A Comparative Randomized Controlled Pragmatic Trial of Neurofeedback and Working Memory Training for Children with Attention-Deficit/Hyperactivity Disorder: Protocol

Abstract

Today, the treatment for children and adolescents with Attention Deficit/Hyperactivity Disorder (ADHD) is predominantly pharmacological. However, not all individuals respond to medication or experience side effects. In addition, the compliance and treatment fidelity to medication is sometimes limited, why effective non-pharmacological treatment options are desirable. Neurocognitive training (NCT) methods such neurofeedback (NF) and working memory (WMt) have shown efficacy to treat the primary symptoms of ADHD in non-blinded trials. Still, larger, comparative and blinded pragmatic randomized trials are needed to ensure their efficacy and effectiveness, and to identify an optimal training rationale. Furthermore, little is known about predictors of treatment response to NCTs, such as genetic variants. In this article we present the protocol of a randomized controlled pragmatic trial. Three NCT methods, namely two NF variants, Slow Cortical Potential training (SCP), and Live Z-Score training (LZS), as well as Working Memory Training (WMt) are evaluated against each other and a waiting list control/treatment as usual only group. In a clinical outpatient setting, N = 200 children and adolescents with ADHD aged 9-17 years and common comorbidities are randomized to one of the treatment groups or the inactive control group (n=50/group). The treatment groups (SCP/LZS/WMt) receive a total of 25 highly frequent training sessions (5/week for 5 weeks). A comprehensive assessment comprising ADHD core symptoms, psychopathology, neuropsychology, neurophysiology, quality of life and health related measures are collected pre and post treatment as well as at a 6-month follow-up. Primary outcomes are blinded teacher and unblinded parent ratings as well as self-ratings on the Conners 3 for ADHD. We expect that participants receiving NCT will exhibit improved core ADHD symptomatology compared to waiting list controls. Moreover, we hypothesize that type of NCT (SCP, LZS, WMt) and participant characteristics, such as genetic predisposition, age, IQ, gender, verbal skills, and comorbidity predict patterns of treatment effects the various outcomes.

Key words: ADHD, ADD, comorbidity, attention, treatment, neurofeedback, working memory training, RCT, evidence-based, intervention

Study protocol

Does neurocognitive methods improve AD/HD symptoms?

A comparative, randomized and controlled study in naturalistic setting

Background

Attention-deficit/hyperactivity disorder (AD/HD) is a highly prevalent and heterogenic neuropsychiatric disorder affecting about 5% of school-aged children[1]. The core symptoms of inattention, impulsivity and hyperactivity in AD/HD causes significant problems in several areas of life, affecting adversely children's development and function and causes clear increased risk of developing mental illness. AD/HD is associated with impairment in school performance, increased risk of accidents and misuse, teenage pregnancy, bullying, social isolation, family conflict, anxiety, hopelessness and depression. Nowadays AD/HD is viewed in a life perspective as the core symptoms, mostly difficulties with attention and impulsivity, follow into adulthood. The prevalence of AD/HD in adults is 3-4%. Long-term follow-up studies show that individuals with AD/HD often fail in studies and at work, have increased risk of criminal behavior, long-term sick leave, and problems with handling finances and household chores. Psychiatric comorbidity is estimated to occur in about 80% of adults with AD/HD[2], mainly in untreated AD/HD. AD/HD is, therefore, a condition that untreated can lead to serious consequences for the individual and with large subsequent social costs.

International and local guidelines recommend multimodal treatment combining psychosocial and educational interventions with medication[3]. Most available and commonly used intervention is drug therapy, particularly in the form of stimulants (methylphenidate) which targets behavioral symptoms and has positive effects in the short term, but has limited effect on the long term[4] and after treatment the core symptoms remains. There are also side effects[5], and about 20-30% of children and adolescents with AD/HD do not respond to drug therapy[6], and among those who respond there are still room for improvement. The report by the Swedish Council on Health Technology Assessment[7] emphasizes the need for evidence-based above all non-medical interventions for AD/HD.

Cognitive learning and training (CLT) methods like neurofeedback (NF) and working memory training (WMt) are non-invasive methods which during the recent years experienced a growing empirical support for improving AD/HD symptoms[8]. NF trains the brains electrical activity through an operant/classical learning paradigm and is supposed to enhance the brains self-regulating ability, i.e. flexibly adapt brain activity to better meet the changing demands of the environment. Previous controlled studies and studies with pre-and post-design has found good results mostly by improving impulsivity and inattention[9],[10],[11]. NF has also been demonstrated to induce neuroplastic changes after one session[12] and voluntary control over intrahemispheric functions like the dopamine system[13]. Effects tend to persist after treatment with few side effects (fatigue only after initial training)[14],[15]. WMt focuses on improving working memory functions through challenging exercises in computerized software. Besides encouraging results in enhancing the capacity of foremost visual working memory there has been more sparse evidence that WMt could have beneficial effects on behavioral measures for children with AD/HD[16],[17],[18] and questions remain of the nature of the effects and long term effects[19].

Guidelines recommend multimodal treatment combining psychosocial and educational interventions with medication. Compared with psychopharmacological treatment studies there are quite a limited number of studies on alternative treatments for children and adolescents with AD/HD[20]. CLT´s are non-invasive methods and above all NF has shown good preliminary evidence in several international studies in reducing the core symptoms of AD/HD in children, and has encouraging results in contrast to psychopharmacological treatment that the positive effect persists[21]. WMt has promising evidence of improving working memory capacity and that the good effects also can generalize into other functions but there are a clear shortage of studies comparing WMt with other active interventions and controls (Melby-Lervåg, 2012). If the results would be positive then CLT´s could broaden the range of treatment for children and adolescents with AD/HD in Sweden. To date there are several different kinds of neurofeedback training options and two mainstream methods are Slow Cortical Potential training (SCPt) and frequency training (Ft) whereas the latter offers more commercially available options. For the clinical validity of this rather extensive training it is of major importance that potential improvements also last. There is a lack of follow-up studies concerning CLTs (Hodgson et al, 2012, Lofthouse et al, 2012, Melby-Lervåg et al, 2012) and the aim of this sub study is to measure long term outcome from CLT methods

Aims and objectives

Primary aim of the study is to evaluate if neurocognitive training improves core symptoms in AD/HD. Key objectives are (i) are there differences in outcome between the different neurocognitive methods, (ii) can we find predictors that differentiate learners from non-learners, (iii) are neurocognitive methods feasible in clinical settings. Additional important research questions are a) if possible improvements generalize to other settings like

school and home environment, b) does effects last six months after training, c) does the training affect the bioelectrical communication in the brain, d) are there more generalized beneficial outcomes as in perceived quality of life, stress in parents, sleep patterns.

Method/design

The KITE study is a randomized, controlled and comparative study conducted in collaboration between Child and Adolescent Psychiatry (BUP) Division in Stockholm and Center of Neurodevelopmental Disorders at Karolinska Institutet (KIND). The study protocol was approved by Ethical Review Board in Stockholm (Dnr.2013/739-31, amendment: Dnr.2013/1729-32). The trial is registered with ClinicalTrials.gov (NCT01841151).

Eligibility and Recruitment

Participants are recruited by referrals from Child Psychiatric Clinics, ADHD-center (Habilitering & Hälsa) and children clinics (Barn- och ungdomsmedicinska mottagningar) in Stockholm County. Self-referrals are also welcome. Parents or legal guarding comes to an information meeting that is held at BUP-KIND. Before entering the study, written consent is obtained from the parent or legal guardian of the participant, and verbal assent for children under 13 or written assent for children 13 years and older. Evaluation about inclusion and exclusion criteria's is made after signed informed consent forms arrives with most recent report of neuropsychiatric evaluation confirming the ADHD diagnose.

A total of n=200 children and adolescents with AD/HD between 9-17 years of age will participate in the study alongside with treatment as usual (TAU) such as drug treatment. The duration for the participant in the study is about 30 weeks a total of; (a) baseline testing, (b) five weeks training/TAU, (c) post testing and (d) six months follow-up testing. Measurements are made with self-, parent- and teacher estimations, psychometric tests and neurophysiological measurements at measure points (a), (c) and (d). Each child and parent or guardian participate in an evaluation session to determine eligibility for the study and to establish a baseline score. To confirm AD/HD diagnosis and to ensure IQ>80 a psychiatric interview is done with parents by Kiddie Schedule for Affective Disorders and Schizophrenia for children of 6-18 years (K-SADS)[22] and the participant are tested by Vocabulary and Block Design-tests from WISC IV or WAIS IV from where IQ estimate is calculated.

After referral or self-referral and initial evaluation based on requisitioned report on previously made assessment to establish AD/HD diagnoses the study participants are randomized to four different groups N=50 in each. Two groups of NF (SCP and Ft), WMt group, and the fourth, control group will be measured during treatment as usual (TAU) and will be able to train with self-preferred method after the last measure point. The duration of KITE study is 36 months. After initial screening the duration for participants in the study is approximately 30 weeks a total of; (a) baseline testing, (b) 5 weeks of CLT/TAU, (c) post testing and (d) six months follow-up testing. All the participants attend the study in parallel with TAU, such as drug treatment.

Inclusion criteria

Clinical diagnosis of AD/HD according to DSM-IV-TR and the K-SADS
interview, drug naive or under stable medication with stimulants or equivalent for at least 1 month.

Exclusion criteria

IQ <80 (WISC-IV or WAIS-IV), clinically unstable psychiatric condition such as suffering from acute depression, bipolar disorder, severe obsessive compulsive disorder, clinically judged severe self-harming behavior, severe somatic (neurological) disease, or has a very limited knowledge of the Swedish language.

Interventions

Subjects randomized to the training groups, i.e. NF1, NF2 and WMt, comes to the clinic five times per week for five weeks, 25 sessions in total. Each session lasts about 50 minutes.

Two NF methods

NF 1: Slow cortical potential (SCP)

SCP is slower bioelectrical activity in the brain, it is a form of event related potentials (ERPs) and locked in time. It is related to phasic regulation of cortical excitability and apical dendrites of pyramidal cells are believed to be the source of the activity. SCP is characterized of negative and positive shifts lasting from 350(?) milliseconds to several seconds. The negative shift is believed to reflect brain state of allocating attentional resources and increased cortical excitability, and positive shifts reflects inhibition, reduced excitability. In this

study setting children sits in front of a computer screen and are asked to use their brain activity to either move an object up on the screen for negative shift or down for positive. The training segments lasts in total 8 seconds (2 seconds for baseline, 6 seconds of training). One session consists of 36 segments with 50% positive and 50% negative shifts that are trained in random order. Also transfer trials are trained where children has to imagine positive or negative shift according to guidelines presented on the screen. Vertical, horizontal eye movement and eye blinks are recorder and computed before every session and corrected online during training. For segments containing artifacts exceeding…. And … no feedback is calculated. For closer description see supplement section.

NF 2: Live z-score (LZS)
LZS is thought to compute, view, and process normative z-scores in real time and give feedback to the ongoing electroencephalogram (EEG). The software instantaneous measure different aspects of EEG e.g. relative and absolute amplitude and connectivity measures and give feedback on measured brain activity normative values interpreted to population mean z-score deviations of choice. A metric that is about 0 for the general population, and the trainer decides how many standard deviations and rate of feedback is best to work with. Feedback consists of getting information if the brain meets or not conditions decided by the trainer, e.g. and provides real-time proportional feedback… all feedback is governed by statistical ranges that are defined as plus/minus z-scores or standard deviations. ….

The training protocol has been design in collaboration with Tom Collura, founder of Brainmaster (www.brainmaster.com). It consists of training with 2 channels in two 20 minute sections (first is with following placements; C3 and C4, second part: Fz and Cz), 40 minutes of training in total. Feedback is provided partially by Flashgames and movies with a dimmer (the positive feedback is a brighter screen). For more information see supplement section.

Working memory training (WMt)
KITE study use a computerized software program for working memory training called Memory Quest Flex (www.flexprogram.org). Every session consists of ten different modules with eight (for younger children) or 10 (from 12 years old) different exercises in each. The different exercises stresses on either visual or auditory working memory, and the difficulty level adjusts automatically as a response to individual performance. Various kinds of positive rewards, e.g. oral and collect objects, is provided by the program. After follow-up measure participants in the WMt group are offered NF2 training in the same way as NF2 group are training.

Control
For those randomized to control group are measures collected at the same time points as for the active groups. After final data collection participants in the control group are offered NF training same as the active NF groups have obtained.

Measures
Participants using methylphenidate has a 48 hours wash-out period before measurement.

Primary outcome measures
The primary outcomes for KITE study is changes in AD/HD core symptoms measured by self-, parents- and teacher estimates by full-length Conners 3[23] forms. Conners 3 is a well-studied rating scale aimed to capture manifestations of the behavioural symptoms in AD/HD. It consists of three questionnaires (child, parent and teacher) for children between 6-17 years old.

Secondary outcome measures
Rating scales
Behavior Rating Inventory of Executive Function (BRIEF)[24] is used for parents and teachers to fill to identify dysexecutive functioning and possible improvements with neurocognitive training. It is an 86-item questionnaire.

KIDSCREEN-27[25],[26]; is a self-report questionnaire consisting of 27 items applicable to children between 8-18 years about perceived quality of life (QoL). Items are scored on a five-point scale; higher scores indicate better experienced QoL. The KIDSCREEN-27 has been shown to have robust psychometric properties[27].

The Swedish Parenthood Stress Questionnaire (SPSQ)[28] is developed from Parenting Stress Index (PSI)[29] and consists of 35 questions divided into five domains. The aim is to detect perceived stress related to parenthood.

Diet and exercise questionnaire[30]; Swedish National Food Administration's published diet and exercise questionnaire for adults has been slightly adjusted to suit children, and parents fills it at the first measure point.

Sleep questionnaire – simple schedule of registration sleep onset, time and perceived sleep quality for one week (seven nights) is filled one week before, after training and at the follow-up time point.

Cognitive measures

Conners CPT II[31]: is a task-oriented computerized continuous performance test. It measures inattentiveness, impulsivity, sustained attention and vigilance.

Find the phone task: Is a computerized test where the task is to avoid selecting several times the phone that already has rung among many phones on the screen. The number of times an already rung phone is selected is used as a measure of deficits in the working memory. The task is similar to the spatial working memory task in Cambridge Neuropsychological Test Automated Battery (CANTAB[32]).

Working memory; forward and backward digit and block span subscales from the WISC-IV[33] or WAIS-IV[34] were administered. The dependent measure is the level where participant fails to correctly repeat digits or block on two consecutive trials at one level of difficulty.

IQ; IQ estimate[35] is calculated from the subtests vocabulary and block design in WISC-IV or WAIS-IV.

Tapping[36] This is a computerized auditory task. Every 1,200ms a tone is presented, and the child has to tap at the same pace by pressing right mouse button. After 15 cued trials the child is asked to continue tapping at the previously cued rate for 41 uncued trials. Within-subject standard deviation will be calculated of the variability in tapping.

Duration Discrimination[37] Two unfilled intervals (target and comparison) defined by two brief tones (50 milliseconds; 1000 Hz) before and after are presented to the child. The task is to discriminate between longer and shorter, target interval (400 milliseconds, ms). The participant responds by pressing left mouse button if the first tone is longer and right button if they think the second one is longer. The trial intervals are separated by 800 ms and inter-trial interval is 1000 ms. The target interval shifts randomly from first to second place, and the longer is adjusted up or down in 10 ms increments depending on the accuracy of response. An adaptive procedure was used to track 80% accuracy[38] and after six reversals of direction the test ended. The dependent measure is the average of the last five reversal values.

Time anticipation[39]. A computerized task where the child has to beam oxygen to a spaceship to save the crew. In the beginning the target ship becomes visible at the same rate for the first trials and the child has to press a button. After ten trials the child has to estimate when the so called cloaked or invisible ship appears at the same interval as on the uncued, visible trials. Feedback is given in both visible as invisible trials. In the first block the response rate was every 400 ms and on the second block 2000 ms. the dependent measure is calculated as the mean percentage of responses made before the ally arrived (i.e. too early responses).

Biomarkers

Quantitative electroencephalogram (QEEG) measured through 21 electrodes, placed according to international 10-20 system. Three minutes eyes open, three minutes eyes closed.

Event-related potentials (ERP) is neuronal processes underlying measurable overt behaviour such as speed and accuracy of processing information. ERPs provides direct measure of brains covert activity and its precise timing, specifically preparatory and inhibitory processes.

- P300 measured from central location (Cz) and is seen as an index of neurophysiological response inhibition (or no-go). Reduced P3 amplitude to cues in CPT-OX test is associated with resource allocation and covert attentional orienting is the most consistent neurophysiological deficit in childhood AD/HD[40].

- Contingent Negative Variation (CNV) measured centrally Cz is indication of preparatory processes in the brain, reduced amplitudes indicate deficits in time processing, motor and non-motor preparation in childhood AD/HD[41]
- Error-related negativity (ERN) recorded from CFz[42] when participants make errors in t ex flanker task ERN presents as a negative detection approximately 50-100 ms following the erroneous response. It is thought to reflect error-related brain activity namely individual's ability to monitor behaviour. Deficits in executive functioning i.e. response monitoring is one hallmark in AD/HD

Flankers test which is a kind of reaction time task and where the subject has to respond as quickly as possible, while avoiding errors. The participants are required to indicate the direction of a central target in an array of three stimuli. *Continuous performance test, CPT-OX* consists of 400 letters presented briefly (150ms) every 1,65 s in a pseudorandom sequence at the centre of a computer monitor. Letter "O" is the cue and initiate 40 cue-target i.e. ´O` followed by letter ´X` (go condition) or 40 cued non-target (O followed by different letter than X, no-go condition).

Randomization

Random list of numbers. The date when consent form has arrived.

Statistical analysis

We expect that participants receiving NCT will exhibit improved core ADHD symptomatology and secondary and exploratory outcomes compared with waiting list controls. Moreover, we hypothesize differing effects of Cognitive training in ADHD type of NCT (SCP, LZS, WMt) based on the participant characteristics (e.g. genetic redisposition, age, IQ, gender, verbal skills, and comorbidity) will predict patterns of treatment effects on the various outcomes. The sample size calculation refers to the three primary outcome endpoints: change in Conners 3 total scores and subscales for parent, self-report, and blind teacher ratings between baseline and follow-up assessment, in the Intention to Treat (ITT) sample. MANOVA for repeated measures (three measurement points, withinbetween subjects' interactions, posthoc tests) will be used for the statistical analysis for the RCT study. Based on available evidence about NCT efficacy medium effects for the primary outcomes are expected. With N=200 (n=50 SCP vs. n=50 LZS vs. n=50 WMtr vs. n=50 TAU only controls) and alpha=5%, the power (1-beta) is >99% for medium effects (G Power 3.1.7). All data provided for the participants will be included in the analyses. Data will be tested for normality and homogeneity of variance. To verify that the treatment group and control groups are comparable for continuous and categorical demographic variables at pretreatment, a series of independent-samples t-tests and chi-square tests will be conducted. As for primary outcomes, analyses for secondary outcomes will be conducted according to ITT principles. To analyse for the significance of potential factors predicting outcomes (age, IQ, language abilities, gender, comorbidity, genetic variants) in the active NCTs training groups, these are analysed using a logistic regression to explain dichotomized (by median-split) Conners 3 outcomes as the dependent variable.

Adverse events

Potential adverse events will be continuous monitored with Paediatric side effect checklist (P-SEC[43]). P-SEC is commonly used in monitoring possible side effects of stimulants. Before training and every 5th training session the parents are interviewed or asked to fill in the P-SEC. For every participant in the active groups are a total of six P-SEC followed through. For the control group P-SEC is rated at pre- and post-measure points and once during the active groups training period. Spontaneous remarks of possible adverse events are thoroughly noted in participant's journals. As the study is conducted within newly established research child psychiatric out-door unit the participants are protected through patient insurance.

Discussion

The project aims to optimize brain functioning to facilitate among other things the ability to focus and maintain attention, controlling impulsive behavior and activity level that are the core difficulties in AD/HD. An important role is also giving access to evaluated non-pharmacological methods with scientific basis to children and adolescents with AD/HD. We know today that untreated AD/HD gives suffering and have far-reaching consequences at the individual, group and society level. There is a need for proven interventions for children and adolescents with AD/HD in addition to drug treatment (SBU, 2012[44]). Some do not respond or respond only marginally to drug treatment, others do not want medications that have side effects and that the core problems

remain after the medical treatment has ceased. CTL are non-invasive methods where NF has shown good preliminary evidence in several international studies in reducing the core symptoms of AD/HD in children and in contrast to psychopharmacological treatment the effect seem to persist foremost of NF training. The study is the first of its kind in Sweden and will be conducted in naturalistic clinical environment that ensures external validity to the study results. If the results show effectiveness CLT methods could broaden the range of treatment for children and adolescents with AD/HD in Sweden. In the long term it can lead to decreased suffering, increased function in everyday life, education and work, and quality of life for the individual patient and their family, and reduced social costs.

Trial status

The first participant enrolled in the study in August 2013.

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