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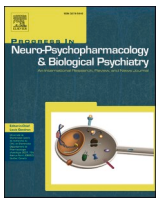

Right prefrontal activation predicts ADHD and its severity: A TMS-EEG study in young adults

Itay Hadas [a,b,*,1], Aviad Hadar [c,d,1], Avi Lazarovits [b], Zafiris J. Daskalakis [a], Abraham Zangen [b]

[a] Department of Psychiatry, Faculty of Health, University of California San Diego, La Jolla, CA 92093-0603, USA
[b] Life Science Department and the Zlotowski Center for Neuroscience, Ben Gurion University in the Negev, Beer Sheva, Israel
[c] Shalvata Mental Health Center, Hod-Hasharon, Israel
[d] Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

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ABSTRACT

Objective: Here we bring a neurophysiological diagnostic tool, based on pathophysiologically-relevant brain region, that is critical for reducing the variability between clinicians, and necessary for quantitative measures of ADHD severity.
Methods: 54 healthy and 57 ADHD adults participated in the study. Electroencephalography (EEG) was recorded when combined with transcranial magnetic stimulation (TMS) over the right prefrontal cortex and also recorded during the Stop Signal task.
Results: TMS evoked potentials (TEPs) and the event related potential (ERP) components in the Stop Signal task were found to be significantly reduced in ADHD relative to the matched healthy controls. Stop signal reaction time (SSRT) and stopping accuracy was found to correlate with the ERP signal, and ADHD severity correlated with the TEP signal. Cortical activity (early TEP and Stop Signal ERP) diagnostic model yielded accuracy of 72%.
Conclusion: TEPs and ERPs reveal that right PFC excitability was associated with ADHD severity, and with behavioral impulsivity – as a hallmark of ADHD pathology. This electrophysiological biomarker supports the potential of objective diagnosis for ADHD.
Significance: Such tools would allow better assessment of treatment efficacy and prognosis, may advance understanding of the pathophysiology of the disease and better the public's attitudes and stigma towards ADHD.
Trial Registration: Trial to Evaluate the Efficacy of the HLPFC Coil Deep Transcranial Magnetic Stimulation System in Treating Attention Deficit and Hyperactivity Disorder (ADHD) in Adults, https://clinicaltrials.gov/ct2/show/NCT01737476, *ClinicalTrials.gov number NCT01737476*

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is a clinically heterogeneous disorder with an estimated prevalence rate of 2.8% among adults worldwide (Fayyad et al., 2017). Its multifaceted pathophysiology has been suggested to consist of complex and distinct neural abnormalities which makes a precise biological diagnosis allusive (Posner et al., 2014). Therefore, ADHD diagnosis is primarily based on symptomatic clinical criteria (Fayyad et al., 2017). The subjective nature of such assessments combined with a growing debate concerning possible inflated diagnosis of ADHD patients (Cotuono, 1993; Desgranges et al., 1995) call for a search for diagnostic procedures which are based on neurobiological measures (Mueller et al., 2017). Indeed numerous studies indicate that the uncertainty regarding the validity and reliability of ADHD diagnosis is a major cause for damaging stigma (social problems, work-place difficulties and internalization of negative stereotypes regarding potential factitious nature of the disorder), in addition to the obvious damage to the patient's wellbeing (Mueller et al., 2012). Moreover, identification of altered neurophysiological activity in brain regions associated with the core cognitive deficits of ADHD could shed light on the pathophysiology of this disorder (Hoekzema et al., 2014).

Several *alternative* diagnostic paradigms have been examined over the past decades involving behavioral, physiological, neural and genetic

* Corresponding author.
E-mail address: ihadas@health.ucsd.edu (I. Hadas).
[1] Equal contributors.

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approaches. One set of paradigms focuses on the behavioral manifestation of impaired cognitive functions in ADHD. A prominent example of this approach are behavioral tasks measuring response inhibition capabilities (e.g., Stop Signal and Go/No go tasks) (Bari and Robbins, 2013). Using these tasks, it has been demonstrated that many ADHD subjects show difficulties in inhibiting responses and that the use of psychostimulants alleviates these difficulties (Alderson et al., 2007). Additionally, imaging studies showed that ADHD patients demonstrate lower brain activity in the right lateral prefrontal cortex (rPFC) during performance of these tasks (Hart et al., 2013).

Another approach, is the use of transcranial magnetic stimulation (TMS) in conjunction with either electroencephalogram (EEG) for the measurement of evoked cortical responses or electromyogram (EMG) for the measurement of neuromuscular activity (Tremblay et al., 2019). Such methodologies enable the measurement of several excitatory and inhibitory neural measures associated with the disorder (Casarotto et al., 2011a; Huber et al., 2013a). For example, several EMG studies reported reduced cortical inhibition in the *motor* cortex of children and adults suffering from ADHD (Gilbert et al., 2011; Dutra et al., 2016; Vera et al., 2020). Notably, earlier TMS studies mainly used EMG, which records muscular activity corresponding to motor cortex activity without recording direct cortical activity. This was mainly due to technical limitations in EEG recordings stemming from the TMS artifacts. However, in light of recent advancement of amplifier technology, and developments in signal processing (Korhonen et al., 2011), the use of TMS-EEG for assessment of cortical activity in non-motor regions is gradually increasing (Tremblay et al., 2019). It is now possible to reliably assess prefrontal neural anomalies (Rogasch et al., 2014) without the unnecessary involvement of upstream sensory activation which may map more precisely onto the physiological functions impaired in ADHD.

The current study has therefore two objectives: First, to identify a reliable neural anomaly in the right prefrontal neural circuitry of adults with ADHD, which may help in elucidating the neurophysiological underpinnings of ADHD and even aid it defining the diagnosis. Second, to establish whether this neural measure is correlated with behavioral deficits central to ADHD and particularly in inhibitory control. These objectives were achieved through two paradigms: (1) concurrent TMS-EEG recording, where a single TMS pulse was aimed at the rPFC and a neural response was evoked and analyzed; (2) EEG recording during performance of the Stop Signal task, in which both impaired behavioral inhibitory control and rPFC hypoactivity have been consistently reported (Aron et al., 2014; Aron et al., 2004; Bush et al., 2005; Dickstein et al., 2006; Pliszka et al., 2007). These hypotheses driven, pathophysiologically relevant measures were then used to collectively identify ADHD in a simple and readily understood linear discriminant model (without the need for automated selection of arbitrary signal features).

2. Materials and methods

2.1. Participants

One hundred and eight participants including 52 healthy control subjects (17 females; mean age 26 (SEM = 0.3) years) and 56 ADHD subjects (11 females; mean age 25.7 (0.5) years) were recruited for this study. Subjects were recruited by advertisement on university boards and an online newsletter. Majority of participants (both groups) were students at Ben Gurion University. The use of psychoactive medications (e.g., methylphenidate) was prohibited a week prior to participation. A local ethical committee (Helsinki) approved the protocol and written informed consent was obtained from all subjects.

All subjects completed the Hebrew version of the "Conners' Adult ADHD Rating Scale - Self Report: long version questionnaire" (CAARS) (Conners et al., 1999) for assessment of severity of ADHD symptoms. ADHD subjects were also interviewed by a psychiatrist in order to verify ADHD diagnosis and to rule out neuropsychiatric comorbidities, and use of psychiatric drugs as per the inclusion/exclusion criteria of the protocol.

2.2. Apparatus

Electroencephalogram (EEG) activity was recorded both during performance of the Stop Signal task and during the TMS-EEG sessions, using a 64 electrodes Waveguard^{tm} cap and a TMS compatible EEG amplifier (ANT neuro, Enschede, Netherlands) referenced to Cz electrode and grounded to PO6 electrode. Impedance was kept below 10 kΩ. Recording frequency was set to 2048 Hz. Data were acquired using ASA™ version 4.7.3 (ANT neuro, Enschede, Netherlands).

TMS pulses were administered using a 70 mm figure-of-eight coil (external casing diameter ~ 90 mm for each loop) connected to a Magstim Rapid^2 biphasic stimulator (The Magstim Co. Ltd., Whitland, Carmarthenshire, U.K.).

2.3. Stop signal task

Subjects were required to perform a visual stop signal task (Logan et al., 1997; Berger et al., 2013). They were asked to respond to two visual cues ('x', 'o') by pressing one of two corresponding buttons using either their left or right index fingers. In 25% of trials a stop signal (white square) appeared after the go signal instructing subjects to withhold their response. The delay between go and stop signals (i.e., Stop Signal Delay (SSD)) changed through the experiment in a staircase dynamic-tracking manner, depending on the subject's performance in the preceding stop trial, pursuing 50% success rate in inhibition trials (Berger et al., 2013). Stop Signal Reaction Time (SSRT), which represents the time required for a stopping response, was calculated as the difference between the averaged RT to the Go signal and the averaged SSD (Alyagon et al., 2020). For a detailed description of the task see *Supplement 1*. As mentioned above, neural activity during performance of this task was recorded using EEG.

2.4. TMS-EEG

EEG activity was recorded during administration of TMS pulses targeting the rPFC. Resting motor threshold (RMT) and coil positioning were first established. The coil was then moved 5 cm anterior to the motor spot and 2 cm to the right, handle of the coil pointed backward, perpendicularly to the presumed direction of the central sulcus, approximately 45° to the mid-sagittal line (Alyagon et al., 2020). Stimulation intensity was set to 120% of the RMT. For a detailed description of the TMS procedure see *Supplement 1*.

2.5. Data processing

TMS-EEG and stop-signal EEG data was processed offline with the aid of custom scripts and with the aid of EEGLAB (Delorme and Makeig, 2004) toolbox for Matlab. Noisy channels and epochs were removed, muscle decay artifact was removed using Independent Component Analysis (ICA), and a second round of ICA was applied to remove eye blinks, vertical eye movement, large muscle contractions and other artifacts. For a detailed description of the data processing procedure and TEP extraction see *Supplement 1*. TMS-EEG data of 23 subjects (11 Controls and 12 ADHD) was discarded due to poor recording quality, excessive movements and muscle twitching severely contaminating the data.

2.6. TMS-EEG measures

To assess the local cortical activation induced by the TMS, we computed the local mean field power (LMFP) as follows: $LMFP(t) = \sqrt{\frac{\sum_i^K (V_i(t) - V_{mean}(t))^2}{K}}$ (where K are the ROI channels and V is instantaneous

voltage) (Casarotto et al., 2013; Pellicciari et al., 2013; Fecchio et al., 2017). LFMP timing was around the TEP P30 peak (25–45 ms after the TMS pulse) based on standard timing in the literature, and informed by visual inspection of the waveform. We focused on the very early and prominent peak of the LMFP, positioned specifically under the coil. The earliest TEP peaks are highly reproducible, and localized under the coil, very unlikely to be contaminated with artifactual or unspecific processes, such as sensory (i.e. auditory and somatosensory), or cognitive associated signals (i.e. saliency associated N100- p200 peak) (Nikouline et al., 1999; Conde et al., 2019; Biabani et al., 2019; Freedberg et al., 2020) (see section "Results" and Fig. 2).

2.7. Statistical analysis

2.7.1. Stop Signal behavioral measures

Statistical analysis of the behavioral measures in the Stop Signal Task included the calculation of error proportion, average Go RT, average SSD and SSRT. The analysis procedure used here was identical to the one described at Alyagon et al. (2020) using Statistica version 12.0 (Statsoft, Tulsa, OK, United States).

2.7.2. Stop Signal EEG measures

Two components of ERP bearing specific relevancy to the Stop Signal

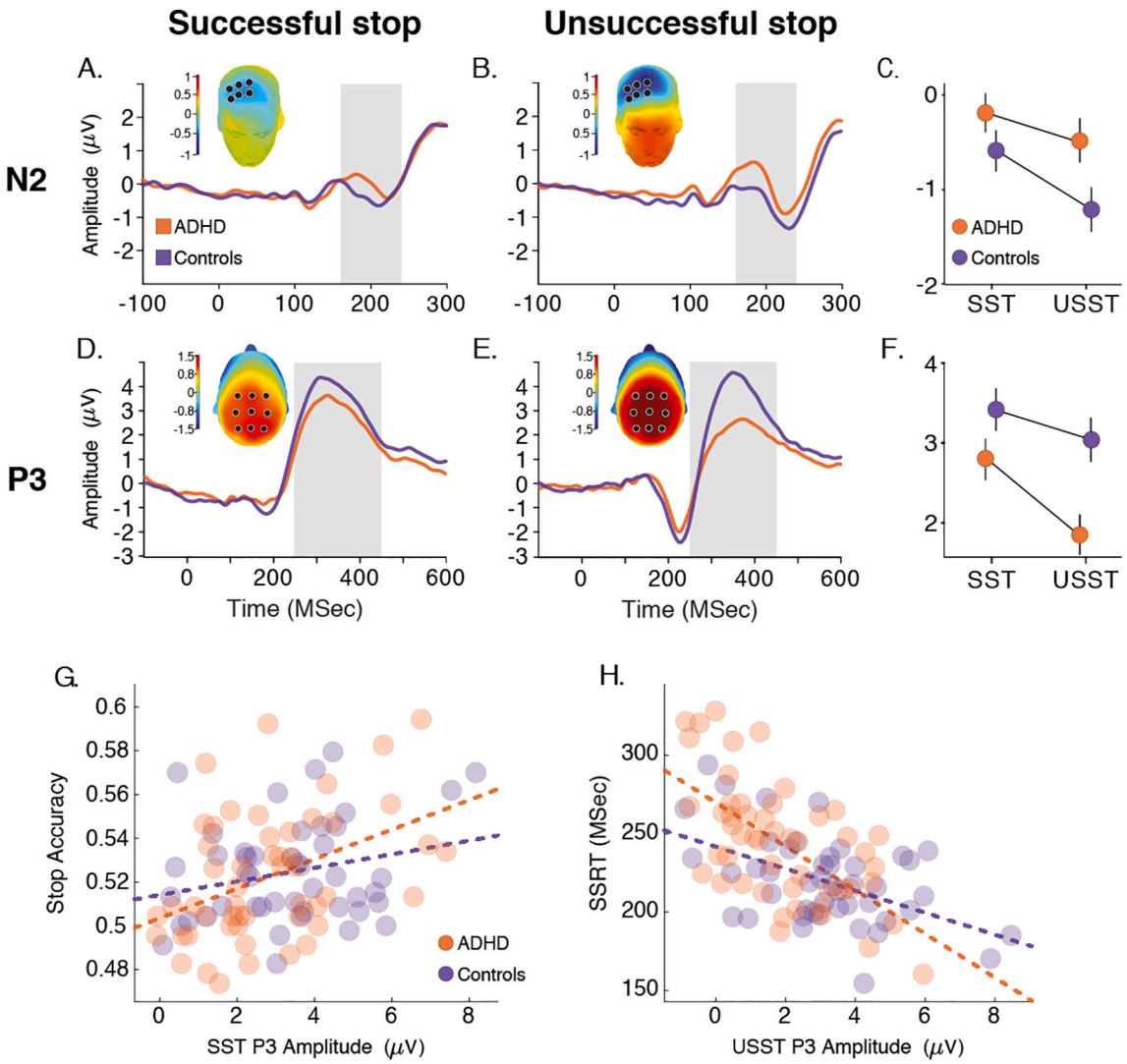

Fig. 1. Event related potentials (ERP) following Stop Signal. The N2 and P3 components evoked by the Stop Signal were significantly reduced in ADHD subjects compared with controls across all performance conditions. N2 amplitude was significantly reduced in both successful (panel A; control, −0.58 (0.24) μV; ADHD, −0.19 (0.17) μV) and unsuccessful (panel B; control, −1.21 (0.26) μV; ADHD, −0.49 (0.20) μV) stops in ADHD (panel C; $F_{(1,\ 99)} = 3.92$, $p = 0.050$). There was no interaction between group and successful stopping (panel C; ($F_{(1,\ 99)} = 1.89$, $p = 0.17$).

P3 amplitude was significantly reduced in both successful (panel D; control, 3.42 (0.26) μV; ADHD, 2.80 (0.25) μV) and unsuccessful (panel E; control, 3.04 (0.29) μV; ADHD, 1.84 (0.25) μV) stops in ADHD (panel F; $F_{(1,\ 99)} = 6.6$, $p = 0.012$). In addition, a significant interaction between group and success in stopping was observed (panel F; $F_{(1,\ 99)} = 7.71$, $p = 0.006$) highlighting a greater group effect in USST. Significant correlation was observed between successful P3 amplitude and overall stop trials accuracy (panel G; ADHD rho = 0.4 $p < 0.004$, Controls rho = 0.15 $p < 0.33$) and between unsuccessful P3 amplitude and SSRT (panel H; ADHD rho = −0.59 $p < 0.00001$, Controls rho = −0.4 $p < 0.006$).

N2 and P3 components were calculated as the mean amplitude within relevant time windows (N2: 160–240 ms after Stop Signal, P3: 250–450 ms).

Grey area denote the time window from which the average was extracted. The headplots in panels A, B, D, E represent the control-ADHD difference wave within this time window.

ERP was averaged across relevant electrodes for the N2 and P3 components (N2: FC2, FC4, FC6, F2, F4, F6; P3: FCz, FC1–2, Cz, C1–2, CPz, CP1–2) based on previous publications and preliminary inspection. See *supplement 2* for higher temporal resolution additional depictions of N2 and P3 activity across conditions and groups. *p < 0.05.

task were analyzed, namely N2 and P3 (Pliszka et al., 2000; Senderecka et al., 2012). N2 and P3 amplitudes were quantified individually for each subject by averaging the right frontal electrodes in the relevant time windows for these components (160–240 and 250–450 ms following the Stop Signal for N2 and P3 components, respectively). The time window and electrodes of interest were based on previous literature (Kaiser et al., 2020) and corroborated by inspection of the grand average (see Fig. 1). Group (ADHD, control) and performance (successful, unsuccessful stopping) differences in N2 and P3 amplitudes were studied using a 2 × 2 mixed design ANOVA. All post-hoc tests were conducted using Tukey HSD with appropriate corrections for multiple comparisons. Stop Signal EEG data of seven subjects (3 Controls and 4 ADHD) was discarded due to poor recording quality and excessive movements severely contaminating the data.

Cross sectional TMS-EEG LMFP comparison was conducted using two-sample, two-tailed *t*-test.

Spearman correlations were conducted in accordance with the distribution of the electrophysiological data. Individual data greater than three scaled median absolute deviations away from the group median was considered outlier and was excluded from the analysis using MATLAB 'isoutlier' function.

2.7.3. Diagnostic ROC curve

The diagnostic value of pathophysiologically relevant neural markers was assessed (Unsuccessful stop P3 and LMFP), and a linear discriminant was fitted over the distribution of the data using MATLAB's 'fitcdiscr' function. A ROC curve was used to estimate the model's optimal thresholds in terms of sensitivity, specificity and accuracy.

3. Results

3.1. Subjective measures

As expected, CAARS total ADHD symptoms in ADHD subjects were significantly higher than that of controls (ADHD subjects, 78.2 (1.39); controls, 52.38 (1.59); $t_{(106)} = -12.26$, $p < 1 \times 10^{-17}$).

3.2. Behavioral measures

ADHD subjects displayed significantly longer SSRT and higher error rates (in discrimination of the Go signals) than that of controls ($t(99) = 2.54$, $p = 0.0125$ and $t(100) = -2.31$, $p = 0.0225$, respectively). Mean RT to the Go signals, mean SSD were not different between the groups (Table 1).

3.3. Stop signal EEG measures

The N2 component in both successful and unsuccessful stopping trials had differential amplitude in ADHD and control subjects under rPFC preselected electrodes, specifically in right frontal channels FC2; FC4;FC6;F2;F4;F6 (see Fig. 1A, B). N2 amplitudes were submitted to a 2 × 2 mixed design ANOVA factoring Group (ADHD or control) by Performance (successful or unsuccessful inhibition). ADHD patients showed lower N2 amplitude than that of healthy controls, as expressed in a marginally significant main effect of Group ($F_{(1, 99)} = 3.92$, $p = 0.050$). In addition, a main effect of Performance was found, highlighting higher amplitude in unsuccessful compared to successful inhibition trials ($F_{(1, 99)} = 15.1$, $p = 0.00018$, see Fig. 1C). No Group by Performance interaction was found ($F_{(1, 99)} = 1.89$, $p = 0.17$).

The P3 component had a central broad spatial distribution (Fig. 1D, E). Data averaged from the relevant central electrodes was subjected to ANOVA in a similar design as the N2 component. ADHD subjects showed lower P3 amplitude than that of healthy controls (group main effect: $F_{(1, 99)} = 6.6$, $p = 0.012$). A main effect of Performance was found, highlighting lower amplitude in unsuccessful compared to successful inhibition trials ($F_{(1, 99)} = 40.75$, $p < 0.00001$, see Fig. 1F). Moreover, a significant Group by Performance interaction ($F_{(1, 99)} = 7.71$, $p = 0.006$) was found, indicating that group differences were more pronounced in unsuccessful compared to successful stopping trials.

The Successful stop trials P3 ERP component was correlated with overall stopping accuracy in the ADHD group, but not in Controls (ADHD rho = 0.4 $p < 0.004$, Controls rho = 0.15 $p < 0.33$; Fig. 1G). The Unsuccessful stop trials P3 ERP component was strongly correlated with SSRT in both ADHD and controls (ADHD rho = −0.59 $p < 0.00001$, Controls rho = −0.4 $p < 0.006$; Fig. 1H).

Correlating the index of total ADHD symptoms and ERP components (i.e. successful / unsuccessful N2 and P3) did not show any significant association (Fig. S9).

3.4. TMS-EEG measures

LMFP around 30 ms (P30 component) in ADHD subjects was significantly lower than that of controls (ADHD = 2.41(1.94); Controls = 3.8(3.28); $t_{(83)} = 2.7352$, $p = 0.007$. Fig. 2A and B.).

A significant moderate correlation (rho = −0.37, $p < 0.0009$. $N_{(ADHD)} = 43$, $N_{(Controls)} = 37$) was found between the rPFC derived LMFP P30 component and the index of total ADHD symptoms according the Connor's questionnaires (Fig. 2D). This correlation remained significant when assessed within the ADHD alone (rho = −0.47, $p < 0.002$) meaning that patients with more severe symptoms showed lower rPFC activation values (Fig. 2D).

A linear model, and a ROC curve analysis was utilized in order to evaluate the diagnostic value of the a-priorily determined neural data obtained (Fig. 3). Optimal thresholding for linear-discriminant model combining the stop-signal P3 and rPFC-LMFP P30 variables, yielded 72% classification accuracy (sensitivity 88%, specificity 54%) (Fig. 3).

Table 1
Group differences between ADHD and control subjects in Stop Signal Task Behavioral measures.

	ADHD	Controls	t (DF = 100)
SSRT	259(99) ms	226 (37) ms	2.182*
Go Accuracy	89 (14)%	94 (4)%	3.96*
Mean RT	587 (90) ms	574 (107) ms	2.52
Mean SSD	362 (177) ms	348 (131) ms	−0.44

SSRT: Stop Signal Reaction time, Accuracy: correct rates in discrimination of the Go signals, RT: Reaction Time, SSD: Stop Signal Delay.
* $p < 0.05$.

4. Discussion

The current study provides novel neurophysiological markers for ADHD in adults and reveals a pathophysiological role for right PFC activity patterns in determining the severity of the disorder. The study demonstrates a central role for rPFC activation in the pathophysiology of ADHD and constructs a straight forward diagnostic model based on this pathophysiologically relevant brain activity. The study taps into rPFC abnormalities in ADHD patients and the successful use of these to form an independent, theory driven, neural marker. In times where the reality of ADHD as a medical entity is constantly challenged and criticized there is great need for both better understanding of its neuropathology and for development of theory-driven objective diagnostic tools.

4.1. rPFC activity is abnormal in adults with ADHD

Here we first showed that neural excitability in the rPFC predicts ADHD severity. This finding rests on three decades of accumulated imaging data consistently showing that rPFC activation abnormalities are central to ADHD pathology (Hart et al., 2013). Critically, the difference between ADHD and control participants was specific to the early TMS evoked LMFP peak which is a widely accepted, reliable and clinically

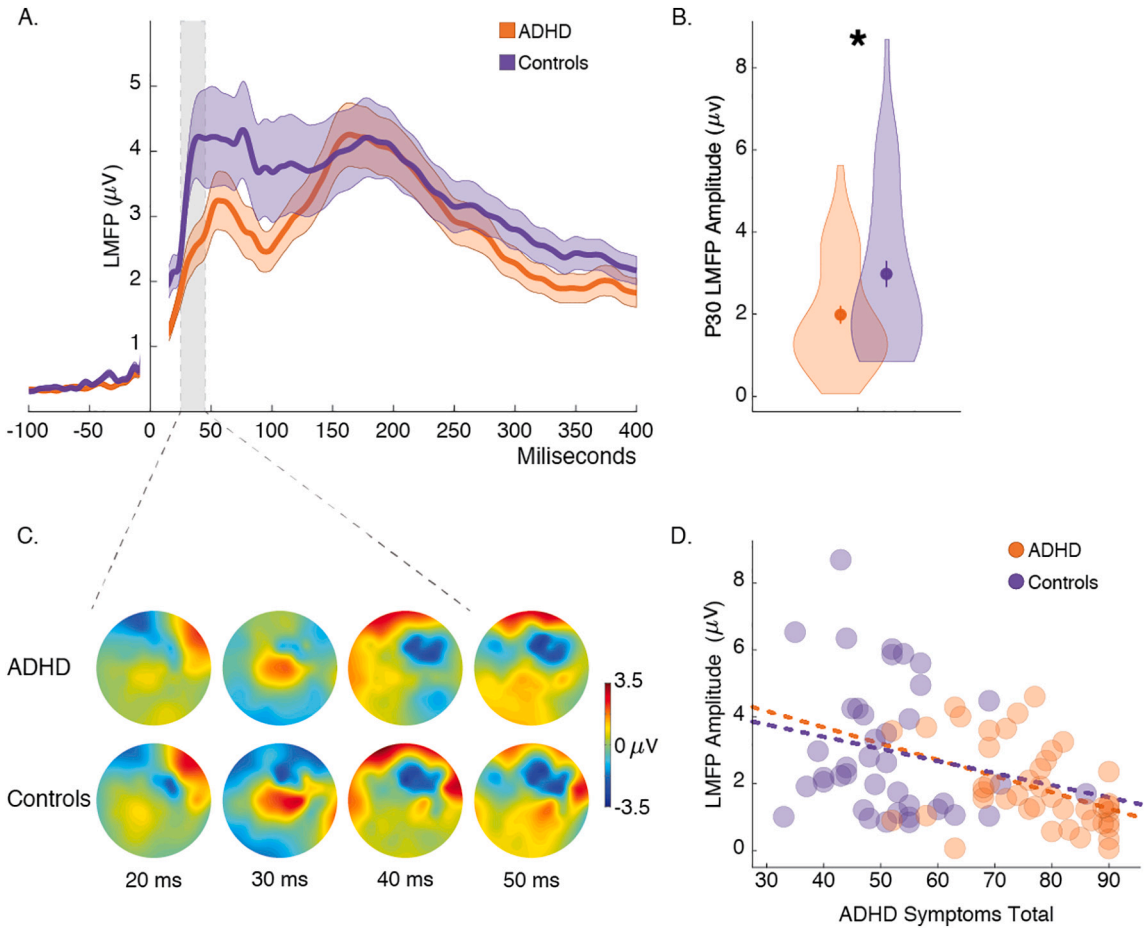

Fig. 2. Local mean field power (LMFP) following a single pulse directed to the rPFC for both experimental groups. Grey area is representing the statistics time window (panel A). Violin plot represent the LMFP group statistics (mean is represented by middle dot, and standard error of the mean is represented by the middle vertical line) (panel B; ADHD = 2.41(1.94); Controls = 3.8(3.28); t(83) = 2.7352, $p < 0.008$)). Topoplots represent TMS response over the scalp during the statistics time window (panel C). Correlation between LMFP amplitude and ADHD symptoms (panel D; rho = −0.37, $p < 0.0009$). significant groups effects. *: $p < 0.01$.

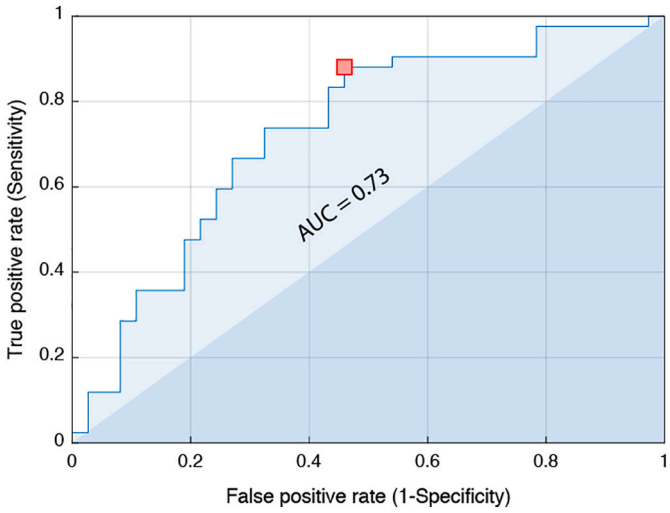

Fig. 3. ROC curve depicting the linear model discriminating power between Controls and ADHD (area under curve (AUC) = 0.73). The small red square represent the optimal threshold for this linear model (72% Accuracy, 88% sensitivity, 54% specificity). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

meaningful neural marker of focal cortical excitability (Lioumis et al., 2009; Tremblay et al., 2019). The magnitude of neural activity adjacent to the TMS pulse is considered to reflect cortical excitability (Casarotto et al., 2011b; Huber et al., 2013b). This independent neural abnormality also showed a significant correlation with ADHD symptoms severity thereby providing the pathophysiologically relevant single neural marker of ADHD.

Several other studies showed that early components of prefrontal TMS-EEG are highly sensitive to changes in cortical excitability (Noda et al., 2017). Altered early TEP components were recorded as a result of both basic pharmacological and electrophysiological manipulations of cortical excitability (Premoli et al., 2018). Our finding of decreased P30 in ADHD patients could reflect an abnormal excitation/inhibition balance in the neural circuitry governing rPFC activity. Previous studies using TMS-EEG in ADHD targeted the motor cortex. For instance, Bruckman et al. (Bruckmann et al., 2012) found reduced motor cortex response in children with ADHD and D'agati et al. (D'Agati et al., 2014) showed a similar non-significant trend. However the TEP preprocessing in D'Agati et al. might be outdated, since their TMS evoked activity lacks the highly replicable waveform, and their signal amplitude suggests it is mainly driven by muscle activation and other technical artifacts (Korhonen et al., 2011; Rogasch et al., 2013, 2014; Mutanen et al., 2016; Mutanen et al., 2013). Here we utilized a highly replicable and well accepted pre-processing of the data (Rogasch et al., 2014) which enables detection of neural anomalies in a focal brain area directly under the coil. Importantly this brain area is specifically implicated in the executive functioning impairments that are the hallmark of ADHD. Indeed our

findings are the first *TMS-EEG derived* evidence to suggest reduced excitability in the rPFC of ADHD subjects.

The current method for simultaneous probing and recording carries several advantages over traditional imaging paradigms for several reasons. First, neural activity provoked by TMS is highly reproducible, relative to activity provoked by cognitive tasks. The TMS-EEG methodology allows to experimentally determine the timing and location of the induced activation independently of upstream sensory or cognitive activation (Rogasch et al., 2015; Farzan et al., 2010; Tremblay et al., 2019; Hadas et al., 2019). Second, performance in cognitive tasks may often be biased by motivational issues (e.g. poor motivation) or secondary gains earned by being diagnosed with ADHD (Harrison et al., 2015). Third, the use of automatic statistical feature selection in imaging data creates a diagnostic "blackbox" with pseudo high accuracy levels on small samples but a rather worrying phenomenon of obvious overfitting in the final classification model (Skocik et al., 2016). Indeed, the relevancy of the derived diagnostic features to the disease pathophysiology is poorly explained or understood. Thus, in the present model, the neural data is specific to disease behavioral and neural pathology and is relatively independent of behavioral or motivation factors.

4.2. Stop signal ERP

The second neural abnormality observed in ADHD subjects was reduced N2 and P3 components of Stop Signal ERP. This pattern was more pronounced in unsuccessful inhibition trials wherein subjects failed to inhibit their response. These results corroborate previous findings in ADHD adults using a closely related inhibition task (Go NoGo task) and data from children with ADHD (Marquardt et al., 2018) (but see also (Falkenstein et al., 1999)). These components are considered to be selectively associated with different sub processes in response inhibition although there is still debate regarding their role in specific inhibitory tasks (Enriquez-Geppert et al., 2010). The N2 component is often considered to reflect conflict monitoring or inhibition of prepotent response, while the P3 is thought to reflect later processes such as motor inhibition, target processing and response evaluation (Botvinick et al., 2004; Ramautar et al., 2006; Solbakk et al., 2014). Importantly, these widely replicated neurophysiological measures correlated here with the stop signal task measure (denoting behavioral inhibition). This finding of significant correlation between behavioral (i.e. SSRT and Successful stopping) and electrophysiological (i.e., P3 amplitude) deficits in adults with ADHD, further supports the validity of the diagnostic model proposed in this study, which includes the P3 feature as a critical electrophysiological measure. To the best of our knowledge, this is the first study in ADHD adults to find a confirmatory behavioral correlate to the widely observed group difference in P3.

4.3. Diagnostic models

The present study proposes a validated neurophysiological-based classification model demonstrating a clinically sufficient classification accuracy within this relatively large sample. Specifically, based on the neurophysiological measures alone our model yielded a 72% accuracy (accounting the clinical interview as ground truth). The high sensitivity (88%) obtained in this neural model for ADHD diagnosis is particularly useful for clinicians given the challenging differential diagnosis for young adults with attention difficulties. That is, a highly sensitive neural model can assist in 'raising the red flags' and ensure clinicians won't accidently omit important diagnosis. Unlike previous classification models, the present model is theoretically driven, parsimonious and does not suffer from overfitting and post-hoc feature selection. In addition to the P3 component, the correlation of the P30 LMFP component with core cognitive impairments of ADHD (Fig. 2D) solidify this component as a neural marker for ADHD and a moderate predictor of its severity.

Notably, a few other studies using TMS and stop signal in children with ADHD also indicated that such measures can aid clinical diagnosis (Dutra et al., 2016). These evolving objective techniques suggest a significant advancement to the diagnostic procedure in children. However, one has to bear in mind their limitations when compared with our study: (a) most TMS-EEG ADHD studies used smaller sample sizes (i.e., 20 subjects for each group (Bruckmann et al., 2012; D'Agati et al., 2014)). (b) They lack reference to diagnostic model of *adults*. (c) They measure cortical activity in the motor cortex and not in a brain region implicated in core cognitive functions, which are impaired in ADHD. (d) The TMS-EEG signals in these studies seems to be driven mainly by TMS related artifacts (muscle activation) (Korhonen et al., 2011; Rogasch et al., 2013, 2014; Mutanen et al., 2016; Mutanen et al., 2013). (e) Applying TMS stimulation during behavioral task will affect cognitive performance, which is a severe design confound. Hence, the present report offers an advancement in the assessment and approximation of ADHD severity in adults.

It is important to differentiate the present model from existing EEG-based neural markers for ADHD (Kaiser et al., 2020; Kiiski et al., 2020; Lenartowicz and Loo, 2014a; Saad et al., 2018). First, as discussed in several reviews studies on the diagnostic utility of theta/beta attempts reported an alarming variance in accuracy, 38% to 91%, while using the same technique (Lenartowicz and Loo, 2014b; Table 1). Indeed more recent attempts to replicate EEG-based classification yielded poor results with substantial heterogeneity and the moderate effect sizes ($d < 0.6$). This replication failure has been explained by the observation that such EEG spectral data and ERP data suffers particularly high inter-individual variability and is poorly reproducible (even within subjects) (Kaiser et al., 2020; Saad et al., 2018). TEP data, in contrast, has been shown in recent years to be reliable and reproducible (Ozdemir et al., 2020). Moreover, some of these imaging based classification models, frequently published in bio-engineering journals (Mueller et al., 2011), rely on automated selection of features using machine learning and complex algorithms that lump together dozens of signal features to achieve a maximal fit. Indeed, a recent review of studies using ERP signals for ADHD concluded that 'The largest biases were lack of representativeness and overfitting' (Gamma and Kara, 2016). This is in strike contrast to a model with a single (or dual) neural marker(s) solely and focally based on the core neuropathology of the disorder.

4.4. Limitations

Our study has several potential limitations concerning control stimulation site and the diagnosis and selection of the ADHD and healthy sample. Firstly, the present study focused on *rPFC* abnormalities in ADHD. However, to ensure that the effects obtained are *location-specific* - one needs to employ a stimulation control *site*. Due to resource limitation for the present study we did not attempt to establish whether the same neuronal pattern can be found in other brain areas, in which case our findings would not be specific for the rPFC. Similarly, our study lacks TMS sham control, however we avoided looking at later TMS-EEG timings that are suspected to be contaminated with sensory and somatosensory activations, and we concentrated on activation directly under the coil, a region that is less affected by such artifacts – particularly the early TEP components. Secondly, the recruitment and diagnosis process of the ADHD sample could be improved. Specifically, it was based on a clinical interview by a psychiatrist without systematic documentation of heteroanamnesis and/or structured diagnostic interview. Finally, control participants in the *healthy group* independently reported the *absence* of psychiatric diagnosis of ADHD and were not diagnosed by a psychiatrist to assure this self-report. Specifically, although all ADHD subjects underwent full psychiatric assessment, healthy subjects were not assessed. Tighter control for potential undiagnosed healthy subject may be pertinent in all participants to thoroughly test diagnostic tools.

5. Summary

In summary, this study identifies independent neural anomalies implicated in the pathophysiology of ADHD and demonstrates their utility for objective diagnosis. The novel use of TMS-EEG in prefrontal regions and the tight relations between rPFC activation, ADHD symptoms, behavioral inhibition and ERP measures provide further evidence for the role of the rPFC in ADHD pathophysiology while advancing objective neural based diagnostic models of ADHD in adults.

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Ethical statement

Written informed consent was provided by all subjects and ethical approval was granted by the local ethical committee of Ben Gurion University in the Negev, in accordance with the Declaration of Helsinki.

Declaration of competing interest

None of the authors has financial affiliations to disclose in association with this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2021.110340.

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