and restricted/stereotyped pattern of behaviour, interests and activities (American Psychiatric Association, 2000). Symptoms usually appear before the age of 3.

Besides these impairments, there are other areas of clinical dysfunction, like intellectual disability, epilepsy, and sensory abnormalities, observed in significant proportion to individuals diagnosed with ASD.

This group of disorders has a significant economic and social impact due to their high prevalence, morbidity and impacts on daily family life (Ruble, 2001). It is estimated that prevalence rates are 36.4 per ten thousand children (Fombonne, 2007). It has been verified that for each girl there are 4.3 reported cases of ASD in boys (Fombonne, 2007). The prevalence estimates in Portugal round out at about ten cases per thousand children (Oliveira, et al., 2007).

3.2 Social Attention in Autism

Selective attention is a set of processes that allows stimulus selection and coordination of performance of multiple tasks (Castelo-Branco, Kozak, Formisano, Teixeira, Xavier, & Goebel, 2009; Luck & Vecera, 2002). Attentional processes are required because the environment contains more information than can be processed and comprehended at any given time. They may protect an organism from information overload and are selective in that they allow processing of some stimuli while disregarding others.

Visual cues are the primary sources of social recognition in humans and it's generally accepted that normal young children can understand that someone is thinking about something from gaze-direction (Baron-Cohen & Cross, Reading the eyes: evidence for the role of perception in the development of a theory of mind, 1992), and that gaze-direction also allows them to guess which of several objects a person wants, or might be interested in, or might be referring to (this is called the joint-attention) (Baldwin, 1991; Bruner, 1983; Butterworth & Jarrett, 1991). However, several clinical research studies proved that autistic children cannot interpret such information from gaze-direction (Baron-Cohen S. , Perceptual role-taking and protodeclarative pointing in autism., 1989; Baron-Cohen, Baldwin, & Crowson, Do children with autism use the Speaker's Direction of Gaze (SDG) strategy to crack the code of language?, 1997; Baron-Cohen, Campbell, Karmiloff-Smith, Grant, & Walker, 1995) *in* (Baron-Cohen S. , 2001). ASD subjects demonstrated also a lack of attentional modulation especially evident for social stimuli (Bird, Catmur, Silani, Frit, & Frith, 2006). Other clinical research studies suggest that autistic patients may have deficits in the cognitive processing of social stimuli: impairments in visual memory for faces (Boucher & Lewis, 1992) and in exogenous orienting of attention to social cues (Leekam & Moore, 2001); atypical brain responses to facial expressions of emotion (Dawson, Webb, Carver, Panagiotides, & McPartland, 2004); and reduced salience of social stimuli/preference for non-social stimuli (Dawson, Abbott, Osterling, Munson, Estes, & Liaw, 2004; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Swettenham, Baron-Cohen, Charman, Cox, & Baird, 1998).

Despite the good quantity of arguments about the impairments of social attention in ASD, little is known about the neural correlates of attention to physical stimuli of variable social meaning and the effects of autism attention deficits in the modulation of P300.

Chapter 4

Study Methodologies

This chapter presents the several steps taken to achieve the proposed objectives; from the planning of experiments, through the solving of the challenges that have emerged, until the final setup of data acquisition.

4.1 Planning

To achieve the proposed objectives, five different oddball paradigms were thought. These paradigms would have variable social complexity, as well as variable interaction complexity. The intention is to optimize the ecological representation of the social content approximating it to reality as close as possible.

Healthy individuals would be recruited to test the validity of the paradigms by recording their electric brain activity. After the validity of paradigms is proven, control subjects will be selected from the typical developing population matched for chronological age, gender and Developmental Quotient/Intelligence Quotient with the autism spectrum disorders group.

The experiment setup would include EEG acquisition and stimuli presentation systems.

The EEG analysis will be done offline using the typical techniques and tools, and also using BCI classification tools.

4.2 Technical issues

Thinking carefully about the solutions to finalize the defined plan, it was decided to create an integrative way to present all the stimuli with no need to change the experiment setup. By doing this, the testing would be more flexible and appealing for both experimenter and participant.

A simple application was developed to allow the user to choose the paradigms, define its parameters, and test the paradigms.

4.2.1 Technologies

The EEG acquisition system is from BrainProducts:

- Electrodes: actiCap - a cap with active electrodes based on high-quality Ag/AgCl sensors with a new type of integrated noise subtraction circuits delivering even lower noise levels than the ”normal” active electrodes achieves. Impedances are measured and displayed at each electrode by using LEDs (Fig. 4.1).

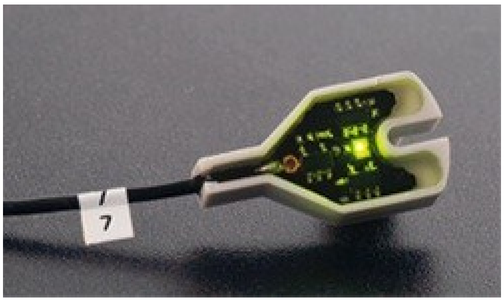


Fig. 4.1 – Active electrode from the BrainProducts’ actiCap (Brain Products GmbH, 2009).

- Amplifier: V-amp - a sixteen channel amplifier with the ability of record several types of signals, such as EEG, EOG, ECG, EMG and the full range of evoked potentials, including brain stem potentials (Fig. 4.2).

Fig. 4.2 - V-amp amplifier from BrainProducts (Brain Products GmbH, 2009).

- Recorder (Software): BrainVision Recorder for V-Amp - A recorder software package.

There are several EEG acquisition systems on the market. The choice of these products of BrainProducts is due to its good results in BCI experiments.

The paradigms development is made using the Vizard Virtual Reality Toolkit, from WorldViz. This toolkit provides an interface for virtual reality environments development in Python. The main reason for the choice of this tool is that it has special complex models of human body, in a special format that allows controlling the each part of the body and animating it. This immediately simplifies the introduction of social meaning in the paradigms, and makes that content as close as possible to the reality.

4.2.2 Stimuli integration

4.2.2.1 Application Objectives

The objectives of the application are to give the user, the researcher in this case, a simplified stimulation system integrating the various stimuli and allowing the unrestrained adjustment of stimuli parameters.

4.2.2.2 Application Requisites

Analysis of the application requisites is detailed in Appendix A. Fig. 4.3 shows the use case diagram for this application.

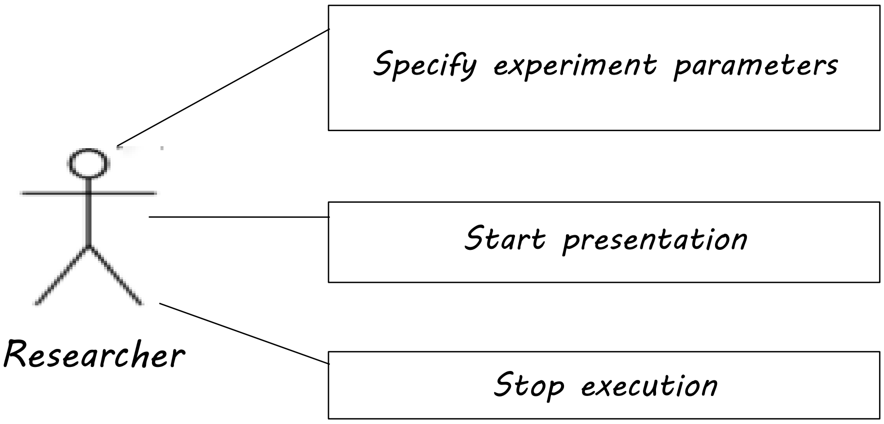


Fig. 4.3 – Use case diagram. The researcher has the possibility to choose the test parameters. At any moment he can start the stimuli presentation. If he wants to stop the experiment it is possible at any moment.

Having the possibility to integrate all the stimuli and to freely adjust their parameters allows the experiment to be more efficient.

The parameters of the experiment are the parameters that specify the paradigms structure. They are **ISI**, **Flash Duration**, **Number of Events**, **Number of Targets, Number of Blocks** and **Target Figure**. The influence of these parameters will be addressed latter in this chapter.

4.2.3 Local Synchronism

It was planned to divide a paradigm's series of events by sending triggers to data acquisition software, as usually is done in ERP acquisition (Luck S. J., 2005). A trigger in this context is a logic electrical signal, 1 or 0, used to initiate a synchronized recording of data.

However, there is another problem that emerges afterwards. We have no definite verification that the Vizard system can show the event on screen and send the trigger simultaneously. Since we are dealing with brain signals in the order of the milliseconds, it is crucial to verify that the presentation of events and the trigger data are saved as precisely as possible in order to avoid a P300 misclassification by the BCI algorithms. If there is a lap between these two variables, the lap must be constant.

4.2.3.1 Synchronism Test Methodology

One photodiode (SM1PD1A Mounted Silicon-Photodiode[1]; See (Thorlabs, 2006) for technical specificities) was placed on the center of the stimuli display that was used in this work (HP L1710 17-inch LCD Monitor; Hewlett-Packard Development Company, L.P.; frame rate of 60 Hz; see (HP, 2010) for technical specifications) and connected by coaxial cable, an electrical cable constituted by a conductor a tubular insulating layer and a tubular conducting shield, to a channel of an oscilloscope (TDS2024C Oscilloscope; TEKTRONIX, INC; see (TEKTRONIX, INC, 2008) for technical specifications).

Using Vizard, a testing stimulus was created, consisting in the change of the screen color from white to black and then from black to white successively every 1.6 seconds (Fig. 4.4). For each color change, a trigger was sent through the parallel port signaling it.

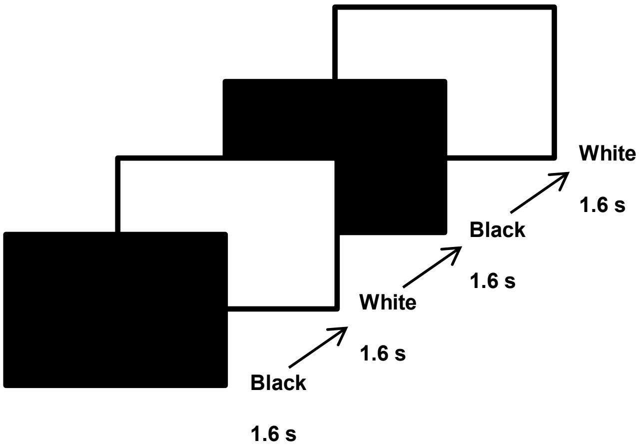


Fig. 4.4 – Test stimulus used to test the synchronism. The screen colour changes every 1.6 seconds, and that colour change is signalled by sending a trigger to the parallel

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[1] Acknowledgement to BlueWorks - Medical Expert Diagnosis, Lda.

A photodiode is an electrical component capable of converting light into electric energy. These components are called photodetectors. The idea was to detect the color change of the screen and see the elapsed time between the trigger signal and the change of color.

Ideally, the instant that the trigger is sent would be at the same time that the stimulus appears on the screen.

To detect the trigger signal, another channel of the oscilloscope was connected by a coaxial cable to a pin of the parallel port corresponding to the bit position of the trigger value.

A parallel port is a computer physical interface used to send several data signals simultaneously over several parallel channels. It is used to connect various peripherals. The most common parallel ports have 25 pins, each one with a specific function in the communications. Pins 2 through 9 are used to transmit data. If there is no charge in a pin, it means that this bit has a value of 0. A charge of 5 volts in a pin means that the value of this bit is 1.

Thus, attributing the decimal value of 2 to the trigger sent by the test stimulus, it means the charged pin is the third because 2 (decimal) = 00000010 (binary). So the cable must be connected to the third pin to detect the sending of the trigger. Fig. 4.5 shows the setup of this experiment.

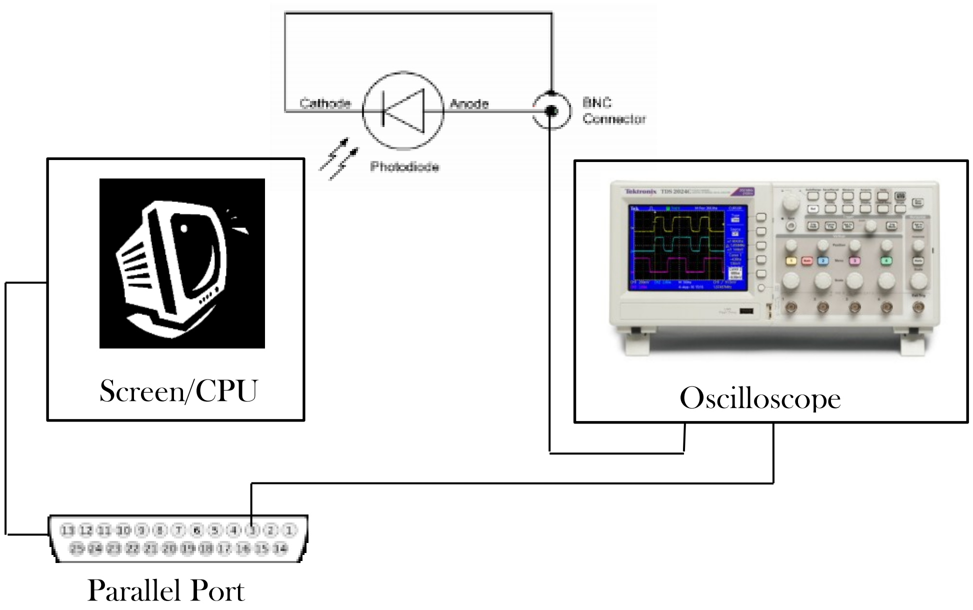

Fig. 4.5 – Synchronism testing setup. The oscilloscope saves the data received from the photodiode and the parallel port, and allows comparing the time distances between those two events.

Whenever the colour of the screen changes to black a trigger is sent with the duration time of 1.6 seconds, the time between the color changes (see Fig. 4.6).

Analyzing the data, the instant defined to be the trigger sending instant was the time point immediately before the abrupt variation of channel voltage that is verified.

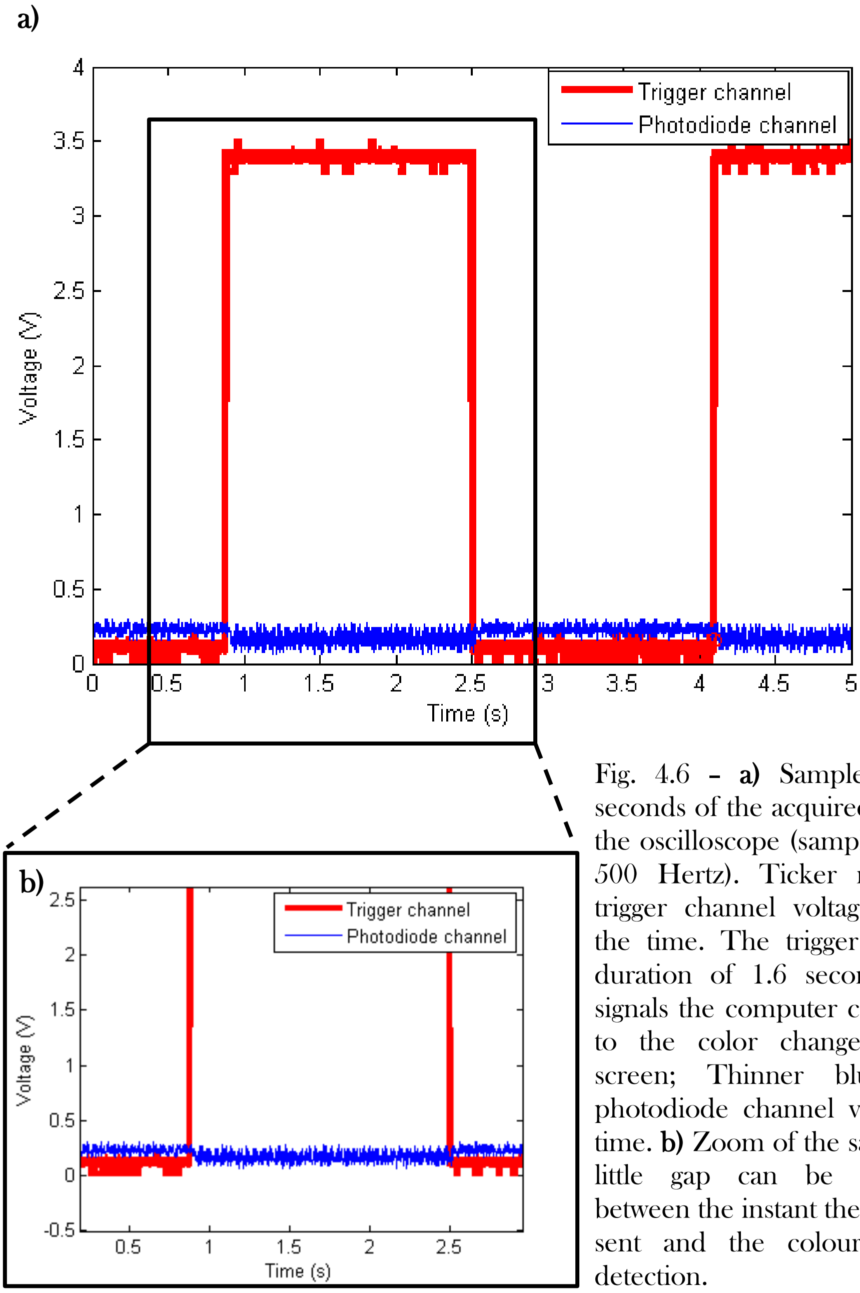

Fig. 4.6 – **a)** Sample of five seconds of the acquired data by the oscilloscope (sample rate of 500 Hertz). Ticker red line: trigger channel voltage during the time. The trigger has the duration of 1.6 seconds, and signals the computer command to the color change of the screen; Thinner blue line: photodiode channel voltage in time. **b)** Zoom of the sample. A little gap can be observed between the instant the trigger is sent and the colour change detection.

To define the instant when the colour of the screen change is detected, the photodiode channel needed to be analyzed carefully (see Fig. 4.7).

The plot showed that in the periods when the screen is white the channel voltage was never inferior to a certain voltage level. This fact was used to specify the instant of the color change detection. Using MatLab (The MathWorks, Inc.), a high-level language and interactive environment that eases the completing of computationally intensive tasks, a threshold level, result of the minimums average in the white screen period, was defined. Under this level, the points are considered being part of the black screen period. This means the first instant under this level can be considered the instant the screen changes its colour.

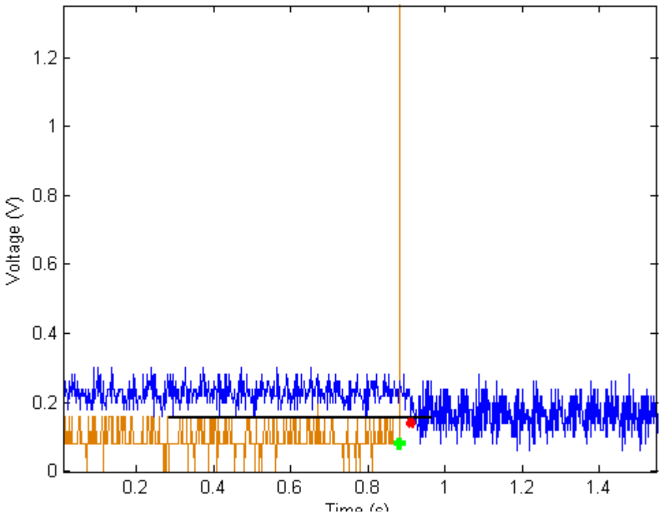

Fig. 4.7 – Zoomed section of signals plot saved by the oscilloscope (sample rate of 500 Hz). Brown line is the trigger channel voltage in time. Gold line is the photodiode channel voltage in time. In red is marked the first point below the threshold level of the black screen period. The black line is the restraining level defined. The red dot marks the time point relative to the delivery of the stimulus after the sending of the trigger(green dot).

The time difference between these instants tells about the lag of the trigger sending, thus the command to change color by computer, and the occurrence of the color changes.

After 162 screen color flashes from white to black, the average time gap between the trigger sending and the color change detection was 0.028 seconds (Standard Error of the Mean (SEM): 0.0006). Fig. 4.8 shows the histogram of gaps' number of occurrences.

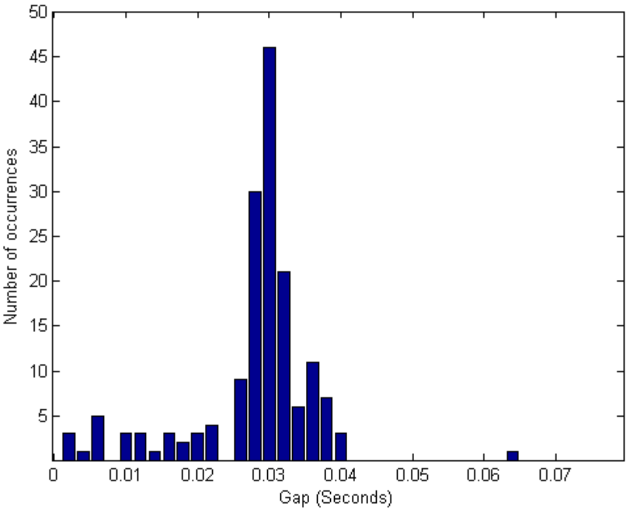

Fig. 4.8 – Histogram of number of occurrences of the time gaps detected. N=162. Average=0.028 seconds, SEM=0.0006.

As referred, the IBILI group has been developing rehabilitation tools for autism, which are intended to be portable. Therefore, wondering if the same behaviour can be found in a laptop, the same test was done in the laptop used for the tests of the application in question (see Fig. 4.9). After 42 screen color flashes, the average time gap between the trigger sending and the color change detection in the laptop was 0.044 seconds (SEM: 0.0006 seconds).

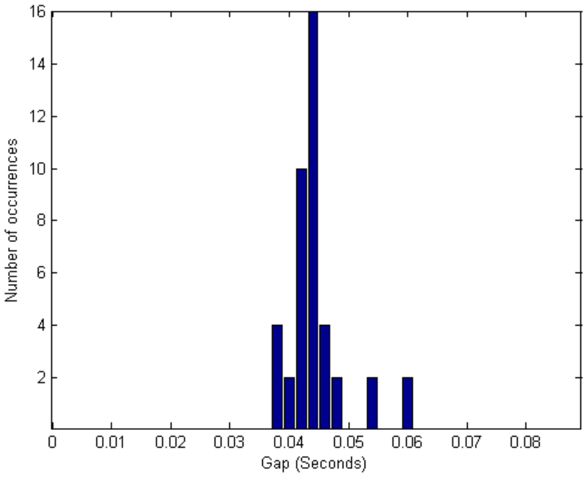

Fig. 4.9 – Histogram of number of occurrences of the time gaps detected in the laptop test. N=42. Average= 0.044 seconds, SEM=0.0008.

4.2.3.2 Conclusions about Synchronism

The results suggest that in the used computer and screen the average gap between the delivery of the command and its effective execution in the screen is around 28 milliseconds. The resulting average value makes believe that the Vizard waits, at least one refresh rate to concretize the command of the script on the screen. As the photodiode was placed on the center of the screen, a little more than an half of the time of the refresh rate is needed to detect the color change of the screen. The small SEM makes believe that this gap is practically constant. The existence of this error is majorly attributed to the possible lack of precision of the algorithm created to detect the exact instants of the moments of each event, due to the relatively low signal to noise level of the photodiode device

In the laptop test the higher average time of the gap (44 milliseconds) can be explained by the use of a parallel port adapter, as the laptop does not have parallel port. This suggests that this adapter makes the sending of the trigger faster than the delivery of the stimulus. The small value of the SEM indicates again that this gap is constant in every command.

These results were important in setting up the EEG experiment. It advises to expect a small delay of the brain responses to the stimuli after the corresponding trigger in the EEG recorded data and its classification.

4.3 The Stimuli

Section 0 explains the option to use Vizard Virtual Reality Toolkit as development tool. It provides an interface for virtual reality environments developed in Python. This interface provides an empty 3D ‘world’ which can be filled with several objects that in turn, can be animated. The creation of all the stimuli followed this line of reasoning.

To ease their individual references in this document, consider the following names:

- 'Balls';
- 'Face';
- 'Eyes';
- 'Animated Avatar';
- '4 Avatars'.

4.3.1 'Balls' Paradigm

This name is explained by the presence of two spheric objects ("balls") as target of attention. Fig. 4.10 shows an example of the 'Balls' paradigm.

A 3D model of a ball from Vizard is added twice as an object. These two balls are placed in the virtual world at an apparent distance of four meters relative to the position of the observer. They are at a distance of 0.5 meters from each other, and the midpoint of the distance between them is placed at the origin coordinates of the virtual world (0,0,0).

Consider these two different states:

- **Non-Target** – The vertical-axis of the balls coordinate system at original configuration;
- **Target** – The vertical-axis of the balls coordinate system is rotated positively thirty two degrees to the right. This means the observer sees the balls rotated to his left.

The functioning of the paradigm consists in consecutive flashes of the two balls, assuming one of the referred states, and spaced by the time defined in the **ISI** parameter. The balls continue to be visible during the time specified in the **Flash Duration** parameter. After that time, the balls disappear.

The number of times each one of the states appears is defined by the **Number of Events** and **Number of Targets** parameters. The **Number of Targets** parameter specifies how many times the **Target** state flashes among the **Non-Target** states. The combined number of flashes of the two states is equal to the **Number of Events**.

The order of appearance of the states is random, and the **Target** state never appears two times consecutively.

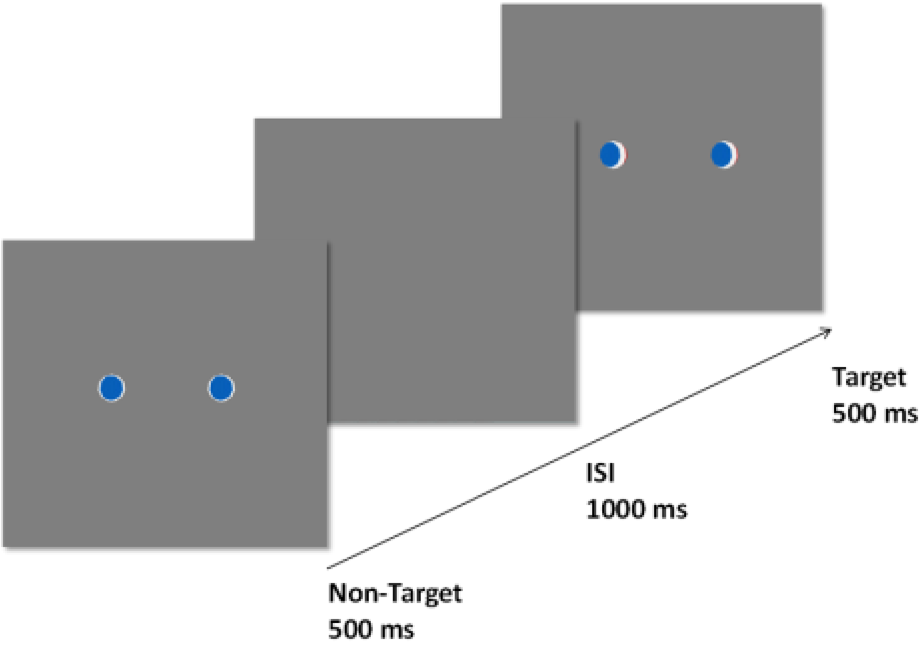

Fig. 4.10 - 'Balls' paradigm representation. The **Target** and **Non-Target** states appear on screen, alternately and randomly, during 500 milliseconds, in spaced intervals of one second. The subjects were asked to "Pay attention to the slightly rotated balls".

The **Number of Events** flashes are repeated the number of times defined in the **Number of Blocks** parameter.

For this paradigm, the chosen time parameters were:

- **ISI** – 1000 milliseconds. The balls appear every 1000 milliseconds.
- **Flash Duration** – 500 milliseconds. The balls remain visible during this time.
- **Number of Events** – 50 flashes. In total, the balls appear 50 times.

- **Number of Targets** – 10 Targets. Among all the ball flashes, the balls appear 10 times in the Target state.
- **Number of Blocks** – 10 Blocks. The sequence of 50 ball flashes is repeated 10 times.

These choices will be explained later in section 4.3.6.

4.3.1.1 'Balls' Paradigm Task Definition

Here, the participants were instructed to simply attend to the balls appearance and pay special attention to their **Target** state. They were told to count how many times the ball appeared rotated.

This simple paradigm represents movement through flashes. There is no significant high level interpretation, but the similarity of the ball movement to the natural movement of eyes can nevertheless introduce a subliminal relation to a social interaction. This low level interpretation is needed to validate the P300 modulation to simple oddball tasks using these Vizard 3D models.

4.3.2 'Face' Paradigm

In order to introduce more obvious social content for this paradigm, the balls from the previous paradigm were replaced by a 3D head model from Vizard. In the virtual environment the head face is placed at an apparent distance of 0.8 meters from the observer, and can assume these two different states:

- **Non-Target** – Face and eyes facing the observer point of view. The observer sees the head model looking to him;
- **Target** – Face and eyes facing a point 0.4 meters to the left of the observer. The head is slightly rotated and facing in a different direction.

The paradigm construction was similar to the previous, with the parameters **ISI**, **Flash Duration**, **Number of Events**, **Number of Targets** and **Number of Blocks** defining its operation in the same way. Fig. 4.11 represents this paradigm.

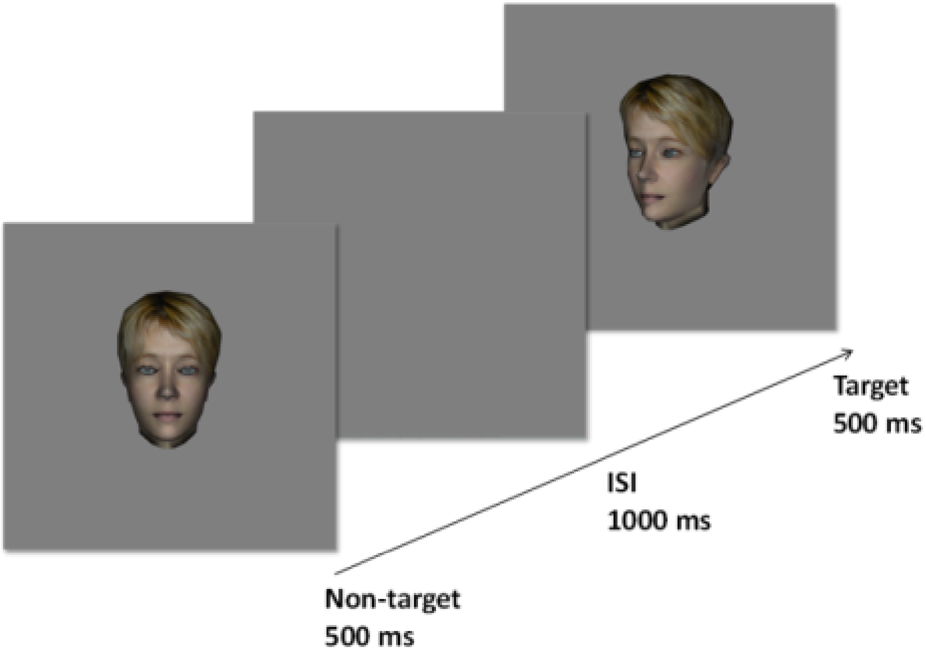

Fig. 4.11 – 'Face' paradigm representation. The **Target** and **Non-Target** states appear on screen, alternately and randomly, during 500 milliseconds in spaced intervals of one second. It is asked that volunteers direct their attention to the face anytime said face rotates.

Parameters were defined similarly to the 'Balls' paradigm:

- **ISI** – 1000 milliseconds. The head flashes every 1000 milliseconds after the previous;
- **Flash Duration –** 500 milliseconds. The head remains visible during this time;
- **Number of Events –** 50 flashes. In total, the 3D model appears 50 times;
- **Number of Targets** – 10 Targets. Among all the head flashes, it appears 10 times as described in Target state;
- **Number of Blocks** – 10 Blocks. The sequence of 50 head flashes is repeated 10 times.

These choices will be analyzed later in section 4.3.6.

4.3.2.1 'Face' Paradigm Task Definition

This paradigm introduces a higher level interpretation. The task formulation is purposefully planned to immerse the subject in an evident social context as it influences to direct his/her attention to a relevant social gesture. This social gesture, a simple turn of the face, is an evident indication of attention redirection.

The volunteers were instructed to pay attention to the head model, and count how many times the face appears looking to another direction. By doing this is intended so that the subject implicitly uses attentional mechanisms for social orienting.

4.3.3 'Eyes' Paradigm

The 'Eyes' paradigm in Fig. 4.12 was used in the same manner as the previously described head model, but the states have a different configuration:

- **Non-Target** – Face and eyes facing the observer point of view. The observer sees the head model looking to him;
- **Target** – Face facing the observer, but the stare is facing a point 0.4 meters to the left of the observer. The observer sees the face facing him, but the stare is deviated to his left.

All the parameters have the same values, thus structuring the paradigm in the same way as the others before:

- **ITI** – 1000 milliseconds. The head model appears every 1000 milliseconds after the previous;
- **Flash Duration** – 500 milliseconds. The 3D model remain visible during this time;
- **Number of Events** – 50 flashes. In total, the head appear 50 times;
- **Number of Targets** – 10 Targets. Among all the model flashes, the head appear 10 times in the Target state;

- **Number of Blocks** – 10 Blocks. The sequence of 50 head flashes is repeated 10 times.

These choices will be analyzed in section 4.3.6.

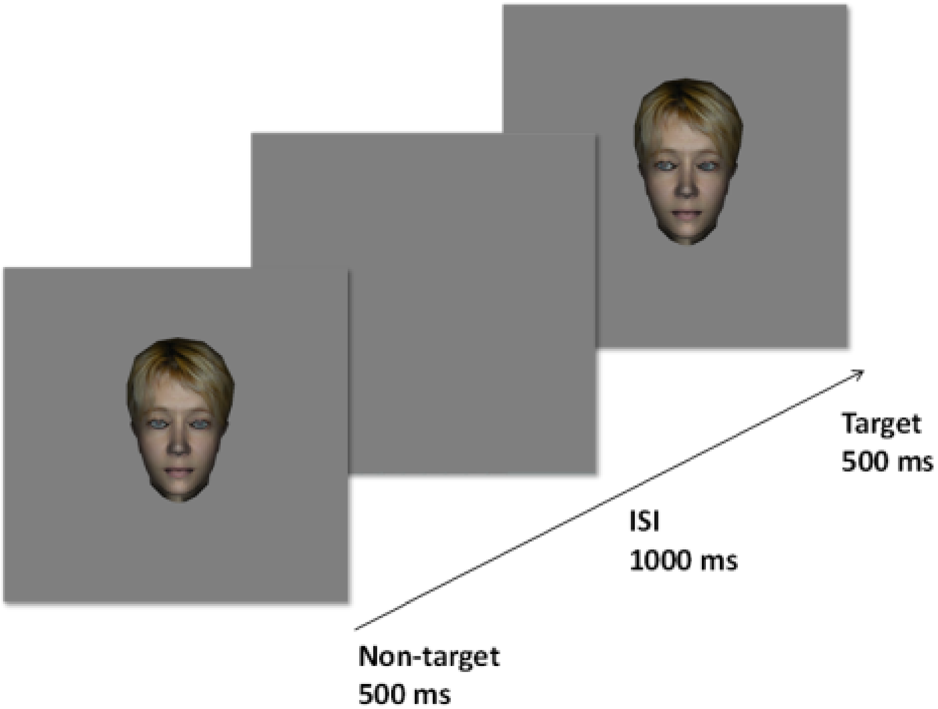

Fig. 4.12 – 'Eyes' paradigm representation. The **Target** and **Non-Target** states appear on screen, alternately and randomly, during 500 milliseconds, in spaced intervals of one second. It is asked that volunteers direct their attention to the face anytime there is a change in the direction of the eyes.

4.3.3.1 'Eyes' Paradigm Task Definition

Just as it is done in the 'Face' paradigm, it is intended to immerse the volunteer in a social context. Here, the level of interpretation is slightly more complex because the subjects are instructed to direct their attention to the gaze. They were told to count the times the 'person' appears with a deviated gaze. In a social context this is a less salient stimulus and could become more difficult to detect for some subjects.

4.3.4 ‘Animated Avatar’ Paradigm

The chosen name for this paradigm explains its structure. The focus of attention is now, a complete 3D Avatar model from Vizard which was animated with natural movements, and objectively arranged to give ‘oddball’ proprieties to the paradigm.

Avatar position in the virtual world is 2.35 meters relative to observer position, and the observer field view is defined so he can only see its body above the heart position, as shown in Fig. 4.13.

Rather than, as in typical oddball paradigms where the stimuli are flashes, in the next paradigms the stimuli are continuous animations. Some more frequent, and others less frequent to where subjects are instructed to pay closer attention.

Generally speaking, this paradigm works in the same way as the others. The main difference is that the object to which the attention is directed never disappears from the screen. The observer has a continuous visual contact with the stimulus, and directs his attention to a specified animation.

The avatar animations consist of:

- **Non-Target** – The head of the avatar turns 30 degrees to the right, which means the observer sees the avatar moving its head to its left;
- **Target** – The head of the avatar turns 30 degrees to the left, which means that the observer sees the avatar moving its head to his right;

As explained before the **Non-Target** animation is more frequent than the **Target**, and the subjects are instructed to direct their attention to the less frequent stimulus, so the oddball effect is safeguarded.

Here, name of parameters are the same, and their use is analogous to the previous. **ISI** defines the time between the animations. The animation duration is specified by the **Flash Duration** parameter. This influences the animation speed. The number of **Target** and **Non-Target** animations occurrences is defined by the **Number of Events** and **Number of Targets** parameters. The **Number of Targets** parameter specifies how many times the **Target** animation is shown among the **Non-Target** animations. The combined number of avatar animations is equal to the **Number of Events.**

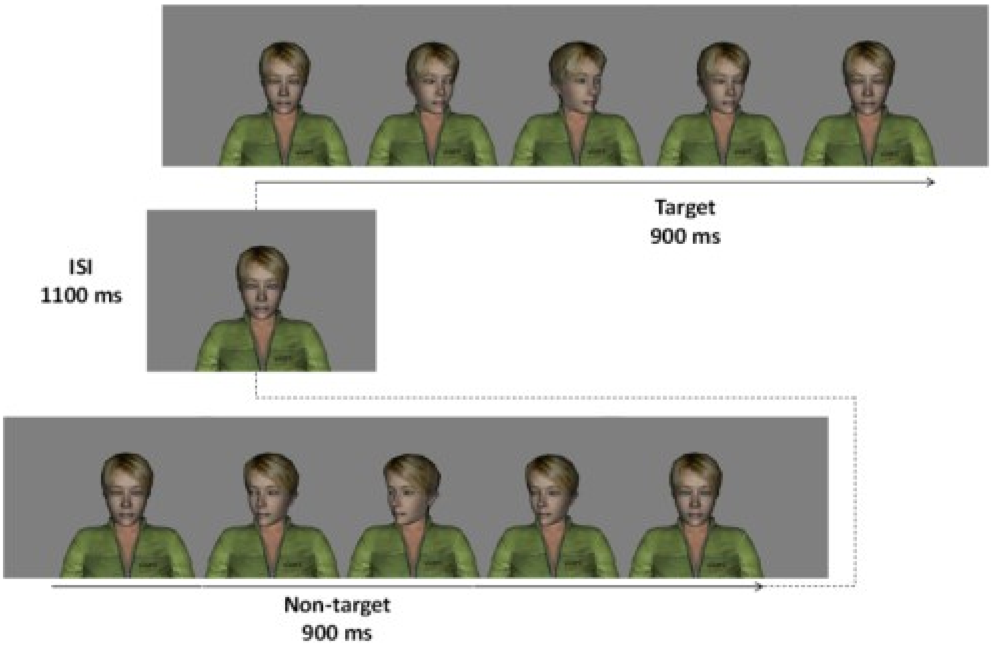

Fig. 4.13 – 'Animated Avatar' paradigm representation. Each 1100 milliseconds the avatar is animated and the subjects are instructed to pay attention to the **Target**

The order of appearance of the two kinds of animation is random, and the **Target** animation never appears two times consecutively.

The **Number of Events** animations are repeated the number of times as defined in **Number of Blocks** parameter.

For the 'Animated Avatar' paradigm, the chosen parameters were:

- **ITI** – 1100 milliseconds. The avatar is animated every 1100 milliseconds after the previous;
- **Flash Duration** – 900 milliseconds. The animation lasts this time. After that, the avatar remains immobile, facing the observer directly until the next animation.

- **Number of Events** – 50 animations. In total, the avatar is animated 50 times.
- **Number of Targets** – 10 targets. Among all the animations, the avatar is animated 10 times as described in **Target** animation.
- **Number of Blocks** – 10 Blocks. The sequence of 50 avatar animations is repeated 10 times.

These choices will be explained later in section 4.3.6.

4.3.4.1 'Animated Avatar' Paradigm Task Definition

Subjects were instructed to count the number of times the 'person' on the screen looks to the right.

The social context is much more realistic than the previous paradigms because it is an animation. It more accurately replicates the natural movement of a human head. The use of attentional mechanisms for social orienting is inevitable.

The introduction of animations as attention focus in oddball stimuli is a quite new concept and it will be interesting to explore the P300 modulation with this type of stimulus.

4.3.5 '4 Avatars' Paradigm

This paradigm simulates a relatively complex social scheme as it presents four different animated avatars. Two are placed in the midline of the observer field view, the closest one at 2.6 meters from the observer, and in a lower position than the avatar furthest away, at 3.1 meters from the point of view of the observer. The other two avatars are placed at a distance of 2.85 meters; each one placed 0.4 meters on each side of the midline and in middle of the screen.

These avatars are animated one at a time and the subject must pay attention to just one. The construction of this paradigm was inspired in the SC paradigm (see section 2.3).

These are the states to consider:

- **Non-Target** – One of three avatars (pre-selected), alternately and randomly, turns the head 30 degrees to the left of the avatar. It means that the observer sees the avatars turning their head to the right;
- **Target** – The target avatar, specified before the paradigm run, turns the head 30 degrees to its left, that is, the observer sees the avatar turning its head to his right.

As previously stated, the **ISI** defines the time between the animations. The animation duration is specified by the **Flash Duration** parameter. It also influences the animation speed. The number of **Target** and **Non-Target** animations occurrences is defined by the **Number of Events** and **Number of Targets** parameters. The **Number of Targets** parameter specifies how many times the **Target** animation is shown among the **Non-Target** animations. The combined number of avatar animations is equal to the **Number of Events**.

The order of avatar animations is random, and the **Target** animation never appears two times consecutively.

As explained before the **Non-Target** animation is more frequent than the **Target**, and the subjects are instructed to direct their attention to the less frequent stimulus, so the oddball effect is ensured. In this case the subject must pay attention to one of the avatars that is turning the head as shown in Fig. 4.14. The choice of target avatar is defined by a new parameter: **TargetF**. This defines which avatar is the target of attention, that is, the avatar which is animated **Number of Targets** times.

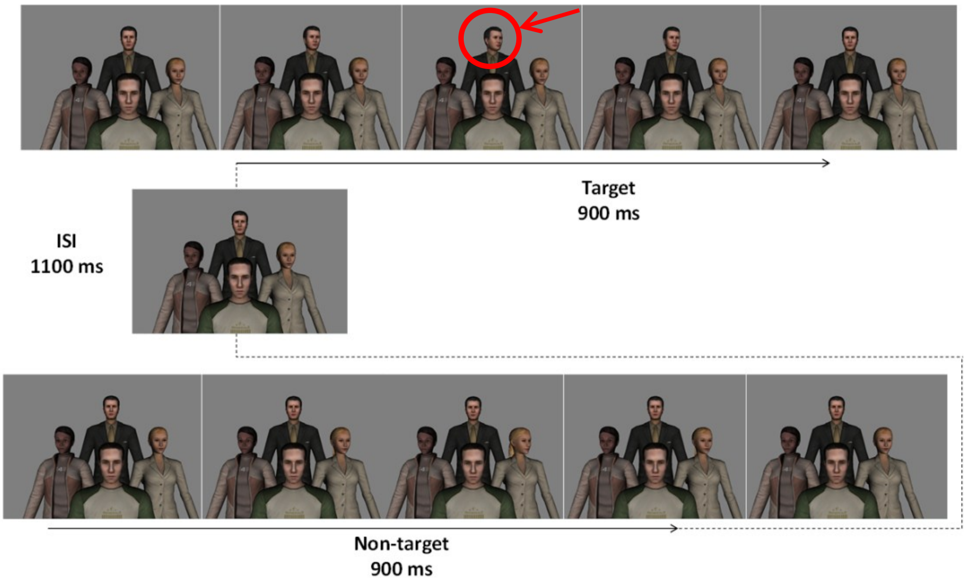

Fig. 4.14 – '4 Avatars' representation. In this example, the target avatar is the top avatar. Each 1100 milliseconds one of the avatar moves its head to the right of the observer, and randomly the target avatar is animated with probability defined by specific parameters. The animation speed is determined by the Flash Duration parameter.

The **Number of Events** animations are repeated the number of times as defined in **Number of Blocks** parameter.

The chosen parameters for this paradigm were the same as the previous one:

- **ITI** – 1100 milliseconds. One of the avatars is animate every 1100 milliseconds;
- **Flash Duration** – 900 milliseconds. The animation lasts this time. After that, all the avatars remain immobile, directly facing the observer, until the next animation.
- **Number of Events** – 50 animations. In total, the avatar animations happen 50 times.
- **Number of Targets** – 10 targets. Among all the animations, the target avatar is animated 10 times as described in **Target** animation.
- **Number of Blocks** – 10 Blocks. The sequence of 50 avatar animations is repeated 10 times.

- **Target Figure** – Top avatar. Determines that the avatar that is animated **Number of Targets** times, is the avatar placed in a higher position on the screen.

These choices will be detailed later in section 4.3.6.

4.3.5.1 '4 Avatars' Task Definition

In human relations, it is common to have multiple and simultaneous contact with many people, so this paradigm replicates these social relationships as realistically as possible, keeping the oddball properties, in order to explore the P300 modulation by this context.

Much like the SC paradigms (Section 2.3), this paradigm requires the subject's ability to direct their attention to just one stimuli present in the screen. In this case the individuals must direct the attention to a person included in the social environment where he is also included (or supposedly should feel included). It is expected the volunteer feels he is facing other people and he is able to direct their attention to one of them by instructing them to count how many times a specific 'person' looks to another place. Therefore, the attentional mechanisms for social orientation must be activated.

4.3.6 Task Definition Overview

As referenced in section 2.2.1.1, the target probability of occurrence, the time between the targets, as well as the time between the stimuli, affects P300 amplitude. An important detail that influenced a lot the construction of the paradigms was the time duration of real social interactions. The **Flash Duration** parameter was carefully chosen so the animation speeds in 'Animated Avatar' and the '4 Avatars' paradigms were not unrealistic.

In the remaining paradigms the chosen times reflect the desire to have some level of coherence between flash and animated paradigms, so their comparison is valid. The animated avatar times are sufficiently long to make top down cognitive modulation of attentional processes occur. The **Flash Duration** needed to be long enough to ensure an interaction between the concerning neural processes.

Having in mind the fact that P300 is sensitive to fatigue and to the subjects level of interest concerning the task (Yagi, Coburn, Estes, & Arruda, 1999; Hillyard, Squires, Bauer, & Lindsay, 1971; Squires, Hillyard, & Lindsay, 1973), the **Numbers of Events** and **Number of Blocks** were decided based on the intention to keep the paradigms as interesting as possible, and at same time to increase the amount of data collected to reduce variability. Splitting the tasks in blocks gives to subjects the chance to take small breaks. This helps the subjects not get tired quickly and to maintain an acceptable level of concentration diminishing the data variability as well.

Parameter **Number of Targets** defines the occurrence probability of the target animations/states. As mentioned before (section 2.2.1.1), this probability influences P300 amplitude: the lower the probability of the target stimulus, the higher the amplitude. The chosen probability of 1/5 to all stimuli is the balanced result between the desire to keep the tasks as motivating as possible and to get good P300 characteristics.

Fig. 4.15 represents a synthesized scheme which helps understand the biggest differences between each developed paradigm.

The ‘Balls’ paradigm is the simplest paradigm in both social complexity and structural complexity amongst oddball paradigms. It does not have an evident social mark and its operation is very similar to the usual flashing oddball paradigms.

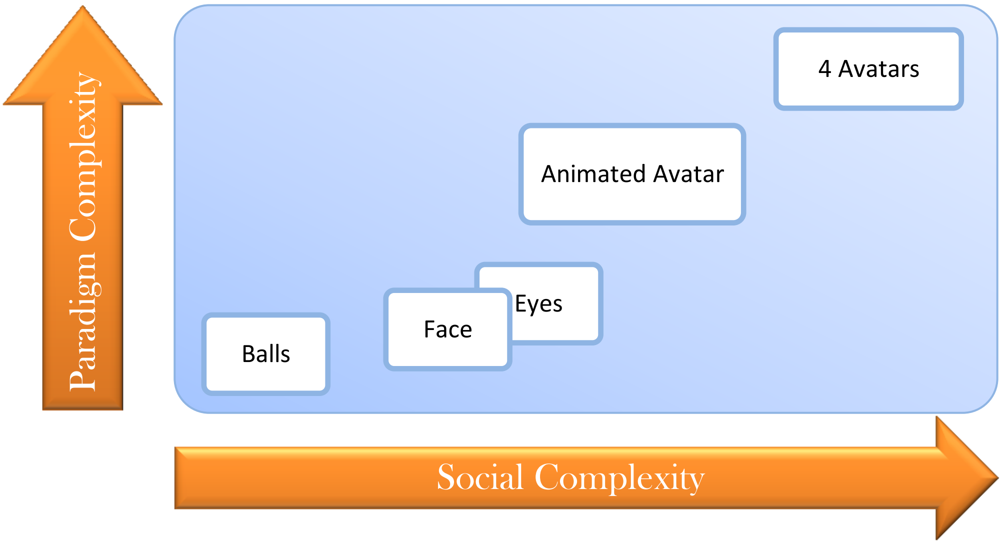

Fig. 4.15 – Scheme representing the overall differences between the created paradigms. Paradigm '4 Avatars' has a higher level of interpretation as well as a higher structural complexity. The 'Balls' paradigm is a 'typical' oddball paradigm introducing subliminal social content.

On the contrary, 'Face' and 'Eyes' paradigms have an evident social content, thus its social complexity is obviously larger. In terms of paradigm complexity this one does not differ too much from the previous one. It still is a normal flashing paradigm. The main distinction is the fact that these two paradigms introduce a high level of interpretation.

The 'Animated Avatar' paradigm introduces a new concept of oddball paradigms, in which the attention targets are animations (instead of flashes). This is the most remarkable distinction. The slightly superior social complexity is due to the fact that the animations turn the social stimuli more realistic.

Finally, the '4 Avatars' paradigm representing a populated environment increases the social complexity substantially as well as the structural complexity of the paradigm. Much like SC paradigms, each stimulus on the screen is eligible to receive attention, and all of them are animated (instead of being flashed), one at a time. The individuals must direct their attention to only one avatar. The presence of several avatars aims to give the subject a feeling of being surrounded by people. This allows investigating the influence of the animation in P300 modulation and also the allocation of social attentional resources in a context similar to real life.

4.4 Data Acquisition

The EEG data acquisition and processing was performed based in the guidelines proposed in (Duncan, et al., 2009).

4.4.1 Participants

To test the validity of the stimuli 17 (N=17) healthy individuals were recruited. They participated voluntary in this study. Six of them were women and eleven were men. Their ages were comprised between 20 and 33 years. The average age is $\overline{X}$= 22.8 (SEM = 0.7). They were naive with respect to paradigms but were informed about the functioning of the experiment.

4.4.2 Experiment Architecture

The recruited individuals were sit about 60 centimetres from the screen (HP L1710 17-inch LCD Monitor; Hewlett-Packard Development Company, L.P.; frame rate of 60 Hz; see (HP, 2010) for technical specifications), and the EEG was recorded with the Brain Products BCI Package (Brain Products GmbH, 2009).

The individuals scalp was previously cleaned and then the actiCAP (Brain Products GmbH, 2009) with 32 possible electrodes locations was placed in their heads. The data was recorded from sixteen active electrodes, placed in Fp1, F3, Fz, F4, FCz, C3, Cz, C4, T8, P7, P3, Pz, P4 P8, O1, and O2 positions according to the international 10-20 standard system.

The choice of these electrodes is explained by the desire to reduce the time of experiment preparation, because is intended to generalize this kind of paradigms for BCI use. Thereby the processing time of the data of too many channels should be considered because it can slow the classification of data. The ground electrode was placed at AFz position and the reference electrode chosen position was the closest position to the earlobe on the cap, T7 position, to ease the experiment preparation. Their impedance was kept lower than 20 K Ω applying the SuperVisc gel (Brain Products GmbH, 2009) (Fig. 4.16).

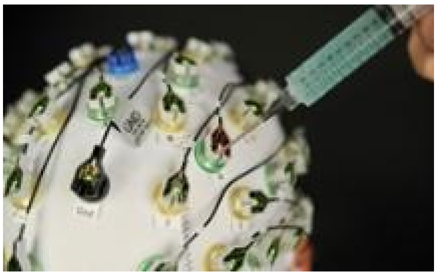

Fig. 4.16 – Placement of gel in the electrodes. If the electrode impedance is above 20 K Ω, the electrode led turns red. If the value of impedance is acceptable (below 15 KΩ), the colour of the led turns green (Brain Products GmbH, 2009).

The Fp1 electrode was used to monitor the eyes movements and blinks. The electrodes were connected directly to the 16 channels V-Amp Amplifier (Brain Products GmbH, 2009) and sampled at 1000 Hz.

EEG data was recorded using the Brain Recorder software (Brain Products GmbH, 2009), while the stimuli were presented to the individuals. For each paradigm the individuals were informed about the respective tasks. Each recording procedure took about 60 minutes to complete. Fig. 4.17 shows a schematic representation of the data acquisition setup.

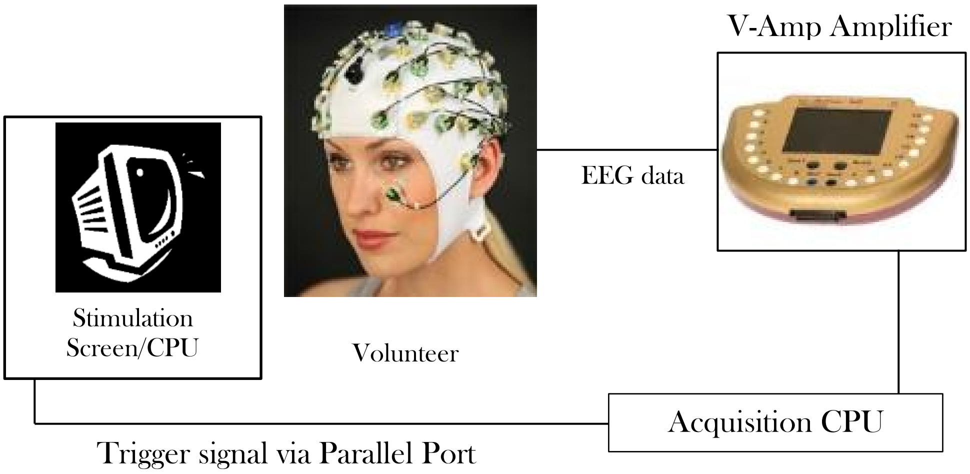

Fig. 4.17 – EEG data acquisition setup. The volunteer attends the screen, and EEG data is amplified by the V-Amp. Trigger signal and EEG data are combined in acquisition computer. Photos from (Brain Products GmbH, 2009)

4.4.3 Data Processing

After storage of the raw data, further processing was performed off-line using Brain Vision Analyzer software (Brain Products GmbH, 2009). The electrode T8 was used to create a new mathematical averaged reference. This strategy is preferred in detriment of physical reference because it has advantages in approximating reference independent potentials.

The data was filtered with low pass filter at 30 Hz (48 dB/octave) and a high pass filter was 0,16 Hz (48 dB/octave).

The data was segmented using the trigger information of each event. The segmentation time was based in the **ISI** of each paradigm. For the ‘Balls’, ‘Eyes’ and ‘Face’ paradigms the segmentation was performed in epochs of 1000 milliseconds with a 100 milliseconds pre-stimulus interval and a 900 milliseconds post-stimulus interval. For ‘Animated Avatar’ and ‘4 Avatar’ paradigms the segmentation was performed in epochs of 1100 milliseconds with a 100 milliseconds pre-stimulus interval and a 1000 ms post-stimulus interval.

Segments with blinks in Fp1 were excluded from further analysis. Artifact rejection was set at 100 microvolts.

Every channel kept more than 36 segments after artifact rejection.

Next, a DC trend correction was performed in each individual segment using the first 100 milliseconds at segment start and the last 100 milliseconds at segment end. DC trend correction consists in the estimate of the DC drift from all pre-stimulus baselines. A regression model is calculated and then subtracted from all data points (Hennighausen, Heil, & Rösler, 1993).

A baseline correction procedure was done using the first pre-stimulus 100 milliseconds.

An average of segments was then calculated and a conventional P300 analysis was performed. The largest positive peak occurring within 250 - 800 milliseconds that increases in amplitude from frontal to parietal scalp areas was identified as the P300 wave.

Chapter 5

Results

The results will be shown separately accordingly to the stimulus type. Average signal waveforms are shown in the appendix. The statistical tests were performed with the software IBM® SPSS® Statistics 19 (SPPS, Inc.) with significance level set at 0.05 level.

5.1 ‘Balls’ Paradigm

In Table 1 are the average amplitudes and latencies of the P300 Target components and the corresponding amplitude of the Non Target waveforms.

Table 1. P300 amplitudes and latencies of the ‘Balls’ paradigm.

Channels	**Amplitude**		**Latency**
	Non-Target	**Target**	
F3	0.22 (0.41)	3.19 (0.49)	516.76 (61.12)
Fz	0.11 (0.53)	4.03 (0.48)	408.71 (50.88)
F4	-0.09 (0.41)	3.46 (0.45)	418.71 (49.59)
C3	0.02 (0.34)	1.80 (0.27)	522.65 (46.70)
Cz	-0.10 (0.28)	3.27 (0.38)	467.24 (43.63)
C4	-0.38 (0.30)	2.92 (0.29)	490.47 (30.48)
P3	-0.78 (0.35)	3.74 (0.50)	427.29 (22.55)
Pz	-0.52 (0.33)	3.84 (0.47)	475.76 (29.27)
P4	-0.03 (0.36)	4.10 (0.44)	402.47 (20.59)

Note: Amplitude values are in microvolts (SEM). Latencies are in milliseconds (SEM).

It was performed a 3 (Region: frontal, central, parietal) × 3 (Laterality: left, midline, right) × 2 (Stimulus Type: Non-Target, Target) ANOVA with repeated measures.

The Region effects was not significant, F(2, 32) = 1.422, p=0.256.

Main effects of Laterality emerged, F(2, 32) = 4.113, p=0.026. The Region × Laterality interaction was not significant:: F(4,64) = 2.431, p=0.72. The topographical distribution of P300 seemed uniform, but the larger amplitude of P300 in the midline was present, even not very evidently.

As expected, a significant main effect of Stimulus Type emerged, F(1,16) = 161.627, p<0.0001; The waveform amplitudes of P300 to Target stimulus (M=3.372 microvolts) was statistically significantly higher than the amplitudes of the Non-Target wave form (M=-0.172 microvolts).

The non-parametric Friedman test revealed that there is no significant statistical differences between the channels' latencies, $X^2(8)$ = 14,934, p=0.060.

5.2 'Face' Paradigm

In Table 2 are the average amplitudes and latencies of the P300 Target components and the corresponding amplitude of the Non Target waveforms.

It was performed a 3 (Region: frontal, central, parietal) × 3 (Laterality: left, midline, right) × 2 (Stimulus Type: Non-Target, Target) ANOVA with repeated measures.

Main effects of Region emerged, F(2, 32) = 26.782, p<0.0001. P300 peak amplitudes were greatest at parietal sites. The effects of Laterality are not significant, F(2, 32) = 3.140, p=0.57. The Region × Laterality interaction was also significant, F(4, 64) = 4.439, p=0.007, which reinforce the notion that these asymmetries are region dependent.

Table 2. P300 amplitudes and latencies of the ‘Face’ paradigm

Channels	**Amplitude**		**Latency**
	Non-Target	**Target**	
F3	-0.51 (0.51)	1.64 (0.51)	628.65 (52.96)
Fz	-0.40 (0.55)	1.13 (0.47)	628.47 (51.14)
F4	-0.29 (0.57)	1.42 (0.51)	689.88 (42.14)
C3	0.12 (0.64)	0.99 (0.25)	564.00 (43.02)
Cz	0.14 (0.61)	1.20 (0.43)	511.12 (48.18)
C4	-0.22 (0.55)	1.63 (0.32)	490.65 (30.90)
P3	0.57 (0.76)	5.62 (0.74)	363.29 (23.66)
Pz	0.51 (0.67)	4.07 (0.60)	373.76 (21.64)
P4	0.65 (0.72)	6.30 (0.94)	362.35 (22.13)

Note: Amplitude values are in microvolts (SEM). Latencies are in milliseconds (SEM).

A significant main effect of Stimulus Type emerged, F(1,16) = 19.835, p<0.0001; The waveform amplitudes of P300 to Target stimulus (M=2.666 microvolts) was statistically significantly higher than the amplitudes of the Non-Target wave form (M=0.062 microvolts).

The non-parametric Friedman test revealed that there is significant statistical differences between the channels’ latencies, $X^2(8) = 37.024$, p<0.0001.

5.3 ‘Eyes’ Paradigm

In Table 3 are the average amplitudes and latencies of the P300 Target components and the corresponding amplitude of the Non Target waveforms.

Table 3. P300 amplitudes and latencies of the 'Eyes' paradigm.

Channels	**Amplitude**		**Latency**
	Non-Target	Target	
F3	-0.25 (0.59)	1.52 (0.49)	679.18 (41.82)
Fz	-0.25 (0.66)	1.41 (0.46)	637.71 (49.17)
F4	-0.14 (0.64)	1.91 (0.49)	656.47 (48.59)
C3	-0.62 (0.68)	0.85 (0.35)	604.18 (34.31)
Cz	0.24 (0.82)	0.88 (0.37)	615.59 (40.17)
C4	0.11 (0.61)	1.72 (0.19)	563.00 (32.85)
P3	0.49 (0.68)	5.22 (0.67)	404.29 (36.02)
Pz	0.59 (0.66)	3.70 (0.49)	436.35 (33.24)
P4	0.78 (0.81)	5.79 (0.63)	417.35 (33.35)

Note: Amplitude values are in microvolts (SEM). Latencies are in milliseconds (SEM).

It was performed a 3 (Region: frontal, central, parietal) × 3 (Laterality: left, midline, right) × 2 (Stimulus Type: Non-Target, Target) ANOVA with repeated measures.

Main effects of Region and of Laterality emerged, F(2, 32) = 31.627, $p<0.0001$ and F(2, 32) = 6.482, $p=0.004$. P300 responses were greatest at parietal sites and at right sites of the scalp. The Region × Laterality interaction was also significant, F(4, 64) = 3.565, $p=0.007$, supporting the notion that these asymmetries are region dependent (Fig. 5.1).

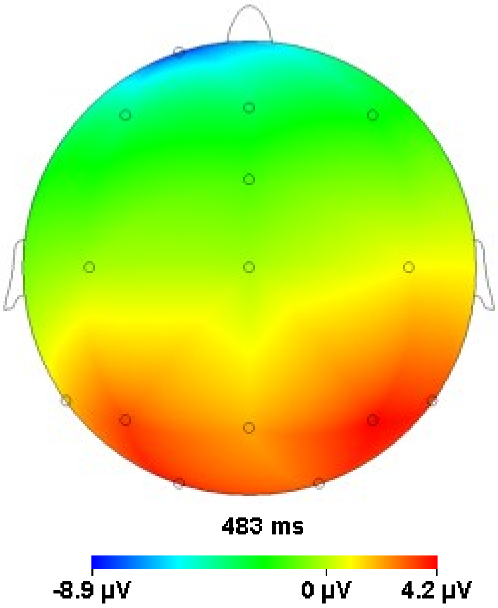

Fig. 5.1 – Topographic distributions of the grand average P300 components (microvolts) from the 'Eyes' paradigm. It's visible the higher amplitude on the parietal areas.

As expected, a significant main effect of Stimulus Type emerged, F(1,16) = 18.383, p=0.001; The waveform amplitudes of P300 to Target stimulus (M=2.556 microvolts) was statistically significantly higher than the amplitudes of the Non-Target wave form (M=0.103 microvolts).

The non-parametric Friedman test revealed that there is significant statistical differences between the channels' latencies, $X^2(8) = 32.221$, $p<0.0001$.

5.4 'Animated Avatar' Paradigm

In Table 4 are the average amplitudes and latencies of the P300 Target components and the corresponding amplitude of the Non Target waveforms.

It was performed a 3 (Region: frontal, central, parietal) × 3 (Laterality: left, midline, right) × 2 (Stimulus Type: Non-Target, Target) ANOVA with repeated measures.

Main effect of Laterality emerged, F(2, 32) = 32.042, $p<0.0001$. P300 peak amplitudes were greatest at midline sites. The Region effects were not significant, F(2, 32) = 2.661, $p=0.109$.

A significant main effect of Stimulus Type emerged, F(1,16) = 65.866, $p<0.0001$; The waveform amplitudes of P300 to Target stimulus (M=3.654 microvolts) was statistically significantly higher than the amplitudes of the Non-Target waveforms (M=0.771 microvolts).

Table 4. P300 amplitudes and latencies of the ‘Animated Avatar’ paradigm.

Channels	**Amplitude**		**Latency**
	Non-Target	**Target**	
F3	0.85 (0.32)	2.03 (0.33)	407.41 (54.08)
Fz	0.84 (0.30)	3.80 (0.49)	340.06 (27.61)
F4	0.55 (0.35)	3.46 (0.48)	427.53 (38.83)
C3	0.92 (0.36)	2.08 (0.19)	472.41 (45.12)
Cz	0.62 (0.31)	4.97 (0.45)	368.71 (22.42)
C4	0.69 (0.31)	4.10 (0.37)	466.18 (21.46)
P3	0.87 (0.30)	2.63 (0.35)	474.53 (25.08)
Pz	0.66 (0.28)	5.62 (0.64)	471.76 (29.98)
P4	0.93 (0.24)	4.20 (0.49)	437.24 (21.14)

Note: Amplitude values are in microvolts (SEM). Latencies are in milliseconds (SEM).

The non-parametric Friedman test revealed that there is significant statistical differences between the channels’ latencies, $X^2(8) = 25.829$, $p=0.001$.

5.5 ‘4 Avatars’ Paradigm

In Table *5* are the average amplitudes and latencies of the P300 Target components and the corresponding amplitude of the Non Target waveforms.

Table 5. P300 amplitudes and latencies of the '4 Avatars Avatar' paradigm.

Channels	**Amplitude**		**Latency**
	Non-Target	**Target**	
F3	0.08 (0.15)	1.19 (0.25)	454.35 (56.37)
Fz	-0.11 (0.19)	1.68 (0.33)	402.88 (46.83)
F4	-0.11 (0.19)	1.69 (0.34)	430.00 (49.75)
C3	0.21 (0.17)	1.54 (0.21)	509.59 (46.10)
Cz	0.16 (0.21)	2.77 (0.36)	438.71 (46.31)
C4	0.04 (0.14)	2.87 (0.24)	447.65 (29.98)
P3	0.33 (0.13)	2.91 (0.28)	499.53 (19.88)
Pz	0.17 (0.13)	4.14 (0.48)	460.00 (18.48)
P4	0.15 (0.16)	4.66 (0.59)	458.71 (15.59)

Note: Amplitude values are in microvolts (SEM). Latencies are in milliseconds (SEM).

It was performed a 3 (Region: frontal, central, parietal) × 3 (Laterality: left, midline, right) × 2 (Stimulus Type: Non-Target, Target) ANOVA with repeated measures.

Main effects of Region and of Laterality emerged, $F(2, 32) = 25.283$, $p<0.0001$ and $F(2, 32) = 7.595$, $p=0.002$. P300 responses were greatest at parietal region, at an intermediate level in the central region, and smallest in the frontal region. The amplitudes were also higher in the midline and right line site. The effect of Region × Laterality, $F(2, 32) = 3.432$, $p<0.024$, reinforces those asymmetries (Fig. 5.2).

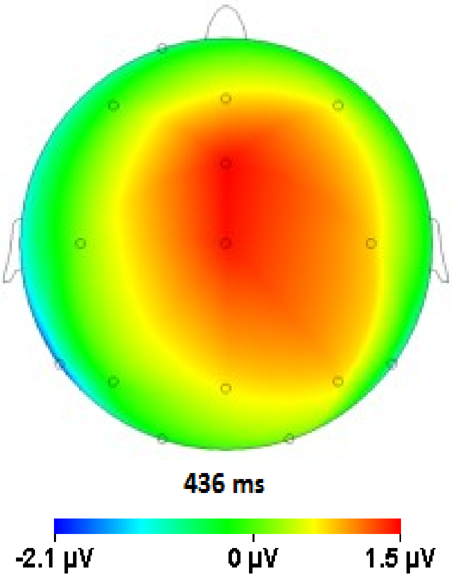

Fig. 5.2 – Topographic distributions of the grand average P300 components (microvolts) from the 'Eyes' paradigm. It is visible the higher amplitude in midline, and right sites, and also in the parietal and central areas.

A significant main effect of Stimulus Type also emerged, F(1,16) = 132.395, $p<0.0001$; The waveform amplitudes of P300 to Target stimulus (M=2.606 microvolts) was statistically significantly higher than the amplitudes of the Non-Target waveforms (M=0.103 microvolts).

The non-parametric Friedman test revealed that there is no significant statistical differences between the channels' latencies, $X^2(8) = 15.442$, $p=0.051$.

5.6 Paradigms Comparison

To explore the differences of P300 amplitudes and latencies between the stimuli proceeded to a non-parametric MANOVA as described in (Maroco, 2007) because, according to the Box's Test of Equality of Covariance Matrices, the assumption of homogeneity of covariance was not valid, Box's M = 304.940; F(189, 11506.859) = 1.269; $p=0.009$.

As described in (Maroco, 2007), a Kruskal-Wallis test followed by multiple comparisons of means was made to identify the channels in which there were significant differences. The type I error was 0.05.

According to the non-parametric MANOVA there were no statistically significant differences in amplitudes ($X^2(36)=16.032$; N=17; $p=0.998$) neither in latencies, ($X^2(36)=11.792$; N=17; $p=0.999$) between the 5 paradigms.

5.7 BCI Classifiers

A key point of this project is to check the validity of the introduction of 3D animations as the focus of attention. One of the practical consequences of this innovation is their use in BCIs. Classification tests were made using classification techniques typically used in BCIs (section 2.3).

The data from four subjects (3 male, 1 female) have been analysed offline on the P300 classifiers developed by Gabriel Pires (Pires, Nunes, & Castelo-Branco, Brain computer interface approaches to control mobile robotic devices, 2008; Pires, Castelo-Branco, & Urbano, Visual P300-based BCI to steer a Wheelchair: a Bayesian Approach, 2008). The results were obtained by crossed validation and in single trials:

Table 6. Classification results of P300 classifiers using the routines described in (Pires, Nunes, & Castelo-Branco, Brain computer interface approaches to control mobile robotic devices, 2008; Pires, Castelo-Branco, & Urbano, Visual P300-based BCI to steer a Wheelchair: a Bayesian Approach, 2008)

Individual	Paradigm	accuracy
1	Balls	91%
	Animated Avatar	91%
	4 Avatars	93%
2	Face	74.30%
	Eyes	77.25%
	Animated Avatar	59%
	4 Avatars	87.80%
3	Balls	87.50%
	Animated Avatar	83%
	4 Avatars	71.12%
4	Animated Avatar	77%
	Balls	76.40%

Similar approaches implemented by Marco Simões, who has been working in IBILI in a project that aims to use similar animated paradigms in BCI, tested the data from four subjects: 3 male, 1 female. The performance of four methods (Fisher Linear Discriminant (FLD), Bayes, Template Coherence and Inner Coherence) with and without Common Spatial Patterns (CSP) spatial filtering was tested with five runs in a 6-fold cross validation. Results are shown in Fig. 5.3.

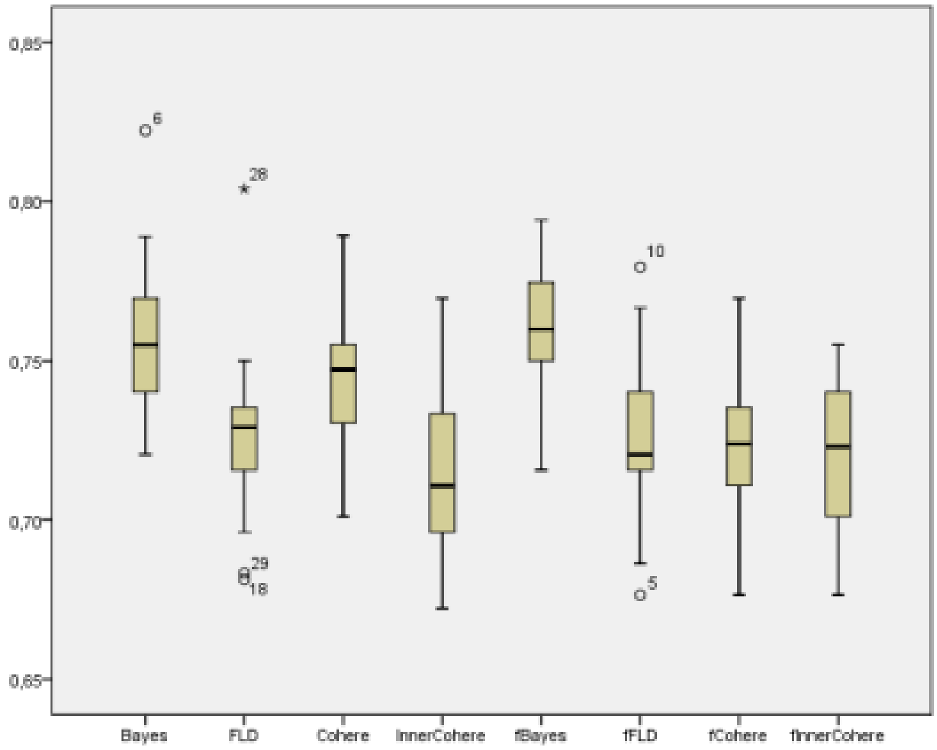

Fig. 5.3 – Boxplot comparing the four methods (Bayes, Fisher Linear Discriminant (FDL), Template Coherence (Cohere) and Inner Coherence (InnerCohere) performances, with (fBayes, fFDL, fCohere, fInnerCohere) and without filtering technics, using EEG data acquired using an animation based oddball paradigm. (Courtesy of Marco Simões.)

The accuracy was around the 73%. The CSP filtering had a statistically significant improvement in the accuracy of the Bayes algorithm.

5.8 Discussion

The main and novel finding of this thesis is that the P300 signal can also be identified in complex social cognition oddball paradigms, indicating that it is a general marker of attentional modulation elicited by rare unexpected events. Indeed, the evident differences between the amplitudes of the Non-Target waveforms and the P300 component indicate that all the paradigms designs were able to elicit P300 responses, regardless of their visual complexity and cognitive analysis requirements. Even the social animation based paradigms revealed significant differences in amplitudes.

The effects of laterality were more evident in social animation based paradigms in which the topographical distribution seemed more evident in midline and right hemispheric sites (in particular the 4 avatar paradigm). In terms of region distribution, the effect seems to be more specifically localized, given the higher amplitudes in centroparietal areas. The introduction of social meaning in the stimulus could influence this distribution. We hypothesize that right hemispheric dominance of processing of social and emotional cues leads to a top down right dominance effect that increases the P300 in particular in midline and right parietal regions. In any case, the largest parietal amplitudes seem to be evident except in the low level 'Balls' paradigm and the topographical distribution of P300 in this paradigm seemed, indeed, more uniform.

In Appendix B, Figure 6.4 represents the grand-averages of the ERP responses of Target stimuli of all the paradigms. Here is possible to verify the expected inter subject variability of P300 response type in all paradigms. The introduction of the effect of interpretation social content in these paradigms might have introduced even additional variability that would render P300 difficult to detect, but this was not the case. Accordingly, we could observe that social content works well as focus of attention in 'oddball' paradigms and that the P300 can also be observed.

Along these lines, the data independent classification results suggest that these paradigms based on stimulus social animations may be a viable possibility in a clinical BCI system.

In summary the results showed that both 3D stimuli representing simple object movement or ecological social animations can elicit a P300 response.

Chapter 6

Conclusions

One of the purposes for this study to prove that structurally complex stimuli, based in 3D/Virtual Reality animated stimuli, can elicit a P300 signal. The results obtained suggest that it is possible. The statistical analysis revealed significant higher amplitudes of P300 components in the waveforms of ERPs generated by both 3D stimuli representing simple object movement and stimuli animated representing social gestures. These results open the bonds of exploration of the 'oddball' social paradigms and their utilization in clinical applications.

The other purpose of this project involves the study of the cognitive networks underlying normal attention to stimuli of increasing complexity of social content. This aspect is part of the future basic research goals. It will be interesting to test the developed paradigms in autistic population so it can be possible to investigate how the introduction of social content in these paradigms influences neural responses in a clinical model of social impairment.

Although it was not possible to achieve this purpose, due to time limitations, the resolution of the challenges that have emerged during this project helped to improve some technical aspects and to create some theoretical background about the nature of the P300 ERP, which opens the perspectives to deepen the knowledge about this subject and investigate the influence of social attention in P300 modulation.

It will be also interesting to verify the applicability of the use of animation based paradigms in the rehabilitation of Autistic individuals. The use of this kind of paradigms would be interesting in neurofeedback approaches BCI-Based. Some results indicate a relation between P300 and feedback processing in autistic children (Larsona, Southa, Krauskopfa, Clawsona, & Crowleyc, 2011). During learning children become less dependent on feedback stimuli, shifting this performance monitoring to their internal system (Groen, Wijers, & Minderaa R.B., 2007). However it seems that the positive feedback stimuli are preferred by children (Russell & Jarrold, 1998). Thus the intention to train the social interaction of autistic children could be based in the positive feedback provided by a BCI EEG system using social stimuli.

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Appendix A

Application Requirements

Actors

Researcher

This actor represents the user that configures the experiment. Is responsible for the experiment and knows how to choose the parameters of the paradigms to be presented. He should know the data acquisition process too.

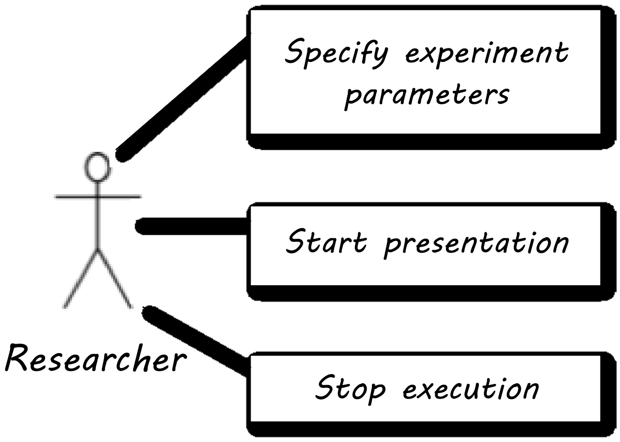


Figure 6.1: Use case diagram.

Use Cases

This section enumerates the use cases of the application, from the case diagram in Figure 6.1.

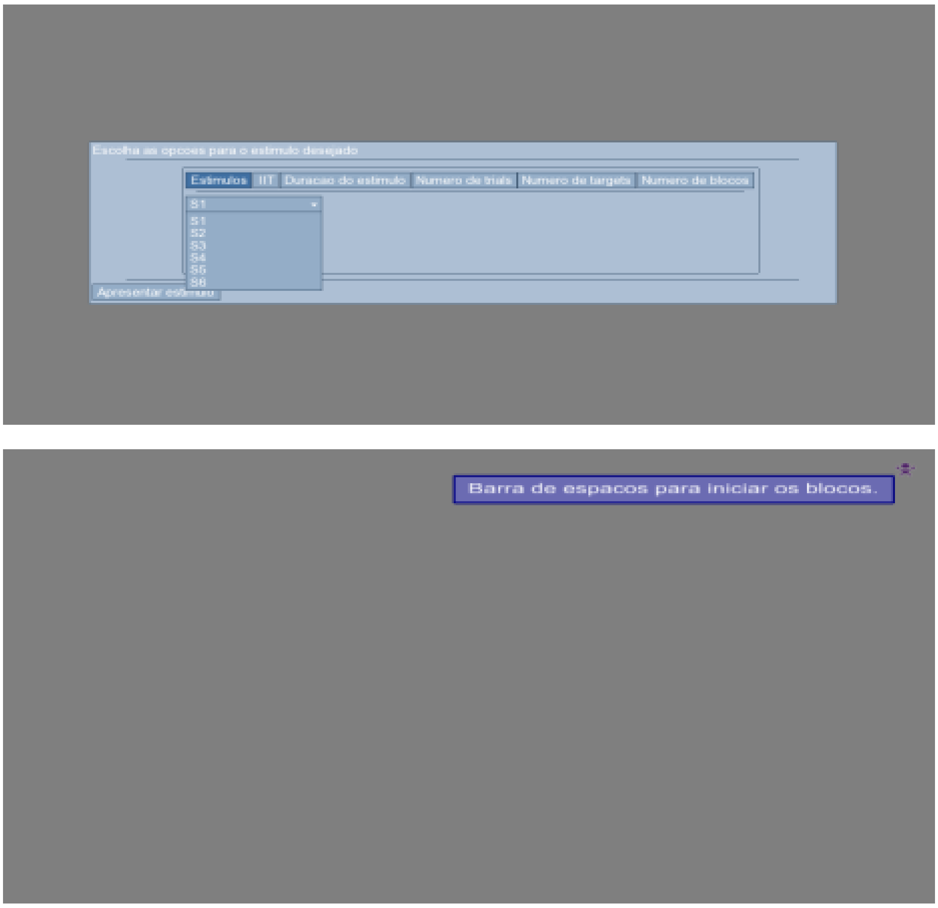
Specify experiment parameters

- Actor: Researcher;

- Brief Description: Allows the researcher to choose the paradigm parameters and to present the paradigm.
- Assumption: The Researcher is someone responsible for the experiment;
- Pre-Conditions: None;
- Post-Conditions:
- The paradigm parameters are defined;
- The scene changes;
- Basic Flow of Events:
    1. The researcher chooses the paradigm and its parameters;
    2. The admin chooses to present the paradigm;
    3. The scene changes and the paradigm is ready to be presented;
- Mock Ups: Some mock ups for this use case are presented in Figure 6.2.

Present the paradigm

- Actor: Researcher;
- Brief Description: This use case includes the paradigm presentation and the re-establishment of the parameters for a new presentation.
- Assumption: The researcher is someone responsible for the experiment;
- Pre-Conditions: The paradigm parameters are chosen;
- Post-Conditions: The scene changes according to the paradigm and the trigger signals are sent;
- Basic Flow of Events:
    1. The researcher presses the specific button;
    2. After the end of presentation, the researcher presses a specific button and the application restores the presentation parameters for a new presentation;
- Mock Ups: Some mock ups for this use case are presented in Figure 6.2.



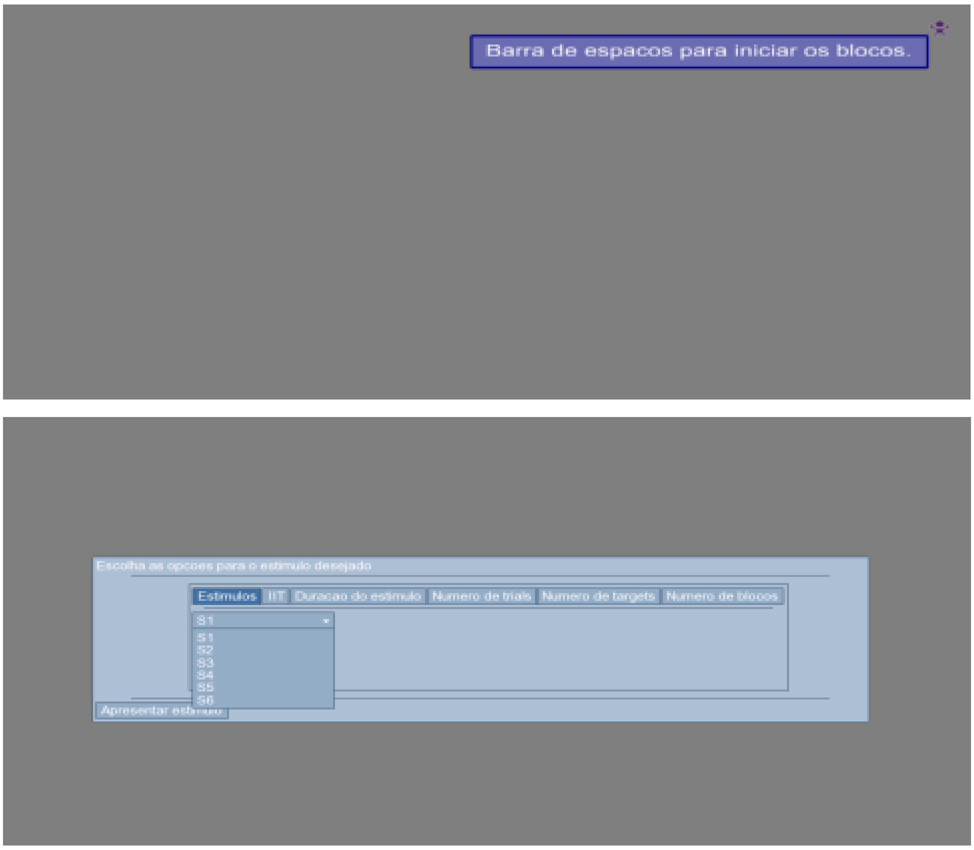
Escolha as opcoes para o estimulo desejado

Barra de espacos para iniciar os blocos.

Figure 6.2: Paradigm' parameters specification mock up. The stimulus is ready to present after the user choose all the parameters.

Stop Execution

- Actor: Researcher;
- Brief Description: The application can be stopped at any time, by pressing a specific key;
- Assumptions: None;
- Pre-Conditions: Application is running:
- Post-Conditions: Application stopped;
- Basic Flow of Events:
    1. User presses termination key;
    2. Task stops;
- Mock Ups: None.



Barra de espacos para iniciar os blocos.

Escolha as opcoes para o estimulo desejado

Figure 6.3: Paradigm presentation mock up. At the end of paradigm presentation, the researcher can restore the presentation parameters.

Appendix B

Grand-Average Plots

Figure 6.4 – Grand-average ERP waveforms for Target stimulus of the five paradigms. Aside P300 a N400 is also present at frontal sites for several conditions. Note the scale differences and that all paradigms show a similar pattern except the animated avatar condition, which shows different time courses and topographies.