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A functional magnetic resonance imaging investigation of prefrontal cortex deep transcranial magnetic stimulation efficacy in adults with attention deficit/hyperactive disorder: A double blind, randomized clinical trial

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ABSTRACT

ADHD is one of the most prevalent neurocognitive disorders. Deep Transcranial Magnetic Stimulation (dTMS) is a non-invasive neuromodulation tool that holds promise in treatment of neurocognitive disorders. Hypoactivity of the prefrontal cortex (PFC) has been observed in ADHD. This study examined the clinical, cognitive, and neural effects of dTMS to the PFC in adults with ADHD by using functional magnetic resonance imaging (fMRI). High frequency repetitive dTMS was applied to either the right or left PFC in 62 adults with ADHD in a randomized, double blind, placebo controlled protocol with 3 study groups: 2 treatment arms (rPFC, or lPFC) and a Sham arm. The study included 15 dTMS/cognitive training treatment sessions. Clinical effects were assessed with the Conners Adult ADHD Rating Scale (CAARS) self-report and the Clinical Global Impression score (CGI) as primary outcome measures. Self-report/observer questionnaires and computerized cognitive testing were also performed to assess clinical and cognitive effects. Neural effects were assessed with fMRI using working-memory (WM) and resting-state paradigms. While the study did not show improvement in the primary endpoints, significant improvements were observed in the CAARS (self-report) inattention/memory sub-scale, as well as increased activations in the rDLPFC, right parietal-cortex and right insula/IFG during WM conditions after treatment in the right stimulation group. Increased rDLPFC activation was associated with larger symptom improvement in the right stimulation group. This study indicates that dTMS is effective in modulating attention related brain networks, and is a feasible technique that may improve attention symptoms in adults with ADHD.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by symptoms of inattention, hyperactivity and impulsivity (American Psychiatric Association, 2013), usually appearing before age 12 and often persisting into adulthood (Ginsberg et al., 2014), with an average prevalence in adults of ~ 4% (Simon et al., 2009). Treatments include pharmacotherapy, behavioral interventions, or a combination. In adults with ADHD, cognitive impairments have been observed (Fuermaier et al., 2015; Mostert et al., 2015) in executive function (Boonstra et al., 2005; Mostert et al., 2015; Rohlf et al., 2012; Stavro et al., 2007; Willcutt et al., 2012), including working memory (Alderson et al., 2013; Skodzik et al., 2017). While medications targeting underlying brain mechanisms, generally by increasing the availability of dopaminergic and noradrenergic neurotransmitters, may improve some aspects of functioning (Coghill et al., 2007), adverse effects leading to treatment discontinuation have been reported in ~50% of patients (Ferrin and Taylor, 2011). Behavioral interventions may be less prone to

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side effects but may not target the relevant brain mechanisms underlying ADHD, possibly explaining their limited efficacy (Pelham et al., 2007). Patients often do not adequately respond to stimulants, or develop disabling side effects (Berman et al., 2010). Thus, there is an urgent need to develop alternative treatment options for people with ADHD.

Noninvasive brain stimulation methods have emerged as novel treatment strategies in ADHD, among other neuropsychiatric disorders (for reviews see Escribano et al., 2019; Tortella et al., 2015). Bloch et al. demonstrated improvement in attention following high-frequency repetitive TMS (rTMS) to the right dorsolateral prefrontal cortex (rDLPFC) (Bloch et al., 2010), using a stimulation protocol based on the notion that the underlying neural mechanisms of ADHD involve the cingulo-frontal-parietal (CFP) brain network (Bush, 2011), which includes the dorsal-anterior mid-cingulate cortex (daMCC), DLPFC, ventrolateral prefrontal cortex (VLPFC) and parietal cortex. Together these regions comprise main components of the CFP cognitive-attention network, which controls goal-directed processes and provides the ability to respond to changing attentional task demands (Bush, 2010). ADHD functional imaging studies have demonstrated regional hypoactivity of attention and motor control areas (Zametkin et al., 1993). fMRI studies have underscored the involvement of the CFP network in ADHD, extending these findings to implicate involvement of aberrant CFP attention network patterns, as well as frontostriatal thalamic deficits, and aberrant default mode network (DMN) connectivity (reviewed in Saad et al., 2020). A Meta-analysis of fMRI data in $>$ 500 ADHD subjects and $>$ 600 controls identified significant PFC hypo-activation, which underscores the PFC as a potential target for rTMS treatment (Norman et al., 2016).

It has been postulated that brain dysfunction in ADHD may consist mainly of hypoactivity in the right hemisphere, allowing for a relative dominance of the left hemispheric activity (Wasserstein and Stefanatos, 2000). Meta-analyses of functional magnetic resonance imaging (fMRI) studies in ADHD have showed decreased activity in a number of network regions in right hemispheric fronto-basal ganglia networks, including rDLPFC (Brodmann areas (BA) 8, 46), right inferior parietal cortex (IPs, BA 40), right precuneus (BA 7), and rVLPFC (BA 29) (Hart et al., 2013; Norman et al., 2016; Westwood et al., 2020) Thus, stimulation of the rDLPFC may be useful in treating ADHD (Bloch et al., 2010; Weaver et al., 2012). There is also suggestion from the literature for a beneficial effect of left hemispheric stimulation on attention functions. Left DLPFC (lDLPFC) stimulation has been associated with improvements in both mood and attention (Levkovitz et al., 2009). Studies of rTMS treatment to the lPFC in depression have reported a beneficial effect on cognitive functions (Tortella et al., 2014). A meta-analysis of fMRI studies using attention tasks found that ADHD subjects exhibited less left medial frontal cortex activation in N-back and Go/no-go studies over controls (McCarthy et al., 2014). Other ADHD neuroimaging studies demonstrated reduced activity of the bilateral PFC (Lei et al., 2015) and left medial frontal cortex (McCarthy et al., 2014) during tasks of inhibitory control, WM and attention. Further, a meta-analysis of tDCS studies has showed that anodal tDCS to lDLPFC improved inhibitory control, and improved working memory task performance in ADHD subjects (Salehinejad et al., 2019).

Accumulating evidence points to a central role of the DLPFC and VLPFC, as these regions are believed to support vigilance, selective and divided attention, attention shifting, planning, executive control, and working memory (Duncan and Owen, 2000; Posner and Petersen, 1990). As such, it may be favorable to use a TMS coil with wider spatial distribution of the electric field, compared to the focal stimulation of rTMS (Deng et al., 2013). Deep TMS (dTMS) is a modification of standard TMS that enables deeper non-invasive cortical stimulation at an effective depth of approximately 5.5 cm (Zangen et al., 2005). It is theorized that long lasting effects of rTMS in general are mediated by increasing cortical excitability in stimulated neurons, which may lead to long term potentiation (LTP) – like effects (Thickbroom, 2007). These phenomena can be further exploited by state-dependent dynamics, where presenting a task relevant to the studied mechanism shortly after the stimulation period may further improve task performance (Thickbroom, 2007).

The current double-blind randomized control study examined the clinical and neural effects of dTMS to the PFC in adults with ADHD, using fMRI. Based on the possible positive effect of both right and left prefrontal activation on cognitive functions, we designed a randomized, double blind controlled study of high frequency, repetitive dTMS to the PFC with 3 study groups: active treatment to the rPFC, active treatment to the lPFC, and sham treatment. Based on the literature we hypothesized that rPFC treatment in adults with ADHD would result in clinical improvement in attention symptoms. The lPFC stimulation group was included as a separate treatment condition to investigate possible clinical effects of stimulation to this region. Clinical effects were assessed with the Conners Adult ADHD Rating Scale (CAARS) self-report and the Clinical Global Impression score (CGI) as primary outcome measures. Furthermore, we aimed to show that dTMS to the rPFC would enhance neural activity in the attention network, which would correlate with symptom improvement.

2. Materials and methods

2.1. Participants

Seventy-five TMS–naïve adults (ages 18–60, mean age 35.1 $\pm$ 9; males = 49) diagnosed with ADHD were recruited from the community (See supplemental file-Fig. 1). After completing the informed consent process, the participants' diagnoses were verified via clinical evaluation based on both DSM-5 criteria and relevant questionnaires including the Adult ADHD Self-Report Scale (ASRS V 1.1). The study was approved by the Institutional Review Board of the Tel-Aviv Sourasky Medical Center. All participants gave written informed consent after receiving a full explanation of the study protocol. In the semi-structured clinical interview, a cognitive neurologist who is experienced in evaluation of adults with ADHD evaluated potential participants after systematically assessing all ADHD criteria, as well other co-morbid conditions including psychosis, affective disorders, anxiety, posttraumatic stress disorder, obsessive compulsive disorder, autistic spectrum personality disorder, and alcohol and substance abuse. Inclusion and Exclusion criteria corresponded to the common guidelines for rTMS studies (Lefaucheur et al., 2014), including exclusion of those with current neurological or additional psychiatric disorder. Specifically, subjects were excluded if there was any history of alcohol or substance abuse. Subjects with a history of any psychiatric disorder were excluded except for those with a history of mild depressive or anxiety symptoms that were well controlled over the previous 3 years. Subjects taking SSRI/SNRI medications that did not exhibit symptoms of depression or anxiety disorder were included in the study. Subjects taking neuroleptics or benzodiazepines were excluded. Hypnotic medications for sleep were allowed provided that the dose was stable for the previous 3 months prior to inclusion and that the dose remained stable over participation in the study. During the study, subjects were prohibited from taking any stimulant medications starting from at least 72 h before their screening (Scr) assessment and until their first follow-up evaluation (V15) (Fig. 1A). Participants were allowed to return to stimulant therapy after the treatment phase as needed. The second (V16) and third (V17) follow-up evaluations also followed a 72-hour period without stimulant intake. Non-stimulant medications for ADHD were not specifically excluded, however none of the enrolled participants were treated with these medications as these medications were not generally available in Israel during the trial. Subjects were compensated about 400 USD for participation in the study to cover transportation expenses for the many study visits.

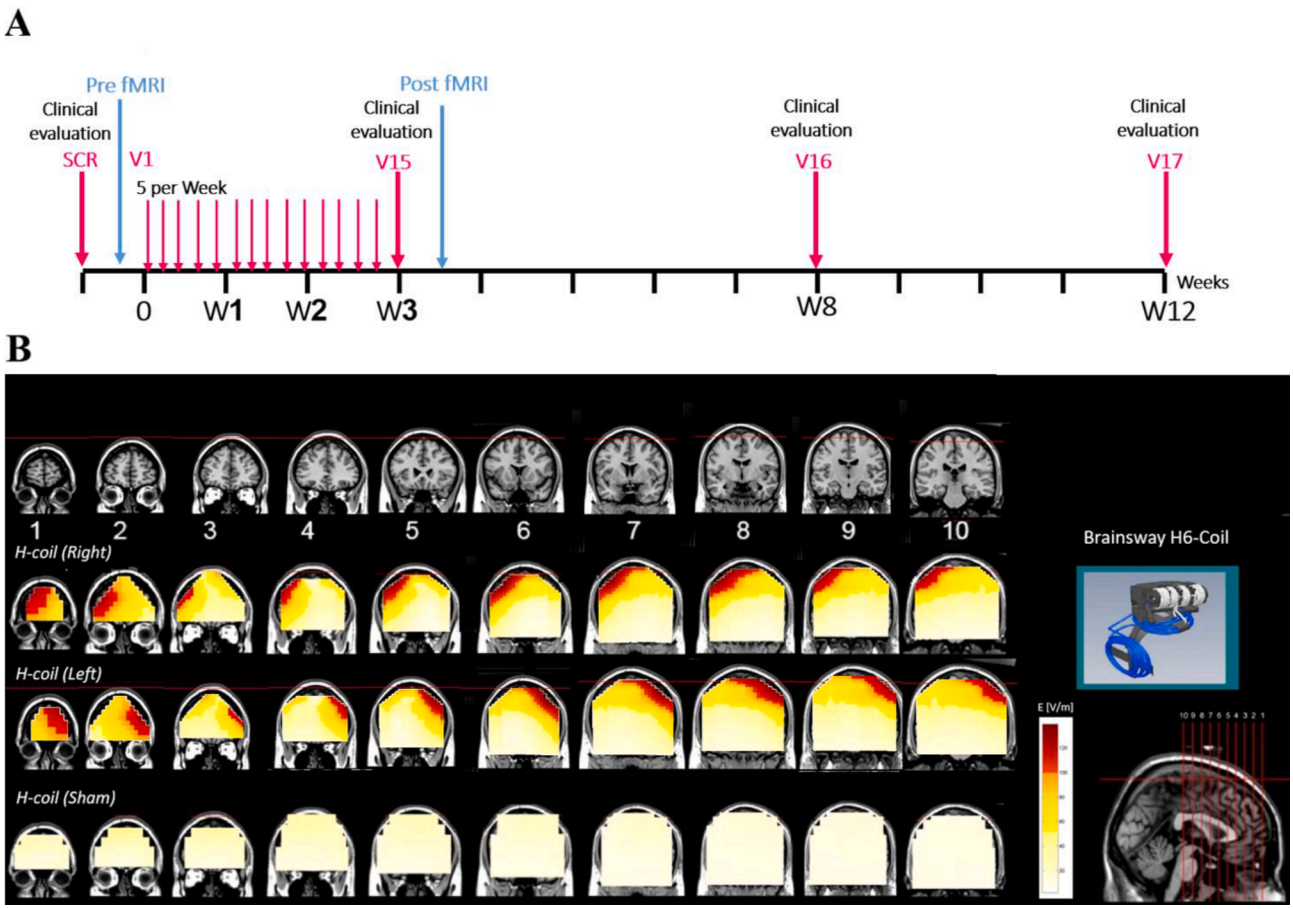

Fig. 1. (A) A time line of the study protocol. (B) Electric field distribution maps at 120% RMT of the right, left and sham H6 coils targeting PFC.

2.2. Treatment groups

The study was run in a double blind manner. Participants were allocated to three study groups: (i) rPFC stimulation, (ii) lPFC stimulation, and (iii) sham stimulation by an external process, without knowledge of the study investigators, according to the minimization method (Treasure and MacRae, 1998) which reduces the differences between groups in pre-defined parameters to the minimum level. The parameters taken in account for minimization were gender, education (years), dominant hand, Conners' Adult ADHD Rating Scale (CAARS self-report; Conners et al., 1999; total score and inattention/memory problems), Adult ADHD Rating Scale (BAARS-4; Barkley, 2011; total, Sluggish Cognitive Tempo (SCT), and hyperactivity scores). Participants and investigators were aware of the side of stimulation (right or left) but were blinded to treatment type. Participants received treatment with dTMS coils that were designed to deliver either real or sham stimulation as designated by an anonymous, pre-assigned key card. The coils were equipped to produce similar noise and scalp sensory effects during sham treatments as to that of real TMS treatments. Each participant was assigned an anonymous key-card which designated the type of treatment (real or sham). A research assistant operated the TMS using the anonymous key card. Unblinding of data occurred at preset time intervals to monitor interim study results.

2.3. Procedure

Subjects underwent 15 daily high-frequency rTMS sessions, which were conducted 5 days a week for three consecutive weeks, using a dTMS H6 coil (Brainsway, IL) fitted to the right or left side of the head, which delivered TMS pulses to either the rPFC or lPFC, respectively (Fig. 1B). The H6 coil was designed to stimulate a wide portion of the PFC, including the DLPFC and VLPFC (Alyagon et al., 2020). Each high-frequency rTMS session consisted of delivering 40 trains of 18 Hz pulses (2 s per train, with a 20 s inter-train interval) at an intensity of 120% of the measured rest motor threshold (RMT) (Schutter and van Honk, 2006). Individual RMT was measured at least once per week by determining the minimal intensity for which a single magnetic pulse over the motor hotspot activates the hand motor cortex in 3/5 trials (evident as a movement of the abductor pollicis brevis muscle). The coil was located 6 cm rostral to the motor cortex, and the total number of pulses was 1440 per session. The sham stimulation group underwent a similar procedure to either the right or left side of the head, but no magnetic pulses were applied during the treatment session. As mentioned, the dTMS H6 coils delivered similar noise and scalp sensory effects during sham treatment to those experienced during real treatment to maintain participant and investigator blinding. In previous studies using dTMS coils designed in a similar fashion, the majority of participants believed that they were receiving real TMS treatments (Levkovitz et al., 2015). In the estimation of the investigators, the majority of subjects believed that they were receiving real TMS, which is in line with previous studies using the same H6 coil (Alyagon et al., 2020), and other deep TMS coils in a similar fashion (Carmi et al., 2018; Levkovitz et al., 2015), where it has been reported that blinding was generally maintained. At each treatment session subjects also performed 6 min of computerized cognitive training (AttengoTM), consisting of an immediate recall task (3 min) and a sustained attention task (3 min) (Stern et al., 2016). Coupling noninvasive brain stimulation (NIBS) with cognitive training has been shown to enhance behavioral effects (Simonsmeier et al., 2018), likely through state-dependent dynamics and long term potentiation (LTP) – like effects (Silvanto and Pascual-Leone, 2008;

Thickbroom, 2007). Cognitive training was not performed concurrently with dTMS stimulation.

Four clinical evaluation visits were performed; at Screening (Scr); after completion of the 3-week treatment phase (V15); 4 weeks after completion of the treatment phase (V16), and 8 weeks after completion of the treatment phase (V17) (Fig. 1A). Clinical evaluations included the assessment of symptom improvement using the following questionnaires: Conners' Adult ADHD Rating Scale (CAARS) (self-report and observer versions), the Adult ADHD Quality of Life Measure (AAQoL; (Brod et al., 2006), Self –Report Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A; Gioia and Isquith, 2011), Beck's Depression Inventory (BDI; Beck, 1961), and the Clinical Global Impression scale (CGI). Additionally, patients performed a full cognitive assessment computerized battery (Mindstreams, Neurotrax; see Schweiger et al., 2007) including the evaluation of memory, executive functions and attention skills. The CAARS self-report and CGI were predesignated as primary outcome measures.

Before and after the treatment phase, each patient underwent fMRI. Maintenance treatment sessions were performed at end of the second and third follow up visits (after 8 and 12 weeks respectively), after all other study procedures were completed, using the same protocols as described.

2.4. Clinical statistical analysis

For each questionnaire and time point we calculated the change from baseline score for analysis using Statistica software (V10.0, StatSoft, USA) in a repeated measures ANOVA with Time and Group as the independent variables.

2.5. fMRI paradigms

2.5.1. N-Back Task

While being scanned, the subjects performed this task composed of two conditions 0-back and 2-back, interspersed with periods of no stimuli. The visual stimuli consisted of 60 achromatic numbers with a red fixation point that was added in the center of the image. Numbers were prepared for presentation by Adobe Photoshop 5.0. The trial consisted of six alternating blocks of the two conditions (three 0-back blocks and three 2-back blocks) and eight baseline blocks. Following instructions, conditions were presented as a series of ten one-digit numbers. During the 0-back condition subjects were required to indicate with a gentle finger tap whenever the number 9 appeared. During the 2-back condition subjects were required to indicate when a number appeared two steps before (e.g. 4 6 8 **6** 2 3). In the baseline condition subjects were instructed to concentrate on the fixation point in the middle of the screen. Stimuli presentation rate was 2 s (1 s per number interposed with 1 s blank). There were 6-s periods of rest between blocks. The stimuli sequences were generated on a PC and projected via an LCD projector (Epson MP7200) onto a translucent tangent screen located on the head coil in front of the subject's forehead. Subjects viewed the screen through a tilted mirror fixed to the head coil. Prior to the fMRI experiment, all participants underwent a preparatory session. During the fMRI experiment, the participants were provided with a response box, and were required to press a button with their right hand. Participants' reaction time and accuracy were recorded.

2.5.2. Resting state

Subjects were instructed to fixate on a red dot in the middle of the screen for six minutes without any specific task.

2.6. fMRI data acquisition and preprocessing

fMRI scanning was performed using a Siemens 3 T Prisma scanner with a 20-channel head coil located at the Tel-Aviv Sourasky Medical Center. Anatomical T1-weighted 3D axial MP-RAGE sequence (TR/TE = 1860/2.74 ms, slice thickness = 1 mm, flip angle = 8°, FOV = 256 × 256 mm) was acquired to provide high-resolution structural images. Functional whole-brain scans were performed in interleaved order with a T2*-weighted gradient echo planar imaging pulse sequence (TR/TE = 3000/35 ms, flip angle = 90°, pixel size = 1.56 mm, FOV = 200 × 200 mm, slice thickness = 3 mm, 39 slices per volume). Active noise canceling headphones (Optoacoustics Ltd., Israel) were used.

Brain Voyager software (ver. QX 2.8; Brain Innovation, Netherlands) was used for preprocessing and co-registration of the standardized anatomical and functional data. Pre-processed functional images were incorporated into the 3D datasets through trilinear interpolation. The complete dataset was transformed into Talairach space. Three-dimensional statistical parametric maps were calculated separately for each subject using a general linear model (GLM) in which the defined predictors were the task conditions (0-back, 2-back) each of them before and after 3-week treatment sessions. The GLM results in a set of beta coefficients (or estimates) corresponding to the set of predictors used, depicting how much of the total variance explained by a specific predictor.

Specific effects were studied in pre-determined regions that are part of the attention and default-mode networks and were defined as 6-mm spherical regions based on peak coordinates taken from Neurosynth.org (Yarkoni et al., 2011) with the search terms 'Working Memory' and 'Default Mode'. Neurosynth is a publicly accessible database that currently lists the results from > 14,000 functional MRI investigations. Neurosynth can be queried for the functional decoding of voxel locations in MNI space (see Table 1 for the full list of brain regions used). Beta estimates for each region of interest for every condition were exported using Brain Voyager for further statistical analysis.

2.7. fMRI statistical analysis

In the N-Back task, repeated measures analysis of variance (ANOVA) was performed on the behavioral measurements as well as for the brain activations with a 2x2 design, using Load and Time as within subject variables and Group as the between subject variable.

2.7.1. Network Connectivity:

In order to reveal changes in network connectivity following treatment, we used both working memory and resting state scans. Given the executive demands of the n-back paradigm and inattentive nature of the patients, we focused on the DLPFC as a main cognitive network node. To evaluate changes in the DMN the mPFC region was chosen as main network node responsible for self-regulation. We sought to investigate the connectivity of this region under both task and rest paradigms.

Table 1
MNI Coordinates for WM network and DMN regions of interest. Regions were based on peak coordinates taken from Neurosynth.org. DLPFC, dorsolateral prefrontal cortex; IPs, intra parietal sulcus; SMA, supplementary motor area; PCC, posterior cingulate cortex; mPFC, medial prefrontal cortex.

Region	MNI Coordinates
Working Memory Network	
Right DLPFC	42, 34, 32
Left DLPFC	−42, 34, 30
Right IPs	40, −48, 44
Left IPs	−42, −48, 44
Left middle cingulate	−14, 16, 32
SMA	0, 16, 52
Right anterior Insula	32, 20, −2
Left anterior Insula	−30, 22, −2
Default Mode Network	
PCC	0, −54, 28
mPFC	0, 50, 8
Right IPs	52, −68, 32
Left IPs	−44, −68, 32

2.7.1.1. Whole brain psycho-physiological interaction (PPI):. Group differences in functional connectivity during *0-back* and *2-back* were examined using an in-house generalized psychophysiological interaction (PPI) analysis tool, previously implemented in our lab for Brainvoyager (Gilam et al., 2015). A whole-brain psycho-physiological interaction (PPI) random effects GLM analysis was conducted on the rDLPFC and the mPFC, using the psychological variables (the original regressors of the fMRI paradigm) and the physiological variable (the activity time course of the seed ROI) as regressors. Correction for multiple comparisons was achieved by cluster-level thresholding at $p = 0.005$ using the Monte Carlo simulation tool implemented in BrainVoyager.

2.7.1.2. Resting-State functional Connectivity:. The mPFC (based on Neurosynth) during the resting state task, was used as a seed region for a voxel-based FC analysis per group.

3. Results

145 individuals were assessed for eligibility from August 2012 to February 2018, of them 76 were enrolled in the study. Three participants were excluded after enrollment due to changes in medication and consent withdrawal. As described, the study comprised of 3 treatment groups: two active treatment arms with (i) rPFC (N = 27) and (ii) lPFC (N = 28) dTMS and (iii) a sham arm (N = 20). 13 patients did not complete the study: 8 patients withdrew consent during the first week of treatments due to stimulation related inconvenience (headache, toothache, etc.); 2 patients missed the final follow-up session (V17); one participant was removed from the study because of a high rest motor-threshold in the first treatment session; one participant was taken out of the study because of an incidental brain finding in the MRI; one participant was removed due to starting psychiatric medications. Thus, the study included 24 patients who received rPFC treatment (age 35.6 ± 8.7; 17 males), 22 patients who received lPFC treatment (age 35.1 ± 10; 15 males), and 16 patients who received sham treatment (age 34.7 ± 9.2; 8 males). Three subjects were excluded from the study due to extreme clinical scores (>2 SD) in their screening assessment. Additionally, three participants completed the study protocol but did not undergo MRI scanning due to incompatibility. No significant differences in clinical impression of ADHD severity were observed between the groups at baseline (Table 2).

3.1. Clinical results

The three groups did not differ significantly in any of the demographic variables (see Table 2). Participants in all groups were not depressed at study entry, as observed by low scores on the BDI, and showed no significant change in depressive symptoms over their participation in the study (see supplementary information). The CAARS observer total and CAARS self-report total subscales did not show a significant group effect on change from baseline scores over the study course ($F(2,56) = 1.325$, $p = 0.27$ and $F(2,56) = 1.495$, $p = 0.23$ respectively; see Fig. 2A,B). We did find a significant group effect on the change from baseline scores of the CAARS self-report Inattention/Memory Problems subscale ($F(2,56) = 4.03$, $p = 0.023$; Fig. 2C), for which post-hoc analysis (Tukey HSD) revealed a significant difference between the right stimulation group and the sham group ($p = 0.018$). In addition, a significant interaction effect was obtained for the same subscale between Time and Group ($F(6, 168) = 2.3475$, $p = 0.03336$). Post-hoc analysis (Tukey HSD) showed that both treatment arms demonstrated decreased scores in V15 (rPFC $p < 0.00005$; lPFC $p < 0.05$), which were sustained through both follow-up visits (V16, V17; rPFC $p < 0.00005$; lPFC $p < 0.05$), while the sham group did not change. The other CAARS subscales did not show significant interaction effects.

Improvements were seen in CGI for all groups and were more robust for the rPFC group but did not reach statistical significance (rPFC − 1.73 points at V15, 1.50 points at v16; lPFC − 1.13 points at V15, 1.05 points at V16; Sham − 1.14 points at V15, 0.87 points at V16) (see supplementary Table 5). Similarly, non– significant improvements in performance on the Mindstreams cognitive battery were observed across the 3 treatment groups (See supplementary Table 3). A non-significant but notable improvement was observed in the Mindstreams attention score from Scr to V15 in the real rPFC group, as compared to the real lPFC and Sham group (5.67 vs 2.55 and 1.42 points respectively). No significant effects were observed on the other quality of life scales.

3.2. fMRI results

3.2.1. Behavioral results

A significant interaction of time and group was detected for reaction time on the N-back task ($F(2, 48) = 3.3492$, $p = 0.04349$). Post-hoc analysis (Tukey HSD) showed that only the rPFC treatment group showed improvement in reaction time for both conditions on the N-back task ($p < 0.01$). No significant difference was observed between groups in performance accuracy.

3.2.2. Imaging results

3.2.2.1. ROIs analysis - N-back paradigm. Pre-determined regions from the attention and default-mode networks were examined in a repeated measures ANOVA with group and time as independent variables. Importantly, no baseline differences were found between the groups in a one-way ANOVA performed on the beta-values of the pre-scan in any of the regions of interest (p-values range 0.08–0.72).

Right DLPFC: Repeated measure ANOVA (group*time) revealed a significant group-by-time interaction for the Beta values ($F(2, 57) = 4.2901$, $p = 0.01838$). HSD post-hoc analysis revealed a significantly greater rDLPFC activation after the treatment phase only in the right treatment group ($p < 0.005$; see Fig. 3A). Furthermore, we found a significant positive correlation between the increased activation in the right DLPFC and the improvement in inattention/memory symptoms ($r = 0.43$, $p < 0.05$; see Fig. 3B).

Right IPs: Repeated measure ANOVA (group*time) revealed a significant group-by-time interaction for the Beta values ($F(2, 56) = 3.2996$, $p = 0.04419$). HSD post-hoc analysis revealed a significantly greater right IPs activation after treatment only in the right treatment arm ($p < 0.05$; see Fig. 4).

Right IFG/ant. Insula: Repeated measure ANOVA (group*time) revealed a significant group-by-time interaction for the Beta values ($F(2, 56) = 3.2418$, $p = 0.04654$). HSD post-hoc analysis revealed a significantly greater right IFG activation after treatment only in the right treatment arm ($p < 0.05$; see Fig. 5). As for the left hemisphere, the homologue brain regions did not present increased activity after treatment period.

3.2.2.2. Whole brain analysis – N-Back paradigm. Whole brain random-

Table 2
Patient demographics. CGI – Clinical Global Impression score; SSRI – Selective Serotonin Reuptake Inhibitor; PFC – prefrontal cortex.

Group	N	Age (years)	Male/Female	Average CGI pre-trial	Handedness % right)	Education (years)	Medications
Right PFC Stimulation	24	35.6 ± 8.7	17/7	4.55	83% right	14.8 ± 2	11 Stimulants; 1 SSRI
Left PFC Stimulation	22	35.1 ± 10.1	15/7	4.38	82% right	14.6 ± 2.7	10 Stimulants; 4 SSRI
Sham Stimulation	16	34.7 ± 9.2	8/8	4.27	93% right	14.7 ± 1.8	4 Stimulants; 5 SSRI

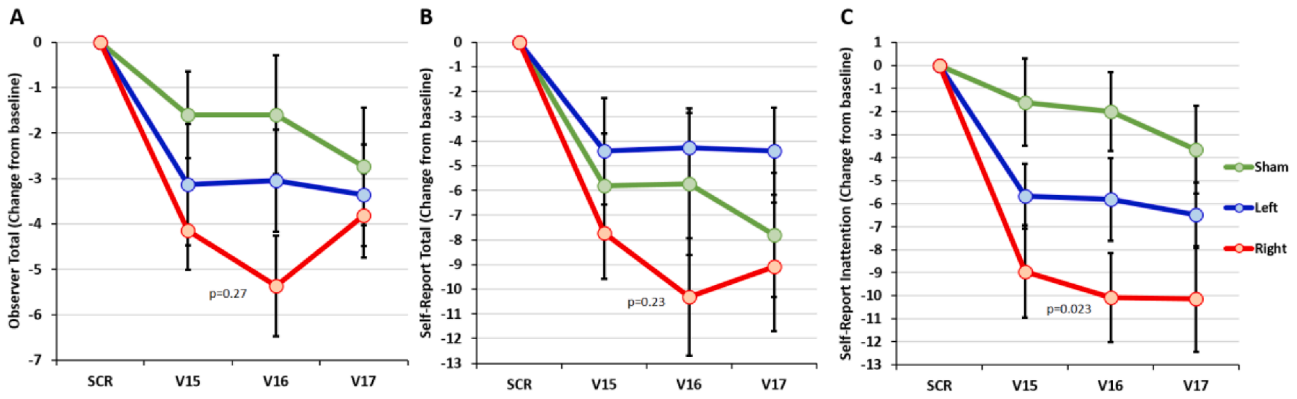

Fig. 2. Clinical sub-scales. A line chart depicting the change from baseline scores of the two treatment groups (Right stimulation in red; left stimulation in blue) and Sham group (green) across time (Screening, visit 15, visit 16 and visit 17) of the (A) CAARS (observer) total subscale (B) CAARS (self-report) total subscale and (C) CAARS (self-report) inattention/memory subscale. Error bars represent standard errors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

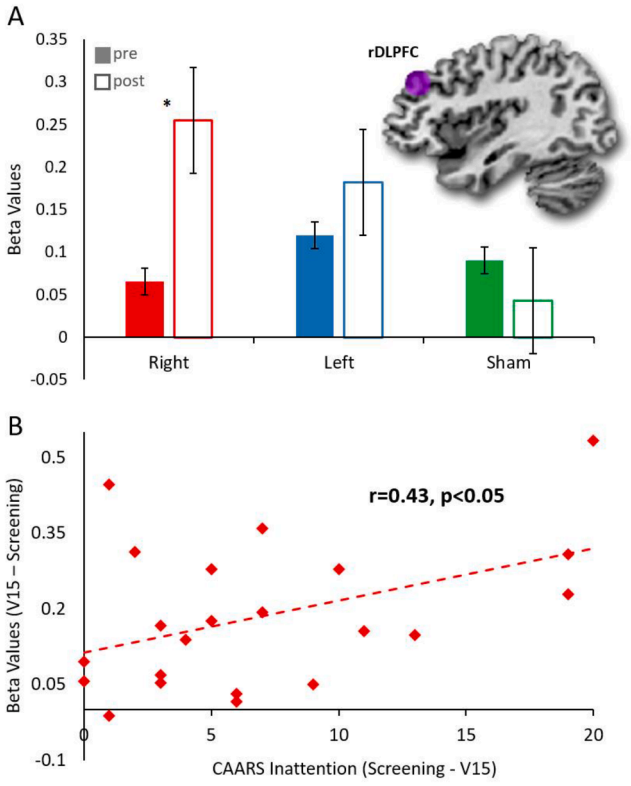

Fig. 3. Right DLPFC activation before and after treatment phase during the WM task. (a) Sagittal slice showing brain region of interest located in the right DLPFC (purple). The bar graph presents the brain activation (beta values) from right DLPFC in the three groups across conditions before (full bars) and after (clear bars) the 3 weeks of treatment. * $P < 0.05$. (b) Significant correlation r = 0.43, ($P < 0.05$) between activation change in the right DLPFC following treatment and improvement in inattention symptoms score shown in the right PFC stimulation group. DLPFC, Dorsolateral Prefrontal Cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

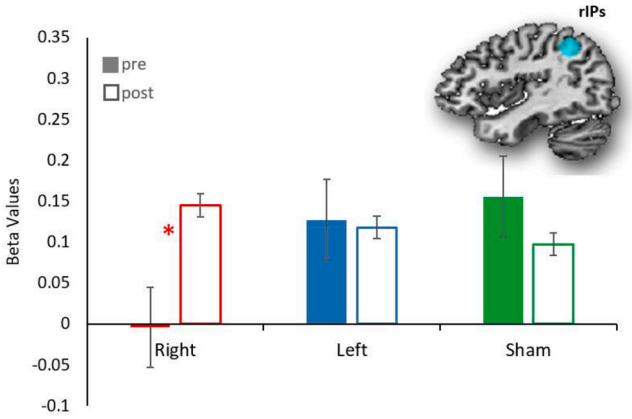

Fig. 4. Right IPs activation before and after treatment phase during the WM task. Sagittal slice showing brain region of interest located in the right IPs (cyan). The bar graph presents the brain activation (beta values) from right IPs in the three groups across conditions before (full bars) and after (clear bars) following the 3 weeks of treatment. * $P < 0.05$ t. IPs, Intra Parietal sulcus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

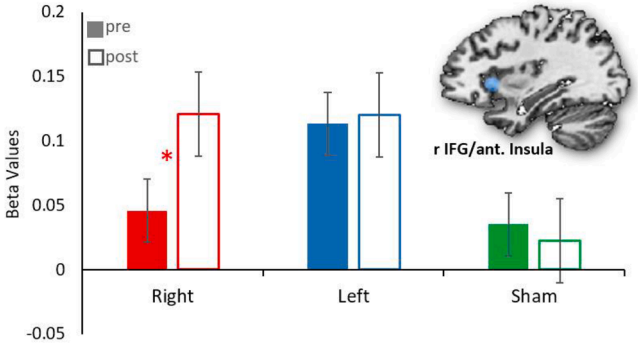

Fig. 5. Right IFG/ant. Insula activation before and after treatment phase during the WM task. Sagittal slice showing brain region of interest located in the right IFG/ant. Insula (light blue). The bar graph presents the brain activation from right IFG/ant. Insula in the three groups across conditions before (full bars) and after (clear bars) following the 3 weeks of treatment. * $P < 0.05$. IFG, Inferior Frontal Gyrus, ant., anterior. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

effects ANOVA with task conditions, time and group revealed no significant interactions.

3.2.2.3. Whole brain psycho-physiological interaction (PPI) - N-back paradigm. The rDLPFC (based on Neurosynth) was used as a seed region for a whole-brain voxel-based Functional Connectivity (FC) analysis for

all groups. Unfortunately, no significant interaction was observed.

The mPFC (based on Neurosynth) was used as a seed region for a whole-brain voxel-based Functional Connectivity (FC) analysis for all groups. Fig. 6 presents a FC map demonstrating significantly increased FC of the mPFC with the right and left middle insula. We then extracted the beta values from the right and left middle insula for all three groups and calculated the difference between the two time points. The results for the right middle insula revealed a significant group effect ($F(2, 58) = 6.3818$, $p = 0.00313$). HSD post-hoc analysis revealed significantly greater connectivity for the right treatment group compared to the left treatment ($p < 0.01$) and sham ($p < 0.05$) groups. The results for the left middle insula revealed a significant group effect ($F(2, 58) = 8.3318$, $p = 0.00066$). HSD post-hoc analysis revealed significantly greater connectivity for the right treatment group compared to the left treatment ($p < 0.005$) and sham ($p < 0.05$) groups.

3.2.2.4. Functional connectivity analysis - Resting-state paradigm. The mPFC (based on Neurosynth) during the resting state task, was used as a seed region for a voxel-based FC analysis per group. Fig. 7 presents a FC map demonstrating significantly increased FC of the mPFC with the posterior cingulate cortex (PCC). We then extracted the beta values from the PCC for all three groups and calculated the deltas between the two time points. The results revealed a significant group effect ($F(2, 52) = 8.0853$, $p = 0.00088$). HSD post-hoc analysis revealed significantly greater connectivity for the right treatment group related to the left treatment ($p < 0.005$) and sham ($p < 0.01$) groups.

4. Discussion

In the current study, we show that dTMS, applied for 15 sessions over 3 weeks to the right PFC in adults with ADHD, improved inattention/memory symptom severity. We also found increased activation during the working memory task in attention related regions; the rDLPFC, rIPs and r insula/IFG. Furthermore, the increased activation observed in the rDLPFC was correlated with clinical improvement in inattention/memory symptoms. FC between the mPFC and the right and left middle insula was also increased after the treatment phase only for the right treatment arm. Lastly, during the resting state paradigm there was increased FC of the mPFC with the PCC after the treatment, again only for the right treatment arm. These findings show that dTMS applied to the rPFC in adults with ADHD was able to increase activity and FC of attention related brain regions, and that these neural changes were associated with clinical improvement in attention symptoms. Taken together, these findings suggest that dTMS to the rPFC may be an effective treatment tool for treating attention symptoms in adults with ADHD.

It is noted that while functional improvements were seen in the rPFC group on the CGI, the study failed to achieve significant clinical improvement on this primary outcome measure. Given the improvements seen in memory/attention symptoms for the rFPC group, it is likely that the effect of the 3 week treatment was either not strong enough or not long enough lasting to lead to significant functional gains. This finding will need to be taken into account in designing future studies using TMS to treat ADHD. It is also possible that by using dTMS, thus stimulating large areas of the cortex with possibly opposing functions, we limit the clinical efficacy of the treatment.

In the left treatment arm, lesser symptomatic improvements were noted, and were not associated with significant changes in brain activation. The more mild symptomatic improvement in the lPFC treatment group may possibly represent a placebo effect, or could alternatively be explained by a milder TMS effect that was not robust enough to lead to significant change in brain activation patterns. It has been proposed that ADHD may be related to neurological involvement of the right hemisphere (Wasserstein and Stefanatos, 2000), although this notion has been controversial. There are existing structural and functional neuroimaging evidence for right hemisphere frontal and striatal dysfunction and/or dysplasia in ADHD (Casey et al., 1997; Castellanos et al., 1996; Filipek et al., 1997). In the same line, Rubia et al., (Rubia et al., 1999) demonstrated a right hemisphere pattern of hypofrontality in adolescents with ADHD during performance of two different executive tasks, with reduced activation in mesial and lateral prefrontal areas in the right hemisphere as compared to controls. Booth and colleagues (Booth et al., 2005) found that ADHD subjects showed decreased activation in a widespread network of frontal regions, predominantly in the right hemisphere. A recent meta-analysis (Norman et al., 2016) of fMRI studies during tasks that require inhibitory control identified reduced rVLPFC activation in ADHD subjects relative to controls. A meta-analysis of whole brain fMRI studies in children and adults with ADHD using a wide range of tasks found reduced activation in ADHD subjects as compared to controls in different functional brain systems, including the bilateral ventral attention system and predominantly right hemispheric fronto-temporo-parietal cognitive control networks, including DLPFC/IFG, basal ganglia, thalamus, ACC and SMA (Cortese et al., 2012). A meta-analysis of N-back WM fMRI studies showed a more bilateral decrease in activation of frontal lobe regions in ADHD subjects relative to controls (McCarthy et al., 2014). A meta-analysis of whole-brain fMRI studies which looked at neural patterns underpinning the different clinical syndromes in ADHD revealed reduced activation for attention tasks in the right hemispheric dorsal attention network, including the DLPFC, posterior basal ganglia, and thalamic and parietal regions, as compared to controls (Hart et al., 2013).

While investigating changes in connectivity in adults with ADHD, we found increased FC between the mPFC and bilateral middle insula

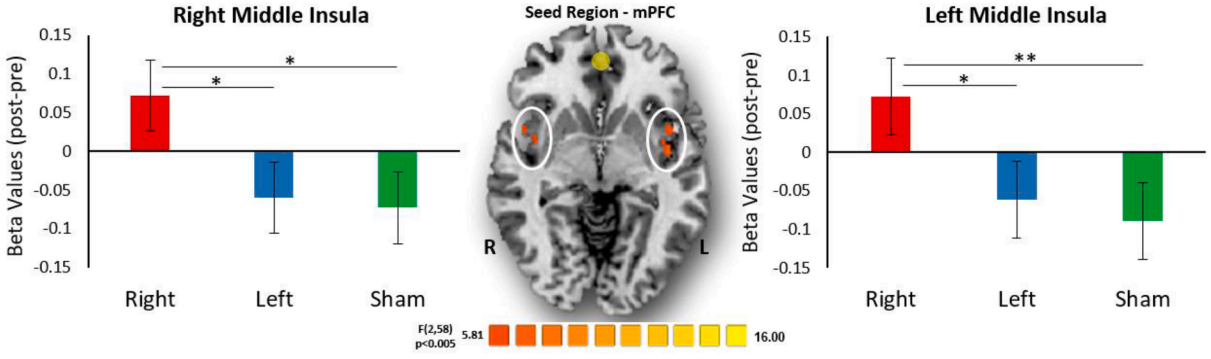

Fig. 6. Connectivity between mPFC & Right and Left Middle Insula during the WM task. Axial slice showing increased functional connectivity between mPFC (yellow) and the right & left middle insula (orange). The image was thresholded at $q < 0.05$, FDR corrected. Extracted beta values from the right middle insula (the left bar graph) and from the left middle insula (the right bar graph) showed that the treatment specifically enhanced mPFC-bilateral middle insula functional connectivity only for the right PFC stimulation group (in red). * $P < 0.05$; ** $P < 0.005$. Error bars represent standard errors. mPFC, medial prefrontal cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

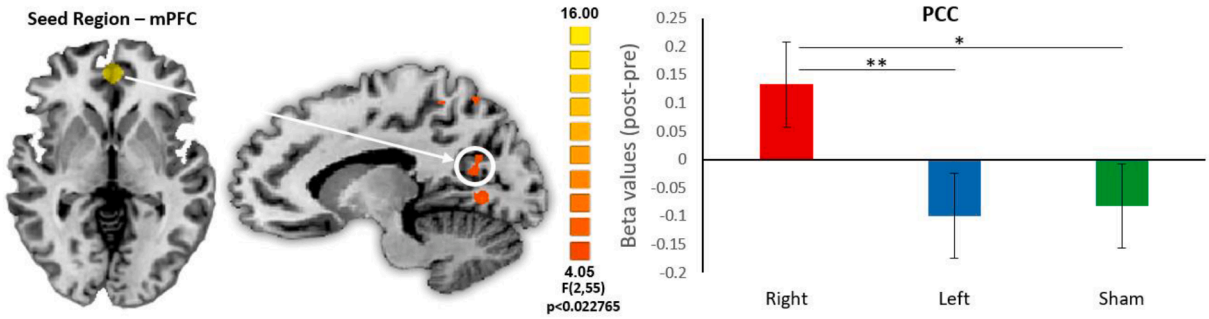

Fig. 7. Connectivity between mPFC & PCC during Resting State. Axial slice showing the seed region, mPFC (in yellow) and in midsagittal view increased functional connectivity with the PCC (orange). The image was thresholded at $q < 0.05$, FDR corrected. Extracted beta values from the PCC showed that the treatment specifically enhanced mPFC-PCC functional connectivity only for the right PFC stimulation group (in red). * $P < 0.01$; ** $P < 0.005$. Error bars represent standard errors. PCC, posterior cingulate cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

during the working memory task after dTMS to the rPFC. During the resting state paradigm, increased FC between two main components of the DMN (mPFC and PCC) after dTMS to the rPFC was observed. Along the same line, hypo-connectivity between the DMN and the ventral attention network (Sripada et al., 2014) as well as the cognitive control network (Castellanos et al., 2008; Uddin et al., 2008) seems to be of particular relevance with regard to a neurocognitive model of attention delays in patients with ADHD. Overall, much of the evidence points toward an altered connectivity within the DMN but also of the DMN with other brain regions that are relevant for the regulation of attentional processes in individuals with ADHD (Posner et al., 2014).

To date, tens of studies have been reported using noninvasive brain stimulation (NIBS) as a therapeutic intervention in people with ADHD, some with positive results, indicating the potential for these techniques (reviewed in Wong and Zaman, 2019). Specifically, Bloch et al. (Bloch et al., 2010) applied rTMS to the right PFC in a single session to 13 adults with ADHD and demonstrated a specific beneficial effect on attention immediately after treatment. Weaver et al. (Weaver et al., 2012) applied rTMS to the right PFC in a 10-session course over 2 weeks using a crossover design to nine adolescents with ADHD and demonstrated some symptomatic improvements but no significant effect of active TMS over sham. It is possible that the 2-week treatment course was too short to identify significant improvement. Transcranial direct current stimulation (tDCS) to the prefrontal cortex has also been evaluated for therapeutic effect in ADHD (for a review see Salehinejad et al., 2019), and has shown improvements in aspects of cognitive functioning, including inhibitory control and working memory. While not demonstrating significant improvement in its functional primary endpoint, our work adds to these previous studies and strengthens the proof of concept in showing improvements in inattention symptoms that correlated with increased activations in the right PFC as well as other brain regions of the attention network.

The strength of this study is the use of fMRI to evaluate the neural effects of dTMS in adults with ADHD. While the use of sham treatment and active comparator arms is also a strength of the study, a possible limitation is that subjects may not have been completely blinded as to whether they were receiving real or sham treatments, due to the local sensory effects elicited by TMS in the skin and soft tissues, possibly leading to placebo effects. We attempted to control for this issue as best as possible, including only recruiting TMS naïve subjects and designing a sham coil that produced similar noise and sensory effects to that of real TMS treatment. In previous deep TMS studies applied to TMS-naïve subjects in a 2 armed, sham controlled protocol (Levkovitz et al., 2015, Carmi, 2018), subjects in both the active and sham arms responded at 70% or greater that they had received real TMS. Overall clinical improvements were seen in all the groups which may be suggestive of a placebo effect, but may also have been related to the use of the same cognitive training applied across all the groups.

To our knowledge, this is the first study that examined the neural effects of dTMS on attention networks in adults with ADHD by using fMRI, and the first study that has demonstrated both clinical improvement and increased activation of attention related brain regions that correlated with clinical improvement. It is noted that clinical improvement was limited to attention related symptoms, which is likely due to the brain regions that were stimulated or the adult nature of the subjects. Further studies are needed to corroborate these effects.

CRediT authorship contribution statement

Maya Bleich-Cohen: Conceptualization, Investigation, Formal analysis, Writing - original draft, Visualization. **Guy Gurevitch:** Investigation, Formal analysis, Software, Writing - original draft, Visualization. **Noa Carmi:** Investigation, Data curation. **Mordekhay Medvedovsky:** Resources, Writing - review & editing. **Noa Bregman:** Resources. **Naomi Nevler:** Resources. **Karin Elman:** Resources. **Amit Ginou:** Project administration, Resources, Funding acquisition. **Abraham Zangen:** Conceptualization, Writing - review & editing. **Elissa L. Ash:** Conceptualization, Investigation, Project administration, Writing - review & editing.

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The present study was pre-registered at ClinicalTrials.gov (trial name: Test Efficiency of Deep Transcranial Magnetic Stimulation (DTMS) Using an H-coil for Prefrontal Cortex (PFC) to Treat Attention Deficit Hyperactivity Disorder (ADHD) in Adults; registration number: NCT01196910; URL: https://clinicaltrials.gov/ct2/show/NCT01196910).

Disclosure

Prof. Zangen is co-inventor of the deep TMS H-coil system, serve as consultant for, and has a financial interest in Brainsway, LTD. All other authors report no biomedical financial interests or potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102670.

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