Efficacy of The Secret Trail of Moon (MOON) a personalized treatment video game for children and adolescents with ADHD based on cognitive training and emotional regulation: Protocol for a randomized clinical trial.

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Abstract

Background: Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder in childhood and adolescence (5%) with associated difficulties and worse prognosis if undetected. Multimodal treatment is the treatment of choice; however, sometimes treatment can be insufficient or have some drawbacks.

Objective: To demonstrate the effectiveness of cognitive training through the serious video game “The Secret Trail of Moon” (MOON) in improving emotional regulation of people with ADHD.

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Statistical power analysis: The study has a power greater than 80% to detect differences.
Statistical analysis: Classical statistics: T student, 2-factor ANOVA and Mann Whitney analyses will be performed according to the characteristics of each variable.
Ethics: The study was approved by the Research Ethics Committee of the Puerta de Hierro University Hospital on December 14th, 2022. The authorization of the Spanish Agency of Medicines and Health Products was February 14th, 2023. Informed consent will be requested from legal guardians and minors protecting their personal data to the provisions of the Organic Law 3/2018 of 5 December, on Personal Data Protection and guarantee of digital rights.

Results: To September 26, 2023, we have enrolled 62 participants. Thirty-one participants have completed the study. This clinical trial has been funded by the Comunidad de Madrid (Spain) IND2020/BMD-17544. The approximate completion date is March 2024.

Conclusions: Serious video games such as MOON can be motivational tools that complement multimodal treatment in ADHD. Clinical Trial: NCT06006871

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Running title: Effectiveness of MOON (serious video game) for ADHD

Keywords: Attention-Deficit/Hyperactivity Disorder, ADHD, Emotional Dysregulation, Serious Video Games, Virtual Reality, Cognitive Training, Music, Chess.

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Abstract

Background: Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder in childhood and adolescence (5%) with associated difficulties and worse prognosis if undetected. Multimodal treatment is the treatment of choice; however, sometimes treatment can be insufficient or have some drawbacks.

Objective: To demonstrate the effectiveness of cognitive training through the serious video game “The Secret Trail of Moon” (MOON) in improving emotional regulation of people with ADHD.

Hypotheses: H1: ADHD patients using MOON improve their emotional regulation more than the control group; H2: ADHD patients using MOON improve in core ADHD symptoms compared with the control group; H3: ADHD patients using MOON improve their cognitive functioning compared to the control group; H4: ADHD patients using MOON improve in academic performance with respect to the control group; H5: The change of platform (face-to-face, online) does not entail

differences in emotional regulation; H6: There are no clinically meaningful side effects associated with the video game.

Methods: Design: prospective, unicenter, randomized, unblinded, PRE-POST intervention study. Randomization of the groups (MOON vs. Control) will be performed by electronic CRD. The MOON intervention will be performed 2 times per week for 10 weeks (30 minutes per session). The first five weeks (10 sessions) will be conducted face-to-face in Puerta de Hierro University Hospital; the remaining weeks will be conducted online at the participants' home. The clinical trial was registered in Clinical Trials NCT06006871.

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Conclusions: Serious video games such as MOON can be motivational tools that complement multimodal treatment in ADHD.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder diagnosed in childhood and adolescence, affecting about 5% worldwide [1]. In addition to the classical clinical triad of ADHD (inattention, hyperactivity and impulsivity) [2], the existence of comorbidity, executive dysfunction or emotional dysregulation can complicate the prognosis [3]. Greater severity of ADHD symptoms is correlated with greater emotional dysregulation in both children [4] and adults [5]. Emotion regulation involves intrinsic and extrinsic processes responsible for managing appraisal and control of emotional reactions, emotion intensity, temporality, and goal orientation [6]. Emotional dysregulation has a severe impact on social skills, academic performance, and adaptive skills leading to a higher rate of usage of treatment services [4]. This impact on emotional regulation affects diversely across broad age ranges in ADHD from children to adults [7–9]. Emotional regulation problems even in patients aged 5 years predict inattention problems[10]. This emotional dysregulation should be treated before the age of 7 years[11]. ADHD is considered a chronic disorder with a high economic cost [12,13], high accident rate, and increased risk of mortality [14].

Multimodal treatment is the most effective treatment for ADHD and includes pharmacological treatment, psychological treatment and psychoeducation of parents and teachers. Pharmacological treatment is the treatment of choice in children and adolescents with severe ADHD [15] and the most common treatment in developed countries [16]. Seventy percent of patients observe a positive change in symptoms in the short term due to stimulants [17]. However, some drawbacks such as the side effects of pharmacological treatment (insomnia, appetite suppression, growth retardation) make some parents reluctant [18]. Moreover, medication is more effective for the core symptoms of ADHD than for the bottom-up mechanisms associated with emotional regulation [19]. Cognitive behavioral therapy (CBT) can help specially in social skills and problem solving [20]. However, motivational difficulties in ADHD [3] and low adherence to treatment [18] have led to additional interventions complementing multimodal treatment. Some research shows promising results with cognitive training [21], metacognitive interventions [22], music [23] or video games [24]. However, the overall results show small effect sizes and difficulties in maintaining long-term benefits and transferability to daily life (generalizability and transferability) [25]. More evidence is needed with a greater control of risk biases.

Video games offer immersive and engaging entertainment tools that are increasingly being used. Video games have been extended as tools in the field of health (e.g. promoting physical exercise through exergames) to others for cognitive training (see Peñuelas-Calvo et al. [24] and Rodrigo-Yanguas et al. [26] for reviews). In particular, a recent systematic review[27] showed the potential use of video games on improving emotional regulation. The potential use of video games in ADHD may be beneficial for several reasons: their attractiveness, customization to suit the player's tastes, and immediate reinforcement[28]. Regarding ADHD, children and adolescents with this diagnosis have difficulties associated with poor verbal working memory (poor internal language), which makes it difficult for them to perform tasks. In addition, they are more dependent on external stimuli (they have low intrinsic motivation) which causes them to become bored earlier[3]. Therapeutic interventions based on gamification and video games can be a good strategy to decrease treatment dropout rates by promoting patients to perform tasks as games.

The Secret Trail of Moon (MOON) is a serious video game based on cognitive training for

people with ADHD. It is composed of a set of different mini-games focused on enhancing the most affected cognitive abilities in ADHD according to Thomas Brown's Model of Executive Functions and Barkley Behavioral Inhibition Model [3,29,30]. The games increase progressively difficulty according to patient needs. MOON has been designed by a multidisciplinary team following a user-centered model (usability study) and an iterative redesign process [28,31]. Prior to the present clinical trial, we completed another clinical trial. In this prospective, single-center, randomized clinical trial with three arms, MOON was tested in clinically stable patients on medication with ADHD, aged 12 to 22 years (NCT04355065) for 3 months. The 105 patients were randomly assigned to the 3 groups: 1) Cognitive training (12 sessions) with face-to-face MOON (n=31); 2) Cognitive training with online Therapeutic Chess (n=24); and 3) Control group with telephone monitoring (n=34). Contrary to our expectations, we did not find any statistically significant improvement in executive functioning, which was the primary outcome. However, we found some improvements in secondary outcomes such as emotional intelligence, emotional regulation, and performance in the school context in both self-reports and parent reports [32]. Following these encouraging results, we designed the present clinical trial (NCT06006871) with the limitations of the previous clinical trial in mind, namely: 1) Increasing sample size; and 2) Increasing the number of cognitive "doses" (20 sessions) and the access to the platform (virtual reality and computer); 3) Improving some aspects of the MOON video game, particularly on emotional regulation, such as the aesthetics of the virtual environment, the introduction of music [23], rhythm-based gameplay, and motivational elements such as the reward system; and 4) Simplifying the design (two arms -case versus contro- instead of three arms). The main objective is to test the efficacy of a serious video-game cognitive training treatment (The Secret Trail of the Moon) in improving emotional regulation in patients with a clinical diagnosis of ADHD aged 7 to 18 years.

Methods

Study design

Prospective, unicentric, randomized, unblinded, pre-post intervention study with concealment of the randomization sequence. Randomization of the groups (MOON vs. Control) will be performed by electronic CRD. The interventional study model is parallel assignment. The allocation ratio will be equal in both groups.

Procedure

All participants will be recruited from the child and adolescent psychiatry outpatient clinics of Hospital Universitario Puerta de Hierro Majadahonda. The number of visits varies in each group; MOON group will have 12 face-to-face visits while Control group will have only 2 presential visits. The total duration of the research will be 90 days in total (3 months for each participant: 12 weeks including pre and post evaluation) (see Figure 1). Table 1 summarized all visits.

[Please, insert Figure 1]

Table 1. Study flow

Visit Day	***Preinclusion D-1***	***Inclusion D0***	***Training D1-D90***	***Final D90***
Explanation protocol	X			
CGI (clinical)	X			
Randomization		X		

Informed consent	X			
Data collection note	X			
CGI (parents)	X			X
SDQ (parents)	X		X	X
CPRS-HI (parents)	X			X
SNAP-IV (parents)	X			X
SDSC (parents)	X			X
BRIEF (parents)	X			X
CPT3 (patients)	X			X
CORSI cubes (patients)	X			X
C-TMT (patients)	X			X
GASA (patients)	X			X
Academic mark	X			X
UKU (patients)			X	
Satisfaction questionnaire				X

For the MOON group, the total number of sessions with the video game will be 20 (twice a week, adjusted according to the availability of the participants). Participants in the MOON group over 12 years old will perform the video game sessions in VR, while participants under 12 will perform the video game sessions in a computer. All participants in the MOON group will perform the cognitive training with MOON following the same order of the games reflected in Table 2. Each session will have a maximum duration of 30 minutes (being approximately 20 minutes of MOON gameplay). The first 10 sessions will be held in person at the hospital. For participants over 12 years of age, the researchers will help to manually calibrate the eye distance of the virtual reality headset to adjust the quality of vision. For those under 12 years of age, researchers will perform computer-based support to ensure proper use and understanding of the video game tasks. The task will be explained by the researcher adapting the instructions to the age of the participant. Once the researcher is assured of the understanding of the task, the difficulty level will be raised in a personalized way for each participant. Progress is signaled to the player by leveling up, parameters (e.g. hits, errors, time taken) and stars earned (0 star=poor performance, must repeat the level; 1 star=acceptable performance; 2 stars=good performance; 3 stars=excellent) (Figures 2,3).

[Please, Insert Figure 2 and Figure 3]

Parents in session 10 receive a flash drive with the video game and training on how to use it at home. The last 10 sessions will take place at the participants' home on their computers and will be monitored online by the researchers. Data collected in the game (e.g. completed levels, hits, errors or reaction times) will be automatically send to a data server (Playfab). Parents of MOON Group participants will be asked in advance to give their consent to the collection of these data.

Table 2. Gameplay order by sessions

Sessions	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*
Mode	*On-site at the Hospital*										*At participants' homes*									
Games																				
Smasher		1	2				1		2			1			2		1		2	
Kuburi		2		1		2			1	2				1		1		2		
Teka-Teki	1			2		1		2			1	2							1	2
Enigma	2				1		2			1			2		1	2				1
Chess			1		2			1			2		1	2			2	1		

In the case of the control group, participants will be followed up with weekly calls to parents during this period. During this follow-up, psychoeducational support about ADHD will be provide to parents.

Hypothesis

Our main hypothesis is that ADHD patients using MOON improve their emotional regulation more than the control group. The efficacy will be evaluated by means of the change produced between the baseline evaluation (Day 0) and the final evaluation visit (Day 90) in the decrease of 3-4 points in the global score of the *Strenghts and difficulties questionnaire* (SDQ) filled by the patients' parents.

As secondary hypotheses, the difference with the control group in measures such as ADHD core symptomatology, cognitive abilities and academic performance will be assessed. As secondary hypothesis we propose:

- H2: ADHD patients using MOON improve in core ADHD symptoms compared with the control group;
- H3: ADHD patients using MOON improve their cognitive functioning compared to the control group;
- H4: ADHD patients using MOON improve in academic performance with respect to the control group;
- H5: The change of platform (face-to-face, online) does not entail differences in emotional regulation;
- H6: There are no clinically meaningful side effects associated with the video game.

Participants

Sample: 152 patients (76 cases versus 76 controls) with a clinical diagnosis of ADHD by DSM 5. All participants will have a clinical diagnosis of ADHD, being on ADHD medication, clinically stable, and scoring between 3 and 6 in the Clinical Global Impression (CGI) before entering into the trial. Medication will not change during the investigation unless changes are required for clinical reasons. A 15% loss rate is expected. Inclusion and exclusion criteria are summarized in Table 3.

Table 3. Criteria for inclusion and exclusion of participants

Inclusion criteria	Exclusion criteria
▪ Age 7-17 years (could turn 18 during the study) ▪ Clinical diagnosis of ADHD in any presentation. ▪ With pharmacological treatment for ADHD. ▪ Ability to follow verbal instructions ▪ Ability to play a video game (not necessary to play regularly). ▪ Clinically stable. ADHD symptomatology severity based on clinician-assessed CGI score (between 3-6).	▪ Severe patients (> or equal to 5 CGI) or very mild patients (CGI < or equal to 1) ▪ Patient at risk of suicide (according to the clinical judgment of the professional in charge of the patient) ▪ Motor difficulties that prevent playing the videogame ▪ Participation in other similar studies ▪ Intention to initiate any psychotherapeutic treatment (including cognitive-behavioral therapy) in the next 3 months of

	the course of participation in the clinical trial.

Randomisation and masking

To warrant clinical trial randomization, a random block sequence of 76 “1” (Experimental) and 76 “2” (Control) in 4 blocks of 38 numbers (19 “1” and 19 “2”) will be generated with the R program by MBF [33]. The sequence will be unknown to the recruiters [34].

In the pre-inclusion phase, patients will be informed about the research by the Principal Investigator (PI), HBF, and their suitability will be assessed according to the inclusion and exclusion criteria (see Table 3). Subsequently, MMM will explain the research procedure in detail and will summon the pre-recruited participants. Once the consent is signed, they will be randomly assigned by blocks using the electronic case report form (CRF) with ratio 1:1. Randomization of the groups (MOON vs. Control) will be performed by electronic CRF Redcap.

Materials

-Hardware

Materials to be used for this study include the video game (MOON) itself, virtual reality goggles, PlayStation 4 controllers (Sony Group Corporation), test consoles, monitor screens, and headsets. The virtual reality software runs on a PlayStation 4 test device (Sony Group Corporation) (Figure 4). A computer with internet connection will also be used in this study for the proper functioning of sending the game data to the Playfab server.

[Please, Insert Figure 4]

-Software: Video game

MOON has been designed to be a therapeutic cognitive training video game for patients with ADHD. This serious video game in this version can be used both on computer and PlayStation 4 virtual reality consoles. The use of virtual reality allows a more focused approach to the task and a greater impact on the motivation of the participants. The use of computer allows more accessibility. The game is set in a natural environment, potentially beneficial for people with ADHD with animals that accompany the player throughout the training session [25]. Different games or tasks compose the game with the purpose of training the most affected cognitive functions in ADHD. MOON has five game mechanics. The games are: 1) SMASHER (sustained attention and inhibitory control) is a task based on *Continuous Performance Tests* [35] with a 2-item sequence (similar to *CSAT test* [36]); 2) In TEKATEKI (planning) the participant is asked to perform a minimum number of possible movements (based on *Hanoi tower*); 3) ENIGMA (working memory) the *span* of items to remember increases according to the difficulty curve [37]; 4) KUBURI (visuospatial ability) is a 3D cube *rotation task*; 5) CHESS (reasoning) consists of tasks related to the rules of chess.

-Psychometric assessments

Pre-inclusion

Clinical Global Impression Scale (CGI) for clinicians [38]

Symptom severity will be measured with the Clinical Global Impression Scale (CGI) approximately 1 minute duration. ADHD symptomatology severity based on clinician-assessed CGI score (between 3-6) for inclusion criteria.

Clinical anamnesis

The clinical anamnesis includes demographic, clinical, school and medical history data.

Psychometric assessments

Strenghts and difficulties questionnaire (SDQ) for parents [39].
This questionnaire has 25 items (duration of approximately 5 minutes). It measures the scales 1) Emotional symptoms, 2) Behavioral problems, 3) Hyperactivity, 4) Problems with peers and 5) Prosocial behavior. A decrease of 3 to 4 points in the post-assessment visit (D70) with respect to the pre-assessment visit (D0) will be considered an improvement in emotional regulation.

The Swanson, Nolan, and Pelham Rating Scale (SNAP-IV) for parents [40,41]
The main ADHD symptomatology (inattention, hyperactivity, impulsivity) will be measured with subjective scales for parents. The SNAP IV is a scale for the assessment of ADHD symptoms. It's an 18-item questionnaire with a Likert scale of 0-4 (approximately 5 minutes long) of which 9 assess attention deficit and another 9 assess hyperactive impulsive component. The cut-off points for attention deficit are 1.78 for parents. For hyperactivity-impulsivity they are 1.44 for parents.

The Conners Abbreviated Symptom Questionnaire (CPRS-HI) for parents [42,43]
The Conners scales are a set of scales for the assessment of patients with ADHD. CPRS-HI is a 10-item questionnaire with a Likert scale of 0-3 (approximately 2 minutes long). This revised and abbreviated version of the Conners scale is designed to be answered by parents of children aged 6-18. It consists on 10 items with a Likert type response: 0= not true at all/never; 1= just a little true/occasionally; 2= Pretty much true/often; 3=very much true/very often.
The cut-off points are divided by gender. For boys, a score above 16 is suspected ADHD, while for girls, a suspected diagnosis of ADHD is above 12 points.

Clinical Global Impression Scale (CGI) for parents [44].
Symptom severity will be measured with the Clinical Global Impression Scale (CGI) adaptation for parents of approximately 1 minute duration, consisting of a "thermometer" with a Likert scale of 1-10.

Behavior Rating Inventory Executive Function 2 (BRIEF-2) questionnaire for parents [45]
The BRIEF-2 is a questionnaire designed for the evaluation of executive functions in children and adolescents. It consists on 63 items with three answer options (never, sometimes and frequently). Its correction provides four general indexes: emotional regulation, cognitive regulation, behavioral regulation and global index of executive function. It also provides two second-order factors and a general index

Conners Continuous Performance Test 3rd Edition (CPT-3) for patients with ADHD [35]
CPT-3 is a screening task for ADHD in addition to measuring sustained attention, impulse control and processing speed. The Conners CPT-3 is a computerized, standardized, and validated application test for different age and gender groups. The task consists on pressing a button each time a letter (target) appears on the screen, except for the letter X (non-target), which must not be pressed. The duration is 14 minutes and the presentation interval between letters is variable (1, 2 and 4 seconds). The test provides results on hits, error of omission (undetected target) and errors of commission (reacted non-target), which are considered a measure of impulsivity. In addition, CPT3-3 provides information on hit mean reaction time and variability.

Corsi Cubes for patients with ADHD [37,46]
Corsi Cubes to measure visuospatial working memory
Comprehensive Trail-Making Test Second Edition (CTMT-2) for patients with ADHD [47]
CTMT-2 to measure cognitive flexibility, with three indexes: inhibitory control, task switching and total index (Figure 5).

The Sleep Disturbance Scale for Children (SDSC) for parents [48]
SDSC is a 26-item questionnaire with a Likert scale of 1-5 (1: never; 5: always) with an approximate duration of 5 minutes.

Udvalg für Kliniske Undersogelser (UKU) for patients with ADHD [49].
UKU is a tool designed to evaluate possible secondary symptoms that happen during the week. This scale is not included in the assessment phases. Only the participants playing VR will have to complete the scale after each cognitive training session.

Game Addiction Scale for Adolescents (GASA) [50,51]
GASA is a 7-item questionnaire to assess video game addiction.

Information about academic performance will be obtained with grades.

[Please, Insert Figure 5]

Interventions

After the initial evaluation, 2 groups randomized by blocks will be formed:

- Group 1: The Secret Trail of Moon (MOON): personalized cognitive training with a video game in person and online. Psychoeducational support on ADHD to parents during the research (n=76).
- Group 2: Control: Usual treatment (pharmacological) without cognitive training intervention. Psychoeducational support on ADHD to parents during the research (n=76).

Analysis

Sample-size calculation

Based on similar investigations whose main hypothesis is based on the administration of the *Strenghts and difficulties questionnaire* (SDQ) [52], the sample size calculation shows the need to perform the study on approximately 152 participants with a diagnosis of ADHD to cover most of the possibilities with an alpha 0.05 and a statistical power of 80% taking into account a 15% drop out. We performed the sample size calculation to contrast a mean in the control group of 11 points on the SDQ global score vs a 2 point mean drop (symptomatologic improvement) in the experimental group with a pooled standard deviation of 4. This estimate covers other less conservative situations such as a difference of up to 4 points.

Study populations

The intention-to-treat (ITT) analysis population is defined as those children who are randomized and receive at least 10 sessions, and the per-protocol (PP) population is defined as those children who complete 100% of the training.
All analyses will be performed on the premise of intention-to-treat analysis.
Two-way ANOVAs will be performed, with time (pre-post) and group (experimental vs. control) as factor and each measure as dependent variable. The difference between the study groups will be

considered significant when the p is < 0.05.

Demographic and baseline characteristics

A data collection notebook will be used to obtain demographic and clinical data. The data will be recorded with electronic CRD (REDCap). Measures to answer the hypotheses will be made through clinical scales for parents and objective tests of cognitive abilities in patients. Additional information on academic performance will be collected.

Primary end point analysis

The main objective is to test the efficacy of the cognitive training treatment (MOON) in improving emotional regulation in patients with a clinical diagnosis of ADHD aged 7 to 18 years. The effectiveness is evaluated by means of the change produced between the baseline evaluation (Day 0) and the final evaluation visit (Day 90) in the decrease of 3-4 points in the global score of the SDQ evaluated by the parents. A decrease of 3 to 4 points on the post-assessment visit (D70) with respect to the pre-assessment visit (D0) will be considered an improvement in emotional regulation based on other similar studies [52].

Three parent SDQ measures will be assessed: initial assessment (D0), mid-term assessment (D45), final assessment (D90) in order to evaluate hypothesis 5 (switching from face-to-face to online does not lead to differences in emotional regulation).

Secondary end point analysis

Two subjective scales will be used to assess hypothesis 2 (ADHD patients using MOON improve in ADHD symptomatology relative to the control group). The main ADHD symptomatology (inattention, hyperactivity, impulsivity) will be measured with: 1) SNAP, an 18-item questionnaire with a Likert scale of 0-4 (approximately 5 minutes long) and 2) CPRS-HI, a 10-item questionnaire with a Likert scale of 0-3 (approximately 2 minutes long). Symptom severity will be measured with the CGI adaptation for parents of approximately 1 minute duration, consisting on a "thermometer" with a Likert scale of 1-10.

Relative to hypothesis 3 (ADHD patients using MOON improve their cognitive abilities more than the control group). Executive dysfunction will be evaluated by means of subjective scales for parents and objective tests for patients. The subjective test for parents will be performed with the BRIEF-2 questionnaire. As for the objective tests for children and adolescents, there will be three: 1) Conners CPT-3 is a task that is usually used to screen for ADHD in addition to measuring sustained attention, impulse control and processing speed; 2) *Corsi Cubes* to measure visuospatial working memory; 3) CTMT-2 to measure cognitive flexibility, with three indexes: inhibitory control, task switching and total index.

Regarding hypothesis 4 (ADHD patients using MOON improve in academic performance relative to the control group) grades will be collected in each subject on the quarterly school report card immediately preceding (pre) and following (post) treatment.

Safety and adherence analysis

Additional measures have been taken with respect to the previous clinical trial [32] in order to assess the occurrence of side effects. Hypothesis 6 (there are no side effects associated with the video game) is related to this aspect. For those associated with the possibility of motionsickness due to the use of virtual reality, the UKU test will be used. In the previous clinical trial, non-significant effects related to sleep were observed, so in the current clinical trial the SDSC scale will be used to assess this symptomatology in depth. Since people with ADHD are more prone to addictive behaviors related to video games [53], two main precautions were taken: adapting the game design so as not to encourage

addictive behaviors [28], and collecting additional information with the GASA test.

Results

To September 26, 2023, we have enrolled 62 participants. Thirty-one participants have completed the study. The approximate completion date is March 2024.

Discussion

ADHD is a neurodevelopmental disorder with great variability. Some authors associate the symptoms of inattention as a disorder of 'cool' executive function (dorsolateral prefrontal cortex pathway) while the symptoms of hyperactivity and impulsivity are associated with deficits of 'hot' executive function (orbital and medial prefrontal cortex pathway)[54]. According to Gross [55,56], emotional regulation is a process in which people modulate their emotions using strategies such as suppression, strategy modulation or reappraisal. This process requires great interaction of executive functions with emotional regulation. In relation to these intrinsic-extrinsic processes, people with ADHD compared with typically developing (TD) children tend to overestimate their performance in different domains (social, school and behavioral); some authors call this term "Positive Illusory Bias" (PIB), with consequent disparity between children's self-reports and parents' assessments [22,57].

The Secret Trail of Moon was developed as a form of cognitive training to improve cognitive abilities such as sustained attention, inhibitory control, working memory, visuospatial ability, reasoning, planning [30,31]. However, after conducting the first clinical trial, our main hypothesis of improving executive functions measured with the BRIEF-2 test was not fulfilled [32]. However, we did find improvements in emotional domains compared to the control group both in self-reports and parent reports (the most relevant being emotional intelligence, emotional regulation and performance in the school context). Accordingly, in this second clinical trial, we wanted to replicate and extend our previous positive findings on different measures of emotion regulation. The global scale of emotional regulation (SDQ) used includes the measurement of emotional symptoms, behavioral problems, hyperactivity, problems with peers, and prosocial behavior [39,52].

We believe that any improvement found in measures should be transferred or generalized to daily life. Thus, in this study we will measure academic performance to assess whether the improvement in cognitive domains includes a transfer to other domains such as arithmetic or reading.

Additional measures have been adopted. Improvements have been added to make the video game more attractive (music, aesthetics, rewards). To avoid the presence of PIB causing questionnaires to be completed by "bad informants", objective tasks as CPT-3 [35], Corsi cubes [37] and C-TMT [47] have been proposed for participants in this second clinical trial. In order to control the possible excessive use of video games or addiction, the design of the video game has been controlled [28] and the GASA test will be incorporated [50,51].

However, this clinical trial has important limitations. First, blinded study has not been possible. Secondly, cognitive domains are difficult to measure in the absence of unified questionnaires; in fact, some laboratory measures related to executive function are moderately related to the main symptoms of ADHD and their impact on daily life. As for the video game, it was not possible to incorporate all the improvements designed. Despite the incorporation of children under 12 years of age in this clinical trial, it is possible that some difficulty levels are not well adjusted due to not having been able to perform a usability study prior to this new clinical trial. In addition, being typical of ADHD symptomatology, it is possible the decay of the video game sessions, especially those online sessions performed at home without supervision of the researchers; the participants could lose motivation for the treatment as the same game is played for a long time [58].

Video games can be a potential tool to improve different skills, such as emotional regulation [27]. In people with ADHD it is especially important to incorporate motivational tools complementary

to multimodal treatment that can facilitate adherence to treatment.

Author's Contributions

MMM, MBF and HBF carried out the research. MMM and HBF will recruit patients. MMM and MBF will perform data collection. MMM will monitor the Calendly appointments and MOON home training data collection via Playfab. MMM designed the electronic CRD (Redcap) and MBF will enter the data into the program. MMM, MRY, CGT and HBF have designed the video game. AS made programming enhancements to this version of MOON. CL and PW provided research design ideas and statistical input. The sample size calculation was carried out by AR. MBF, HBF, MMM and AR will perform the statistical analyses. PLG and HBF supervised the study.

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Special thanks are extended to all children, adolescents and parents for their future participation in this study.

Ethics Approval. Protocol amendments and regulatory aspects

The study was approved by the Research Ethics Committee of the Universitary Hospital Puerta de Hierro on December 14th, 2022 (PI 106/22). The authorization of the Spanish Agency of Medicines and Medical Devices (AEMPS) as clinical research with medical devices without CE marking was February 14th, 2023 (1061/22/EC-R). The version that was approved by both entities was version 4 in the protocol, data collection and recruitment material. The investigator's brochure was approved in version 3. The ethics committee requested the elimination of the rhythm-based game because it had not been previously tested in patients with ADHD. Monitoring of the clinical trial was required. Informed consent will be requested from legal guardians and minors protecting their personal data to the provisions of the Organic Law 3/2018 of 5 December, on Personal Data Protection and guarantee of digital rights.

Consent for Publication

Consent will be obtained from all participants.

Conflict of interest

In the last 24 months, HBF has received lecture fees from Takeda, BIAL, laboratorios Rubio, and laboratorios Rovi. He has also been granted with three prizes regarding the development of a serious videogame for treating ADHD (The secret trail of Moon): the Shibuya Prize by Takeda; the first prize of the college of psychologists of Madrid; and a prize to the best innovative health initiative within the healthstart prize (https://www.youtube.com/watch?v=o_j6WBKIpF0&list=PLFM_B3KwjcXObcNBpbL3VBnrbcRTJmOt4&index=5 accessed on 1 August 2023). He is Principal Investigator (PI) of an iPFIS research contract (www.isciii.es, accessed on 12 August 2022; IFI16/00039), co-PI of a MINECO research grant (RTI2018-101857-B-I00), and PI of a research of the SINCRONIA project, funded by the Start-up Bitsphi, www.bitsphi.com; recipient of (1) a FIPSE Grant and (2) an IDIPHIPSA intensification grant; involved in two clinical trials (MENSIA KOALA, NEWROFEED Study; ESKETSUI2002); Co-Founder of Haglaia Solutions. He is also an employee and member of the advisory board of ITA Salud Mental

(KORIAN).

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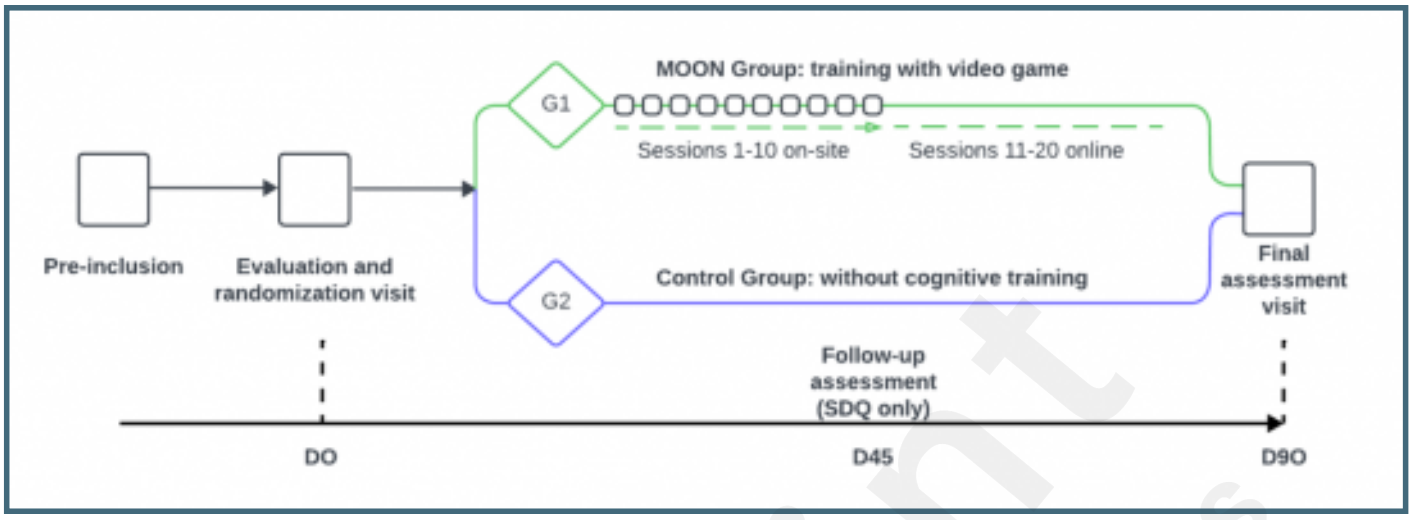
Supplementary Files

Figures

Duration of the research.



MOON's progress.

MOON's star system.

User playing MOON.

Psychometric assessments: Corsi cubes, CPT-3, and CTMT-2.