Artificial Intelligence digital treatment for pediatric ADHD: a pilot study based on neuropsychological and neurophysiological measures

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1. Protocol synopsis

1.1 Synopsis

Protocol Name	**Artificial Intelligence digital treatment for pediatric ADHD: a pilot study based on neuropsychological and neurophysiological measures.**
Sponsor	**Sincrolab Ltd.**
Indication	Children with attention deficit and hyperactive disorder (ADHD), of combined presentation
Purpose	**Exploratory Feasibility:** This study will be carried out to detect differences in cognitive performance among participants with combined presentation ADHD after the use the Sincrolab Kids platform and those who use the Sham control.
Study Product	SINCROLAB tool, cognitive stimulation with artificial intelligence
Design	Single-center, parallel, single-blind, randomized and controlled clinical trial
Sample size	**Estimated sample size:** N = 56 (n = 28) **Sample size due to early stopping:** N = 29 (n = 15)
Intervention	**Conceptualization and Funding:** 2015-2016 **Recruitment:** October 2017-February 2020

Eligibility criteria	***Inclusion criteria*** • Diagnosis of ADHD of combined presentation issued by collegiate health professional and under compliance with criteria of the Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR that states that 6 or more symptoms of inattention and 6 or more symptoms of hyperactivity must be met impulsivity in the last 6 months. • Age between 8 and 11 years under the consent of a legal guardian. • Withdrawal of psychoactive drug 3 days prior the assessment phases prior and after the intervention. Psychoactive medication includes: ADDERALL XR®, VYVANSE®, CONCERTA®, FOCALIN XR®, RITALIN LA®, METADATE CD, Strattera®, or other generic-type analogues approved by the Spanish Agency of Medicines and Medical Devices or the European Medicines Agency. • Do not present additional psychoactive medication. • Do not present psychiatric comorbidities. • Preserved reading-writing. • Provision for compliance with all phases of the study. ***Exclusion criteria*** • Begin or abandon behavioural therapies or psychoactive drugs during the three-month period comprising the Intervention phase. Changes in the pharmacological dose should be reported to the researchers. • Motor difficulties that make the use of the tool impossible. • Use of psychoactive drug that in the opinion of the researcher could be a confounding factor. • Presence or suspicion of substance abuse in the last 6 months. • Presence of blindness or uncorrected visual acuity difficulties. • Medication and / or concomitant therapy.

	• The use of psychotropic medications is not allowed. • The use of other drugs is not allowed except those commonly used (for example: ibuprofen, paracetamol ...) and medical prescription (antibiotics). • Do not initiate, abandon or change types of therapy or medication. ***<u>Concomitant Medication and Treatment:</u>*** • No initiation or change in medication treatment and/or psychotherapy.
Study Regimen	The study procedure complies with the following study phases: 1. Start-point. Enrollment and screening for eligibility (Week 0). 2. Pre-intervention assessment (Visit 1, Week 1). 3. At-home intervention period (Week 2-13). 4. Post-intervention assessment (Visit 2, Week 14-15).
Statistical Considerations	**<u>Analysis of primary objective</u>** Statistical analysis will follow a per-protocol approach, so any participant who has abandoned the study flow before its ending will not be considered as missing data. The primary objective of the study is to assess the efficacy of the neuropsychological rehabilitation tool *SINCROLAB* in the rehabilitation of inhibitory control in paediatric ADHD of combined presentation, measured by Commission score from CPT-III. This study will be carried out to detect differences in cognitive performance among participants

	with combined presentation ADHD who use the Sincrolab Kids platform and those who use the Kongregate platform. First of all, descriptive analysis will be performed with primary measurements and main composite scores, in order to check statistical assumptions such as normal distribution adjustment. Next, each composite score will be entered, as dependent variable, in a mixed-effects model analysis, including as independent variables Treatment, Moment and interaction. Slope and intercept will be checked so models can be adjusted. Due to sample size, robust restricted maximum likelihood (REML) will be chosen as estimation method, instead of maximum likelihood (ML). Generalised least squares (GLS) and generalized estimating equations (GEEglm) methods will be, subsequently, chosen if REML models do not converge. Stepwise method will be used for demographic variables in each mixed model as method applied to explicative models. *Treatment* factor will be taken as explicative variable. Bayesian Information Criterion (BIC) will be used to compare models. Model diagnosis will be performed through Pearson standardized residuals. Mixed model's result for each variable which composes the scores will be also reported. As only one comparison it is intended to be performed for analysis of primary endpoint (one dependent variable), no correction for multiplicity will be applied in this analysis. Respondent analysis will be performed in order to study the proportion of participants who achieved the clinically effect of 0.64 (standardized pre-post mean difference), comparing both intervention arms (Experimental and Control).

1.2 Study Flow Diagram

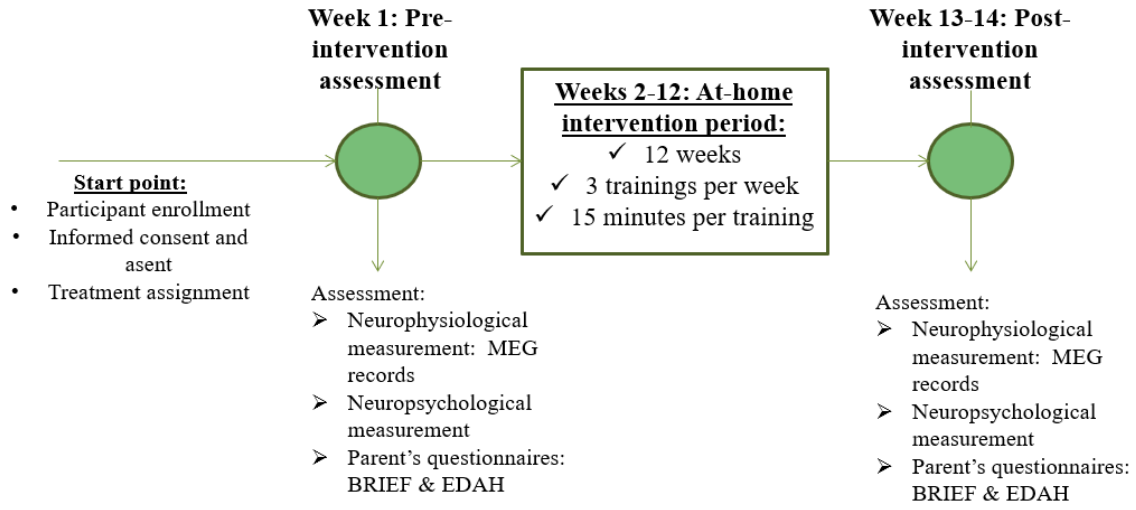

Figure 1. Study Flow Diagram

1.3 Schedule of Activities

Table 1. Schedule of Activities

Schedule of Activities	Study information and prior Week 0	Visit 1. Pre-intervention assessment Week 1	At-home intervention Weeks 2 to 13	Visit 2. Post-intervention assessment Week 14-15
First contact	x			
Patient Information Sheet	x			
Demographics	x			
In-house information questionnaire for eligibility criteria	x			
Informed Consent		x		
Outcome Evaluation: Visits 1 and 2				
Neuropsychological assessment protocol		x		x
Neurophysiological assessment protocol (MEG recording)		x		x
At-home intervention period				
Final verification of eligibility criteria		x		
Randomization		x		
At-home intervention			x	
Adverse events recording			x	
Compliance with intervention protocol			x	

2. Study Glossary

Table 2. Study Glossary

Abbreviation or Term	Definition
PI	Principal Investigator
ADHD	Attention Deficit and Hyperactivity Disorder
CTB-UPM	Center for Biomedical Technology of Polytechnic University of Madrid
LNCyC	Laboratory of Cognitive and Computational Neuroscience
MEG	Magnetoencephalography
DMN	*Default mode* network
WISC-IV	Wechsler Intelligence Scales for Children-IV
NEPSY-II	Developmental Neuropsychological Assessment-II
CPT-III	Conners' Continuous Performance Test, version III
EDAH	Evaluation of Attention Deficit and Hyperactivity Disorder
BRIEF	Behavior Rating Inventory of Executive Functions
AE	Adverse Effects
REML	Robust restricted maximum likelihood

3. Scientific Background

3.1 Attention Deficit and Hyperactivity Disorder

Currently, ADHD is one of the most frequent childhood disorders in public mental health services.

Its prevalence rate, between 8% and 12%, has increased surprisingly in recent years and its treatment is being increasingly studied from a scientific point of view. ADHD is a multidimensional disorder characterized by problems of inattention, impulsivity and hyperactivity (American Psychiatric Association, DSM-IV, 1994). Several investigations have shown the abnormal neuroanatomy of patients with this disorder. Specifically, certain research (Castellanos et al, 2002, Hill et al, 2003) has shown through neuroimaging and cerebral volumetry techniques, how the brain of children with ADHD is smaller on average when compared with normal healthy children. The most widespread symptom explanatory theory of ADHD states that the neuroanatomical circuit that would explain these symptoms would be formed by right prefrontal regions of the brain, basal glanges, cerebellar hemispheres and a subregion of the cerebellar vermis. There has been a special interest in studying the role played by the prefrontal cortex in the neuroanatomy of ADHD. It seems that there is a decrease in the size of the right prefrontal cortex, which could explain the problems for the inhibition control in their responses (Casey et al, 1997). In addition, a decrease in the volume of the right upper prefrontal area has been found in subjects with ADHD, with an increase in left asymmetry greater than right when studying them compared to normal healthy subjects (Hill et al, 2003).

However, we still do not know if these differences are cause or consequence of other previous abnormalities in the information processing pattern. Some studies (Fox et al, 2006, Swanson et al, 2006) have proposed an interesting approach, in which they establish that the lack of capacity of these children with ADHD is due to periodic lapses in attention and these lapses are responsible for the increase in behavioral variability in addition to being the result of the intrusion of low frequency oscillations of the neural network "by default" (Weissman et al, 2006). Therefore, an abnormal distractibility may be responsible for these children suffering from these difficulties in maintaining care.

In this way, a comparative study between two groups, a control group of normal healthy children and an experimental group of children with combined ADHD is proposed, through a task of involuntary auditory attention and distractibility while performing a record of magnetoencephalography.

3.2 Background and Previous Results

The interest in non-pharmacological treatments for ADHD is increasing (van Dongen-Boomsma, Vollebregt, Slaats-Willemse and Buitelaar, 2015), which is why most of the efforts of the clinical sector

are currently focused on the development of new techniques, effective intervention and rehabilitation methods that reduce the symptoms of ADHD for a higher quality of life for these children.

New technologies have invaded our lives completely, and for more than a decade they have been part of the neuropsychological treatment and rehabilitation of multiple diseases and disorders, which guarantees the possible scientific profitability of this future project.

The research of Health Games has grown considerably over the last decade (Kharrazi, et al, 2012), however, there have been few scholars who have focused their efforts on providing scientific evidence to support the impact of rehabilitation computerised (Rabipour and Raz, 2012). The recent research published in Nature (Anguera, et al 2013) showed neural and behavioural evidence of how a video game could have positive effects on cognitive control abilities of older adults. In the field of children and adolescents, specific researchers have demonstrated sustainable/stable behaviour improvements using independent programs, as well as improvements in measures of non-verbal intelligence, language development and executive function after brief interventions (Rabipour and Raz, 2012). Nevertheless, it needs for a change in the research approach in order to achieve reliable and conclusive results (Kharrazi, et al, 2012) and the achievement of clinically useful programs able of generalizing trained skills (Rabipour and Raz, 2012).

Specifically, in ADHD, many of these new tools are focused on the stimulation of working memory through a program consisting of dynamic and attractive interactive games turning rehabilitation into a game.

One of the pioneering programs in using new technologies in the neuropsychological rehabilitation of ADHD is Cogmed. The results of Cogmed are contradictory, while some studies did not find significant improvements in working memory after Intervention with Cogmed in children with ADHD compared to a control group (Van Dongen-Boomsma, et al, 2015), others argue that if a more rigorous comparison condition is used, Cogmed does show effects on certain aspects of memory in children with ADHD. But point out that it does not seem that this improvement is generalised to other cognitive domains (Chacko, et al, 2014). However, an exhaustive review and a recent meta-analysis questions all these results when concluding that the Intervention with Cogmed significantly improves the attention (Shinaver, et al, 2014, Spencer-Smith and Klingberg, 2015), the visual and verbal work memory. It also finds that these effects are generalised to the improvement of sustained attention in up to 6 months (Shinaver, et al, 2014).

In relation to all these findings, a meta-analysis (Cortese et al, 2015), revised the effects of cognitive Intervention in ADHD, through randomized trials and showed that cognitive Intervention has limited effects on the symptoms of ADHD. The authors concluded that there is a need for approaches focused on multiple neuropsychological processes based on rehabilitation and generalization of cognitive profiles.

All these previous findings support the real need to create neuropsychological rehabilitation programs supported by new technologies such as Sincrolab, based on multi cognitive domain stimulation, as well as to initiate a line of research that focuses its efforts on evaluating the effectiveness of these new tools.

3.3 Magnetoencephalography technique: Center for Biomedical Technology from Polytechnic University of Madrid

Over the last few years, the Laboratory of Cognitive and Computational Neuroscience from the Center for Biomedical Technology has carried out multiple studies and projects, under the leadership of Principal Investigator, Fernando Maestú, PhD. Fernando Maestú, PhD, has written and published countless articles (in national and international journals) and books related to the subject presented in this proposal. We can summarise his contribution as follows:

1. *Basic Psychology:* Between 2001 and 2010, Maestú, PhD, was in charge of the direction of the research work of the Department of Basic Psychology of the Complutense University of Madrid where he directed and supervised about 20 doctorates. He has co-authored several books related to memory and language (Maestú et al., 2004, Martín and Maestú, 2005, and Campo, Maestú, and Fernández, 2008). In this same line he has published articles on the involvement of the medial temporal lobe in the coding of long-term memory (Campo, Maestú, Ortiz, Capilla, and Fenández, 2005) and on the use of the MEG as a new tool for the study of basic cognitive processes (Maestú et al., 2005).
2. *Neurodevelopmental Psychology.* In the year 2000, he conducted some studies on the knowledge of the fundamental aspects involved in ADHD, evaluation instruments (2002-2005), differential functional characteristics among the different subtypes (2004-2005), the relationship between cognitive performance and motivation. in this disorder (2004-2005) and the relationship between executive dysfunctions and their involvement in the child's life (2005). In 2006 he launched the book Magnetoencehalography advances in the study of dyslexia (Del Río, Carboni, Capilla, Maestú, and Ortiz, 2006) and in recent years has published a dozen articles on neurodevelopmental disorders, among which we highlight those that focus in the study of ADHD and autism spectrum disorders using the MEG technique (Muñoz-Yunta et al., 2004, Capilla et al, 2004, Etchepareborda et al, 2004, Muñoz-Yunta et al, 2006, Mulas et al, 2006; and Muñoz -Yunta et al., 2008).
3. *Magnetoencephalography.* It should be noted that Maestú, PhD, is part of the only group of specialists in the MEG functional neuroimaging technique that will be used in this project, and that in the last 5 years have collaborated and participated in about 10 projects and have made more than 30 articles and publications (national and international) with this methodology. Both the collaboration in these projects, putting together his own studies based on this technique, and the contribution in a dozen books (Ortiz, Fernández, Maestú, Amo and Sequeira, 2001, Ortiz, Amo, Maestú and Fernández, 2003, Maestú , et al, 2006, Sancho, Sanchez-Quesada, Fernández, Maestú

and Ortiz, 2006, Del Río, Carboni, Capilla, Maestú and Ortiz, 2006, Mestú, et al, 2006, Maestú, Ríos and Cabestrero, 2008, Maestú, Maestú and Pozo, 2008, Maestú and Ríos, 2009, and Maestú, Fernández and Aine, 2009), have granted Dr. Maestu undoubted and great knowledge and practice on the technique, its use and the interpretation of it.

4. Objectives of the Study

4.1 Primary objective

Protocol amendment 1.1: The main objective of this study is to assess the efficacy of the neuropsychological rehabilitation tool *SINCROLAB* in the rehabilitation of Inhibitory Control in paediatric ADHD of combined presentation.

By comparing two intervention arms of random allocation (Intervention with SINCROLAB tool and Sham control), we plan to assess pre-post interaction effect of SINCROLAB neuropsychological intervention on inhibitory control.

Protocol amendment 1.1: Main outcome measure for this objective will be Commision score from Conners' CPT-III (Conners, 2014).

4.2 Secondary objectives

The first secondary objective is to test the efficacy of intervention with SINCROLAB tool for the rehabilitation of other cognitive processes involved in paediatric ADHD. These cognitive processes comprise:

- Inhibitory Control.
- Visuospatial and Verbal Working Memory.
- Cognitive Flexibility.
- Semantic and Phonological Verbal Fluency.
- Sustained Attention.

The second secondary is to study how neuropsychological rehabilitation *SINCROLAB tool* produces functional connectivity changes in altered networks in ADHD. There are already previous studies showing evidence about the effects of cognitive rehabilitation in functional connectivity, so our secondary hypothesis goes this way.

4.3 Exploratory objectives

The first exploratory objective is to study the correlation matrix between changes in functional connectivity and changes in neuropsychological primary scores.

The second exploratory objective is the adherence analysis by comparing the compliance with at-home intervention protocol in both arms.

The third exploratory objective is to record potential adverse events which may be produced during at-home intervention period. Adverse events record sheet is attached to Annex III.

5. Trial Plan

5.1 Overall Design

The present study is a single-center, single-blinded, parallel, randomized, controlled clinical trial in which subjects are randomly allocated in one of the two experimental conditions: Experimental group (SINCROLAB cognitive treatment intervention) or Control group (Sham control intervention).

Baseline assessment for each participant will be performed before the intervention phase. Neuropsychological assessment protocol will be applied at CTB-UPM. Neurophysiological assessment protocol (magnetoencephalography data) will be also recorded at the Center for Biomedical Technology (CTB-UPM).

After that, both study groups will participate in a 3-month intervention phase (at-home intervention period), consisting of scheduled training sessions with Sincrolab cognitive rehabilitation tool or with Sham control. Experimental group will train with the Sincrolab cognitive rehabilitation tool and Control will do the same but with a Sham control (commercial, ludic videogames). This intervention phase consists of 15-minutes-at-home training sessions, 3 times per week for 12 weeks (total of 48 training sessions).

Identical assessments (magnetoencephalography and neuropsychological measures) will be performed at CTB-UPM once the treatment phase is over (post-intervention assessment).

5.2 Study Ethics

This study is ruled by the principles of the Declaration of Helsinki (Edinburgh, 2013) and the International Council on Harmonisation - Good Clinical Practice (ICH-GCP) Guideline (ICH-E6-R2).

This trial is registered with ISRCTN (ISRCTN71041318, http://www.isrctn. com). This study is approved by Ethical Committee of Clinical Research Hospital Clinico San Carlos (08/01/2016, ref: C.P.-C.I. 15/575-E).

5.3 Study Procedures

The study procedure complies with the following study phases:

5. Start-point. Enrollment and screening for eligibility (Week 0).
6. Pre-intervention assessment (Visit 1, Week 1).
7. At-home intervention period (Week 2-13).
8. Post-intervention assessment (Visit 2, Week 14-15).

Every contact via e-mail with parents/legal guardians, for each study phase, is detailed in the communication protocol (Annex IV).

5.3.1 Start point. Enrollment and screening for eligibility

Assessment for eligibility is part of enrollment procedure (see *7.1 Methods of Enrollment* for more details). During screening procedure, each participant will be assigned to a study number which codes participant's ID.

E-mail and phone number from legal guardians will be collected prior to Visit 1. This information will be stored just for needed communications, such as breaches of the study protocol and/or set the appointment for post-intervention evaluation

Demographic data are collected from parents/legal guardian's participants, prior to pre-intervention assessment (Visit 1) in order to check inclusion and exclusion criteria (see *Section 6*). This data collection for screening is performed via e-mail communications. Participant's legal guardians will receive by e-mail the Participant Information Sheet (Annex II). This document contains a brief questionnaire which is required for legal guardians to fulfill. This questionnaire of eligibility information shall be sent back to Sincrolab Ltd and PI, so eligibility criteria may be checked. Right after receiving the questionnaire with demographic data, a researcher from Sincrolab Ltd will appoint the date for Visit 1 at the facilities of CTB-UPM (Pozuelo de Alarcón, Madrid, Spain).

Participant's legal guardian will sign Informed Consent model in Week 1, Visit 1, prior to any other activity. After that, pre-intervention assessment stage will begin.

5.3.2 Pre-intervention assessment (Visit 1, Week 1)

Visit 1 comprises pre-intervention assessment. In order to reduce the noise produced by the variability in the time of completion of the initial evaluation all subjects will perform the evaluation in the hours of 9:00 a.m. to 12:00 AM. The secondary objective of this procedure is to avoid post-school fatigue effects that could affect the performance of the evaluation tests.

Right after legal guardian/s sign the Informed Consent, pre-intervention assessment will begin.

Neuropsychological assessment protocol is composed by batteries and neuropsychological standardized tests. Some of the characteristics that will be part of this evaluation are the following:

- The evaluator will go to the waiting room where the child is with their legal guardians. At this time, the BRIEF and EDAH questionnaire will be given to the parents for completion and the child will be picked up to be taken to the room where the neuropsychological evaluation will be carried out.
- There will be a conversation of approximately 5 minutes with the child in which they will explain what is going to be done, as well as how to ask non-binding questions such as "What is your favourite food?" Or "Which player is your favourite? " The objective of these 2-3 minutes of non-binding conversation seeks to reduce the tension or anxiety for the assessment and will be applied in all participants in the same way.
- In both cases, prior to every task there will be a period of instruction and testing, in which it will be verified that the participant has understood the task to be performed or the need to not perform any task at that moment of the evaluation.
- The order in which neuropsychological tasks are administered is shown in Table 3, *Section 11. Outcome Measures.*

Those participants who first performed the neuropsychological assessment protocol will subsequently and without delay to the MEG registration room and vice versa. To avoid fatigue effects, an informal talk of about 5 minutes with the participants on non-binding topics will be maintained again. Also, they will be asked about their need to use the bathroom.

Neurophysiological assessment protocol is composed by MEG records. MEG recording procedure is as it follows:

i. First, participants will go through oddball task recording, for approximately 30 minutes. Oddball task is composed by four 7-minutes blocks. At the end of each block, participants will be encouraged.
ii. After task-recording, eyes-opened resting state phase will be performed for 5 minutoes.

iii. Finally, eyes-closed resting state phase will be performed for another 5 minutes.

After both MEG and neuropsychological protocols are administered, the parents will be informed:

- Research staff will decide if all the inclusion and exclusion criteria are met. No personal data that allows to recognize the subject will be registered.
- They will receive an instruction document in order to carry out the at-home intervention period. This document shall include the access' keys to the proper randomized intervention (SINCROLAB or Sham control) and explanatory instructions for the platform.
- A copy of the Informed Consent.

Parents will be instructed that during the next 12 weeks their children should perform 3 sessions of 15 minutes each week. They will be warned that this Intervention time will be divided into three games. You will be instructed that the instruction sheet to access the platforms and the instructions for beginning and ending the Intervention session will be provided the next day through the contact e-mail provided. Likewise, they will be provided with a mobile phone +34 627 73 68 85 in case they need to get in touch at any point of the study.

5.3.3 At-home intervention period (Weeks 2 to 13)

Once pre-intervention assessment is over, legal guardians will receive an e-mail with the access' keys to the corresponding platform. These keys come within an instruction document in order to download the platform and perform the training sessions. Due to the nature of the intervention platforms (Sham control is outside *Sincrolab Kids* application), different documents are sent to Experimental or Control (see Annex V for Experimental intervention instructions document and Annex VI for Control intervention instruction document).

Right after the previous e-mail is received, intervention period begins. For the following twelve weeks participants will perform the at-home intervention, which consists in 3-weekly training sessions, at the most convenient time, with a duration of 15 minutes per each.

These 15 minutes do not include time for reading instructions and / or receiving feedback. The number of games played during the 15 minutes will be 3, approximately 5 minutes each.

There will be a follow-up through the platforms themselves. Both platforms (*Sincrolab* and Sham control platform) register if there has been a session during the previous day. Therefore, each day a Sincrolab researcher must check if the session was carried out the day before.

Sincrolab research staff will notify, via e-mail, to the participants' parents/legal guardian if, at the 4th day of the week, they have not complied with the provided intervention protocol (i.e participant has not

performed any scheduled training session). This notification (and the day it is sent) allows the participant to comply with intervention protocol for the present week. This procedure will be carried out unless the participant's intervention pattern comprises the last three days of the week.

If the participant fails to comply with the intervention protocol for a week, an e-mail will be sent to the legal tutors in order to know the reason and explain the need for such an event not to recur, as it could mean the end of participation in the study. If the e-mail is not answered, a phone call will be made.

After the 12th intervention week, participants' legal guardians will be appointed at the CTB-UPM in order to perform post-intervention assessment.

This post-intervention assessment will be performed within 2 weeks since intervention protocol's ending.

5.3.4 Post-intervention assessment (Visit 2, Week 14-15)

Visit 2 comprises post-intervention assessment. In order to reduce the noise produced by the variability in the time of completion of the initial evaluation all subjects will perform the evaluation in the hours of 9:00 a.m. to 12:00 AM. The secondary objective of this procedure is to avoid post-school fatigue effects that could affect the performance of the evaluation tests.

Neuropsychological assessment protocol is composed by batteries and neuropsychological standardized tests. Some of the characteristics that will be part of this evaluation are the following:

- The evaluator will go to the waiting room where the child is with their legal guardians. At this time, the BRIEF and EDAH questionnaire will be given to the parents for completion and the child will be picked up to be taken to the room where the neuropsychological evaluation will be carried out.
- There will be a conversation of approximately 5 minutes with the child in which they will explain what is going to be done, as well as how to ask non-binding questions such as "What is your favourite food?" Or "Which player is your favourite? " The objective of these 2-3 minutes of non-binding conversation seeks to reduce the tension or anxiety for the assessment and will be applied in all participants in the same way.
- In both cases, prior to every task there will be a period of instruction and testing, in which it will be verified that the participant has understood the task to be performed or the need to not perform any task at that moment of the evaluation.
- The order in which neuropsychological tasks are administered is shown in Table 3, *Section 11. Outcome Measures.*

Those participants who first performed the neuropsychological assessment protocol will subsequently and without delay to the MEG registration room and vice versa. To avoid fatigue effects, an informal talk of

about 5 minutes with the participants on non-binding topics will be maintained again. Also, they will be asked about their need to use the bathroom.

Neurophysiological assessment protocol is composed by MEG records. MEG recording procedure is as it follows:

iv. First, participants will go through oddball task recording, for approximately 30 minutes. Oddball task is composed by four 7-minutes blocks. At the end of each block, participants will be encouraged.
v. After task-recording, eyes-opened resting state phase will be performed for 5 minutoes.
vi. Finally, eyes-closed resting state phase will be performed for another 5 minutes.

After both MEG and neuropsychological protocols are administered, the parents will be informed:

- The report derived from the CPT-III that the system facilitates after the execution of the test. Likewise, for those who require it, an explanation of the results will be provided privately and on time, warning that said explanation will not have diagnostic validity. Likewise, it will be recommended that said report be reported to your reference professional for a correct interpretation of it.
- If participant was allocated in Control group and has received Sham control intervention, they will be informed that they have the possibility of receive SINCROLAB intervention under the same conditions as Experimental participants.

The end of Visit 2 points the end of study procedures.

6. Study Population

6.1 Inclusion criteria

Inclusion criteria are as follows:

- Diagnosis of ADHD of combined presentation issued by collegiate health professional and under compliance with criteria of the Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR that states that 6 or more symptoms of inattention and 6 or more symptoms of hyperactivity must be met impulsivity in the last 6 months.
- Age between 8 and 11 years under the consent of a legal guardian.
- Withdrawal of psychoactive drug 3 days prior the assessment phases prior and after the intervention. Psychoactive medication includes: ADDERALL XR®, VYVANSE®, CONCERTA®, FOCALIN XR®, RITALIN LA®, METADATE CD, Strattera®, or other

generic-type analogues approved by the Spanish Agency of Medicines and Medical Devices or the European Medicines Agency.

- Do not present additional psychoactive medication.
- Do not present psychiatric comorbidities.
- Preserved reading and writing.
- Provision for compliance with all phases of the study.

6.2 Exclusion criteria

Exclusion criteria are as follows:

- Begin or abandon behavioural therapies or psychoactive drugs during the three-month period comprising the Intervention phase. Changes in the pharmacological dose should be reported to the researchers.
- Motor difficulties which would make the use of the tool impossible.
- Use of psychoactive drug that in the opinion of the researcher could be a confounding factor.
- Presence or suspicion of substance abuse in the last 6 months.
- Presence of blindness or uncorrected visual acuity difficulties.
- The use of psychotropic medications is not allowed.
- The use of other drugs is not allowed except those commonly used (for example: ibuprofen, paracetamol ...) and medical prescription (antibiotics).
- Do not initiate, abandon or change types of therapy or medication.

6.3 Lifestyle and Concomitant Treatments Considerations

Participants should have withdrawaled medication for 3 days prior to each Visit (Week 1, Visit 1 or Week 14-15, Visit 2). If this is not the case, the evaluator has to consider if the assessment procedure is compromised; and if so, he has to postpone it (Visit 1a or Visit 2a).

Concomitant Medication and Treatments:

No initiation, abandonment or substantial modification in pharmacological ADHD treatments shall be allowed at time of screening stage and/or during treatment period. For stimulant medication which is considered in *Inclusion criteria*, legal guardians will be asked for participant to withdrawal medication intake for 3 days prior to Visits (pre-treatment and post-intervention assessments).

Regular use of other drugs and or chronic pharmacological treatments are not allowed. The exceptions are common medication (such as ibuprofen) and medical prescribed medication for non-chronic treatment of minor medical conditions (such as antibiotics). Short-term use of medication for minor conditions (such

as allergies treatments) have to be reported to research staff. PI and/or research staff shall consider case-by-case exceptions.

Regarding with behavioural therapies, initiation is not allowed since the 4th week prior to pre-treatment assessment (Visit 1). Therapies which have been initiated for more than 4 weeks prior to Visit 1 are allowed if, in consideration of PI and/or research staff, engagement is enough to prevent substantial changes or abandonments during study procedures.

In general terms, initiation, abandonment or substantial modification of behavioural or pharmacological therapies between screening and pre-treatment assessment and/or during the three-month treatment period. Changes in current therapies (i.e Pharmacological doses) should be reported to the researcher staff. PI, alongside researcher staff, shall consider if the change is substantial enough.

6.4 Screen failures

Participants whose legal guardian/s agrees with participation but does not meet eligibility criteria will be considered as screen failures. Screen failures may occur in the following stages of the study procedures:

1. **Prior to Visit 1:** First, during study information and first screening stage, some criteria which are checked by information questionnaire may result in participant's exclusion. If that is the case, no appointment for Visit 1 (final screening and pre-intervention assessment) will be setted. Screen failures in this stage will not be compensated.
2. **After Visit 1 and prior to randomization.** If screen failures are produced in this stage, excluded participants will receive SINCROLAB intervention out of study procedures, in compensation for possible inconveniences. These screen failures have not been yet randomized, so they will not be considered as intervention dropouts.
3. **After randomization and for the rest of study procedures.** Any screen failure which is produced after randomization, due to, for example, concomitant treatment substantial changes.

7. Recruitment Procedure

7.1 Methods of Enrollment

The recruitment of the sample will be done through the principal investigators. The recruitment method will be carried out by telephone with accredited centers and/or professionals as a health or educational center by the Community of Madrid. The contacted institutions are private or arranged and the order of contact is alphabetical.

The first contact will be maintained with the therapists or heads of orientation of each center. In a first initial call, the object of the study will be explained. If they are interested, Participant Information Sheet (see Annex II) will be sent to the children's legal guardians who may be able to participate in the study (assessment for eligibility). Participant Information Sheet attaches a brief self-report questionnaire for parents/legal guardians, which intends to check for the whole eligibility criteria (see also Annex II). Parents/legal guardians must send this signed questionnaire and this signature is taken as an agreement (prior to informed consent) to record demographic information.

Signed and fulfilled questionnaire must be sent to the email address investigacion@sincrolab.es. Once the e-mail is received, the research staff from Sincrolab Ltd will contact parents/legal guardians to set an appointment in order to carry out the pre-intervention assessment, (always scheduled between 9:00 AM and 13:00 AM. In this first appointment, any doubt will be solved prior to Informed Consent sign.

7.2 Informed Consent

In the first face-to-face visit (pre-intervention assessment; Visit 1, Week 1), a Sincrolab researcher will inform participant and their legal guardians about all aspects of the study, including the existence of an Experimental group and Control (whose allocation will be revealed after post-intervention assessment).

They will be also informed that, if they have been allocated in Control group, participant will receive a period of three months (equal to Experimental intervention) for the *Sincrolab's* free use.

Every legal guardian must sign an informed consent prior to any type of activity developed within the study which involves direct contact with children.

7.3 Registration Method

Each participant, after participation signature (prior to informed consent), will receive a number in order of arrival, beginning in 01.

All information will be coded with this number. If eligibility criteria are complied, allocation to Experimental or Control will be performed. Likewise, a digital folder with this coding will be created to house the information and data collected from the assessment protocol (neuropsychological and neurophysiological).

7.2 Strategies for Recruitment and Retention

Material for recruitment will be only the Patient Information Sheet (Annex II).

8. Randomization and Blinding

8.1 Randomization and Intervention allocation

The Intervention allocation (Experimental or Control) will be performed following a simple randomization process, with a 1:1 ratio and an allocation probability of 0.50. Participants will be allocated according with their registration number, starting with the Experimental group, as it follows: 01-experimental, 02-control, 03-experimental (…), etc.

No procedure will be followed to adjust or match the proportion of participants with and without medication, neither with nor without complementary behavioral treatment.

Participants allocation will be performed once eligibility criteria are satisfied, following CONSORT 2010 Statement (Schulz, Altman & Moher, 2010).

8.2 Blinding and masking procedure

The study will be single-blinded. The participants will not know in which of the groups they are assigned. It will only be revealed once post-intervention assessment is over. Unmasking will be considered as the end of study procedures.

Right after unmasking, participants which have been allocated in Control group will receive SINCROLAB intervention for a period of equal duration as for Experimental group.

9. Study Intervention

9.1 Study Intervention. Products of the Study

Study Intervention is based on the administration of SINCROLAB cognitive stimulation intervention. SINCROLAB is a software which provides a complete computerized cognitive stimulation therapy, which have to be supervised by a health proffessional. SINCROLAB software has been developed by Sincrolab Ltd.

Participants in Experimental arm will receive SINCROLAB cognitive stimulation intervention, while participants in Control arm will receive a Sham control intervention with the same administration parameters.

All participants will receive a 3-month intervention based on cognitive stimulation therapy. Participants who have been allocated in Experimental group will receive SINCROLAB intervention. Control participants will receive a placebo intervention.

- SINCROLAB intervention is composed by 14 different video-games which have been designed following cognitive rehabilitation literature. SINCROLAB treatment games are based on scientific-supported neuropsychological tasks (such as go/no-go task, n-back task, etc). SINCROLAB intervention uses an Artificial Intelligence engine which adjusts the difficulty level of each task according with participant's cognitive performance on previous intervention sessions.
- Sham control is constituted by three ludic videogames from open-access *Kongregate* computer website. These videogames were Knightmare Tower, Bloons Super Monkey and Super Staker 2. Knightmare Tower is a runner-like videogame in which the player has to ascend to the top of a tower while avoiding enemies and traps. Bloons Super Monkey is a videogame, similar to the classic Space Invaders, in which the player has to defeat enemies and obstacles by moving left or right. Last, Super Stacker 2 is a puzzle-like videogame in which the player has to locate a certain number of geometrical pieces in order to keep them balanced. These videogames are not specifically designed in order to improve cognitive performance, following Mishra, Anguera and Gazzaley's (2016) criteria. These three videogames have been chosen by Sincrolab research staff. *Kongregate* platform has been chosen because of two main reason: it's open-access and it allows to check if users have played the previous day.

The administration and dosing are identical for both intervention arms (Experimental and Control).

9.2 Administration and Dosing

All participants, either Experimental or Control, will be instructed for an equal way of administration and dosing.

Administration: SINCROLAB software is hosted in a tablet/smartphone application which is available for both Apple and Android devices; while Kongregate access (Sham control) is performed though computer or laptops. Experimental participants (under legal guardians supervision) have to download the *Sincrolab Kids* application, following the instruction manual which will be provided to legal guardian after Visit 1.

For both intervention arms, instruction manual/document will contain intervention posology and dosing:

- Three 15-minutes-sessions per week for 12 weeks.
- Intervention sessions shall be performed in a quiet environment, with minimum distractions.
- Legal guardians shall not help or interrupt participant during intervention session (gameplay). They will be only allowed to help for task-instruction reading. It is imperative that legal guardians do not perform any intervention session, so this statement will be included.

Dosing: Each participant will have to perform one 15-minute session per day of their randomly assigned intervention (SINCROLAB intervention or Sham control), 3 days per week for 12 weeks (3 months). The total amount of intervention sessions is 36 (100% of intervention sessions per protocol).

10. Sample Size Justification

A priori decision on sample size was made based on previous literature in ADHD pharmacological treatment with methylphenidate on Commission score from Continuous Performance Test (Losier, McGrath & Klein, 1996), which is our main outcome measure.

Sample size was estimated in order to detect a standardized mean difference of 0.64 SD in main outcome measure, with significance level of $\alpha = 0.05$ and power of 0.8 ($1 - \beta = 0.8$). This standardized mean difference is the meta-analytic effect of pharmacological ADHD treatment with methylphenidate on infant ADHD (Losier, McGrath & Klein, 1996).

Calculation procedure follows sample size estimation for a two-tailed, two-samples mean difference with a correction factor for repeated measures (Ecuation 1) (Twisk, 2006, 2019). Setting these parameters, total sample size required is $N = 56$ ($n_i = 28$).

$$N_{EXP} = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \cdot \sigma^2 \cdot (r+1) \cdot [1 + (T-1) \cdot \rho]}{d^2 \cdot r \cdot T}$$

Where r is the ratio between experimental and control samples (which is equal to 1 in this study), ρ is intra-class correlation coefficient within measures (constrained to 0.50) and T is the number of repeated measures (2, in this case).

Setting these parameters, total sample size required is $N = 56$ ($n_i = 28$).

Protocol amendment in version 1.2: The last enrolled participant ended study procedures in February 2020. At this time, 40 participants had been recruited and 29 comprised with protocol requirements. COVID-19 crisis and consequences in Spain (since March 2020), Sponsor and PI decided to stop the sample recruitment due to the impossibility to assure protocol compliance for MEG and neuropsychological assessments in 2020 and Q1 2021.

Therefore, assuming the exploratory nature of this pilot randomized trial, it was decided to apply the Statistical Analysis Plan on the sample which was recruited from October 2017 until February 2020. Sample sizes of between 10-15 subjects per condition are well-supported in similar literature (Westerberg,

et al, 2007, Castellanos, et al, 2010, Looi, et al, 2016, Nyquist, Lappin, Zhang, Tadin, 2016; Anguera, Gunning & Arean, 2017).

11. Outcome Measures

11.1 Outcome Measures Obtention

Outcome Measurement will be performed at different study stages. Outcomes related with primary and secondary objectives will be obtained from pre-intervention and post-intervention assessments. The following assessment protocol will be administered:

- ***Neurophysiological measurement protocol***. Magnetoencephalography records were collected in order to estimate functional connectivity maps and indexes. Each subject's MEG record consisted in three phases, in the following order:
    1. Record during the execution of an oddball task. Oddball task is an experimental paradigm in which participant have to watch intermittent images of dogs and cats. Participant must answer if the shown image is a cat or a dog. Each stimulus image presentation goes with a whistle nor an odd sound. Oddball task record lasts for, approximately, 30 minutes. This task is segmented in four equal 7-minutes-blocks. At the end of each block, participant have the choice to rest for a few seconds.
    2. Resting state phase with eyes opened.
    3. Resting state phase with eyes closed.
- ***Neuropsychological measurement protocol***. Conductual and cognitive measures were taken by these neuropsychological standardised tests:
    - Conner's Continuous Performance Test (CPT-III) (Conners, 2014). Dectectability index (d'), Omissions rate (O), Commisions rate (C), Perseverations rate (P), Hit Reaction Time (HRT), Standard Deviation of HRT (SDHRT), Variability score (Var) and HRT slope by inter-stimuli Interval (HRTISI) will be taken from CPT-III.
    - Digit Span Test, Digit-Symbol from Wechsler Intelligence Scale for Children-IV (WISC-IV) (Weschler, 2008) and Corsi Block Test from Wechsler Non-Verbal Scale (WNV) (Wechsler & Naglieri, 2006). *Direct, Inverse, Direct Span and Inverse Span* scores will be taken from these tests.
    - Digit-Symbol Coding Test and Symbol Search Test from Wechsler Intelligence Scale for Children-IV (WISC-IV) (Wechsler, 2008). From these tests, Number of correct answers, Number of errors and Number of total processed stimuli will be taken.
    - Inhibition Test from Developmental Neuropsychological Assessment-II (NEPSY-II). Time, Total errors and Number of self-corrected errors will be taken as measures from this test.

- Card Classification Test from Developmental Neuropsychological Assessment-II (NEPSY-II) (Korkman, Kirk & Kemp, 2007). Number of correct answers and repetition, *other classification* and total errors will be taken.
- Auditory Attention Test & Cognitive Flexibility Test from Developmental Neuropsychological Assessment-II (NEPSY-II) (Korkman, Kirk & Kemp, 2007). Number of correct answers, commission, omission and perseveration errors will be taken from these tests.
- Verbal Fluency Test from Developmental Neuropsychological Assessment-II (NEPSY-II) (Korkman, Kirk & Kemp, 2007). Number of correct answers from each condition (Semantic and Phonological) will be taken.
- Parent's Behavior Rating Inventory of Executive Functions (BRIEF) (Gioia, Isquith, Guy & Kenworthy, 2000). Direct score from each subscale will be taken.
- Parent's Evaluation of Attention Deficit and Hyperactivity Disorder (EDAH) (Farré & Narbona, 2013). Direct score from each subscale will be taken.

During at-home intervention period, the following variables will be recorded, in order to accomplish with exploratory objectives:

- Adverse events' recording.
- Compliance with intervention protocol: Number of intervention sessions per week and Days in which sessions are performed
- Potential medication and other treatment changes. This information will also be collected from eligibility data (medication posology and dosage).

Outcome measures are summarized in **Table 3.**

Table 3. Outcome Measures at each study stage

Outcome Measure	**Enrollment and screening**	**Pre-intervention assessment**	**At-home intervention period**	**Post-intervention assessment**
	Start point	Week 0	Weeks 1-12	Week 13-14
General information				
Participant sheet	X			

Demografic & contact information	X			
Informed consent and assent		X		
Neurophysiological measurement				
MEG recording		X		X
Neuropsychological measurement				
Parent's BRIEF		X		X
Parent's EDAH		X		X
Conner's Continuous Performance Test-III (CPT-III)		X		X
Digit Span Test (WISC-IV)		X		X
Digit-Symbol Test (WISC-IV)		X		X
Symbol-Search Test (WISC-IV)		X		X
Corsi Cubes Test (WNV)		X		X
Inhibition Test (NEPSY-II)		X		X
Card Classification Test (NEPSY-II)		X		X
Auditory Attention Test (NEPSY-II)		X		X
Cognitive Flexibility Test (NEPSY-II)		X		X
Verbal Fluency Test (NEPSY-II)		X		X
At home intervention monitoring				
Number of trainings per week			X	
Days of training			X	

11.2 Main Outcome Measure

Protocol amendment in version 1.1: The main outcome measure of this study is the variances difference found in the Commission score from Conners' Continuous Performance Test (CPT-III) between both groups (Conners, 2014). Inhibitory control (Commissions in CPT-III) was used as the main outcome due to its used as efficacy treatment´s measure in several previous studies about the methylphenidate effect in ADHD (Losier, McGrath & Klein, 1996).

11.3 Secondary Outcome Measures

Protocol amendment in version 1.1: Secondary outcome measures are as follow:

- From CPT-III (Conners, 2014), scores of omissions and perseveration errors, detectability index, hit reaction time (HRT), standard deviation of HRT (HRT SD), response variability and HRT Inter-Stimulus Interval (ISI) change (HRT-ISI).
- From Inhibition Test (Korkman, Kirk & Kemp, 2007), scores of time, total errors and self-corrected errors.
- From Card Classification Test (Korkman, Kirk & Kemp, 2007), scores of correct answers, repeated errors, *other classification* errors and total errors.
- From Verbal Fluency Test (Korkman, Kirk & Kemp, 2007), scores of correct answers in each condition (Semantic and Phonological).
- From Auditory Attention Test and Flexibility Test (Korkman, Kirk & Kemp, 2007), scores of correct answers and commission, omission and inhibition errors.
- From Digit Span Test, scores of total direct digits, direct digit span, total inverse digits and inverse digit span were taken.
- From Digit-Symbol Coding Test, scores of correct answers, errors and total processed stimuli were taken.
- From Symbol Search Test, also scores of correct answers, errors and total processed stimuli were taken.
- From Corsi Block Tapping Test, scores of total direct, direct span, total inverse and inverse span were taken.
- From Parents' version of BRIEF test, scores of Inhibition, Shifting, Emotional Control, Initiating, Working Memory, Planning, Organization of Materials and Monitoring were computed and taken.
- EDAH questionnaire (*Evaluación del Déficit de Atención e Hiperactividad*) [50]. From EDAH scale, scores of Hyperactivity, Attention Deficit, Hiperactivity + Attention Disorder and Behavioural Disorder were computed and taken.
- From magnetoencephalography recordings, functional connectivity between regions of interests (ROIs) estimated through the calculation of the L index for generalized connectivity between the

MEG signals between each ROI. This index calculation will be programmed using García-Prieto, Bajo and Pereda [60] algorithms for each time period previously reviewed and considered not to have noise. This connectivity index, which requires the previous reconstruction of the state spaces through the time series of the system to be studied, makes it possible to establish the degree of dependence between systems and the directionality of the system [60]. Finally, the arithmetic mean of the connectivity of all the time periods will be taken and a single connectivity matrix will be defined (232x232) for each subject and condition.

11.4 Exploratory Outcome Measures

During at-home intervention period, adverse events, number of intervention sessions per week, days of intervention and potential changes in medication and/or other therapies will be collected. These variables will be used in order to accomplish with exploratory objectives.

Potential adverse events will be monitored and recorded during intervention period.

Pre-post individual changes in neuropsychological outcome measures will be calculated, as well as individual functional connectivity changes in order to perform the analysis for the third exploratory objective.

End of protocol amendments in version 1.1.

12. Abandonments of the Study

Participants who leave the study for reasons unrelated to those defined in the research protocol may do so without having to justify leaving the study. However, the causes that are believed that may occur, are the following:

- Impossibility to comply with the intervention protocol due to time availability.
- The occurrence of an adverse event in the family environment.
- The occurrence of adverse events in the participant.

When the intention to abandon participation in the study is notified, a call will be made to the minor's legal guardian to try to comply with it. If this is not possible, we will try to receive feedback on the object of leaving the study.

13. Data Management

13.1 General Protocol of Data Collection and Storage

The study will collect data in the pre-intervention phase (week 0), intervention phase (week 1-12), post-Intervention phase (week 13-14).

Data derived from the neuropsychological assessment protocol will be stored in physical individual folders with the corresponding numerical code. Likewise, individual digital folders will be created to store neuropsychological data for each participant. Information related with intervention allocation (SINCROLAB or Sham control) will be stored separately for each participant's code number in an independent digital file.

Neurophysiological data (MEG records) will be collected using a Vectorview MEG system (Elekta AB, Stockholm, Sweden) with 306 channels (102 magnetometers and 204 gradiometers) placed in a magnetically shielded room (Vacuum Schmelze GmbH, Hanau, Germany) in the Center for Biomedical Technology's Cognitive (CTB), Computational and Neuroscience Laboratory (LNCyC), at the Polytechnic University of Madrid, Spain (UPM). Head shape was digitized found using a Fastrak 3D digitizer (Polhemus, Colchester, Vermont). Three fiducial landmarks were acquired (nasion, left and right pre-auricular points) and several at least 300 points on the surface of the scalp of each participant. Four head position indicator (HPI) coils were also placed on the scalp, two on the mastoids and two on the forehead. The position of the HPI coils was also acquired using the Fastrak device, and continuous estimation of the head position during recording was used to track head movements. A vertical electrooculogram on of the left eye was used to capture blinking and eye movement. Two additional electrodes were used to measure cardiac activity. The MEG data will be acquired at a 1000 Hz sampling frequency using an online bandpass anti-aliasing filter from 0.1 to 330 Hz. Data derived from these neurophysiological assessments (MEG records) will be stored in digital format with a folder labeled with its identifier for each of the records. These records will be stored on a hard drive independent of the CTB and will later be transferred to Sincrolab S.L for analysis, leaving a backup stored on the hard drive of the CTB. All this information will be available in the supplementary material with the exception of the data that would allow access or recognize one of our participants. Likewise, AI algorithms will not be provided, for reasons of security and copyright.

13.2 Required Data at each Study Stage

13.2.1 Enrollment and screening for eligibility

Information regarding to eligibility criteria and demographic information of the participant will be collected and stored. Additional information about the legal guardians of the participants will be collected

- E-mail.
- Phone number.
- Questionnaire attached to Participant Information Sheet.
- Demographic information of the participant: age, sex, manual dominance, years since diagnosis, medication and dosage, complementary psychological treatments, reference center from which he is contacted.

13.2.2 Pre-intervention assessment (Visit 1, Week 1)

The following data will be collected in this stage:

- Data derived from neuropsychological assessment protocol.
- Data derived from neurophysiological assessment protocol (MEG record).

13.2.3 At-home intervention period (Weeks 2-13)

The following data will be collected in this stage:

- Adverse events and other unanticipated problems
- Compliance with intervention protocol: number of intervention sessions and days in which sessions have been performed. Compliance information with SINCROLAB tool will be stored in Sincrolab's database. Information related with the use of Kongregate platform will not be accessible due to be a platform alien to the organization itself.

13.2.4 Post-intervention assessment (Visit 2, Week 14-15)

The following data will be collected in this stage:

- Data derived from neuropsychological assessment protocol.
- Data derived from neurophysiological assessment protocol (MEG record).

14. Statistical Analysis Plan

14.1 Study Population

Statistical analysis will follow a per-protocol approach, so any participant who has abandoned the study flow before its ending will not be considered as missing data.

14.2 Analysis of main outcome measure

The main objective of the study is to assess the efficacy of the neuropsychological rehabilitation tool *Sincrolab* in the rehabilitation of inhibitory control in paediatric ADHD of combined presentation, measured by Commission score from CPT-III. This study will be carried out to detect differences in cognitive performance among participants with combined presentation ADHD who use the Sincrolab Kids platform and those who use the Kongregate platform.

First of all, descriptive analysis will be performed with primary measurements and main composite scores, in order to check statistical assumptions such as normal distribution adjustment.

Next, each composite score will be entered, as dependent variable, in a mixed-effects model analysis, including as independent variables Intervention, Moment and interaction. Slope and intercept will be checked so models can be adjusted. Due to sample size, robust restricted maximum likelihood (REML) will be chosen as estimation method, instead of maximum likelihood (ML). Generalised least squares (GLS) and generalized estimating equations (GEEglm) methods will be, subsequently, chosen if REML models do not converge.

Stepwise method will be used for demographic variables in each mixed model as method applied to explicative models. *Intervention* factor will be taken as explicative variable. Bayesian Information Criterion (BIC) will be used to compare models. Model diagnosis will be performed through Pearson standardized residuals.

Mixed model's result for each variable which composes the scores will be also reported. As only one comparison it is intended to be performed for analysis of primary endpoint (one dependent variable), no correction for multiplicity will be applied in this analysis.

Respondent analysis will be performed in order to study the proportion of participants who achieved the clinically effect of 0.64 (standardized pre-post mean difference), comparing both intervention arms (Experimental and Control).

14.3 Analysis of secondary outcome measures

Neuropsychological measures

For the neuropsychological secondary outcome measures, the same procedure as primary objective analysis will be followed. Neuropsychological secondary outcome measures comprise the first secondary objective. In cases of no normality, the non-parametric Wilcoxon Sign test will be applied to pre and post measures, separately, for each.

As multiple variables (although composites) will be compared, a correction procedure for multiplicity will be included. Multiple testing may lead to an inflation of the overall Type I error rate ($\alpha = 0.05$). Therefore, a multiplicity correction method will be applied: the *false discovery rate* method (FDR; Benjamini & Hochberg, 1995). As this pilot randomized trial is intended for exploratory feasibility purposes, uncorrected p-values will be used; although corrected p-values (q-values) will be also reported for a better interpretation.

For measures derived from BRIEF and EDAH questionnaire, individual scores will be standardized according with correction manuals. Standardized paired samples t-test between pre and post individual scores will be estimated for each intervention arm.

Neurophysiological measures. MEG data

MEG data shall be pre-processed prior to connectivity calculations. MEG signal pre-processing procedure is as follows:

1. First, continuous MEG signals will be inspected visually by a researcher experienced in MEG, rejecting noisy channels.
2. Using MaxFilter 2.2 software (Elekta Neuromag), each recording will be processed using *Temporal Space Signal Separation (tSSS)*, in order to reduce noise from external sources (Tesche et al., 1995; Uusitalo & Ilmoniemi, 1997; Taulu & Hari, 2009) and to diminish the cardiac artefact in all the subjects.
3. Afterwards, the MEG signal will be filtered using a 1.001 order linear-phase band-pass filter applied in both time directions, equivalent to a no-pass filter with cutoff frequencies at 1 Hz and 45 Hz.
4. A second visual inspection was made, enabling selection of only those time segments with no noise for later analysis. Within these time segments with no noise, the MEG signal was divided into 1-second windows favouring the existence of repetition by subject and eliminating possible variances in later connectivity calculations.

Once MEG data is pre-processed, sources shall be calculated in order to define ROIs. Sources will be calculated using the FieldTrip tool (http://fieldtrip.fcdonders.nl/) in combination with in-house MATLAB © code (The Mathworks, Natick, MA). Source calculation procedure is as follows:

1. Initially, the source model is made from a template provided within the Brainnetome atlas tool (Fan et al., 2016).
2. Once the brain region is segmented using FieldTrip, a uniform network is constructed with 2,700 sources inside the Brainnetome brain, distributed with a separation of 1 cm between each source. Subsequently, the Brainnetome atlas was adapted, so that the digitized points of each subject's

head by the Fastrak acquirer were superimposed on the head of the Brainnetome atlas. This way, not only it is possible to adapt the particularities of each subject but, at the same time, the direct comparison of results between subjects, since all the sources of each subject have a well-defined common origin in the Brainnetome atlas. Additionally, sources are calculated using the Linearly Constrained Minimum Variance ("LCMV") algorithm (Van Veen & Buckley, 1988).

3. Finally, taking advantage of the fact that the Brainnetome atlas presents regions of interest (ROIs) defined, the 2,700 sources were divided into 232 ROIs. Thus, the MEG activity of each ROI was isolated through the arithmetic mean of the MEG activity of each source belonging to the same region. As a result, 232 temporal series were defined covering the totality of both hemispheres of each subject, having been each source previously adapted to the profile of each subject.

Functional connectivity between regions of interests (ROIs) is estimated through the calculation of the L index for generalized connectivity between the MEG signals between each ROI (Chicharro & Andrzejak, 2009). This index calculation will be programmed using García-Prieto, Bajo and Pereda (García-Prieto, Bajo & Pereda, 2017) algorithms for each time period previously reviewed and considered not to have noise. This connectivity index, which requires the previous reconstruction of the state spaces through the time series of the system to be studied, makes it possible to establish the degree of dependence between systems and the directionality of the system (García-Prieto, Bajo & Pereda, 2017). Finally, the arithmetic mean of the connectivity of all the time periods will be taken and a single connectivity matrix will be defined (232x232) for each subject and condition.

Single connectivity matrices for each subject and condition will be used as secondary outcome measures for the analysis of the second secondary objective. For the analyses derived from the connectivity calculations, the Wilcoxon Sign nonparametric test will be used on connectivity in each of the 53.592 links (232x232). The connectivity between each ROI with itself will be not taken into consideration in the comparisons as they are always for each subject and condition. Multiple comparison correction will be done between the two groups based on 1.000 permutations of subjects.

14.4 Exploratory analysis

Descriptive analysis for adverse events and compliance with intervention protocol will be performed for the first and second exploratory objectives. Dropouts analysis will be also performed.

For the third exploratory objective, a Pearson's correlation analysis will be performed in order to find the relationships between changes in connectivity measurements and changes in scores on the neuropsychological batteries. The false positives associated with the problem of multiple comparisons were controlled by the False Discovery Rate method (FDR; Benjamini & Hoechberg, 1995), with a value of q = 0.05. The correlation analysis was applied to the regions which in the previous analysis had shown

significant differences between pre-intervention and post-intervention and the scores of all the variables that made up the Neuropsychological assessment protocol.

14.5 Missing Data Handling

Missing data patterns will be analyzed in order to establish the mechanism in which these data may have been missed (*Missing Completely At Random or MCAR, Missing At Random or MAR and Missing Not At Random or MNAR*).

Parameter matrix estimated with robust restricted maximum likelihood (REML) is robust and unbiased in the presence of missing data. So REML will be the method to deal with MCAR/MNAR missing values. If any model's parameter matrix is estimated with other method or with non-parametric techniques, multiple imputation by chained equations (MICE) procedure will be applied in order to deal with potential missing data.

14.6 Baseline Descriptive Analysis

Demographics and clinical characteristics (such as age, sex and medication) will be analysed between Intervention arms (Experimental or Control). Randomization has the objective of no differentiation between groups at baseline. So then, these variables will be analysed between groups at baseline with independent *t-tests* for cuantitative variables and with Pearson's χ^2 for categorical ones. Alfa-level (α) will be setted in 0.05 and no correction for multiplicity will be performed in baseline descriptive analysis.

15. Intervention Safety

Any adverse medical effects with or without a direct cause of intervention must be documented after the reception of the Informed Consent. Researchers should ensure that all these effects are properly recorded and ensure that these effects are not stable over time. If there is any medical emergency, it must be answered in an appropriate manner to attend the participant.

Safety Assessment is defined as the procedure with the objective of recording adverse events. Participants' legal guardian will report at each study site any adverse event which occurs during Intervention phase. A researcher from each study site will fulfill the adverse events' record sheet (Annex III), with the supervision of the PI.

16. Quality Control

16.1 Key Roles and Study Governance

The study is oversighted by the following roles:

Principal Investigator	Sponsor
Fernando Maestú Unturbe, PhD	*Ignacio de Ramón Burgos, MSc*
Complutense University of Madrid and Polytechnic University of Madrid.	*Sincrolab Ltd.*
Centre for Biomedical Technology *Polytechnic University of Madrid (UPM)* *Campus Montegancedo* *28223 Pozuelo de Alarcón* *Madrid, Spain*	*23, Irun Street* *28008 Madrid* *Madrid, Spain*
+ 34 (0)91 336 4632	*+ 34 (0)630364425*
fernando.maestu@ctb.upm.es	nacho@sincrolab.es

The study is governed by the following guidelines, principles and Boards:

- Declaration of Helsinki (2013).
- International Council on Harmonisation - Good Clinical Practice (ICH-GCP) Guideline *(ICH-E6-R2)*.
- Ethics Committee Board from Hospital Clínico San Carlos, from Madrid (Spain).

Although Sponsor is responsible, Study Monitor will overview study activities related with safety oversight and quality of the data.

15.2 Study Suspension and/or Stopping

The whole study protocol may be temporarily suspended or definitively stopped prior to primary endpoint achievement if there are sufficient reasonable causes.

The procedure for temporal study suspension or premature stopping will contain the following actions:

- Suspension decision for the whole study will be made up by Sponsor and PI.
- Ethics Committee Board may also request request for temporal or permanent suspension.
- Every decision of suspension shall be made up in agreement with all involved parties (Sponsor, PI).
- In case of suspension, written notification must be provided by the Sponsor to legal guardians whose children are currently in any stage of study procedures and to research staff. This notification must document the reason or reasons why study has been suspended and if this suspension is temporal or definitive.
- The Sponsor shall inform the Ethics Committee about the reasons of suspension or stopping.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Unacceptable insufficient compliance of research staff to the present study protocol (for example, significant protocol deviations).
- Severe technical issues related with SINCROLAB software which affect to all participants (for example, a server crash).
- Cases of force majeure, external to the study context.

Protocol amendment in version 1.2: Study was early stopped due to COVID-19 crisis and consequences. Sponsor and PI are not able to assure compliance with the current protocol regarding with in-person Visits 1 and 2 during the rest of 2020 and Q1 2021.

15.3 Safety Oversight

Sponsor will take the responsibilities for safety oversight. Due to the low risks related with the use of SINCROLAB software, no independent Safety Monitoring Committee will be established. In relation with safety oversight, Study Monitor will be in charge of the following roles (under the responsibility of Sponsor):

- Periodical checking and validation of the adverse events' record sheets.
- Communication with the Ethics Committee Board about adverse events which may be causes of stopping the trial.
- Communication with other study sites about unanticipated problems which may happen at one study site.
- Anticipation and, if it is not possible, quick resolution of potential technical issues with the software.

15.4 Data Quality

Sponsor, PI as well as the research staff will review the progress of the study to ensure the safety and quality of the registration of all data, under the responsibility of Sponsor. On a weekly basis, a Sincrolab researcher will review reports, MEG records and documents provided to patients and family members. In addition, weekly periodic calls can be made to the relatives of the patients to monitor the evolution of the study. Any incident is recorded in the weekly incident report.

All the participants will provide a diagnosis ruled by a medical doctor, which shall be verified by the questionnaires of executive functions and symptoms of ADHD (Annexes VII & VIII). In addition, these doctors will have to evaluate the clinical adequation of not to change the dose of medication during the intervention period. Those participants who do not correctly fill in their medical records, send their diagnosis or fill out their questionnaires properly will not participate in the trial.

During the MEG registration, patients were continuously monitored by video and audio. Any incident during the registration of MEG is reflected in the observations of the Lab's daily notebook and if that were the case, the MEG record will be stopped so that the subject could leave the register immediately if he wished.

Any substantial change to the protocol must be formally submitted in writing to Sincrolab and the PI. All results will be monitored by PI and by Sincrolab. Given the low risks and the size of the trial, there is no need to establish an Internal Security Committee.

17. Participants' Rights and Confidentiality

Any participant may leave the study at any time during the study under their own free will. In addition, any participant may leave the study if they do not meet the requirements of the inclusion criteria (*Section 6*) and *Section 12*.

All participants of the Control group (Sham control intervention; without *Sincrolab*) have the right to perform the intervention with Sincrolab after the intervention period, under the same conditions as the Experimental group.

This protocol may be modified by formal writing to Sincrolab or the IP. Once the formal document has been received, the PI and Sincrolab will decide on the partial or total modification of the protocol. The resolution must be in writing and sent to the CEIC of the San Carlos Clinical Hospital of Madrid. The study may be stopped at any time by Sincrolab, the PI or the Ethics Committee.

All reports, assessments and questionnaires in paper format will be stored in locked cabinets to which only authorized staff access by the PI or by Sincrolab will have access. MEG records will be stored on hard

drives or computers with strong passwords and will only have personal access authorized by the PI or by Sincrolab. No name or any other identifier will appear in evaluation reports or MEG records. ID will be used to identify each participant. All records will be available to any regulatory institution. All the staff is trained in ensuring the maximum confidentiality of the participants.

18. Publication Policy

PI and Sincrolab will coordinate the dissemination of data from this study, and they will review the data for validity and subsequent publication. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Publication of this proof-of-concept randomized trial will be splitted in two communications: one for neuropsychological results (analysis derived from neuropsychological main and secondary measures) and other for MEG results.

19. Funding

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21. Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
1.0	05/2015		Version 1.0 was approved by Ethics Committee Board.
1.1	02/2019	Main and secondary outcomes were defined. Recruitment process was going on.	Outcomes were reorganized in main and secondary due to requirements of study pre-registration.
1.2	04/2020	Early permanent stopping due to COVID-19 crisis in Spain and posterior consequences.	Due to COVID-19 crisis and consequences, it is not possible to comply with the whole protocol (MEG records and assessments) in 2020 and Q1 2021.

SUMMARY OF CHANGES

Version 1.1

1) Measures were reorganized in main and secondary outcome measures. Commission score from CPT-III were set as main outcome measure, due to its importance in the theoretical framework. No new measures were added from Version 1.0 to Version 1.1.

2) Objectives and Analysis for primary and secondary objectives were also modified according with this new organization of main and secondary.

Version 1.2

1) Sponsor and PI decided to stop the study permanently due to COVID-19 crisis, which started in March 2020 in Spain. The current protocol does not fit within the new social distancing requirements. MEG recording implies physical contact and neuropsychological assessments are not prepared for 2 meters of social distance. Required changes in assessment protocol would mean significant deviations from the original protocol. In addition, we estimate that this social distancing rules will last until Q1 2021 in Spain.

2) Changes in Sample Size Justification were applied due to early termination of the study.

Annexes

Annex I. Informed Consent Model (Spanish version)

DECLARACIÓN DE CONSENTIMIENTO INFORMADO

D./Dª_____con DNI_____, en la condición de padre, madre, tutor o representante legal de_____con DNI_____manifiesto que he sido informado/a sobre todos los procedimientos que se aplicarán en este estudio. Asimismo, he tenido la oportunidad de efectuar preguntas acerca del mismo y he obtenido respuestas satisfactorias.

Declaro que he leído la hoja informativa que me ha sido entregada. (Adjuntada a este documento)

Declaro que he tenido la oportunidad de realizar preguntas sobre el estudio, y he recibido al respecto respuestas satisfactorias.

Declaro que he recibido suficiente información en relación con el estudio.

Entiendo que mi participación, o en su caso, la de mi representado es voluntaria, pudiendo abandonarse el estudio en cualquier momento sin dar explicaciones y sin que ello tenga ninguna consecuencia.

En cumplimiento de lo establecido en la Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal, se me ha informado de que mis datos serán incluidos en un fichero titularidad de Sincrolab, S.L. dichos datos serán tratados y custodiados con respeto a mi intimidad y a la vigente normativa de protección de datos, y exclusivamente con la finalidad de participar en la investigación objeto del presente consentimiento informado. Se me ha informado que puedo ejercer mis derechos de acceso, rectificación, cancelación y oposición dirigiéndose por escrito a Sincrolab, S.L. en calle Padre Jesús Ordoñez, 5 6C, 28002 Madrid.

Los datos identificativos serán destruidos una vez dejen de ser necesarios para la finalidad para la que han sido recabados.

Información general

La Magnetoencefalografía (MEG) permite el estudio de la actividad cerebral a partir de los campos magnéticos que de forma natural genera el cerebro. Este método es totalmente inofensivo y no ocasiona ningún efecto secundario.

Objeto de estudio

A partir de los datos obtenidos mediante la MEG podemos saber más sobre el funcionamiento del cerebro. El estudio en el que va a participar se realiza con fines de investigación y de él no se derivan consecuencias para el diagnóstico y/o tratamiento.Su participación es totalmente voluntaria y podrá abandonar el estudio en el momento que lo desee.

Asimismo, los datos obtenidos serán tratados con absoluta confidencialidad.

Procedimiento de estudio

La MEG se realiza en una habitación aislada de los campos magnéticos externos, en la que permanecerá sentado y solo mientras dure el estudio. La actividad magnética de su cerebro será registrada por medio de un sensor que cubrirá su cabeza a modo de casco. En todo momento permanecerá en contacto con el investigador responsable del estudio por medio de un sistema de cámaras y micrófonos que permiten la comunicación.

De forma previa se perfilará el contorno de su cabeza con un lápiz digital se le colocarán algunos cables que servirán para conocer la localización de su cabeza dentro del sensor.

Durante el registro deberá estar lo más tranquilo posible y permanecer relajado sin realizar movimientos. La duración de la prueba es de aproximadamente una hora, variando en función del tipo de estudio a realizar.

Criterios de exclusión.

Para garantizar unos resultados adecuados es necesario:

- No haberse realizado una resonancia magnética (RM) en las 48 horas previas a este estudio. En caso contrario únicamente afectará a la calidad de los datos y en ningún caso a su seguridad.
- Desprenderse de cualquier objeto metálico en las cercanías del aparato de medida.
- Informe al investigador si es portador de un marcapasos cardiaco, prótesis metálicas, prótesis dentales, aparatos de estimulación acústica o cualquiera de los siguientes objetos que pueden interferir un estudio mediante MEG:

marcapasos	DIU - dispositivo intrauterino
prótesis ortopédicas	alambres de embolización
prótesis de oído	neuroestimuladores
prótesis de globo ocular	estimulador de crecimiento óseo
prótesis dental	filtros vasculares
prótesis metálica cardiaca	bomba de infusión de medicamentos
grapas quirúrgicas	esquirla metálica ocular u orbitraria
grapas para aneurismas cerebrales	bala, perdigón, metralla, etc.
suturas metálicas	tatuaje
válvulas de derivación	otras prótesis (vascular, biliar, etc.)
catéteres	

En caso de que no haya comprendido algo o tenga alguna pregunta, solicite información al investigador.

Declaración:

Como persona destinataria de la información declaro que he recibido una copia de dicho documento y que he comprendido adecuadamente la información.

Tomando todo ello en consideración, OTORGO MI CONSENTIMIENTO a que se lleve a cabo el estudio. En_____, a__ de_____de _____

Fdo. (investigador) Fdo. (niño mayor de 14 años) Fdo.D/Dª(padre, madre o tutor)

□ Marque esta casilla si desea ser informado/a de los resultados obtenidos por su hijo/a una vez finalizada la investigación. Esta información sólo podrá ser comunicada durante los tres meses siguientes tras la finalización de la investigación. Pasado este plazo, todos los datos personales serán destruidos.

Si desea obtener más información, puede solicitarla poniéndose en contacto con Sincrolab, S.L. a través del teléfono 630364425 de lunes a viernes de 9:30 a 13:30 y de 16:00 a 20

Annex II. Participant Information Sheet

HOJA INFORMATIVA SOBRE EL ESTUDIO CON *SINCROLAB*

Estimado Sr. /Sra.,

El motivo de la presente carta es invitar a su hijo o hija a participar en un estudio que vamos a llevar a cabo en su centro educativo para validar una herramienta de entrenamiento cognitivo (basado en memoria, atención, planificación, control de los impulsos…) dirigida a incrementar las competencias cerebrales superiores y la excelencia académica.

Con este estudio estamos valorando la capacidad de mejora de las funciones cognitivas de cada niño tras el uso de la herramienta tras un periodo de entrenamiento de 12 semanas de duración, con tres sesiones, de máximo 20 minutos, por semana. El objetivo de esta herramienta es estandarizar el entrenamiento cognitivo para niños con Trastorno por Déficit de Atención e Hiperactividad (TDAH) de subtipo **combinado**.

Se realizarán tres evaluaciones: una previa y dos posteriores al entrenamiento. Al existir un grupo que no realizará el entrenamiento con Sincrolab entre las tres evaluaciones, sino que lo hará con otra aplicación, cualquier alumno que desee llevarlo a cabo podrá tener acceso a este tras la tercera evaluación. La participación y asignación a cada uno de los grupos es **completamente aleatoria** e independiente de la decisión del centro escolar.

La **evaluación previa** consta, por un lado, de una valoración neuropsicológica y, por otro lado, de un registro de magnetoencefalografía. Ambas valoraciones se llevarán a cabo en la misma mañana. La valoración neuropsicológica tendrá una duración máxima de una hora y se evaluarán la memoria, la atención, el funcionamiento ejecutivo, el control inhibitorio, y la memoria de trabajo. El **registro de magnetoencefalografía (MEG)** tendrá una duración aproximada de una hora en total. La MEG es una técnica de neuroimagen no invasiva que permite captar el campo magnético que el cerebro emite de manera natural como consecuencia del flujo de corriente eléctrica generado por las neuronas. Durante el registro, el niño tendrá que llevar a cabo una tarea sencilla.

El período de **entrenamiento** para los grupos a los que va destinado consistirá en 36 sesiones de entrenamiento de 3 tareas diferentes dirigidas a estimular:

1. La memoria operativa o de trabajo.
2. Control inhibitorio y mejora de la impulsividad.
3. Flexibilidad cognitiva y adaptación al cambio de set atencional.

El entrenamiento, que no tiene una duración mayor de 15-20 minutos por sesión, se puede realizar en un dispositivo iPad 2 o superior, o en un dispositivo Android.

Se realizará a todos los niños una **segunda evaluación,** igual a la primera, para valorar las diferencias existentes tras la realización o no de dicho entrenamiento. Y por último se realizará una **tercera evaluación** a los tres meses de haber realizado la segunda con el objetivo de medir la estabilidad de los cambios a largo plazo.

¿Por qué participar?

La participación en este estudio puede arrojar luz sobre nuevas formas de mejorar la capacidad cognitiva de estos niños mediante el uso de nuevas tecnologías que sean más estandarizados, objetivas, eficientes y altamente personalizadas y adaptadas a cada perfil individual y ejecución.

La información obtenida en esta investigación será custodiada bajo las máximas garantías para su confidencialidad y la de su hijo o hija. Los datos sólo se emplearán en el proyecto de investigación y en ningún caso se publicarán de forma que pueda ser identificado individualmente. Toda la información relacionada con el estudio es estrictamente confidencial.

Cada uno de los resultados de las pruebas que realice su hijo recibirá un número y nunca el equipo investigador que lleve a cabo los análisis estadísticos conocerá su identidad. El Investigador coordinador guardará su hoja de Consentimiento firmada en un archivo especial seguro.

En cualquier caso, si su hijo se retira del estudio antes de su finalización, puede solicitar que se eliminen del mismo todos los datos obtenidos sobre él/ella hasta ese momento.

La participación en el estudio es **totalmente voluntaria**. Estaremos muy agradecidos por la participación en el estudio que permitirá valorar la eficacia de este nuevo entrenamiento.

Si decide que su hijo o hija participe, le pedimos que rellene y firme el consentimiento informado y el cuestionario que acompaña a esta carta. Puede volver a enviar la documentación cumplimentada a investigacion@sincrolab.es y nos pondremos en contacto de nuevo para concertar la cita para la evaluación.

Agradeciendo de antemano su colaboración reciba un cordial saludo,

NACHO DE RAMÓN BURGOS
CEO & Co-fundador de Sincrolab S.L.

Si usted tiene cualquier duda sobre el estudio, puede ponerse en contacto con las personas responsables.
Jaime Bouhaben Olmedo (teléfono: 607488521; e-mail: jaimebou96@gmail.com)
Rafael Medina Martín (teléfono: 648489786; e-mail: investigacion@sincrolab.es)
Nacho de Ramón Burgos (teléfono: 630364425; e-mail: nacho@sincrolab.es)

Estimada/o Sra. /Sr.,

Este cuestionario forma parte del estudio de investigación que está llevando a cabo Sincrolab y el centro CTB-UPM. Tiene como objetivo completar la información obtenida a través de las pruebas administradas a su hijo/a, y servirá para la correcta interpretación de los resultados. Es **necesario rellenar todos los campos**. Le recordamos que todos los datos serán tratados de forma confidencial. **Muchas gracias por su colaboración**.

CUESTIONARIO DATOS PERSONALES
Nombre:
Apellidos:
Edad:
Fecha de Nacimiento:
Peso al nacer: (marque una de las dos opciones)
☐ > 2.500 gr. ☐ < 2.500 gr.
Sexo:
Nombre del Padre y de la Madre:
Nacionalidad:
Curso:
¿Ha repetido algún curso? Indique cuál.
Lengua materna/ principal:
¿Es bilingüe?
¿Ha tenido alguna enfermedad grave?
¿Tiene algún diagnóstico anterior?

¿Toma alguna medicación? Indique cuál y qué dosis
¿Presenta dificultades de aprendizaje?

Los datos identificativos serán destruidos una vez dejen de ser necesarios para la finalidad para la que han sido recabados.

Tomando todo ello en consideración, accedo a que se lleve a cabo el estudio en los términos arriba indicados.

En _____, a __ de _____ de _____

Fdo. (Investigador)

Fdo. (Niño mayor de 12 años)

Fdo. /Dª (padre, madre o tutor)

Si desea obtener más información, puede solicitarla poniéndose en contacto con Sincrolab, S.L a través de los teléfonos 607488521 o 648489786, de lunes a viernes de 9:00 a 14:00; o en el correo electrónico investigacion@sincrolab.es.

Annex III. Adverse events' record sheet

<This record sheet is fulfilled by Sincrolab research staff according with legal guardians' communications>

Fecha	**Código**	**Breve descripción del evento**	**Severidad** (Leve = 1, Moderado = 2 y Grave = 3)	**¿Impidió realizar la actividad con normalidad?**

Annex IV. Communication protocol with legal guardians

1. Inicio: Correo de reclutamiento cuando proceden del servicio de neuropediatría

Buenos días:

Soy Rafael Medina, de Sincrolab S.L. En base a lo comentado con <responsable del servicio de procedencia>, le envío la información sobre el estudio. Adjuntada a este mail, encontrará la carta informativa, con información extendida sobre el mismo, que redactamos para los tutores legales que puedan estar interesados/as en participar. En caso de aceptar, le rogaríamos que nos reenviase de vuelta el cuestionario cumplimentado que acompaña la carta para poder confirmar su participación. Dicha carta se envía tanto en formato PDF como en formato DOC para facilitar su modificación.

El objetivo de este correo es ofrecerles participar, de manera gratuita, en la investigación que estamos llevando a cabo desde Sincrolab S.L, junto con el Laboratorio de Neurociencia Cognitiva y Computacional del Centro de Tecnología Biomédica de la Universidad Politécnica de Madrid.

Sincrolab S.L es una empresa dedicada al desarrollo de aplicaciones destinadas al entrenamiento de procesos cognitivos. Nuestro objetivo es estudiar de forma empírica la eficacia de la rehabilitación neuropsicológica a través de nuevas tecnologías en el tratamiento del TDAH, como forma de tratamiento no farmacológico. Nuestra principal preocupación gira en torno a la necesidad de disponer, tanto en el ámbito sanitario como en el ámbito educativo, de herramientas, procedimientos y metodologías de intervención neuropsicológica rápidos, eficaces y accesibles económicamente.

En Sincrolab nos centramos en el uso de las nuevas tecnologías y de la comunicación como herramienta para el entrenamiento de las funciones cognitivas. En el caso concreto del entrenamiento cognitivo en niños, se han desarrollado múltiples herramientas, enfocadas al entrenamiento o rehabilitación de la memoria de trabajo a través de un programa formado por videojuegos interactivos dinámicos y atractivos que consiguen dar un nuevo sentido a la rehabilitación convirtiéndola en un juego. Sin embargo, han sido pocos los estudiosos que han centrado sus esfuerzos en proporcionar evidencia científica para apoyar el impacto del entrenamiento y la rehabilitación informatizada.

De tal manera, hemos desarrollado la app Sincrolab Kids, una plataforma de entrenamiento cognitivo que está centrada muy especialmente en la recuperación y el desarrollo de funciones ejecutivas y procesos atencionales (capacidad de flexibilidad, control inhibitorio, iniciativa, toma de decisiones, memoria operativa, atención alternante, atención selectiva,...) y cuya misión es ser la herramienta tecnológica líder para la rehabilitación neuropsicológica en TDAH. El objetivo de esta investigación es estudiar la eficacia y efectividad de la herramienta de rehabilitación neuropsicológica de Sincrolab para la rehabilitación de los procesos cognitivos implicados en el TDAH.

Este estudio está enfocado a niños de entre 8 y 11 años, que hayan sido diagnosticados de TDAH combinado. Los requisitos para participar son:

- Tener un diagnóstico de un facultativo médico de TDAH-C
- No haber sido diagnosticado de ningún otro trastorno o dificultad del aprendizaje
- No tener ninguna pieza metálica que no pueda ser extraída del cuerpo (P.ej. brackets) para el registro mediante magnetoencefalografía. En el caso de brackets y fundas dentales, coméntenoslo para para que lo consultemos, por favor.
- No ser bilingüe
- Tener una tablet en casa
- En caso de tomar medicación prescrita para TDAH, retirada de la misma durante los 3 días previos a las evaluaciones.

El estudio consta de tres fases. En primer lugar, se realizaría una evaluación previa en el Centro de Tecnología Biomédica de la UPM, que implicaría una evaluación neuropsicológica y un registro mediante

magnetoencefalografía. La segunda fase, de entrenamiento, duraría 3 meses en los que el niño, desde su casa, realizaría el entrenamiento durante 15 minutos, aproximadamente, tres días por semana. En esta fase, el niño puede haber sido clasificado como grupo control o como tratamiento.

Finalmente, existiría una nueva fase de evaluación posterior, igual a la primera, al finalizar el entrenamiento. Tanto las evaluaciones neuropsicológicas como el periodo de 3 meses de estimulación cognitiva con la plataforma se les ofrece de manera totalmente gratuita. Cuando el participante finaliza su participación en el estudio y ha formado parte del grupo control, recibe 3 meses gratuitos de estimulación cognitiva con Sincrolab en las mismas condiciones.

Desde Sincrolab tenemos la firme creencia de que la herramienta es de gran ayuda en el proceso terapéutico de estos niños; así, agradeceríamos, por tanto, su participación.

Para cualquier cuestión, no dude en ponerse en contacto conmigo por este correo o en los teléfonos xxxxxxxxx o yyyyyyyyy. Esperamos su respuesta.

Muchas gracias por adelantado.

Un saludo,

Rafael Medina, de Sincrolab S.L.

Participant Information Sheet is attached to this first e-mail

2. Recordatorio si no responden al correo inicial

Buenas tardes:

Soy Rafael Medina, de Sincrolab S.L. Contacto con usted de nuevo para saber si vio mi e-mail invitándoles a participar en la investigación que estamos llevando a cabo con la herramienta Sincrolab Kids.

Gracias de antemano y un saludo.

3. Segundo recordatorio si no responden al correo inicial

Buenos días,

Soy Rafael Medina, de Sincrolab S.L. Le escribo para recordarle acerca del proyecto de investigación que estamos llevando a cabo con participantes con TDAH. Quería comunicarle que abril será el último mes que incluiremos nuevos candidatos, hasta septiembre. Por tanto, en caso de querer participar, le pediría confirmación cuanto antes

En caso de no desear participar, le pediría si pudiera hacérmelo saber, ya que así no le enviaría más correos.

Disculpe las molestias.

Gracias y un saludo.

4. Correo para concertar cita de la primera evaluación

Buenos días

Soy Rafael Medina, de Sincrolab. Les escribo para concertar la cita relativa a la primera evaluación del ensayo al que han accedido a participar. Tenemos disponibilidad el día de la semana X, fecha X de X, a las 10:00-12:00 de la mañana.

Como recordatorio, esta evaluación tiene lugar en el Centro de Tecnología Biomédica, de la Universidad Politécnica de Madrid. Su duración está en torno a 1h40-2h. Con la confirmación de la cita, les enviaré información sobre cómo llegar y por quién preguntar. En caso de albergar cualquier duda, quedamos a su disposición, tanto en las direcciones de e-mail como en los teléfonos proporcionados.

Muchas gracias y un saludo.

5. Correo de confirmación de la cita para la evaluación pre-entrenamiento

Buenos días:

Le escribo para confirmar la cita para el X de XX a las 10:00-12:00 AM. Le envío información relativa a la localización del centro. El Centro de Tecnología Biomédica está en Parque Científico y Tecnológico de la UPM, Crta. M40, Km. 38, 28223 Pozuelo de Alarcón, Madrid

- Enlace de Maps: https://goo.gl/maps/ED3VWZ8zRYy
- Enlace de la web que viene con las indicaciones: http://www.ctb.upm.es/?page_id=47

El centro cuenta con plazas de aparcamiento cercanas. Respecto a la persona por la que preguntar, estaremos bien yo, bien mi compañero Jaime Bouhaben, para recibiros en recepción.

La duración total estimada está entre 2h y 2h15; y el centro cuenta con salas de espera acondicionadas para el acompañante/s. Les recordamos, nuevamente, que 3 días antes de la fecha concertada, el participante deberá dejar de tomar medicación psicoactiva (en caso de tomarla). Podrá retomarla una vez finalice la evaluación.

Muchas gracias y un saludo.

6. Correo de recordatorio de la cita para la evaluación pre-entrenamiento

Buenos días:

Les escribo desde Sincrolab para hacerles un recordatorio de que la fecha de la primera evaluación para el ensayo con Sincrolab Kids, programada para el día X de XXXX a las XX:XX AM, está próxima. Como les comentó la doctora, su hijo/a debe dejar de tomar medicación psicoactiva (en caso de tomarla) 3 días antes de la misma. Por tanto, dicho periodo sin medicación comenzaría hoy y se prolongaría hasta el XXX día XX tras finalizar la primera evaluación.

Les rogamos acudan al Centro de Tecnología Biomédica aproximadamente 15 minutos antes de la hora programada, para poder hacer el registro de visitantes en la recepción y empezar las pruebas en hora.

Mi compañero Jaime Bouhaben será el que les reciba en la puerta. Su número de teléfono es el xxxxxxxxx.

Muchas gracias y un saludo.

7. Correo para iniciar la fase de entrenamiento

Buenos días;

Les escribo para iniciar la segunda fase del ensayo: los entrenamientos en el grupo correspondiente. Les envío en primer lugar un documento con las instrucciones para acceder a la aplicación correspondiente.

Por otro lado, les envío un documento con las posibles recompensas en caso de cumplir con las condiciones del estudio.

Daría así comienzo hoy XX día XX/XX esta fase, que se prolongará 12 semanas, hasta el XX/XX. Para la evaluación post-intervención, les daremos cita para la semana del XX/XX (la fecha y hora exactas será más adelante, pero con suficiente antelación).

Muchas gracias por su participación y un saludo.

Annex V for SINCROLAB intervention or Annex IV for Sham control intervention are attached to this e-mail

8. Correo de feedback del primer mes

Buenos días

Les escribo para comunicarle que han realizado con éxito y sin incidencias el primer mes del ensayo del total de tres meses. Aparte de un feedback positivo, con este email me gustaría volver a recordarles nuestra disponibilidad para resolverles cualquier cuestión que les pueda ir surgiendo.

Muchas gracias de antemano por continuar su participación y un saludo.

9. Correo de feedback del segundo mes

Buenos días

Les escribo de nuevo para comunicarles que han realizado con éxito y sin incidencias el segundo mes del ensayo del total de tres meses. Estamos muy agradecidos por la dedicación, tanto suya como de su hijo X. Aparte de un feedback positivo, con este email me gustaría volver a recordarles nuestra disponibilidad para resolverles cualquier cuestión que les pueda ir surgiendo.

Muchas gracias de antemano por continuar su participación y un saludo.

10. Correo recordatorio de evaluación final

Buenos días:

Les escribo desde Sincrolab para hacerles un recordatorio de que la fecha de la evaluación final para el ensayo con Sincrolab Kids, programada para el día XX de XXXX a las XX:XX AM, está próxima. Les recuerdo que Iván debe dejar de tomar medicación psicoactiva (en caso de tomarla) 3 días antes de la misma. Por tanto, dicho periodo sin medicación comenzaría el XX y se prolongaría hasta el XX tras finalizar la evaluación.

Les rogamos acudan al Centro de Tecnología Biomédica aproximadamente 15 minutos antes de la hora programada, para poder hacer el registro de visitantes en la recepción y empezar las pruebas en hora.

Les recuerdo que el Centro de Tecnología Biomédica está en Parque Científico y Tecnológico de la UPM, Crta. M40, Km. 38, 28223 Pozuelo de Alarcón, Madrid

- Enlace de Maps: https://goo.gl/maps/ED3VWZ8zRYy
- Enlace de la web que viene con las indicaciones: http://www.ctb.upm.es/?page_id=47

Mi número de teléfono es el xxxxxxxxx. La duración total estimada está entre 2h y 2h15; y el centro cuenta con salas de espera acondicionadas para el acompañante/s.

Muchas gracias y un saludo.

Annex V. Instructions for SINCROLAB Intervention

PROCEDIMIENTO PARA INICIAR LA FASE DE ENTRENAMIENTO

Este documento informativo tiene como objetivo proporcionar una serie de indicaciones breves para comenzar a utilizar la aplicación correspondiente; en este caso, *Sincrolab Kids*.

1. La aplicación se descarga directamente en la tablet. Si ésta es Android, la descarga se hace desde *Google Play Store*. Si la tablet es Apple (iOS), se descarga desde la *App Store*. En ambos casos, es preciso introducir en el buscador las palabras clave *Sincrolab Kids* para encontrar la aplicación con este icono:

2. Una vez se haya descargado, al pulsar en ella se iniciará. Tras un breve momento de carga, aparecerá una pantalla donde hay que introducir el usuario y la contraseña.

3. Las claves son las siguientes:
   - Usuario: xxxxxxxxxx
   - Contraseña: abcdefghi12345

4. Les recordamos que la pauta son **tres sesiones de entrenamiento semanales**, durante 12 semanas. El tiempo de cada sesión oscila entre los 15 y 20 minutos. La propia plataforma controla que sea ese el tiempo de uso diario. Ustedes únicamente deben asegurarse de que el niño/a no deja la sesión sin finalizar.

5. Para cualquier duda, seguimos en contacto a través del correo investigacion@sincrolab.es o en los números de teléfono proporcionados.

6. Les adjuntamos además un archivo pdf con las recompensas posibles por finalizar el estudio. Cabe recordar que se podrá elegir una recompensa de la lista con la condición de cumplir las sesiones de entrenamiento (3 semanales durante 12 semanas; 36 sesiones en total) y de pasar por la evaluación post-intervención (idéntica a la primera).

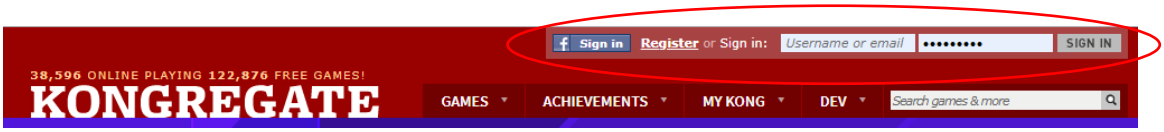
Annex VI. Instructions for Sham control Intervention

PROCEDIMIENTO PARA INICIAR LA FASE DE ENTRENAMIENTO

Este documento informativo tiene como objetivo proporcionar una serie de indicaciones breves para comenzar a utilizar la aplicación correspondiente.

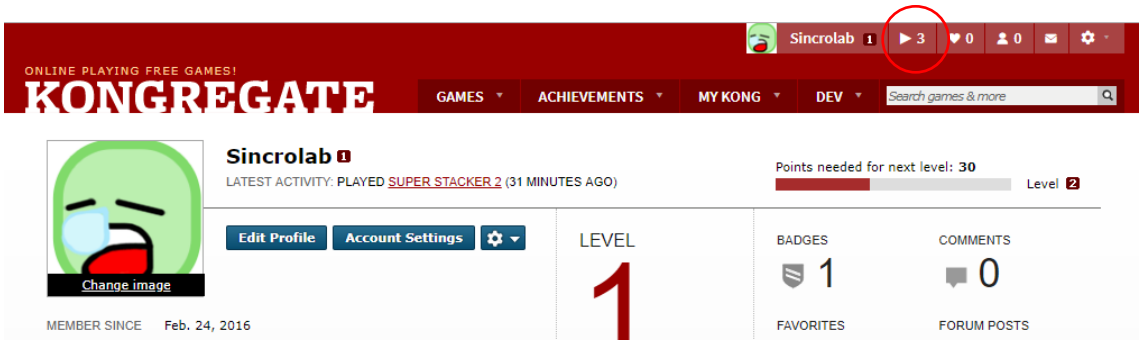
1. Desde el navegador web (Chrome, Mozilla, o el que tengan) de su **ordenador**, deben acceder al siguiente enlace: https://www.kongregate.com/

2. Una vez se haya cargado la página, en la esquina superior derecha aparecerán dos rectángulos para introducir su nombre de usuario y contraseña:

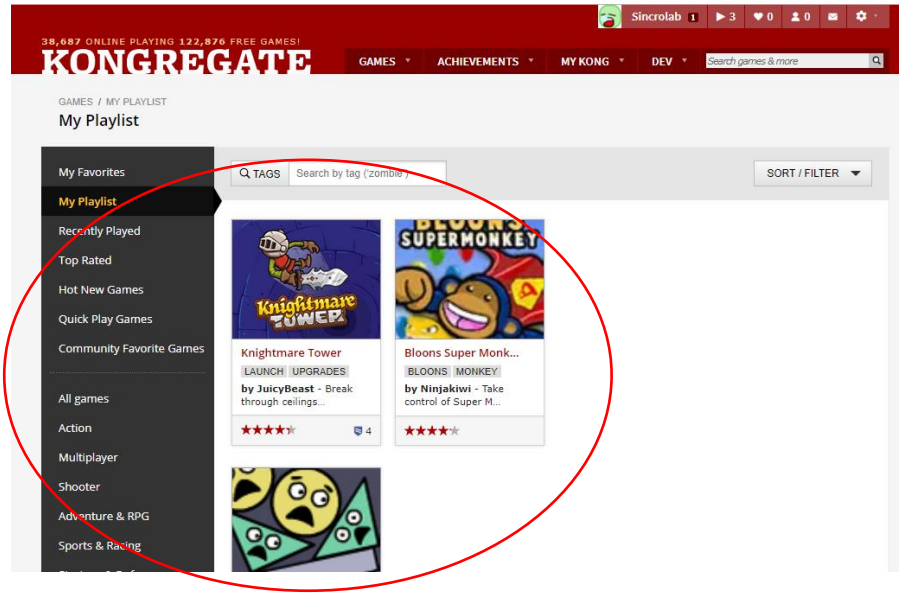


3. Su nombre de usuario y contraseña son los siguientes:
   - Usuario: sincrolab_al
   - Contraseña: sincrolab

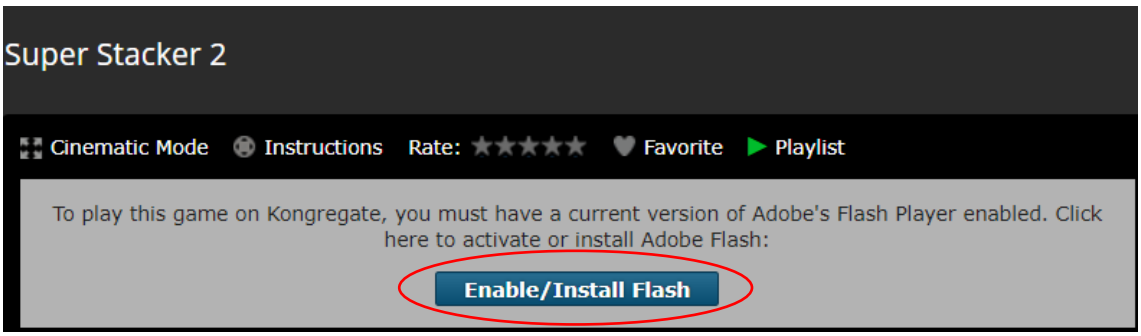
4. Una vez accedan con su nombre de usuario y contraseña, verán la siguiente pantalla. Deberán pulsar en el rectángulo con el número 3:



5. Al pulsar en dicha pestaña, aparecerá la pantalla con los juegos que componen el entrenamiento:



6. Es posible que, al iniciar el primer juego, les aparezca la siguiente pantalla:



La plataforma pide la activación de Adobe Flash. Adobe Flash no es más que un *plug-in* o complemento que permite el uso de contenido multimedia en el navegador web. Pulsen sobre *Enable/Install Flash* para activarlo. Si ya está descargado, al pulsar, el juego empezará automáticamente. En caso de no tenerlo, deberán instalarlo (se instala de manera fácil, rápida y gratuita).

7. Al pulsar sobre cada uno de estos juegos, dará comienzo. El sonido de cada juego puede silenciarse.

8. La pauta de entrenamiento es la siguiente: 3 días por semana durante 15 minutos al día. Puede ser un único juego al día o varios en un mismo día, pero en ningún caso se repetirán dos días consecutivos el mismo juego exclusivamente. Rogamos que, en ningún caso, se superen estos 15 minutos de juego al día.

9. Para cualquier duda, seguimos en contacto a través del correo investigacion@sincrolab.es o en los números de teléfono proporcionados.

10. Les adjuntamos además un archivo pdf con las recompensas posibles por finalizar el estudio. Cabe recordar que se podrá elegir una recompensa de la lista con la condición de cumplir las sesiones de entrenamiento (3 semanales durante 12 semanas; 36 sesiones en total) y de pasar por la evaluación post-intervención (idéntica a la primera).

Annex VII. EDAH record sheet

Escala de evaluación del trastorno por déficit de atención con hiperactividad (EDAH)

Farré-Riba A y Narbona J. Versión revisada y abreviada de la Escala Escolar de Conners para profesores.

	NEGATIVO				POSITIVO			
	Nada		Poco		Bastante		Mucho	
1. Tiene excesiva inquietud motora								
2. Tiene dificultades de aprendizaje escolar								
3. Molesta frecuentemente a los niños								
4. Se distrae fácilmente, escasa atención								
5. Exige que sus peticiones se cumplan inmediatamente								
6. Tiene dificultad para actividades en equipo/grupo								
7. Está en las nubes, ensimismado								
8. No acaba las tareas que ha empezado								
9. Es mal aceptado por el grupo								
10. Niega sus errores y echa la culpa a otros								
11. Emite sonidos molestos y en situación inapropiada								
12. Se comporta con arrogancia, es irrespetuoso								
13. Intranquilo, siempre en movimiento								
14. Discute y pelea por cualquier cosa								
15. Tiene explosiones impredecibles de mal genio								
16. Le falta sentido de las reglas del "juego limpio"								
17. Es impulsivo e irritable								
18. Se lleva mal con la mayoría de sus compañeros								
19. Sus esfuerzos se frustran fácilmente, es inconstante								
20. Acepta mal las indicaciones del profesor								

Annex VIII. BRIEF record sheet

BRIEF

Escala conductual de funcionamiento ejecutivo (versión para padres)

(Gioia GA, Isquith PK, Guy SC)

Instrucciones

En la página siguiente, hallará una lista de frases que describen el comportamiento. Nos gustaría saber si ha tenido problemas con estas conductas a lo largo de los últimos 2 meses. Como habrá podido comprobar, las preguntas son las mismas que las que completó hace dos meses. El objetivo de este cuestionario es comprobar si se ha producido algún cambio en el comportamiento de su hijo en los últimos dos meses.

Por favor conteste a todas las cuestiones lo mejor que pueda. NO OMITA NINGUNA.
Piense en su comportamiento mientras lee cada frase y marque con un círculo su respuesta.

N si su conducta **Nunca** es un problema

A si su conducta **A veces** es un problema

F si su conducta **Frecuentemente** es un problema

Por ejemplo, si nunca tiene dificultades para completar los deberes a tiempo, debe poner un círculo en la N para esta frase:

Tiene dificultades para completar los deberes a tiempo **N A F**

Si Ud. comete un error o quiere cambiar su respuesta, NO BORRE NADA. Dibuje una "X" sobre la respuesta que quiere cambiar y luego marque con un círculo la respuesta correcta:

Tiene dificultades para completar los deberes a tiempo **N A** ~~**F**~~

Antes de empezar a responder, por favor, indique su nombre, edad, fecha de nacimiento, curso académico y fecha en los espacios habilitados en la parte superior de la página siguiente.

Nombre del niño o niña_____Curso

_____Edad_____ Sexo

_____Fecha de nacimiento_____Fecha de hoy _____ Su

nombre_____Relación con el niño

N = Nunca **A = A veces** **F = Frecuentemente**

1. Sobrerreacciona a pequeños problemas	N	A	F
2. Cuando se le pide que haga tres cosas, solo recuerda la primera o la última	N	A	F
3. No toma la iniciativa por sí solo	N	A	F
4. Deja el cuarto de juguetes hecho un desastre	N	A	F
5. Se resiste o tiene dificultades para aceptar una forma diferente para resolver un problema con las tareas escolares, domésticas o con amigos	N	A	F
6. Se enfada o disgusta en nuevas situaciones	N	A	F
7. Tiene arranques de rabia explosivos	N	A	F
8. Intenta solucionar un problema de la misma forma una y otra vez aunque no funcione	N	A	F
9. Tiene poca capacidad de atención	N	A	F
10. Hay que recordarle empezar una tarea aunque esté dispuesto	N	A	F
11. No trae a casa las tareas escolares, hojas con deberes, materiales, etc.	N	A	F
12. Se molesta cuando hay un cambio de planes	N	A	F
13. Se disgusta por un cambio de maestro o de clase	N	A	F
14. No repasa los errores de un trabajo	N	A	F
15. Tiene buenas ideas pero no las puede poner en papel	N	A	F
16. Le cuesta tener ideas sobre a qué jugar o qué hacer en su tiempo libre	N	A	F
17. Tiene dificultad en concentrarse en tareas de casa, deberes, etc.	N	A	F
18. No relaciona hacer los deberes ahora con sacar después buenas notas	N	A	F
19. Se distrae fácilmente con ruidos, actividad, vistas, etc.	N	A	F
20. Tiene lágrima fácil	N	A	F
21. Comete errores por descuido	N	A	F
22. Se olvida de entregar los deberes aún cuando los ha terminado	N	A	F
23. Se resiste a un cambio en la rutina, las comidas, lugares, etc.	N	A	F
24. Tiene dificultades para afrontar tareas que requieren más de un paso	N	A	F
25. Explota por poca cosa	N	A	F
26. Tiene frecuentes cambios de humor	N	A	F
27. Necesita la ayuda de un adulto para mantenerse centrado en una tarea	N	A	F
28. Se queda atrapado en los detalles y pierde la visión global	N	A	F

29. Mantiene su habitación en desorden	N	A	F

N = Nunca **A = A veces** **F = Frecuentemente**

30. Tiene dificultades para adaptarse a nuevas situaciones (clases, grupos, amigos)	N	A	F
31. Mala caligrafía, hace mala letra	N	A	F
32. Se olvida de lo que estaba haciendo	N	A	F
33. Cuando estaba haciendo algo, se olvida qué debía buscar	N	A	F
34. No se da cuenta de que su conducta afecta a otros	N	A	F
35. Tiene buenas ideas pero no acaba los trabajos (le falta continuidad)	N	A	F
36. Se abruma con tareas grandes	N	A	F
37. Dificultades para acabar tareas (quehaceres, deberes)	N	A	F
38. Hace más locuras o tonterías que los otros cuando está en grupo (cumpleaños, patio)	N	A	F
39. Piensa demasiado en el mismo tema	N	A	F
40. Subestima el tiempo que necesita para terminar las tareas	N	A	F
41. Interrumpe a los demás	N	A	F
42. No se da cuenta cuando su conducta provoca reacciones negativas	N	A	F
43. Se levanta del asiento en momentos inadecuados	N	A	F
44. Pierde el control más que sus amigos	N	A	F
45. Reacciona más acusadamente a situaciones que otros niños	N	A	F
46. Empieza tareas o quehaceres en el último minuto	N	A	F
47. Dificultades para empezar los deberes, tareas, o quehaceres domésticos	N	A	F
48. Dificultades para organizar actividades con amigos	N	A	F
49. Dice cosas bruscamente	N	A	F
50. Su estado de ánimo es fácilmente influenciable por la situación	N	A	F
51. No planifica las tareas escolares	N	A	F
52. Escasa comprensión de sus propios puntos fuertes y débiles	N	A	F
53. Sus trabajos escritos están mal organizados	N	A	F
54. Actúa como un salvaje o descontrolado	N	A	F
55. Dificultades para poner freno a sus actos	N	A	F
56. Se mete en problemas si no está supervisado por un adulto	N	A	F

57. Dificultades para recordar cosas, incluso por unos minutos	N	A	F
58. Dificultades para llevar a cabo las acciones necesarias para llegar a una meta (ahorrar para comprar algo especial, estudiar esta noche para sacar buena nota en el examen)	N	A	F
59. Hace muchas tonterías	N	A	F
60. Su trabajo es descuidado	N	A	F
61. No toma iniciativa	N	A	F
62. Sus explosiones de enojo o lágrimas son intensos pero acaban de repente	N	A	F

N = Nunca **A = A veces** **F = Frecuentemente**

63. No se da cuenta de que ciertas acciones molestan a otros	N	A	
64. Cosas sin importancia provocan grandes reacciones	N	A	
65. Habla en momentos inapropiados	N	A	
66. Se queja de que no se le ocurre nada que hacer	N	A	
67. No puede encontrar cosas en su habitación o su pupitre	N	A	
68. Deja un rastro de pertenencias allá donde va	N	A	
69. Genera desórdenes que otros tienen que recoger	N	A	
70. Se molesta muy fácilmente	N	A	
71. Vaguea mucho por la casa	N	A	
72. Tiene el armario desordenado	N	A	
73. Dificultades para esperar su turno	N	A	
74. Pierde la merienda, el dinero los pases de permiso, los deberes, etc.	N	A	
75. No puede encontrar ropa, gafas, zapatos, juguetes, libros, lápices, etc.	N	A	
76. Hace mal los controles/exámenes, aún sabiendo las respuestas correctas	N	A	
77. No termina los proyectos a largo plazo	N	A	
78. Hay que supervisarle constantemente	N	A	
79. No piensa antes de actuar	N	A	
80. Dificultades para pasar de una actividad a otra	N	A	
81. Inquieto (mueve dedos, pierna maquinalmente…)	N	A	
82. Es impulsivo	N	A	
83. Pasa de un tema a otro durante una conversación	N	A	
84. Se encalla en el mismo asunto cuando habla	N	A	

85. Repite las mismas cosas una y otra vez	N	A	
86. Dificultades para realizar las rutinas matutinas preparándose antes de ir a la escuela	N	A	

Annex IX: WNV record sheet

Memoria espacial — Edad 8-21

Comienzo
Edad 8-21
Orden directo: Ítem de demostración, ítem de ejemplo e ítem 1.
Orden inverso: Ítem de demostración, ítem de ejemplo e ítem 1.

Terminación
Después de **2** puntuaciones de **0** en *los dos* intentos del *mismo ítem*.

Puntuación
0 o **1** punto por cada intento.
MESOD y **MESOI**: puntuación directa para OD y OI.
SpanMESOD y **SpanMESOI**: número de cubos tocados en el último ítem puntuado con **1** punto para OD y OI

ORDEN DIRECTO

Ítem	Intento	Respuesta	Punt. intento	Punt. ítem
Demo. (8-21)	10 – 1			
Ej.	1 – 6			
	5 – 8			
1.	3 – 10		1 0	0 1 2
	7 – 4		1 0	
2.	1 – 9 – 3		1 0	0 1 2
	8 – 2 – 7		1 0	
3.	4 – 9 – 1 – 6		1 0	0 1 2
	10 – 6 – 2 – 7		1 0	
4.	6 – 5 – 1 – 4 – 8		1 0	0 1 2
	5 – 7 – 9 – 8 – 2		1 0	
5.	4 – 1 – 9 – 3 – 8 – 10		1 0	0 1 2
	9 – 2 – 6 – 7 – 3 – 5		1 0	
6.	10 – 1 – 6 – 4 – 8 – 5 – 7		1 0	0 1 2
	2 – 6 – 3 – 8 – 2 – 10 – 1		1 0	
7.	7 – 3 – 10 – 5 – 7 – 8 – 4 – 9		1 0	0 1 2
	6 – 9 – 3 – 2 – 1 – 7 – 10 – 5		1 0	
8.	5 – 8 – 4 – 10 – 7 – 3 – 1 – 9 – 6		1 0	0 1 2
	8 – 2 – 6 – 1 – 10 – 3 – 7 – 4 – 9		1 0	

SpanMESOD (Máximo = 9) ____ Punt. directa MESOD (Máximo = 16) ____

ORDEN INVERSO

Ítem	Intento	Respuesta	Punt. intento	Punt. ítem
Demo. (8-21)	10 – 1			
Ej.	5 – 8			
	1 – 6			
1.	7 – 4		1 0	0 1 2
	3 – 10		1 0	
2.	8 – 2 – 7		1 0	0 1 2
	1 – 9 – 3		1 0	
3.	10 – 6 – 2 – 7		1 0	0 1 2
	4 – 9 – 1 – 6		1 0	
4.	5 – 7 – 9 – 8 – 2		1 0	0 1 2
	6 – 5 – 1 – 4 – 8		1 0	
5.	9 – 2 – 6 – 7 – 3 – 5		1 0	0 1 2
	4 – 1 – 9 – 3 – 8 – 10		1 0	
6.	2 – 6 – 3 – 8 – 2 – 10 – 1		1 0	0 1 2
	10 – 1 – 6 – 4 – 8 – 5 – 7		1 0	
7.	6 – 9 – 3 – 2 – 1 – 7 – 10 – 5		1 0	0 1 2
	7 – 3 – 10 – 5 – 7 – 8 – 4 – 9		1 0	
8.	8 – 2 – 6 – 1 – 10 – 3 – 7 – 4 – 9		1 0	0 1 2
	5 – 8 – 4 – 10 – 7 – 3 – 1 – 9 – 6		1 0	

SpanMESOI (Máximo = 9) ____ Punt. directa MESOI (Máximo = 16) ____

Puntuación directa Memoria espacial (Máximo = 32) ____

Annex X: NEPSY-II record sheet

Edad 7-16 — Clasificación de animales

Materiales	Comienzo	Retorno	Terminación	Parada	Cronometraje
Manual de aplicación y corrección Tarjetas de *Clasificación de animales* (8) Cronómetro	Ítem de práctica	Ninguno	Después de 360 segundos de tiempo de clasificación acumulado, cuando se hayan completado todas las clasificaciones correctas, tras 120 segundos sin una respuesta, o cuando el niño afirme que ha terminado.	Ninguna	Dejar 360 segundos de tiempo de clasificación acumulado.

Número de clasificación	Tarjeta de cebras	Número de tarjeta	Otra clasificación	Clasificación repetida	Clasificación correcta
IP	1	2 4 5			
1.	1		S N	S N	0 1
2.	1		S N	S N	0 1
3.	1		S N	S N	0 1
4.	1		S N	S N	0 1
5.	1		S N	S N	0 1
6.	1		S N	S N	0 1
7.	1		S N	S N	0 1
8.	1		S N	S N	0 1
9.	1		S N	S N	0 1
10.	1		S N	S N	0 1
11.	1		S N	S N	0 1
12.	1		S N	S N	0 1
13.	1		S N	S N	0 1
14.	1		S N	S N	0 1
15.	1		S N	S N	0 1
16.	1		S N	S N	0 1
17.	1		S N	S N	0 1
18.	1		S N	S N	0 1
19.	1		S N	S N	0 1
20.	1		S N	S N	0 1

Total de errores otras clasificaciones CA		Total de errores clasificaciones repetidas CA		Total de errores CA	Total de clasificaciones correctas CA (Máx. = 12)
	+		=		

Edad 5-16 — Fluidez verbal

Materiales	Comienzo	Retorno	Terminación	Parada	Cronometraje
Manual de aplicación y corrección Cronómetro	Ítem 1	Ninguno	Ninguna	**5-6 :** después del ítem 2.	Dejar 60 segundos para cada ítem.

Semántica		Letra inicial	
1. Animales	2. Comidas o bebidas	3. Palabras con «P» inicial	4. Palabras con «M» inicial
	5-6 STOP		

Puntuación total FV Semántica	Puntuación total FV Letra inicial

Edad 5-16 — Atención auditiva y Flexibilidad cognitiva

Materiales	Comienzo	Retorno	Terminación	Parada	Cronometraje
Manual de aplicación y corrección Cuaderno de estímulos 1 Archivo de audio de *Atención auditiva y Flexibilidad cognitiva* Reproductor de audio	Ítem de práctica de *Atención auditiva.*	Ninguno	Ninguna	**5-6:** después de *Atención auditiva.*	Ninguno

Atención auditiva-Ítems del test

Respuesta	Punt.		Error	
negro			c	i
cosa			c	
pronto			c	
tarde			c	
oye			c	
ROJO	1	o	c	
roca			c	
ahora			c	
verde			c	i
pero			c	
azul			c	i
ROJO	1	o	c	
bajo			c	
toma			c	
verde			c	i
roca			c	
bajo			c	
muerde			c	
ahora			c	
negro			c	i
ROJO	1	o	c	
azul			c	i
ROJO	1	o	c	
toma			c	
bajo			c	
eso			c	
blanco			c	
ahora			c	
azar			c	
ROJO	1	o	c	
roca			c	
ROJO	1	o	c	
toma			c	
ROJO	1	o	c	
verde			c	i
bajo			c	

Respuesta	Punt.		Error	
limpio			c	
azar			c	
negro			c	i
no			c	
ahora			c	
azul			c	i
roca			c	
negro			c	i
ahora			c	
bien			c	
negro			c	i
roca			c	
cosa			c	
sueño			c	
verde			c	i
azul			c	i
azar			c	
ahora			c	
ROJO	1	o	c	
limpio			c	
ROJO	1	o	c	
verde			c	i
vamos			c	
ROJO	1	o	c	
caja			c	
blanco			c	
azar			c	
azul			c	i
azar			c	
ROJO	1	o	c	
ahora			c	
ROJO	1	o	c	
cosa			c	
pronto			c	
tarde			c	
aquí			c	

Respuesta	Punt.		Error	
ROJO	1	o	c	
ahora			c	
verde			c	i
pero			c	
bajo			c	
eso			c	
toma			c	
ROJO	1	o	c	
negro			c	i
cosa			c	
pronto			c	
tarde			c	
oye			c	
ROJO	1	o	c	
roca			c	
ahora			c	i
verde			c	
pero			c	
azul			c	i
bajo			c	
eso			c	
toma			c	
ROJO	1	o	c	
verde			c	i
roca			c	
bajo			c	
muerde			c	
ahora			c	
azul			c	i
ROJO	1	o	c	
roca			c	
ROJO	1	o	c	
azul			c	i
ROJO	1	o	c	
toma			c	
bajo			c	
eso			c	
blanco			c	
ahora			c	
azar			c	

Respuesta	Punt.		Error	
ROJO	1	o	c	
roca			c	
toma			c	
verde			c	i
bajo			c	
ROJO	1	o	c	
azar			c	
ROJO	1	o	c	
no			c	
ahora			c	
azul			c	i
roca			c	
ahora			c	
bien			c	
negro			c	i
roca			c	
cosa			c	
sueño			c	
verde			c	i
azul			c	i
azar			c	
ahora			c	
limpio			c	
negro			c	i
ahora			c	
verde			c	i
vamos			c	
ahora			c	
ROJO	1	o	c	
roca			c	
negro			c	i
ROJO	1	o	c	
cosa			c	
caja			c	
blanco			c	
azar			c	

Respuesta	Punt.		Error	
ROJO	1	o	c	
azar			c	
ROJO	1	o	c	
ahora			c	
ROJO	1	o	c	
negro			c	i
tarde			c	
aquí			c	
ROJO	1	o	c	
roca			c	
ahora			c	
verde			c	i
pero			c	
bajo			c	
ROJO	1	o	c	
toma			c	
eso			c	
negro			c	i
cosa			c	
pronto			c	
tarde			c	
oye			c	
ROJO	1	o	c	
roca			c	
ahora			c	
verde			c	i
pero			c	
azul			c	i
ROJO	1	o	c	
eso			c	
toma			c	
verde			c	i
roca			c	
bajo			c	
muerde			c	
ROJO	1	o	c	

5-6 STOP

Observaciones conductuales

Total de conductas fuera de tarea por inatención o distracción AA

Total de conductas fuera de tarea por movimiento físico en el asiento o por levantarse AA

Total de respuestas correctas AA (Máx. = 30) — A.1 — Puntuación escalar/ Percentil total de respuestas correctas AA

Total de errores comisión AA (Máx. = 180) — A.1 — Percentil total de errores comisión AA

Total de errores omisión AA (Máx. = 30) — A.1 — Percentil total de errores omisión AA

Total de errores inhibición AA (Máx. = 35) — A.1 — Percentil total de errores inhibición AA

5–12 B.2

13–16 B.3

Puntuación escalar combinada AA

Atención auditiva y Flexibilidad cognitiva *(continuación)*

Flexibilidad cognitiva-Ítems del test

Respuesta	Punt.		Error		Respuesta	Punt.		Error		Respuesta	Punt.		Error		Respuesta	Punt.		Error		Respuesta	Punt.		Error	
bajo			c		AZUL	1	o	c		ROJO	1	o	c	i	negro			c	i	vamos			c	
ahora			c		pero			c		negro			c	i	AZUL	1	o	c		AZUL	1	o	c	
bien			c		bajo			c		cosa			c		pronto			c		no			c	
negro			c	i	eso			c		caja			c		tarde			c		aquí			c	
roca			c		toma			c		AZUL	1	o	c		aquí			c		busca			c	
cosa			c		negro			c	i	azar			c		ROJO	1	o	c	i	ROJO	1	o	c	i
sueño			c		roca			c		tarde			c		roca			c		blanco			c	
VERDE	1	o	c	i	muerde			c		ahora			c		ahora			c		negro			c	i
azar			c		bajo			c		ROJO	1	o	c	i	tarde			c		VERDE	1	o	c	i
ahora			c		ahora			c		bajo			c		pero			c		azar			c	
AZUL	1	o	c		AZUL	1	o	c		ahora			c		toma			c		uno			c	
limpio			c		toma			c		bien			c		eso			c		ahora			c	
negro			c	i	eso			c		negro			c	i	AZUL	1	o	c		toma			c	
ahora			c		blanco			c		roca			c		uno			c		baúl			c	
VERDE	1	o	c	i	baúl			c		cosa			c		ahora			c		no			c	
vamos			c		azar			c		VERDE	1	o	c	i	azar			c		AZUL	1	o	c	
ROJO	1	o	c	i	roca			c		sueño			c		negro			c	i	pero			c	
roca			c		AZUL	1	o	c		quieto			c		roca			c		toma			c	
negro			c	i	algo			c		azar			c		oye			c		eso			c	
cosa			c		toma			c		AZUL	1	o	c		azar			c		ROJO	1	o	c	i
caja			c		ROJO	1	o	c	i	limpio			c		blanco			c		roca			c	
ROJO	1	o	c	i	bajo			c		negro			c	i	no			c		azar			c	
azar			c		no			c		ahora			c		ahora			c		VERDE	1	o	c	i
no			c		ahora			c		VERDE	1	o	c	i	pero			c		limpio			c	
azar			c		azar			c		vamos			c		pronto			c		cosa			c	
VERDE	1	o	c	i	negro			c	i	ROJO	1	o	c	i	AZUL	1	o	c		verbo			c	
ahora			c		ahora			c		roca			c		azar			c		caja			c	
negro			c	i	AZUL	1	o	c		negro			c	i	negro			c	i	muerde			c	
cosa			c		no			c		cosa			c		cosa			c		toma			c	
dime			c		VERDE	1	o	c	i	caja			c		VERDE	1	o	c	i	AZUL	1	o	c	
ROJO	1	o	c	i	roca			c		blanco			c		tarde			c		blanco			c	
tarde			c		limpio			c		azar			c		nada			c		baúl			c	
aquí			c		bien			c		AZUL	1	o	c		blanco			c		ROJO	1	o	c	i
VERDE	1	o	c	i	blanco			c		azar			c		VERDE	1	o	c	i	eso			c	
roca			c		negro			c	i	aquí			c		hace			c		es			c	
ahora			c		roca			c		ahora			c		ahora			c		todo			c	

Observaciones conductuales

Total de conductas fuera de tarea por inatención o distracción FC

Total de conductas fuera de tarea por movimiento físico en el asiento o por levantarse FC

Total de respuestas correctas FC (Máx. = 36) — A.1

Puntuación escalar/ Percentil total de respuestas correctas FC

Total de errores comisión FC (Máx. = 180) — A.1

Percentil total de errores comisión FC

Total de errores omisión FC (Máx. = 36) — A.1

Percentil total de errores omisión FC

Total de errores inhibición FC (Máx. = 37) — A.1

Percentil total de errores inhibición FC

7–12 — B.4

13–16 — B.5

Puntuación escalar combinada FC

Puntuación escalar combinada AA

Puntuación escalar combinada FC

C.1 — Puntuación escalar de comparación AA vs. FC

Inhibición

Edad 5-16

Materiales	Comienzo	Retorno	Terminación	Parada	Cronometraje
Manual de aplicación y corrección Cuaderno de estímulos 1 Cronómetro	Ítem de práctica Denominación de la parte 1: Figuras	Ninguno	Ninguna	**5-6:** después del ítem del test Inhibición de la parte 1: Figuras y la parte 2: Flechas.	**Ítem del test Denominación:** dejar 180 segundos. **Ítems del test Inhibición y Cambio:** dejar 240 segundos.

Parte 1: Figuras

Ítem de práctica Denominación

Cu Cu Ci Ci Cu Ci Ci Cu

Señala los estímulos ☐S ☐N

Ítem del test Denominación

Cu	Ci	Ci	Ci	Cu	Ci	Cu	Cu
Ci	Cu	Ci	Ci	Cu	Cu	Cu	Cu
Ci	Ci	Cu	Ci	Cu	Ci	Cu	Ci
Cu	Cu	Cu	Ci	Ci	Ci	Ci	Ci
Cu	Ci	Ci	Ci	Cu	Ci	Cu	Cu

Errores no corregidos (Máx. = 40)

Errores autocorregidos (Máx. = 40)

Total de errores (Máx. = 40)

Tiempo empleado (Máx. = 180")

Ítem de práctica Inhibición

Ci Ci Cu Cu Ci Cu Cu Ci

Señala los estímulos ☐S ☐N

Ítem del test Inhibición

Ci	Cu	Cu	Cu	Ci	Cu	Ci	Ci
Cu	Ci	Cu	Cu	Ci	Ci	Ci	Ci
Cu	Cu	Ci	Cu	Ci	Cu	Ci	Cu
Ci	Ci	Ci	Cu	Cu	Cu	Cu	Cu
Ci	Cu	Cu	Cu	Ci	Cu	Ci	Ci

Errores no corregidos (Máx. = 40)

Errores autocorregidos (Máx. = 40)

Total de errores (Máx. = 40)

Tiempo empleado (Máx. = 240")

5-6 STOP **Aplicar el Ítem 2: Flechas**

Ítem de práctica Cambio

Ci Cu Cu Cu Ci Ci Ci Ci

Señala los estímulos ☐S ☐N

Ítem del test Cambio

Ci	Cu	Cu	Ci	Cu	Cu	Ci	Cu
Cu	Cu	Cu	Ci	Ci	Cu	Ci	Ci
Ci	Ci	Ci	Cu	Ci	Cu	Ci	Ci
Cu	Ci	Ci	Ci	Cu	Ci	Cu	Ci
Ci	Cu	Cu	Ci	Cu	Cu	Ci	Cu

Errores no corregidos (Máx. = 40)

Errores autocorregidos (Máx. = 40)

Total de errores (Máx. = 40)

Tiempo empleado (Máx. = 240")

Parte 2: Flechas

Ítem de práctica Denominación

Ar Ar Ab Ab Ar Ab Ab Ar

Señala los estímulos ☐S ☐N

Ítem del test Denominación

Ar	Ab	Ab	Ab	Ar	Ab	Ar	Ar
Ab	Ar	Ab	Ab	Ar	Ar	Ar	Ar
Ab	Ab	Ar	Ab	Ar	Ab	Ar	Ab
Ar	Ar	Ar	Ab	Ab	Ab	Ab	Ab
Ar	Ab	Ab	Ab	Ar	Ab	Ar	Ar

Errores no corregidos (Máx. = 40)

Errores autocorregidos (Máx. = 40)

Total de errores (Máx. = 40)

Tiempo empleado (Máx. = 180")

Ítem de práctica Inhibición

Ab Ab Ar Ar Ab Ar Ar Ab

Señala los estímulos ☐S ☐N

Ítem del test Inhibición

Ab	Ar	Ar	Ar	Ab	Ar	Ab	Ab
Ar	Ab	Ar	Ar	Ab	Ab	Ab	Ab
Ar	Ar	Ab	Ar	Ab	Ar	Ab	Ar
Ab	Ab	Ab	Ar	Ar	Ar	Ar	Ar
Ab	Ar	Ar	Ar	Ab	Ar	Ab	Ab

Errores no corregidos (Máx. = 40)

Errores autocorregidos (Máx. = 40)

Total de errores (Máx. = 40)

Tiempo empleado (Máx. = 240")

5-6 STOP

Ítem de práctica Cambio

Ab Ar Ar Ar Ab Ab Ab Ab

Señala los estímulos ☐S ☐N

Ítem del test Cambio

Ab	Ar	Ar	Ab	Ar	Ar	Ab	Ar
Ar	Ar	Ar	Ab	Ab	Ar	Ab	Ab
Ab	Ab	Ab	Ar	Ab	Ar	Ab	Ab
Ar	Ab	Ab	Ab	Ar	Ab	Ar	Ab
Ab	Ar	Ar	Ab	Ar	Ar	Ab	Ar

Errores no corregidos (Máx. = 40)

Errores autocorregidos (Máx. = 40)

Total de errores (Máx. = 40)

Tiempo empleado (Máx. = 240")

Parte 1: total de errores Figuras
(5-6: máx. = 80)
(7-16: máx. = 120)

Parte 2: total de errores Flechas
(5-6: máx. = 80)
(7-16: máx. = 120)

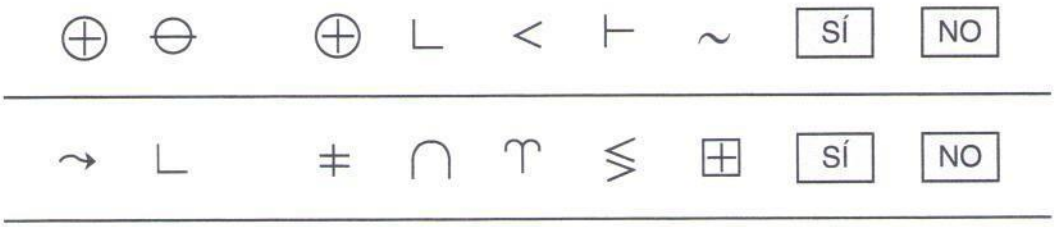
Annex XI. WISC-IV record sheet

WS -

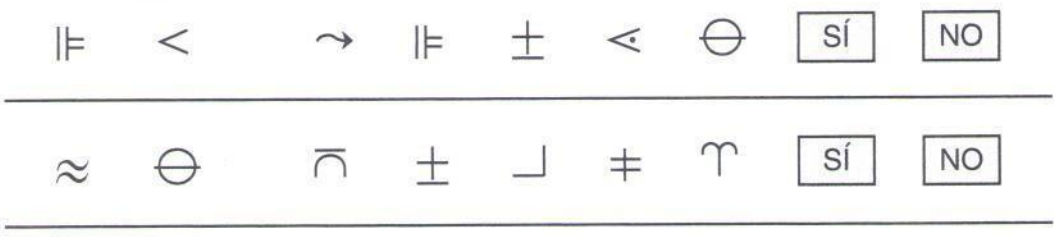
Búsqueda de símbolos

PARTE B: 8 a 16 años

EJEMPLOS



ELEMENTOS DE PRÁCTICA

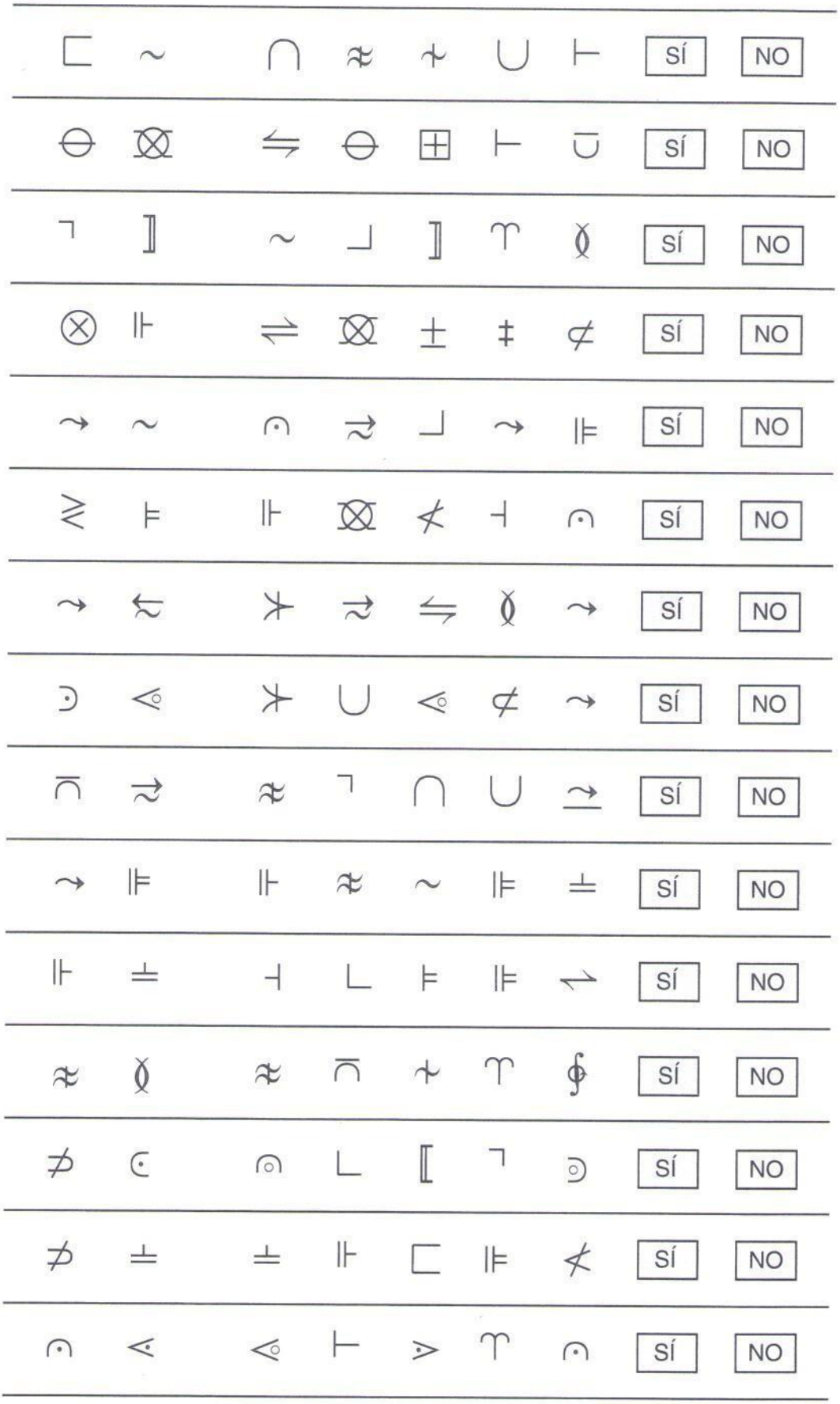


Continúe

B *(Continuación)*

⊖ ⊕	≫ ⅂ ⊖ ≉ ⌋	SÍ	NO
⊣ ⌊	⊣ ≁ ≻ ∩ ⊗	SÍ	NO
∩ ∪	⇛ ⌐ ⊨ ⊞ ≺	SÍ	NO
⊗ ~	⊀ ⊗ ⊔ ≠ ⊖	SÍ	NO
⊅ ⅂	⊫ ⇄ ⊂ ⌋ ⇝	SÍ	NO
≻ ≽	~ ∪ ≫ ≠ ≈	SÍ	NO
≉ ⊐	∩ ∪ ⌋ ⊀ ⇁	SÍ	NO
⊀ ≁	≠ ⊖ ⅂ ⊐ ≁	SÍ	NO
⊏ ⊀	≺ ⊃ ⅂ ≻ ∪	SÍ	NO
⊞ ~	≠ ⊢ ⊂ ⊞ ⌋	SÍ	NO
⊀ ≽	≻ ⊀ ≺ ≠ ⊀	SÍ	NO
⇌ ⇁	≁ ≫ ∪ ~ ⩽	SÍ	NO
⊃ ⌝	⊣ ⊁ ≺ ⊅ ≉	SÍ	NO
⇌ ⊗	⊞ ⊗ ⊁ ⌝ ⊀	SÍ	NO
⌋ ⊨	⊀ ⊢ ⊀ ⌝ ⇄	SÍ	NO

B *(Continuación)*

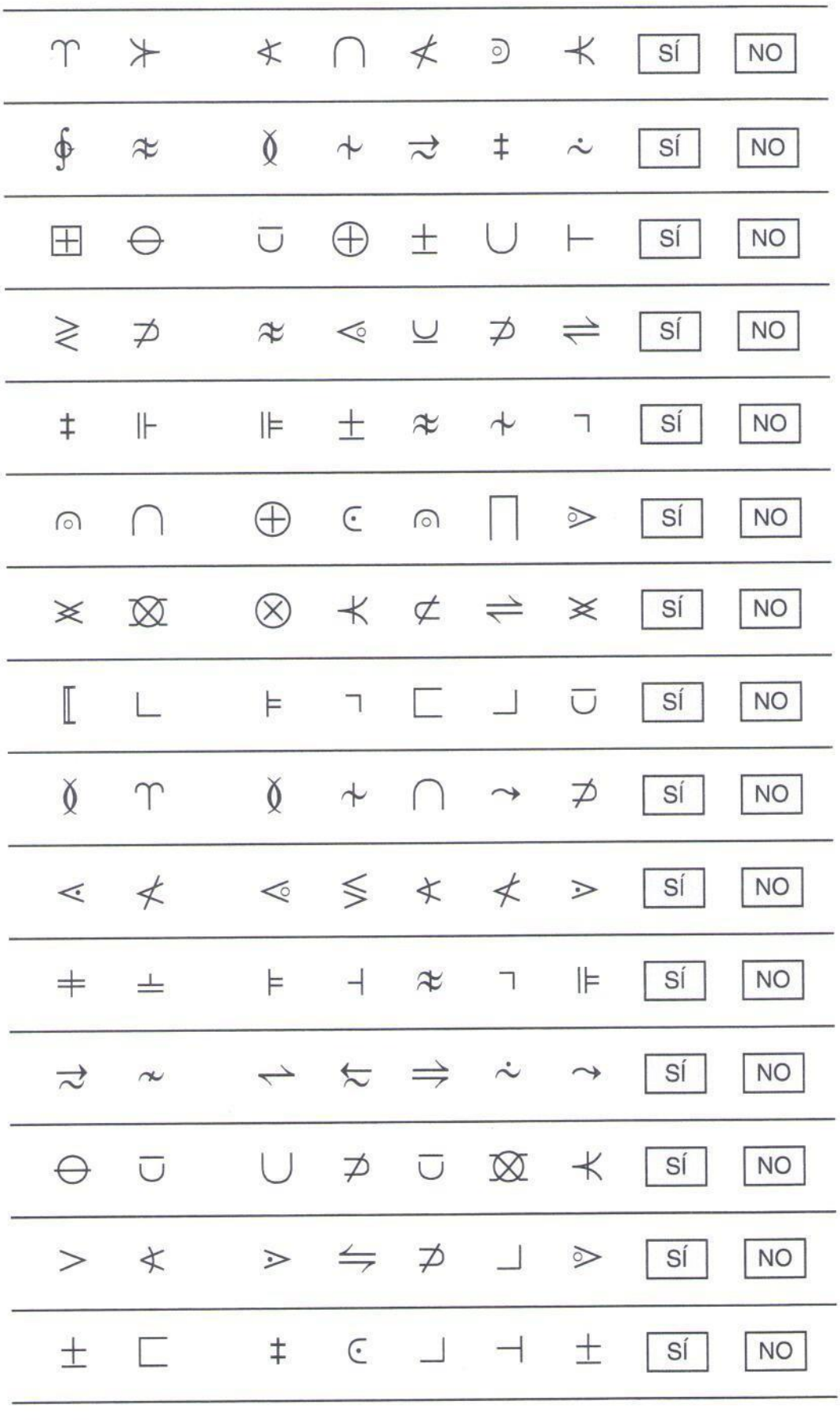


B *(Continuación)*

							SÍ	NO
							SÍ	NO
							SÍ	NO
							SÍ	NO
							SÍ	NO
							SÍ	NO
							SÍ	NO
							SÍ	NO
							SÍ	NO
							SÍ	NO
							SÍ	NO
							SÍ	NO
							SÍ	NO
							SÍ	NO
							SÍ	NO
							SÍ	NO

WS -

B *(Continuación)*



Claves B

8 a 16 años

1	2	3	4	5	6	7	8	9
÷	)	+	⊢	⅂	V	(	÷	⊣

EJEMPLOS

2	1	4	6	3	5	2	1	3	4	2	1	3	1	2	3	1	4	2	6	3

1	2	5	1	3	1	5	4	2	7	4	6	9	2	5	8	4	7	6	1	8

7	5	4	8	6	9	4	3	1	8	2	9	7	6	2	5	8	7	3	6	4

5	9	4	1	6	8	9	3	7	5	1	4	9	1	5	8	7	6	9	7	8

2	4	8	3	5	6	7	1	9	4	3	6	2	7	9	3	5	6	7	4	5

2	7	8	1	3	9	2	6	8	4	1	3	2	6	4	9	3	8	5	1	8

Annex XII: Conners' Continuous Performance Test's III

CONNERS
CPT 3™
Conners Continuous
Performance Test 3rd Edition™