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THE NEURAL CORRELATES OF ATTENTION TO PHYSICAL STIMULI OF VARIABLE SOCIAL MEANING: A TRANSLATIONAL APPROACH TO AUTISM

Tese no âmbito do Doutoramento em Engenharia Biomédica orientada pelo Professor Doutor Miguel de Sá e Sousa Castelo-Branco e apresentada ao Departamento de Física da Faculdade de Ciências e Tecnologia da Universidade de Coimbra

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Para ti, avó...

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Abstract

Autism Spectrum Disorder (ASD) is well known by persistent social cognition deficits which are characteristic of its behavioural phenotype and are likely related to the neural mechanisms underlying social attention. Since social attention plays a fundamental role in social orientation and perception of others' intentions, these impairments cause a series of unadjusted social behaviours which render difficult the building of successful interactions and relationships. These difficulties are hard to overcome, and generally, the outcome in adult life are high levels of dependency on their families or other support services, low rate of employment and reduction of close and satisfying social contacts. The impacts of ASD in families' daily life are enormous ranging from increased parenting stress to significant financial strain and time pressure largely due to the necessity of intense and continuous early training of behavioural and social skills of autistic individuals. Usually, this training is facilitated by a therapist or teacher and may involve training peers, siblings, or parents to interact with youth with ASD. However, for the whole intervention process to succeed, it implies having a regular and considerable amount of human resources, which makes it a hard task to coordinate, longlasting and more prone to be less systematized.

The aim of this thesis is to present a solution to train social skills (specifically joint attention - JA) of ASD subjects that gathers a series of properties that have been advocated by several authors in the field to represent requisites to overcome the generalization problem (among other problems) of the rehabilitation of social skills in ASD subjects in real life settings. These characteristics include high standardization, predictability, immersivity, controlled, and a personalized therapeutic approach. We were able to suggest this solution with the creation of a Brain Computer Interface (BCI), coupled with virtual reality that includes social interactions challenging JA responses, and specific feedback based on the neurophysiological response (P300)

to the challenge presented. We expected to promote behavioural learning of automatic responses to JA cues.

Naturally, we had to pass through several incremental steps to achieve our goals. It included some conceptual aspects like the dissection of the mechanisms underlying the cognitive processing of realistic and complex social scenes and BCIs, and the validation of the paradigm concept of using social cues to direct the focus of attention to relevant scene signals. Also, some other practical aspects were fundamental to address, such as the search for the best technical solution for the combination of virtual reality with electroencephalography (EEG) based BCI and the viability tests of our BCI as a potential social attention training tool for autism.

In sum, we were able to show that realistic animated oddballs with social content generate a specific response that can be successfully classified, even at the single-trial level, and that this specific response is right lateralized for more complex scenes. We also show the feasibility of the introduction of realistic social cues and immersive setups in BCI paradigms and their use in ASD participants. Finally, we investigated whether this type of tool could be used in a structured clinical intervention and how would it be accepted by the target population by running a feasibility clinical trial. To do so, we acquired feasibility metrics which ended up being very positive in terms of assiduity and compliance. We also collected a series of standard neuropsychologic and neurobehavioral data from the participants to scrutinize any potential clinical effect in ASD and these data revealed some positive effects on patient's mood and mental state translated, for example, by improvements in autism symptoms, sociability, and depression. We also created a new method to evaluate the rate of responses to JA cues (based on eye tracking data) as a tool to ascertain any effect of the BCI intervention, although it lacked sensitivity.

Our work gives positive insights into the potential use of realistic stimuli in ecologic environments for clinical applications, and so we hope this work could inspire the investigation of new neurophysiologic-based rehabilitation tools coupled with virtual reality for improving social behaviour in ASD or for intervention in other disorders.

Resumo

A perturbação do espectro do autismo (PEA) é bem conhecida pela ocorrência persistente de comportamentos sociais desajustados que estão provavelmente relacionados com deficiências nos mecanismos neuronais subjacentes à atenção social. Uma vez que a atenção social é fundamental para a perceção social das intenções dos outros, estas deficiências levam a comportamentos sociais que dificultam a construção de relações interpessoais satisfatórias. É difícil para os indivíduos do espectro do autismo lidar com estas dificuldades e, normalmente, a consequência a longo prazo são elevados níveis de dependência em relação às suas famílias ou outros serviços de apoio, baixa taxa de emprego e a inexistência de relações sociais próximas e satisfatórias. Para além disso, o impacto no dia a dia das famílias das pessoas com PEA é enorme. A necessidade prioritária de recorrer à intervenção precoce nos indivíduos com autismo colocam estas famílias numa pressão financeira e com cargas horárias pesadas. Isto aumenta significativamente o stress parental nestas familias. Normalmente a intervenção precoce envolve o treino intensivo de competências socais e é facultado por meio de terapeutas ou professores especializados e pode implicar a formação de colegas, familiares ou pais para a forma como interagir com a criança com PEA. No entanto, para que todo o processo de intervenção tenha sucesso é necessária uma quantidade de recursos humanos consideravel o que torna o mesmo processo dificil de coordenar, demorado e mais susceptivel de se tornar pouco sistematizado.

O objectivo desta tese é apresentar uma solução para o treino de competências sociais (especificamente a atenção conjunta) na PEA que reúne uma série de caracteristicas que têm vindo a ser preconizadas por alguns especialistas da área e que podem ajudar a resolver o problema (entre outros) da generalização das competências sociais treinadas para contextos socias reais. Estas caracteristicas são a uniformidade, a previsibilidade, a imersividade, a controlabilidade e a capacidade de

personalizar a terapêutica. Nós apresentamos esta solução na forma de uma interface cérebro-computador (ICC), incluída num sistema de realidade virtual, que apresenta interaçõees sociais que promovem a atenção conjunta e que devolve uma resposta retroativa baseada na informação neurofisiológica resultante da interação social promovida. A espectativa é que, com este conceito, ocorra a aprendizagem operante de comportamento adaptativo das pessoas do espectro do autismo e que isso leve ao aumento de probabilidade de ocorrência de episódios bem-sucedidos de atenção conjunta em contextos sociais reais.

O sucesso da nossa proposta dependeu, naturalmente, da realização de alguns passos incrementais. Esses passos incluíram o domínio de aspetos conceptuais tais como a compreensão de como é feito o processamento neuro-cognitivo de cenas socias complexas e realísticas e da validação do paradigma de estimulação da ICC tendo como base pistas sociais como guias da atenção. Para além destes passos, foi fundamental abordar aspetos pragmáticos tais como a busca da melhor solução técnica para a combinação da realidade virtual com a ICC havendo a ocorrência simultânea de aquisição de eletroencefalografia (EEG) e, também, os testes de viabilidade de utilização desta ferramenta como forma de treino de competências sociais no autismo.

Em suma, fomos capazes de demonstrar que estímulos raros do tipo *oddball* (gerador da resposta neuronal P300) que incluem conteúdo social dão origem a uma resposta neuronal especifica que pode ser detetada ao nível de *single trial* e que essa resposta especifica é lateralizada à direita quando a cena no estímulo é mais complexa (inclui animações realistas de movimentos sociais). Também provámos a viabilidade da introdução destes estímulos complexos e animados de forma realista numa ICC, assim como a viabilidade do acoplamento de aparelhos de simulação de imersividade completa (realidade virtual 360º) numa ICC, e a possibilidade da sua utilização na população com PEA. Por fim dedicámo-nos à aferição da possibilidade do uso desta tecnologia como forma de intervenção clínica e de como seria tolerada pela população de estudo alvo recorrendo a um ensaio clínico de exequibilidade. Aqui registámos medidas de viabilidade que se mostraram bastante positivas em termos de assiduidade e adesão. Também recolhemos um conjunto de medidas neuropsicológicas e comportamentais padrão com o objetivo de desvendar algum eventual efeito clínico nos pacientes com PEA. A informação recolhida destas medidas revelou-se bastante interessante a nível do estado mental e do humor dos pacientes, mostrando melhorias em medidas de sintomas de autismo, de depressão e de sociabilidade. Também observámos a necessidade de criar um novo método para avaliar o rácio de respostas bem-sucedidas a pistas de atenção conjunta (baseado em medidas de *movimentos oculares*) de forma a verificar algum potencial efeito da intervenção com a ICC. No entanto este método não se revelou suficientemente sensível.

Fazendo o balanço, acreditamos que o nosso trabalho introduz contributos relevantes acerca da utilização de estímulos realistas e de ambientes de realidade virtual imersivos em aplicações clínicas. Esperamos que isso possa inspirar a investigação e criação de novas ferramentas de reabilitação deste tipo, e que essas ferramentas tenham como base, cada vez mais, a utilização de medidas neurofisiológicas com o objetivo de melhorar a eficiência do treino de qualquer tipo de competência em patologias do neurodesenvolvimento.

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List of abbreviations

ABA – Applied Behaviour Analysis

ADI-R – Autism Diagnostic Interview-Revised

ADOS – Autism Diagnostic Observation Schedule

ASD – Autism Spectrum Disorder

BA– Balanced Accuracy

BCI – Brain Computer Interface

CSP – Common Spatial Patterns

CSTP – Common Spatiotemporal Patterns

dB – Decibels

DISCO – Diagnostic Interview for Social and Communication Disorders

DSM – Diagnostic and Statistical Manual of Mental Disorders

EEG – Electroencephalography

ERP – Event-Related Potentials

FEF – Frontal Eye Field

FN – False Negatives

FP – False Positives

Gb – Gigabytes

HMMs – Hidden Markov models

Hz – Hertz

ICA – Independent Component Analysis

ISI – Inter-Stimulus Interval

JA– Joint Attention

kNN – k-Nearest Neighbours

kΩ – Kiloohms

LDA – Linear Discriminant Analysis

Mdn – Median

MLP – Multi-Layer Perceptron

mRMR – Minimum Redundancy and Maximum Relevance

ms – Milliseconds

NB – Naïve Bayesian Classifier

NN – Neural Networks

PCA – Principal Component Analysis

PDD – Pervasive Developmental Disorders

PECS – Picture Exchange Communication System

qNB – Quadratic Naïve Bayesian Classifier

SCP – Slow Cortical Potentials

SEF – Supplementary Eye Field

SMO – Sequential Minimal Optimization

SNR – Signal-to-Noise Ratio

SOA – Stimulus Onset Asynchrony

SP – Specificity

SPL – Superior parietal lobule

SS – Sensitivity

SSEP – Steady State Evoked Potentials

SSVEPs – Steady State Visual Evoked Potentials

STS – Superior Temporal Sulcus

SVM – Support Vector Machines

TCP/IP – Transmission Control Protocol/Internet Protocol

TEACCH – Treatment and Education of Autistic and related Communication-handicapped CHildren

TN– True Negatives

TP – True Positives

VE – Virtual Reality Environments

VR– Virtual Reality

µV – Microvolts

3D – Three Dimensional

Chapter 1

Introduction: BCI in Autism, Why?

This chapter introduces the themes of autism spectrum disorder, joint attention, Brain Computer Interfaces, and virtual reality. This serves as an introductory context to the problem we addressed and to our approach to solve it. In this chapter, one can find also the explanation of the objectives of our work and the description of the structure of the thesis.

1.1 Motivation for the Thesis

Autism Spectrum Disorder (ASD) is well known by the persistent social deficits component of its behavioural phenotype (Sugawara & Nikaido, 2014). Social deficits of autism are intrinsically related to the neural mechanisms of social attention (Dawson et al., 2004; Greene et al., 2011) (section 1.3). Since social attention plays a fundamental role in social orientation and perception of others' intentions, these impairments cause a series of unadjusted social behaviours which difficult the building of relationships. These difficulties are hard to overcome, and generally, the outcome in adult life are high levels of dependency on their families or other support services, low rate of employment and absence of close and satisfying social contacts (Bauminger & Kasari, 2000; Howlin, Goode, Hutton, & Rutter, 2004).

Although prevalence estimates under the more recent Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-V, (American Psychiatric Association, 2013)) diagnosis criteria are not yet available, most recent studies reveal an ASD incidence between 0.7 and 2.6% among children in developed countries around the world (Baxter et al., 2015; Christensen et al., 2016; Lyall et al., 2017). This condition has a significant economic and social impact due to its high prevalence, morbidity, and impacts on daily family life (Boshoff, Gibbs, Phillips, Wiles, & Porter, 2016; Harrop, McBee, & Boyd, 2016; S. Jones, Bremer, & Lloyd, 2016; Karst & van Hecke, 2012; Schlebusch, Samuels, & Dada, 2016). The prevalence of ASD in Portugal was estimated at ~10 per 10000 children by Oliveira et al. in 2007. The authors referred the choice of age range in their study as a possible explanation for the lower prevalence in relation to the other studies in developed countries, as studies in younger cohorts tend to report a higher prevalence of autism. However, their results matched similar studies using stricter diagnosis criteria.

The impact of ASD in families' daily life are enormous, ranging from increased parenting stress to significant financial strain and time pressures (Harrop et al., 2016; S. Jones et al., 2016; Karst & van Hecke, 2012; Schlebusch et al., 2016), largely due to the necessity of intense and countinuous early behavioural and social skills training by autistic individuals. This necessity is justified by the emerging evidence about the effectiveness of this type of interventions (Bass & Mulick, 2007; Bellini & Akullian, 2007; Eikeseth, 2009; McConnell, 2002; Reichow, Doehring, Cicchetti, & Volkmar, 2011; Reichow & Volkmar, 2010; Reichow & Wolery, 2009; Scattone, Tingstrom, & Wilczynski, 2006). Generally speaking, these social skills interventions are facilitated by a therapist or teacher and may involve training peers, siblings, or parents to interact with youth with ASD. However, in order for the whole intervention process to succeed, it implies a regular and considerable amount of human resources, which makes it a hard task to coordinate, long lasting and more prone to be less systematized.

Our thoughs about this problem converge to the attempt to find a solution that can be adapted to the interests of each individual with ASD, focusing on their specificities in a way that it can help to systematize the intervention on their social skills. So, we were searching for something that needed to be flexible, personalized, atractive and easy to control.

Our initial research on this theme led us to identify some points that turned out to be fundamental to establish the objetives of this thesis work:

- there are promising results of neurofeedback strategies on neurorehabitilitation of social dysfunctions in ASD (Pineda, Friedrich, & LaMarca, 2014);
- computer technology is often highly motivating and rewarding for individuals with ASD (Hetzroni & Tannous, 2004; S. Parsons & Mitchell, 2002);
- there is an apparent positive effect of virtual reality in social skills interventions (Kandalaft, Didehbani, Krawczyk, Allen, & Chapman, 2013; Lorenzo, Lledó, Pomares, & Roig, 2016; Maskey, Lowry, Rodgers, McConachie, & Parr, 2014; Wallace et al., 2010).

Analysing the knowledge basis from our host research group, namely the application of P300-based brain computer interfaces (BCI) (section 1.5) to neural diseases (Pires, Nunes, & Castelo-Branco, 2011b), the possibility to adapt this technology also to autism started to make sense due to its relation to neurofeedback attempts. But how? Neurofeedback, by definition, involves a closed loop self-regulation of brain activity to get some outcome in the interface. If one could adapt a BCI task that drives users to self-regulate their behaviour and give any kind of feedback to the interface, one could potentially achieve an induced brain activity regulation by this task. It will work in a different manner than neurofeedback because BCI only requires some sort of interaction with the interface, without having a closed loop in terms of brain activity. Anyway, with BCI, we can get a behavioural feedback that might interest us.

But, what kinds of behavioural feedback should we look for? Is there any behaviour that can be changed in ASD using a P300-based BCI? When thinking about P300, we immediately identify the word "attention". So, one can pick some attention related behaviour that is impaired in ASD. In this sense, social attention seemed to be a logic choice. The deficits regarding non-verbal communication processing in ASD are clear and are particularly obvious in joint attention (JA) skills (section 1.1). Thus, it became obvious that the idea to design a P300-based BCI focusing in the modulation of JA behaviours in people with ASD could be a viable solution. The repetitive nature of oddball paradigms and the P300 operant learning properties related to integration of information with context and memory (Halgren et al., 1995) gives a huge support to this hypothesis.

In fact, this concept was already idealized by Friedrich et al. (2014) in their review where they postulated that quantitative electroencephalography (EEG)-based neurofeedback training is viable as a personalized therapeutic approach in ASD. They also suggested the development of a game platform that includes social interactions and specific feedback based on behaviour, neurophysiological, and/or peripheral physiological responses of the users with the goal to reinforce significant behaviours, such as social interactions, using neurobehavioral signals to promote behavioural, cognitive, and emotional improvement in ASD people. Along with this line, several studies do advocate (Bekele et al., 2014; Georgescu, Kuzmanovic, Roth, Bente, & Vogeley, 2014; Wainer & Ingersoll, 2011) that the use of ecological, realistic, and interactive virtual environments may be the solution for the well-known generalization problem of the rehabilitation of social skills in ASD subjects to real life settings. Golan and Baron-Cohen (2006) suggested that the use of computerized intervention in ASD individuals enables the development of skills in a highly standardized, predictable, and controlled environment, while simultaneously allowing an individual to work at his own pace and ability level. With all this, the main challenge to address should be to find a good and realistic behavioural or neurophysiologic feedback to promote significant improvements of JA skills in people with ASD in a way that they can generalize it for their day-to-day life.

So, we propose a cognitive training tool for JA abilities of people with ASD that combines virtual reality and a realistic and salient neurophysiologic based feedback. In sum, we need to develop a P300-based BCI paradigm coupled with virtual reality that gives a feedback with a relevant social meaning in order to promote a behavioural adaptation of ASD subjects regarding the attention to JA cues.

1.2 Objectives and Thesis Organization

To address this challenge, we propose:

1. to study neural correlates of the P300 signal in response to realistic social cueing.
2. to build a BCI based on these realistic social cueing correlates.
3. test the viability of this BCI as an intervention model for social attention capabilities in ASD population.

This thesis was organized following the natural sequence of this research challenge. Chapter 2 describes our effort to dissect the mechanisms underlying the cognitive processing of realistic and complex social scenes and BCIs. We did it by constructing a series of oddball paradigms with increasing social complexity in order to verify the P300 characteristics in response to social cues with variable perceptual complexity.

The third chapter covers the preliminary tests with the P300-based BCI. We wanted to validate the paradigm concept of using social cues to direct the focus of attention and the combination of interactive immersive virtual reality in the system. This way we were able to find the best technical solution for the BCI setup. Our final intention was to maximize the probability of acceptability by the target population, having in account their hyperreactivity to particular types of sensory stimulation.

Chapter 4 summarizes the viability tests of our BCI as a social attention training tool in a feasibility clinical trial.

In the current chapter, we now introduce different concepts that will be useful to understand the steps taken during the development of the work to which we proposed.

1.3 Autism Spectrum Disorder

ASD is a chronic and neurodevelopmental disorder with a heterogeneous clinical phenotype. It is characterized by impairments in social interaction and reciprocal communication, and by patterns of stereotyped behaviours (American Psychiatric Association, 2013).

1.3.1 Brief Historic Overview

In 1912, the Swiss psychiatrist Bleuler wrote a long essay (Bleuler, 1912) presenting the concept 'autism' to the scientific community, based on direct observation and contact with patients. He used this expression to categorize a set of thought disorders that were present in schizophrenic patients (Coleman & Cillberg, 1994).

The concept 'autism' has been taken over in the publications of Kanner (1943) and Asperger (1944), where they also described common symptoms across the patients they observed. These symptoms included the prevalence of repeated and stereotyped behaviours, difficulties in the development of language and the impairment of social behaviours. They labelled this disorder as a certain syndrome of infantile developmental disturbance (Kuhn & Cahn, 2004) and distinguished it from the schizophrenia in the sense of the inappropriate social behaviour: in autism the patients do have an inability to understand and adapt to the current rules in their environment and the schizophrenic patients have afraid of the surrounding world. So, both conditions tend to have inappropriate social behaviour, but for different reasons.

Despite this, during the 50's and 60's autism continued to be confused with schizophrenia and theories supporting the cause of autism as the result of the inadequate affective relationship between the infants and the mothers (Bettelheim, 1959) became popular.

After this, clinical researchers like Michael Rutter (1978), Edward Ritvo, Betty Jo Freeman, (1977), Lorna Wing (1980), amongst others, put their efforts into the classification of autism as a set of early life developmental disorders and, in 1980 the third edition of Diagnostic and Statistical Manual of Mental Disorders (DSM), included autism in the new Pervasive Developmental Disorders (PDD) class – this category comprises a set of "*distortions* in the development of (...) social skills and language, such as attention, perception, reality testing, and motor movement" (pag.

86 in American Psychiatric Association, 1980). Here the diagnostic criteria for autism were defined as the pervasive lack of responsiveness to other people, gross deficits in language development, and bizarre responses to various aspects of the environment. These criteria were considered controversial at the time because it considered the onset before the 30 months of age and it stated the lack of social interaction instead of deficit.

Over the years the concept of autism has been extended into a more and more wide clinical spectrum and there have been adaptations in the diagnostic subclasses of PDD related to autism:

- in the revision of the DSM-III (American Psychiatric Association, 1987), the subclass 'Infantile Autism' was modified to 'Autistic Disorder', assuming autism as a chronic lifelong disorder. 'Pervasive Developmental Disorder Not Otherwise Specified' subclass replaced the 'Infantile Autism, Residual State' and 'Childhood Onset Pervasive Developmental Disorder' subclasses of the manual's previous edition.
- In the fourth edition of DSM (American Psychiatric Association, 2000; Association, 1994) there were five diagnostic disorders related to autism: 'Autistic Disorder', 'Rett's Disorder', 'Childhood Disintegrative Disorder', 'Asperger's Disorder Diagnostic' and 'Pervasive Developmental Disorder Not Otherwise Specified (Atypical Autism)'.

Despite the mutating subclasses, the clinical characterization of autism has been based in three crucial behavioural categories:

1. abnormal or impaired development in social interaction;
2. abnormal or impaired development in social communication;
3. restricted repertoire of activity and interests.

Currently, the fifth edition of DSM (American Psychiatric Association, 2013) classifies autism as a neurodevelopmental disorder with a wide clinical phenotype instead of a PDD (this classification disappeared). The previous diagnostic subclasses are now encompassed in the Autism Spectrum Disorder concept (with except of Rett Syndrome that was individualized), which reinforces the idea that autism is a wide spectrum of variable perturbations with a common set of signals and symptoms. Considering this, specifiers that describe the severity of autistic symptoms (f. ex.: level of social communication impairments and level of restricted, repetitive patterns of behaviour, association with any known medical or genetic condition, etc…) must be used to give clinicians opportunity to individualize the diagnosis. The base behavioural criteria that defines autism became only two as the result of the fusion of social interaction and social communication impairments in one criterion.

1.3.2 Diagnosis Criteria

The clinical criteria for the diagnosis of ASD according to the DSM-V (American Psychiatric Association, 2013) are summarized in Table 1.1.

Table 1.1 – Diagnosis criteria of the Autism Spectrum Disorder according to DSM-V

Diagnostic Criteria
A. Persistent deficits in social communication and social interaction manifested by: 1. Deficits in social-emotional reciprocity. 2. Deficits in nonverbal communicative behaviours used for social interaction. 3. Deficits in developing, maintaining, and understanding relationships. Specification about severity based on social communication impairments and restricted, repetitive patterns of behaviour must be done.[1]
B. Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by at least two of the following: 1. Stereotyped or repetitive motor movements, use of objects, or speech.

[1] There are three levels of severity specifiers ("requiring support", "requiring substantial support" and "requiring very substantial support") that should be used separately to rate severity of social communication difficulties and restricted, repetitive behaviours.

	2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behaviour. 3. Highly restricted, fixated interests that are abnormal in intensity or focus. 4. Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment. **Specification about severity based on social communication impairments and restricted, repetitive patterns of behaviour must be done.**[1]
C.	Symptoms must be present in the early developmental period.
D.	Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E.	Symptoms are not better explained by intellectual disability or global developmental delay. Give: • Information about presence or not of intellectual impairment. • Information about presence or not of language impairment. • Information about association with a known medical or genetic condition or environmental. • Information about association with another neurodevelopmental, mental, or behavioural disorder. • Information about presence or not of catatonia.

The fundamental symptoms for an ASD diagnosis are the persistent presence of impaired social communication, social interaction (criterion A, Table 1.1) and repetitive and restricted patterns of behaviour, interests or activities (criterion B, Table 1.1). These symptoms must be present and be clinically significant in a persistent manner since early childhood (criterion C and D, Table 1.1). However, these symptoms manifest itself in a very diverse way depending on neurodevelopmental and behavioural specificities of each patient. This gives support to the concept "Autism Spectrum Disorder" being a spectrum of disorders as presented in DSM-V.

1.3.3 Symptomatic Features

A wide range of characteristics (with variable degree of severity) are encompassed in each one of the diagnosis criteria (American Psychiatric Association, 2013; Rutter, 1978). As examples we have:

Impairments in communication and social interaction

Communication problems may include language deficits, such as complete lack of speech, language delays, poor comprehension of speech, echoed speech, or stilted and overly literal language. The field of nonverbal communication is also impaired and it is common to find abnormalities in eye contact, body language and in the understanding and use of gestures. It is evident the absence of pointing, showing, or bringing objects to share interest with others, or the inability to follow someone's pointing or eye gaze (this is called as joint attention and will be addressed later on this thesis). The decreased or absent use of facial expressions is also frequent.

Social interaction deficits manifests in deviant social-emotional behaviours like little or no initiation of social interaction, no sharing of emotions, interests, and affects, reduced or inexistent imitation of others' behaviour, atypical social approach and failure maintaining a normal conversation. It is normal to find, difficulties in developing, maintaining, understanding relationships, and adjusting behaviour to the social contexts (which frequently leads to anxiety episodes). There may be also a preference for solitary activities and no interest in peers. An evident difficulty in sharing imaginative play is also characteristic.

Restricted, repetitive patterns of behaviour, interests, or activities

This group of symptoms encompasses all kind of behaviours that are abnormally repeated. As an example, there are motor stereotypies (hand flapping, spinning, run without direction…), repetitive use of objects and child's play, repetitive speech. It is frequent to find highly restricted and fixated interests for something in particular, but with no functional interest (e.g.: symbols, objects, brands, specific placement of any object, shapes, smells…), which creates inadequate social behaviours (e.g.: irrelevant questioning about the obsession in incorrect social contexts, lining up objects…). Extreme responses to or rituals involving taste, smell, sounds, texture, or food are common, as well as apparent indifference to pain, heat or cold too. These reactions may be related to hyper- or hypo-reactivity to sensory input and are a presenting feature of autism spectrum disorder.

1.3.4 Pathophysiology

Recent work in genetics, as well as imaging, molecular biology, and neuroanatomy have shed some light on the pathophysiology of ASD.

The genetic contribution to ASD etiology is strongly supported historically by twin and family studies. The more recent estimates point to 50% to 95% heritability rates in the United States and Europe (Colvert et al., 2015; Hallmayer et al., 2011; Sandin et al., 2014) and the risk of recurrence among siblings of autistic children ranges from 3 to 18% (Grønborg, Schendel, & Parner, 2013; Sally Ozonoff et al., 2011; Sandin et al., 2014). Over the last years genetic studies have been identifying rare genetic variations, such as inherited and de novo mutations and copy number variations, related to autism or autistic features (Bourgeron, 2015). The evidences are starting to reveal three common biological pathways — chromatin remodelling, synaptic cell adhesion and scaffolding, and neuronal signalling and development (Bourgeron, 2015; Pinto et al., 2014). It is speculated that these processes are linked to networks of brain development genes (Voineagu et al., 2011), which are implicated in specified mid-fetal brain development (Willsey et al., 2013), a critical period for initiation of ASD neuropathology.

In terms of anatomy, the evidence has been consistent describing an early brain overgrowth in ASD (Sacco, Gabriele, & Persico, 2015). Additionally, anatomic changes within the cerebral cortex and cerebellum have been found in ASD brains but with variable differences (Chen, Peñagarikano, Belgard, Swarup, & Geschwind, 2015; Lefebvre, Beggiato, Bourgeron, & Toro, 2015). Imaging studies indicate changes in functional connectivity, and hypoconnectivity across brain structures of ASD individuals (Di Martino et al., 2014). Nevertheless, it remains necessary to better clarify neuroanatomic features influencing behaviours in ASD and, for this, longitudinal imaging studies examining specific brain structures may help (Elison et al., 2013).

Chaidez, Hansen, & Hertz-Picciotto, (2014) described a higher prevalence of gastrointestinal symptoms among children with ASD, and more associated challenging behaviours (irritability, social withdrawal, stereotypy, and hyperactivity). However, the prevalence and potential causes of gastrointestinal pathologies among children with ASD are not fully understood (Buie et al., 2010). The meta-analysis from Rossignol & Frye, (2012) reported mitochondrial and metabolism dysfunctions in ASD cases. Unfortunately, it remains controversial how these multisystem comorbidities can help understand the pathophysiology or potential etiologic subgroups of ASD.

The evidence until now is strongly directing to a multifactorial basis on ASD and environmental factors are increasingly being pointed as moderators of etiological agents by themselves, such as vaccinations, exposure of rich metals or pesticides, viral agents and food products, among others (Rutter, 2005). However, the role of such factors remains highly controversial.

1.3.5 Neuropsychology

Over the years several psychological theories have been developed trying to better explain ASD symptom domains.

Theory of Mind

'Theory of Mind' has been referred to as the cognitive capacity to attribute mental states (beliefs, desires, knowledge and toughs) to self and others and predict the behaviours based on this ascription (Baron-Cohen, Leslie, & Frith, 1985; Goldman, 2012). When Baron-Cohen and colleagues (1985) developed the Sally-Ann test and challenged children with ASD to analyse the social context of the task, they observed that these children had serious difficulties understanding what the character from the task was thinking and predicting its behaviour. The replication of this results (Rogers

& Pennington, 1991) proved that ASD children have impairments in coordinating social representations of self and other at increasingly complex levels (Baron-Cohen, 1995). This theory supposes ASD individuals have an impairment in self-consciousness which implies a severe loss in interpersonal relationships capabilities because they are not able to understand actions and behaviours that reveal simple mental states.

The Empathizing–Systemizing Theory

'Theory of Mind' succeeded in the understanding of the social and communication difficulties of ASD. However it fails explaining the stereotyped and repetitive behaviours and interests of this disorder. In (Baron-Cohen, 2002, 2009) Baron-Cohen suggested 'The Empathizing–Systemizing Theory' that justifies the social and communication difficulties of ASD with the delays and deficits in empathy (usually below average in ASD individuals (Davis, 1994)), while explaining the non-social characteristics (stereotyped and repetitive behaviours and interests) with reference to the positive results in the systemizing psychological factor (commonly average or above average) (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001).

Systemizing is the ability to objectively analyse and create operational systems. Empathy is the capability to have an appropriate emotional reaction to another person's thoughts and feelings. This theory upholds that it is the discrepancy between empathy and systemizing that defines the progress of autism spectrum symptoms.

In fact, the Empathizing–Systemizing Theory is strong in explaining the non-social and generalization problems of ASD. The systemizing concept helps to understand the preference by repetition, the resistance to change and the difficulties generalizing the solutions learned: if we see an ASD child as an individual that deals with situations as if they were systems, we must understand that each situation they face is always considered as new and without significant overlap of characteristics to past experiences.

Nevertheless, the lack of scientific evidence (due in part to its recent formulation) makes this theory still easily questionable.

The Central Coherence Theory

According to this theory ASD individuals have huge difficulties integrating the perceptual stimuli in a global and coherent manner that can be generalized to different contexts (Frith & Happé, 1994).

Happé & Frith (1996) and Garner & Hamilton (2001) showed that people with ASD may have difficulties finding the relation between the parts and wholes (such as proximity, similarity or sequence), due to their focused analytical strategies, emphasizing detail. These findings must be reconciled with the better results of people with ASD in the scales evaluating grouping and classification of image series (Frith & Happé, 1994), locating hidden figures (Shah & Frith, 1993) and memorizing meaningless words (Hermelin & O'Connor, 1970).

So, this theory focusses both on the limitations and the strengths of ASD individuals. However, it is weak clarifying the social and communication deficits and uses the theory of mind to indirectly address this question.

The Executive Functions Theory

Usually, people with ASD show impairments in the capacity to prepare and execute complex behaviours – executive function – which include planning, organization, automatization, mental representation of tasks and objectives, and cognitive flexibility (Sally Ozonoff, Rogers, & Hendren, 2003). In consequence, ASD individuals face serious problems in the resolution of real-life problems.

In ASD, there is a direct relationship between the executive functions deficits, attention and working memory, and the fact that these deficits occur early on age impact not only the behaviour planning, but also the acquisition of concepts that require long term integration of information (Russell, 2000). Having these problems in working memory since young ages implies deficits in the ability to imitate and understand the intentionality of actions. Thus, the executive disfunction theory in ASD can explain the impairments in imitation, joint attention, theory of mind and symbolic play. The stereotyped and repetitive behaviours can also be explained by the absence of inhibition of these behaviours due to the lack of working memory representation of behavioural repertoires (Russell, 2000).

1.3.6 Diagnostic Tools

Despite ASD being a wide spectrum of cognitive, linguistic and neurobehavioral disorders and symptoms, over the recent years, the uniformization of diagnosis criteria helped the development of diagnostic instruments. However, clinical diagnosis remains based mainly on developmental and behavioural analysis in the form of interviews and observational scales.

The Autism Diagnostic Observation Schedule (ADOS, Lord et al., 2000) and the Autism Diagnostic Interview-Revised, (ADI-R, Le Couteur, Lord, & Rutter, 2003) has been the most used and are accepted as the "gold standard" diagnosis instruments for ASD (Charman & Gotham, 2013; Filipek et al., 1999). Other autism diagnosis instruments include the Diagnostic Interview for Social and Communication Disorders (DISCO, Lorna Wing, Leekam, Libby, Gould, & Larcombe, 2002), and the developmental, dimensional, and diagnostic interview (3di, Skuse et al., 2004), for example.

ADOS

This standardized observation schedule can be applied to children above 12 months by a trained professional. It consists in five development- and language-dependent modules that take about 30 to 45 minutes to complete. The professional must choose the appropriate modules for the individual's age in order to create a semi-structured social interaction with the use of standardized objects (e. g.: toys, books...). The modules include items related to communication, reciprocal social interaction, and restricted and repetitive behaviour domains. After the administration, each item is scored on a 0-3 scale, with higher scores indicating greater symptom severity.

ADI-R

This instrument is a standardized and semi-structured interview administered to parents or caregivers that have knowledge about the developmental history of the individual being evaluated. ADI-R is comprised of several items focused on development, language/communication, reciprocal social interactions and restricted and repetitive behaviours. Scores are assigned on a 0-3 scale by a trained clinician based on self-judgment of the behavioural reports obtained from the informant.

ADOS and ADI-R have a strong discriminant validity (K. M. Gray, Tonge, & Sweeney, 2008; Oosterling et al., 2010; Risi et al., 2006) and their specificity improve when used in combination (De Bildt et al., 2004). However, the administration of these instruments requires a clinician with a solid experience and knowledge about the variations and specificities of development and behaviour. It is crucial to have a critical view over the data collected and for that it is important to have experience dealing with children with autism and other developmental disorders.

1.3.7 Comorbidity and Differential Diagnosis

Autism spectrum disorder is frequently associated with some other conditions such as neurological disorders (prevalence of ~15.7%; e.g.: epilepsy, auditory problems, etc…), psychiatric (prevalence of ~10%; e.g.: anxiety disorder, mood disorder, depression, mutism, etc…), developmental (total prevalence of ~80%; e.g.: intellectual disability, language disorder, attention-deficit/hyperactivity disorder, etc…) and is often associated with other medical conditions (total prevalence of ~3%, e.g.: down syndrome, fragile X syndrome, etc…). The prevalence of the diagnoses is not mutually exclusive, and one patient can accumulate more than one type of diagnosis. The work from Levy and colleagues (2010) gives a good overview about the prevalence of these non-ASD diagnostic entities among ASD cases.

This coexistence of symptoms may render difficult the diagnosis of the main disorder (autism). Hence, there is a necessity to perform a careful differential diagnosis having in account clinical entities such as intellectual disability, language disorders and social (pragmatic) communication disorder, stereotypic movement disorder, attention-deficit/hyperactivity disorder, schizophrenia, selective mutism, obsessive compulsive disorder, or emotional deprivation. Some symptoms from these clinical conditions overlap with the symptomatology of autism spectrum (e.g.: in language disorders there may be social difficulties derived from the inherent problems of communication), so it is important to ensure all ASD diagnosis criteria are met to advance for an ASD diagnostic.

1.3.8 Prognosis

The best prognostic indicators for an individual diagnosed within the autism spectrum are the absence of intellectual disability and language impairment (American Psychiatric Association, 2013). The percentage of employment varies from 0 to 32% counting with the temporary jobs in the best cases. However, the occupations tend to be poorly paid and do not provide adequate financial support which leads to an high dependency ratio (around 50%) (Ballaban-Gil, Rapin, Tuchman, & Shinnar, 1996; Gillberg & Steffenburg, 1987; Howlin et al., 2004; Seltzer, Shattuck, Abbeduto, & Greenberg, 2004). Early detection and specialized intervention improve children evolution provided that innate cognitive, social and language capabilities are positive (Bryson & Smith, 1998).

1.3.9 Interventions on autism

Although there is no cure to this disorder some forms of intervention are available to help increase the quality of life of these individuals and their families. The existing methods that have been showing effectiveness are based on early structured and intensive behavioural programs that tend to provide the environmental conditions necessary for an efficient acquisition of communication skills, social interaction rules and adaptive functioning. A well-known intervention methodology is the so-called Applied Behaviour Analysis (ABA; (Lovaas, 1987)), a series of evidence-based approaches addressed through intensive trials of antecedent-behaviour-consequence chains. A range of selected materials are presented repeatedly with the objective of promoting the success of a specific task and a tight control is maintained over the antecedent stimuli, prompt hierarchy, and the reinforcers. The correct responses are reinforced using tokens and edibles paired with verbal praise. Traditionally the application of ABA approaches is done within a non-distracting environment, disembodying behaviour from meaningful activities during initial skill acquisition. However, the contemporary ABA approaches modified the execution of ABA principles such that the intervention is focused on child's interests and activities to overcome children's difficulties in generalizing skills created precisely because of the disengagement of the intervention from the meaningful contexts in the traditional ABA approach. Contemporary applications of ABA are seen in approaches such as Incidental Teaching (Mcgee, Morrier, & Daly, 1999), Natural Language Paradigm (Koegel, O'Dell, & Koegel, 1987), Pivotal Response Training ("Teach. Child. with autism Strateg. Initiat. Posit. Interact. Improv. Learn. Oppor.," 1995), the Milieu Teaching approach (Warren & Bambara, 1989), and Picture Exchange Communication System (PECS; Bondy & Frost, 1998), which employ strategies aimed to facilitate spontaneous language and communication development always focused on the child's motivation as active communication partner. These approaches are designed to be easily adapted to child's preferences and choices so that the interactions are more natural and fluidly structured to encourage the communication initiation by the child. There is some evidence that generalization of some communication skills can occur using these contemporary approaches while acquired throughout the day in meaningful communicative contexts (Fey et al., 2006; Koegel et al., 1987; Neef, Walters, & Egel, 1984; Pierce & Schreibman, 1995). Moreover, there is evidence that early intervention may benefit early communication development when other intervention strategies are incorporated (Stahmer & Ingersoll, 2004).

Another well-known complementary approach is called Treatment and Education of Autistic and related Communication-handicapped CHildren (TEACCH, Goldson, 2001; Sally Ozonoff, Cathcart, & Cathart, 1998). The TEACCH approach is based on evidence and observation that "individuals with autism share a pattern of neuropsychological deficits and strengths" (in Mesibov & Shea, 2010) and is called Structural Teaching. The essential mechanisms of this approach are (a) structuring the environment and activities in ways that are understandable and predictable to the individual; (b) using individuals' relative strengths in visual skills and interest in visual details to supplement relatively weaker skills; (c) using individuals' special interests to engage them in learning; and (d) supporting self-initiated use of meaningful communication; (e) focusing on teaching small units of learning systematically; (f) arranging the target skills on a carefully constructed and personalized behaviour analytical curriculum; (g) including a substantial component of parent support; (h) specialized training of the intervention team; (i) early (before 3 and 4 years of age) and intensive teaching (from 15 to 40 weekly hours of training) (L. a LeBlanc & Gillis, 2012; Mesibov & Shea, 2010).

Since social skills deficits are a core feature of ASD, the training of this competence is an important component for this population. The intervention programs include many strategies to teach social skills to youth with ASD such as:

- Peer mentoring – Teach typically developing peers how to interact with children with ASD as a way to promote positive transmission of social skills in a classroom (Wolfberg & Schuler, 2003).
- Social skills groups – 4 or 5 members groups of children with ASD participate in social skills lessons. The topics of these lessons include greeting others, being friendly, joining or initiating play with others, reading nonverbal cues, and

starting and maintaining conversations (Gajewski, Hirn, & Mayo, 2008; Winner, 2008).

- Video modelling - children with ASD watch video recordings of themselves or peers successfully performing appropriate social skills, and then imitate the skills demonstrated in the video (Buggey, 2009).
- Social stories and Picture books – parent or teacher write a short story about the child with ASD, in the first person, teaching an appropriate use of a social skill or activity (C. Gray, 2010). Instead, a picture illustrating an example of the social situation or skill can be used (Baker, 2001).

There is a large body of positive scientific evidence (Eldevik et al., 2009; Larsson, 2013; L. A. LeBlanc & Gillis, 2012) demonstrating that the early behavioural intervention improves the net health outcome as much as or more than established alternatives. The improvements include increase on direct measures of joint attention, play, imitation and language, and at the same time decreases in stereotyped behaviours (MacDonald, Parry-Cruwys, Dupere, & Ahearn, 2014).

In the field of pharmacological intervention there is no specific medication addressing the core features of autism. The pharmacologic therapy is based on the control of seizures and symptoms that dysregulates the behaviour in order to optimize the educative intervention commitment (Gillberg & Coleman, 2000; Mcdougle, Kresch, & Posey, 2000; Tsai, 2005). The most widely used pharmaceuticals include neuroleptics, which act as dopaminergic antagonists to control the aggressive behaviours, (Kaplan & Mccracken, 2012; McDougle, 1997); and serotonin reuptake inhibitors, to control the repetitive behaviour and aggressive behaviours, (Mcdougle et al., 2000; Scahill & Boorin, 2011; Tsai, 2005).

1.4 The Brain, Cognitive Systems with a Focus on Attention

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 immune protection of the central nervous system; and the ependyma, involved in the production of cerebrospinal fluid.

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 nearly symmetrical cortex, left and right hemispheres, can be divided into four 'lobes':

- Frontal lobe: in front of each hemisphere and positioned in front of the parietal lobe and superior to temporal lobes. Among other functions, the frontal lobe is associated with reward processing, planning, and other executive functions.
- Parietal lobe: positioned above the occipital lobe and behind the frontal lobe. The central fissure (or central sulcus) separates the parietal lobe from the frontal lobe, and the primary motor cortex from the primary somatosensory cortex. Among other functions, the parietal lobe integrates the sensory information from various parts of the body, shaping the spatial orientation and navigation of the organism, within the dorsal processing stream.
- 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 lobe is anterior to the occipital lobe, inferior to the frontal lobe and parietal lobe, 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 object vision, within the ventral processing stream. The temporal lobe plays an important role in the perception of auditory stimuli. It is also associated with coordination and balance, emotions, memory and face recognition. This lobe incorporates the hippocampus playing an important role in the formation of long-term memory.

1.4.1 Attention

The term attention is a conceptual construct from psychology. According to the original statement of William James (1890), 'Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one of what may seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others.' This definition, yet simplistic, exposes the apparent familiarity that this concept presents, due to its frequent presence in everyday discourse (e. g.: when a teacher asks his students to 'pay attention' to something important during a class).

However, after more than a century the research in the field has put forward several meanings for this term (Ashcraft, 2006), and it is now quite consensual that the core of attention involves the focused concentration of mental activity (Matlin, 2005) in several types of cognitive processes. Current neuroimaging research can now identify the activation of specific brain regions for different attentional processes (e. g., frontal and parietal brain regions during visual search tasks (Corbetta & Shulman, 2002) and ventral frontal cortex during the redirection of attention for an unexpected stimulus (E. E. Smith & Kosslyn, 2009)). Different types or dimensions of attention can be identified (A. Moran, 2013):

- **Concentration**: decision to invest mental effort on what is most important in any given situation;
- **Selective attention**: perceptual ability to discriminate relevant stimuli from distractors that compete for our attention in the environment;
- **Divided attention**: ability to perform two or more time-sharing actions equally well.

During the last 70 years, cognitive psychologists used several conceptual models attempting to unravel the nature of attention. These models influenced the way attention has been conceptualized and studied throughout time.

The filter conceptual model, proposed by Broadbent (1958), states that humans possess a limited ability to process information and that there is a mechanism that facilitates the selection of information while inhibiting the selection of competing information. Broadbent explained this mechanism drawing an analogy between attention and the neck of a bottle that restricts the flow a liquid. Attention should be therefore a hypothetical filter mechanism that limits the quantity of information to which we can allocate resources at any given time. This theory specified that the selection by this filtering was based on the physical properties of the information being processed, like the pitch or loudness. Although initially influential, this model encountered several difficulties to account for the flexibility and sophistication of human attention, such as the capacity to discriminate concurrent information, which was not previously selected by the attention mechanism, while intentionally paying attention to the physical characteristics of another stimulus. Given this, other theories gained popularity over the filter metaphor.

The spotlight model of visual attention (Posner, 1980) presents the selective attention mechanism as a mental beam that illuminates a circumscribed part of the visual field and that this attentional beam can be redirected voluntarily to any reachable source of information. At the same time, this theory assumes that the information lying outside the illuminated region is ignored. This theory, which can in principle be generalized outside the visual domain, showed several advantages while defining the beam of concentration as something voluntarily controlled that can be directed or not at the 'wrong' source of information. The assumption that one can control one's visual attention forms the basis of Nideffer (1976) view, where he defines four different types of attentional focus required for a given task:

- **'broad external':** attentional focus on several sources of information in the environment to create a mental map about the individual surroundings;
- **'narrow external':** attentional focus in one specific source of information (e. g.: a physical object) in the immediate environment;
- **'broad internal'** attentional focus on a series of thoughts recalling relevant information for a specific task;
- **'narrow internal':** attentional focus on a single tough or image relevant for a specific task;

However, the visual spotlight metaphor of attention struggles to explain some conceptual and empirical problems. For example, it does not explain or predict which processes rule the direction of the spotlight of attention. Also, like the filter metaphor, it neglects the possibility that unconscious processes might influence people's attentional focus. In this case, the limitation lies on the fact that the spotlight and zoom theories assume that what lies outside the beam of attention is ignored.

A third model, encapsulating a sort of capacity metaphor of attention (Kahneman, 1973), was developed trying to explain the mechanisms underlying people's ability to perform two or more tasks at the same time (divided attention). This model sees the attentional focus as a resource that can be allocated to concurrent tasks depending on a combination of factors such as 'momentary intentions' (subjective factors important at the time) or enduring dispositions (factors that are always important to a person). The big strength of this proposal is that it can contemplate the practice acquired to perform a task as an influential factor of the capacity to allocate attention to several sources of information relevant for the task. On the other hand the capacity metaphor is somewhat simplistic because it fails to explain the data proving the independence between the attentional mechanisms related with selection of a finger movement and the regulation of the verbal skill to pronounce a word (Schimidt, R. A., & Lee, 1999). Thus, Luck, S.J., Vecera, 2002 proposed that attention should be considered as a collection of multiple separable resources that operate within different cognitive subsystems.

In sum, the cognitive models of attention created until now have some important gaps, but the reviews of relevant research (B. Abernethy, 2001; Bruce Abernethy, Maxwell, Masters, Kamp, & Jackson, 2007; A. P. Moran, 1996) condense basic principles in five building blocks:

- **Decision to concentrate or focus**: it is essential to make a deliberate decision to invest mental effort in any task;
- **Focus on only one thought at a time:** based on the research showing the limited 'bandwidth' of working memory (Garavan, 1998; McElree, 1998), the conscious focus on only one thing at a time is fundamental for an effective concentration. The performance of several actions simultaneously is possible as long as one or more of the tasks do not require conscious control;
- **Match between thoughts and actions:** there must be no differences between the thinking and the actions performed to have a truly focused concentration;
- **Focus only on factors within the control of oneself:** if the focus wanders around stimuli or thoughts irrelevant for a task the performance on that task tends to decrease;

- **Focus outwards on actions when experiencing anxiety:** anxiety can be a source of doubts and self-criticism, so the outward focus is necessary to build an effective concentration.

In terms of brain imaging research, areas in the parietal, frontal and cingulate cortices have been related to selective attention processing (Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999). These regions include the frontoparietal network which includes areas such the superior parietal lobule (SPL), the frontal eye field (FEF), and the supplementary eye field (SEF) and regions extending into the anterior cingulate cortex. In the case of visual attention, these are among the areas that are thought to provide feedback signals that influence the allocation of attention for the processing of the physical properties of the sensory environment within each specialized area of the human visual cortex.

The limited capacity of attention has been explained by limited capacity of the cortical structures (Treisman & Gelade, 1980). In other words, it is possible that neurons can be overloaded with information from different sources simultaneously and be disabled to transmit accurate information about each one of these sources.

1.4.2 Joint Attention

Joint attention (JA) is an early-developing social communication skill defined by the coordination of attention of two individuals toward a third object or event through non-verbal social cues (Bakeman & Adamson, 1984; Scaife & Bruner, 1975). Non-verbal social cues include pitch, speed, tone and volume of voice, gestures and facial expressions, body posture, stance, and proximity to the listener, eye movements and contact, and dress and appearance. The most influent cues in JA are eye and head movements, and body gestures (pointing, body position).

The lowest level of JA occurs when two individuals are simply looking at an object. The next level of JA is called dyadic JA, where the interaction takes place alternately with facial expressions, noises, and/or speech. The triadic attention (highest level of JA) implies both individuals understand the other is looking to the same object and acknowledge that there is an element of shared attention (Oates & Grayson, 2004). Usually this is marked by one individual looking back to the other individual after looking to the object. So, JA requires the ability to follow eye gaze and the identification of intention.

It is believed that the behaviour of JA is related to innate brain mechanisms attuned to the visual appearance of eyes (Baron-Cohen, 1995). In fact, young infants and neonates prefer and smile more at faces with visible eyes (Batki, Baron-Cohen, Wheelwright, Connellan, & Ahluwalia, 2000; Farroni, Csibra, Simion, & Johnson, 2002; Spitz & Wolf, 1946), and have an enhanced processing of direct gaze comparing to averted gaze (Farroni et al., 2002; Farroni, Johnson, & Csibra, 2004). This is coherent with the evidences proving the existence of a cortical region (within and near the Superior Temporal Sulcus (STS)) responsive to relevant and familiar types of biological motion such as movements of the hands, body, eyes and mouth (Eva Bonda, Ostry, & Evans, 1996; Oram & Perrett, 1994; K. a Pelphrey, Morris, & McCarthy, 2005; Puce, Allison, Bentin, Gore, & McCarthy, 1998). Also, humans have neurons that code for specific gaze directions (i.e., left vs. right) rather than simply distinguishing between direct and averted eye gaze (Calder et al., 2007; Jenkins, Beaver, & Calder, 2006; Seyama, 2006; Seyama & Nagayama, 2006). There is also a lot of evidence about the significant influence of gaze perception in human behaviour: direct gaze both captures attention and delays disengagement of attention from the face stimulus (George, Hugueville, Conty, Coelho, & Tijus, 2006; Senju & Hasegawa, 2005; Senju, Hasegawa, & Tojo, 2005); humans have better performance recognizing and making gender categorization when the face stimuli display direct rather than averted gaze (Hood, Macrae, Cole-Davies, & Dias, 2003; Macrae, Hood, Milne, Rowe, & Mason, 2002; Mason, Hood, & Macrae, 2004; A. D. Smith, Hood, & Hector, 2006); observers avoid to withdraw attention from the gazed-at location (Frischen & Tipper, 2004).

Despite the belief about the innate nature of the processes involved in JA, its full establishment in humans is a long and complex process. Reports refer the first emerging joint attention signals after around 2 to 4 months (Amano, Kezuka, & Yamamoto, 2004; Scaife & Bruner, 1975). Amano, Kezuka, and Yamamoto (2004) described 3 months-old babies looking from an adult's head to their hand and pointed it as a JA precursor. This development continues growing and at 6 months-old babies start to orient towards an object of a caregiver's attention (Baldwin, 1995; Butterworth & Cochran, 1980; Butterworth & Jarrett, 1991) and it is shown that the acquisition of this competency at this age is correlated with vocabulary size at 18 months (Morales et al., 2000; Morales, Mundy, & Rojas, 1998). At 20 months, JA abilities are sufficient to predict theory of mind abilities at 44 months (Charman et al., 2000).

Once these basic JA mechanisms are formed, children start to use other people's orienting behaviour to infer about more complex intention predictions. For example, Baron-Cohen and colleagues (1995) reported that 3 and 4 years children were capable to deduce the desire for food trough the gaze direction of a schematic face (looking to a bar of chocolate).

Around the 5th year of age children's use of gaze cues is still very susceptible to interference when faced with contradictory information (Pellicano & Rhodes, 2003) but around the 7th year children start to present brain patterns similar to adults when analysing gaze direction (Mosconi, Mack, McCarthy, & Pelphrey, 2005b).

Although, in the literature, it has long been assumed that gaze cueing is universal in typically developed people it is now clear that this may be not the case. In fact there is data showing a great range of cueing magnitudes (A. P. Bayliss, Pellegrino, & Tipper, 2005; Hietanen, Nummenmaa, Nyman, Parkkola, & Hämäläinen, 2006). So, it is important to see gaze cueing as a robust effect given an appropriately sized random sample. In fact there are works showing that gaze cueing is influenced by the task instruction (Bukowski, Hietanen, & Samson, 2015; Hermens, 2015), by mental state attributions (Morgan, Freeth, & Smith, 2018) and emotions (Macdonald & Tatler, 2015; Pecchinenda & Petrucci, 2016).

STS seems to have a great influence in the initial analysis of social cues and it is in a privileged anatomical location to integrate information derived from both the ventral "what" and the dorsal "where" visual pathways (T. Allison, Puce, & McCarthy, 2000). Haxby et al. in (Haxby, Hoffman, & Gobbini, 2000) postulated that the posterior STS is responsible for the processing of quickly changing social features, such as facial expressions. Nummenmaa & Calder in (Nummenmaa & Calder, 2009) believe that the posterior STS is related to the processing of the intentionality of others' actions. Hein and Knight in (Hein & Knight, 2008) agreed that the function of STS depends largely upon the co-activations of connected areas. On the other hand, Lahnakoski and colleagues (2012) suggested that the posterior STS region is functionally tightly coupled with other brain regions and might work as a convergence (integration) hub of social information processed in other functionally connected sub-systems. This hypothesized integrative role of STS makes it a central high-level system responsible for the creation of mental representations of other people's behaviour, intentions, and mental states – identification of intention – all fundamental skills in JA.

Altogether, these data demonstrate the relevance of gaze following in the development of social cognition. Humans are prone to detect and encode other people's eyes, and direction of gaze in particular, since early in life, and these skills serve as building blocks for the development of other higher level social cognition abilities such the identification of intention and mental states. Therefore, the correct development of these gaze perception and gaze-following skills have a crucial importance so the individual social cognition reaches its full potential. It is evident that these mechanisms are impaired in ASD.

1.4.2.1 Joint Attention Deficits in Autism

The evidence is clear showing people with autism have a highly impaired cognitive profile regarding gaze processing. People with ASD tend to dislike and avoid eye contact (Baron-Cohen, 1988; Dalton et al., 2005; K. A. Pelphrey et al., 2002) and show greater galvanic skin response and greater neural activity (compared to normal individuals) in the fusiform gyrus and amygdala when asked to explore the eyes region (Dalton et al., 2005) which suggests that autistic people avoid eye-region to control their arousal levels. Also, adults and children with autism have worse performance attributing emotions to people based on the eye region compared to normal individuals (Baron-Cohen et al., 1995, 2001; Baron-Cohen, Wheelwright, & Jolliffe, 1997). Moreover, children with autism make little eye contact with a person performing an action regardless the semantic context they are embedded whereas normal children engage gaze more readily when a person's action is ambiguous (Phillips, Rutter, & Baron Cohen, 1992).

Given this, it is predictable that JA development is impaired in ASD (Charman et al., 1997; Dawson et al., 2004; S R Leekam, Lopez, & Moore, 2000; Roeyers, Van Oost, & Bothuyne, 1998). For example: autistic children only start to respond to JA cues after their cognitive development reaches the equivalent to 30 to 36 months in normal development (Mundy, Sigman, & Kasari, 1994); the impairments on initiation and response to JA are also evident until the adolescence (Charman, 2003; Mundy, Sigman, Ungerer, & Sherman, 1986) and adulthood (Caruana et al., 2017); autists have less attention sharing interactions with other children and caregivers (Mundy et al., 1986). Imitation – a JA dependent skill – is also impaired in ASD children (Charman et al., 1997; Stone, Ousley, & Littleford, 1997), a sign of mirror system disruption; and individuals with autism perform more shifts of attention with objects rather than with people (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; J. Swettenham et al., 1998).

Despite the quantity of evidence about patterns of gaze avoidance in autism some other studies (Chawarska, Klin, & Volkmar, 2003; Susan R. Leekam & Hunnissett, 1998; John Swettenham, Condie, Campbell, Milne, & Coleman, 2003) were able to find normal levels of orienting towards another's gaze in children with high functioning autism (individuals with Intelligence Quotient within the normal range). This can be because of the relevance of low-level motion characteristics of the cues from which JA develops in normally developing children. Nevertheless, the use of gaze cues in typically developing children is much more nuanced, in contrast to participants with autism. For example, normally developing children have asymmetric preference orienting to gaze cues (A. P. Bayliss & Tipper, 2006; Okada, Sato, Kubota, Toichi, & Murai, 2012) while people with ASD tend to orient equally both to right and left (Vlamings, Stauder, Van Son, & Mottron, 2005). More, children with autism are not influenced by counter-predictive gaze or arrow cues (Senju, Tojo, Dairoku, & Hasegawa, 2004) and do not alter their performance when reaching an object gazed or gazed away (Pierno, Mari, Glover, Georgiou, & Castiello, 2006). In sum, these results suggest that the system that allows a gaze cue to shift attention may be different in people with autism. This system seems to be less flexible and is not able to recruit such higher-level processing mechanisms as the normal population's system does.

The existence of normal levels of social orienting in children with autism (Chawarska et al., 2003; Susan R. Leekam & Hunnissett, 1998; John Swettenham et al., 2003) remains a surprising fact having in account the reports showing atypical orienting in adult samples (Ristic et al., 2005; Vlamings et al., 2005). The first thought would be that the compensation mechanisms that individuals acquire during their development would help to improve the use of the gaze in older people with autism and, because of their social development delay, children with autism would show weaker effects of gaze cueing. The evidence shows the opposite: despite the developmental delay autistic children at 2 years age and above show gaze cueing whereas adults show no gaze cueing. The possible explanation for this age differences in gaze behaviour could be related to different degree of voluntary control over joint attention in the adulthood. While normally developed adults retain a more reflexive cueing response, autistic adults exert a non-automatic control over joint attention mechanisms. This is supported by the data from Dalton et al. (2005) where they reported greater amygdala activity in autistic individuals when they attended to the eyes. Amygdala activity may be linked to the described increased arousal when people with autism make eye contact. It is possible that individuals with autism may develop an adaptive strategy to reduce the greater emotional response caused by eye gaze namely the avoidance of the eye region of other person. This avoidance could be driven by an inhibitory mechanism preventing the person orienting to the eye region in the first place.

Having this avoidance strategy in account one can partially understand the individual variability in gaze-cuing magnitudes in the normal population (A. P. Bayliss et al., 2005; Bukowski et al., 2015; Hermens, 2015; Macdonald & Tatler, 2015; Morgan et al., 2018; Pecchinenda & Petrucci, 2016) and predict the implications this can have in autism. That is, if the visual system is not able to acquire quality information from other's eye region (because it was induced to not fixate this region) the gaze cueing system will receive a weaker signal and will not be able to compute the appropriate direction. Each individual can develop their own specific mechanism to deal with eye gaze, which in turn creates the variable gaze-cuing magnitudes across individuals. Nevertheless, it is still unclear whether variations in the reflex to orient to the eye region can explain the differences in cueing or if those individual differences are the consequence of variations in the gaze-cueing system itself.

Some neuroimaging studies noted that the observation of gaze direction originates neural maps that resembles to the exogeneous orienting maps. Covert shifts of attention have a similar activation patterns as the saccadic eyes movements (Grosbras, Laird, & Paus, 2005), which is congruent to the findings that the observation of a particular action elicits the same patterns of activity in the premotor areas as the patterns originated when performing the same action (Gallese, Keysers, & Rizzolatti, 2004; Iacoboni & Dapretto, 2006; Rizzolatti & Craighero, 2004). This could mean that human mirror system may be involved in the observation of gaze because it triggers involuntary saccades in the corresponding direction. (Mansfield, Farroni, & Johnson, 2003; Ricciardelli, Ro, & Driver, 2002).

Adding to this, several works revealed that both visual and oculomotor neurons are active in the frontal eye field during covert shifts of attention and saccade preparation (Connolly, Goodale, Menon, & Munoz, 2002; Gitelman et al., 1999; Schall, 1997). STS was also reported to be active in gaze perception, eye movements, covert shifts of attention and some of their neurons do project directly to the frontal eye field (see: Grosbras et al., 2005; Komatsu & Wurtz, 1989; Nobre, Gitelman, Dias, & Mesulam, 2000; Samus et al., 2006).

All these studies give support to the view that the preparation of goal-oriented actions and attention shifts are linked. This idea is known by the premotor theory of attention (Rizzolatti, Riggio, Dascola, & Umiltá, 1987; Rizzolatti, Riggio, & Sheliga, 1994). Accordingly, the spatial mechanisms of attention are able to originate neural responses coding visually guided movements in space. That is, the observation of another person's saccade activates the corresponding motor program, which in turn results in an attention shift in the corresponding direction. The dysfunction of this mirror system has been suggested to be a root cause in the development of autism (Williams, Whiten, Suddendorf, & Perrett, 2001). Indeed, mirror system activation is decreased in individuals with autism during observation and imitation of movements of the lips and hands as well as of emotional facial expressions (Dapretto et al., 2006; Nishitani, Avikainen, & Hari, 2004; Oberman et al., 2005; Théoret et al., 2005).

Mirror neuron activity play a pivotal role in imitation, in decoding actions goals and, therefore, understanding another person's intentions. These are the skills impaired in autism and also key elements in theory of mind. With these data and arguments theory of mind has been became very popular in explanatory frameworks of the difficulties in ASD.

1.5 Brain Computer Interfaces

We all have, at least occasionally, the desire to know what another person is thinking about. Machine learning approaches and Brain Computer Interfaces (BCI) are, possibly, the closest thing humans have created to achieve that. The concept of a BCI was formalised in 1973 by Vidal (Vidal, 1973) after some attempts to produce music in real time using brain activity patterns. Taking Wolpaw definition "a BCI is a communication system in which messages or commands that an individual sends to the external world do not pass through the brain's normal output pathways of peripheral nerves and muscles" (in J. R. Wolpaw, Birbaumer, McFarland, Pfurtscheller, & Vaughan, 2002). In other words, BCI translates individuals' brain information to the external world without the necessity to recruit natural means of communication (speech, gestures, etc...), and use this information as messages or commands for interactive applications (computers or robotic devices) turning them in a communication channel.

BCIs can be classified according to dependability, invasiveness, and synchronization (Ramadan & Vasilakos, 2017).

Dependent BCI and independent BCI

The dependent BCI requires certain level of motor control from the subject and could facilitate subjects doing some tasks (playing video games and moving a wheelchair for example). Independent BCI does not require any motor control and are indicated to subjects with severe disabilities (B. Allison, Graimann, & Gräser, 2007).

Invasive BCI and non-invasive BCI

BCI is classified to invasive or non-invasive according to the way of the brain activity is measured. BCI based on invasive sensors, to perform intracranial recordings e.g. electrocorticography (Leuthardt, Miller, Schalk, Rao, & Ojemann, 2006; Schalk et al., 2008; Simeral, Kim, Black, Donoghue, & Hochberg, 2011), in which grid electrodes or even microelectrodes are implanted in the brain, under the skull, or implanted inside the brain cortex during neurosurgery for functional mapping purposes. In this case, the signal might be produced with high quality but can give some risks for the users (such as infections, haemorrhages or bio-incompatibility).

Non-invasive BCIs, do not represent any risk for the user and include brain signals recording techniques such as:

- functional magnetic resonance imaging (fMRI) - measures metabolic activity through the blood oxygen level dependent (BOLD) signal. This technique allows to determine the source of the brain signal very precisely in space (good spatial resolution), but it has a limitation: BOLD signal is observed with a relatively fixed delay after the neural activation and has low temporal resolution. This limits its utilization on BCI applications, to the second time scales. However, Weiskopf and coleagues (2004) were able to successfully achieve real-time BCI operation and this field is increasingly growing.
- functional near infrared spectroscopy (fNIRS) - measures the cortical activity through the changes in absorption and reflection of the emitted light by the devices' light source (infrared emitting diode placed in direct contact with scalp) and follows similar principles as BOLD imaging. The utilization of this technique is attractive because it uses simple optodes, is portable and inexpensive, but the research around fNIRS-BCI systems it is still at its infancy (Naseer & Hong, 2015). Such as fMRI, fNIRS is highly dependent of the nature of the hemodynamic response.
- magnetoencephalography (MEG) – detects the magnetic fields generated by the electric currents in active neurons. Because the order of magnitude of the magnetic fields being very small (<10-12 fTesla) the acquisition devices must

be very sensitive which makes them very expensive and bulky. Despite this, their temporal and spatial resolution are quite attractive, as well as its frequency range which some studies have been exploiting for BCI algorithm development (Buch et al., 2008; Florin, Bock, & Baillet, 2014; Reichert, Dürschmid, Heinze, & Hinrichs, 2017).

- electroencephalography (EEG) - EEG is the recording of brain electric potential oscillations. The recording is made through electrodes placed directly on the scalp over the cortex. EEG is considered the most common method for recording of brain signals because it has high temporal resolution, it is easy to use, safe, and affordable. EEG will be addressed in more detail further ahead.

Synchronous and asynchronous BCI

A BCI system is called a synchronous when the system imposes the subject interaction within a certain period of time, otherwise, the system will not be able to receive the subject signals. An asynchronous BCI, gives the liberty to the user to perform the mental tasks at any time and the system reacts to his/her mental activities.

A well designed BCI requires it to have two functioning phases: 1) an offline training phase during which the system is calibrated and 2) the operational online phase in which the system recognises brain activity patterns and translates them into commands for a computer. An online BCI is a closed-loop system generally composed by six fundamental steps: brain activity measurement, pre-processing, feature extraction, classification, translation into a command and feedback. Figure 1.1 shows a generic architecture of a BCI system.

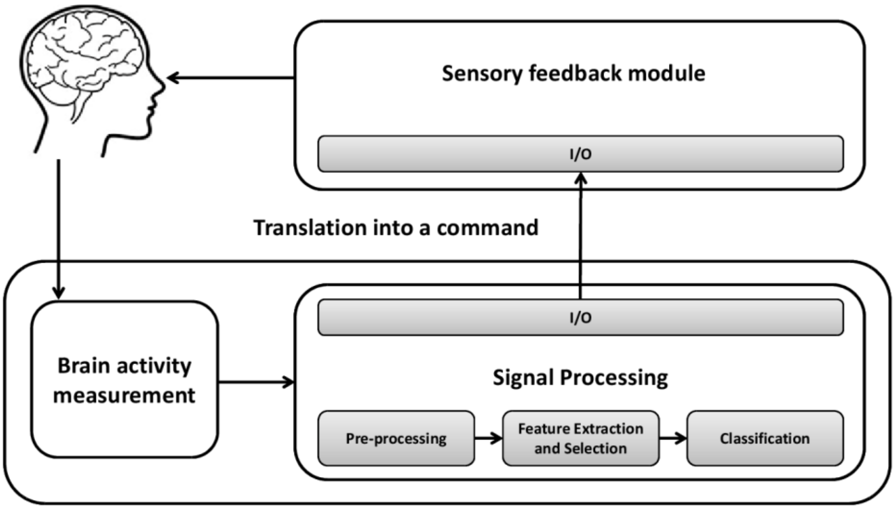

Figure 1.1 – Generic architecture of an online Brain Computer Interface. Designing a BCI requires multidisciplinary knowledge in computer science, engineering, signal processing, neuroscience and psychology.

Currently, the training phase is generally a fundamental step of a BCI system in order to obtain a reliable BCI operation and it is generally done offline. In this stage, pre-recorded data from the user are used as a training data set so the optimal features are selected, and the classification algorithm is calibrated to detect a mental state of interest. This implies the training data set contains brain signals recorded while the user performs each mental task of interest several times, according to given instructions. The recorded EEG signals are then used as mental state representations of the task and the calibration parameters are set for each user from these representations. In consequence BCI systems are highly user-specific. The information about the optimal features and the calibration parameters are then used in the online phase of BCI and optimize the detection of the user's brain state through its brain signal.

It is important to have in mind that, although BCIs seems to be a promising technology, they still have serious limitations that prevent it to be used reliably in practical applications and in real life scenarios. The main reasons for that are the modest robustness and reliability: very rare occurrences of 100% correct recognition of user´s mental states (C. Guger, Edlinger, Harkam, Niedermayer, & Pfurtscheller, 2003; Christoph Guger et al., 2012, 2009); some users are completely unable to use some types of BCIs (B. Z. Allison & Neuper, 2010); BCI performance decreases when used outside laboratory conditions, when the users are moving and when used over long periods (Brandl, Hohne, Muller, & Samek, 2015; Fatourechi, Bashashati, Ward, & Birch, 2007; Fabien Lotte et al., 2009); BCIs are less reliable when used by severely motor-impaired users such as locked in patients (Neumann & Kubler, 2003); the calibration time of EEG-based BCIs is relatively long (Fabien Lotte, 2015) and may also require long to very long human training time (Kindermans, Tangermann, Müller, & Schrauwen, 2014; Neuper & Pfurtscheller, 2009). So, the challenges the research community must tackle to yield a robust practical and functional BCI are vast and serious.

The next sections will address fundamental concepts for the understanding of BCIs functioning that are related to each one of the BCI operation steps. We will increasingly focus on the topics related to EEG analysis in BCI, since this is the field we are working at.

1.5.1 Brain Activity Measurement

The central focus of a BCI loop is the user and his/her brain. The brain signals that are being measured and processed by the BCI are the source of information that guides the operation of this technologic system.

1.5.1.1 Electroencephalography

As already stated, EEG is the most common method for recording brain signals in humans because it is safe, affordable, easy to use, and because it has a temporal resolution of the order of milliseconds (Niedermeyer & da Silva, 2005).

The typical recording system of an EEG includes the electrodes that capture the electrical signal on the scalp; differential amplifiers, sensitive to voltage differences, but not to the spatially constant potentials over the scalp; analog filters, removing superfluous artefacts 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 Figure 1.2.

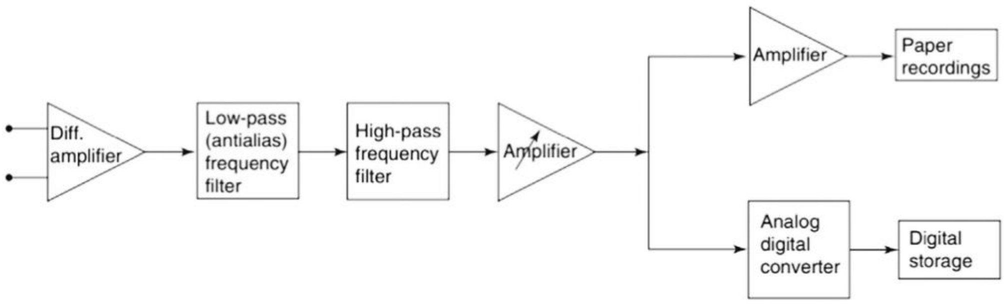

Figure 1.2 – Schematic diagram of a generic EEG recording. The electrical signal is captured by the electrodes and the potential difference between the electrodes and the ground electrode is amplified. The signal is filtered and then amplified, before being converted to digital. The EEG signal can be displayed and stored.

EEG electrodes, placed on the scalp, can be either "passive" or "active". Passive electrodes, mostly made of an Ag/AgCl alloy, are connected to an amplifier by a cable. Active electrodes have an inbuilt preamplifier to make them less sensitive to environmental noise and cable movements. The electrodes are placed in the scalp with a conductive paste or gel to decrease impedance, the resistance to electrical current. These electrodes are called wet electrodes. The used gels have conductivity similar to skin, and their gelatinous consistency helps improve the contact of electrodes with the skin which diminishes the loss of signal power. 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. Special materials are used in dry electrodes including conductive foams, spring-loaded fingers, and micro-machined structures, conductive rubber, conductive carbon nanotubes, and bristle structures (Gargiulo et al., 2010; S. Lee, Shin, Woo, Kim, & Lee, 2013; Liao, Wang, Chen, Chang, & Lin, 2011; Lopez-Gordo, Sanchez Morillo, & Pelayo Valle, 2014; Mihajlovi, n.d.; Zander et al., 2011). Dry electrodes usually are combined with the active electrodes technology and used without any conductive gel or glue.

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 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 (Cooper, Osselton, & Shaw, 1974; Klem, Luëders, Jasper, & Elger, 1999; F. W. Sharbrough et al., 1994). The intermediate 10% or 5% electrode positions can be also used (Oostenveld & Praamstra, 2001). See Figure 1.3.

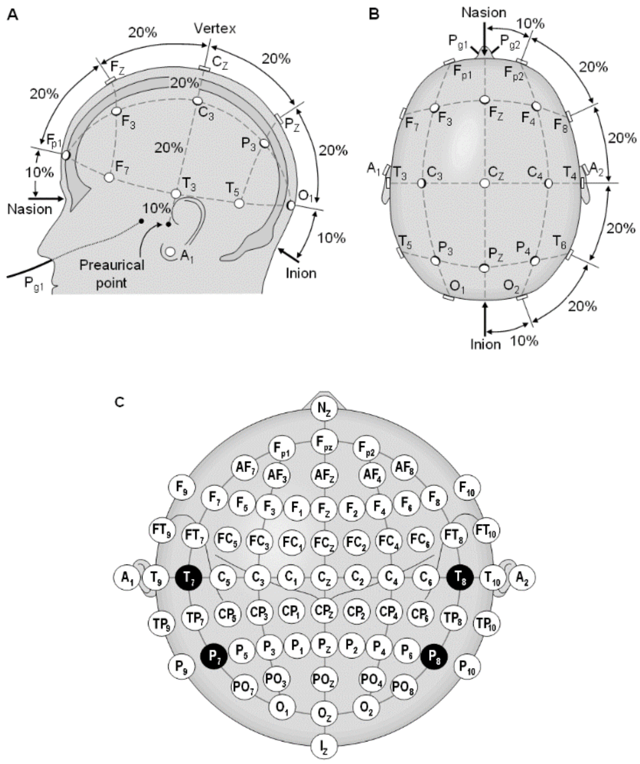

Figure 1.3 – Left (A) and top (B) of the head views of the international 10-20 system. (C) Location and nomenclature of the intermediate 10% electrodes, as standardized by the American Electroencephalographic Society (in F. Sharbrough et al., 1991).

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.

1.5.1.2 Using attentional signals to control BCIs – The P300 Component

The brain signals that can be measured from EEG and used in BCI can be categorized into three categories: evoked signals; spontaneous signals; and hybrid signals.

Evoked signals or evoked potentials are the direct response to an external stimulus such as a light flash or an auditory tone. Evoked potentials are considered an early component (occur within the 100 ms after the onset of the stimulus) of an Event Related Potential (ERP). 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; Scott, 1999). Because of this, the ERPs may even last beyond stimulus duration.

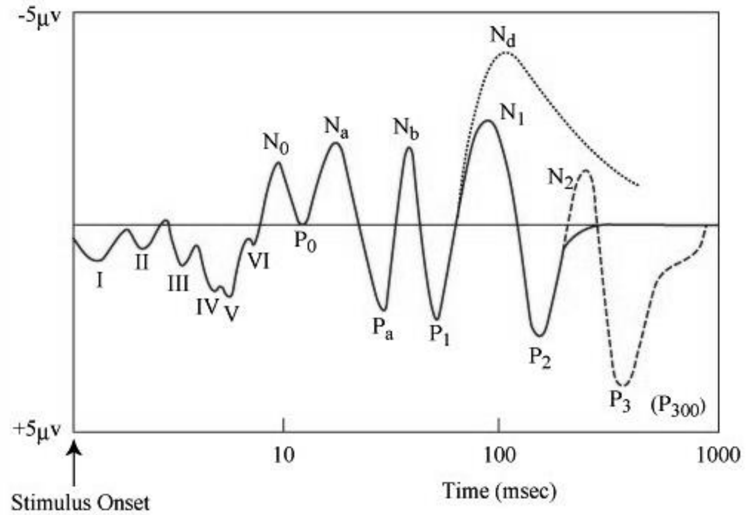

Figure 1.4 – Idealized representation of ERPs components. Each component is dependent on stimulus context and subject attention. The name of the components is based in amplitude polarity and the latency of the peak. The vertical axis is the potential of the EEG record. Adapted from (M I T - Massachusetts Institute of Technology, 2016).

An ERP consists of a wave form containing a series of characteristic peaks occurring after the presentation of each stimulus (Figure 1.4).

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). The parameters that define an ERP are its positive or negative potential difference, its latency (time between the stimulus presentation and the 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 to specific cognitive processes. The bigger the latency of the ERP the later the processing stage of 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.

A well known evoked signal are the Steady State Evoked Potentials (SSEP) that can be weither visual (SSVEPs), somatosensory SSEP or auditory SSEP. SSEP signals are brain signals that are generated when the subject perceives periodic stimuli such as flickering images, modulated sounds, and even vibratory stimuli (Kuś et al., 2017). SSVEP are by far the most used SSEP for BCI design (Bin, Gao, Wang, Hong, & Gao, 2009; Jinghai Yin, Derong Jiang, & Jianfeng Hu, 2009). SSVEP are generated at the visual cortex with the same frequency of the flickering visual stimuli (usually between 6 and 30 Hz). The popularity of SSVEP is because it can be used without user training, and can provide a large number of commands. The mandatory need for a stimulus, and the reliance on the user's visual attention are the main limitations of this brain signal.

The spontaneous signals are the signals generated by subject voluntarily without any external stimulations. Among this type of signals, we can find the motor and sensorimotor rhythms, Slow Cortical Potentials (SCP), and non-motor cognitive tasks.

The motor and sensorimotor rhythms (Golub, Chase, Batista, & Yu, 2016) are related to the desynchronization and synchronization coming from over sensorimotor cortex with frequency bands located at μ (≃8–13 Hz) and β (≃13–30 Hz). The controlling of amplitude of these rhythms can be learned by performing tasks such as motor imagery (e. g.: imagine the movement of a hand) or similar strategies under operant conditioning (choose the personal best mental strategy so achieve the desired control). However, some people are unable to achieve this control. SCP is a signal within a frequency range below 1 Hz (Kim et al., 2004) detected in the frontal and central parts of the cortex as the result of depolarization shifts in the upper cortical dendrites. The subject can learn to control the generation of SCP signals under operant conditioning, but this which might require very long training procedures. Motor and sensorimotor signals are preferred over the SCP to be used in BCIs.

When a BCI works with **hybrid signals** it means that a combination of brain generated signals are used for control. The main purpose of the usage of hybrid brain signals for control is to mitigate the disadvantages of each signal individually with the advantage of the other used brain signal. The review from Amiri, Fazel-Rezai, & Asadpour (2013) addresses these types of systems.

The P300 Component

The positive deflection of the ERP waveform about 300 milliseconds after the presentation of oddball types of stimuli is called the P300 wave (Figure 2.4). It was first reported in 1965 by Sutton (Sutton, Braren, Zubin, & John, 1965). P300 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 for oddball responses can vary from approximately 250 to 1000 milliseconds (Duncan-Johnson & Donchin, 1982; Kutas & McCarthy, 1977; Kenneth Squires, Petuchowski, Wickens, & Donchin, 1977). P300 has a scalp distribution over the midline electrodes, and its magnitude decreases from the parietal to frontal electrode sites (Johnson Jr, 1993).

As stated above the stimulus that gives rise to the P300 component is called an oddball. This paradigm consists of a random sequential presentation of visual or auditory stimuli. For these tasks the individuals are instructed to respond to target (target) stimuli with less frequent occurrences (thereby called oddballs), 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. Figure 1.5 ilustrates the stimulation sequence of an oddball paradigm. SOA and stimulis duration represent the time between the onset of two diferent stimuli (SOA = Stimulus Onset Asynchrony), and the time duration of the stimulus presentation, respectively.

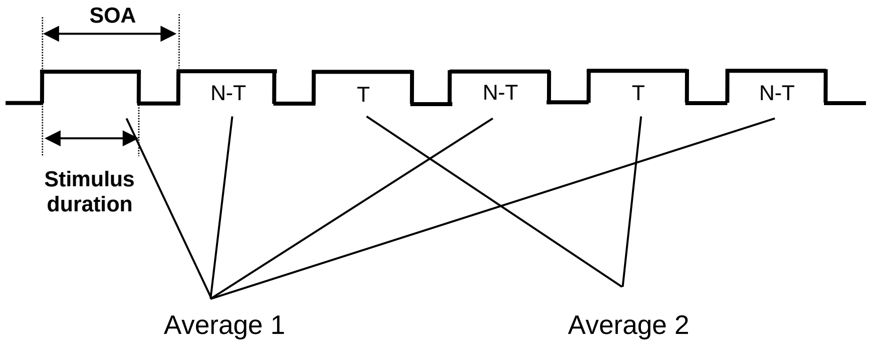

Figure 1.5 – Schematic illustration of traditional oddball paradigm. Two different stimuli are presented in a random sequence, with the target stimulus occurring less frequently (Target = T) than the standard stimuli (Non-Target = N-T). Each stimulus is specifically identified by markers in the EEG data (so called triggers) 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: P300 amplitude is positively correlated with SOA (B. Z. Allison & Pineda, 2006). The number of events, number of total stimuli, is also important to the paradigm sctructure and the relative Number of Targets, , defines the probability of the target stimuli appearance. 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 is broken the elicited P300 is larger (K. Squires, Wickens, Squires, & Donchin, 1976). The works of Donchin and Pritchard are pivotal in the clarification of the roles of stimulus probability and task relevance in the oddball paradigm (Donchin, Ritter, McCallum, & McCallum, 1978; Pritchard, 1981).

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), but in turn it increases the time needed to complete the experiment which may potentiate the participants fatigue which in turn have negative impact on P300 amplitude.

1.5.2 Pre-Processing

After the acquisition of brain signals, they must be analysed and processed in order to identify the brain activity patterns they contain. The pre-processing of the signal must be planned having in mind noisy signals unrelated to brain activity: muscular activity of the head and neck, eye movements and eye blinks which generate electric charge variations. It is important to be aware of these artefacts and be careful not to process them indistinctly from brain signals (Fatourechi et al., 2007). Detecting muscular artefacts can be done with amplitude thresholds on band-power or time-courses of certain channels. For ocular artefacts, additional electrodes can be placed close to the eyes, allowing to recognise a trace of that activity on the EEG channels. Once an artefact has been detected, the portion of data corrupted with this artefact should be rejected or one can subtract the effect of the artefact from the EEG by using special techniques such as Independent Components Analysis or specific filters (A. Schlögl et al., 2007). Basic temporal filtering, such as low-pass, high-pass, band-pass (e.g.: between 0.1-30 Hz) and notch, are usually applied to EEG, to eliminate signals that are outside the frequency range of interest, or to eliminate specific interferences. Epoching the raw data is often a fundamental step in pre-processing of EEG data in ERP based BCIs. When we extract the time points surrounding the stimulus onset, we are able to associate the mental state contained in the epoch to some property of the stimulus or task that originated the response. The whole EEG data is cut by using a fixed time window (e.g. 0-1000 ms) corresponding to each trigger onset and each segment is named as an epoch. The remaining steps that lead to the classification (feature extraction and classification) are applied to the resulting epochs.

1.5.2.1 Feature Extraction

Despite the use of the above pre-processing techniques, it may not be sufficient to provide adequate features for classification. The feature extraction aims at representing the pre-processed EEG signals by an ideally small number of relevant values, which describe the task-relevant information contained in the signals. These features should be selected to minimise the intra-class variance while maximising inter-class variance. In other words, the intention of feature extraction is to increase the signal-to-noise ratio (SNR) of ERPs and maximize the difference between the classes. At the same time, feature extraction aims to reduce the dimensionality of feature space, by mapping the input data into a lower dimensional space which may avoid overfitting to training data, increases algorithm robustness, and provides faster and more effective algorithm computation (A. Schlögl et al., 2007).

BCI based on oscillatory activity (e.g., BCI based on SSVEP or motor and sensorimotor rhythms) mostly use spectral and spatial information as features. Spectral estimation techniques are applied on raw EEG data and include techniques like discrete Fourier transform, auto-regressive models, wavelets and periodogram based methods such like Welch (Bashashati, Fatourechi, Ward, & Birch, 2007; Brodu, Lotte, & Lécuyer, 2011; Herman, Prasad, McGinnity, & Coyle, 2008).

Since ERP components are time-locked and phase locked with the events, ERP based BCIs mostly use the temporal and spatial information. This information benefits from being extracted after spatial filtering. Spatial filtering results in a combination of the original sensor signals with a higher signal-to-noise ratio than that of individual sensor. One can find data independent filters (based on the physical consideration of the EEG acquisition) like the Laplacian filter (McFarland, McCane, David, & Wolpaw, 1997). There are also data-driven and unsupervised spatial filters such as principal component analysis (PCA) or independent component analysis (ICA) (Kachenoura, Albera, Senhadji, & Comon, 2008). Filters obtained in a data-driven manner and with supervised learning include the well-known common spatial patterns (CSP)

(Blankertz, Tomioka, Lemm, Kawanabe, & Müller, 2008) dedicated to band-power features and oscillatory activity BCI, and spatial filters such as xDAWN (Rivet, Souloumiac, Attina, & Gibert, 2009) or Fisher spatial filters (Hoffmann, Vesin, & Ebrahimi, 2006) for ERP classification based on time point features. In which concerns P300 detection, the work of Pires (2009) and Krusienski (2007) proposed a successfully adaptation of CSP called Common Spatiotemporal Patterns (CSTP).

1.5.2.1.1 C-FMS beamformer

In (Pires, 2011; Pires et al., 2011b) our collaborator Gabriel Pires proposed the C-FMS beamformer methodology that cascades a spatial filter based on the Fisher Criterion (FC) with another spatial filter that maximizes the ratio of signal power and noise power (Max-SNR) satisfying simultaneously sub-optimally both criteria.

The FC aims to increase the separation between classes while minimizing the variance within a class, much like the Fisher's linear discriminant - FDL (Duda, Hart, & Stork, 2001). The FC takes into consideration the difference between target and non-target spatio-temporal patterns and it is expected that this filter maximizes the differences between them and enhances the subcomponents present in the ERPs

The FC is given by the Rayleigh quotient

$J(W) = \frac{W' S_b W}{W' S_w W}$,

where W is the weighting vector, $'$ represents the transpose operator and with S_b being the between-class scatter matrix and S_w the within-class scatter matrix computed taking the data matrices X_k (with dimension N(number channels) $\times T$ (number of time points)) from each epoch:

$$S_b = \sum_i p_i(\bar{X}_i - \bar{X})(\bar{X}_i - \bar{X})'$$

and

$$S_w = \sum_i \sum_{k \in T_i} (X_{i,k} - \bar{X}_i)(X_{i,k} - \bar{X}_i)'$$

where $i \in \{+, -\}$ and T_+ and T_- represent the target and non-target classes, and p_i is the probability of occurrence of each class. $\bar{X}_i$ and $\bar{X}$ are the average of the epochs in each class and the average of all epochs, respectively, and k represent the individual epochs.

The solution is achieved by finding the generalized eigenvalue decomposition that satisfies the equation

$$S_b W = S_w W \boldsymbol{\Lambda} \, ,$$

having $\boldsymbol{\Lambda}$ as the eigenvalue matrix.

We can obtain the eigenvectors W from the eigenvalue decomposition of $(S_w)^{-1} S_b$. The principal eigenvector maximizes the SNR, and therefore the output of the spatial filtering, is calculated by

$$y = W_{FC}^{(1)\prime} X \, .$$

The result y is a $1 \times T$ projection of the EEG channels on X that maximizes the difference between target and non-target classes and minimizes the variance within a class.

Analogously, the Max-SNR methodology starts with the concept that the spatial filtering of P300 is a spatial denoising problem, and the solution for this problem is a beamformer that maximizes the output SNR, that can be translated by the Rayleigh quotient:

$$SNR = \frac{W' \bar{R}_+ W}{W' \bar{R}_- W} \, ,$$

where + and – represent the target and non-target classes.

The matrices $\bar{R}_+$ and $\bar{R}_-$ are the $N \times N$ average of the spatial covariances for each epoch inside each classs (k), calculated with $R_k = \frac{X_k X_k'}{tr(X_k X_k')}$.

The solution is achieved by finding the generalized eigenvalue decomposition that satisfies the equation

$$\bar{R}_+ W = \bar{R}_- W \boldsymbol{\Lambda} ,$$

having $\boldsymbol{\Lambda}$ as the eigenvalue matrix.

We can obtain the eigenvectors W from the eigenvalue decomposition of $(\bar{R}_-)^{-1}\bar{R}_+$. The principal eigenvector maximizes the SNR, and therefore the output of the beamformer is calculated by

$$y = W_{SNR}^{(1)}{}'X .$$

X is the data matrix with the dimension $N \times T$, where N is the number of EEG channels and T the number of time points. The result y is a $1 \times T$ projection of the EEG channels on X that maximizes the SNR.

We used this strategy proposed by Gabriel Pires to cascade the two spatial filters and simultaneously satisfy both criteria. The idea is to apply FC method, compute the spatial filter W_{FC} and obtain the first filtered projection of the data:

$$Y = W_{FC}' X .$$

The first feature vector to be used, y_1, is the first projection of Y

$$y_1 = W_{FC}^{(1)'} X .$$

Then, from the remaining projections, $Y^{(2:N)}$, calculate the Max-SNR filter and get the corresponding projection

$$z_1 = W_{SNR}^{(1)'} Y^{(2:N)} .$$

The features to be used in the subsequent steps are the result of the concatenation of these two projections from each filter

$$feature\ vector = [y_1 \ \ z_1] \ .$$

These features maximize simultaneously and sub-optimally both FC and max-SNR criteria. From here we have also a substantial reduction of feature space, fundamental in feature extraction.

Figure 1.6 schematizes this logic in a simplistic way.

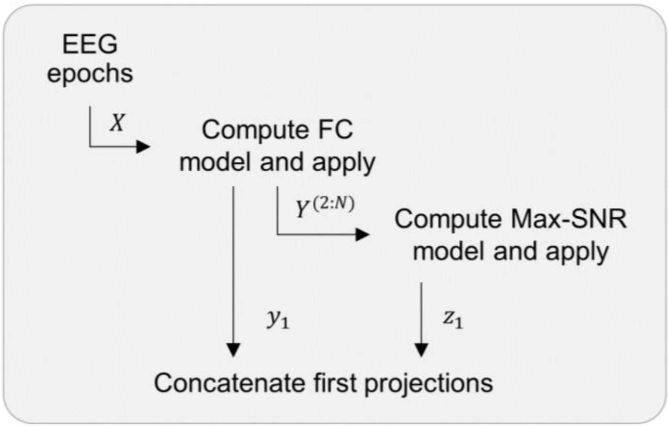

Figure 1.6 – Schematic representation of the C-FMS beamformer methodology for the feature extraction.

The data-driven nature of this methodology implies that the calculation of C-FMS beamformer models must be done from the training phase data of the BCI.

The regularization of spatial filters has been successfully applied to spatial filters (Blankertz et al., 2008; Fabien Lotte, Guan, & Member, 2011; Lu, Eng, & Guan, 2010; Lu, Plataniotis, & Venetsanopoulos, 2009; Mak et al., 2011b; Schäfer & Strimmer, 2005; Yu Zhang, Zhao, Zhou, Wang, & Cichocki, 2012). It consists in the regularization of the covariances matrices in order to compensate their systematic bias. This is specially common when the calculation of the filters models is done with a reduced volume of training cases in comparison to the dimensionality of the data (in EEG, usually the dimensionality of the data is around 32 channels × 1000 time points per epoch vs. some dozens of epochs for training). In practice, it results in the inclusion of a regularization parameter on the eigenvalue problem equations

$$S_b W = [(I-\theta)S_w + \theta I]W\boldsymbol{\Lambda}\,,$$

$$\bar{R}_+ W = [(I-\lambda)\bar{R}_- + \lambda I]W\boldsymbol{\Lambda}\,,$$

where θ and α are the regularized parameters that can be adjusted taking account the training data and I the identity matrix. This parameter acts mostly under the extreme eigenvalues (large or small) and modifies them (shrinking or elongating) towards a (potentially) better representation of the feature space (see Blankertz, Lemm, Treder, Haufe, & Müller, 2011). Regularization can prevent overfitting and the influence of outliers and controls the complexity of the models. The negative aspect of this approach is the computational complexity for cross validation estimation of the regularized parameter.

1.5.2.1.2 Feature Selection

The feature extraction methods can lead to a set of variables that can give no more than suboptimal predictors of the mental states. That is because among the various features that one can extract from EEG signals, some may be redundant or may not be related to the mental states targeted by the BCI. Thus, a feature selection step can be applied after the feature extraction step (Guyon & Elisseef, 2003). Methods for feature selection usually fall into three feature selection approaches (Kohavi & John, 1997; F Lotte et al., 2018): filters, wrappers and embedded approaches. In general, the benefits of using these methods include the facilitation of data visualization and data understanding, the reduction of measurement and storage requirements and reduction of training and utilization times.

Filter methods rely on measures of relationship between each feature and the target class, independently of the classifier to be used which makes it computationally more efficient and offer a better generalization. The square of the estimation of the Pearson correlation coefficient - r^2- (Fieller, Hartley, & Pearson, 2014), can be used as a feature ranking criterion. The higher the value the higher the inter-class variance and thus the discriminative power of the individual feature. Ranking criteria based on information theory can also be used e.g. the mutual information between each feature and the target variable - minimum redundancy and maximum relevance (mRMR) (Guyon & Elisseef, 2003; Hanchuan Peng, Fuhui Long, & Ding, 2005). Many filter feature selection approaches require estimations of the probability densities and the joint density of the feature and class label from the data. It is important to note, however, that the filter approaches can still lead to a selection of redundant features because of their linear complexity with respect to the number of features.

With respect to wrapper and embedded methods the redundancy question can be surpassed with the cost of more computation time. Wrapper methods use a cross-validation logic to find the best subset of features to use with a classifier and keep the search according to a stopping criterion or purpose. We can enumerate support vector machine for channel selection (Lal et al., 2004), linear regressor for knowledge extraction (Liang & Bougrain, 2012), genetic algorithms for spectral feature selection and P300-based feature selection (Corralejo, Hornero, & Alvarez, 2011; Rao & Berger, 1971), and evolutionary algorithms for feature selection based on multiresolution analysis (Ortega, Asensio-Cubero, Gan, & Ortiz, 2016). Embedded methods integrate the features selection and the evaluation in a unique process such as a decision tree (Quinlan, 1987) or a multilayer perceptron (Cibas, Soulié, Gallinari, & Raudys, 1994).

We decided to use the r^2 in our work because it has been widely used and it offers a computationally efficient solution for our needs: correlation-based feature selection was one of the top performers in an evaluation made on the BCI competition III data sets (Koprinska, 2010).

1.5.3 Classification

After the feature extraction and selection form the EEG data it is time to try to uncover the relevant mental state related to the task performed. This is a challenging task since BCI features often present several unfavourable properties even if the extraction and selection methods are well applied. The more important aspects to consider are: the noise and outliers due to low SNR of EEG data; non-stationarity of the features since EEG signals may rapidly vary over time and sessions; and small training sets.

The detection of the P300 signal is a binary classification problem, where the P300 ERP is one class and is associated to target events and the EEG component associated to the non-target events is the other class.

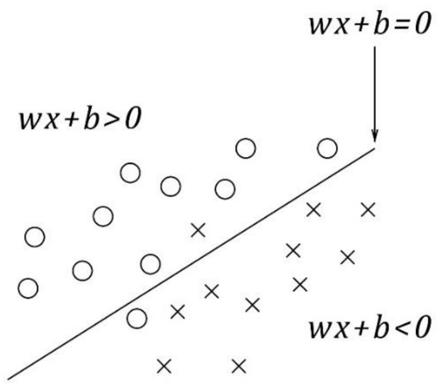

Figure 1.7 – A hyperplane which separates two classes: the 'circles' and the 'crosses' (adapted from (F Lotte, Congedo, Lécuyer, Lamarche, & Arnaldi, 2007).

Generically, the classification problem is solved finding a projection vector (or hyperplane) in the feature space that separates the two classes (Figure 1.7). Assuming x a feature vector, a linear discriminant function is obtained from

$f(x) = wx + b$.

where b is a bias term. To estimate the projection vector a classification algorithm must find w and b following an optimization criterion. Each algorithm has its own criterion and strategy to reach it.

One can consider nonlinear separation as the best solution or a determined problem, so the feature vector x can be modified into a new dimensional space using a kernel function $\delta(\cdot)$

$f(x) = w\delta(x) + b$.

The more commonly employed classification algorithms in BCIs include: linear classifiers, neural networks, non-linear Bayesian classifiers, nearest neighbour classifiers and classifier combinations. A good overview about the more traditional classification algorithms used in EEG-based BCIs can be found in (F Lotte et al., 2007).

Linear classifiers are discriminant algorithms that use linear functions to distinguish the feature vectors of each class. These types of classifiers are probably the most popular algorithms for EEG-based BCI systems. They include linear discriminant analysis (LDA) (Fukunaga, 1990), regularized LDA (Blankertz, Curio, & Müller, 2002; Müller, Krauledat, Dornhege, Curio, & Blankertz, 2004) and support vector machines (SVMs) (Bennett & Campbell, 2000; Burges, 1998; Cortes & Vapnik, 1995). While LDA seeks the separating hyperplane that maximise the interclass variance using the 'one versus the rest' (OVR) strategy, the regularized LDA introduces a regularization parameter that can allow or penalize classification errors on the training set, which gives better generalization capabilities to deal with EEG data outliers. On the other hand, SVMs tries to maximize the margins between the nearest features and the hyperplanes. Both LDA and SVM were, and still are, the most popular types of classifiers for EEG based-BCIs, particularly for online and real-time

BCIs (F Lotte et al., 2018, 2007). SVM have several advantages that will be addressed further ahead.

Neural networks (NN) are assemblies of artificial neurons, arranged in layers, which can be used to produce various non-linear decision boundaries (Bishop, 1995; A. K. Jain, Jianchang Mao, & Mohiuddin, 1996). The multi-layer perceptron (MLP) is a NN composed by several layers of neurons. MLP are the most common type of NN used for BCI (Anderson & Sijercic, 1996; Haselsteiner & Pfurtscheller, 2000; Palaniappan, 2005). In MLP each neuron's input is connected to the output of the previous layer's neurons. The neurons of the output layer determine the class of the input feature vector. When composed of enough neurons and layers, MLP can approximate any continuous function. Added to the fact that they can classify any number of classes, this makes NN very flexible classifiers that can adapt to a great variety of problems. However, due to the fact NN being universal approximators they are sensitive to overtraining, especially with noisy and non-stationary data (Balakrishnan & Puthusserypady, 2005). Another type of NN architecture that deserves a specific attention is the Gaussian classifier NN, that has been specifically designed for the BCI field. According to Millan et al. (2000) this NN outperforms MLP on BCI data.

Non-linear Naïve Bayesian classifiers (NB) model the probability distributions of each class and use Bayes' rule (assumes that feature variables are independent of each other given the target class) to assign a feature vector to the class with highest probability (Hanchuan Peng et al., 2005; Rish, 2001). Such classifiers notably include Bayes quadratic classifiers and hidden Markov models (HMMs). NB will also be addressed further ahead.

Nearest neighbour classifiers are a set of non-linear classifiers that assign to an unseen point the dominant class according to the its nearest neighbour(s). Such neighbours could be training feature vectors from the training data as in k nearest neighbours method (kNN), or class prototypes such as Mahalanobis distance classifiers. In kNN the nearest neighbours are usually obtained using a metric distance (Blankertz et al., 2002), but this method is known to be very sensitive to the curse-of-dimensionality (Friedman, 1997). The Mahalanobis distance based classifiers apply a transformation to the training data of each class towards a Gaussian distribution. The unseen feature vector is then allocated to the class that corresponds to the nearest transformed class according to the so-called Mahalanobis distance (De Maesschalck, Jouan-Rimbaud, & Massart, 2000). This is not a very popular classifier among the BCI literature despite its good performances and the suitability for multiclass categorization (Salazar-Varas & Gutierrez, 2015; Alois Schlögl, Lee, Bischof, & Pfurtscheller, 2005).

The classifier combinations are a self-explanatory concept. They are an aggregation of different classifiers aiming to maximize their complementarity. The combination strategies used in BCI include boosting (cascade of classifiers with focus on the error committed by the previous ones (e.g.: Boostani & Moradi, 2004; Hoffmann, Garcia, Vesin, Diserens, & Ebrahimi, 2005)), voting (several classifiers give their output for the same input vector and the final class is that of the majority (e. g.: Pfurtscheller, Flotzinger, & Kalcher, 1993; Qin, Li, & Cichocki, 2005; Rakotomamonjy, Guigue, Mallet, & Alvarado, 2005)) and stacking (a level-0 layer of several classifiers classify the same input feature vector and then a level-1 classifier (or meta-classifier) uses the output of each classifier as input to make the final decision (Wolpert, 1992)). The practical application of these techniques proved that they can reduce the variance and thus the classification error (Friedman, 1997; H. Lee & Choi, 2003).

The last decade has been prolific in the search of new classification methods for EEG-based BCIs. Lotte et al. (2018) offer a very good and actualized review about the new methodologies being studied in the recent years. Some novel classifiers referred in this review include:

- adaptive classifiers: the weights attributed to each discriminant hyperplane, are incrementally re-estimated and updated as new EEG data become available (Alois Schlögl, Vidaurre, & Müller, 2009; Shenoy, Krauledat, Blankertz, Rao, & Müller, 2006));

- **Riemannian geometry classifiers**: instead of estimating spatial filters and/or select features these classifiers map the data onto a geometrical space by means of with a suitable metric such like manifold of Hermitian (Bhatia, 2009), the Stiefel or the Grassmann manifolds (Edelman, Arias, & Smith, 1998);
- **tensor classifiers:** tries to generalize lower-order data formats to higher-order structured multiway arrays (tensors) (Cichocki et al., 2016; Onishi, Phan, Matsuoka, & Cichocki, 2012);
- **transfer learning methods:** a set of methodologies that aims to enhance the performance of a classifier model trained on one task based on information gained while learning another task (Kindermans, Schreuder, Schrauwen, Müller, & Tangermann, 2014; Weiss, Khoshgoftaar, & Wang, 2016);
- **deep learning:** machine learning architecture based on a cascade of trainable feature extractor modules and nonlinearities with increasing levels of concepts. The principles of deep learning include the use of a composition of visible NN layers used for transforming its input data into a more abstract representation and other set of layers to capture some dependencies between input and output variables from each one of the layers. The architecture is then structured in a **greedy** layer-by-layer method to continuously select the features that improve classification. Popular deep learning approaches for BCI include convolutional neural networks (Fukushima, Miyake, & Ito, 1983; LeCun et al., 1989; Manor & Geva, 2015) and restricted Boltzmann machines (Fischer & Igel, 2012; Manor & Geva, 2015).

1.5.3.1 Naïve Bayes classifiers

NB is based on the Bayes rule and assumes that feature variables are independent of each other given the target class. Given a feature vector $x =$

$\{x_1, x_2, \dots, x_m\}$ for m features, the posterior probability that x belongs to class $T_k, \in \{1,2\}$ is

$$P(T_k|x) = \frac{P(T_k)p(x|T_k)}{p(x)}$$

with

$$p(x) = \sum_k p(x|T_k)P(T_k)$$

where $p(x|T_k)$ is the class conditional probability density learned from examples in the training process and $P(T_k)$ is the prior probability of the class. The objective is to maximize the *a posteriori* probability function (discriminant function): $f(x) = \arg max\, P(T_k|x)$.

The big challenge in this problem is to specify the class conditional density $p(x|T_k)$. The usual assumption, the naïve Bays or idiot Bayes assumption, is that the parameters of each such conditional distribution are independent given the class label:

$$p(x|T_k) = \prod_i^m p(x_i|T_k)$$

Even though this is usually false (since features are usually dependent), the resulting model is easy to fit and works surprisingly well (Rish, 2001). One can possibly attribute different distributions to the class-conditional densities. If a Gaussian distributing is chosen, the NB classifier assumes a quadratic form (qNB) because this leads to quadratic decision boundaries. Even though this classifier is not widely used for BCI, it has been applied with success to motor imagery (Lemm, Schäfer, & Curio, 2004; Solhjoo, 2004), mental task classification (Barreto, Frota, Medeiros, & de Medeiros, 2004; Keirn & Aunon, 1990), and P300 identification (Kindermans, Verstraeten, & Schrauwen, 2012; Pires, Castelo-Branco, & Nunes, 2008; Pires et al., 2011b; Throckmorton, Colwell, Ryan, Sellers, & Collins, 2013).

NB gives a probabilistic output which gives liberty to reject output options according the uncertain of the prediction. It also allows to compensate the class imbalance calling the resulting model $P(T_k|x)$ and adjusting to the data distribution and combine the output from different classification models (Murphy, 2006). The clear advantages in terms of noise tolerance (Langley, Iba, & Thompson, 1992), simplicity, learning speed, classification speed, storage space and incrementality (Walker, Ohzawa, & Freeman, 1999) give us the arguments to choose this classification methods for our work.

To maintain the focus of the thesis, we decided to reduce the details about the resolution of the estimation problem of NB. One can find detailed information about this in (Murphy, 2006; Rish, 2001; Srivastava, 2007).

1.5.3.2 Support Vector Machines

A SVM maps the input space (x) into a high-dimensional features space ($x = \varphi(x)$) linearly separable by an optimal hyperplane defined by $w.z - b = 0$; this hyperplane separates the l training examples in two classes. The SVM optimization problem is defined by

$$\min \quad \frac{1}{2}\|w\|^2 + C\sum_i \xi_i$$

$$\text{s.t.} \quad y_i(w.z_i - b) \geq 1 - \xi_i, \qquad \xi_i \geq 0 \; \forall \, i$$

where y_i are the class labels $y_i \in \{+1, -1\}$, and ξ_i is the error variable associated to each example $i, j = 1, \dots, l$, and C is a margin regularization constant which determines the trade-off between minimizing the training error and minimizing model complexity. The computational solution for this problem can be achieved from the dual formulation

$$\max \quad \sum_i \alpha_i - \frac{1}{2}\sum_i \sum_j \alpha_i \alpha_j y_i y_j k(x_i x_j)$$

$$\text{s.t.} \quad 0 \leq \alpha_i \leq C \; \forall \, i, \; \sum_i y_i \alpha_i = 0,$$

where $k(x_i x_j) = \varphi(x_i) \cdot \varphi(x_j)$ is the kernel function that performs the non-linear mapping of the feature space and α_i are the Lagrange multiplier of each training point. Each $\alpha_i \geq 0$ are called 'support vectors' and are part of the two hyperplanes that define the boundaries between the classes. For these machines, the support vectors are the critical elements of the training set. They lie closest to the decision boundary; if all other training points ($\alpha_i \geq 0$) were removed and training was repeated, the same separating hyperplane would be found (Burges, 1998).

Depending on the chosen kernel function the SVM can remain a linear or non-linear classifier. Popular non-linear functions are:

- Gaussian kernel: $k(x_i x_j) = \exp\left(-\frac{\|x_i - x_j\|^2}{2\sigma^2}\right)$,
- Polynomial kernel: $k(x_i x_j) = (1 + x_i \cdot x_j)^d$.

There are several details about SVM not addressed here to keep the focus of the work, but one can observe several hyperparameters that can be tuned in order to obtain a good classification performance (C, σ, d). We can deduce that the search of the best values for each parameter can be very time consuming. The method used in our work was sequential minimal optimization (SMO) algorithm (Platt, 1998) better performing than k-fold cross-validation or the leave-one-out methods. This is outweighed by the good generalization properties, the resistance to overtraining and to the curse-of-dimensionality (Burges, 1998; A. Jain, Duin, Duin, & Mao, 2000). And these were the proprieties that attract us to use SVMs in our work.

LIBSVM is a popular open source machine learning library developed at the National Taiwan University written in C++ though with a C API that implements the SMO algorithm for SVMs (Chang & Lin, 2011). The work described on chapter 2 uses the MATLAB interface for LIBSVM.

Please refer to (Duan, Keerthi, & Poo, 2003) for a better understanding about SVMs.

1.5.4 BCI Output, Feedback and Performance

The BCIs should be regarded as co-adaptive systems (J. Wolpaw & Wolpaw, 2012), that means that the user must learn how to produce recognizable EEG patterns and the machine must learn to recognize such patterns. Only in this way it is possible to associate a command to a brain state that can successfully be used to control a given BCI application. This is why the translation of the classification output and the sensory feedback are strictly interconnected: the way the feedback about the user's mental state recognized by the BCI is presented to the user directly influences the BCI control skills (Fazel-Rezai et al., 2012; Fabien Lotte, Larrue, & Mühl, 2013; Neuper & Pfurtscheller, 2009).

The sensory feedback of BCIs depends of its applicability. Some of the most significant fields of applicability of BCI include:

- restoration of communication – patients who suffer any kind of disease that limits the communication abilities (e. g.: Amyotrophic Lateral Sclerosis, Locked-in Syndrome, brainstem stroke, brain or spinal cord injury, cerebral palsy…) benefit from this kind of BCI systems, namely the BCI spellers (a good review in Rezeika et al., 2018). The spellers allow patients to select letters of the alphabet presented in a screen given them a mean to communicate. The row-column speller was pioneer (Farwell & Donchin, 1988) and serves as inspiration for the several other types of spellers such like the checkerboard spellers (Townsend et al., 2010). P300 and therefore the oddball paradigm as stimulation detection serves as the basis for these systems, however SSVEP and sensorimotor rhythms have also been successfully used in spellers (Yu et al., 2017; Yangsong Zhang, Xu, Cheng, & Yao, 2014).

- motor substitution (or neuroprosthesis) – a BCI prosthesis is a device built for improving or replacing a defective organ or a missing body part. It can be also a system for helping to restore mobility like a wheelchair controlled by BCI (Al-qaysi, Zaidan, Zaidan, & Suzani, 2018; Al-Quraishi, Elamvazuthi, Daud, Parasuraman, & Borboni, 2018). In these systems auditory, visual feedback and cutaneous sensory feedback could work as the alternative pathway from stimuli to the brain;
- neurorehabilitation – a stroke (cerebral infarction or cerebral haemorrhage) is a severe common brain disorder which causes many situations of disability, namely loss of motor control of the arm and hand. BCIs can be used by stroke patients with residual corticomotor patterns to perform exercises with various feedbacks (gauge, virtual limb, robotised arm, or even functional electrical stimulation of the real limb) as a way to guide brain plasticity towards restoring efficiently and effectively motor control, or improving the control of a neuroprosthesis if not enough motor control can be recovered (Ang & Guan, 2013; Remsik et al., 2016);
- gamming, virtual reality and environmental control – BCI can also be adapted as input for several systems that may or not be used by clinical populations. For example it can serve as the controller of ambient assisted living devices (Fabien Lotte et al., 2012; Memon, Wagner, Pedersen, Aysha Beevi, & Hansen, 2014; Mora, Bianchi, De Munari, & Ciampolini, 2014), the controller of games and/or other virtual reality (VR) applications (Fabien Lotte et al., 2012; Van Erp, Lotte, & Tangermann, 2012). P300 and SSVEP neuromechanisms can be used to control such systems using computer screens with icons that can be selected trough modulation of those neurosignals.
- neurotherapy in behavioural disorders – Several neurofeedback (real-time feedback of brain activity) interventions have reduced symptoms in children with Attention Deficit Hyperactivity Disorder (medical condition characterized by the presence of frequent inattentive, impulsive, and hyperactive behaviours) (Gevensleben et al., 2009; M. J. Larson, South, Krauskopf,

Clawson, & Crowley, 2011; Monastra, 2005; Tankus, Fried, & Shoham, 2014). In these studies EEG rhythms related to attention were translated to game commands, and the children were asked to maintain a threshold level of attention to keep a game object in the air (Q. Wang, Sourina, & Nguyen, 2011). This empowered the control over attention.

In sum, the visual feedback is the most utilized form of sensory feedback (apart from auditory (e. g.: Nijboer et al., 2008; Xiao et al., 2016) and haptic feedback (e. g.: Gomez-Rodriguez et al., 2011; Kauhanen et al., 2006)) and most of the times it works only in a corrective manner, i.e., it only informs the user whether the mental task was or not performed correctly. For example, in spellers the resulting output is the letter the BCI identified as the chosen letter. The user then analyses the result and takes a decision about what to do next, adapting his/her strategy for this. This is the basis of the feedback step in BCI: inform the users about their behaviour when performing the BCI task so they can know if their objective while using the BCI system was accomplished or not. The objective is derived by the applicability of the BCI system itself (e. g.: write a letter in a speller, move a robotic limb in a motor substitution BCI, chose the object in a virtual world or game…).

The ultimate goal of a BCI is to return accurately the choice made by the user and do it with a relatively small time required as a way to provide an effective communication channel. The success of applicability of the BCI system can be delivered through several evaluation criteria (Alois Schlögl, Kronegg, Huggins, & Mason, 2007). The most popular statistical metric used to measure the performance of the classification functions is the accuracy. It is defined by the percentage of correct labelling of the feature vectors' classes. However, this measure does not distinguish types of error and is sensitive to the number of classes. In some applications the type I and II error may not have a negative impact, but in P300-based BCIs the target and non-target classes are highly imbalanced due to the oddball paradigm structure itself (target class is less frequent than non-target). For example, if the target and non-target probability in the oddball paradigm were 1/10 and 9/10 respectively, and if the classifier output for all input vectors were the non-target class, it will result in an accuracy of 90%, even failing to classify correctly the target belonging feature vectors. This mean accuracy is not a valid measure of performance to P300-based BCIs. Balanced accuracy is a more appropriate performance measure to use in classification problems with imbalanced classes (Brodersen, Ong, Stephan, & Buhmann, 2010). Based on a confusion matrix

	actual	
	+	-
predicted +	*TP*	*FP*
predicted -	*FN*	*TN*

where TP, TN, FP, FN are the true positives, true negatives, false positives and false negatives, respectively, the balanced accuracy (BA), can be defined as the average accuracy obtained on either class

$$BA = \frac{SP + SS}{2}$$

where SP is the specificity and SS is the sensitivity obtained from

$$SP = \frac{TN}{TN + FP} \qquad SS = \frac{TP}{TP + FN}\,.$$

1.6 Virtual Reality and BCI in Autism

Virtual Reality (VR) technology is regarded as computer simulations that provide a totally artificial environment with the objective to provide users a sensory experience similar to the real-world experience (or "physical" reality). The idea is to give to the brain artificial sensory input that will make it 'feel' as if receiving 'real' input. A way to do it is to monitor the movements of the users and adjust the sensory displays in a manner that gives the feeling of being immersed in the simulation by stimulating the human senses. The stimulation can be done through panoramic 3D displays (visual), surround sound acoustics (auditory), haptics and force feedback (tactile), smell replication (olfactory) and taste replication (gustation). Nowadays, the most common applications combine visual, auditory and tactile technology (Craig, Sherman, & Will, 2009). The monitoring of user's movements is done by using several technologies/sensors: head-trackers (sensors which capture the head direction and movements) and position trackers (sensors which capture the user's position and movements in the real world). The point-of-view of the user in the virtual environment is moved or rotated along the tracked movements of the user's head and position.

Most current virtual reality environments (VE) comprise primarily visual and auditory experiences, displayed either on a computer screen or through special stereoscopic displays. Stereoscopy is a technique that creates the illusion of depth showing displaced images to the right and left eyes. Receiving the displaced images, the brain combines them both thereby creating a 3D percept. Virtual reality systems utilize 3-dimensional images because they can create a more realistic representation of the environments. Nowadays immersive experience that VR can offer with head-mounted displays such as Microsoft® Hololens and HTC's VIVE Pro Eye can be rated at a very good level and is well popularized.

More recently, VR training has been explored as a possible adjunct therapy for people with motor and mental health dysfunctions. The concept tries to take advantage from the meaningful and relevant stimulation that VR can deliver to an individual's nervous system and thereby capitalize on neuroplasticity to promote both cognitive and motor rehabilitation. In fact some research was done with disorders such as cerebral palsy, Parkinson's disease, stroke, schizophrenia and anxiety disorders (Teo et al., 2017). In relation to ASD, VR has been increasingly used in the improving of various skills like social context understanding (Didehbani, Allen, Kandalaft, Krawczyk, & Chapman, 2016; Mitchell, Parsons, & Leonard, 2007), emotional skills (Lorenzo et al., 2016), understanding facial expressions (Fabri, Elzouki, & Moore, 2007), communication (Wainer & Ingersoll, 2011), reducing phobia (Maskey et al., 2014), travel training and fire alarm procedures (Simões, Bernardes, Barros, & Castelo-Branco, 2018; Strickland, McAllister, Coles, & Osborne, 2007). The advantages of using VR with ASD have been revealed when comparing with traditional social skill interventions such as simple emotion recognition tasks or role-play: (1) it can provide safe, unlimited, controlled, and commonly encountered day-to-day contexts to practice social scenarios, which are relevant in autism, such as inviting someone for one's birthday party or find someone to sit with (Kandalaft et al., 2013; Sarah Parsons, Mitchell, & Leonard, 2004; Wallace et al., 2010); (2) provide the opportunity for repeated practice in dynamic, constantly changing social exchanges and provide a supportive environment for individuals with ASD to make social mistakes without the intense social anxiety associated with face-to-face social interactions (Georgescu et al., 2014; Maskey et al., 2014); (3) the dynamic practice of different VR contexts may facilitate the generalization of social skills learned in VR to everyday life interactions (Bekele et al., 2014; Pineda et al., 2014; M. Wang & Reid, 2011b); (4) computer technology is often highly motivating and rewarding for individuals with ASD (S. Parsons & Mitchell, 2002).

Overall, VR offers an engaging, interactive, and individualized platform for training and improving social cognition in children with ASD, nevertheless, in their review, Teo et al. (2017) pointed that the cost-saving benefits and the applicability of such VR therapies in real world settings may not be warrantied yet and claimed that VR therapy must be complemented by other forms of technologies (such as neuroimaging) in order to augment training benefits and reach more targeted approaches to neurorehabilitation. They also pinpoint the necessity of large-scale longitudinal studies to determine the effects of VR therapy (in combination with neuroimaging techniques) and the translation of VR therapy in a non-clinical environment (i.e., home setting).

In fact, going against this problematic, one can find some studies where VR has already been tested as a feedback medium in BCI systems (Fabien Lotte et al., 2012; R, A, & A, 2005). Research (J. D. Bayliss & Ballard, 2000) showed that a more straightforward, vivid, motivating, and dynamic scene feedback can significantly enhance BCI's performance. VR can offer these conditions by giving an attractive visual point of view of the task that is supposed to be performed in the BCI dispositive. Because of the greater immersion and enjoyment of the VR setting the user's brain effort and vividness is empowered and such enhancement can improve the brain's pattern recognition performance and enable BCI learning and testing towards new BCI-VR prototypes (Millán et al., 2010). So, VR technology provides BCI research tools with practical meaning, simulation and testing capabilities due to the low-cost, safe, controllable, easy to manipulate and construct dynamic environments that can be created for example with Unity3D or Vizard (software tools for building VE).

Surprisingly, despite the big quantity of favourable arguments, the study of combined VR and BCI applications has only been used with children with attention deficit hyperactivity disorder (Jiang, Guan, Zhang, Wang, & Jiang, 2011; Rohani, Sorensen, & Puthusserypady, 2014) (which includes the presence of frequent inattentive, impulsive and hyperactive behaviours (American Psychiatric Association, 2013)).

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Chapter 2

Neural signals induced by scenes of increasing social complexity

This chapter describes our effort for detection of oddball stimuli with increasing social scene complexity at single or near single-trial level. Our objective was to bridge the cognitive processing of realistic and complex social scenes and BCI environments. With this work we were able to open new perspectives for the creation of a new form of cognitive training using realistic scenarios and virtual reality. The subsequent chapters present our proposed approach for this new type of cognitive training tool.

This chapter was based on: ***Amaral, C. P.****, Simões, M. A., & Castelo-Branco, M. S. (2015). Neural Signals Evoked by Stimuli of Increasing Social Scene Complexity Are Detectable at the Single-Trial Level and Right Lateralized. PLOS ONE, 10(3), e0121970. https://doi.org/10.1371/journal.pone.0121970*

2.1 Abstract

Classification of neural signals at the single-trial level and the study of their relevance in affective and cognitive neuroscience are still in their infancy. Here we investigated the neurophysiological correlates of conditions of increasing social scene complexity using 3D human models as targets of attention. Challenging single-trial statistical classification of EEG neural signals was attempted for detection of oddball stimuli with increasing social scene complexity. Stimuli had an oddball structure and were as follows: 1) flashed schematic eyes, 2) simple 3D faces flashed between averted and non-averted gaze (only eye position changing), 3) simple 3D faces flashed between averted and non-averted gaze (head and eye position changing), 4) animated avatar alternated its gaze direction to the left and to the right (head and eye position), 5) environment with 4 animated avatars all of which change gaze and one of which is the target of attention.

We found a late (> 300 milliseconds) neurophysiological oddball correlate for all conditions irrespective of their complexity as assessed by repeated measures ANOVA. We attempted single-trial detection of this signal with automatic classifiers and obtained a significant balanced accuracy classification of around 79%, which is noteworthy given the amount of scene complexity. Lateralization analysis showed a specific right lateralization only for more complex realistic social scenes.

In sum, complex ecological animations with social content elicit neurophysiological events which can be characterized even at the single-trial level. These signals are right lateralized. These findings pave the way for neuroscientific studies in affective neuroscience based on complex social scenes and given the detectability at the single trial level this suggests the feasibility of brain computer interfaces that can be applied to social cognition disorders such as autism.

2.2 Introduction

Investigating the sensitivity of neurophysiological responses to complex social scenes is now becoming an increasingly recognized topic in affective neuroscience (Kaspar, 2013; Semrud-Clikeman, Fine, & Zhu, 2011). It is also of paramount importance in important fields such as developmental neuroscience (Stoesz & Jakobson, 2014) and autism research, where complex social attention deficits are present (Rice, Moriuchi, Jones, & Klin, 2013; Semrud-Clikeman et al., 2011). Moreover, if these responses could be studied at the single or near single-trial level, this might pave the way to develop brain computer interfaces to train social cognition deficits in these disorders, which are characterized by deficits in social attention. The problems associated with low signal to noise of neurophysiological responses are now overcome by advanced statistical classification methods that can classify these signals at the single-trial level (Pires et al., 2011b; Pires, Nunes, & Castelo-Branco, 2012a).

Attention to social stimuli such as faces has often been studied with oddball paradigms which use simple face presentation as target stimuli and the average of many responses for the analysis (e.g., (Campanella et al., 2002; Chai et al., 2012; Fishman, Ng, & Bellugi, 2011; Susac, Ilmoniemi, Pihko, & Supek, 2004)). As an example, the P300 oddball signal is a well-known neural signature of attention processes for detection of rare items in a series of distinct stimuli types. The P300 has been classically reported as an enhanced positive-going component with a latency of about 300 milliseconds (ms) and normally a scalp distribution over the midline electrodes (for a review see (Duncan et al., 2009; Patel & Azzam, 2005; John Polich, 2007)).

The main goal of this manuscript was to study attention to social complex stimuli and scenes at the single-trial level, and the relevance of hemispheric laterality in this process. This is an important qualitative step, because we focus on single or few trials in addition to average neurophysiological responses. The suitability of oddball paradigms for such single-trial analyses, has been empirically proven and is well documented in the literature. The reason for their use is that it is possible to quickly "calibrate" and model the P300 in individual subjects and use it in statistical classification approaches (Pires, 2011; Pires et al., 2012a). Conflict paradigms or attentional-bias paradigms have not yet been proven to be suitable for single-trial analyses, unlike P300 approaches. Accordingly, P300 based oddball paradigms are often used in brain computer interfaces (BCI) which are systems that allow individuals to communicate without having to use verbal or motor means of communication (Farwell & Donchin, 1988; Kleih et al., 2011; Mak et al., 2011a; J. Wolpaw & Wolpaw, 2012). The fact that P300 is a robust signal that can be identified even at single-trial level makes it a favourable neurophysiological component to provide good communication speeds for BCIs. Wang and colleagues in (P. T. Wang, King, Do, Nenadic, & Feb, 2012) were able to achieve an information transfer rate of 12 characters per minute with this type of paradigm, which is very significant in this field. These approaches do therefore take advantage of the recent progress in statistical classification methods (for review see (Tangermann et al., 2012)) to identify P300 waveforms even at the single-trial level (e. g., (Pires et al., 2011b, 2012a)).

The usage of faces as target of attention was already successful in oddball-based BCIs (Kaufmann, Schulz, Grünzinger, & Kübler, 2011; Onishi & Zhang, 2011; Yu Zhang, Zhao, Jin, Wang, & Cichocki, 2012) and has also been used to study healthy social cognition (Conty, N'Diaye, Tijus, & George, 2007) and disorders such autism (Gunji et al., 2013; Senju, Tojo, Yaguchi, & Hasegawa, 2005), prosopagnosia (Bobes et al., 2004) and social phobia (Sachs et al., 2004). Moreover, a few studies aiming at BCI applications tried to integrate three-dimensional (3D) stimuli in oddball paradigms (Jessica D Bayliss & Ballard, 2000; Donnerer & Steed, 2010; Piccione et al., 2008). They showed that it is possible to measure a P300 response to 3D stimuli though none used realistic or complex social scenes as targets of attention.

The eyes are a powerful route of non-verbal information and draw most of our attentional resources during social interactions. They can be used to determine the focus of someone's attention, which is called joint attention. This ability is already established very early in development (for review see (Emery, 2000)) which indicates the high relevance this kind of gaze processing occupies in the human evolutionary process. Gaze shifts of others towards any point in the environment can trigger a reflexive redirection of one's own attentional focus (Driver et al., 1999; Friesen & Kingstone, 2003). Thus, we believe that this reflexive attentional process can be studied in terms of the mechanisms involved in novelty processing embedded in oddball paradigms. Therefore, we envisaged the introduction of complex social scenes containing non-natural (flashed) or natural eye/head-gaze shifts as target of attention in oddball paradigms.

Several studies have already described the involvement of the superior temporal sulcus (STS) in the processing of relevant and familiar types of biological motion such as human body motion (E Bonda, Petrides, Ostry, & Evans, 1996; Grossman et al., 2000), expression of emotions (LaBar, Crupain, Voyvodic, & McCarthy, 2003; K. A. Pelphrey, Morris, Mccarthy, & Labar, 2007; Schultz & Pilz, 2009), facial motion due to speech production (Campbell et al., 2001; Hall, Fussell, & Summerfield, 2005), or in complex scenes such as movies (Bartels & Zeki, 2004; Hasson, Nir, Levy, Fuhrmann, & Malach, 2004). Additionally, this region has been shown to respond to natural images of facial motion (Puce et al., 1998). Taken together, such studies suggest that initial analysis of social cues occurs in the STS region, which is in a privileged anatomical location to integrate information derived from both the ventral "what" and the dorsal "where" visual pathways (T. Allison et al., 2000). Hein and Knight in (Hein & Knight, 2008) agreed that the function of STS depends largely upon the co-activations of connected areas. On the other hand, Haxby et al. in (Haxby et al., 2000) postulate that the posterior STS is responsible for the processing of quickly changing social features, such as facial expressions. Nummenmaa & Calder in (Nummenmaa & Calder, 2009) believe that the posterior STS is related to the processing of the intentionality of others' actions. Lahnakoski et al. in (Lahnakoski et al., 2012) suggested that the posterior STS region is functionally tightly coupled with other brain regions and might work as a convergence (integration) point of social information processed in other functionally connected sub-systems.

To our knowledge, studies of complex social cognition close to the single-trial level have not been attempted from the cognitive neuroscience point of view. We based the current study on the introduction of hierarchically complex and realistic stimuli with social content. In this way we could dissect the cognitive networks underlying normal attention to stimuli of complex social significance. We believe, as Kingstone proposed in (Kingstone, 2009), that the study of the neural correlates of increasingly complex representations of social interactions can provide critical insights into the nature of cognitive processing in the domain of social attention. Furthermore, Mattout in (Mattout, 2012) highlighted the strong need for experiments that could help identify realistic and efficient models of social interactions that BCI can then use to instantiate more productive interactions between an adaptive machine and a patient. If one could detect the neural signals related to complex social cognition processing at the single-trial level, it would potentially pave the way for the use of these kind of stimuli in future approaches of cognitive training in diseases of social cognition such autism. An interesting and updated review about the use of innovative computer technology for the development of social skills to individuals (Wainer & Ingersoll, 2011) reveals the promising potential of this type of approach, in particular if realistic scenes are used. The studies mentioned in this review reported significant improvements in the addressed social skills, however, altogether, the same studies did not verify the transfer of these skills to more realistic and meaningful contexts. On the other hand, some other studies have in fact explored methods for systematically teaching joint attention to children with autism (E. a Jones, Carr, & Feeley, 2006; Koegel, Vernon, & Koegel, 2009; Whalen, Schreibman, & Ingersoll, 2006). These studies included embedding motivating social interactions into the interventions, which effectively improved children's social competences. However, the infrequent implementation of the protocols compromised the persistence of positive carryover effects after the end of the interventions. Thereby, the use of BCI interfaces that provide detection of complex social cognition related neural signals would enable the use of structured, well-controlled, realistic and immersive social interactions in computerized systems. This would in turn facilitate the repetition of the interventions as many times as required.

Thus, we directly attempted to test the expected right hemispheric lateralization which is typical of social and emotional stimuli and detect the neurophysiological correlates of attention to complex social stimuli at a single-trial level as a way to prove the usability of this concept in BCI applications.

2.3 Methods

2.3.1 Ethics Statement

This study and all the procedures were reviewed and approved by the Ethics Commission of the Faculty of Medicine of the University of Coimbra (Comissão de Ética da Faculdade de Medicina da Universidade de Coimbra) and was conducted in accordance with the declaration of Helsinki. All participants were recruited from our database of voluntary participants, with no monetary compensation. All of them agreed and signed a written informed consent.

2.3.2 Participants

All participants (n=17, 11 males, 6 females, average age 22.8 years (SD = 4.1), range 20-33 years) had normal or corrected-to normal vision and no history of neurological disorders nor any other major health problems. All participants were naive regarding the purpose of the study. Participants took part in EEG recordings during five different experimental paradigms.

2.3.3 Experimental paradigms

We constructed five oddball experimental paradigms using the Vizard Virtual Reality Toolkit, from WorldViz. They ranged from simple flashing stimulus paradigms to realistic animations of human models as targets for focus of attention. The flashing paradigms were labelled as follows: 'Flashed Schematic Eyes', 'Flashed Face – Eye position change', 'Flashed Face – Eye and Head position change' (flashing paradigms) (Figure 2.1). The paradigms with animations as target of attention were labelled as: 'Animated 3D body – gaze change in 1 avatar' and 'Animated 4 avatar environment – gaze change in 4 avatars'.

Flashing oddball paradigms were as follows:

- 'Flashed Schematic Eyes': The non-target events of this paradigm consisted in the appearance of two 3D models of "balls" (resembling eyes) in a grey background screen, during 500 ms. In the target event the balls appeared slightly rotated in relation to the position it had in the non-target events. The task was to mentally count the occurrence of these target events;
- 'Flashed Face – Eye position change': The non-target events of this paradigm consisted in the appearance of a 3D model of a face in a grey background screen, "looking" to the participant during 500 ms. In the target event the face appeared with the eyes gazing to its right (left of the participant). The task was to mentally count how many times the face appeared with the eyes gazing to participants' left;
- 'Flashed Face – Eye and Head position change': The non-target events of this paradigm consisted in the appearance of a 3D model of a face looking to participant during 500 ms. In the target event the face appeared facing towards the left side. The participant task was to mentally count the times the face appeared facing to participants' left.

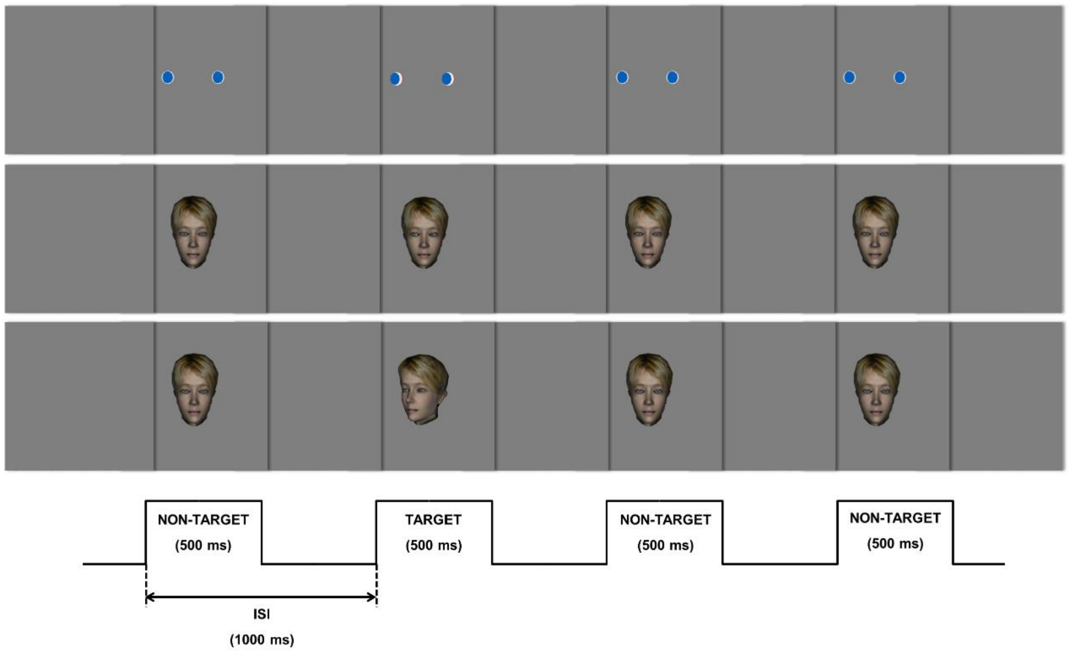

Figure 2.1 – Schematic illustration of the 3 flashing oddball paradigms. Top – 'Flashed Schematic Eyes' paradigm: The subjects were asked to count the occurrence of slightly rotated balls. Middle – 'Flashed Face – Eye position change' paradigm: the target event is a change in the direction of the eyes. Bottom – 'Flashed Face – Eye and Head position change': The target event is the slight head rotation.

Animated paradigms description:

- **'Animated 3D body** – gaze change in 1 avatar': One 3D model of a human-like avatar is facing the participant (presented from the shoulders up), in a scenario with a grey background. The events are the animation of this avatar. The non-target event is the rotation of avatar's head to the left side (continuous realistic animation that lasted 900 ms). The target event was the rotation of the head to the right side (also a continuous realistic animation of

900 ms). The task of the participant was to mentally count "how many times the person looks to its right" (Figure 2.2– 'Animated 3D body – gaze change in 1 avatar' paradigm. The participants were instructed to pay attention to the turning of the head of the avatar to the left of the participant. Non-target animation is the rotation of the head to the right of the participant.).

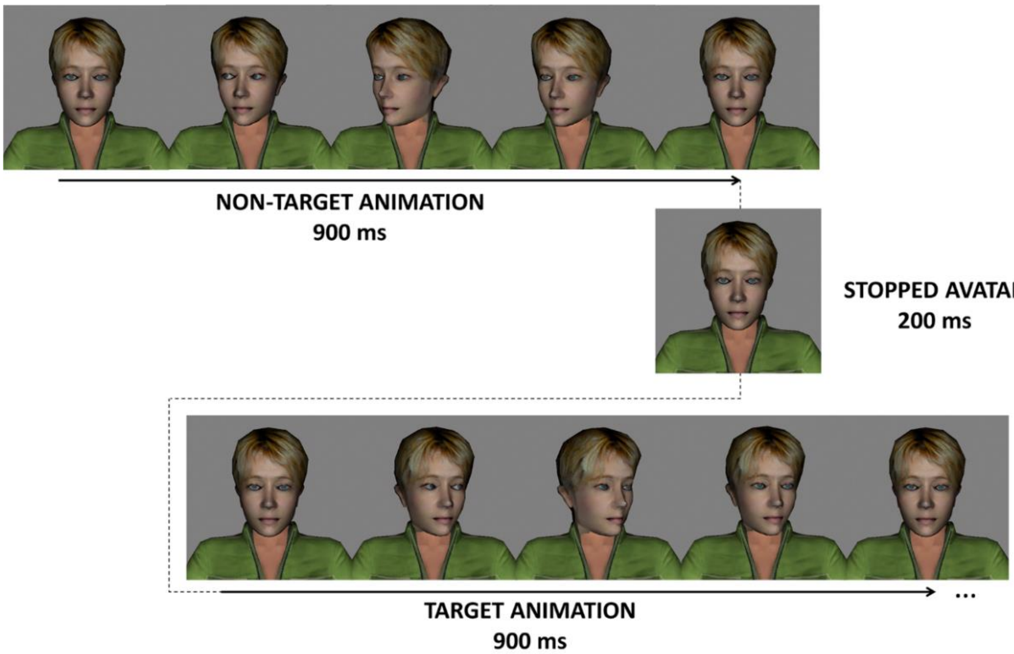

Figure 2.2 – 'Animated 3D body – gaze change in 1 avatar' paradigm. The participants were instructed to pay attention to the turning of the head of the avatar to the left of the participant. Non-target animation is the rotation of the head to the right of the participant.

- 'Animated 4 avatar environment – gaze change in 4 avatars': Four different avatars are arranged in diamond, in a scenario with a grey background. The events consisted in the rotation of the head of one of the four avatars to the right (continuous realistic animation that lasted 900 ms). The target event was the rotation of the head of the diamond's top edge avatar, to the right

(Figure 2.3). The task here was to mentally count "*how many times the person in the top looks to its right side*".

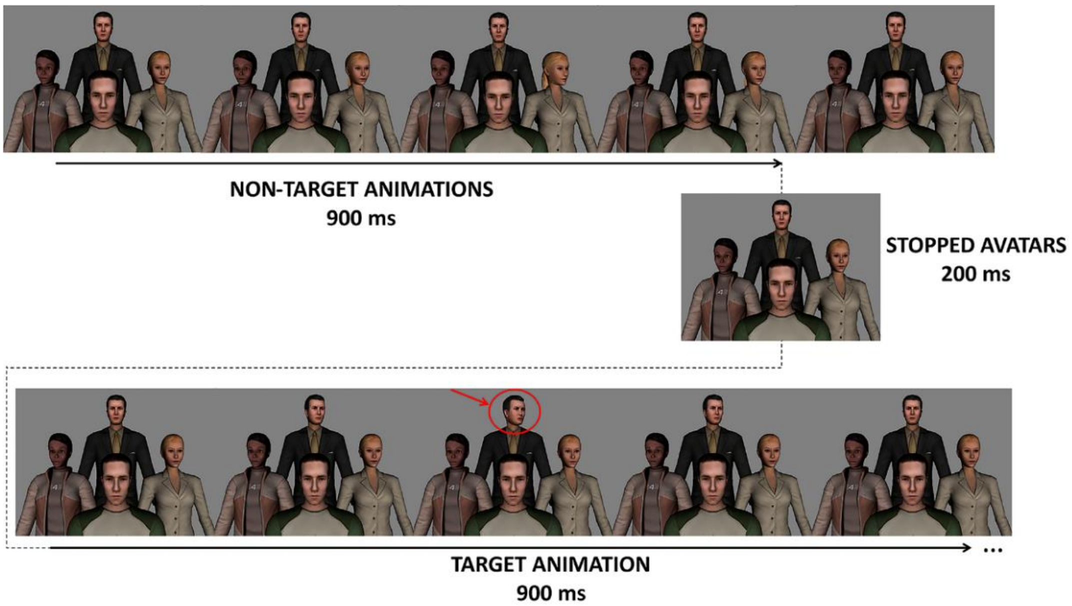

Figure 2.3 – 'Animated 4 avatar environment – gaze change in 4 avatars' paradigm. The target of attention is the animation of top avatar. The task was to count how many times the top avatar averted its gaze.

We ran 10 blocks of 50 events for each paradigm. We allowed the participant to rest at each 5 blocks. In all the paradigms the target events were displayed randomly among the non-target. In each block the number of target events was 10, which gives an occurrence probability of 1/5. Two target events never occurred consecutively. In the 'Animated 4 avatar environment – gaze change in 4 avatars' paradigm, the same avatar never turned its head two times consecutively. The stimulus onset asynchrony (SOA) of the flashing paradigms was 1000 ms and the inter-stimulus interval (ISI) was 500 ms. In the animated paradigms the SOA was

1100 ms and the time between the animations of the avatars was 200 ms (thus animation time is 900 ms). The animation time of these two paradigms is the balance between the time needed to maintain a realistic movement of the avatar head and the need to maintain the time as small as possible to avoid uncomfortable total experiment times.

We planned to introduce hierarchical social scene complexity in these paradigms to uncover the degree of complexity that can be introduced in oddball paradigms such that the neural correlates for attention to social stimuli can still be detected at single-trial level. The social scene complexity of these paradigms was organized according to a matrix which ordered three objective parameters present in the scene. This matrix considers the number of items in the scene (including multipart social objects), elements that define the trajectory of social object and presence of movement. See Table 2.1.

After each block the participants were asked how many target events they counted.

2.3.4 Data Acquisition

Participants were sat at about 60 centimetres from the screen (HP L1710 17-inch LCD Monitor; frame rate of 60 Hz), and the EEG was recorded using a Brain Products Package.

The individuals scalp was first cleaned using abrasive gel and then the actiCAP cap was placed on their heads. The data was recorded from 16 Ag/AgCl active electrodes (Brain Products), placed in Fp1, F3, Fz, F4, FCz, C3, Cz, C4, T4, P7, P3, Pz, P4, P8, O1, and O2 locations according to the international 10-20 standard system. The ground electrode was placed at AFz position and the reference electrode at T3 position. Their impedance was kept under 10 kΩ. The electrodes were connected directly to the 16 channels Brain Products V-Amp Amplifier and sampled at 1000 Hz.

EEG data was recorded using the Brain Products Brain Recorder software with notch filter at 50 Hz, while the stimuli were presented to the subjects. For each paradigm the individuals were informed about the respective tasks. Each experimental procedure (preparation + 5 paradigms) took around 70 minutes to complete.

Table 2.1 - Matrix describing ordinal criteria for paradigms social scene complexity. These criteria define the hierarchy of social complexity of the paradigms.

Stimuli	Amount of items in the scene (including multipart social objects)	Elements that define the trajectory of social object	Movement	Overall social scene complexity
Flashed Schematic Eyes	* (2 balls)	* (2 balls)	*	***
Flashed Face – Eye position change	** (face)	* (2 eyes)	*	****
Flashed Face – Eye and Head position change	** (face)	** (eyes and face)	*	*****
Animated 3D body – gaze change in 1 avatar	*** (face and upper chest)	** (eyes and face)	**	*******
Animated 4 avatar environment – gaze change in 4 avatars	**** (4 faces and upper bodies)	** (eyes and face)	**	********

2.3.5 Data analysis

We performed an off-line analysis with Brain Vision Analyzer 2 from Brain Products software. The average of T4 and T3 channels was used to form a new reference to simulate as close as possible the linked ears reference due to the proximity of these electrodes to the ears. This averaged re-reference was applied to all the remaining electrodes.

The data were filtered with a low pass filter at 30 Hz (24 dB/octave) and a high pass filter at 0.16 Hz (24 dB/octave). The data segmentation was based in the SOA of each paradigm. For the flashed stimuli paradigms, the segmentation was performed in epochs of 1100 ms with a 100 ms pre-stimulus interval and a 1000 ms post-stimulus interval. For the animated stimuli paradigms, the segmentation was performed in epochs of 1200 ms with a 100 ms pre-stimulus interval and an 1100 ms post-stimulus interval. Segments contaminated with eye blinks or excessive muscular activity were excluded from further analysis. Artefact rejection was set at 100 microvolts (µV). Both Target and Non-target conditions yielded more than 60 segments after artefact rejection for each condition. Next, a DC trend correction was performed in each individual segment using the first 100 ms at segment start and the last 100 ms at segment end (Hennighausen, Heil, & Rösler, 1993). A baseline correction procedure was done using the first pre-stimulus 100 ms.

An average of the target and non-target segments was then calculated and a conventional P300 analysis was performed. For this purpose the largest positive peak occurring within 250 - 800 ms that increases in amplitude from Frontal to Parietal scalp areas was identified as the P300 peak. We selected the Non-Target waveforms amplitudes with the same latency as the P300 peak to make the amplitude comparisons.

General statistical analysis was performed with the software IBM® SPSS® Statistics 19 (SPPS, Inc.) after verifying normality assumptions, with the significance level set at 0.05 level. If the normality assumption were met we performed a 3 (area: frontal (F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4)) × 3 (location relative to midline: left (F3, C3, P3), midline (Fz, Cz, Pz) and right (F4, C4, P4)) × 2 (stimulus type: non-target, target) repeated measures ANOVA for all paradigms and a more detailed 3 (area: frontal, central, parietal) × 2 (location relative to midline: left, right) repeated measures ANOVA of the target averaged amplitudes. The *post-hoc* tests were then performed with Bonferroni correction. When the normality assumptions were not met we performed the Friedman tests and the post-hoc Wilcoxon signed-rank tests with Bonferroni correction.

The automatic classification was performed in MathWorks Matlab, using the PRTools toolbox (Heijden, Duin, Ridder, & Tax, 2004). The EEG data was split in segments from 200 ms to 800 ms after stimulus onset. Each epoch was decimated by a factor of 20 and the 16 channels were joined, forming the feature vector. Classification of the event as target or non-target was performed using a Support Vector Machine (SVM) classifier with a polynomial kernel of one degree (Cortes, Vapnik, & Saitta, 1995). Data were classified using several values of averaged ERPs (1, 2, 3, 4, 5, 10 and 15). Classification performance measures for target detection were obtained through leave one out 6-fold cross validation. The metrics used were accuracy - $(TP + TN) / N$, specificity - $TN / (TN + FP)$, sensitivity - $TP / (TP + FN)$ and balanced accuracy - $(SP + SS) / 2$, having TP, TN, FP, FN, SP, SS and N as True Positives, True Negatives, False Positives, False Negatives, Specificity, Sensitivity and total number of events, respectively (section 1.5.3). The unbalanced nature of the data set (the non-target segments are four times more than the target ones, because of the different occurrence probability) makes the balanced accuracy the more reliable metric for assessing the classifier performance.

Permutation tests were performed in order to evaluate the statistical significance of the classification's results, following the permutation-based p-value definition presented in (Ojala & Garriga, 2009):

Permutation-based p-value – Let $D^* = \{D_1', \dots, D_k'\}$ be the set of k randomized versions of the data matrices, $D = \{(X_i, y_i)\}_{i=1}^n$, where X_i are the observations of a series of features, and y_i the class labels associated to each observation, sampled from a given null distribution. The empirical p-value for the function learned by the classification algorithm, *f*, is calculated by

$$p = \frac{|\{D' \in D^* : e(f, D') \leq e(f, D)\}| + 1}{k+1},$$

with e being the error function, which is the ratio of wrong classified observations. This *p* value represents the fraction of randomized versions where the classifier had better performance in the random labelled data than in the original data. If the *p*-value is small enough the null hypothesis is rejected. In this case the null hypothesis was that the classifier is performing at the chance level.

2.4 Results

Statistical analysis revealed a significant main effect for stimulus type in all paradigms. The lateralization analysis revealed significant main effects of location relative to midline only in the target peaks of the animated paradigms, being significantly higher at right electrode sites (for control analyses concerning gaze directions see below). Regarding the area effects, the amplitudes of P300 peaks were generally significantly higher at parietal sites in all paradigms. Latency analysis showed that latencies were significantly higher at frontal and central sites comparing to parietal sites in the less salient condition ('Flashed Face – Eye position change' paradigm). Detailed statistical results are shown next.

Table 2.2 – Means (SEM) of the non-target and target peak amplitude (in microvolts) responses for the different paradigms.

Stimuli	Non-target	Target
Flashed Schematic Eyes	0.55 (0.23)	6.15 (0.24) ***
Flashed Face – Eye position change	1.61 (0.33)	5.31 (0.27) ***
Flashed Face – Eye and Head position change	1.18 (0.30)	5.81 (0.35) ***
Animated 3D body – gaze change in 1 avatar	1.69 (0.16)	6,72 (0.26) ***
Animated 4 avatar environment – gaze change in 4 avatars	-0.30 (0.07)	4.15 (0.20) ***

*** P-value < 0.0001

Concerning the significant main effect of stimulus type that emerged in all conditions it can be summarized as follows: 'Flashed Schematic Eyes' – $F(1,16) = 73.2$, $p < 0.0001$; 'Flashed Face – Eye position change' – $F(1,16) = 25.9$, $p < 0.0001$; 'Flashed Face – Eye and Head position change' – $F(1,16) = 25.5$, $p < 0.0001$; 'Animated 3D body – gaze change in 1 avatar' – $F(1, 16) = 52.2$, $p < 0.0001$; 'Animated 4 avatar environment – gaze change in 4 avatars' – $F(1,16) = 110.6$, $p < 0.0001$. Accordingly, the waveform amplitudes of P300 to target stimuli were significantly higher than the amplitudes of the Non-Target waveforms for all the paradigms (see Table 2.2).

Grand-average responses in parietal sites of the flashing paradigms are shown in Figure 2.4.

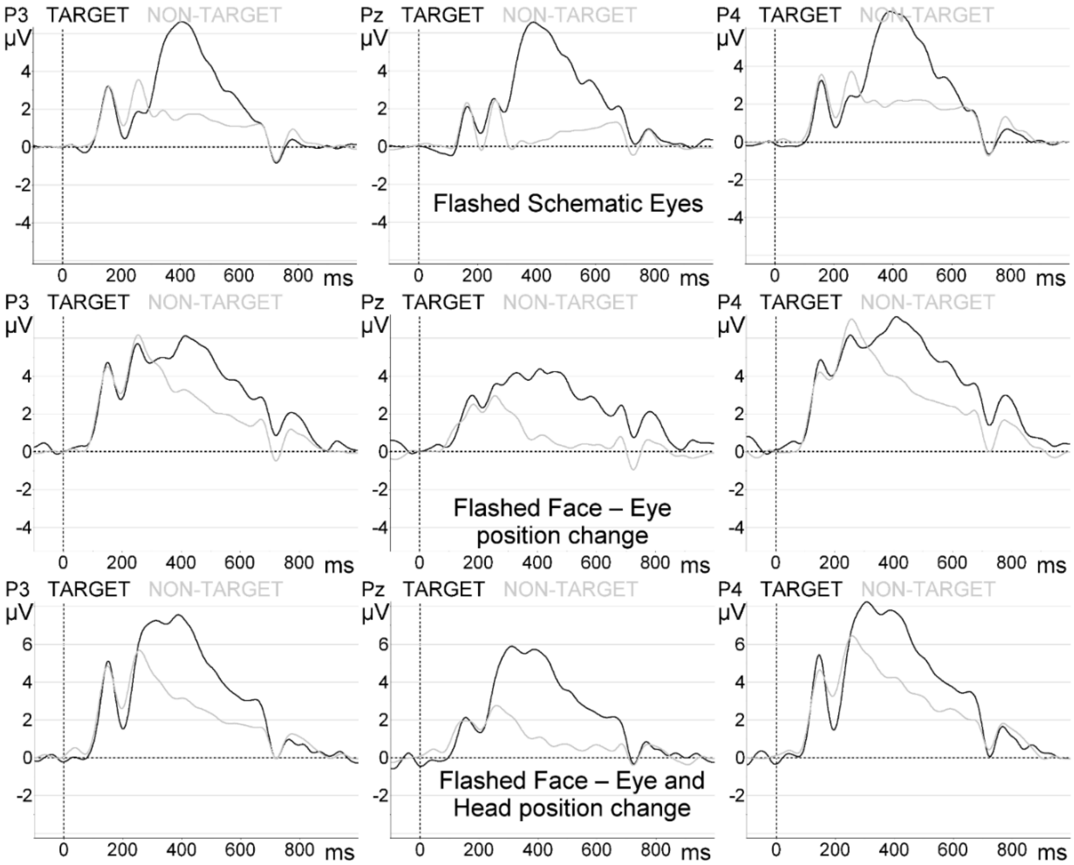

Figure 2.4 – 'Target and non-target grand-average ERP waveforms at parietal sites. Top: 'Flashed Schematic Eyes' paradigm. Middle: 'Flashed Face – Eye position change'. Bottom: 'Flashed Face – Eye and Head position change'.

More detailed analysis of the target averaged amplitudes revealed marginal effects of area ($F(2, 32) = 3.513$, $p = 0.073$) and location ($F(1, 16) = 4.439$, $p = 0.051$) for the 'Flashed Schematic Eyes' paradigm. Concerning the 'Flashed Face – Eye position change' paradigm we observed area effects ($F(2, 32) = 18.953$, $p < 0.0001$), but not location ($F(1, 16) = 1.457$, $p = 0.245$). Areal effects for the 'Flashed Face – Eye and Head position change' paradigm were also detected ($F(2, 32) = 16.857$, $p < 0.0001$), contrary to location ($F(1, 16) = 4.965$, $p = 0.321$). The area effects were also significant for the 'Animated 4 avatar environment – gaze change in 4 avatars' paradigm ($F(2, 32) = 19.350$, $p < 0.0001$), but not for the 'Animated 3D body – gaze change in 1 avatar' condition. Still, as visible in Fig. 5 and Fig. 6, a location effect was indeed found in both animated paradigms: 'Animated 3D body – gaze change in 1 avatar' – $F(1, 16) = 20.518$, $p < 0.0001$); 'Animated 4 avatar environment – gaze change in 4 avatars' – $F(1, 16) = 14.549$, $p = 0.002$.

Post hoc tests with Bonferroni correction for 'Flashed Schematic Eyes' paradigm revealed that peak amplitudes were larger at parietal sites (7.09 ± 0.82 µV) in comparison to the central sites (5.26 ± 0.44 µV, $p = 0.038$). For 'Flashed Face – Eye position change' the amplitudes were higher at parietal sites (8.33 ± 0.93 µV) in comparison to the central sites (3.93 ± 0.40 µV, $p < 0.0001$) and frontal sites (3.99 ± 0.52µV, $p = 0.004$). For 'Flashed Face – Eye and Head position change' we observed greater P300 peak amplitudes at parietal sites (9.54 ± 1.22 µV) in comparison to the central sites (4.49 ± 0.62 µV, $p < 0.0001$) and frontal sites (3.78 ± 0.65 µV, $p = 0.003$). The analysis showed equivalent hemispheric responses, which are consistent with the expected symmetry from more conventional P300 paradigms.

For the animated paradigms ('Animated 3D body – gaze change in 1 avatar' and 'Animated 4 avatar environment – gaze change in 4 avatars') the post hoc tests confirmed an unexpected asymmetry in the amplitude distribution. For 'Animated 3D body – gaze change in 1 avatar' paradigm the P300 peaks amplitudes were higher at right (6.98 ± 0.65 µV) sites compared to left (5.01 ± 0.44 µV, $p < 0.0001$) sites. Also for 'Animated 4 avatar environment – gaze change in 4 avatars' the amplitudes were superior at right (4.54 ± 0.45 µV) electrode positions compared to Left (3.34 ± 0.36 µV, $p = 0.002$) sites. The amplitudes were superior at Parietal sites (5.41 ± 0.542 µV), comparing to Central (3.65 ± 0.40 µV, $p = 0.001$) and Frontal areas (3.77 ± 0.39 µV, $p = 0.001$). In sum, the P300 peak amplitudes of the animated paradigms ('Animated 3D body – gaze change in 1 avatar' and 'Animated 4 avatar environment – gaze change in 4 avatars') were significantly higher at right sites suggesting that a new component was superimposed to P300 signals in these social animated stimuli. Grand-averages concerning these paradigms are shown in Figure 2.5 and Figure 2.6, respectively.

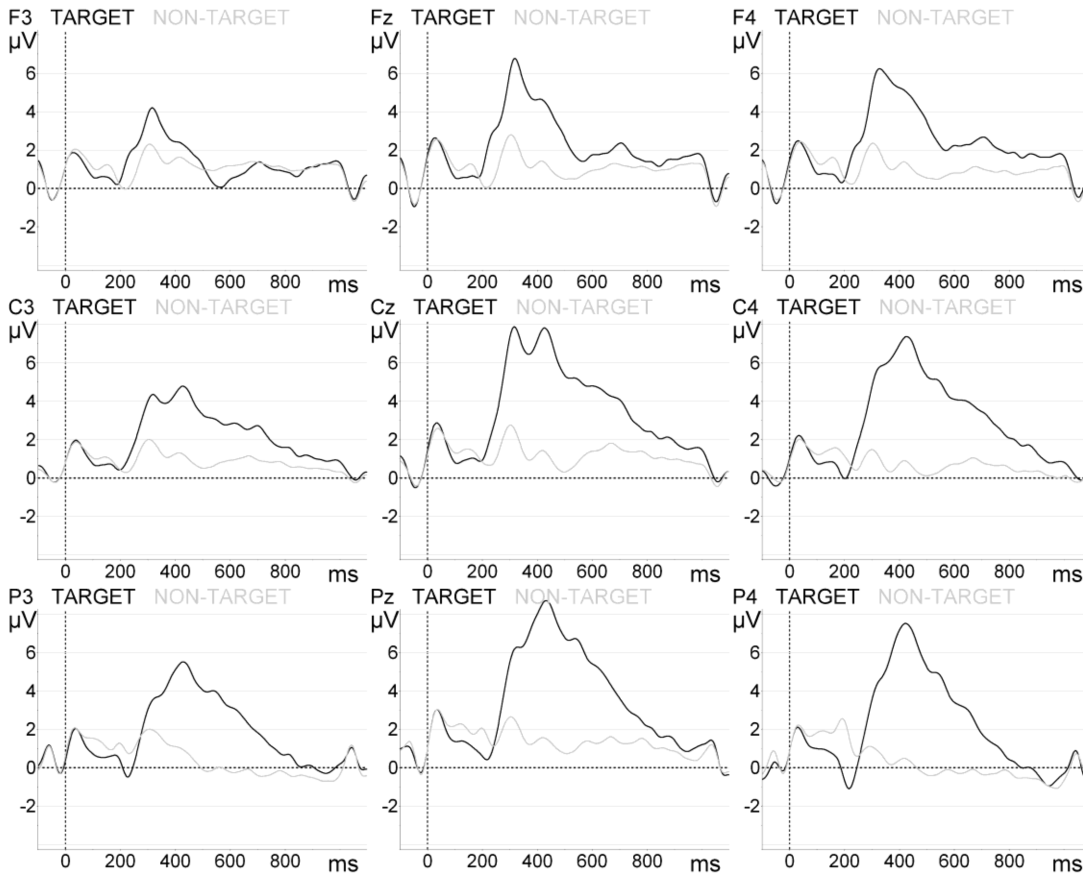

Figure 2.5 – Target and non-target grand-average ERP waveforms for the 'Animated 3D body – gaze change in 1 avatar' paradigm.

Concerning latencies, Friedman tests of the mean latencies at the defined areas (frontal – F3, Fz, F4; central – C3, Cz, C4; parietal – P3, Pz, P4) and locations relative to midline (left – F3, C3, P3; right – F4, C4, P4) showed no effects of area and location for 'Flashed Schematic Eyes' paradigm ($\chi^2(2) = 2.471$, $p = 0.291$, $\chi^2(1) = 0.059$, $p = 0.808$).

For 'Flashed Face – Eye position change' the area effects were significant ($\chi^2(2) = 8.588$, $p = 0.014$) but location effects were not observed ($\chi^2(1) = 2.882$, $p = 0.090$).

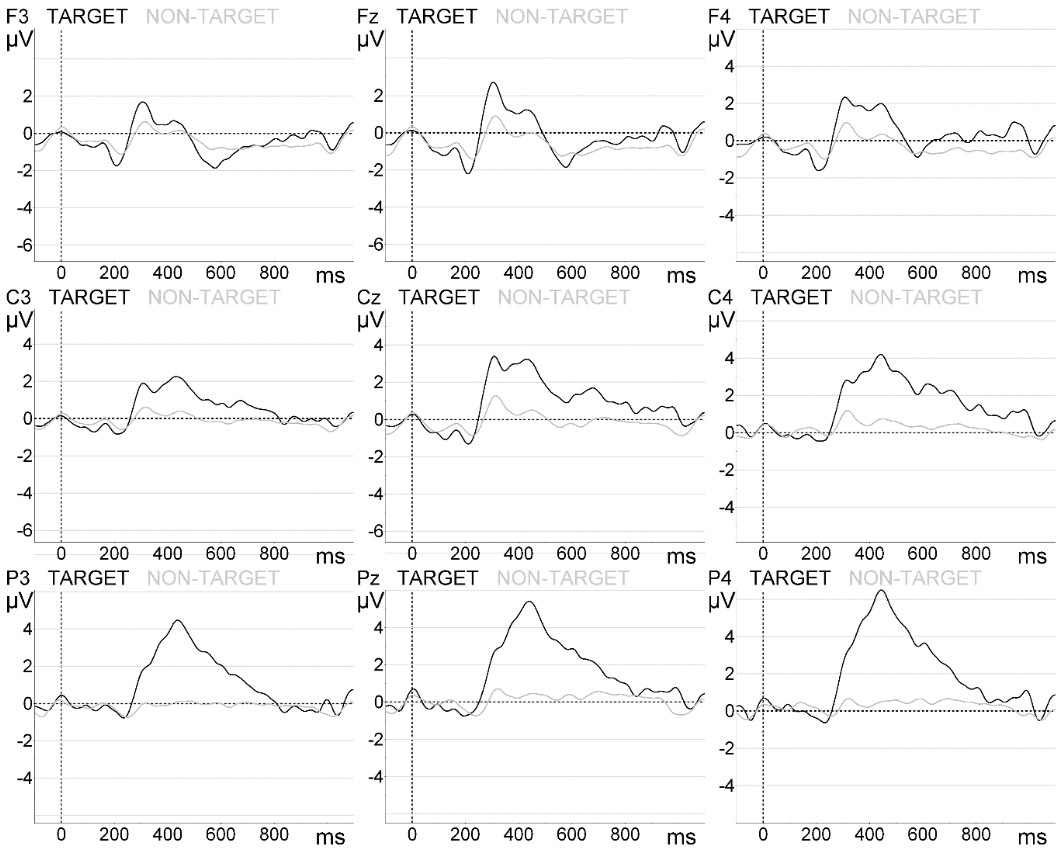

Figure 2.6 – Target and non-target grand-average ERPs waveforms for the 'Animated 4 avatar environment – gaze change in 4 avatars' paradigm.

For 'Flashed Face – Eye and Head position change' paradigm neither area effects ($\chi^2(2) = 3.294$, $p = 0.193$), nor location effects were significant (χ^2 (1) = 0.250, $p = 0.617$).

The 'Animated 3D body – gaze change in 1 avatar' condition showed significant differences between areas (χ^2 (2) = 9.882, $p = 0.007$). Location effects were not observed (χ^2 (1) = 0.059, $p = 0.808$). We observed area effects in the 'Animated 4 avatar environment – gaze change in 4 avatars' paradigm ($\chi2(2) = 6.706$, $p = 0.035$), but not location effects ($\chi2$ (1) = 1.471, $p = 0.225$).

The post hoc analysis with Wilcoxon signed-rank tests with Bonferroni correction were applied, resulting in a significance level set at $p < 0.017$. For 'Flashed Face – Eye position change' the post hoc analysis revealed faster latencies at Parietal areas (374.78 ± 107.38 ms) comparatively to Central (505.65 ± 164.42 ms, $Z = -2.675$, $p = 0.007$) and Frontal (566.96 ± 201.55 ms, $Z = -2.438$, $p = 0.015$) sites. For the 'Animated 4 avatar environment – gaze change in 4 avatars' and 'Animated 3D body – gaze change in 1 avatar' there were no significant differences in any of the mean latencies of the defined Areas.

Figure 2.7 provides an overall summary of the main results reported in this study.

All participants were able to detect the 10 target events of each block in more than 99% of the cases. We had already shown that no detections imply the absence of a P300 matching the absence of behavioural report (Teixeira et al. 2014). Therefore, the potential confound of no detection of target events is not present in our experiment.

We also performed control analyses comparing conditions whereby avatars gaze either to the left or to the right. Amplitude values for both types of gaze were virtually identical and were therefore not significantly different.

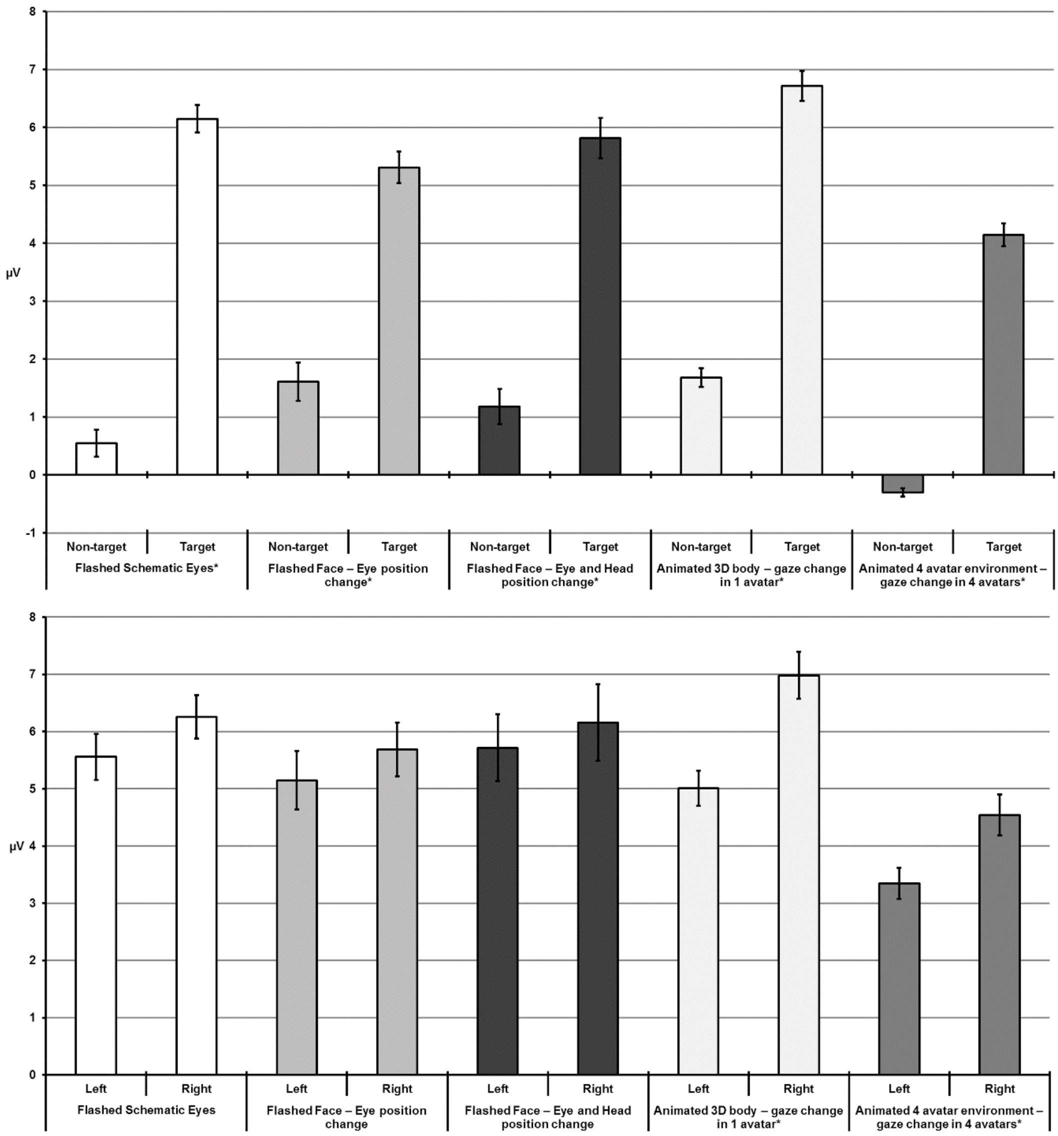

Figure 2.7 – Summary of results. Top: target and non-target waveform amplitudes comparison. Bottom: P300 amplitudes were significantly higher in the right hemisphere for realistic animations ('Animated 3D body – gaze change in 1 avatar' and 'Animated 4 avatar environment – gaze change in 4 avatars'). Error bars are the standard error of the mean.

2.4.1 Waveform classification

Significant classification performance was found already at the single-trial level (see Figure 2.8). The metrics used were accuracy (TP + TN) / N, specificity TN / (TN + FP), sensitivity TP / (TP + FN) and balanced accuracy (SP + SS) / 2 (TP, TN, FP, FN, SP, SS and N as True Positives, True Negatives, False Positives, False Negatives, Specificity, Sensitivity and total number of events, respectively). Permutations tests for each subject and paradigm, yielded p-values bellow 0.05 in 99,9% of the cases which means that the classifier performs well and is reliable. An improvement in classification performance was observed, as expected, when increasing the number of averaged EEG single-trial epochs due to the noise reduction effect of averaging. Yet, this increase is no longer relevant after 5 averaged epochs because of the probable loss of relevant information in averaging and the decreasing of the dataset size. As expected, classification results are worse but still significant for animated paradigms due to the complexity of the scene. The results are presented in Figure 2.8.

Classification results comparison between stimuli conditions revealed a significant main effect ($F(4, 80) = 2.483$, $p = 0.050$). Post hoc analysis with Bonferroni correction showed that classification results were significantly better for 'Flashed Schematic Eyes' (0.91 ± 0.02) comparing to the more complex 'Animated 4 avatar environment – gaze change in 4 avatars' conditions (0.82 ± 0.19, $p = 0.039$).

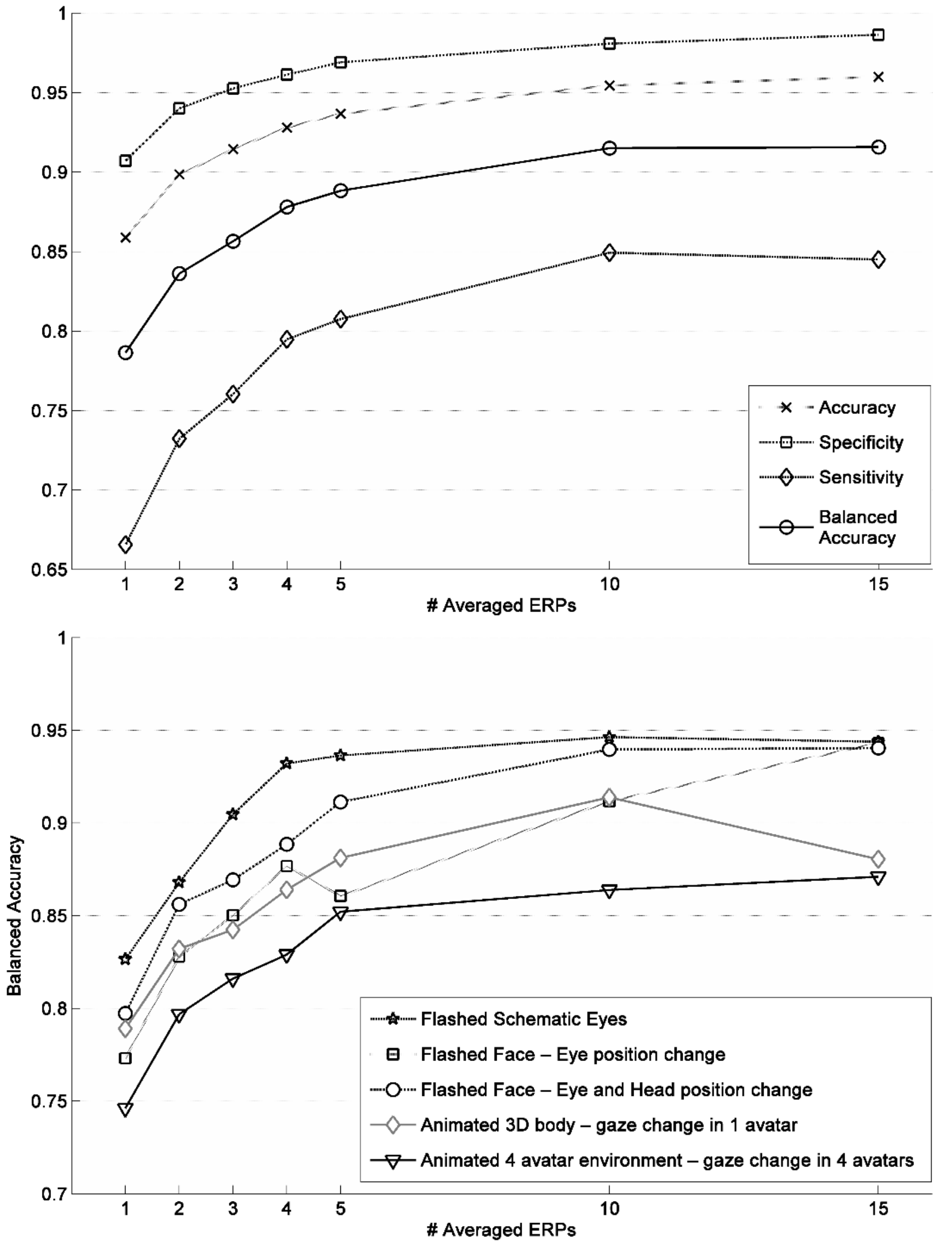

Figure 2.8 – Classification results. Top: Results of several metrics with all paradigms averaged, for the different number of trials used. Bottom: Comparison of balanced accuracy between paradigms for the different number of events average.

2.5 Discussion

The goal of the present study was to study and identify the neurophysiological correlates of attention to realistic social scenes which degree of complexity was defined in a defined ordinal manner (Table 2.1), taking into account the number of items in the scene (including multipart social objects), elements that define the trajectory of social object and presence of movement. This was attempted at a single or near single-trial level, which would potentially allow pinpointing complex directed attention responses at the single event level. We found an oddball response for all the conditions and, importantly, we proved that the processing of realistic multi-agent actions (that can or not be interpreted as social) can be detected in human oddball responses both in average responses and at the single-trial level.

We found an oddball response for all the tested paradigms, irrespective of their complexity. Our waveforms analysis revealed a distinct P300-like waveform when it was elicited by animated stimuli representing realistic gestures. This signal does differ from the classic P300 by being right lateralized, which is not explained by low level features of the stimuli, given that it was neither found in our study, using the simpler paradigms, nor reported in the literature (see below discussion of potential confounds).

We hypothesize that the right lateralization is due to high level characteristics introduced by the realism of the animated paradigms, such as the reflexive attention generated by social gaze orientation. This hypothesis is supported by recent findings in fMRI studies (Carlin, Rowe, Kriegeskorte, Thompson, & Calder, 2012; Laube, Kamphuis, Dicke, & Thier, 2011; Mosconi, Mack, McCarthy, & Pelphrey, 2005a) about the regions involved in gaze orienting. These studies described the influence of the right STS and other regions in processing of dynamic social attention cues (for a review see (Carlin & Calder, 2013; Nummenmaa & Calder, 2009).

There is solid evidence for hemispheric asymmetries underlying the domain of social perception (for a review see (Brancucci, Lucci, Mazzatenta, & Tommasi, 2009). Our results are consistent with the idea that the neural substrates of the perception of gaze, faces and related gestures are characterized by a general pattern of right-hemispheric functional asymmetry. It has been postulated that such substrates might benefit from other aspects of hemispheric lateralization in affective processing, instead of constituting an *isolated specialization* for social information. Individual recognition or social judgment is prioritized by the human brain and may benefit if it were localized only in one hemisphere (Brancucci et al., 2009). Even simple face detection is already lateralized to the right hemisphere (Graewe et al., 2013; Rebola, Castelhano, Ferreira, & Castelo-Branco, 2012). Processing of facial expressions of emotion, which is also relevant for social cognition, is known to be lateralized (Demaree, Everhart, Youngstrom, & Harrison, 2005; Narumoto, Okada, Sadato, Fukui, & Yonekura, 2001).

Concerning social cognition, gaze plays a central role in decoding others' attention, goals and intentions, supporting the idea of a right-hemispheric bias for eye gaze perception. Hemispheric asymmetries in the neural substrates of gaze perception are present even in domestic chicks (Rosa Salva, Regolin, & Vallortigara, 2007) and confirmed by human data (Ricciardelli et al., 2002). In the latter work it was shown that eye gaze is processed better when presented in the left visual field. Following this idea, a right hemisphere involvement in social responses seems to be well-established among all vertebrates studied so far (Lesley J. Rogers, Giorgio Vallortigara, 2013; Salva, Regolin, Mascalzoni, & Vallortigara, 2012).

Biological motion was also a feature in our displays, in particular in the more complex animated versions. These stimuli are of evolutionary importance since social animals, such as humans, take decisions based on the interpretation of the actions of others. Saygin in (Saygin, 2007) examined 60 unilateral stroke patients, and found no evidence suggesting lateralization for basic biological motion perception. Nevertheless, Pelphrey and colleagues in (K. A. Pelphrey, Viola, & Mccarthy, 2004) found such a lateralization when studying perception of naturalistic social movements in complex context, which led Saygin et al. to infer that the right lateralization of biological motion perception may be explained by the 'social' aspects elicited by human motion rather than by body movement *per se*. It is demonstrated that BOLD response to dynamic faces is higher than to static faces in right STS (Schultz & Pilz, 2009). Puce et al. in (Puce et al., 1998), described higher right STS activation during perception of moving eyes and mouth within a face. This is consistent with our results, since lateralization emerges for the more complex displays. Our data support the idea that social gaze orientation characteristics coupled to the ecological nature of our conditions elicited an increased asymmetric temporo-parietal response that adds to the reflexive attentional processes inherent to the 'oddball' structure of the paradigm.

Altogether the available evidence indicates that social orienting relies on asymmetric cortical mechanisms. Future studies should elucidate the nature of the realistic social processing network model underlying the identified neurophysiological component. Anyway, our results suggest that these signals are highly generalizable to realistic oddball contexts.

One could argue that the P300-like ERP lateralization is not related to the complexity of the stimulus presented, but to the direction where in the target stimuli the gaze is directed. It should be noted that both viewer and avatar frames of reference (left-right reversed) are distinct and simultaneously present, which makes predictions based on gaze direction not obvious (and if present would mask rather than emphasize our results). In any case, our new data and analyses comparing conditions where avatars gaze either to the left or to the right revealed that the amplitude values for both types of gaze were virtually identical. This potential confound is therefore ruled out under the conditions of the experiment (where both viewer and avatar frames of reference are distinct and simultaneously present).

An important validation of the relevance of these oddball signals was their data driven identification with high fidelity with few or even single-trials. The success of single-trial classification of P300 signals evoked by realistic gestures is important not only in cognitive neuroscience but also for the potential development of clinical applications including BCIs. Since cognitive processes depend critically on the specific situational context in which a subject is embedded (Kingstone, 2009), we can use this kind of stimuli to create realistic, structured and efficient models of social interactions that can be detectable with excellent temporal resolution. It potentiates the use of BCIs in clinical applications of adaptive social behaviour in normal subjects and disorders of social cognition such as in autism (Duncan et al., 2009; Mattout, 2012).

The usage of 16 electrodes can be viewed as a potential limitation of this study, but on the other hand the identification of these neural signals with very few electrodes at the single-trial level reinforces the idea that it is possible to use these signals as markers of attention within complex social events/scenes in BCI applications, with as few electrodes as possible. Further work should be made to find the best features that define this signal and the electrode positions that are best suited to provide such features. With this, one might drastically reduce the number of electrodes to use in clinical applications such as in autism, which will reduce the preparation time of the sessions, usually one of the major drawbacks of EEG applications in clinical BCI.

To conclude, we have shown that realistic animated oddballs with social content generate a specific response that can be successfully classified even at the single-trial level. We verified that this specific response is right lateralized for more complex scenes. We do believe that this work paves the way to study social cognition at the single or near single-trial and opens the door for future forms of cognitive training in diseases of social cognition.

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Chapter 3

Tests with a novel BCI paradigm combined with virtual reality for social skills training in autism

This chapter addresses the feasibility tests with a P300-based BCI paradigm developed by us. The paradigm challenges the responses of the user to joint attention cues performed by an avatar in the virtual scenario.

The tests conducted aimed to verify the usability and comfort of this VR P300-based BCI as a way to predict the best EEG setup to use with ASD subjects. The chosen setup was well tolerated by ASD participants which proved its feasibility for a clinical setting test that is described in the next chapter.

This chapter was based on: ***Amaral, C. P.****, Simões, M. A., Mouga, S., Andrade, J., & Castelo-Branco, M. (2017). A novel Brain Computer Interface for classification of social joint attention in autism and comparison of 3 experimental setups: A feasibility study. Journal of Neuroscience Methods, 290, 105–115. https://doi.org/10.1016/j.jneumeth.2017.07.029*

3.1 Abstract

We present a novel virtual-reality P300-based Brain Computer Interface (BCI) paradigm using social cues to direct the focus of attention. We combined interactive immersive virtual-reality (VR) technology with the properties of P300 signals in a training tool which can be used in social attention disorders such as autism spectrum disorder (ASD).

We tested the novel social attention training paradigm (P300-based BCI paradigm for rehabilitation of joint-attention skills) in 13 healthy participants, in 3 EEG systems. The more suitable setup was tested online with 4 ASD subjects. Statistical accuracy was assessed based on the detection of P300, using spatial filtering and a Naïve-Bayes classifier.

We compared: 1 - g.Mobilab+ (active dry-electrodes, wireless transmission); 2 - g.Nautilus (active electrodes, wireless transmission); 3 - V-Amp with actiCAP Xpress dry-electrodes. Significant statistical classification was achieved in all systems. g.Nautilus proved to be the best performing system in terms of accuracy in the detection of P300, preparation time, speed and reported comfort. Proof of concept tests in ASD participants proved that this setup is feasible for training joint attention skills in ASD.

This work provides a unique combination of 'easy-to-use' BCI systems with new technologies such as VR to train joint-attention skills in autism.

Our P300 BCI paradigm is feasible for future Phase I/II clinical trials to train joint-attention skills, with successful classification within few trials, online in ASD participants. The g.Nautilus system is the best performing one to use with the developed BCI setup.

3.2 Introduction

Electroencephalography (EEG) based brain computer interfaces (BCI), represent widely studied communication technologies (Farwell & Donchin, 1988; Kleih et al., 2011; Mak et al., 2011a; J. Wolpaw & Wolpaw, 2012). An online BCI can be defined as a closed-loop, composed of six main steps: brain activity measurement, pre-processing, feature extraction, classification, translation into a command and the presence of feedback inside the experiment (Fabien Lotte et al., 2015). Virtual reality (VR) has also been increasingly used in neuro-rehabilitation, in particular of motor control and has shown promising results (Astrand, Wardak, & Ben Hamed, 2014; E. B. Larson, Feigon, Gagliardo, & Dvorkin, 2014; M. J. Larson et al., 2011; Salisbury, Dahdah, Driver, Parsons, & Richter, 2016; Tankus et al., 2014). Concerning cognitive applications in the field of neuro-rehabilitation the use of combined VR and BCIs has mainly been used with children with attention deficit hyperactivity disorder (which includes the presence of frequent inattentive, impulsive and hyperactive behaviours (Sugawara & Nikaido, 2014)). For example, Cho et al. (2002) tested an attention enhancement system using a head mounted Virtual Reality device and EEG biofeedback to increase the attention span of children who have attention difficulties.

In (Wainer & Ingersoll, 2011; M. Wang & Reid, 2011a) one can find a summary of several studies that have examined the feasibility and effectiveness of VR as a social skill training option for people with ASD (Bernard-Opitz, Sriram, & Nakhoda-Sapuan, 2001; Lorenzo et al., 2016; Mitchell et al., 2007; S Ozonoff & Miller, 1995; Sarah Parsons et al., 2004). The majority of these studies focused on teaching emotion recognition and simple language skills such as learning vocabulary words and receptive language. More recently, Kandalaft (2013) and Didehbani (2016) tested the efficacy of a Virtual Reality Social Cognition Training tool in children with high functioning autism and measured changes in affect recognition, social attribution, and executive function pre and post training. These studies revealed some promising improvements in social capabilities of ASD subjects, but almost all of them pointed some problems in the translation of these improvements for the individuals' daily living joint attention skills, which represent 'real-world' life demands. Joint attention refers to the ability to share a common point of reference, e.g. the human capacity to coordinate attention cued by a social partner. Joint attention is pivotal in social information processing in learning situations.

Despite these limitations, several studies do postulate (Bekele et al., 2014; Georgescu et al., 2014; Wainer & Ingersoll, 2011), that the use of ecological, realistic and interactive virtual environments may be the solution for this typical generalization problem in the rehabilitation of social skills in ASD subjects to real life settings. Golan and Baron-Cohen (2006) proposed that the use of computerized interventions in ASD individuals permit the development of skills in a highly standardized, predictable, and controlled environment, while simultaneously allowing an individual to work at his own pace and ability level.

In this feasibility study we propose a novel virtual reality P300-based BCI paradigm that tries to couple the potentialities of ecological, realistic and interactive virtual environments with the attention related nature of the P300 brain waveform to create a cognitive training tool for ASD, for use in future efficacy Phase II clinical trials. The P300-based paradigm that we present here consists on an immersive environment were the subject must follow a non-verbal social agent cue (head turn) and direct his/her attention to the target object. The attentional mental state of the subject is monitored through the detection of oddballs, which leads to a P300 signal. This allows giving feedback about his/her attentional focus. The P300 signal is a well-known neural signature of attention processes for detection of rare items in a stimulus series – oddball paradigm – (for a review see (Duncan et al., 2009; Patel & Azzam, 2005; John Polich, 2007)). We decided to couple the training of joint attention skills to P300 signal because the latter is widely used in performance studies, and is related to integration of information with context and memory (Halgren et al., 1995). Moreover, with the automatic detection of P300 signals one can provide direct feedback about individual's attentional focus. This provides information that the subject can use to self-monitor his/her performance about where to look and subsequently allow ASD subjects to adjust behaviour. Given the repetitive nature of this type of oddball paradigm, and its operant learning properties, our motivation for the construction of this paradigm is based on the hypothesis that ASD subjects can assimilate joint attention skills by automating the response to the social cue that is given during the task we created. Joint attention is an early-developing social communication skill defined by the non-verbal coordination of attention of two individuals towards a third object or event (Bakeman & Adamson, 1984). People with ASD show severe deficits in joint attention abilities (Baron-Cohen, 1989; Baron-Cohen, Baldwin, & Crowson, 1997; Dawson et al., 2004; Klin, 2002; S. Leekam & Moore, 2001; J. Swettenham et al., 1998) which plays a critical role in social and language development (Charman, 1998).

From the target population's point of view, the comfort associated to the use of immersive technology plus the EEG setup is crucial because ASD subjects may show sensory hyper-reactivity (Sugawara & Nikaido, 2014). Thereby, it is important to reduce the time needed to prepare the BCI and virtual reality setup. This may help reduce stress levels and increase task compliance. Taking this into account, the use of active electrodes that do not require skin preparation may be an efficient way to reduce the EEG preparation time. The combined use of head mounted virtual reality setups with EEG acquisition devices is still a huge challenge due to the difficulties in coupling both systems in the same subjects. In this study, we addressed the feasibility of our novel P300 based paradigm with joint attention cues by comparing its performance and usability across 3 different 'easy-to-use' EEG systems coupled with a head mounted virtual reality setup. The objective was to find the most appropriate EEG system to use with this type of novel paradigm and then to test its feasibility online in ASD participants.

In sum, our study had two main goals: 1. to ascertain the usability of 3 distinct EEG setups to be used combined with a VR headset as part of a novel BCI system with a paradigm that uses social joint attention cues as an indicator of the target event; 2. to test its feasibility online in ASD participants as a prior step for future efficacy trials. Concerning this prior goal, we tested three distinct 'easy-to-use' EEG systems. The tests were conducted to verify the comfort and the time needed to use the VR P300-based BCI tool with each one of the EEG systems. The acquired EEG data were tested with the automatic BCI's P300 identification module to investigate which system showed better accuracy in which concerns BCI's performance.

We therefore first focused on a healthy participant cohort and finally performed exploratory assessments in four ASD subjects to prove the feasibility in a clinical setting.

3.3 Material and methods

This study and all the procedures were approved by the Ethics Commission of the Faculty of Medicine of the University of Coimbra (Comissão de Ética da Faculdade de Medicina da Universidade de Coimbra) and was conducted in accordance with the declaration of Helsinki. All participants were recruited from our database of voluntary participants, with no monetary compensation. All of them agreed and signed a written informed consent.

3.3.1 Participants

All healthy participants (n = 13, 7 males, 6 females, average age 22,5 years (SD = 1.8 years), range 21–26 years) had normal or corrected-to normal vision and no history of neuropsychiatric disorders.

Pilot studies with clinical participants included 4 young males with high-functioning Autism Spectrum Disorder (Full-Scale Intelligent Quotient [FSIQ] > 70; FSIQ: Mean = 106.75; SD = 17,85), ranging in age from 15 years to 22 years, average age 18,8 years (SD = 2.6 years). ASD diagnosis was assigned on the basis of the gold standard instruments: parental or caregiver interview (Autism Diagnostic Interview – Revised, ADI-R (Lord, Rutter, & Le Couteur, 1994)), direct structured subject assessment (Autism Diagnostic Observation Schedule, ADOS (Lord et al., 1989)), and the current diagnostic criteria for ASD according to the Diagnostic and Statistical Manual of Mental Disorders 5, DSM-5 (Sugawara & Nikaido, 2014).

3.3.2 Virtual environment and software details

The immersive virtual environment was presented to the participant via the Oculus Rift Development Kit 2 headset (from Oculus VR). Participants did not report any problems with the near vision conditions of the setup, due to the small distance between the headset display and the eyes. The virtual environment consists in a bedroom with common type of furniture (shelves, a bed, a table, a chair, and a dresser) and objects (frames, books, lights, a printer, a radio, a ball, a door, a window, and a laptop).

Figure 3.1 – Panoramic view of the virtual bedroom

The room environment (Figure 3.1) was designed with 3ds Max (from Autodesk Inc.) and SketchUp (from Trimble Navigation Limited). The objects in the room were obtained and adapted from 3D Warehouse (from Trimble Navigation Limited). The environment texture rendering was done in 3ds Max with Mental Ray 3D rendering software (from NVIDIA ARC GmbH). The stimulation software was written using the Vizard Virtual Reality Toolkit software (from WorldViz) and the real-time scene rendering was implemented using Vizard and Oculus Rift middleware software integration.

The communication between the stimulation and the EEG acquisition module (event markers and results of data processing) was achieved via a TCP/IP communication protocol. The TCP/IP protocol was chosen in order to allow the system to work in the future in separate computers, if the need arises, due to larger number of channels and/or sampling rate.

The overall system setup can be seen in Figure 3.2.

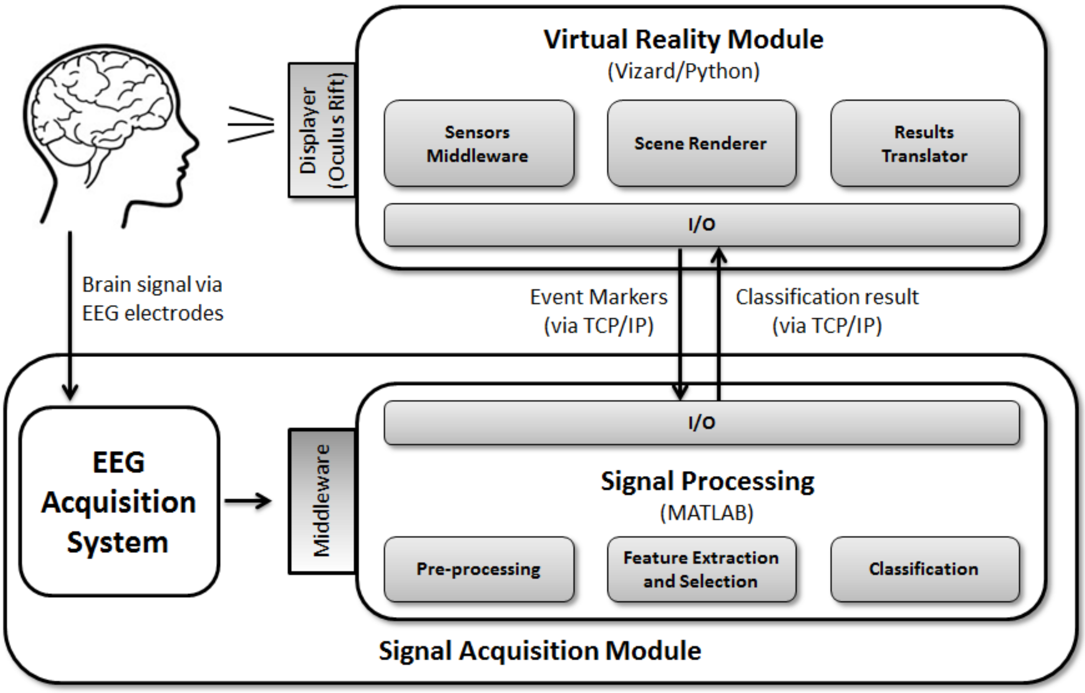

Figure 3.2 – BCI system integration

The acquisition and the VR stimulus display was controlled by a single computer (Intel ® Core™ i7-4710HQ CPU @ 2.50 GHz, 6M Cache, up to 3.50 GHz, RAM: 16 Gb, graphics card: GeForce GTX 870M, 1344 CUDA cores @ 941 MHz, 192 Bit memory interface @ 2500 MHz, 6 Gb of dedicated memory). Prior tests showed that the smooth rendering of the graphical VR stimulation is ensured, as well as the EEG acquisition.

3.3.3 EEG Data acquisition

The tested systems were: 1) g.Mobilab+ (gTEC, Austria) with g.SAHARA active dry-electrodes and wireless transmission of the signal; 2) g.Nautilus (gTEC, Austria) with active electrodes that do not require abrasive skin treatment (completely wireless signal transmission); 3) V-Amp with wired actiCAP Xpress dry-electrodes (BrainProducts, Germany).

EEG data were recorded from the same 8 electrodes positions (C3, Cz, C4, CPz, P3, Pz, P4, POz) with all the systems. The reference positions were placed at the right ear. The ground positions was placed at the left ear, except with the g.Nautilus system (placed at AFz, because this could not be changed). Sampling rate was set at 250 Hz, the closest possible to predefined g.Mobilab sampling rate (256 Hz). Data were acquired notch filtered at 50Hz and passband filtered between 2Hz and 30Hz. The filtering was performed via the proprietary Simulink HighSpeed Online Processing block modules for g.MOBIlab and g.Nautilus systems, and via MATLAB code for the Xpress system. Table 3.1 summarizes the acquisition settings for each system.

Participants took part in 3 EEG recordings, each one with one of the EEG systems, in random order, performing the same task. The number of trials resulting from each EEG recording is the same across all the setups, which gives a total number of events/trials per subject of 1600 trials × 3 acquisitions = 4800 trials. More details about the events are described in the next sections. In order to reduce the fatigue effect, and sequence effects, the order by which each system was tested was randomized between all the participants with the constraint that all systems had been tested in the first place the same number of times.

Table 3.1 - Acquisition systems characteristics

Characteristics	Acquisition system		
	g.MOBIlab+	g.Nautilus	Xpress
Amplifier	g.MOBIlab+ 8 unipolar channels	g.Nautilus 16 Research Headset	V-Amp 16 unipolar channels
Cap	g.GAMMAcap² (10-20 system)		actiCAP Xpress cap (10-20 system)
Electrodes	8 active dry electrodes (g.SAHARAelectrodes) + 2 adhesive Ag/AgCl electrodes (GND and REF)	8 gel-based active electrodes (g.LADYbird) + g.LADYbird (GND) + g.GAMMAearclip (REF)	8 active dry electrodes (mushroom-headed QuickBits) + 2 T-shaped QuickBits (GND and REF)
Electrode positions	C3, Cz, C4, CPz, P3, Pz, P4, POz, GND: left ear, REF: right ear	C3, Cz, C4, CPz, P3, Pz, P4, POz, GND: AFz, REF: right ear	C3, Cz, C4, CPz, P3, Pz, P4, POz, GND: left ear, REF: right ear
Pre-amplifier	g.SAHARAbox - Active dry electrode driver box	-	-
Sampling rate	256Hz	250Hz	250Hz
Signal transmission	Bluetooth 2.0	Bluetooth 4.0	USB 2.0
Middleware	g.MOBIlab+ Simulink HighSpeed Online Processing for MATLAB		TCP/IP Remote Data Access interface from BrainVision Recorder
Filtering	Notch: 50 Hz; 2Hz–30Hz, 8th order Butterworth band-pass filter		Post-recording filtering: 2Hz to 30Hz 8th order Butterworth band-pass filter, 50 Hz Notch

The time needed to place the cap on the volunteer's head was measured with a chronometer, as well as the time to place Oculus headset over the EEG caps, and the time to achieve the desired signal quality, using the same criteria. The time between the start and the end of the total session procedure was also recorded. Pilot recordings revealed that when the subject is still with the eyes opened and using active electrodes the EEG signal could be kept stable between ±20 μV and the impedances kept under 30 kΩ. We therefore defined the desired signal quality as the moment when the EEG signal was visually kept stable between ±20 μV more than 10 consecutive seconds, having the subject still and with the eyes opened. During the time to achieve the desired signal quality we explained the task to the participant and adjusted the positions of the electrodes and the contact with the scalp. With the g.Nautilus system, during this time we also placed the conductive gel.

Friedman Tests were conducted with a significance level set at 0,05 to compare the total session time, the time needed to place the cap on volunteer's head, the time to place the Oculus headset over the EEG caps, and the time to achieve the desired signal quality with each of the systems. These tests were followed by post hoc analysis with Wilcoxon signed-rank tests with a Bonferroni correction applied, resulting in a significance level set at $p < 0.017$.

At the end of the acquisitions we asked the participants which system was the most comfortable to use.

3.3.4 Proof of concept studies with clinical participants

The setup used in the pilot sessions with ASD individuals was chosen based on the results obtained from the tests with healthy subjects. As it will be shown in results section, the BCI configuration using g.Nautilus offered better signal reliability, faster setup preparation and more comfort to the participants. This way, ASD participants used the configuration with the above described g.Nautilus.

3.3.5 Paradigm and task

The participants were submitted to the calibration phase of the BCI. It is a fundamental step of a BCI system since the data and derived models of the filter and classifier resulting from this phase are used separately for training and test data, being in turn used in the BCI online phase (for the clinical proof of concept of this study). This is a mandatory phase since the filter and the classifier are user-dependent. Only this way it is possible obtain the set of parameters that optimize the detection of P300 for each user.

The calibration phase of our BCI system is divided in two parts where the task is similar, but the instructions are slightly different.

First part (Figure 3.3): This part had 10 blocks. Each block consisted in 10 sequential runs, and each such run consisted of flashing all of the 8 objects in the scene (green flashes) in a randomized order: 1. a wooden plane hanging from the ceiling; 2. a printer on a shelf; 3. a corkboard on the wall; 4. a laptop on a table; 5. a ball on the ground; 6. a radio on top of a dresser; 7. a picture on the wall; 8. books on a shelf. The highlight (flash) of each object occurred with a Interstimulus Interval of 200 ms. Each flash had the duration of 100 ms. The order which by all the objects were highlighted was random. This gives a total of 80 flashes (events) per block. In each block it was directly told to the participants to look to one of the already mentioned objects that would be flashed and count the number of times it would happen. The object that was explicitly mentioned to the user in this phase was the target one. The target object in each block was randomly chosen by the computer using the pseudorandom number generator Mersenne Twister algorithm and was displayed only to the investigator on the laptop screen (the participant is wearing the Oculus device). Since the participant was only attending to the flashes of only one object per block, this event is the rarest one (target event probability of 1/8) and thus it generates the P300 brain response we aim to monitor. Here, by directly instructing the user to the target object during calibration, we intentionally remove potential errors identifying the target object related with social attention deficits that are present in ASD. At the end of each block it was asked to the participant to which object they looked (as a behavioural control). This part was designed to ensure the correct recording of each subject's P300 response, without interference of social cognition aspects. This is fundamental because the data from this part will be used as the training data of the filter and the classifier of the BCI system, explained in the next section.

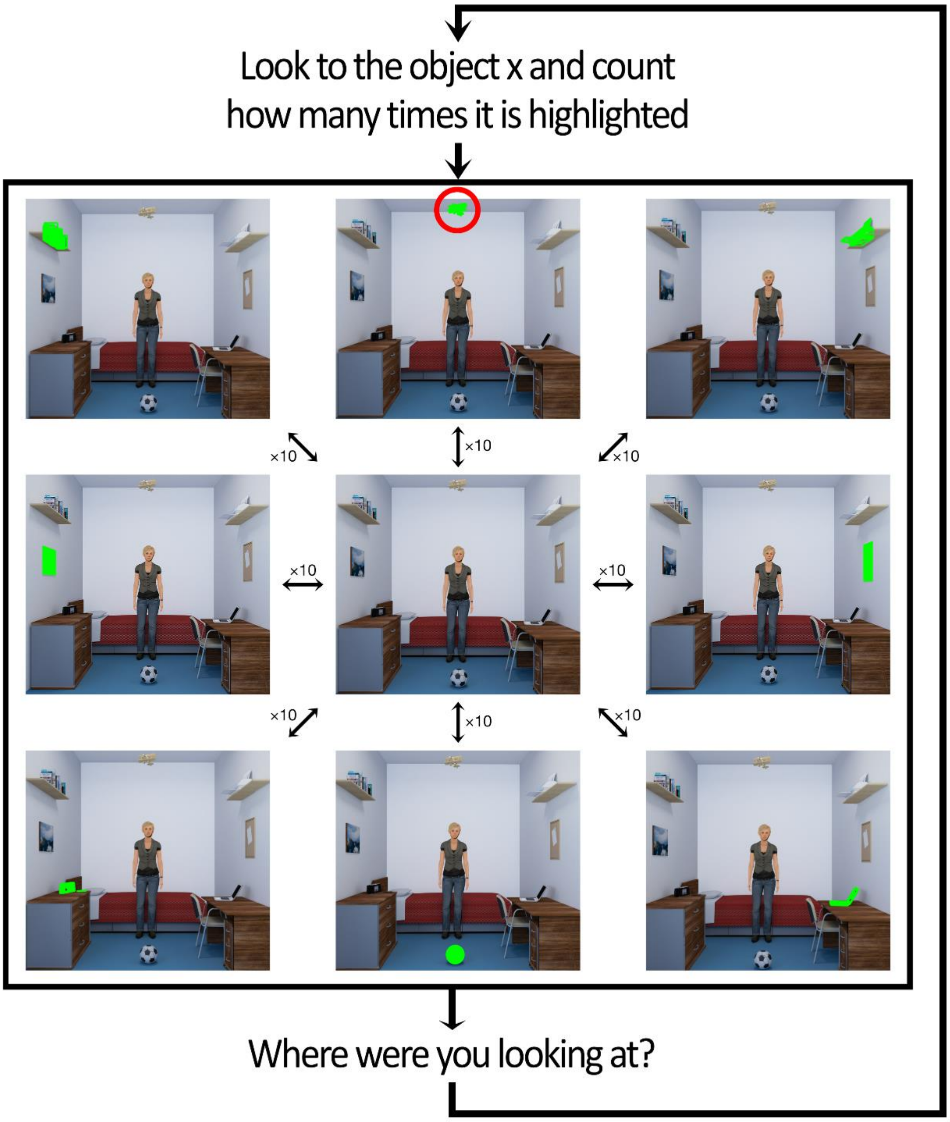

Figure 3.3 – Example of one block of the first part from the calibration phase of the BCI. Inside each block the same object never flashed two consecutive times. The randomization of the order of the objects highlighting was controlled in order so this never happened.

Second part (Figure 3.4): This part also had 10 blocks. In each block the participants were instructed to look to the virtual character's (avatar) face and attend to which of the objects it turned its head (joint attention cueing). The avatar then moved its head with a realistic and animated movement to one of the 8 objects already mentioned in the first part. The object to where the avatar turned its head was chosen randomly by the computer in each block using the pseudorandom number generator Mersenne Twister algorithm. Then they were asked about which object was chosen by the avatar. This cycle was repeated until the participant has given two consecutive correct answers. This response is meant to obligate the user to learn to read the social joint attention cue of the avatar and use this information correctly. In other words, these are the instructions for use of the BCI. It is crucial so the acquired data can be effectively used to properly test the classifier.

After this, the participants were told to look to the object the avatar had chosen and count the times it was highlighted. This step is followed by 10 sequential runs of flashing all of the 8 objects in the scene (green flashes) in a randomized order. This gives a total of 80 flashes (events) per block. The object to which the avatar turned its head was the target object (event) of the block. Since the participant was only attending to the flashes of only one object per block, this event is the rarest one and thus it generates the P300 brain response we want to monitor.

At the end of the objects highlighting period it was asked to the participant to which object they looked (as a behaviour control). This part was designed to add the joint attention training component of the online BCI paradigm. By introducing the ecological and immersive virtual reality environment and the realistic animation of avatars' head towards an object, as a cue to the target object, we intended to introduce the realistic component that can add joint attention mechanisms during social information processing. The understanding of this mechanism is fundamental so the participants can succeed in the online BCI task (performed in proof of concept tests with ASD individuals; see below) where the blocks are similar to the blocks of this second part but without the cycle of questioning to where the avatar turns its head. The participant must follow the head cue instantaneously and pay attention to the target object. In the online phase of BCI the P300 detection model created with the data from the calibration phase (explained in the next section) will be in charge to give the feedback about the attentional focus of each participant, at the end of each block (target object turns green if the user correctly directed their attention to it, or any non-target object turns red if the attention focus was one of them). This closed-loop ensures feedback about the attentional focus of the subject and its monitoring during the BCI game with no need for any explicit response, which helps keeping attention focused, critical for clinical applications (Figure 4.4).

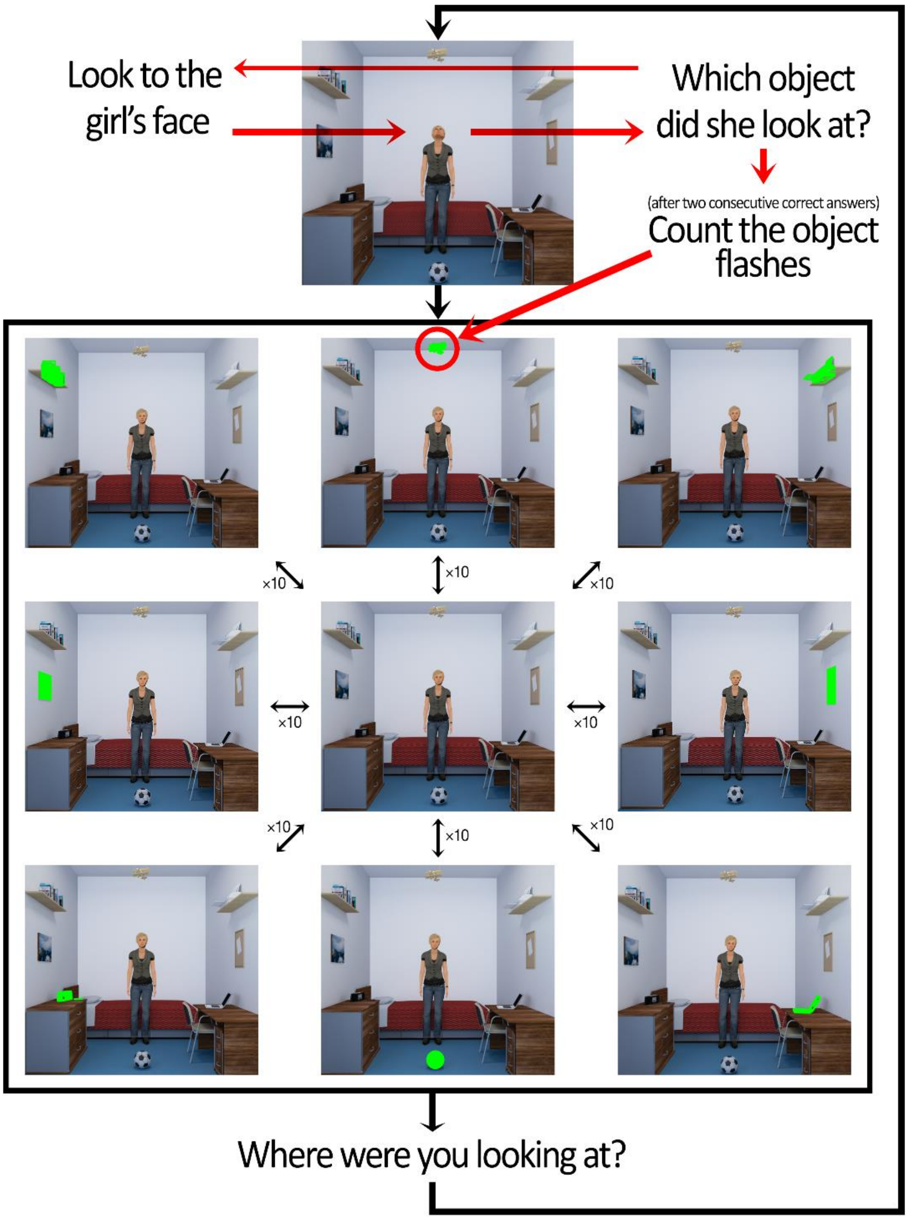

Figure 3.4 – Example of one block of the second part from the training phase of BCI. Inside each block the same object never flashed two consecutive times. The randomization of the order of the objects highlighting was controlled in order so this never happened.

3.3.6 EEG data analysis

Offline analysis of the data from the healthy subjects was performed using the C-FMS beamformer methodology proposed in Pires et al. (2011), that cascades a spatial filter based on the Fisher Criterion (FC) with another spatial filter that maximizes the ratio of signal power and noise power (Max-SNR) satisfying simultaneously sub-optimally both criteria (C-FMS beamformer) .

The EEG data from both parts were segmented in epochs (related to each event of the blocks) of 1100 ms with a 100 ms pre-stimulus interval and a 1000 ms post-stimulus interval. Each epoch was normalized to zero mean and unit standard deviation. Each epoch is labelled as target or non-target accordingly to the trigger stored during the EEG acquisition and the target event of each block. From the events labels and the responses of the classifier for each event we could calculate the accuracy of the classifier responses.

From the structure of the tasks we get two datasets. We defined the data from the first part as the training dataset and the data from the second part as the test dataset. Both datasets have 10 blocks of data. Inside each block we have 10 runs of 8 distinct events from which only one is the target event (the target event of the block). This leads to a total of 800 epochs of data. This way we were able to test the classifier performance across different events averages (from single event to 10 event averages) inside each block.

The training dataset is used to compute the FC filter model. The FC filter is applied to the data and a first feature vector is obtained from the projection associated to the largest eigenvalue of FC filter. The Max-SNR filter model is calculated from the remaining projections. The filter is then applied to the same projections and a second feature vector is extracted from the projection associated to the largest eigenvalue of Max-SNR filter. The two feature vectors are concatenated (forming the C-FMS beamformer) and scored according to the r-square discrimination (square of the Pearson's correlation coefficient) between target and non-target events. Finally, a Naïve Bayes (NB) classifier is trained using the features with higher r-square score and the best feature indices are also stored.

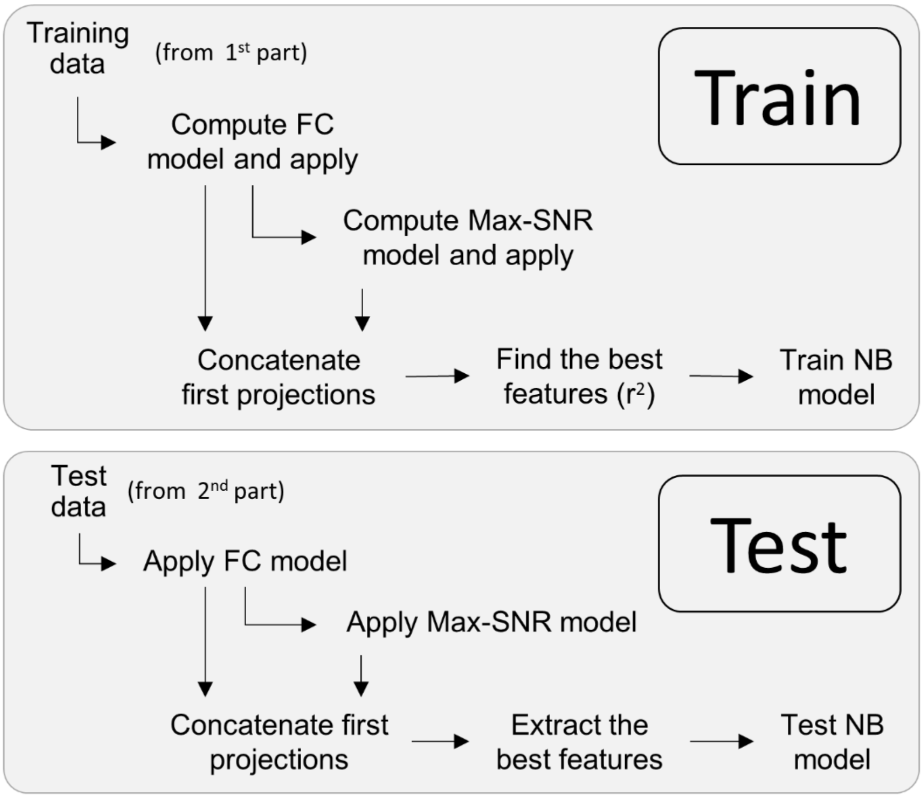

Figure 3.5 – Data processing workflow.

Thereafter, the FC and Max-SNR filters calculated from the training dataset are then applied in cascade to the test dataset to obtain the vector of features. The features with the same indexes of the best features in the training dataset processing are used to test the NB classifier model. The decision about the attended object is obtained from the combination of the *a posteriori* probabilities returned by the NB classifier according to:

$$\#object = max_j \in \{1, \ldots, 8\} P_+^j +$$

where P_+^j are the *a posteriori* probabilities associated to the events (index j, corresponding to the 8 objects). In other words, the method chooses the event most likely to be a target.

The classifier's accuracy of target object detection by run was computed with the data from the three systems, for each subject. The classification performance is assessed using the NB classifier. We tested several averages of events (from a single event to 10 event averages) to verify the influence of signal to noise ratio in the accuracy of the classifier.

The area under the curve of the accuracy levels across event averages was calculated to compare the global performance of the classifier across the different systems. A Friedman Test was conducted followed by *post hoc* analysis with Wilcoxon signed-rank tests with a Bonferroni correction applied, resulting in a significance level set at $p < 0.017$.

3.4 Results

3.4.1 Tests with healthy subjects

The Friedman Tests comparing the measured times from all the 13 participants, for each of the 3 systems, revealed statistically significant differences in overal session time (Figure 3.6), $\chi^2(2) = 5.320$, $p = 0.045$, in the time needed to place the EEG cap, $\chi^2(2) = 9{,}692$, $p = 0.007$, in the time needed to place the Oculus Rift headset over the EEG cap, $\chi^2(2) = 9.385$, $p = 0.009$, and in the time needed to signal stabilization, $\chi^2(2) = 7.538$, $p = 0.025$.

The post hoc tests with Bonferroni correction indicated that the sessions with the g.Nautilus EEG system (Mdn – 28 minutes = 1680 seconds) was significantly shorter than the sessions with the Xpress system (Mdn session time – 32 minutes = 1920 seconds), Z = -2.518, *p* = 0.008.

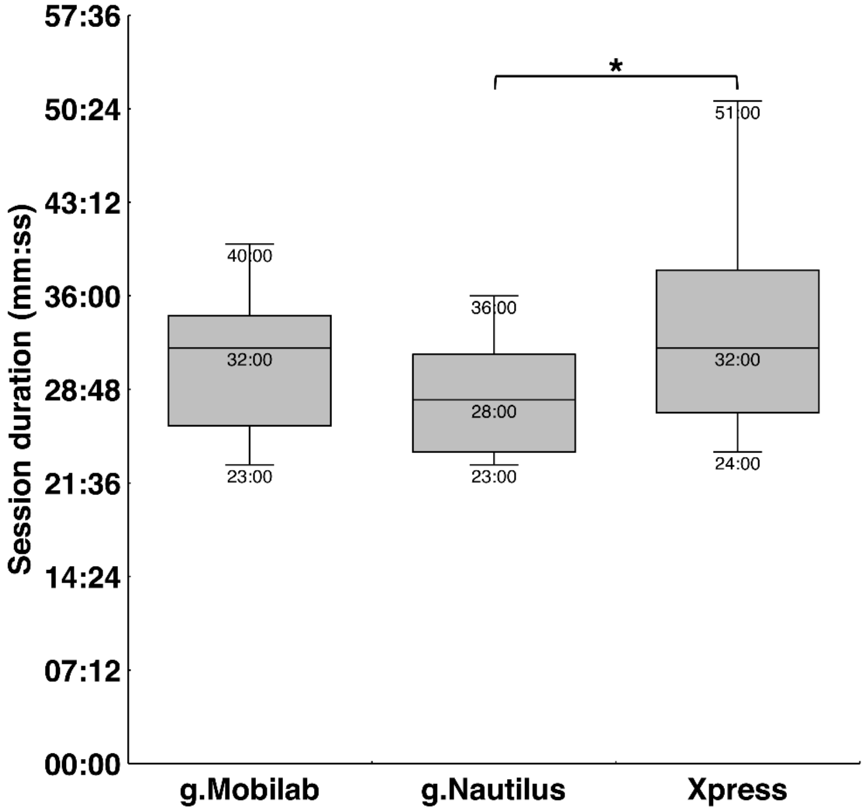

Figure 3.6 – Boxplot of the session times with the different systems.

There were no significant differences between the total session time with g.Mobilab (Mdn – 32 minutes = 1920 seconds) and Xpress (Mdn – 32 minutes = 1920 seconds), *Z* = -0.735, p = 0.486, neither between the session times with g.Nautilus and g.Mobilab, *Z* = -1.297, *p* = 0.218. It took less time to correctly place the g.Nautilus system's cap in the participants head (Mdn – 1 minute and 3 seconds = 63 seconds) than all the others systems' caps (vs g.Mobilab: Mdn – 1 minute and 41 seconds = 101 seconds, *Z* = -2.342, *p* = 0.016; vs Xpress: Mdn – 1 minute and 40 seconds = 10 seconds, $Z = -2.132$, $p = 0.033$). There were no differences between the time needed to place the caps of g.Mobilab and Xpress systems, $Z = -0.769$, $p = 0.465$ (Figure 3.7).

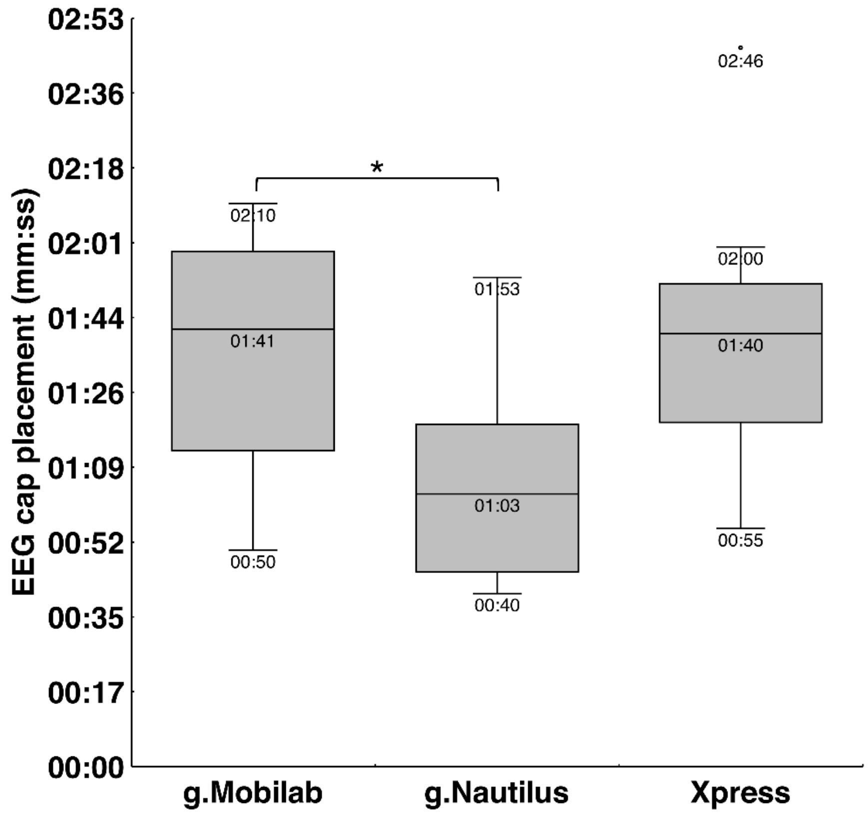

Figure 3.7 – Boxplot of the times needed to place the different systems' EEG caps.

Concerning the time needed to place the Oculus Rift headset over the EEG caps (Figure 3.8), it was faster (Mdn – 30 seconds) to place when the participants were with the g.Nautilus cap on (vs g.Mobilab: Mdn – 46 seconds, $Z = -2.730$, $p = 0.004$; vs Xpress: Mdn – 45 seconds, $Z = -2.834$, $p = 0.003$. There were no differences when the participants were wearing g.Mobilab or Xpress, $Z = -0.280$, $p = 0.800$).

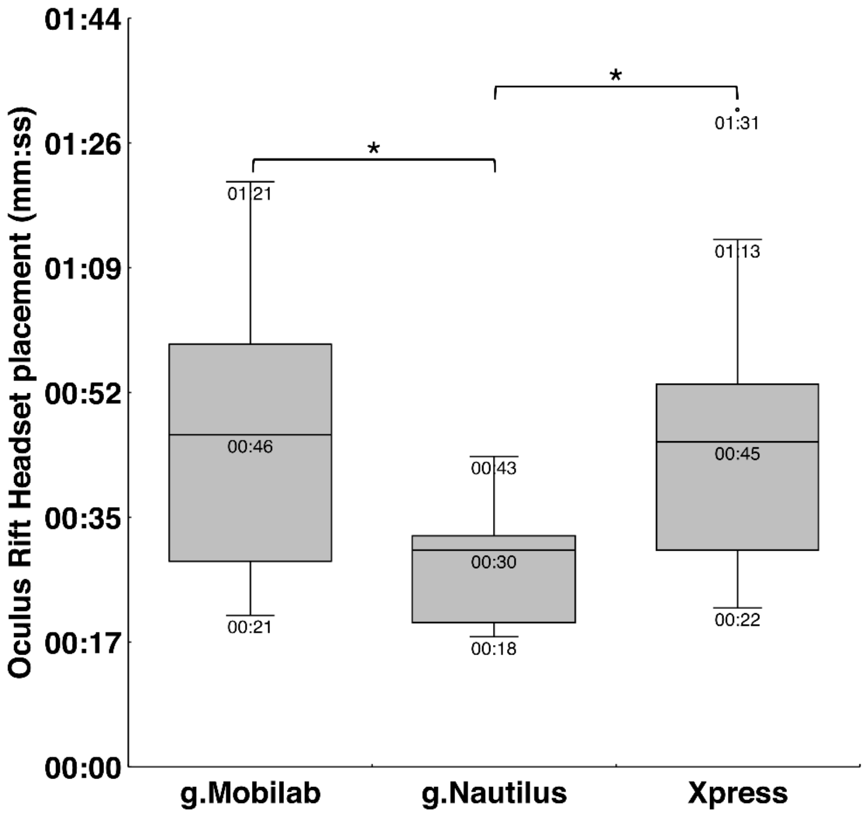

Figure 3.8 – Boxplot of the times needed to place the Oculus Rift headset over the EEG cap.

The comparison tests between the time needed for the EEG signal stabilization (Figure 3.9) revealed that there were statistically significant differences between the times for signal stabilization of g.Nautilus (Mdn – 1 minute and 43 seconds = 103 seconds) and g.Mobilab (Mdn – 3 minutes and 20 seconds = 200 seconds), $Z = -2.201$, $p = 0.027$; but not between g.Nautilus and Xpress stabilization times (Mdn – 2 minutes and 48 seconds = 168 seconds), $Z = -1.748$, $p = 0.083$, nor between g.Mobilab and Xpress, $Z = -0.524$, $p = 0.635$).

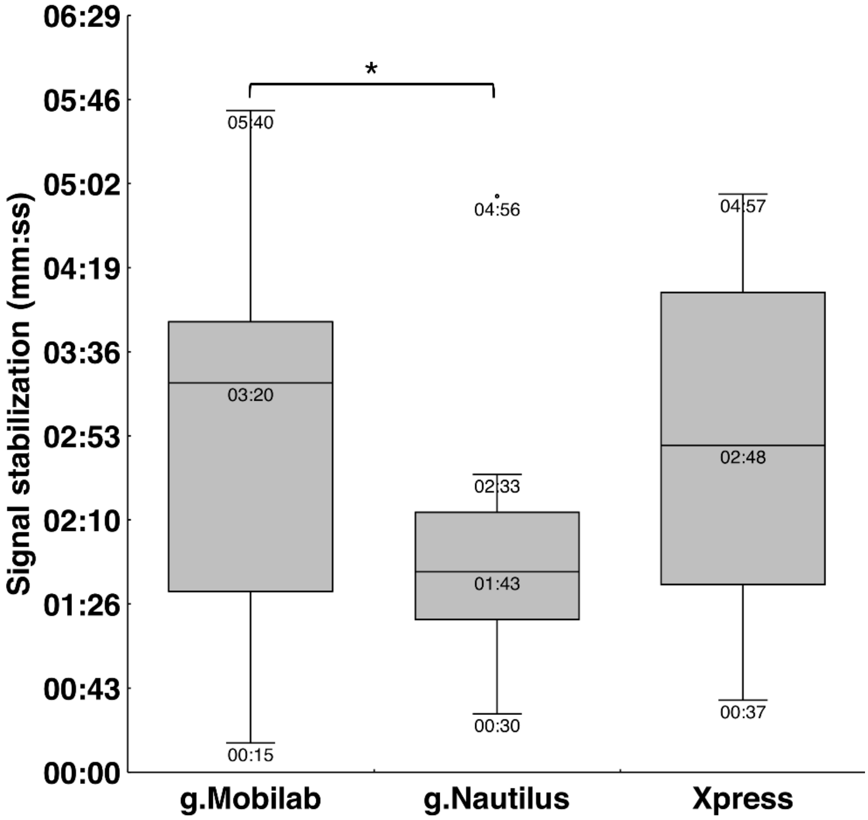

Figure 3.9 – Boxplot of the times for the signal stabilization occur.

Average accuracies of target object detection by block across event averages are summarized in Figure 3.10. Even at the single trial level all systems were well above the 1/8 chance level.

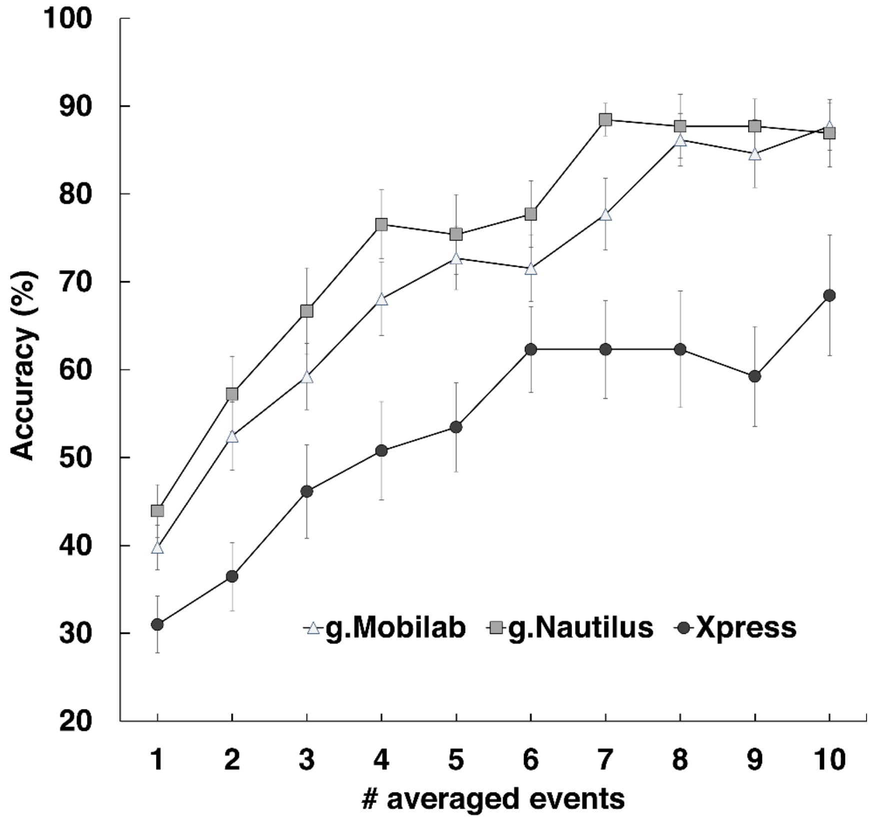

Figure 3.10 – Averaged accuracies and standard errors of the mean of object detection per block, with the signal from g.Mobilab, g.Nautilus and Xpress. Chance level is 12.5%.

Statistically significant differences were found between the AUCs of accuracy levels across event averages, $\chi^2(2) = 14{,}000$, $p = 0{,}001$. Post hoc tests unveiled that, globaly, the classifier performed significantly worse with the signal from Xpress: Median areas under the curve: g.Mobilab – 6.49; g.Nautilus – 6.88, Xpress – 5.09. Xpress vs g.Nautilus, $Z = -3.040$, $p = 0.001$; Xpress vs g.Mobilab, $Z = -2.900$, $p = 0.002$. The AUCs of g.Mobilab and g.Nautilus were not significantly different, $Z = -1.992$, $p = 0.048$ (Figure 3.11).

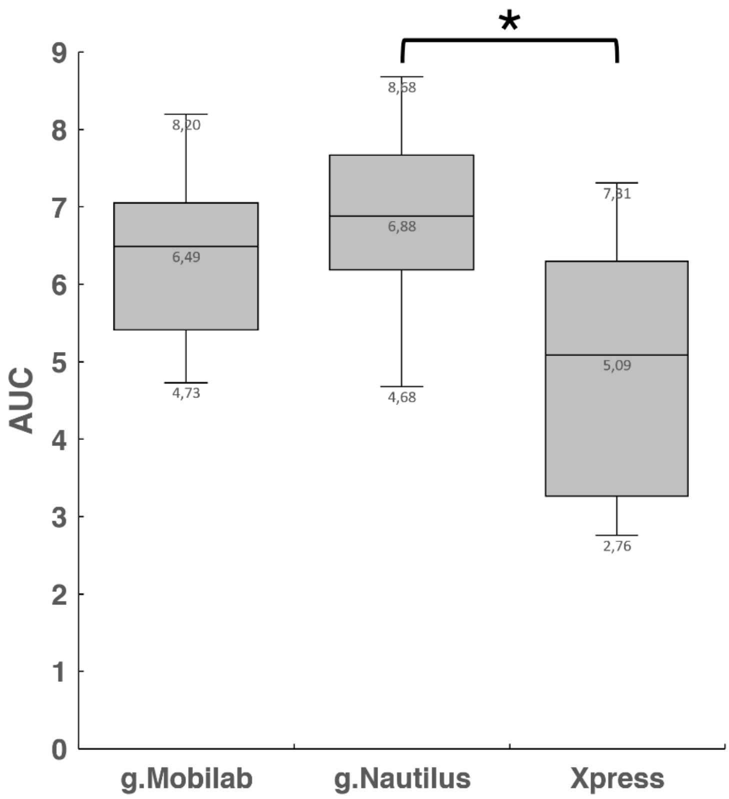

Figure 3.11 – Boxplot of the AUCs of accuracy levels across event averages, for each system.

Twelve participants pointed g.Nautilus as the most comfortable system to use with the VR setup, performing the BCI task. One participant preferred the g.Mobilab system.

3.4.2 Proof of concept in Autism Spectrum Disorder Participants

We took the opportunity to test the overall BCI configuration online in ASD participants. Based on the results shown in the previous section we picked g.Nautilus system to perform these experiments.

We were able to make four online sessions with four ASD subjects. Figure 3.12 shows the accuracy of target object detection on calibration phase of BCI. The number of averaged events 1 and 2 was not tested in the calibration phase to prevent excessive elongation of the overall online session time.

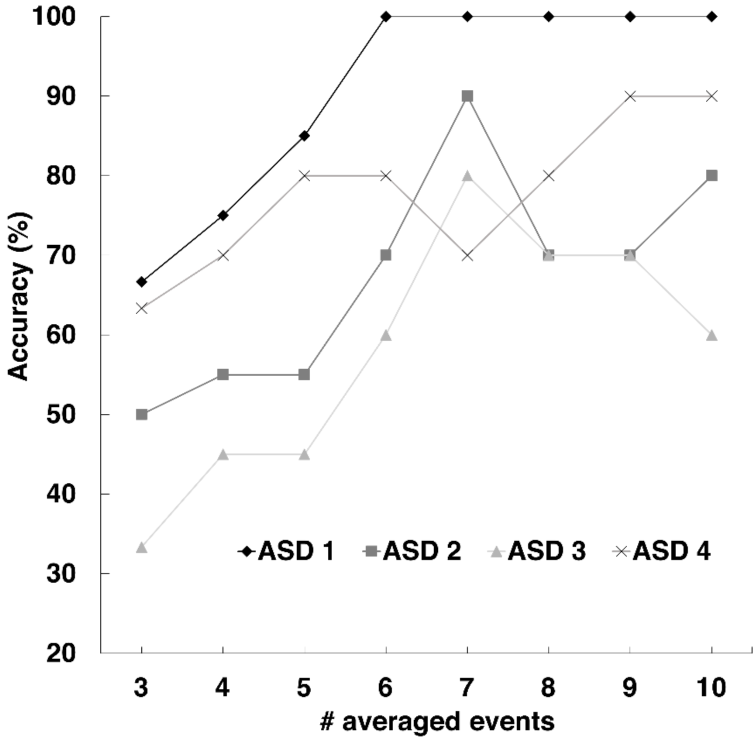

Figure 3.12 – Accuracies of target object detection across different number of averaged events per block on calibration phase, for each ASD participant. Chance level is 12.5%.

The number of averaged events to use in the online phase of BCI was chosen from the results of each calibration phase: we selected the lowest number of averaged events with the accuracy levels above 87.5% (100% minus 12.5%) or the lowest number of averaged events with the best possible accuracy.

Table 3.2 presents the detection accuracy of attention to the target object on the online phase of BCI using the number of averaged events chosen from each calibration phase. All participants were all well above chance.

Table 3.2 - Accuracy of detection of attention to the target object on the online phase and the number of averaged epochs for each ASD subject that performed the online BCI sessions.

ASD subject	Target object detection accuracy*	# averaged events
ASD1	0,34	6
ASD2	0,72	7
ASD3	0,36	7
ASD4	0,46	9

* chance level: 1/8

3.5 Discussion

This study had 2 main goals: 1. To develop a novel BCI with a paradigm that uses social joint attention cues as an indicator of the target event and ascertain the usability of 3 distinct EEG setups to be used combined with a VR headset; 2. Test this setup with an emphasis on comfort and usability with healthy subjects, and to test its feasibility online in ASD participants, for application in a future efficacy testing Phase I/II trial.

Regarding the comparisons tests in healthy participants two systems performed well above chance even at the single trial level. Tests with EEG data from each system revealed an overall better performance with the signal from g.Nautilus and g.Mobilab as compared to the signal derived from Xpress. A possible explanation might be that in the latter case artifacts are more likely during the recordings possibly because of stability of Xpress electrodes pin configuration or because of the wires that connect them to the amplifier. The Xpress' electrodes single pin configuration seemed to be less effective in maintaining stable contact with the skin to obtain good signal quality. A slight move of the subject (e.g.: turn the head to look to the target object) makes the wires stretch, move the electrodes and, eventually, even make them occasionally lose contact with the skin. Because Xpress electrodes have only one pin they are prone to leave their position and hardly return to the original one. In contact, despite the fact that g.Mobilab electrodes are also dry electrodes and have wires connected to the transmitter, their 8 pin configuration makes it possible the electrodes to tilt and drag, which makes them less prone to lose contact with the skin.

The mean accuracy of 80% after 4 trials averages with the g.Nautilus system shows the possibility of using this paradigm with this setup in an applied setting to give direct feedback about the attentional focus of the subject. Nonetheless these accuracy values are significant having into acount the scene complexity and the relatively high probability of target occurrence in relation to the usual target probability in some of others P300 based BCI paradigms (Guan, Thulasidas, & Wu, 2004; Pires, Nunes, & Castelo-Branco, 2011a, 2012b; Townsend et al., 2010). One could possibily increase the accuracy rates by reducing the target event probability since the lower the probability of the target event the higher the amplitude of P300 wich, in turn, is one of the most relevant features for P300 detection (Croft, Gonsalvez, Gabriel, & Barry, 2003; Mars et al., 2008; J Polich, Ellerson, & Cohen, 1996). One way to do this would be increasing the number of objects flashing in the bedroom. We decided to keep the high probability of the target event by choosing only 8 objects in the room to have a fair tradeoff between the scene realism and the performance of the BCI. This decision was also suported by the already mentioned sensory hypersensitivity of the potential target population of the system. Having a big number of flashes in front of their eyes might disturb the ASD subjects and decrease the adherence to the task. Increasing the number of objects in the scene would also increase the total number of events of the task and thus the total time. It might negatively affect the attention levels of the subject due to the fatigue acumulation during the task.

In terms of the usability of all the experimental setups, globally, the sessions with the g.Nautilus EEG system were shorter than with other systems. During the acquisitions with Xpress and g.Mobilab and by monitoring the online EEG plot we noticed that the electrodes had lost their contact with the scalp sometimes. It was often necessary to correct these faults, pausing the task and adjusting the electrodes positions. This might have contributed to the larger range of session duration times of Xpress and g.Mobilab and contributed to the statistically significant longer sessions of Xpress sessions as compared to the sessions with g.Nautilus.

Concerning recording time g.Nautilus showed to be the easiest EEG system to use together with the remaining BCI apparatus since it was quicker to place its cap than the g.Mobilab cap, and it was quicker to place VR headset over g.Nautilus cap than the other systems' caps. Despite the fact that these differences were only of some seconds, they are still quite important considering the BCI's target population. ASD subjects may have a hyper-reactivity to sensory stimulation so it is important to minimize the direct contact with the participant. These results together with the narrower range of g.Nautilus' signal stabilization time constraints (Figure 3.9) indicate an overall lower direct contact time with the users of the BCI when the g.Nautilus system is used.

We believe that some technical factors related to EEG systems' configuration might have influenced the usability differences between all systems. The electrode configuration of Xpress and g.Mobilab system complicated the cap placement. Each Xpress electrode have one pin with mushroom heads designed "to ensure a stable contact with the scalp even if the sensors are not completely perpendicular to the surface" (Brain Products, 2014). However, when placing the cap, the pins often caused unwarranted pressure on the participants' scalp and sometimes even discomfort. So, we had to carefully raise from the skin each electrode that was causing such discomfort to the participant and only then move the cap to the correct position. Regarding g.Mobilab electrodes the same happened but less frequently because these electrodes have 8 pins instead of a single one. It distributed the forces applied in the scalp which reduced the potentially inflicted discomfort. Besides that, the electrode pins of both systems revealed to be not the best to have the VR headset elastic bands over them. The bands increase the pressure on the electrodes which caused additional discomfort to the participant when placing the Oculus system, which required extra care, and implied an increase of the time needed to place the Oculus Rift headset over the electrodes caps.

The differences between the stabilization times of g.Nautilus and g.Mobilab suggest that the use of the gel optimizes the stabilization of the EEG signal. Additionally, the differences between overall sessions times of g.Nautilus and Xpress support the idea that it is still worth to use gel in these applications, because it reduces the occurrence of the loss of contact between the electrodes and the skin during the EEG acquisitions. We have experienced that this often occurs with the Xpress system. This is reflected in the overall session time with Xpress and in the respective differences to the g.Nautilus. With the gel, we did not have to interrupt the session to re-establish the contact between the electrodes and the skin and this is why the overall session time with g.Nautilus is inferior. At the same time, the gel reduces the skin impedance which justifies the best classification results (best signal-to-noise ratio).

Online tests in ASD participants

The configuration with g.Nautilus was tested online with ASD subjects and proved to be well accepted by these participants. The task was performed without any problems, and the BCI classifier was able to correctly identify the attention marker well above the chance level in the online sessions, with all the four ASD participants. This means they understood the task and learned to read the joint attention social cue and use the information to correctly direct their attention to the target object.

This is noteworthy and proves the potential for a possible BCI based training tool to improve joint attention impairments. Future Phase I/II clinical trials should be done to prove the efficacy of this potential training tool.

3.6 Conclusions

We have developed a P300 BCI paradigm that introduces joint attention social cues to the participants. We showed that it is possible to introduce this kind of cues in immersive and realistic P300 based paradigms and that those cues can be effectively used. The results of the offline tests indicate significant classification results, even within few trials, and suggest the feasibility of online BCI sessions using this type of joint attention social cues as an indicator of the target object. We could show that it is feasible to use this paradigm online with autistic participants with joint attention impairments. The next step should be to investigate, within the scope of a clinical trial, the possibility of training joint attention skills of ASD subjects based on such social cueing to target events in the BCIs. At the same time, it was possible to test the feasibility of introducing virtual reality in this kind of applications.

Among the compared systems, the g.Nautilus system is the more suited system and was chosen as the final BCI setup for clinical testing. It is less intrusive to the participants and ensures good signal reliability. Among the three EEG systems compared, the criteria suggest that the g.Nautilus is better placed to afford a quicker set-up and a better classification performance which in turn are good characteristics of a BCI planned to be used with ASD population. These characteristics might reduce the probability of hypersensitivity responses by the potential target population

This work highlights the importance to test the usability of these 'easy-to-use' EEG systems with new technologies such as VR to increase the cognitive rehabilitation possibilities, in particular the ability to follow social cues, in clinical populations.

In sum, we have shown that joint attention signals (critical in autism, which is a social attention disorder) can be used in a BCI. The introduction of realistic social cues and immersive setups in BCI paradigms is a novelty and this study also showed the feasibility of this new approach in autistic participants. In the future similar setups could be used to train and test efficacy of joint attention skills in ASD population within the context of clinical Phase I/II clinical trials.

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Chapter 4

A feasibility clinical trial to improve social attention skills in ASD

This chapter follows up the effort to build a BCI coupled with virtual reality that was used to train joint attention skills in ASD. Here we describe the feasibility clinical trial we conducted to ascertain the viability of an intervention based on this type of technology. The neurophysiological and neuropsychological measures made during this trial allowed us to understand how ASD participants accept this type of technology how we can improve the procedures involving its utilization, in particular concerning to target desired improvements and choosing the best outcome measures.

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4.1 Abstract

Deficits in the interpretation of others' intentions from gaze-direction or other social attention cues are well-recognized in ASD. Here we investigated whether an EEG Brain Computer Interface (BCI) can be used to train social cognition skills in ASD patients. We performed a single-arm feasibility clinical trial and enrolled 15 participants (mean age 22y 2m) with high-functioning ASD (mean full-scale IQ 103). Participants were submitted to a BCI training paradigm using a virtual reality interface over seven sessions spread over 4 months. The first four sessions occurred weekly, and the remainder monthly. In each session, the subject was asked to identify objects of interest based on the gaze direction of an avatar. Attentional responses were extracted from the EEG P300 component. A final follow-up assessment was performed 6-months after the last session. To analyse responses to joint attention cues participants were assessed pre and post intervention and in the follow-up, using an ecologic "Joint-attention task." We used eye-tracking to identify the number of social attention items that a patient could accurately identify from an avatar's action cues (e.g., looking, pointing at). As secondary outcome measures we used the Autism Treatment Evaluation Checklist (ATEC) and the Vineland Adaptive Behaviour Scale (VABS). Neuropsychological measures related to mood and depression were also assessed. In sum, we observed a decrease in total ATEC and rated autism symptoms (Sociability; Sensory/Cognitive Awareness; Health/Physical/Behaviour); an evident improvement in Adapted Behaviour Composite and in the DLS subarea from VABS; a decrease in Depression (from POMS) and in mood disturbance/depression (BDI). BCI online performance and tolerance were stable along the intervention. Average P300 amplitude and alpha power were also preserved across sessions. We have demonstrated the feasibility of BCI in this kind of intervention in ASD. Participants engage successfully and consistently in the task. Although the primary outcome (rate of automatic responses to joint attention cues) did not show changes, most secondary

neuropsychological outcome measures showed improvement, yielding promise for a future efficacy trial.

4.2 Introduction

Autism spectrum disorder (ASD) is a set of pervasive and sustained neurodevelopmental conditions characterized by persistent deficits in social communication and social interaction, alongside restricted, repetitive patterns of behaviour, interests, or activities (Sugawara & Nikaido, 2014). This condition has a significant economic and social impact due to its high prevalence (estimated at ~1.5% in developed countries around the world (Baxter et al., 2015; Christensen et al., 2016; Lyall et al., 2017) and ~10 per 10000 children in Portugal (Oliveira et al., 2007)). It is associated with high morbidity and impact on daily family life (Boshoff et al., 2016; Harrop et al., 2016; S. Jones et al., 2016; Karst & van Hecke, 2012; Schlebusch et al., 2016).

Joint attention (JA) is an early-developing social communication skill defined by the non-verbal coordination of attention of two individuals towards a third object or event (Bakeman & Adamson, 1984). People with ASD show severe deficits in JA abilities (Baron-Cohen, 1989; Baron-Cohen, Baldwin, et al., 1997; Dawson et al., 2004; Klin, 2002; S. Leekam & Moore, 2001; J. Swettenham et al., 1998) which plays a critical role in the development of their social and language capabilities (Charman, 1998, 2003).

Electroencephalography (EEG) based brain computer interfaces (BCI), represent widely studied communication technologies (Farwell & Donchin, 1988; Kleih et al., 2011; Mak et al., 2011a; J. Wolpaw & Wolpaw, 2012). Virtual reality (VR) has been increasingly used in neuro-rehabilitation, in particular of motor control and has shown promising results (Astrand et al., 2014; E. B. Larson et al., 2014; M. J. Larson et al., 2011; Salisbury et al., 2016; Tankus et al., 2014). However, concerning cognitive applications in the field of neuro-rehabilitation the use of combined VR and BCIs has only been used with children with attention deficit hyperactivity disorder (which includes the presence of frequent inattentive, impulsive and hyperactive behaviours (Sugawara & Nikaido, 2014)).

The review provided by Friedrich et al., 2014, grounded on a series of neurofeedback training studies, postulates that quantitative EEG-based neurofeedback training is viable as a personalized therapeutic approach in ASD. They also suggest the development of a game platform that includes social interactions and specific feedback based on behaviour, neurophysiological and/or peripheral physiological responses of the users. The ultimate goal is to reinforce significant behaviours, such as social interactions using neurobehavioral signals to promote behavioural, cognitive and emotional improvement in ASD people. Along this line several studies do advocate (Bekele et al., 2014; Georgescu et al., 2014; Wainer & Ingersoll, 2011) that the use of ecological, realistic and interactive virtual environments may be the solution for the well-known generalization problem of the rehabilitation of social skills in ASD subjects to real life settings. Golan and Baron-Cohen (2006) suggested that the use of computerized intervention in ASD individuals enables the development of skills in a highly standardized, predictable, and controlled environment, while simultaneously allowing an individual to work at his own pace and ability level.

Based on these suggestions, we propose a virtual reality P300-based BCI paradigm (which technical implementation is described in (C. P. Amaral, Simões, Mouga, Andrade, & Castelo-Branco, 2017) that tries to couple the advantages of ecological, realistic and interactive virtual environments with the attention related nature of the P300 brain waveform to create a cognitive training tool for ASD. The P300-based paradigm that we present here consists on an immersive environment were the subject must follow a non-verbal social agent cue (head turn) and direct his/her attention to the target object. The attentional mental state of the subject is monitored through the detection of oddballs, which leads to a P300 signal which allows giving feedback about his/her attentional focus. The P300 signal is a well-known neural signature of attention processes for detection of rare items in a stimulus series – oddball paradigm – (for a review see (Duncan et al., 2009; Patel & Azzam, 2005; John Polich, 2007)). We decided to couple the training of joint attention skills to the P300 signal because the latter is widely used in focused attention studies, and is related to integration of information with context and memory (Halgren et al., 1995). Moreover, with the automatic detection of P300 signals one can provide direct feedback about the participant's attentional focus. This provides information that the subject can use to self-monitor his/her performance about where to look and subsequently allow ASD subjects to adjust behaviour. Given the repetitive nature of this type of oddball paradigm, and its operant learning properties, our motivation for the construction of this paradigm is based on the hypothesis that ASD subjects can assimilate joint attention skills by automating the response to the social cue that is given during the task we created.

The current trial set out to assess the feasibility and potential clinical effects of the use of this type of technology in ASD and attempts to evaluate the use of neurophysiologic-based rehabilitation tools for improving social behaviour in ASD.

4.3 Apparatus and methods

This was a single-arm clinical feasibility trial study conducted in Portugal.

Prior to subject recruitment, ethical approvals were obtained from the Ethics Commission of the Faculty of Medicine of the University of Coimbra (Comissão de Ética da Faculdade de Medicina da Universidade de Coimbra), the INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. (Portuguese Authority of Medicines and Health Products) and CEIC – Comissão de Ética para a Investigação Clínica (Portuguese Ethics Committee for Clinical Research).

This study and all the procedures were approved and was conducted in accordance with the declaration of Helsinki.

All subjects agreed and signed a written informed consent prior to screening procedures and recruitment (clinical-trial ID: NCT02445625 — clinicaltrials.gov).

4.3.1 Participants

Study included 15 adolescents and adults (mean age = 22 years and 2 months, ranging from 16 to 38 years old) with high-functioning ASD (Full-Scale Intelligent Quotient [FSIQ] (Wechsler, 2008): Mean = 102.53; SD = 11.64).

These participants met the inclusion criteria: positive diagnostic results for ASD assigned on the basis of the gold standard instruments: parental or caregiver interview - Autism Diagnostic Interview-Revised (Le Couteur et al., 2003); direct structured subject assessment - Autism Diagnostic Observation Schedule (Lord & Rutter, 1999); and/or the current diagnostic criteria for ASD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (Sugawara & Nikaido, 2014).

All diagnostic and neuropsychological assessments were performed by a psychologist (SM or IB) under the supervision of a medical doctor – a neurodevelopmental paediatrician (GO) in a face to face standardized situation in our clinical research institute.

Participants were excluded if they had intellectual disability, with a FSIQ inferior to 80 (Wechsler, 2008) and associated medical conditions such as epilepsy, neurocutaneous or other genetic known syndromes, or other usual comorbidity in ASD samples.

4.3.2 Intervention and apparatus

The baseline visit was used to obtain consent and collect baseline data. Collected baseline data included demographics, medication, neuropsychological measures related to the ASD diagnosis (ADI-R (Le Couteur et al., 2003); ADOS (Lord & Rutter, 1999) and DSM-5 (Sugawara & Nikaido, 2014) criteria) and intellectual ability (IQ measured by WAIS-III (Wechsler, 2008)) and the outcome measures detailed below.

The intervention comprised seven BCI sessions spread over four months. The first four sessions weekly and the remaining monthly. Adherence and compliance were evaluated using the following definitions: Adherence was defined as attending all seven BCI sessions. Compliance was assessed based on the percent of subjects who have performed the scheduled number of interventional sessions.

Participants outcome assessments were performed at baseline (session 0), post-training (session 7), and follow-up (6 months post-training).

The baseline visit was in the same day of the session 1. The 7 sessions included BCI intervention, before and after which the participants were asked to complete a questionnaire about how were they feeling in the moment - Profile of Mood States (POMS) (Faro Viana, Almeida, & Santos, 2012; McNair, Lorr, & Droppleman, 1992).

The Primary outcome measure was a customized ecologic "Joint-attention assessment task" (JAAT), assessing the detection of initiation of joint attention cues (from avatars - gazing or pointing cues). We recorded (using eye-tracking) the number of items of social attention that a patient could accurately identify from an avatar's action cues (e.g. looking at, pointing at).

JAAT consisted in four virtual scenarios. The scenarios were as follows:

Cafe: interior of a café with a maid (avatar) inside the balcony. The viewer's position is in front of the balcony. Several common objects in a cafe (packets of chips, several drinks, chewing gums, bottles and a lamp) are distributed the around the avatar's position (Figure 4.1A);

Classroom: standing in front of a table with a professor (avatar) and with a ruler, a book, a notebook, a protractor, a pencil and an eraser on top of the table (Figure 4.1 B) The scenario also has another tables and chairs;

Kiosk: standing in front of a street kiosk with the employee inside and several newspapers and magazines scattered on the kiosk, around the employee position (Figure 4.1 C);

Zebra crossing: standing in one side of a street, waiting to cross the zebra crossing, with one person on the other side. The other side of the street has a traffic light, a traffic signal, a garbage can, and a map in a bus stop (Figure 4.1 D).

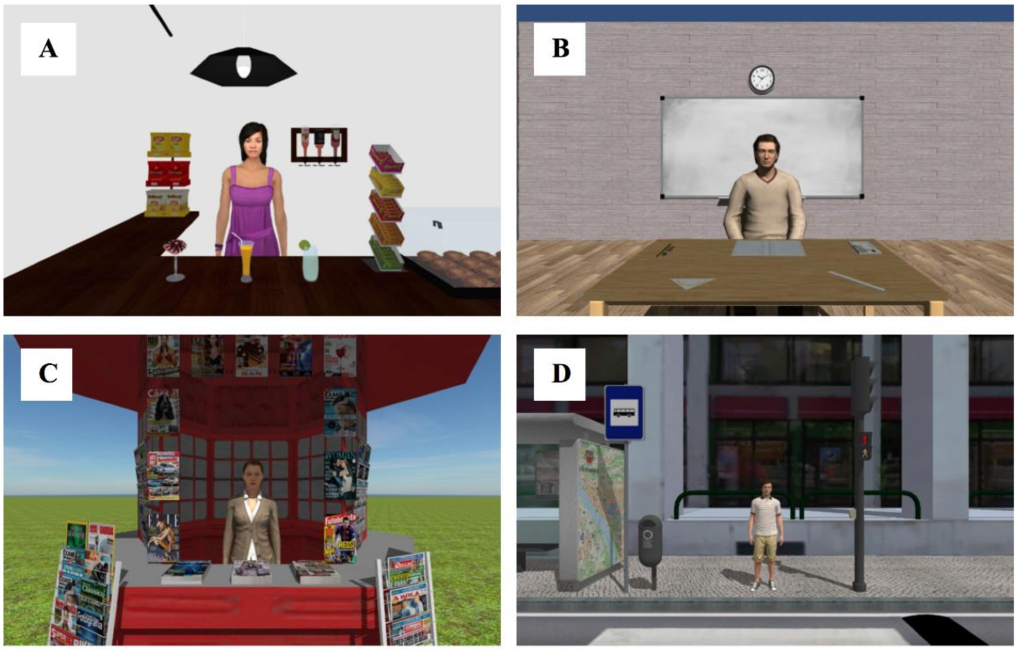

Figure 4.1 – Representation of the JAAT scenarios. (A) Cafe scenario; (B) Classroom scenario; (C) Kiosk scenario; (D) Zebra crossing scenario.

Participants were sat in an adjustable rotary office chair wearing the Oculus Rift DK 2 headset. Eye movements were recorded with Eye Tracking HMD package from SMI embedded in the Oculus Rift itself, with sampling rate of 60 Hz, and accuracy of 0.5-1°. The scenes had a 360° perspective and a real-time fully immersive experience. JAAT started with the eye-tracker calibration and validation (5-point validation method built in-house). Next, the presentation of each scenario was done. The order by each scenario was presented was random. The task started with a 30 seconds free-viewing period followed by a series of avatar animations spaced by between 2 and 2.5 s. The animations were divided in joint attention animations and control animations. The joint attention animations comprise the head turning of the avatar or pointing to one object of interest in the scene.

The animations were repeated two times in a random order which gives a total of 18 joint attention animations in the café scenario, 10 in classroom scenario, 16 in kiosk, and 10 joint attention animations in zebra crossing scenario. The overall joint attention events were 54, and control (no joint attention) animations 32. Control animations included the avatar coughing, rolling the head, scratching the head and yawning. Participants were instructed to act naturally. They were not aware that their eye movements were being recorded.

The number of items of social attention that a patient could accurately identify from an avatar's action cues were obtained by defining areas of interest (AI) with 3D boxes. These AI overlap with objects in the scenes that were relevant in the context. For example, the drinks in the cafe, the notebook and the ruler in the classroom, the magazines in the kiosk and the traffic lights on the zebra crossing scenario. AI in each scenario are shown in Figure 4.2.

Figure 4.2 – Areas of interest in each scenario of JAAT.

The number of items of social attention were defined as eye fixations inside the AI after the start of the joint attention animation and until between 2 and 2.5 s. We assumed a fixation duration as a fixation with more than 300 miliseconds (ms) (based on the range of mean fixation duration in scene perception presented in Rayner, (2009)). Inside the JA responses we considered two types of responses:

JAAT_No face – Fixation on the target object of the joint attention animation after the animation starts.

JAAT_Face – Fixation on the target object of the joint attention animation after the animation beginning that is preceded by a fixation on the face of the avatar.

As secondary outcome measures we included the Autism Treatment Evaluation Checklist (ATEC) (Rimland & Edelson, 1999), specifically designed to measure treatment effectiveness, and Vineland Adaptive Behaviour Scales (VABS), which focuses on adaptive functioning (Sparrow, Balla, & Cicchetti, 1984). Other neuropsychological measures related to mood, anxiety and depression were also assessed: Profile of Mood States (POMS) (Faro Viana et al., 2012; McNair et al., 1992); Hospital Anxiety & Depression Scale (HADS) (Pais-Ribeiro et al., 2007; Zigmond & Snaith, 1983) and Beck Depression Inventory (BDI) (A.T. Beck & Steer, 1990; Aaron T Beck, 1961; Vaz-Serra & Abreu, 1973).

The experimental apparatus used for the BCI interventions is shown in Figure 4.3.

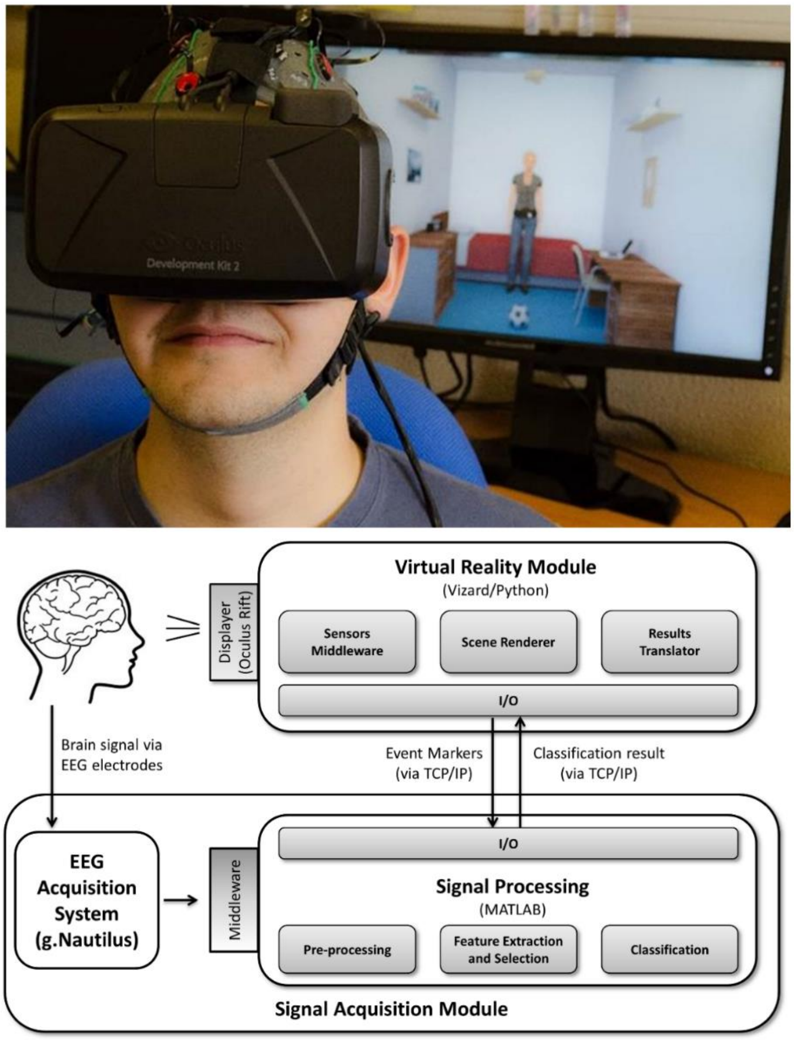

Figure 4.3 – BCI apparatus overview. Top: person wearing Oculus Rift and g.Nautilus EEG system (part of the virtual reality P300-based BCI) and the observer's viewing window on the screen. Bottom: block design of the system. Informed consent was obtained from the individual for the publication of this image.

BCI sessions were carried out in a spacious and quiet room with minimal electrical interference and participants were seated in an adjustable office chair in front of a table.

The virtual reality P300-based BCI paradigm used comprises an immersive virtual environment presented to the participants via the Oculus Rift Development Kit 2 headset (from Oculus VR) which participants wear in front of the eyes during the intervention sessions. An EEG cap was also placed in participants head. The cap had 16 active electrodes that do not require abrasive skin treatment and with completely wireless signal transmission (g.Nautilus from gTEC, Austria). The EEG data were acquired from 8 electrodes positions (C3, Cz, C4, CPz, P3, Pz, P4, POz), the reference was placed at the right ear and the ground electrode was placed at AFz. Sampling rate was set at 250 Hz. EEG data were acquired notch filtered at 50Hz and passband filtered between 2Hz and 30Hz.

The virtual environment consists in a bedroom with common type of furniture (shelves, a bed, a table, a chair, and a dresser) and objects (frames, books, lights, a printer, a radio, a ball, a door, a window, and a laptop). The BCI task was divided in 3 phases. The first two were part of the calibration process of the BCI, and the last one the online phase. In the first phase the participants were directly and explicitly instructed to attend the target object in order to remove potential errors identifying the target object related with social attention deficits present in ASD. In the second phase the participants were asked about which object was chosen by the avatar (after avatar's animation) to guarantee the user learned to read the social joint attention cue of the avatar and use this information correctly. In the third phase the participants were asked to respond to the head cue of the avatar in the center of the scene, looking to the object of interest. In all the three phases of BCI, after the redirection of attention of participant in each trial, they were asked to mentally count the blinks of the object of interest. Each trial consisted in 10 sequential runs, and each such run consisted of flashing all the 8 objects in the scene (green flashes) in a randomized order: 1. a wooden plane hanging from the ceiling; 2. a printer on a shelf; 3. a corkboard on the wall; 4. a laptop on a table; 5. a ball on the ground; 6. a radio on top of a dresser; 7. a picture on the wall; 8. books on a shelf. The highlight (flash) of each object occurred with an inter-stimulus interval of 200 ms. Each flash had the duration of 100 ms. This gives a total of 80 flashes per trial. Participants performed a total of 70 trials (10 in the first phase, 10 in the second and 50 in the online phase).

The data recorded from the first 20 calibration trials stores the P300 responses that occurs when the object of interest flashed, and statistical classifiers are used to identify this response. These classifiers are then used in the online phase to identify whether participants were counting the flashes of avatar's object of interest. If it was done properly by the participant the BCI gave a positive feedback (object of interest turns green at the end of the trial). If not, the object turned red. This mechanism is shown in Figure 4. The overall functioning of BCI is explained in detail in Amaral et al. (2017), where we tested the best setup to use in this BCI and also performed pilot tests in ASD participants.

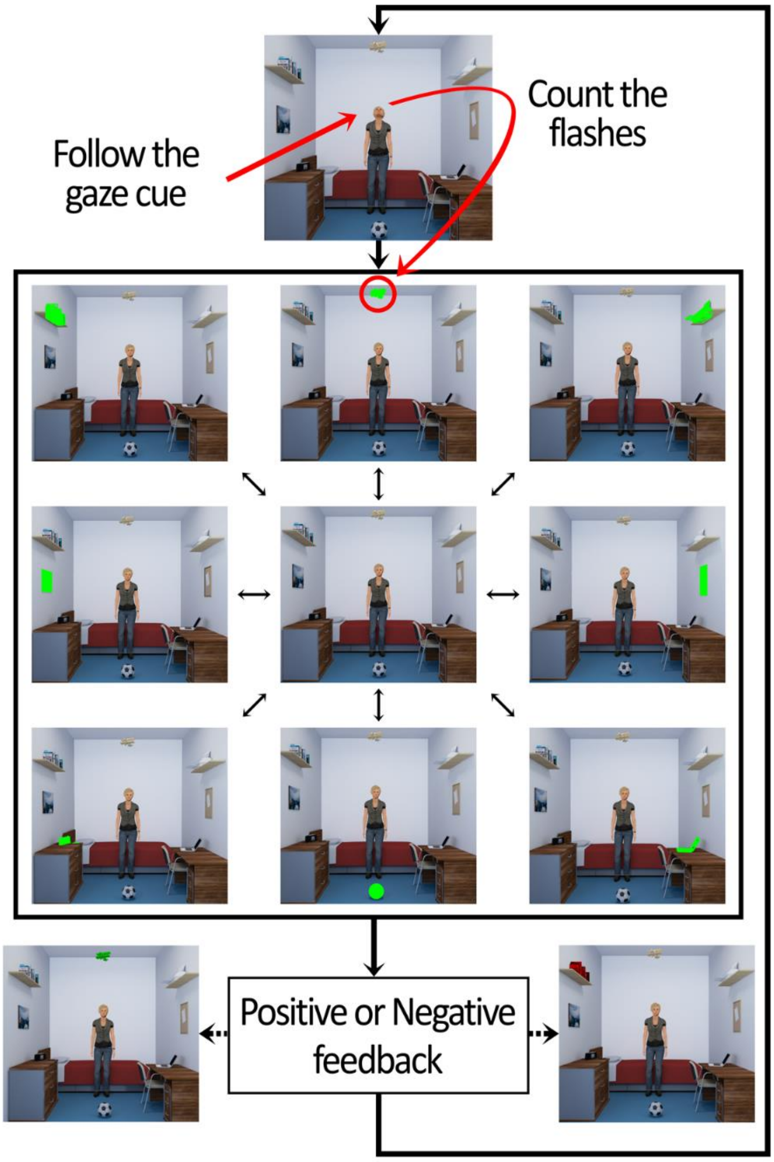

Figure 4.4 – Sequence of events of the trials in the BCI online phase.

4.3.3 Statistical Analysis

Our initial sample size was calculated using the G*Power tool (Faul, Erdfelder, Lang, & Buchner, 2007). Based in other effects described in the literature, the effect size considered is 0.8 (the mean difference is 0.8 standard deviations). In these conditions, for power of 0.8 the estimated sample size is 15. Without the normality assumption of the distribution of the means differences, we would also need 15 subjects, considering a non-parametric test. However, these calculations were used only as a guide for sample size and in keeping with the feasibility design no explicit hypothesis testing was used.

The specific aim of the study was to assess the feasibility and effects of the use of virtual reality P300-based BCI paradigm in ASD. Based on this aforementioned aim, 95% confidence interval for differences in means are presented.

The assumptions of the statistical techniques used were validated. All statistical analysis was realized with the support of the version for Microsoft Windows® of the Statistical Package for Social Sciences, version 19 (SPSS ®, Chicago, IL, USA).

4.3.3.1 Brain Computer Interface Evaluation of Signal Stability

We tested the stability across the seven sessions of three parameters: the BCI's balanced accuracy (see definition below) of target object detection, the average P300 maximum amplitude across trials and the mean alpha power variation in the band [8 12] Hz per trial. For the latter two, a cluster of the 8 channels was formed. For each subject, a linear regression was computed using the value of each parameter across sessions. The first order coefficient of the linear regressed model was extracted, and its distribution was tested against the hypothesis that its median value was equal to zero, using a Wilcoxon signed rank test. Graphical illustration of the stability of measures across sessions is provided. The tests were performed in Matlab 2014a.

4.4 Results

Demographic data are provided in Table 4.1. Fifteen adolescents and adults (mean age = 22 years and 2 months, ranging from 16 to 38 years old) with high-functioning ASD (Full-Scale Intelligent Quotient [FSIQ] (Wechsler, 2008): Mean = 102.53; SD = 11.64) participated in the study between February 2016 and January 2017. Five patients were medicated (three with a neuroleptic, one with a psychostimulant and another with an antidepressant). We recruited 17 patients, because of two dropouts, which meets the target sample size. Dropouts were due to an eye abnormality in one patient, not reported during the recruitment, and a misdiagnosis of ASD in another patient.

Table 4.1 Baseline demographic data

	n	% or Mean (SD)
Age	15	22 years and 2 months (5 years and 6 months)
Gender	15	100% Male
Education	15	Junior Highschool (9 years) 6.67% Incomplete Highschool (11 years)13.33% Highschool (12 years) 66.67% Bachelor 6.67% Master 6.67%

Table 4.2 depicts the basic statistics related to core baseline and study specific outcome measures.

Table 4.2 Baseline outcome measures

	n	Mean (SD)	Data completeness %
CORE OUTCOMES			
ADIR_Social interaction	14	16.14 (4.56)	93%
ADIR_Communication	14	12.14 (5.39)	93%
ADIR _Repetitive and restricted behaviour	14	6.14 (2.41)	93%
ADIR_Developmental delay	14	2.21 (1.89)	93%
ADOS _Communication	15	3.20 (0.86)	100%
ADOS_Social interaction	15	6.27 (1.34)	100%
ADOS_Total	15	9.47 (1.92)	100%
DSM_5 Criteria	15	5.73 (0.59)	100%
WAIS-III (FSIQ)	15	102.53 (11.64)	100%
WAIS-III (VIQ)	15	102.33 (16.63)	100%
WAIS-III (PIQ)	15	102.47 (10.97)	100%
HADS_Total	15	10.93 (5.78)	100%
BDI_Total	15	9.13 (6.56)	100%
POMS_Tension	15	6.40 (3.23)	100%
POMS_Depression	15	7.53 (6.13)	100%
POMS_Anger	15	4.00 (3.46)	100%
POMS_Vigour	15	12.53 (6.80)	100%
POMS_Fatigue	15	4.47 (3.96)	100%
POMS_Confusion	15	6.80 (2.68)	100%
POMS_Total	15	116.67 (18.54)	100%
STUDY SPECIFIC OUTCOMES			
JAAT_NoFace	15	16.33 (9.36)	100%
JAAT_Face	15	10.67 (9.35)	100%

ATEC_SPEECH/LANGUAGE/COMMUNICATION	15	4.07 (1.82)	100%
ATEC_SOCIABILITY	15	12.64 (6.20)	100%
ATEC_SENSORY/COGNITIVE AWARENESS	15	9.50 (5.13)	100%
ATEC_HEALTH/PHYSICAL/BEHAVIOR	15	9.36 (6.25)	100%
ATEC_Total	15	35.57 (12.53)	100%
VABS_COM_S1	15	68.27 (21.53)	100%
VABS_DLS_S1	15	77.53 (14.05)	100%
VABS_SOC_S1	15	65.80 (16.79)	100%
VABS_ABC_S1	15	65.73 (15.56)	100%

Concerning measures of feasibility, they are reported in Table 4.3.

Table 4.3 – Primary outcome - feasibility

	% (n/n)
Recruitment/Consent	100%
Retention (primary end point)	100%
Retention (secondary end point)	100%
Intervention uptake	100%
Adherence/ Completion	100%
Compliance	100%
Intervention delivery	100%
Acceptability	100%

Although an effect was not found for our primary measure of choice (JAAT), most secondary measures demonstrated a change (Table 4.4).

Table 4.4 shows the analysis of the clinical outcomes for complete baseline and primary follow-up. The analysis revealed no noticeable change in the total number of social attention items that a patient can accurately identify from avatar's action cues (JAAT_NoFace and JAAT_Face). On the other hand, there was variation in total ATEC scores, as well as in Sociability, Sensory/Cognitive Awareness and Health/Physical/Behavior. Significant effects in Adapted Behavior Composite and in DLS (total and a subarea from VABS) were also observed. The depression subscale from POMS scores (POMS_Depression) showed a difference between the baseline and the primary follow-up time point. The mood disturbance/depression (BDI) scale also showed a change after the intervention.

Table 4.4 – Outcomes for complete baseline and primary follow-up dataset

	Baseline/Session 1		Primary follow-up time point (Session 7 - post intervention)		Mean difference and 95% CI	
	n	Mean (SD)	n	Mean (SD)	Mean difference	95% CI
CORE OUTCOMES						
HADS_Total	15	10.93 (5.78)	15	9.13 (4.22)	1.80	(-0.40, 4.00)
BDI_Total	15	9.13 (6.56)	15	6.67 (5.25)	2.47	(0.38, 4.56)
POMS_Tension	15	6.40 (3.23)	15	5.20 (5.51)	1.20	(-2.06, 4.46)
POMS_Depression	15	7.53 (6.13)	15	3.80 (5.20)	3.73	(0.49, 6.97)
POMS_Anger	15	4.00 (3.46)	15	2.93 (6.12)	1.07	(-2.47, 4.60)
POMS_Vigour	15	12.53 (6.80)	15	12.87 (7.97)	-0.33	(-3.67, 3.00)
POMS_Fatigue	15	4.47 (3.96)	15	4.67 (5.92)	-0.20	(-3.20, 2.80)
POMS_Confusion	15	6.80 (2.68)	15	6.07 (3.60)	0.73	(-1.26, 2.72)
POMS_Total	15	116.67 (18.54)	15	109.80 (25.77)	6.87	(-7.20, 20.93)
STUDY SPECIFIC OUTCOMES						
JAAT_NoFace	15	16.33 (9.36)	15	13.73 (8.19)	2.60	(-2.20, 7.40)
JAAT_Face	15	10.67 (9.35)	15	7.80 (8.77)	2.87	(-0.07, 5.80)
ATEC_SPEECH/LANGUAGE/COMMUNICATION	15	4.07 (1.82)	15	2.93 (1.64)	1.07	(-0.23, 2.37)
ATEC_SOCIABILITY	15	12.64 (6.20)	15	8.50 (5.30)	4.33	(2.32, 6.35)
ATEC_SENSORY/COGNITIVE AWARENESS	15	9.50 (5.13)	15	6.14 (4.93)	3.47	(0.90, 6.03)
ATEC_HEALTH/PHYSICAL/BEHAVIOR	15	9.36 (6.25)	15	6.57 (5.39)	2.80	(0.65, 4.95)
ATEC_Total	15	35.57 (12.53)	15	24.29 (12.90)	11.53	(5.33, 17.74)
VABS_COM	15	68.27 (21.53)	15	71.33 (21.62)	-3.07	(-8.37, 2.24)
VABS_DLS	15	77.53 (14.05)	15	81.60 (14.46)	-4.07	(-6.40, -1.73)
VABS_SOC	15	65.80 (16.79)	15	67.67 (16.18)	-1.87	(-4.44, .70)
VABS_ABC	15	65.73 (15.56)	15	69.00 (15.20)	-3.27	(-5.48, -1.06)

In sum, we observed a 32% average decrease in total ATEC, rated autism symptoms (34% in Sociability; 37% in Sensory/Cognitive Awareness; 29% in Health/Physical/Behaviour); 5% average improvement in Adapted Behaviour Composite and 5% in DLS, subarea from VABS; 50% average decrease in Depression subscale from POMS and 27% average decrease in mood disturbance/depression (BDI).

Table 4.5 shows the analysis of the clinical outcomes for complete baseline and secondary follow-up. JAAT_NoFace and JAAT_Face scores also revealed no differences between baseline and the secondary follow-up time point. There were positive effects in all subscales (Speech/Language/Communication, Sociability, Sensory/Cognitive Awareness and Health/Physical/Behaviour) from ATEC and in ATEC total scores. There were also changes in Adapted Behaviour Composite and in all subareas from VABS (COM, DLS, SOC).

No serious adverse events were reported.

Table 4.5 – Outcomes for complete baseline and secondary follow-up dataset

	Baseline		Secondary follow-up time point (post intervention)			Mean difference and 95% CI
	n	Mean (SD)	n	Mean (SD)	Mean difference	95% CI
STUDY SPECIFIC OUTCOMES						
JAAT_NoFace	15	16.33 (9.36)	15	15.00 (10.02)	1.33	(-4.47, 7.14)
JAAT_Face	15	10.67 (9.35)	15	7.53 (8.11)	3.13	(-2.00, 8.27)
ATEC_SPEECH/LANGUAGE/COMMUNICATION	15	4.07 (1.82)	14	1.79 (1.42)	2.29	(.94, 3.63)
ATEC_SOCIABILITY	15	12.64 (6.20)	14	6.57 (5.14)	6.07	(3.23, 8.91)
ATEC_SENSORY/COGNITIVE AWARENESS	15	9.50 (5.13)	14	5.21 (4.28)	4.29	(1.31, 7.26)
ATEC_HEALTH/PHYSICAL/BEHAVIOR	15	9.36 (6.25)	14	4.86 (4.35)	4.50	(2.65, 6.35)
ATEC_Total	15	35.57 (12.53)	14	18.43 (11.77)	17.14	(10.38, 23.91)
VABS_COM	15	68.27 (21.53)	14	73.14 (17.29)	-7.36	(-12.53, -2.18)
VABS_DLS	15	77.53 (14.05)	14	86.29 (14.02)	-10.14	(-12.58, -7.71)
VABS_SOC	15	65.80 (16.79)	14	71.14 (16.11)	-6.79	(-10.13, -3.44)
VABS_ABC	15	65.73 (15.56)	14	72.00 (13.65)	-8.21	(-10.66, -5.77)

4.4.1 Brain Computer Interface Evaluation of Signal Stability

We analysed whether the signal quality and performance of our BCI remained stable across intervention sessions. Figure 4.5 shows across session balanced accuracy of our online classifier.

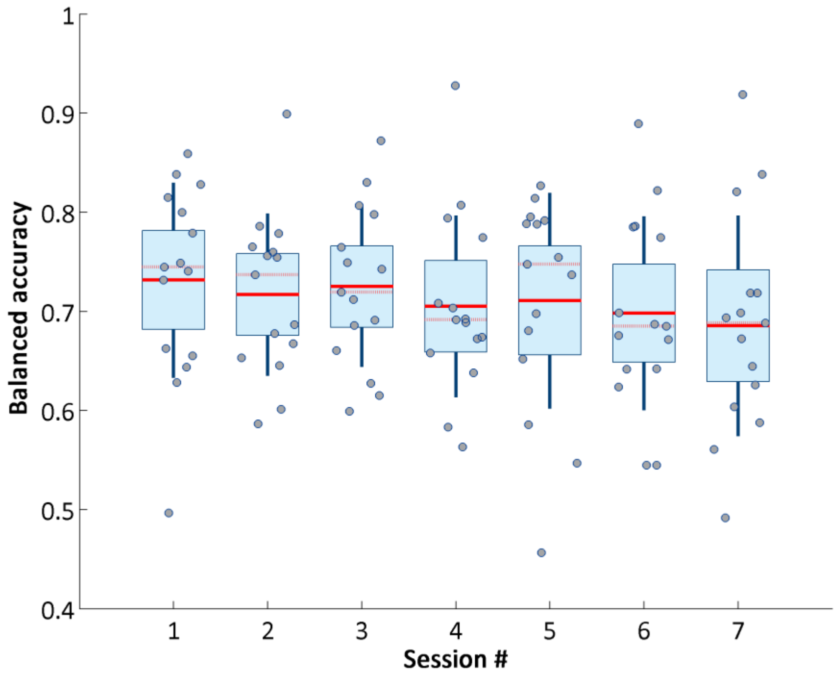

Figure 4.5 – Balanced accuracy of target object detection on online phase across sessions

The unbalanced nature of the data set (the non-target objects flashes are 8 times more than the target ones, because of the different occurrence probability) makes the balanced accuracy the more reliable metric for assessing the classifier performance (section 1.5.3). Balanced accuracy is calculated following the formula $BA = \frac{SP + SS}{2}$. This value did not vary greatly across sessions. Although the overall trend decreased very slightly from session 1 to 7, our system retained stable performance across visits.

Concerning the P300 signal, which is pivotal for decoding attention related information, it also remained stable across sessions, as shown in Figure 4.7. Average P300 maximum amplitude was calculated averaging the maximum amplitude values (between 250 and 500 ms after the flashes onset) of the averaged event-related potentials of the target object flashes in the third phase of BCI (online).

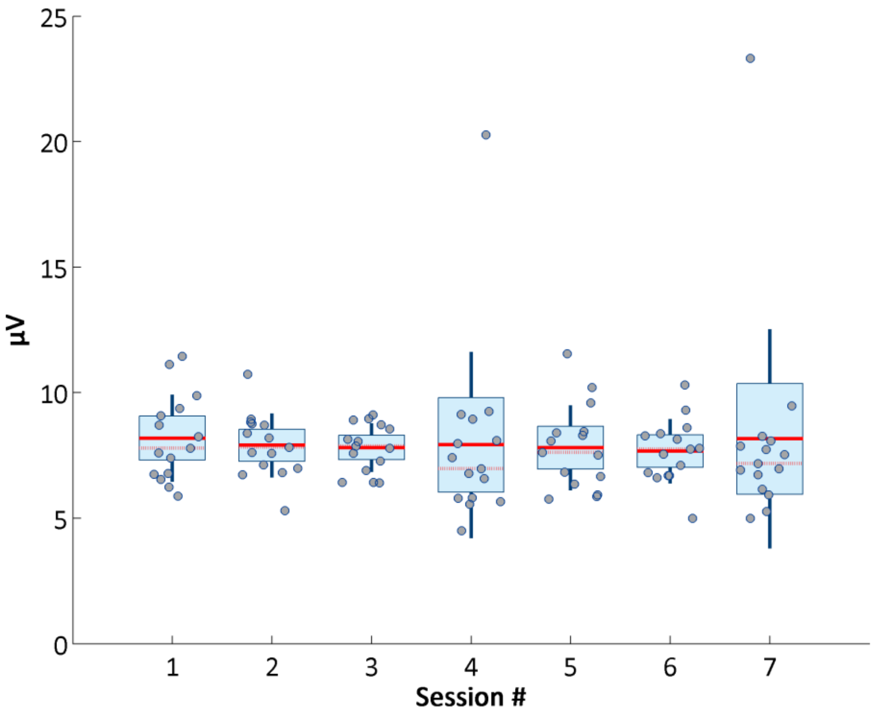

Figure 4.6 – Average P300 maximum amplitude across sessions

In Figure 4.7 it is possible to observe the P300 waveform across sessions.

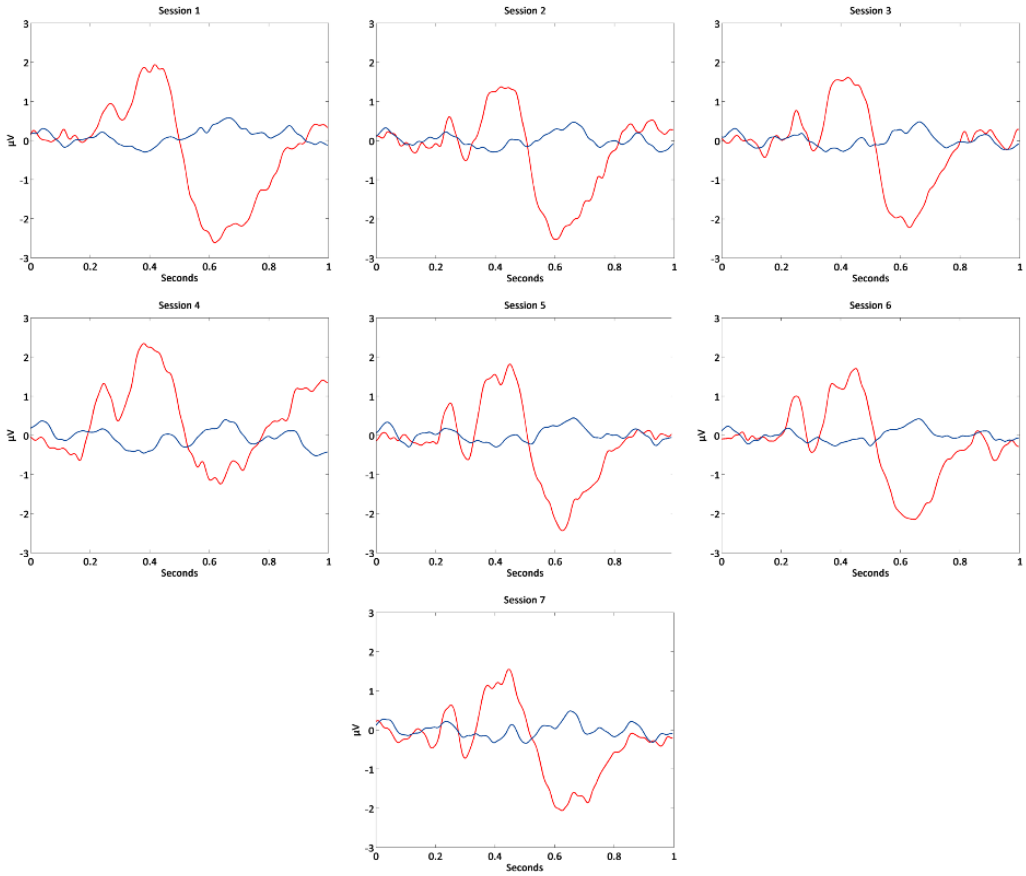

Figure 4.7 – Grand-average of event-related potentials in each BCI session of Cz channel. Red represents target events and blue the non-target events.

Accordingly, P300 maximum amplitude did not vary and was statistical verified, demonstrating the presence of stable attention related signals across visits. Stability of neurophysiological patterns was further examined by investigating changes in alpha modulation (Figure 4.8), and remained around similar levels across sessions.

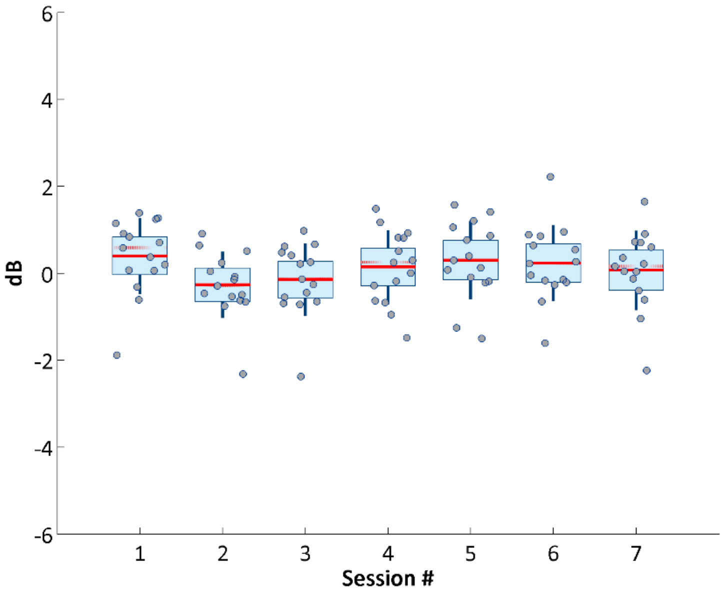

Figure 4.8 – Average alpha power across sessions

4.5 Discussion

In this study we assessed a virtual reality P300-based BCI paradigm in ASD. Our device coupled an interactive virtual environment with the attention signature of the P300 brain waveform, featuring a cognitive training tool for ASD. Participants had to follow a non-verbal social agent cue. As a cautionary note, the fact that a P300 signal can be detected with high accuracy does not necessarily imply that the stimulus is suitable and well tolerated. Nevertheless, the current trial proved the feasibility and potentially useful clinical effects of the use of this type of technology in ASD.

Although the main goal of the study was not to test efficacy measures, some relevant effects were observed, even in spite of the fact that our eye-tracking based assessment tool did not show a change in the total number of social attention items that a patient can accurately identify from avatar's action cues (JAAT_NoFace and JAAT_Face, only a small non-significant trend is visible possibly due to familiarity).

However, in the primary follow-up time point, there was an effect on total ATEC scores, which translates to a decrease in the severity of autism symptoms (specifically the ones related to Sociability and Sensory/Cognitive Awareness) as wells as the ones reported as more general symptoms (Health/Physical/Behaviour). Effects in Adapted Behaviour Composite and in DLS (subareas from VABS) were observed. The daily living skills (DLS) are one of the most compromised areas in ASD and an improvement in this area translates in a better integration in the daily routines, and improved self-sufficiency.

In the secondary follow-up time point, analysis replicated the maintenance of positive changes observed at the in the primary follow-up time point, which is noteworthy, because a decay of effects did not occur, and significance was still present.

JAAT_NoFace and JAAT_Face scores did not alter between baseline and the secondary follow-up time point.

There were positive effects in all subscales from ATEC and in ATEC total scores. There were also changes in Adapted Behaviour Composite and in all subareas from VABS.

Our study suggests a long-term beneficial effect in patient's mood/mental state. This effect cannot at this stage be causally attributed to specific mechanisms related the intervention but gives a good insight about the structure of the intervention, the compliance and reliability of the measures used, which show long term significant effects.

4.5.1 Strengths and limitations

As strengths, we can list the high compliance, low/null dropout rates, and signal to noise stability and decoding accuracy of our BCI system across all 7 sessions. Moreover, and in spite of the fact that our custom primary outcome measure failed to show improvement, most secondary clinical outcome measures (ATEC and VABS) suggested improvement. This improvement was maintained in the six-months follow-up assessment, which reinforces the potential utility of these kind of interventions and the validity of this measures.

As limitations, we note the customized nature of our chosen primary outcome measure, which had no prior clinical validation, unlike the secondary measures. Moreover, in spite of the relatively realistic nature of our VR environment it can further be improved to train in a more effective way social attention skills.

4.5.2 Implications for practice and research

Given the very low rate of dropouts and the good classification accuracy over sessions, with stable neurophysiological signals, the system proves to be feasible as a tool in future efficacy trials. Given that several of the secondary clinical outcome measures showed improvement, we propose to use one of them (ATEC, VABS) or a combination of scores as the primary outcome measure in a future Phase 2 b clinical trial.

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Chapter 5

General Discussion and Conclusion

This chapter summarizes the findings of our work and their relevance for further studies.

5.1 Overview of the main achievements of the thesis

The study of the neurophysiological processing networks related to realistic and complex social scenes is still a topic with much to be unveiled and we felt this loophole at the start of our investigation: the neurophysiological correlates of attention (specifically of P300) to realistic social scenes were unknown. We were searching for a realistic stimulus that, somehow, could replicate a social gesture that people with ASD has difficulty to process, but we were uncertain about how to extract the neurophysiological representation of this stimulus and use it as feedback tool. In (C. P. Amaral, Simões, & Castelo-Branco, 2015), the oddball stimuli with increasing social scene complexity described in Chapter 2 allowed us to find the expected oddball responses for all the conditions and, importantly, observe a distinct P300-like waveform when it was elicited by animated stimuli representing realistic and animated social gestures. We believe that the high-level characteristics introduced by the realism of the animated paradigms, such as the reflexive attention generated by social gaze orientation, induced the activation of the inherent networks which neurophysiologic manifestation was added to the P300 waveform. This might explain the right hemispheric bias that we found for our modified P300 signal. This hypothesis seemed quite plausible due to the solid evidence for hemispheric asymmetries underlying the domain of social perception (for a review see (Brancucci et al., 2009). Additionally, our success trying the single-trial classification of these P300 signals was also of large relevance because it unlocked the possibility to use these types of realistic, structured and efficient models of social interactions in BCIs.

So, having the capacity to automatically detect a neural signal sensitive to social perception stimuli, the next step went through developing a stimulation paradigm able to be used in a BCI loop that integrated meaningful social attention perception in a realistic and ecologic manner. In (C. P. Amaral et al., 2017) we described an oddball paradigm embedded in a virtual reality setup that uses social cues as the indicator of the target event. Our first intention was to use a JA cue gesture as the target of attention among other non-target JA cues (following an oddball paradigm structure). However, in that first attempt the neurophysiologic response to reflexive social gaze orientation overpowers the oddball effect of attending only to the target cue (unpublished data). This prevents the distinction between target and non-target cues, which in turn makes it impossible to use this paradigm hypothesis in a viable BCI. Our alternative to overcome this drawback was to use a JA cue as the indicator of the target event (an object in a virtual environment) and to let the attentional mental state of the subject to be monitored through the detection of a traditional P300 signal elicited by flashing the objects in the scene with an oddball paradigm structure.

In fact, the tests performed with the several paradigms and ultimately with different EEG systems and setups let us understand how nuances in the design of hardware can influence the user experience in a significant way. Our choice fell to the EEG system that provided less time to prepare the EEG acquisition and that gave a more comfortable experience to the users during the BCI session. Regarding the basic logistic and patient-centred issues regarding EEG preparation and virtual reality setup this was a priority due to the possibility of hypersensitive responses by the potential target population for which this BCI was designed. Indeed, ASD is characterized by abnormal sensory sensitivity, and preparation of the experimental setup therefore has to take this clinical aspect into account. In equal terms we were also focused to find the EEG system that offers a reliable signal. Conveniently, the chosen system reunited the characteristics which simultaneously allowed us to maximize the performance and the acceptability of the BCI.

The study described in Chapter 3 had a crucial importance since it helped us to validate the combination of a virtual reality paradigm within a BCI, trying to couple the potentialities of ecological, realistic and interactive virtual environments with the attention related nature of the P300 brain waveform. This allowed giving feedback about the user attentional focus immersed in an ecologic environment which we believe can enhance the user self-monitoring of his/her performance regarding the response to joint attention cues and subsequently allow them to adjust their behaviour more efficiently. This and the results obtained from the tests with ASD participants amplified the perspectives of cognitive rehabilitation possibilities in ASD since the introduction of realistic social cues and immersive setups in BCI paradigms was a novelty and we showed its feasibility with autistic participants.

Our hypothesis relied heavily on the repetitive nature of the oddball paradigm, and the P300 operant learning properties related to integration of information with context and memory (Halgren et al., 1995). We conjectured that ASD subjects could assimilate joint attention skills by automating the response to the social cue that is given during the task we created. It was then obvious that we needed to verify this assumption in a rigorous manner. Chapter 4 shows the feasibility verification of a structured clinical intervention using the technology we created (C. Amaral et al., 2018). We took the opportunity to create a protocol for a controlled clinical trial which helped us to reduce the probability of any mistake during the intervention and ensure the reliability of the collected data. Nevertheless, the main goal of the trial was not to test the efficacy of the intervention, efficacy measures were also used in the study. We first aimed to assess the feasibility and secondarily potential clinical effects of the use of this type of technology in ASD because of its logistic and hardware complexity. We didn't know how ASD participants would react to successive BCI sessions during several weeks and wanted to prevent any undesired event.

We planned to collect a series of standard neuropsychologic and neurobehavioral data from the participants. We also found the need to create a procedure to evaluate the rate of automatic response to JA cues in order to evaluate any potential alteration in the capability of ASD participants to react to JA cues. The 'JAAT', based on eye-tracking measurements, was thought to overcome this gap in evaluation of JA, but this novel measure was not sensitive enough to reveal changes in the total number of social attention items that a patient can accurately identify from avatar's action cues along the intervention. Nevertheless, the remaining measures revealed positive effects in patient's mood and mental state translated, for example, by improvements in autism symptoms, sociability and depression. This and the perfect assiduity from all participants, showing perfect compliance to attend all sessions, are important facts to point out since it provides a good insight about the structure of the intervention and the compliance and reliability of the measures used (which showed long term significant effects).

5.2 Final considerations for future work

Altogether, and despite the fact that additional work is needed to prove that a P300-based BCI can help improve the response to JA cues of people with ASD, the work presented in this thesis opens the way to the investigation of new neurophysiologic-based rehabilitation tools coupled with virtual reality for improving social behaviour in ASD.

In a final retrospective of the work we presented identify some critical aspects that need to be solved in future work:

- BCI paradigm - As already referred, it remains a challenge to directly use JA cues as direct targets of attention. Since we intended to change the behavioural response of ASD users to JA cues, the logic option to couple with P300 signal would be the own social cue. The results from (C. P. Amaral et al., 2015) strongly indicated this possibility. But the preliminary tests with the first sketches of the paradigms that used JA as target of attention showed the apparent impossibility to distinguish the target and non-target cues. Future work should address this limitation in the design of future BCI paradigms and the chosen alternative presented in C. Amaral et al. (2018) and C. Amaral et al. (2017). This would optimize the characteristics to effectively potentiate the desired behavioural changes.

- **Evaluation of the response to JA cues** – There is always a trade-off in developing new tools to assess JA when the available ones are based on qualitative clinical observation. Future work should improve the design of our customized ecologic *joint-attention assessment task* and attempt clinical validation.

In spite of the improvements that are still necessary, overall, our work gives positive insights into the potential use of realistic stimuli in ecologic environments for clinical applications. We have shown that realistic stimuli generate meaningful neural responses related to social cognition and we were able to develop a system that uses this type of stimulus and test it in a clinical trial successfully, with high patient compliance and evidence for potential clinical benefits.

More work is still to be done to find the best neurophysiological feedback system that provides an effective mean to promote JA skills and adaptive behaviour to make this cognitive training tool a viable mean of intervention.

5.3 References

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