CLINICAL TRIAL PROTOCOL

Title: Comparative Effects of BCI-Based Attention Training, Methylphenidate, and Citicoline on Attention, Executive Function, and Emotional/Behavioral Outcomes in School-Age Children with Attentional Difficulties

Protocol Version: 1.0
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Institution: Uludağ University

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Trial Phase: Exploratory clinical study (quasi-experimental)
Registration: Registered online

1. SYNOPSIS

Study Design:
Prospective, quasi-experimental, non-randomized, parallel-group, pre–post clinical study with four intervention arms.

Study Arms (4 groups):

1. COGO + Methylphenidate (Mph)
2. COGO + Citicoline
3. COGO-only
4. Citicoline-only

Target Population:
School-age children (approximately 6–18 years) with clinically significant attentional difficulties and/or ADHD symptoms, referred to child and adolescent psychiatry or pediatric neurology clinics.

Planned Sample Size:
Total n = 170–180 (approximately 40–45 participants per group), reflecting a naturalistic convenience sample and expected attrition.

Study Duration per Participant:

Screening period: up to 4 weeks

Intervention period: 8 weeks

Total participation: approximately 10–12 weeks

Primary Objective:

To compare within- and between-group changes in attention performance (CPT-3 indices) following 8 weeks of COGO BCI-based attention training and/or pharmacological/nutraceutical intervention.

Secondary Objectives:

To evaluate changes in behavioral, emotional, and executive-function outcomes between baseline and post-treatment.

To compare the pattern of change across the four treatment modalities.

Primary Outcome:

Change from baseline to week 8 in Conners Continuous Performance Test–Third Edition (CPT-3) T-scores, focusing on:

Omission errors

Commission errors

Hit Reaction Time (HRT)

HRT Standard Deviation (HRT SD)

Variability

HRT Block Change

HRT ISI Change

Secondary Outcomes:

Change from baseline to week 8 on:

SNAP-IV (Inattention, Hyperactivity/Impulsivity)

Sluggish Cognitive Tempo (SCT) Scale

Revised Child Anxiety and Depression Scale (RCADS)

Strengths and Difficulties Questionnaire (SDQ)

Behavior Rating Inventory of Executive Function (BRIEF: BRI, MI, GEC and subscales)

Statistical Methods (summary):

Descriptive statistics for all variables

Within-group pre–post changes: paired t-tests

Between-group differences: ANCOVA/one-way ANOVA (adjusted for age)

Group-by-time effects: repeated-measures ANOVA

Significance threshold: $p < 0.05$ (two-sided)

2. BACKGROUND AND RATIONALE

Attention-deficit/hyperactivity disorder (ADHD) and attentional difficulties are prevalent in childhood and are associated with deficits in sustained attention, inhibitory control, and executive function, impacting academic and socio-emotional functioning. Pharmacological treatment with stimulants such as methylphenidate is considered first-line but has important limitations, including side effects, variable response, and concerns about long-term use.

Citicoline (CDP-choline) is a nutraceutical agent with potential cognitive-enhancing properties via effects on phospholipid metabolism and dopaminergic/cholinergic pathways, but evidence in pediatric ADHD is still limited and mixed. Brain–computer-interface (BCI)-

based attention training and EEG-based neurofeedback have emerged as non-pharmacological modalities aiming to improve attention by modulating neurophysiological markers through real-time feedback and gamified training tasks.

The COGO Cognitive Training Program is an EEG-based BCI attention training system using adaptive game-based tasks, typically delivered over 8 weeks (3 sessions/week, total 24 sessions). Preliminary data suggest feasibility and potential benefit on attention and related behavioral domains. Integrating COGO with methylphenidate or citicoline may yield additive or synergistic effects on attention, executive functioning, and emotional regulation, but direct comparative clinical data are scarce.

This protocol describes a quasi-experimental clinical study comparing four treatment strategies: COGO + methylphenidate, COGO + citicoline, COGO-only, and citicoline-only, using both neuropsychological (CPT-3) and parent-report measures (SNAP-IV, SCT, RCADS, SDQ, BRIEF).

3. STUDY OBJECTIVES AND HYPOTHESES

3.1 Primary Objective

To assess and compare the effects of four intervention modalities on attention performance, as measured by CPT-3 T-scores, after 8 weeks of treatment.

3.2 Secondary Objectives

1. To evaluate changes in behavioral and emotional symptoms (SNAP-IV, SCT, RCADS, SDQ).
2. To evaluate changes in executive functioning (BRIEF indices and subscales).
3. To explore whether combined interventions (COGO + methylphenidate and COGO + citicoline) show greater improvements than single-modality interventions (COGO-only, citicoline-only).

3.3 Hypotheses

H1: COGO + methylphenidate will produce the largest improvements in CPT-3 omission errors and HRT-related measures compared with other groups.

H2: COGO + citicoline will yield greater improvements in commission errors and emotional/internalizing symptoms compared with other groups.

4. STUDY DESIGN

4.1 Overview

This is a single-center (or multicenter, if applicable), prospective, quasi-experimental clinical trial with four parallel treatment arms. Treatment allocation is based on routine clinical decision-making rather than randomization (naturalistic design).

4.2 Study Arms

1. **COGO + Methylphenidate Group**
    - COGO BCI-based attention training for 8 weeks
    - Concurrent methylphenidate treatment at clinically appropriate doses
2. **COGO + Citicoline Group**
    - COGO training for 8 weeks
    - Concurrent citicoline at age-appropriate doses
3. **COGO-only Group**
    - COGO training for 8 weeks
    - No methylphenidate or citicoline
4. **Citicoline-only Group**
    - Citicoline at age-appropriate doses for 8 weeks
    - No COGO training and no methylphenidate

4.3 Study Visits and Timepoints

- **Visit 1 (Screening / Baseline, Week 0):**
    - Eligibility assessment
    - Informed consent/assent
    - Sociodemographic and clinical data

    - Baseline CPT-3
    - Baseline parent-rated scales: SNAP-IV, SCT, RCADS, SDQ, BRIEF
- **Visits 2–[n] (Intervention Period, Weeks 1–8):**
    - COGO sessions (3/week) for arms 1–3
    - Medication dispensation/monitoring for arms 1, 2, and 4
    - Adverse event (AE) assessment at each contact
- **Visit Final (Post-treatment, Week 8 ± 1 week):**
    - Repeat CPT-3
    - Repeat SNAP-IV, SCT, RCADS, SDQ, BRIEF
    - AE and concomitant medication review
    - Study termination procedures

5. STUDY POPULATION

5.1 Inclusion Criteria

1. Children and adolescents aged approximately 6-18 years.
2. Referred for attentional difficulties and/or suspected/diagnosed ADHD based on clinical evaluation.
3. Clinically significant attention problems (e.g., elevated SNAP-IV inattention scores or comparable clinician-rated criteria).
4. Enrolled in regular school education (any grade).
5. Able to comply with study procedures and attend scheduled COGO sessions (where applicable).
6. At least one parent/legal guardian able to give informed consent; child able to provide assent according to local regulations.

5.2 Exclusion Criteria

1. Known intellectual disability (IQ < approx. 70) that would impede participation.
2. Severe neurological disorders (e.g., epilepsy with frequent seizures, major brain injury) interfering with EEG-based training.
3. Severe psychiatric comorbidity requiring immediate intensive intervention (e.g., psychosis, acute suicidality).

4. Current or recent (within 4 weeks) use of psychotropic medications other than methylphenidate or citicoline, unless on a stable non-interacting medication regimen approved by the investigator.
5. Known allergy or contraindication to methylphenidate or citicoline (for relevant groups).
6. Sensory or motor impairments preventing the use of the COGO system.
7. Participation in another interventional clinical trial within the last 3 months.

6. INTERVENTIONS

6.1 COGO Cognitive Training Program

Modality: EEG-based BCI attention training using game-based tasks.

Schedule: 3 sessions per week, over 8 consecutive weeks (total of 24 sessions).

COGO study

Session Duration: Approximately [20–40] minutes per session (to be specified by site standard).

Setting: Outpatient clinic (or supervised home-based where applicable).

Content: Adaptive attention, working memory, and inhibitory-control tasks that integrate real-time EEG markers into game mechanics.

Compliance: Attendance will be recorded; adherence thresholds (e.g., ≥75% of sessions completed) will be predefined for per-protocol analyses.

6.2 Pharmacological Interventions

6.2.1 Methylphenidate (Mph)

Indication: ADHD/attentional problems, according to national guidelines.

Formulation: Immediate-release or extended-release as per routine clinical practice.

Dosing: Initiated and titrated by treating child psychiatrist or pediatrician according to body weight, symptom severity, and tolerability.

Duration: Continuous over the 8-week intervention period.

6.2.2 Citicoline

Formulation: Oral solution, capsules, or tablets, according to age and local availability.

Dosing: Age-appropriate total daily dose as per product labeling or current clinical practice (e.g., mg/kg/day or fixed pediatric dose), divided in 1–2 administrations.

Duration: Continuous over the 8-week intervention period.

6.3 Concomitant Medications

Stable doses of non-psychotropic medications (e.g., for asthma, allergies) are permitted.

Initiation of new psychotropic medications during the trial is discouraged and should be documented and evaluated case by case.

Any change in methylphenidate or citicoline dose will be documented.

7. OUTCOME MEASURES AND ASSESSMENTS

7.1 Primary Outcome Measure

Conners Continuous Performance Test–Third Edition (CPT-3)

Outcome Measure 1 Name: Conners Continuous Performance Test–Third Edition (CPT-3) – Omission Errors Description: Number of omission errors reflecting inattention, reported as T-scores derived from CPT-3 normative data. Unit of Measure: T-score

Outcome Measure 2 Name: Conners Continuous Performance Test–Third Edition (CPT-3) – Commission Errors Description: Number of commission errors reflecting impulsivity, reported as T-scores derived from CPT-3 normative data. Unit of Measure: T-score

Outcome Measure 3 Name: Conners Continuous Performance Test–Third Edition (CPT-3) – Perseverations Description: Number of perseverative responses reflecting response control difficulties, reported as T-scores derived from CPT-3 normative data. Unit of Measure: T-score

Outcome Measure 4 Name: Conners Continuous Performance Test–Third Edition (CPT-3) – Hit Reaction Time (HRT) Description: Mean reaction time for correct responses, reported as T-

scores derived from CPT-3 normative data. Unit of Measure: T-score

Outcome Measure 5 Name: Conners Continuous Performance Test–Third Edition (CPT-3) – Hit Reaction Time Standard Deviation (HRT SD) Description: Variability of reaction time across correct responses, reported as T-scores derived from CPT-3 normative data. Unit of Measure: T-score.

- Assessed at baseline and at week 8.

7.2. **Secondary Outcome Measures**

Outcome Measure

7. 2. 1. Swanson, Nolan, and Pelham Rating Scale–Fourth Edition (SNAP-IV)

Description: Description: The Swanson, Nolan, and Pelham Rating Scale–Fourth Edition (SNAP-IV) is a parent- or teacher-rated scale assessing symptoms of inattention, hyperactivity/impulsivity, and oppositional defiant behavior. Items are rated on a 4-point Likert scale (0–3), with higher scores indicating greater symptom severity. Score Range: Item scores range from 0 to 3; subscale scores are calculated as mean scores ranging from 0 to 3. Direction of Outcome: Higher scores indicate worse outcomes (greater symptom severity). Outcome Measure: Change in SNAP-IV total score from baseline to post-intervention.**Time Frame:** 8 weeks

Outcome Measure

7. 2. 2. Barkley Sluggish Cognitive Tempo Scale

Description: Description: The Barkley Sluggish Cognitive Tempo Scale is a parent- or teacher-rated questionnaire assessing sluggish cognitive tempo symptoms, including excessive daydreaming, mental confusion, lethargy, and slowed behavior. Minimum–Maximum Score Range: Items are rated on a 4-point Likert scale ranging from 0 (never or rarely) to 3 (very often). Total and mean scores range from 0 to 3. Direction of Outcome: Higher scores indicate greater symptom severity and therefore worse outcomes. Outcome Measure: Change in Barkley SCT total score from baseline to post-intervention.**Time Frame:** 8 weeks

Outcome Measure

7. 2. 3. Revised Child Anxiety and Depression Scale (RCADS), Parent Version

Description: Description: The Revised Child Anxiety and Depression Scale (RCADS) – Parent Form is a parent-rated questionnaire consisting of 47 items, assessing symptoms of anxiety and depression in children and adolescents across multiple DSM-based subscales (separation anxiety, social phobia, generalized anxiety, panic disorder, obsessive–compulsive disorder, and major depressive disorder). Minimum–Maximum Score Range: Items are rated on a 4-point Likert scale ranging from 0 (never) to 3 (always). Subscale and total raw scores range from 0 to 141. Raw scores may be converted to age- and sex-adjusted T-scores. Direction of Outcome: Higher scores indicate greater anxiety and depressive symptom severity and therefore worse outcomes. Outcome Measure: Change in RCADS total score from baseline to post-intervention.**Time Frame:** 8 weeks

Outcome Measure

7. 2. 4. Strengths and Difficulties Questionnaire (SDQ)

Description: Description: The Strengths and Difficulties Questionnaire (SDQ) is a parent-rated behavioral screening questionnaire consisting of 25 items, assessing emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior in children and adolescents. Minimum–Maximum Score Range: Items are rated on a 3-point Likert scale ranging from 0 (not true) to 2 (certainly true). The Total Difficulties Score (sum of four difficulty subscales) ranges from 0 to 40. The Prosocial Behavior subscale ranges from 0 to

10. Direction of Outcome: For the Total Difficulties Score, higher scores indicate greater behavioral and emotional difficulties (worse outcomes). For the Prosocial Behavior subscale, higher scores indicate better outcomes. Outcome Measure: Change in SDQ Total Difficulties score from baseline to post-intervention.**Time Frame:** 8 weeks

Outcome Measure

7. 2. 5. Behavior Rating Inventory of Executive Function (BRIEF)

Description: Description: The Behavior Rating Inventory of Executive Function (BRIEF) is a parent-rated questionnaire consisting of 86 items, designed to assess executive functioning in everyday settings in children and adolescents. It yields index scores including the Behavioral Regulation Index (BRI), Metacognition Index (MI), and a Global Executive Composite (GEC). Minimum–Maximum Score Range: Items are rated on a 3-point Likert scale. Raw scores are converted to age- and sex-adjusted T-scores, which typically range from 30 to 100. Direction of Outcome: Higher T-scores indicate greater executive function difficulties and therefore worse outcomes. Outcome Measure: Change in BRIEF Global Executive Composite T-score from baseline to post-intervention.**Time Frame:** 8 weeks

All questionnaires will be completed by parents or primary caregivers at baseline and at week 8.

8. SAMPLE SIZE AND POWER

This is primarily an exploratory, naturalistic clinical study. In the manuscript, no a priori sample size calculation was performed, and group sizes of approximately 42–44 participants per arm were obtained.

For this protocol, a target total sample size of approximately 160–180 participants (≈40–45 per group) is set, which is expected to provide adequate power (around 0.80) to detect medium within-group effect sizes (Cohen's d ≈ 0.5) and small-to-medium group-by-time interactions in repeated-measures analyses, assuming alpha = 0.05 and modest attrition.

9. STATISTICAL ANALYSIS PLAN

9.1 Analysis Populations

Full Analysis Set (FAS): All enrolled participants with baseline and at least one post-baseline primary outcome assessment.

Per-Protocol Set (PPS): Participants with high adherence (e.g., ≥75% of planned COGO sessions where applicable, and continuous medication use without major protocol deviations).

9.2 Descriptive Analyses

Continuous variables: mean, standard deviation, median, interquartile range.

Categorical variables: counts and percentages.

9.3 Primary Analysis

Within each group, pre–post changes in CPT-3 T-scores will be analyzed using paired-samples t-tests.

Between-group comparisons of change scores will be conducted using ANCOVA or one-way ANOVA, adjusting for baseline age (and grade if appropriate).

COGO study

9.4 Secondary Analyses

Pre–post changes in SNAP-IV, SCT, RCADS, SDQ, and BRIEF scores will be examined using paired t-tests within groups.

Group-by-time interactions will be assessed using repeated-measures ANOVA (time × group) for each outcome.

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Effect sizes will be reported as Cohen's d for paired comparisons and partial η^2 for ANOVA models.

9.5 Handling Missing Data

Missing baseline data will preclude inclusion in FAS for that outcome.

For missing post-treatment data, analyses will primarily use available cases; sensitivity analyses may consider simple imputation (e.g., last observation carried forward) if appropriate.

Reasons for missing data will be documented.

9.6 Significance Level

Two-sided tests with alpha = 0.05.

No formal multiplicity correction is planned, as the study is exploratory; interpretation will remain cautious.

10. SAFETY MONITORING

10.1 Adverse Events (AEs)

All AEs reported by participants or observed by investigators will be recorded from the time of consent until the final visit.

10.2 Serious Adverse Events (SAEs)

SAEs (death, life-threatening events, hospitalization, disability) will be reported to the ethics committee and relevant regulatory bodies per local regulations and within mandated timelines.

Causality (related, possibly related, unrelated) will be assessed by the PI.

10.3 Early Withdrawal Criteria

Participants may be withdrawn in case of:

Serious or intolerable AEs.

Non-compliance with study procedures (e.g., missing most COGO sessions).

Withdrawal of consent by parent/guardian or assent by the child.

Investigator's judgment that continued participation is not in the child's best interest.

If appropriate, a Data and Safety Monitoring Plan (DSMP) or Data Monitoring Committee (DMC) may be established, depending on institutional requirements.

11. ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and applicable local regulations.

The study protocol, informed consent/assent forms, and recruitment materials will be approved by the institutional ethics committee before initiation.

Written informed consent will be obtained from parents/legal guardians; age-appropriate assent will be obtained from children.

Participants may withdraw from the study at any time without consequences for their routine clinical care.

The quasi-experimental design reflects standard clinical decision-making, minimizing additional risks.

12. DATA MANAGEMENT AND CONFIDENTIALITY

Each participant will be assigned a unique study ID; identifiable information will be stored separately from research data.

Paper questionnaires and CPT-3 printouts will be stored in locked cabinets; electronic data will be kept on password-protected computers/servers with restricted access.

Data quality checks (range checks, missing data review) will be performed regularly.

Data will be retained for at least the minimum period required by national regulations and institutional policy.

13. STUDY TIMELINE

Protocol approval and registration: 10.10.2023

Participant recruitment: February 2025-November 2025

Data analysis and manuscript preparation: November 2025

14. PUBLICATION PLAN

Results will be analyzed and submitted for publication in peer-reviewed journals and presented at scientific meetings. Authorship will follow standard international authorship criteria. Participant confidentiality will be strictly maintained in all publications.