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Study Identification

Unique Protocol ID:	vpradtdcs0102012
Brief Title:	ADHD Electrophysiological Subtypes and Implications in Transcranial Direct-current Stimulation (tdcs&adhd)
Official Title:	Implications of Electrophysiological ADHD Endophenotypes to Predict Response to Transcranial Direct-Current Stimulation
Secondary IDs:	

Study Status

Record Verification:	July 2023
Overall Status:	Completed
Study Start:	June 2012 []
Primary Completion:	December 2012 [Actual]
Study Completion:	December 2012 [Actual]

Sponsor/Collaborators

Sponsor:	Spanish Foundation for Neurometrics Development
Responsible Party:	Sponsor
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	

Unapproved/Uncleared Device:	No
U.S. FDA IND/IDE:	Yes
IND/IDE Information:	FDA Center: CDRH IND/IDE Number: CH1332 Serial Number: 6092827 Has Expanded Access: No
Human Subjects Review:	Board Status:
Data Monitoring:	Yes
FDA Regulated Intervention:	Yes
Section 801 Clinical Trial:	Yes

Study Description

Brief Summary:	In the present study the aim is to examine whether transcranial direct-current stimulation (tDCS) generated excitability changes and induce modifications of functional cortical architecture in Attention Deficit Hyperactivity Disorder (ADHD) patients. To achieve this, the investigators used an event-related potential (ERP) analysis based on 20 channel EEG recordings in ADHD subjects before and after bipolar tDCS-anode stimulation over F3/F4 or T5/T6 or P4/P3, during resting state and measure clinical scores and visual CPT tasks changes. Time courses and topography of independent component visual ERPs were compared before and after tDCS.
Detailed Description:	Important advances in the understanding of ADHD pathophysiology, such fMRI studies showing a focal frontotemporal loops dysfunction in brain activity, suggest that frontal brain stimulation might be helpful for the treatment of ADHD. In a recent study of Lyon's university with tDCS they concluded that tDCS is "cheaper and easier-use than transcranial magnetic stimulation (TMS) and the impact on symptomatology seems larger (impact on negative symptoms of schizophrenic patients) and longer (at least 3 months duration) than that TMS currently permits. It is possible that tDCS could in the future be used at home by patients themselves. The efficacy of tDCS depends of parameters like electrode position and current strength. In this trial, The investigators investigated the effects of 12 days of anodal stimulation of the left dorsolateral prefrontal cortex in ten patients with ADHD (aged 8 +/- 3 years). tDCS was applied through a saline-soaked pair of surface sponge electrodes (35 cm2). The anode electrode was placed over F3/F4 or T5/T6 or P4/P3(based on the 10-20 International EEG System) of each subject. The cathode was placed over the contralateral mastoid area. A constant current between 1.1 and 2.0 mA was applied for 25 min/day (administered for 12 alternated days). Prior to the first session, ADHD subjects were asked to complete and return a series of questionnaires, including the Conners Brief Symptom Inventory, a health history questionnaire, and the QEEG questionnaire. Subjects were then tested in a first session which lasted approximately three hours. During this period, a comprehensive structured clinical interview was carried out, comprising of an assessment of current and past ADHD symptoms, the history of problems at school, the past psychiatric history (including drug and medication use), as well as past and present comorbidities. Subsequently, EEG data was acquired. EEG data was first recorded while the subject was in eyes-closed and eyes-open resting conditions, lasting four minutes each. Then data was recorded while subjects performed a visual continuous performance task (VCPT). The VCPT took approximately

22 minutes to complete. In addition, subjects randomly performed either an auditory or an emotional continuous performance task.

The control group had a shortened procedure. Subjects were tested in a single session lasting approximately two and a half hours. During this period, a series of questionnaires (Brief Symptom Inventory, Health History questionnaire, Current Symptoms Scales) were filled out and thereafter, EEG data was acquired. Subsequently, a working memory task, which is not relevant here, was administered.

EEG was recorded using a Mitsar 201 19-channel electroencephalographic system. The input signals referenced to the linked ears were filtered between 0.5 and 50 Hz and digitized at a sampling rate of 250 Hz. Impedance was kept below 5 kOhm for all electrodes. Electrodes were placed according to the International 10-20 system using a electrode cap. Quantitative data was calculated using WinEEG software. Linked ears reference montage was changed to average reference montage prior to data processing. Eye-blink artefacts were corrected by zeroing the activation curves of individual ICA component score responding to eye blinks. In addition, epochs of the filtered electroencephalogram with excessive amplitude (>100 μV) and/or excessive fast (>35 μV in 20 to 35 Hz band) and slow (>50 μV in 0 to 1 Hz band) activity were automatically marked and excluded from further analysis. Finally, EEG was manually inspected to verify artefact removal.

Behavioral task

The VCPT is a modification of the visual two-stimulus GO/NOGO paradigm. Three categories of visual stimuli were selected: 20 pictures of animals, 20 pictures of plants, and 20 pictures of humans (presented together with an artificial "novel" sound). The trials consisted of presentations of pairs of stimuli: animal-animal (GO trials), animal-plant (NOGO trials), plant-plant (IGNORE trials), and plant-human (NOVEL trials). The trials were grouped into four blocks. In each block a unique set of five animal stimuli, five plant stimuli and five human stimuli was selected. Each block consisted of a pseudo-random presentation of 100 stimuli pairs with equal probability for each trial category.

The task was to press a button as fast as possible in response to GO trials.

According to the task design, two preparatory sets were distinguished in the trials. In the "Continue set" a picture of an animal is presented as the first stimulus and the subject is supposed to prepare to respond. In the "Discontinue set" a picture of a plant is presented as the first stimulus and the subject does not need to prepare to respond.

During the task, subjects were seated in a comfortable chair, 1.5 m in front of a computer screen. The stimuli were presented on a 17 inch monitor using the Psytask (Mitsar Ltd.) software.

The primary outcome was change in score on the QEEG Rating Scale (AMEN questionnaire). The ERP and questionnaire/ behavioural assessments will be made at baseline (before stimulation)and 3 months after stimulation.

This study involved 30 subjects, all aged between 7 and 13. All have been diagnosed with ADHD by a medical professional.

Conditions

Conditions: ADHD
ADD

Keywords: tdcs
tms
qeeg

neuroplasticity
brain networks
add
adhs

Study Design

Study Type:	Observational
Observational Study Model:	Case-Control
Time Perspective:	Prospective
Biospecimen Retention:	None Retained
Biospecimen Description:	
Enrollment:	60 [Actual]
Number of Groups/Cohorts:	2

Groups and Interventions

Groups/Cohorts	Interventions
active tDCS The patients with ADHD received electro-stimulation at 20 sessions with 2 mAmp 1 session per day alternative days. The investigators used an ERP analysis derived of 20 channel EEG recordings during resting state and visual CPT to define the tDCS site and polarity at refractory ADHD patients to conventional treatments. Time courses, topography and amplitude of ERPs, correlated with clinical scores, were compared with the controls average (data base)to guide the selection of personal tDCS parameters. The following relation shown how many patients were submitted to intervention in each electrode, according to their polarity: Anodal tDCS: T5, T6, etc. Cathodal tDCS: T5, T6, etc.	Device: Active tDCS tDCS applied to left dorsolateral prefrontal scalp area through a saline-soaked pair of surface sponge electrodes (35 cm2). The anode electrode was placed over F3 (based on the 10-20 International EEG System) of each subject. The cathode was placed over the contralateral mastoid area. A constant current of 1.1 mA was applied for 25 min/day (administered for 12 alternated days). Other Names: • Chattanooga Iontophoresis
controls Healthy people that not receive tDCS	

Outcome Measures

[See Results Section.]

Eligibility

Study Population: ADHD children from 5 to 13 years old and controls

Sampling Method: Probability Sample

Minimum Age: 8 Years

Maximum Age: 68 Years

Sex: All

Gender Based:

Accepts Healthy Volunteers: Yes

Criteria: Inclusion criteria:

1. ADHD diagnosis.
2. Age between 7 and 65 years.
3. Comorbidities were no reason for subject exclusion.

Exclusion criteria:

1. Presence of psychosis.
2. Subjects taking medication,they had refrained from taking methylphenidate during 24 hours before testing.
3. Subjects taking other psychotropics were not included in the study.
4. Subjects which had suffered of a head injury with subsequent loss of consciousness, and subjects suffering from neurological or systemic medical diseases were excluded from the study.

Contacts/Locations

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IPDSharing

Plan to Share IPD:

References

Citations: Mueller A, Candrian G, Grane VA, Kropotov JD, Ponomarev VA, Baschera GM. Discriminating between ADHD adults and controls using independent ERP components and a support vector machine: a validation study. Nonlinear Biomed Phys. 2011 Jul 19;5:5. doi: 10.1186/1753-4631-5-5. PubMed 21771289

Mueller A, Candrian G, Kropotov JD, Ponomarev VA, Baschera GM. Classification of ADHD patients on the basis of independent ERP components using a machine learning system. Nonlinear Biomed Phys. 2010 Jun 3;4 Suppl 1(Suppl 1):S1. doi: 10.1186/1753-4631-4-S1-S1. PubMed 20522259

Links:

Available IPD/Information:

Study Results

Participant Flow

Recruitment Details	Subjects were screened and enrolled at 3 clinics in Spain

Reporting Groups

	Description
Active tDCS	Transcranial Direct-Current Stimulation. Patients with ADHD that receive electro-stimulation 20 sessions with 2 mAmp 1 session per day alternative days. 55 % of subjects led the anode in temporal lobe (60% right temporal lobe and 40% in left temporal lobe). 8 % of subjects led de anode in parietal lobe (80 % in left hemisphere), and the rest of subjets 37 % of them led the anodo in frontal and prefrontal lobe (55 % in right frontal lobe and 45 % in left frontal lobe).
Controls	Healthy people that not receive tDCS

Overall Study

	Active tDCS	Controls
Started	30	30
Completed	28 [1]	30
Not Completed	2	0
Physician Decision	2	0

[1] technical problems or excessive artifacts, two data sets were excluded from further analysis.

Baseline Characteristics

Reporting Groups

	Description
Active tDCS	Transcranial Direct-Current Stimulation. Patients with ADHD that receive electro-stimulation 20 sessions with 2 mAmp 1 session per day alternative days
Controls	Healthy people that not receive tDCS

Baseline Measures

		Active tDCS	Controls	Total
Overall Number of Participants		30	30	60
Age, Categorical Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	30 participants	30 participants	60 participants
	<=18 years	19 63.33%	14 46.67%	33 55%
	Between 18 and 65 years	11 36.67%	16 53.33%	27 45%
	>=65 years	0 0%	0 0%	0 0%
Age, Continuous Mean (Standard Deviation) Unit of measure: years	Number Analyzed	30 participants	30 participants	60 participants
		20.06 (13.03)	33.12 (22.80)	25.14 (18.09)

		Active tDCS	Controls	Total
Sex: Female, Male Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	30 participants	30 participants	60 participants
	Female	9 30%	12 40%	21 35%
	Male	21 70%	18 60%	39 65%
Region of Enrollment Measure Type: Number Unit of measure: participants	Number Analyzed	30 participants	30 participants	60 participants
Spain		30	30	60

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Clinical Assessment (Amen Questionnaire)
Measure Description	The Amen Attention Deficit Disorder (ADD) Type Questionnaire is a 71-question self-test that evaluates the ADD syndrome. 0 never, 1 rarely, 2 Occasionally, 3 Often and 4 Very Often. Consists of a series of questions that evaluate five brain systems: basal ganglia (23 items), Cingular System (17 items), Temporal System (16 items), Prefrontal Cortex (24 items) and deep limbic system (20 items). Each system has a maximum score of 4, and if this punctuation is greater than 1.7 it is possible that the system is deviated from normality and implicated in AD/HD behavior. The minimal average score is 5 (Best) and the maximum is 20 (Worst). More than four is suspicious of diagnosis, six or more of a score of three or four is needed to make diagnosis. Meets the criteria for inattentiveness (six or more on questions 1-14) and also scores six or more on the cingular system questions (24-36 items), over-focused ADD subtype is suspected.
Time Frame	From September to December 2012

Analysis Population Description

The number of participants needed for study completion is between 20 and 40 for pilot study if it is homogeneous in patients with clinical signs and symptoms, to test efficacy and safety of noninvasive Brain Stimulation.

Reporting Groups

	Description
Active tDCS	Transcranial Direct-Current Stimulation. Patients with ADHD that receive electro-stimulation 20 sessions with 2 mAmp 1 session per day alternative days
Control Group	Healthy people that not receive tDCS

Measured Values

	Active tDCS	Control Group
Overall Number of Participants Analyzed	30	30
Clinical Assessment (Amen Questionnaire) Mean (Standard Deviation) Unit of measure: units on a scale		
Amen Average Scale Pre_tDCS	9.85 (1.55)	3.55 (1.20)
Amen Average Scale Post_tDCS at 3 months	5.15 (1.83)	3.54 (1.21)

2. Secondary Outcome Measure:

Measure Title	Event-related Potentials Amplitude (ERPs)
Measure Description	ERPs to the GO/NOGO task will be examined for changes as a result of treatment. Assessments were made at baseline (before stimulation), after the 10-12 days of stimulation, and at 1 and 3 months after stimulation. Event related potentials (ERP) generated from a visual continuous performance task (VCPT) are employed to access the early stages of information processing (Mueller et al., 2011; Kropotov, 2008) and performing at a GO/NOGO paradigm may be used to study the mechanisms of the brain's executive functions (Falkenstein et al., 1995). Amplitude and latency of ERP activity recorded from a subject can be compared to normalized databases to predict a possible hyper or hypo function of cerebral circuits. These ERP were recorded on 19 separeted channels according international 10-20 system. Electrode names are derived by brain lobule which is is located below and position, e.g., Pz is Parietal on position zero (midline) and Cz is Central Midline.
Time Frame	From September to December 2012

Analysis Population Description

The number of participants needed for study completion is between 20 and 40 for pilot study if it is homogeneous in patients with clinical signs and symptoms, to test efficacy and safety of noninvasive Brain Stimulation.

Reporting Groups

	Description
Active tDCS	Transcranial Direct-Current Stimulation. Patients with ADHD that receive electro-stimulation 20 sessions with 2 mAmp 1 session per day alternative days
Controls	Healthy people that not receive tDCS
Active tDCS at 3 Months	Transcranial Direct-Current Stimulation. Patients with ADHD that receive electro-stimulation 20 sessions with 2 mAmp 1 session per day alternative days

	Description
Controls at 3 Months	Healthy people that not receive tDCS

Measured Values

	Active tDCS	Controls	Active tDCS at 3 Months	Controls at 3 Months
Overall Number of Participants Analyzed	30	30	30	30
Event-related Potentials Amplitude (ERPs) Mean (Standard Deviation) Unit of measure: microVolts				
Pz GO amplitude	6.07 (2.20)	5.40 (2.28)	4.96 (2.28)	4.77 (2.12)
Cz NOGO amplitude	9.22 (3.59)	7.01 (4.52)	7.23 (2.49)	7.21 (2.19)

3. Secondary Outcome Measure:

Measure Title	Event-related Potentials Latency (ERPs)
Measure Description	ERPs to the GO/NOGO task will be examined for changes as a result of treatment. Assessments were made at baseline (before stimulation), after the 10-12 days of stimulation, and at 1 and 3 months after stimulation. Event related potentials (ERP) generated from a visual continuous performance task (VCPT) are employed to access the early stages of information processing (Mueller et al., 2011; Kropotov, 2008) and performing at a GO/NOGO paradigm may be used to study the mechanisms of the brain's executive functions (Falkenstein et al., 1995). Amplitude and latency of ERP activity recorded from a subject can be compared to normalized databases to predict a possible hyper or hypo function of cerebral circuits. These ERP were recorded on 19 separeted channels according international 10-20 system. Electrode names are derived by brain lobule which is is located below and position, e.g., Pz is Parietal on position zero (midline) and Cz is Central Midline.
Time Frame	From September to December 2012

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
Active tDCS	Transcranial Direct-Current Stimulation. Patients with ADHD that receive electro-stimulation 20 sessions with 2 mAmp 1 session per day alternative days
Control Group	Healthy people that not receive tDCS

	Description
Active tDCS at 3 Months	Transcranial Direct-Current Stimulation. Patients with ADHD that receive electro-stimulation 20 sessions with 2 mAmp 1 session per day alternative days
Control Group at 3 Months	Healthy people that not receive tDCS

Measured Values

	Active tDCS	Control Group	Active tDCS at 3 Months	Control Group at 3 Months
Overall Number of Participants Analyzed	30	30	30	30
Event-related Potentials Latency (ERPs) Mean (Standard Deviation) Unit of measure: milliseconds				
Pz GO latency	323.78 (10.60)	324.44 (16.49)	321.56 (13.33)	326.21 (15.11)
Cz NOGO latency	348.67 (17.89)	354.00 (15.17)	348.22 (16.38)	352.17 (14.91)

4. Secondary Outcome Measure:

Measure Title	Reaction Time (Behavior Task)
Measure Description	All subjects performed a Visual continuous performance task (VCPT) with GO/NOGO paradigm. It consists of three types of stimuli: 1) twenty animals (A), 2) twenty images of different plant (P), 3) Twenty images of people of different professions (H) which is present with an artificial sound called "Novel" 20msec and.Thus, each pair of stimulus is presented for 100 milliseconds, at intervals of one second of duration between each block. The objective of is to press a button as quickly as possible while observing the pairs AA, situation called GO, while trying not to press when observes other types of pairs. This latency of response (reaction time) was mensured. Pairs are called GO(AA) NOGO(AP), IGNORE(PP) and NOVEL(PH + Sound). Errors by omission (lack of response in test GO) and by commission (lack of suppression in NOGO test) were be automatically counted for each subject.
Time Frame	From September to December 2012

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
Active tDCS Group	Transcranial Direct-Current Stimulation. Patients with ADHD that receive electro-stimulation 20 sessions with 2 mAmp 1 session per day alternative days

	Description
Control Group	Healthy people that not receive tDCS
Active tDCS at 3 Months	l Direct-Current Stimulation. Patients with ADHD that receive electro-stimulation 20 sessions with 2 mAmp 1 session per day alternative days
Control Group at 3 Months	Healthy people that not receive tDCS

Measured Values

	Active tDCS Group	Control Group	Active tDCS at 3 Months	Control Group at 3 Months
Overall Number of Participants Analyzed	30	30	30	30
Reaction Time (Behavior Task) Mean (Standard Deviation) Unit of measure: milliseconds				
Reaction Time Before tDCS	466.95 (109.70)	354.68 (39.02)	444.65 (110.56)	356.58 (40.01)
Reaction time after tDCS	467.04 (124.44)	352.29 (35.49)	412.49 (98.41)	351.27 (35.02)

5. Secondary Outcome Measure:

Measure Title	Number of Omission and Commission Errors of Behavior Task
Measure Description	After VCPT task, errors by Omission (lack of response in test GO) and by commission (lack of suppression in NOGO and NOVELTY test) were automatically counted for each subject.
Time Frame	From September to December 2012

Analysis Population Description

The number of participants needed for study completion is between 20 and 40 for pilot study if it is homogeneous in patients with clinical signs and symptoms, to test efficacy and safety of noninvasive Brain Stimulation.

Reporting Groups

	Description
Active tDCS	Transcranial Direct-Current Stimulation. Patients with ADHD that receive electro-stimulation 20 sessions with 2 mAmp 1 session per day alternative days
Control Group	Healthy people that not receive tDCS

Measured Values

	Active tDCS	Control Group
Overall Number of Participants Analyzed	30	30
Number of Omission and Commission Errors of Behavior Task Mean (Standard Deviation) Unit of measure: Number of omission and commision errors		
Omission Errors pre tDCS GO cues	11.22 (10.64)	1.07 (1.27)
Omission Errors post tDCS at 3 months GO cues	12.22 (16.54)	1.04 (1.29)
Comission Errors pre tDCS NOGO cues	0.83 (3.34)	0.04 (0.19)
Comission Errosr post tDCS at 3 months NOGO cues	0.30 (1.02)	0.04 (0.19)

Reported Adverse Events

Time Frame	From September to December 2012
Adverse Event Reporting Description	The adverse events are reported by nurse like at the end of every session.

Reporting Groups

	Description
Active tDCS	Transcranial Direct-Current Stimulation. Patients with ADHD that receive electro-stimulation 20 sessions with 2 mAmp 1 session per day alternative days
Controls	Healthy people that not receive tDCS

All-Cause Mortality

	Active tDCS		Controls	
	Affected/At Risk (%)	# Events	Affected/At Risk (%)	# Events
Total All-Cause Mortality	/		/	

Serious Adverse Events

	Active tDCS		Controls	
	Affected/At Risk (%)	# Events	Affected/At Risk (%)	# Events
Total	0/30 (0%)		0/30 (0%)	

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 3%

	Active tDCS		Controls	
	Affected/At Risk (%)	# Events	Affected/At Risk (%)	# Events
Total	3/30 (10%)		0/30 (0%)	
General disorders				
fatigue or nausea †	2/30 (6.67%)	2	0/30 (0%)	0
Nervous system disorders				
headache †	3/30 (10%)	3	0/30 (0%)	0
headedness / dizziness †	3/30 (10%)	3	0/30 (0%)	0

† Indicates events were collected by systematic assessment.

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

All Principal Investigators ARE employed by the organization sponsoring the study.

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