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Scaffolding the attention-deficit/hyperactivity disorder brain using transcranial direct current and random noise stimulation: A randomized controlled trial

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HIGHLIGHTS

- Transcranial random noise stimulation (tRNS) improved clinical symptoms in unmedicated children with ADHD.
- The improvement using tRNS was greater than transcranial direct current stimulation (tDCS) with a montage that was highlighted as promising in previous meta-analyses.
- The effect of intervention yielded further improvement after completion of treatment, suggesting a neuroplasticity-related effect.

ABSTRACT

Objective: Improving symptomology and cognitive deficits in neurodevelopmental disorders is a crucial challenge. We examined whether neurostimulation protocols, which have been shown to yield long-term effects when combined with cognitive training, could benefit children with Attention-deficit/hyperactivity-disorder (ADHD), the most common neurodevelopmental disorder in childhood.
Methods: We used a randomized double-blind active-controlled crossover study of 19 unmedicated children with ADHD, who received either anodal transcranial direct current stimulation (tDCS) over the left dorsolateral prefrontal cortex (dlPFC) or random noise stimulation (tRNS) over the bilateral dlPFC, while completing executive functions training.
Results: For our primary outcome, tRNS yielded a clinical improvement as indicated by the reduced ADHD rating-scale score from baseline, and in comparison to the changes observed in tDCS. The effect of brain stimulation one week after completion of treatment yielded further improvement, suggesting a neuroplasticity-related effect. Finally, tRNS improved working memory compared to tDCS, and a larger tRNS effect on ADHD rating-scale was predicted for those who showed the greatest improvement in working memory.
Conclusions: We found that our intervention can have a lasting effect, rather than a merely immediate effect as was shown for in previous medical interventions in ADHD.
Significance: Our results provide a promising direction toward a novel intervention in ADHD.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in childhood, with significant negative lifetime outcomes (Greydanus et al., 2007). Despite proven effects of combinations of pharmacological and psychoso-

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cial interventions, there is still a need for improvement of cognitive dysfunction and behavioral symptoms that are only partially covered by current interventions (Moldavsky and Sayal, 2013). These factors highlight the pressing need for novel, efficacious interventions, and transcranial electrical stimulation (tES) has been highlighted as one of possible intervention (Krause and Cohen Kadosh, 2013).

tES involves the application of a weak current (mostly 1–2 mA) to the brain via skin-electrode interface, creating an electric field that modulates neuronal activity (Polania et al., 2018). tES has an excellent safety profile, which makes it an appealing treatment method for children and adolescents (Krishnan et al., 2015). Here we used two types of tES: transcranial direct current stimulation (tDCS) and transcranial random noise stimulation (tRNS). tDCS is the most frequently used form of tES, and it has been suggested that the cortex beneath the anodal electrode typically becomes more excitable whereas the cathodal site has decreased excitability (Polania et al., 2018). The delivery of tRNS uses the same equipment as tDCS to stimulate neuronal activity. However, the mechanisms by which tRNS influences brain activity are different (Chaieb et al., 2015). In addition, in tRNS both electrodes can be used to increase cortical excitability (Terney et al., 2008). Previous studies, mainly in adults, have shown that when several sessions of tDCS or tRNS are applied during cognitive training, the effects can last from weeks to months (e.g., Brevet-Aeby et al., 2019, Reis et al., 2009, Snowball et al., 2013).

One of the most influential theories of the neural basis of ADHD suggests that deficient inhibitory control mechanisms give rise to executive dysfunction, which is likely genetically influenced (Sonuga-Barke, 2005). Inhibitory control is processed during the maturation of basal ganglia-thalamo-cortical circuit. Previous studies have shown that ADHD is associated with structural and functional abnormalities within this circuit (Aron et al., 2004, Christakou et al., 2004). An updated meta-analysis suggests that anodal tDCS over the left dlPFC can yield a small-to-medium effect size on neuropsychological deficits, such as inhibition and working memory, in ADHD (Salehinejad et al., 2019). Another recent meta-analysis, which focused on clinical symptoms in ADHD, has suggested that tDCS over the left dlPFC improves inattention and impulsivity (Brauer et al., 2021). These results reflects the enthusiasm and promise from tDCS as a potential neurointervention method in ADHD (see also Salehinejad et al., 2020).

To date tRNS has not been used in the case of ADHD, as it is a more novel form of brain stimulation (Polania et al., 2018). However, tRNS in healthy adults successfully improved cognitive functions including attentional control, with stronger effects shown for individuals with poorer attentional control (Harty and Cohen Kadosh, 2019). In a small sample of children with dyscalculia, tRNS over bilateral dlPFC during numerical training has shown positive effects on numerical training compared to sham (placebo) stimulation (Looi et al., 2017). Moreover, accumulated evidence have suggested that tRNS could yield stronger effects than tDCS (Fertonani et al., 2011, Simonsmeier et al., 2018).

The goal of our study was to compare the beneficial effects of tRNS and tDCS when combined with executive function (EF) training in ameliorating symptoms and EF in unmedicated children with ADHD. Each tES method was applied for 5 consecutive days along with EF training. We limited each arm to 5 days as previous tDCS and tRNS studies on healthy adults have yielded lasting effects with protocols of a similar duration or even shorter (Cappelletti et al., 2013, Reis et al., 2009, Snowball et al., 2013). Endurance of effects was measured one week after the end of the intervention protocol. We expected that both stimulation protocols will lead to clinical and cognitive improvement, and our motivation was to examine any potential differential effects between tRNS and tDCS.

2. Methods

2.1. Study design

We conducted a randomized double-blind active-controlled crossover study of children diagnosed with ADHD. Twenty-two children were assessed for eligibility, 21 children were recruited for the study, and 19 participants completed it (see Fig. 1 for the Consolidated Standards of Reporting Trials (CONSORT) flow diagram). Two participants were excluded from the study: one of them due to complaints of an uncomfortable topical sensation and headaches during the tDCS protocol. The second participant was excluded as the parents reported in the third session behaviour that might meet one of the exclusion criteria (the expression of self-harm thoughts), which was present already two months before study participation but was not reported at screening.

All children were newly diagnosed and drug naïve (**Table S1**). Given the difficulties in recruiting this population, and for cognitive training that requires longer protocols, we chose in the present study to use a within-subject design. This approach allowed us to control better for individual differences that are impossible to perfectly match in a between-subject design, and at the same time allowing more powerful design, with the given sample size. For example, in a between-subject design the sample size required to detect an effect with $\alpha = 0.05$, power $(1-\beta) = 0.8$, and an effect size of Cohen's $d = 0.68$ using a t-test with a non-directional hypothesis is 72, more than 3.5 times the sample size required using a within-subject design.

Following screening, eligible participants were assessed at baseline and then randomized into receiving either tDCS or tRNS first in week 1, along with computerized EF training. Each group received either tDCS or tRNS treatment for 5 consecutive days (one treatment session each day). Following a one-week break, there was a crossover between the groups in week 3: those who received tDCS in the first week received tRNS in the third week, while those who received tRNS in the first week received tDCS in the third week (Fig. 2). Parents and children were blinded to treatment method order. This allowed us to compare the different treatment in a within-subject design, as well as to examine one-week post-treatment effects to assess lasting effects. The assessment battery was repeated at the end of each week. The total duration of subject participation in the study was 4 weeks. All study-related activities were conducted in a research lab at the School of Occupational Therapy of the Hebrew University of Jerusalem.

2.2. Study population

The study included children aged 7–12 years old. Participants were recruited (between 03/2018–03/2019) among children referred to the ADHD clinic by paediatricians, general practitioners, teachers, psychologists, or parents. All participants agreed to participate in the study (verbal assent) and their parents gave written informed consent to the study. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human patients were approved by approved by the Helsinki Committee (IRB) of the Hebrew University and Hadassah Medical Center (Jerusalem, Israel).

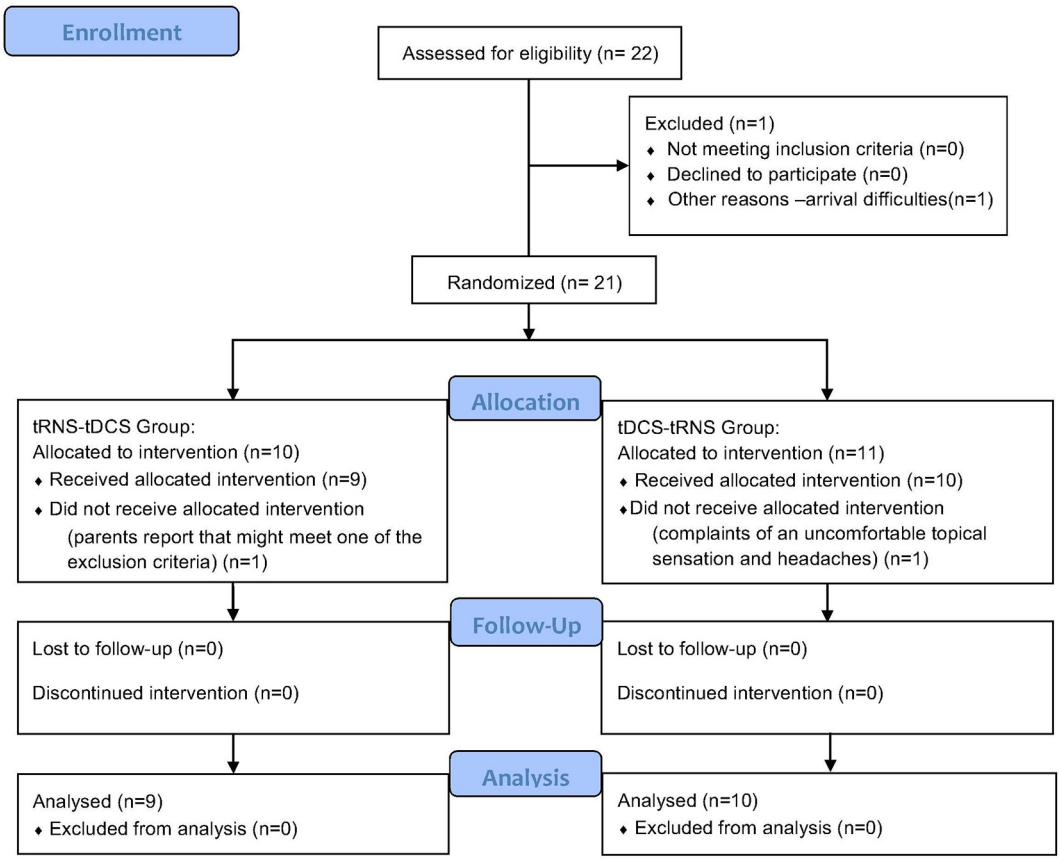

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the progress through the phases of the randomized crossover study of the two groups.

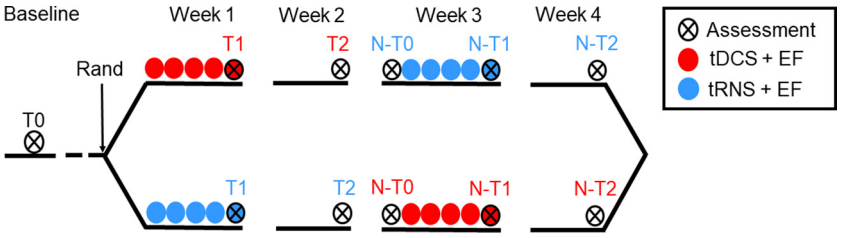

Fig. 2. Study Design. Eligible participants with Attention-deficit/hyperactivity-disorder (ADHD) were randomized (Rand) into one of two treatment groups. Baseline measures were acquired (T0) before the randomization into one of the two groups. Participants in both groups received 5 daily treatment sessions in Week 1 and were assessed at the end of this week (T1). At Week 2 no treatment was given and the lasting effect from week 1 was measured (T2). On Week 3 the participants received the treatment that the other group received in Week 1. That is, if participants received transcranial random noise stimulation and executive functions training (tRNS + EF) on Week 1, they received transcranial direct current stimulation and executive functions training (tDCS + EF) on Week 3. To allow an accurate assessment of the new treatment on Week 3, we recalibrated the participants' baseline measures by using their latest assessment data from T2. This new baseline measure was called New T0 (N-T0). We reassessed the participants at the end of Week 3 (N-T1). At Week 4 no treatment was given and the lasting effect from week 3 was measured (N-T2).

Initially, the local IRB approved a total number of 100 participants for this study. For safety reasons we were asked to summarise the data of the first 20 participants in order to assess safety and tolerability. Upon clinical review by the study team and the IRB - if all safety criteria are met, the study could proceed to recruit another 80 participants. That is the reason we chose to include all 20 participants in the tDCS-tRNS arm, so safety and tolerability, as well as efficacy, will be assessed for both methods and will allow us to revise accordingly the testing plans for the future participants. However, due to the repeated lockdowns and termination of funding we could not continue and recruit the full number. The study is registered at ClinicalTrials.gov (identifier NCT03104972).

A power analysis revealed that the obtained sample size, power = 0.8, and α = 0.05 would allow to detect an effect with an obtained effect size of 0.68. This is due to the within-subject design, which allows, with the given sample size, for more power to detect an effect compared to previous studies, including a recent trial that used a between-subject design (n = 32 in one group and n = 30 in another) and led to Food and Drug Administration (FDA) approval of its use in brain stimulation to treat ADHD (McGough et al., 2019).

Inclusion criteria: Each child scored above the standard clinical cut-off values for ADHD symptoms on ADHD DSM–5 scales (American Psychiatric Association, 2013, DuPaul et al., 2016), and met the criteria for ADHD according to DSM–5, using the "gold standard" procedure as described by the American Academy of

Pediatrics, and including a semi-structured interview of the patient and parents by a specialist in paediatric neurology and child development, a neurological examination, and ADHD rating scale (ADHD-RS) diagnostic questionnaires (DuPaul et al., 2016).

Exclusion criteria: Children were excluded from the study if they had one of the following: a chronic neurological disease, epilepsy in the participant or in a first-degree relative, intellectual disability, other chronic conditions, chronic use of medications, or other primary psychiatric diagnosis (e.g., depression, anxiety, psychosis). The Hebrew translation of the Kiddie-SADS-Lifetime Version (Kaufman et al., 2000) was used to assess axis-I disorders in participants according to DSM–5 criteria (Kaufman et al., 2000).

Prospective resting-state electroencephalography was performed at screening in order to rule out an unknown existence of epileptiform activity. Electroencephalography records were standardized and recorded with g.Recorder software (gTec, Schiedlberg, Austria), using a 64-channel wireless electroencephalography cap system (g.Nautilus) with gel-based electrodes.

2.3. Primary outcome measure

The primary outcome measure of the study is the total score of the ADHD-RS diagnostic questionnaire completed by the parents (DuPaul et al., 2016). This scale is of well-accepted validity and reliability, regarded as standards in ADHD diagnosis and treatment effect. The ADHD-RS-5 contains 18 items based on the wording used to describe those items in the DSM–5. The 18 items are presented in the context of a two-factor structure beginning with the nine inattention (IN) symptoms followed by the nine hyperactive-impulsive (HI) symptoms. Parents rate each of these items on a 4-point Likert frequency scale that can be scored 0 (never or rarely), 1 (sometimes), 2 (often), or 3 (very often). IN and HI total symptom severity scores categorically generate IN and HI symptom counts. The symptom count for IN is determined by summing the number of IN items receiving ratings of 2 (often) or 3 (very often). The symptom count for HI is calculated in a similar fashion. Thus, for both IN and HI, symptom counts range from 0 to 9 in accordance with DSM–5 criteria and 18 is the maximal possible scoring for the entire scale (Anastopoulos et al., 2018). Two participants were excluded from this analysis as their parents did not provide the ADHD-RS post-intervention immediately after the intervention and 1 week later.

2.4. Secondary outcome measures

1. CGI-S (Clinical Global Impression–Severity) scale: a 3-item observer-rated scale that measures illness severity, as assessed by the treating clinician (Guy, 1976). Scoring the CGI-S is rated on a 7-point scale, with the severity of illness scale ranging from 1 (normal) to 7 (severely ill).
2. MOXO-CPT (NeuroTech Solutions Ltd): a standardized computerized test that measures attentional performance (Berger et al., 2017). The MOXO-CPT includes four performance indices: attention, timing, impulsivity, and hyperactivity.
3. Digit Span: a subtest of the Wechsler Intelligence Scale for Children (WISC)–Fourth edition that measures short-term auditory memory and attention (Wechsler, 2003).

2.5. Study interventions

Participants completed computerized EF training along with either tDCS or tRNS.

2.6. Computerized EF training

Participants completed training using the ACTIVATE™ training program, delivered on a tablet (Wexler et al., 2016). This gamified EF training includes different mini-games that target different EF components: working memory, cognitive flexibility, response inhibition, and sustained attention (Wexler et al., 2016). Each training session included 4 mini-games, each played for 5 minutes, which coincided with the tES protocol. The training starts at a basic level and adaptively progresses to move advanced levels, which include more complex tasks, depending on individual performance. While the present cognitive training has been used in previous studies that aimed to improve academic performance in typically developing children (Wexler et al., 2016), and in some preliminary studies in children with ADHD (de Oliveira Rosa et al., 2019), the outcome measures in previous studies never included ADHD-RS, which prevented us from estimating the effect size expected from such training alone. As our study focused on comparing the efficacy of two tES methods, a detailed description of the EF training protocol is beyond the scope of this paper, but can be found in the Supplementary Information.

2.7. Transcranial electrical stimulation

Both tDCS and tRNS were applied using semi-dry 5X5 cm electrodes using the NovoStim device (Tech InnoSphere Eng. Ltd., Haifa). The NovoStim device is a research and investigational device, pending FDA and medical CE approval. Stimulation was delivered for 20 minutes each session, while participants completed the cognitive training (Fig. 3). The total stimulation time for each tES protocol was 100 minutes (5 sessions of 20 min each).

tDCS. The current was set to 0.75 mA based on previous computational modelling of tDCS in children and is estimated to equal that of approximately 1.5 mA in adults (Kessler et al., 2013).

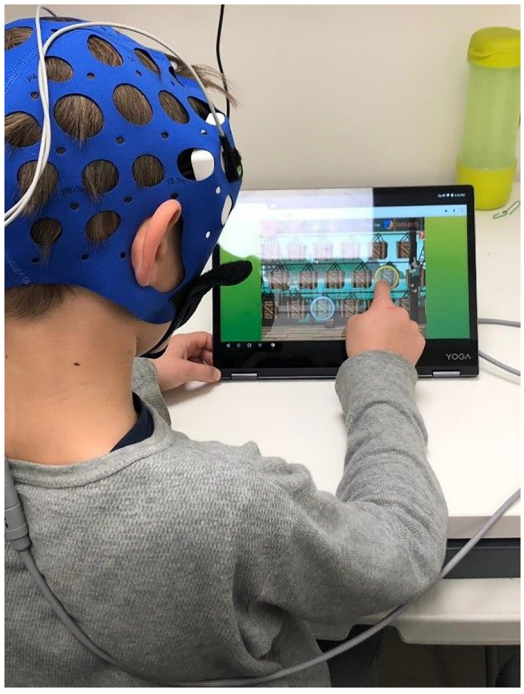

Fig. 3. A treatment session of transcranial electrical stimulation combined with executive functions (EF) training. Participants completed 20 minutes of EF training while transcranial random noise stimulation or transcranial direct current stimulation was delivered to them during this period.

Ramp-up and ramp-down durations were 30 seconds each. These durations were chosen after considering the parameters that would influence current distribution and density at the site of stimulation, such as thinner scalp, less cerebrospinal fluid, and smaller head size of the paediatric population (Kessler et al., 2013). A similar dosage of tDCS was well tolerated by the children and was not associated with adverse effects (Krishnan et al., 2015). The anodal electrode was positioned above the left dlPFC (F3 based on the International 10–20 system), while the cathodal electrode was placed over the right supraorbital (Fp2). This montage has been deemed to be the most successful so far based on a meta-analysis of tDCS studies in ADHD (Brauer et al., 2021, Salehinejad et al., 2020, Salehinejad et al., 2019, But see for weaker effects in Westwood et al., 2020b).

tRNS. Stimulation was applied at an amplitude of 0.75 mA of high-frequency (100–640 Hz) tRNS over the left dlPFC and the right inferior frontal gyrus (IFG), attached under designated electrode positions (F3-F8 based on the International 10–20 system) of the tES cap. These stimulation locations were chosen based on their involvement in executive control and inhibition processes (Aron et al., 2004, Christakou et al., 2004). Ramp-up and ramp-down durations were the same as in the tDCS condition. This montage was chosen due both to the advantage of this neurostimulation polarity-independent method and to its ability to yield excitatory stimulation without parallel inhibitory effects (Terney et al., 2008). Moreover, a similar montage was used in previous tRNS studies in the field of cognitive training in healthy young adults and children with dyscalculia (Looi et al., 2017, Snowball et al., 2013).

To mitigate the possibility that the research assistant will notice the differences in the montages between tDCS and tRNS, and would be biased toward a given montage, we alternated three naive research assistants throughout this study.

2.8. Statistical analysis

To examine treatment effects, we used linear mixed effects models, which account for within-subject correlations more optimally compared to ANOVA and automatically handle missing values, allowing maximum use of available data (Seltman, 2009). We used the R-package *nlme* (Pinheiro et al., 2017) to perform the linear mixed effects analysis with maximized log-likelihood on the outcome measures, and subjects as the random factor. We examined outcomes immediately post-treatment and one week later for each stimulation type, and included stimulation type (tDCS, tRNS) and time (immediately after treatment and one week post-treatment) as predictors. We included baseline performance as a covariate in our model, rather than use a subtraction score (i.e., post-treatment minus baseline). Including baseline performance as a covariate allows for a better adjustment for minor differences in the pre-treatment means. In contrast, subtraction score contains measurement error from both the baseline performance and the post-treatment score and is also negatively correlated with baseline performance because of the measurement error (Edwards, 2001, Jamieson, 2007). As we used a within-subjects design, we used the baseline measures at T0 for the first arm, but to allow an accurate assessment of second arm, we recalibrated the participants' baseline measures by using their latest assessment data from T2 as the new baseline for the second arm (Fig. 2).

For all the measures we verified that the residuals were normally distributed using a q-q plot and the Shapiro–Wilk normality test. The only exception was the MOXO-CPT residuals, which were not normally distributed; we therefore applied the Tukey ladder of powers transformation, which is recommended in this case (Tukey, 1977). We also tested for the inclusion of an interaction term in our analysis. In our primary outcome, ADHD-RS, the interaction between stimulation type and time was not significant [$\beta = 0.14$, SE = 0.18, $t(35) = 0.78$, $p = .44$, 95% confidence intervals (CI) (−0.21, 0.5)]. A model comparison showed no benefit from a more complex model, favouring the more parsimonious model, which included the main effects of stimulation and time (chi-squared test = 0.66, p = .41). We therefore report this parsimonious model also for the secondary outcome measures. However, as with the other measures, the inclusion of the interaction term between stimulation and time was not significant. We also explored the effect of order (tRNS first followed by tDCS, vice versa), but this variable was not significant [$\beta = -0.12$, SE = 0.12, $t(34) = -1.04$, $p = .3$, 95% CI (−0.37, 0.11)], and a model comparison preferred the simpler model that did not include this variable (chi-squared test = 1.12, p = 0.29).

3. Data availability

Data is available upon reasonable request from the first author.

4. Results

4.1. Side effects and safety issues

There were 61 records of side effects reported, none of which were considered clinically significant (**Table S2**).

4.2. Primary outcome measure

For the primary outcome, we measured the ADHD-RS total score post-treatment immediately after the intervention (tRNS/tDCS) and one week later, while covarying for the baseline score. The analysis revealed a main effect of stimulation type, indicating greater improvement for tRNS than for tDCS [$\beta = -0.42$ (SE = 0.18), $B = -1.98$ (SE = 0.87), $t(35) = -2.28$, $p = .028$, 95% CI (−3.67, −0.29)] Table 1, Fig. S1-2). The main effect of time, i.e., immediately after the end of the intervention to one week later, showed a further improvement one week after the end of the treatment [$\beta = -0.19$ (SE = 0.09), $B = -1.78$ (SE = 0.86), $t(35) = -2.07$, $p = .045$), 95% CI (−3.46, −0.1)]. In terms of improvement from baseline, tRNS yielded a mean improvement of 3.47 points [SE = 1.03, $t(15) = 3.35$, $p = .004$, 95% CI (1.31, 5.64)], while tDCS yielded a mean improvement of 0.57 points [SE = 1.19, $t(15) = 0.47$, $p = .64$, 95% CI (−1.92, 3.06)].

4.3. Changes in secondary outcome measures

The secondary outcome measures were considered more exploratory. As such, we present them below without applying a correction for multiple comparisons, yet highlight that none of the results was significant at a $\alpha \leq 0.05$ after applying Bonferroni correction for multiple comparisons.

4.4. Changes in attentional performance

The results for the MOXO-CPT subscales and CGI-S (see **Tables S3–S7**) did not show a significant post-treatment effect of stimulation type (all ps > 0.44), aside from the MOXO timing index, which showed larger changes following tRNS compared with those seen following tDCS [B = 1.92 (SE = 0.91), $t(47) = 2.11$, $p = .04$, 95% CI (0.14, 3.7)].

Table 1
Beta Weights (Standardized) of the Regression Model with Post-treatment Attention-deficit/hyperactivity-disorder rating scale (ADHD-RS) Score as the Outcome Measure. The results indicate a significant effect for stimulation due to greater reduction in the ADHD-RS score for transcranial random noise stimulation in comparison to transcranial direct current stimulation, and greater improvement, as opposed to deterioration, as time passed following the treatment (one week later). Std = standard; DF = degrees of freedom.

	β	Std Error	DF	t-value	p-value
Intercept	−0.08	0.173	35	−0.484	0.631
ADHD-RS (baseline)	0.228	0.105	35	2.166	0.037
Stimulation	−0.422	0.185	35	−2.285	0.028
Time	−0.192	0.092	35	−2.075	0.045

Table 2
Beta Weights (Standardized) of the Regression Model with Post-treatment Backward Digit Span Score**.** The results indicate a significant effect for stimulation due to greater increase in the backward digit span score for transcranial random noise stimulation in comparison to transcranial direct current stimulation. Std = standard; DF = degrees of freedom.

	β	Std Error	DF	t-value	p-value
Intercept	−0.197	0.108	51	−1.811	0.076
Stimulation	0.331	0.156	51	2.123	0.038
Backward digit span (baseline)	0.84	0.077	51	10.928	<0.001
Time	0.052	0.077	51	0.673	0.504

4.5. Changes in working memory and in short-term memory

Performance on the digit span subscale of the WISC (total score of forward and backward span) after the intervention showed a significant effect of stimulation, favouring tRNS over tDCS [β = 0.34 (SE = 0.14), B = 1.07 (SE = 0.44), t(50) = 2.44, p = .018, 95% CI (0.22, 1.92)].

Further analysis indicates that tRNS led to a significantly better performance in the backward digit span only, compared to tDCS [Table 2, backward digit span: β = 0.33 (SE = 0.16), B = 0.63 (SE = 0.3), t(51) = 2.12, p = .038, 95% CI (0.04, 1.22); forward digit span: β = 0.04 (SE = 0.16), B = 0.058 (SE = 0.24), t(51) = 0.24, p = .81, 95% CI (−0.41, 0.52), **Table S8**].

4.6. Examining the link between clinical and cognitive changes

Next, we examined whether the improvement in the ADHD-RS score under the tRNS protocol depends on the changes in working memory (WM) performance (the backward digit span score). We ran a moderation analysis and predicted the post-treatment ADHD-RS score by stimulation type and the post-treatment backward digit span score, while controlling for the ADHD-RS and backward digit span scores at baseline. This analysis revealed a trend toward a significant interaction between stimulation type and the post-treatment backward digit span score [β = −0.41 (SE = 0.23), B = −1.01 (SE = 0.56), t(53) = −1.81, p = .075, 95% CI (−2.09, 0.06), **Table S9 and Fig. S3**]. A simple slopes analysis revealed that this trend stemmed from a significant improvement in ADHD-RS for tRNS vs. tDCS in those who had showed the largest improvement in the backward digit span test [β = −0.62 (SE = 0.29), B = −2.91 (SE = 1.36), t(53) = −2.14, p = .037), 95% CI (−0.24, −5.57)].

5. Discussion

The most notable results in our study are the improvements on ADHD-RS scores following tRNS and EF training relative to baseline and to tDCS and EF training. These promising results on the tRNS protocol support those of several studies in healthy young adults (Brevet-Aeby et al., 2019, Snowball et al., 2013, Terney et al., 2008). Importantly, the results showed a further significant improvement 7 days after the end of the treatment, mirroring a similar lasting tRNS effect in previous studies on healthy adults (Brevet-Aeby et al., 2019, Snowball et al., 2013).

Our results are further supported by a tRNS effect on the MOXO timing index score, which reflects cognitive processing speed, i.e., the speed at which a person is able to perceive and react to stimuli in the environment (Nielsen et al., 2017). More importantly, we observed a tRNS effect on the backward digit span test, which measures WM capacity. This last effect is expected given that our cognitive training targeted WM as one of the EFs that have been shown to be impaired in children with ADHD (Barkley, 1997). Moreover, a greater improvement of ADHD-RS by tRNS was predicted by a greater improvement in the backward digit span test from baseline. However, the interaction between brain stimulation and WM in predicting ADHD-RS was only marginally significant.

5.1. Potential mechanisms

The most prevalent explanation for tRNS is stochastic resonance (Fertonani and Miniussi, 2017, Pavan et al., 2019, Terney et al., 2008, van der Groen and Wenderoth, 2016). Stochastic resonance describes the phenomenon of introducing an appropriate level of random noise to enhance the output of subthreshold signals. With respect to tRNS, it suggests that the application of weak electric currents amounts to an introduction of neural noise, which improve information processing at the neuronal level (Terney et al., 2008). According to this framework the effect of tRNS in the present study might be attributed to amplifying underactive basal ganglia-thalamo-cortical circuits that has been associated with ADHD (Aron et al., 2004, Christakou et al., 2004). In this scenario, targeting the prefrontal cortex impact the dorsal neostriatum via excitatory glutaminergic cells, the basal ganglia to the dorsomedial thalamus via inhibitory projections, and the thalamus back to the prefrontal cortex via excitatory projections (Castellanos et al., 2002).

A second mechanistic explanation for the tRNS in the present study is coming from a combined electroencephalography-tRNS study that found that the behavioural improvements of tRNS above the dlPFC vs. sham tRNS are associated with alterations in amplitude of attention and preparatory markers. Those results suggest that the enhancement effect of tRNS when applied above the dlPFC acts by effecting general attentional mechanisms during cognitive training (Sheffield et al., 2020). However, it is important to highlight that the abovementioned study included healthy young adults.

However, another possibility is that tRNS impacted oscillations between 140–220 Hz (“ripples”), which are involved in learning and long-term potentiation (Jadhav et al., 2016). Ripple oscillations

underlie learning via Hebbian requirements for synaptic modification, and are attributed to the hippocampus as well as the prefrontal cortex (Jadhav et al., 2016). If tRNS modulated ripple oscillations and by that causally alter learning and long-term potentiation in ADHD then a more optimal tRNS frequencies would be within 140–220 Hz, rather than 100–640 Hz as in this study. Namely, while in the non-cognitive domain high-frequency tRNS (101–640 Hz) has been suggested to be more beneficial than low-frequency (0.1–100 Hz) (Terney et al., 2008), the prediction of the ripple oscillations hypothesis is that the most optimal parameters will appear in the range of 140–220 Hz (Jadhav et al., 2016). It might be that transient tRNS effect, as was found in other studies, might be due to other mechanisms such as stochastic resonance, while the neuroplasticity effects could be due to ripple oscillations.

In addition, a recent study in mice that aimed to progress the understanding of tRNS effect on the developing brain has revealed that identical tRNS current density and duration per day over multiple sessions (in this case 9 sessions, twice a week) over the prefrontal cortex has yielded changes in reduction in glutamic acid decarboxylase (GAD) 65/67 but not vesicular glutamate transporter 1. Such effect was maximal in the location beneath the electrode but not in a deeper location (Sanchez-Leon et al., 2020). Such findings strengthening our suggestion that tRNS impacts neuroplastic mechanisms, and at least in mice involves the GABAergic system.

While describing the potential mechanisms for tRNS, an existing question is *why* tRNS was better than tDCS in the present study. While we do not have the needed data to shed light on this question, in addition to the potential mechanisms that tRNS might have played in our observed results, we would like to suggest a couple of potential reasons. First, tRNS allowed us to use two electrodes that have shown to have excitatory effect, rather than one excitatory and one inhibitory effect in tDCS. It is unclear if the additional excitatory effect of the tRNS over the right IFG and/or the cathodal effect of tDCS over the supraorbital have contributed to the increased efficacy of tRNS. Second, tRNS provide alternating current in a wide range of frequencies. Such feature could have allowed more variability in terms of the stimulation protocol, compared to the fixed direct current in tDCS and therefore impacting more individuals despite their assumed heterogeneity. Similarly, tRNS is less sensitive to cortical folding than tDCS (Terney et al., 2008), and therefore reducing the impact of anatomical variations between participants. Third, by inducing random noise at the neuronal level, tRNS may increase uncertainty, which is associated with greater level of plasticity (Chang and Merzenich, 2003, Frankenhuis and Fraley, 2017). This effect might allow greater opportunity for the central nervous system to change. While such effect of increased uncertainty might be also induced by tDCS, the effect of tRNS might be greater due to its greater impact on inducing neuronal noise. To our knowledge, this idea is novel and has not been yet examined in the field of brain stimulation.

Note, that the aim of the current study was to improve clinical symptoms in ADHD by combining theoretically-motivated EF cognitive training with the currently most promising transcranial electrical stimulation protocols. tDCS and tRNS have been shown to work, at least partially, on different mechanisms (Antal and Herrmann, 2016, Chaieb et al., 2015, Liebetanz et al., 2002, Nitsche et al., 2004). We therefore did not match either of the protocols with regard to different factors such as electrode positions. In this respect, our approach is very similar to the approach that is adopted in pharmacological studies, where not the dose of different drugs are matched, but the best dose for each drug with maximal effects on brain and behavior is investigated (Chamberlain et al., 2006). As such, our goal was to test the efficacy of tRNS and tDCS protocols using the parameters that yielded promising results in previous studies. Therefore, instead of equating the tRNS and tDCS protocols (if possible at all) and comparing the involved mechanisms, which would be an interesting and challenging question per se, our motivation was different; to yield the best clinical results. In this respect, future studies should examine whether further optimizing tDCS and tRNS protocols using different parameters could yield different conclusions, and whether the present beneficial effect of tRNS is limited to the developing brain as well as other ADHD characteristics (Lipka et al., 2021). However, few studies that have found greater benefit of tRNS vs. tDCS in adults may suggest that its advantage may not be necessarily restricted to the developing brain (Brem et al., 2018, Fertonani et al., 2011, Ghin et al., 2018, Inukai et al., 2016).

5.2. Comparing the present approach to previous studies

There are a few differences that are worth emphasizing when comparing our approach to the recent promising findings on trigeminal nerve stimulation as a treatment for ADHD (McGough et al., 2019). Our results are based on lower stimulation intensity (0.75 mA vs. 2–4 mA) and shorter treatment duration (100 min vs. 13,440 min in total), and they show persistent and even increasing improvement after treatment, indicating plasticity-related effects. This is in contrast to the short-lived immediate improvement and significant deterioration one week after the end of the treatment associated with trigeminal nerve stimulation (McGough et al., 2019). Moreover, the estimated effect size in our study on ADHD-RS is higher than the one reported in (McGough et al., 2019) (estimated Cohen's d = 0.82 on an 18 points scale, and 0.75 on a 54 points scale vs. 0.51). This difference is less likely to be due to an inflated effect size due to an underpowered design as the experimental design in our study was more suitable for detecting the observed effect size. The sample size in the present study is the upper range of the sample size used in paediatric ADHD neurostimulation studies (with n = 9–21, Salehinejad et al., 2019). Notably, most of these studies did not require the patients and their guardians to come to the lab multiple time as in the present study, which increase difficulties in terms of recruitment, and parental and child's commitment. Moreover, all the children in our study were newly diagnosed and drug naïve.

5.3. Potential limitations and future directions

While we stressed the strength of our approach to ensure balance, we would like to discuss also possible limitations.

One potential caveat in the present study is the lasting effect of a given intervention (e.g., tRNS). To take this into account we "rescaled" in our statistical model the baseline performance before the beginning of the second intervention, and also examine how the factor order, which was not significant, could influence the results.

In addition, in the present study we chose to compare the effect of tRNS vs. tDCS, rather than sham stimulation. In our view, such an approach is more rigorous as it compares the effect of two stimulation protocols that at the theoretical and the empirical level had an a priori likelihood of leading to successful treatment. Therefore, the obtained results are expected to be stronger when compared to sham stimulation. However, a potential criticism is that tDCS, in contrast to sham stimulation, might yield impairment, rather than improvement. While a future study that includes a sham group is needed to exclude this possibility with great confidence, the criticism is likely unfounded given the accumulated evidence that suggests a beneficial effect of tDCS on ADHD clinical symptoms and neuropsychological deficits under the montage we used (Brauer et al., 2021, Salehinejad et al., 2020, Salehinejad et al., 2019). However, this potential concern cannot be excluded entirely given that

studies that used tDCS with anodal electrode over the right inferior frontal gyrus has found a detrimental effect compared to sham in adolescents with ADHD (Breitling et al., 2020, Westwood et al., 2020a).

Our present results offer a further motivation to examine the results vs. sham group to strength the confidence in the present results and replicate them, as well as examining the potential benefit of tRNS in a large sample size as a function of ADHD subtype. In addition, compared to the mechanisms involved in other brain stimulation methods, such as tDCS, the neurocognitive mechanisms in tRNS are less known. While we discuss potential mechanistic explanation to our results, further work in humans and animals could shed further light on the involved mechanisms, and how tRNS can ameliorate ADHD symptoms, and potentially other clinical conditions.

Declaration of Competing Interest

IB serves on the advisory board of Tech InnoSphere Engineering Ltd. RCK serves on the scientific advisory boards of Neuroelectrics Inc. and Tech InnoSphere Engineering Ltd. RCK filed a UK Patent via the University of Oxford for "method for obtaining personalized parameters for transcranial stimulation, transcranial system, method of applying transcranial stimulation". All the other authors reported no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.01.005.

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