AN INTERVENTIONAL STUDY TO IMPROVE SOCIAL ATTENTION IN AUTISM SPECTRUM DISORDER (ASD): A BRAIN COMPUTER INTERFACE (BCI) APPROACH

PROTOCOL VERSION NUMBER

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This protocol has been authorised by:			
Name	**Role**	**Signature**	**Date**
Miguel Castelo-Branco	PI for University of Coimbra		

General Information This protocol describes the **'An interventional study to improve social attention in autism spectrum disorder (ASD): a Brain-Computer Interface (BCI) approach'** study, and provides information about procedures for entering participants. The protocol should not be used as a guide, or as an aide-memoire for the care of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the local study team and the most current approved version will be available on the BRAINTRAIN extranet.

Compliance This study will adhere to the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95). It will be conducted in compliance with the protocol and other regulatory requirements as appropriate.

The conducting of clinical trials on medicines for human use is governed by Law n.º 46/2004 of 19 August that implements Directive 2001/20/EC of the European Parliament and of the Council of 4 April in Portuguese legislation. In addition to the above legislation there are a series of guidelines covering various matters related to clinical trials which can be found in volume X of Eudralex (see link in PNEC portal below). To that end, and as part of the harmonised European system, the conducting of clinical trials in Portuguese research centres requires authorisation from INFARMED, I.P. (Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.) and a favourable, prior opinion from the CEIC (Clinical Research Ethics Committee).

We will register our trial to http://www.pnec.pt/portal/page/portal/PORTAL_PNEC. PNEC portal is a forum that allows all players to work together to transform research in Portugal, through a strategic approach that identifies national clinical research opportunities and barriers. All of the procedures described in this project have already been approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra.

The **'An interventional study to improve social attention in autism spectrum disorder (ASD): a Brain-Computer Interface (BCI) approach'** study is funded by the European Commission 7th Framework Programme for Research, Technological Development and Demonstration, and is a component of Work Package 4.

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Clinical queries:

Clinical queries
Miguel Castelo-Branco (MD PhD) and Guiomar Oliveira (MD PhD).

Serious Adverse Events:

SAE reporting
Where the adverse event meets one of the serious categories, an SAE form should be completed within 24 hours of becoming aware of the event (See section 14 for more details).

Table of Contents

Glossary of abbreviations

AE	Adverse Event
ASD	Autism Spectrum Disorder
ATEC	Autism Treatment Evaluation Checklist
BCI	Brain Computer Interface
BDI	Beck Depression Inventory
CRF	Case Report Form
DMC	Data Monitoring Committee
EEG	Electroencephalography
EU	European Union
FEEST	Facial Expressions of Emotion – Stimuli and Tests
FP-7	7th Framework Programme for Research, Technological Development & Demonstration
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
ICH	International Conference on Harmonization
ISRCTN	International Standard Randomised Controlled Trial Number
PIS	Patient Information Sheet
POMS	Profile of Mood States questionnaire
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SEWTU	South East Wales Trials Unit
SOP	Standard Operating Procedure
STAIC	State/Trait Anxiety Inventory for Children
TCQ	Thought Control Questionnaire
TCAQ	Thought Control Ability Questionnaire
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

USM Urgent Safety Measure

VABS Vineland Adaptive Behaviour Scales

WAIS-III Wechsler Adult Intelligence Scale

1 Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
	V 1.0			

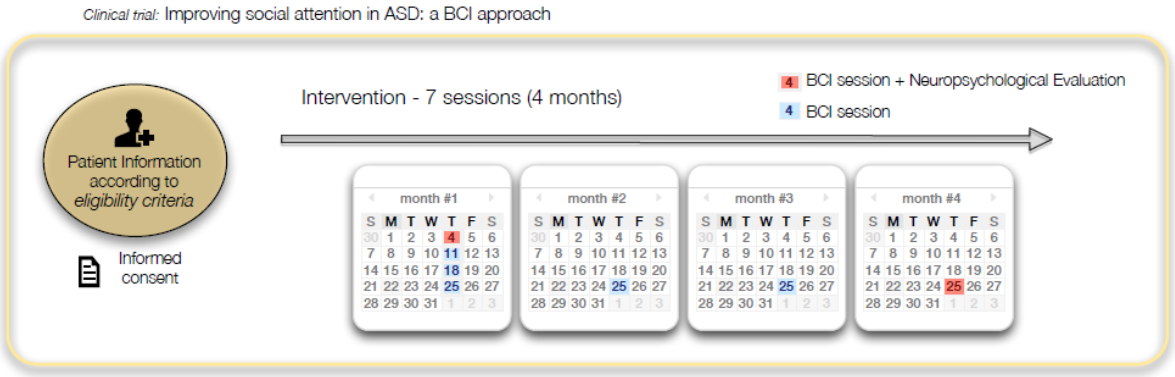
2 Synopsis

Short title	BCI (Brain Computer Interface) Intervention in Autism (BCIAUT)
Acronym	BCIAUT
Internal ref. no.	IBILI - VB - 2015 – 01
Study design	SINGLE ARM WITHIN – SUBJECT "BEFORE-AFTER" DESIGN.
Trial/study participants	ASD (experimental)
Planned sample size	15 (plus 3 in case of drop outs)
Follow-up duration	6 months after last intervention session
Planned trial/study period	4 months
Primary objective	Increase the number/rate of responses to initiation/response to joint attention cues in a serious game
Secondary objectives	Improve general social cognition functions
Primary endpoint	Number/rate of responses to initiation/response to joint attention cues
Secondary endpoints	ATEC, Vineland Scores
Interventions	BCI to train joint attention mechanisms

3 Study summary & schema

3.1 Study schema

3.2 Participant flow diagram



3.3 Study summary

Clinical research has demonstrated that ASD children have deficits in the interpretation of others' intentions from gaze-direction or other social attention cues (Baron-Cohen, Baldwin, & Crowson, 1997; Baron-Cohen, 1989).

The purpose of the study is to investigate whether a brain computer interface (BCI) using electroencephalographic (EEG) signals can be used to train social cognition skills (in particular interpretation of gaze direction pointing to objects of interest) in ASD patients and whether this improves clinical symptoms.

The intervention comprises seven BCI sessions spread over four months. The first four sessions are planned to occur weekly, and the rest monthly. In each session, the subject is asked to identify objects of interest based on the gaze direction of an avatar. The subject response is interpreted from the EEG signal (using the P300 component, as established in our previous work).

4 Introduction

4.1 Background

Autism Spectrum Disorder and Joint Attention

Autism spectrum disorder (ASD) is a severe, early-onset and life-long neurodevelopmental disorder with a high worldwide prevalence and a distribution of four males (M) to one female (F) (Baron-Cohen et al., 2009; Fombonne, 2003; Oliveira et al., 2007). ASD is characterized by deficits in social interaction and communication as well as by a repetitive pattern of behaviour and interests (American Psychiatric Association, 2013).

Joint attention is an early-developing social communication skill defined by the coordination of attention of two individuals towards a third object or event (Bakeman & Adamson, 1984). This skill is critical in the development of language and communication abilities later in life, and people with ASD show severe deficits in joint attention abilities.

Clinical research studies proved that ASD children show a deficit in interpreting others intentions from gaze-direction (Baron-Cohen et al., 1997; Baron-Cohen, 1989). ASD subjects also demonstrated a lack of attentional modulation in a fMRI study especially evident for social stimuli (Bird, Catmur, Silani, Frith, & Frith, 2006). Other studies suggest that ASD patients may have deficits in the cognitive processing of social stimuli: impairments in exogenous orienting of attention to social cues but not to objects (Leekam & Moore, 2001) and reduced saliency of social stimuli/preference for non-social stimuli (Dawson et al., 2004; Klin, 2002; Swettenham et al., 1998). Altogether, this inability means they are unable to predict or understand other people's actions suggesting dysfunctional social behaviours.

Gaming and Intervention Strategies

ASD subjects often experience discomfort with unpredictable social environments (Charlop-Christy, Le, & Freeman, 2000). The use of computerized intervention enables the development of skills in a highly standardized, predictable, consistent and controlled environment. Simultaneously, it allows individuals to work at their own pace and ability level (Golan & Baron-Cohen, 2006). This is a crucial point for this population. For many years the use of technology in ASD intervention relied primarily on the use of videotapes for instructional video modelling (Bellini & Akullian, 2007), but now the potential of technology extends far beyond simple video modelling to areas such as interactive computer programs and virtual reality.

Individuals with ASD often have relatively strong visual processing skills and a preference towards electronic media, thus it is likely that the dissemination of intervention via computer technology would be particularly appropriate and motivating for these individuals (Shane & Albert, 2008). 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 kind of approach, in particular if realistic scenes are used. The studies mentioned in this review reported significant improvements in the social skills addressed, but, altogether, some studies did not verify the transfer of these skills to more realistic and meaningful contexts. In the field of joint attention, some other studies have explored methods for systematically teaching joint attention to children with autism (Jones, Carr, & Feeley, 2006; Koegel, Vernon, & Koegel, 2009; Whalen, Schreibman, & Ingersoll, 2006).

These studies included embedding motivating social interactions into the intervention which effectively improved childrens' social areas. However, the infrequent implementation of the protocols compromised the carryover after the end of the interventions.

Brain-Computer Interfaces, Electroencephalography and the P300 signal

The EEG P300 oddball signal is a well-known neural signature of attention processes for detection of rare items in a series of distinct stimuli types. It has been classically reported as an enhanced positive-going component with a latency of about 300 milliseconds and a normal scalp distribution over the midline electrodes (for a review see Duncan et al., 2009; Patel & Azzam, 2005; Polich, 2007). P300 based oddball paradigms are often used in BCI which are systems that allow individuals to communicate without having to use verbal or motor means of communication (Blankertz et al., 2010; Farwell & Donchin, 1988; Kleih et al., 2011; Mak et al., 2011; Wolpaw & Wolpaw, 2012). P300 can be identified even at single-trial level (high signal-to-noise ratio) allowing good communication speeds for BCIs.

4.2 Rationale for current study

The main hypothesis is that training of initiation and response to joint attention cues using gaming/BCI interfaces can be used to improve joint attention social cognition skills in ASD participants.

The BCI setup will be used to train initiation and repeated responses to a joint attention object. An independent game platform will be used to test whether enhanced rates of joint attention (initiation and responses) were achieved.

This study aims to demonstrate that improvements in identification of social cues (and improvement of overall social behaviour) in subjects with ASD can be achieved using social games together with a BCI setup. The primary goal is to ensure increased rate of responses to joint attention cues.

To evaluate the improvements, we will use a new task/realistic game that will challenge the detection of initiation of joint attention cues (from avatars – gaze or pointing). The number of correct responses (to particular objects and not to non-object parts of the scene, will be recorded). We will also record incorrect responses to non-pointing body gestures. Participants will be challenged with about 20 events per minute (one every three seconds), of variable degree of difficulty. Given that the experiment lasts 10 minutes, and some events are control measures, we will have a total of 150 test events and 50 control events. We expect that ASD subjects will be able to correctly report a mean of 75 of the target events, based on tailored task difficulty.

Considering the longitudinal design proposed, with alpha 0.05, power of 80%, and standardized effect of 0.8 (improvement of 8 points for an estimated SD of 10 points) we would need 15 subjects. We will consider three additional subjects to account for drop-offs. The sample size calculations were performed based on a matched 2 sided paired t-test. To determine these values we used the G*Power tool (Faul, Erdfelder, Lang, & Buchner, 2007). The sample size calculations were performed under the assumption that the distribution of the mean differences is normal. Without the normality assumption, we would also need 15 subjects, considering a non-parametric Wilcoxon test.

The structure proposed for this study is the following: (1) initial eligibility screening, (2) pre-intervention, (3) intervention process, (4) post-intervention, and (5) follow-up.

5 Study objective(s)

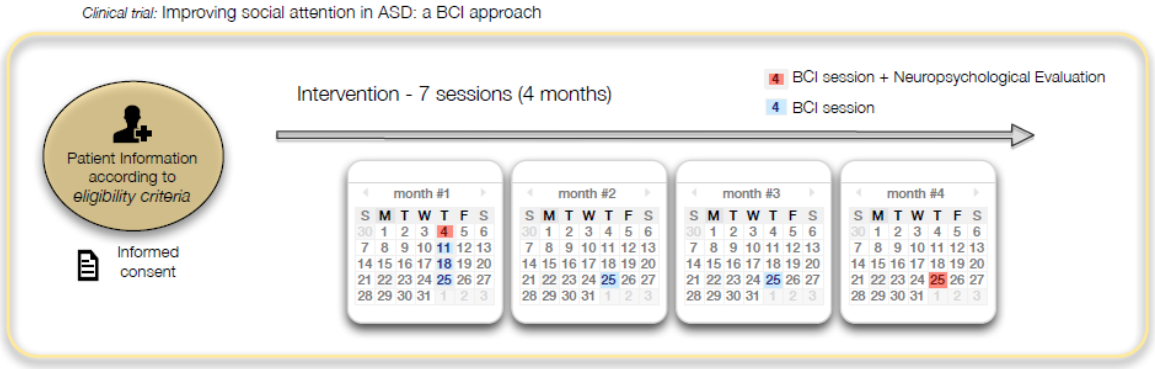
5.1 Primary objective(s)

Improvement of social attention skills (training joint attention mechanisms) by increasing the rate of responses to joint attention cues. We expect that ASD subjects will be able to increase the number of target events correctly reported, based on a tailored task difficulty.

5.2 Secondary objectives

Improvements in general aspects of social cognition (as measured by neuropsychological tests) derived from a generalization of the skills learned.

6 Study design



Allocation: not applicable

Endpoint Classification: Efficacy Study

Intervention Model: Single arm

Primary Purpose: Basic Science and clinical feasibility study

Participants: 15 ASD subjects (plus 3 in case of drop outs)

7 Participant selection

The eligible patients for the study should be high functioning ASD adolescents and adults. These participants should also meet all the following inclusion criteria and none of the exclusion criteria. All queries about patient eligibility should be directed to Susana Mouga before registration.

7.1 Inclusion criteria

- Positive diagnostic results for ASD in:
    - Autism Diagnostic Interview-Revised;
    - Autism Diagnostic Observation Schedule;
    - The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.

7.2 Exclusion criteria

- Global Intelligence Quotient < 80
- Associated medical condition such as epilepsy, neurocutaneous or other genetic syndromes, or other usual comorbidity in ASD samples

8 Recruitment

8.1 Number of participants

A total of 15 (plus 3 in case of drop outs) participants will be recruited. We expect to recruit one subject each three weeks. The study is expected to start on the second semester of 2015 and last up to 82 weeks (including follow-up).

8.2 Recruitment process

Participants will be recruited from the National Clinical Program for ASD at University of Coimbra. The Lead Researcher is responsible for contacting the participants.

8.3 Informed consent

Informed Consent can be found attached in the appendices. This Informed Consent must be signed by each participant/legal representative before the beginning of the study.

8.4 Screening logs

The data related to screening logs (paper format) will be kept in a secured room only accessible by BRAINTRAIN researchers. Additionally, data required to support analysis of the study will be entered and stored in an MS SQL Server database hosted on servers at Cardiff University. The hosting server is on a locked, secure machine room at Cardiff University.

The database will be backed up daily and access to the database will be via secure logon (username and password) and restricted to named study personnel only, as detailed in the study's PRA log. Each study will only see data and actions relating to their own study.

9 Withdrawal & loss to follow-up

Participants have the right to withdraw consent for participation in any aspect of the BCI intervention at any time. The participant's care will not be affected at any time by declining to participate or withdrawing from the study.

If a participant initially consents but subsequently withdraws from the study, clear distinction must be made as to what aspect of the study the participant is withdrawing from. These aspects could be:

- Withdrawal from study intervention
- Withdrawal from study follow-up
- Withdrawal from entire study and does not want data to be used.

A patient may withdraw or be withdrawn from the intervention for the following reasons:

- Withdrawal of consent for intervention by the participant
- Any alteration in the participants condition or circumstances which justifies the discontinuation of the intervention in the Investigators' opinion

In all instances participants who consent and subsequently withdraw should complete a withdrawal form or the withdrawal form should be completed on the participant's behalf by the researcher/clinician based on information provided by the participant.

10 Intervention

10.1 EEG

During the EEG acquisition, researchers will stay in the same room as participants. Researchers will be able to see and monitor participant's behaviour and their performance. The acquisition can be stopped at any time, should participants' request this or researchers become concerned about participant's health.

10.2 Possible undesirable effects

Serious adverse effects are highly unlikely.

- The acquisition is not painful but requires participants to remain as motionless as possible for up to 50 minutes.
- Virtual Reality setup may induce momentary dizziness.

10.3 Intervention arms

Experimental: BCI intervention

This group will undergo seven sessions of BCI intervention. Each subject will also undergo neuropsychological evaluations and "Joint-attention task" before the first BCI session (week 0) and after the last BCI session (week 16). The first four sessions are weekly while the other three are monthly. The intervention will take a total of four months.

10.4 Brain area/s of interest

Brain areas of interest include the parietal lobe of the brain because P300 has been classically reported as an enhanced positive-going component with a centro-parietal scalp distribution that is maximal over midline scalp sites. This way EEG electrodes of BCI will be strategically placed in the central, parietal and occipital electrodes positions (following the international 10-20 system), specially over the midline positions.

10.5 Adherence

Adherence is defined as attending all seven BCI sessions.

After the enrolment, the participant will be given a schedule with the sessions plan. Additionally, the participant or caregiver will be reminded of each session by telephone-call one week earlier and by message the day before.

On the basis of following the study protocol, follow-up plan should depend on specific situation of participants such as avoiding the holiday or the inconvenient day. When the intervention is over, researchers should remind patients of the next appointment time. For eventual absent participants, researchers should do telephone interviews in time, ask the reason and try to reschedule.

11 Outcome measures

11.1 Primary outcome measure

The results [Number of items of social attention that a patient can accurately identify in the avatar's action, e.g. looking at, pointing at] in a separate "Joint-attention task" will be the primary outcome measure. The experimental group will be evaluated in the pre and post evaluation time with this test.

11.2 Secondary outcome measures

Secondary outcomes comprise the core measures detailed in Table 1 below.

- The results in Autism Treatment Evaluation Checklist (ATEC) [Sociability and Cognitive Awareness Subtests] will be one of the secondary outcome measures. The group will be evaluated in the pre and post evaluation time with this test.

- The results in Vineland Adaptive Behavior Scale (VABS) [Socialization and Daily Living Skills Domains] will be one of the secondary outcome measures. The group will be evaluated in the pre and post evaluation time with this test.

Table 1. Other BRAINTRAIN core outcomes

Measure	**Outcomes**	**Description**	**Timepoint**
Demographic questionnaire	Age, gender, education, SES		Baseline
Thought control questionnaire (TCQ)(Wells & Davies, 1994)	Thought control (distraction, punishment, worry; re-appraisal; social control)	30-item measure to assess effectiveness of strategies used for the control of unpleasant/unwanted thoughts	Baseline
Thought control ability questionnaire (TCAQ)(Luciano et al., 2005)	Thought control	25-item measure of individual differences in perceived ability to control unwanted & intrusive thoughts	Baseline
Wechsler Adult Intelligence Scale (WAIS-III)(Wechsler, 1997)	IQ	Global intelligence/IQ measure	Baseline

Profile of Mood States (POMS)(Heuchert and McNair, 2012)	Anger; confusion; depression; fatigue; tension and vigour		Pre-post assessment (each session)
Hospital Anxiety & Depression Scale (HADS)(Zigmond and Snaith, 1983)	Anxiety; depression	24-item scale (7 depression & 7 anxiety items)	Pre-post assessment (across intervention)
Beck Depression Inventory (BDI-II)(Beck et al., 1996)	Depression	21-item measure of clinical depression	Pre-post assessment (across intervention)
Autism Treatment Evaluation Checklist (ATEC) (Rimland and Edelson, 1999)	Autism Traits	77-items: speech/language/communication (14 items); sociability (20 items); sensory/cognitive awareness (18 items); health/physical/behaviour (25 items)	Pre-post assessment (across intervention)
Vineland Adaptive Behaviour Scales (VABS) (Sparrow et	Adaptive Behaviour	297 items measure of adaptive behaviour Three main domains: Communication (COM), Daily Living Skills (DLS) and Socialization (SOC)	Pre-post assessment (across intervention)

al., 1984)		and total score, the Adaptive Behaviour Composite (ABC)	
Debriefing interview questionnaire		Covers: strategies; general experience of the process; adverse effects; awareness of group allocation	Post-assessment (ideally each session)

12 Study procedures

12.1 Data collection

Each BCI session consists of selecting targets of social cues through an oddball paradigm designed in a virtual reality scenario. The BCI virtual reality scenario will be presented via Oculus Rift DK2. The EEG acquisition will be made via EEG electrodes placed on participant's head using an EEG cap. The task was initially thought to be based on mentally counting how many times a virtual human character directs its attention (gaze) to a specific object in the scene. Based on a pilot study the task is to mentally count the blinks of the object to which the virtual human character directed its attention (gaze) at the beginning of each run. The computer reads/stores the EEG signal and detects if the subject was counting the correct object via detection of P300 elicited by the target object blink. Each session is composed by the following steps:

- Subject and BCI setup preparation (10 minutes)
    - Explain the task to participant;
    - Place the cap with electrodes on participant's head;
    - Check EEG signal quality.
- Data Acquisition (up to 40 minutes)
    - BCI Training phase - ~ 20 minutes;
    - BCI Testing – 5 minutes (single trial classification) to 20 minutes (ten trials classification). The number of trials needed to validate depends on a predefined accuracy (equal for every subject). Subjects may need different number of trials to achieve this accuracy, thus the higher the number of trials, the longer the experiment is. The task consists in the presentation of 50 target events

The sessions will be controlled by the EEG technician responsible for the BCI interventions of the BrainTrain research team at UCo.

All data collected from training and testing phases will be stored in digital format inside the stimulation machine. Upon concluded the session, data will be copied into a hard-drive for posterior analysis.

Stored data will be processed and analysed by the BrainTrain research team at UCo.

Personal identification of each participant will be hidden. Unique ID will be used to identify each participant's data for the whole course of the clinical trial and future references.

12.2 Screening

Not applicable.

12.3 Pre-test

The experimental group will undergo an initial diagnostic and neuropsychological evaluation, followed by a customized "Joint-attention" assessment test and Autism Treatment Evaluation Checklist (ATEC) [Sociability and Cognitive Awareness Subtests], Vineland Adaptive Behaviour Scale (VABS) [Socialization and Daily Living Skills Domains].

12.4 Post-test

Once concluded the intervention, the group performs the a posteriori evaluation, to assess the hypothesized improvements on the measures, as compared to pre-test assessment.

12.5 Follow-up

We will perform a final follow-up 6 months after the intervention. Not applicable otherwise.

12.6 Samples & storage

Not applicable.

12.7 Facilities & equipment

BCI sessions will be carried out in spacious and quiet room with minimal electrical interference. The room must have at least one table and one chair.

The BCI acquisition module consists of a cap with eight active electrodes that will be placed in the head of participant. The electrodes are connected to g.tec amplifier that sends the data wirelessly for the computer.

The computer contains the data processing module (Matlab) and the virtual-reality module (Vizard).

The BCI loop is closed with the Oculus Rift DK2 (Oculos VR, Inc), placed on participant's head.

12.8 Incidental findings

Not applicable.

13 Statistical considerations

13.1 Randomisation

Not Applicable

13.2 Sample size

Considering the longitudinal design proposed, with alpha 0.05, power of 80%, and standardized effect of 0.8 (improvement of 8 points for and estimated SD of 10 points) we would need 15 subjects (plus 3 in case of drop outs). We will add three additional subjects to account for drop-offs. The sample size calculations were performed based on a matched 2 sided paired t-test. To determine these values we used the G*Power tool (Faul et al., 2007). The sample size calculations were performed under the assumption that the distribution of the mean differences is normal. Similarly, without the normality assumption, we would also need 15 subjects, considering a non-parametric Wilcoxon test.

13.3 Missing, unused & spurious data

Detail provided in the Statistical Analysis Plan (SAP).

13.4 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

13.5 Termination of the study

Reasons for early termination of the study include unexpected, unacceptable side effects.

14 Adverse Events

14.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a participant which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease.

Serious Adverse Event (SAE): Any adverse event that:

- Results in death
- Is life-threatening*
- Required hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other medically important condition ***

* Note: The term "life-threatening" in the definition of serious refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** Note: Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened or elective procedures does not constitute an adverse event.

*** Note: other events that may not result in death are not life-threatening, or do not require hospitalisation may be considered as a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

14.2 Causality

The assignment of causality should be made by the Investigator responsible for the care of the participant.

Table 2. Causality

Relationship	Description

Unrelated	There is no evidence of any causal relationship with the study or intervention.
Unlikely	There is little evidence to suggest there is a casual relationship (e.g. the event did not occur within a reasonable time after intervention) with the study or intervention. There is another reasonable explanation for the event (e.g. the participant's clinical condition, other treatment).
Possible	There is some evidence to suggest a causal relationship with the study or intervention (e.g. because the event occurs within a reasonable time after intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a judgement of the causal relationship.

14.3 Expectedness

The assessment of whether or not an SAE is an expected consequence of receiving the intervention will be provided by the Lead Researcher.

Depending on the nature of the event, the reporting procedures outlined in this protocol should be followed. Any queries concerning adverse event reporting should be directed to Miguel Castelo-Branco - Principal investigator.

14.4 Reporting procedures

14.4.1 Events exempt from reporting (non-serious AEs)

All such events, whether expected or not, should be recorded on the relevant case report form.

An SAE form should be completed for all SAEs within 24 hours. Events exempt from SAE reporting are set out in Table 2 and information relating to them should instead be captured on the relevant CRF.

Table 3. Adverse Events exempt from reporting

Adverse Event	Information
Nausea	Immersive Virtual Reality setup may induce momentary nausea to the participants.
Discomfort	EEG cap and electrodes, as well as Virtual Reality setup may cause discomfort to the participants

Additional information should be sent within 5 days if the event has not resolved at the time of reporting. All events should be followed up through to resolution.

In the case of serious, unexpected and related adverse events, the procedures will be taken as referred in the Informed Consent Form. This document can be found attached in the appendices.

14.5 Urgent Safety Measures (USMs)

An urgent safety measure is an immediate change in a trial procedure or temporary halt to a trial procedure, put in place prior to approval in order to protect participants from any immediate hazard to health and safety following new safety information (SAE or other information received from an external source). The Principal Investigator may carry out USMs to protect participants from immediate harm.

15 Analysis

15.1 Main analysis

A priori, we will analyse the data normality. Considering a normal distribution of the mean differences, the main analysis will consist on a t-test on the means - difference between two dependent means (matched pairs).

The null hypothesis of this test is that the means μ_x, μ_y of pre- and post- intervention, respectively, are identical.

The null hypothesis that $\mu_x = \mu_y$ can be reformulated in terms of the difference $d_i = x_i - y_i$. The null hypothesis is then given by $\mu_d = 0$. The alternative hypothesis states that μ_d has a value different from zero:

$H_0 : \mu_d = 0$

$H_1 : \mu_d \neq 0$

However, without the normality assumption, we will consider a non-parametric Wilcoxon test.

Further details will be found in the SAP

15.1.1 Sub-group & interim analysis

Not applicable.

16 Data storage & retention

Data collected on paper will be kept in a secured room only accessible by BRAINTRAIN researchers, for a minimum period of 5 years after publication.

Data required to support analysis of the study will be entered and stored in an MS SQL Server database hosted on servers in a secure machine room at Cardiff University. This room is locked and entry is via a swipe card system.

The database will be backed up daily and access to the database will be via secure logon (username and password) and restricted to named study personnel only, as detailed in the study's PRA log.

17 Study closure

The trial will end up to 82 weeks after its start.

18 Regulatory issues

18.1 Ethical and research governance approval

The study will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Ethical approval for this study was given by the Ethical Committee of the Faculty of Medicine of University of Coimbra. Research governance approval (granted by CEIC/Infarmed) will be sought after document approval.

18.2 Consent

Consent will only be considered informed following provision of adequate participant information (see attached information sheet/s and consent form). Participants will be informed that they are free to withdraw at any time and that this will not impact on current or future care.

18.3 Confidentiality

Data Confidentiality is assured as stated in the Informed Consent form, according with the Portuguese data protection regulations as per the EU directive. This document can be found attached in the appendices.

18.4 Indemnity

Although not expected due to the participation, if the subject suffers any injury as a result of any study procedures, performed according to the protocol, the subject will be reimbursed for medical expenses necessary to treat them. All procedures are reviewed by staff and all incidents reported to the persons and / or entities.

18.5 Trial sponsorship

Faculty of Medicine of University of Coimbra.

18.6 Funding

The ***'An interventional study to improve social attention in autism spectrum disorder (ASD): a brain computer interface (BCI) approach'*** study is funded by the European Commission 7th Framework Programme for Research, Technological Development and Demonstration.

18.7 Audits & inspections

The study may be participant to inspection and audit by CEIC/Infarmed.

19 Study/trial management

LBIM (Laboratory of Biostatistics and Medical Informatics of the Faculty of Medicine of University of Coimbra) will manage the study.

We will keep, weekly project team meetings, monthly study management group meetings. These meetings will be attended by researchers directly involved in running the study.

20 Data monitoring & quality assurance

LBIM (Laboratory of Biostatistics and Medical Informatics of the Faculty of Medicine of Coimbra) will manage the quality of the study.

20.1 T/SSC (Trial/Study Steering Committee)

The TSC/SSC will be established centrally for the BRAINTRAIN consortium and include external clinical and methodological experts, at least one service user and an independent statistician. Members will be required to sign up to the remit and conditions as set out in the TSC Charter.

20.2 IDMC (Independent Data Monitoring Committee)

The nature of this study makes it unlikely that a separate Data Monitoring Committee (DMC) will be required; however, this will be discussed with the TSC at their first meeting and a DMC will be set up if deemed necessary. Members will be required to sign up to the remit and conditions as set out in the DMC Charter.

21 Publication policy

The Publication Policy is detailed in <<document title>> and can be found on the BRAINTRAIN extranet <<file location>>.

22 Milestones

Table 4. Milestones

TASK	START	DURATION	Months
			1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Recruiting	1	5	
Intervention	2	15	
Follow-up	8	15	

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24 Appendices

- Informed Consent Form
- Ethical Committee Approval