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Challenging the Diagnostic Value of Theta/Beta Ratio

Challenging the Diagnostic Value of Theta/Beta Ratio: Insights From an EEG Subtyping Meta-Analytical Approach in ADHD

Marit Boxum[1,2] · Helena Voetterl[2,3] · Hanneke van Dijk[2,3,4] · Evian Gordon[5] · Roger DeBeus[6] · L. Eugene Arnold[7] · Martijn Arns[2,3]

Abstract

The frequently reported high theta/beta ratio (TBR) in the electroencephalograms (EEGs) of children with attention-deficit/hyperactivity disorder (ADHD) has been suggested to include at least two distinct neurophysiological subgroups, a subgroup with high TBR and one with slow alpha peak frequency, overlapping the theta range. We combined three large ADHD cohorts recorded under standardized procedures and used a meta-analytical approach to leverage the large sample size (N = 417; age range: 6–18 years), classify these EEG subtypes and investigate their behavioral correlates to clarify their brain-behavior relationships. To control for the fact that slow alpha might contribute to theta power, three distinct EEG subgroups (non-slow-alpha TBR (NSAT) subgroup, slow alpha peak frequency (SAF) subgroup, not applicable (NA) subgroup) were determined, based on a halfway cut-off in age- and sex-normalized theta and alpha, informed by previous literature. For the meta-analysis, Cohen's d was calculated to assess the differences between EEG subgroups for baseline effects, using means and standard deviations of baseline inattention and hyperactivity-impulsivity scores. Non-significant, small Grand Mean effect sizes ($-0.212 < d < 0.218$) were obtained when comparing baseline behavioral scores between the EEG subgroups. This study could not confirm any association of EEG subtype with behavioral traits. This confirms previous findings suggesting that TBR has no diagnostic value for ADHD. TBR could, however, serve as an aid to stratify patients between neurofeedback protocols based on baseline TBR. A free online tool was made available for clinicians to calculate age- and sex-corrected TBR decile scores (Brainmarker-IV) for stratification of neurofeedback protocols.

Keywords ADHD · Biomarker · TBR · EEG · Stratified Psychiatry

Marit Boxum and Helena Voetterl have shared first authorship.

✉ Martijn Arns
martijn@brainclinics.com

1. Radboud University, Nijmegen, The Netherlands

2. Research Institute Brainclinics, Brainclinics Foundation, Bijleveldsingel 32, 6524 AD Nijmegen, The Netherlands

3. Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands

4. Synaeda Psycho Medisch Centrum, Leeuwarden, The Netherlands

5. Brain Resource Ltd, San Francisco, CA, USA

6. The University of North Carolina at Asheville, Asheville, NC, USA

7. Department of Psychiatry &, Behavioral Health, Nisonger Center, Ohio State University, Columbus, OH, USA

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common childhood psychiatric disorder, affecting approximately 5% of children worldwide (Faraone et al., 2015) About 40–60% of these individuals continue to experience symptoms into adolescence and adulthood (Faraone et al., 2006). ADHD is characterized by persistent symptoms of inattention, hyperactivity and/or impulsivity that may interfere with daily functioning in academic, occupational, and social settings (Faraone et al., 2015). The underlying causes of ADHD are not fully understood, but research suggests that genetic and environmental factors interact in its etiology (Thapar et al., 2012). To gain more insight into the underlying neurophysiology of ADHD, electroencephalography (EEG) has been used over the past decades to investigate the neural activity of individuals with and without ADHD.

Most children with ADHD exhibit an aberrant pattern of baseline cortical activity, characterized by elevated slow-wave activity primarily in the theta band and reduced fast-wave activity mainly in the beta band. These patterns often occur concomitantly and are referred to as high theta/beta ratio (TBR) (Barry et al., 2003). During wakeful rest, slow-wave theta activity may indicate fatigue or drowsiness, while activity in the beta band is generally associated with mental activity and concentration (Loo & Arns, 2015). The low beta activity, as is typically found in ADHD, could be indicative of a cognitive processing dysfunction (Hobbs et al., 2007; Markovska-Simoska & Pop-Jordanova, 2017). Originally, TBR was proposed as a diagnostic biomarker to discriminate individuals with ADHD from healthy controls and was eventually approved by the Food and Drug Administration (FDA) as a diagnostic biomarker (Monastra et al., 1999, 2001; Snyder et al., 2008, 2015; Suffin & Emory, 1995). However, a meta-analysis (Arns et al., 2013) showed that TBR could not differentiate between children with and without ADHD and is therefore not a reliable diagnostic biomarker for ADHD. Still, elevated TBR has been suggested as predictor for different treatment outcomes (Arns et al., 2008, 2012; Clarke et al., 2002; Janssen et al., 2016), suggesting prognostic value.

Another EEG metric that has shown promising results as an age- and sex-standardized biomarker is the individual alpha peak frequency (iAF) (Voetterl et al., 2022), the modal frequency of an individual's alpha oscillations. Alpha activity is generated in the thalamocortical feedback circuitry (Silva, 1991; Steriade et al., 1990), implying that iAF may be indicative of bidirectional information flow between the cortex and thalamus. A higher iAF may indicate faster information processing and is associated with enhanced cognitive performance (Clark et al., 2004; Jin et al., 2006; Klimesch, 1996). In contrast, slow iAF is frequently observed in mental disorders, such as Alzheimer's, mild cognitive impairment (Rodriguez et al., 1999), psychosis/schizophrenia (Murphy & Öngür, 2019; Yeum & Kang, 2018) and ADHD (Bazanova et al., 2018). Moreover, slow iAF was traditionally related to non-response to treatment with stimulants in ADHD (Arns et al., 2008, 2018). However, recent studies have shown that iAF has potential to differentially predict outcome to different treatments and that iAF stratification between methylphenidate (MPH) and neurofeedback (NFB) might enhance remission rates (Krepel et al., 2020a; Voetterl et al., 2022).

Several studies comparing the EEG between children with and without ADHD used traditional fixed frequency ranges to estimate EEG power rather than individual frequency ranges (Chabot et al., 1999; Clarke et al., 2002, 2003). However, it has been suggested that the low alpha range overlaps with the theta range (Doppelmayr et al., 1998; Klimesch, 1999), leading to the potential misinterpretation of slow alpha as theta activity. At least two distinct EEG subtypes in ADHD, a subgroup with high TBR and a subgroup with slow alpha peak frequency, might thus contribute to the observed increase in "theta" power, and consequently, a higher TBR (Arns et al., 2008). In a paper by Lansbergen et al. (2011), the increased TBR was replicated in boys with ADHD using fixed frequency ranges, but this effect was lacking when TBR was based on individualized frequency ranges informed by the iAF. This result also suggests that findings of high TBR in children with ADHD might depend on a slow alpha subgroup and that clear dissociation between high TBR and slow iAF is needed as these two subtypes have completely different etiologies (Steriade et al., 1990). In line with this, a review that summarized research investigating the presence of patient clusters based on EEG differences, concluded that EEG profiles of ADHD patients represent the heterogeneity of the disorder (Clarke et al., 2020). A study investigating EEG phenotypes already suggested that different subtypes responded differentially to stimulant medication (Arns et al., 2008). Still, the question remains whether iAF and TBR combined can aid in correctly classifying these subtypes, reflected in behavioural traits.

Here, we calculated the age- and sex-corrected iAF (Brainmarker-I, for details also see: Voetterl et al. (2022)), and applied the same corrections to TBR (referred to as Brainmarker-IV) using a large lifespan database of N > 4000. Next, we investigated behavioral correlates of these biomarker-based EEG subtypes including clinical samples of children and adolescents with ADHD from several large ADHD trials that utilized standardized methodology and equipment (iSPOT-A, N = 278; ICAN, N = 90; and the TDBRAIN + , N = 49), facilitating combination of these samples using a meta-analytical approach. We used a dimensional approach focused on symptoms measured by AHDH rating scales, allowing us to leverage a large combined sample size and potentially achieve greater sensitivity. For comparability to prior research, we examined two-way divisions by segregating individuals based on high versus low Brainmarker-I and high versus low Brainmarker-IV. Additionally, we implemented a three-way grouping approach, comprising a subgroup with non-slow-alpha TBR (NSAT), a subgroup with slow alpha peak frequency (SAF) and a subgroup which shows neither slowed alpha nor excessive theta, termed not applicable (NA) subgroup. Since an earlier study suggested a correlation between slow alpha peak frequency and hyperactivity-impulsivity (Stevens et al., 1968), we expected higher levels of baseline hyperactivity-impulsivity in the SAF compared to the NA subgroup. Based on a study by Arns et al. (Arns et al., 2008), which argued that individuals with high TBR are specifically those with the inattentive component, we expected that the NSAT subgroup will show higher baseline inattention scores compared to the NA subgroup.

Materials and Methods

Datasets

Data that was collected for the *International Study to Predict Optimized Treatment in ADHD* (iSPOT-A), the *International Collaborative Neurofeedback Study* (ICAN) and the *TDBRAIN+-Neurofeedback Study* was used. Data from the different datasets was measured using the same EEG equipment, and EEG preprocessing was conducted in the same way to reduce variance. Full details of the study protocols can be found elsewhere (Arns et al., 2018; Group et al. 2021; Krepel et al., 2020b).

iSPOT-A Study

The iSPOT-A Study was a phase-IV, multi-site, international, open-label effectiveness trial, which consisted of 336 individuals with ADHD and 158 healthy controls (6–18 years) from seven international research sites. ADHD patients were treated with MPH for 6 weeks and were required to have a minimum treatment duration of 4 weeks. The ADHD-Rating Scale-IV (ADHD-RS) was administered by a non-prescribing clinician before and after treatment with MPH to assess ADHD symptoms. EEG assessments were completed before treatment start.

ICAN Study

The ICAN Study was a double-blind randomized controlled trial, which consisted of 140 children (6–12 years) with ADHD who were selected based on a high TBR value equal to or above 4.5. Children were blindly randomized to a multimodal treatment of sleep and nutrition counseling along with either TBR NFB (MM-NFB) or NFB administered based on a prerecorded EEG (control) to facilitate blinding of all. The study compared the effects of MM-NFB to the control treatment for up to 38 treatments in a 14-week period, with 6-, 13-, and 25-month follow-up. Primary outcome was inattentive symptom severity measured by the C-3 Parent and Teacher DSM-V inattention subscales (Conners et al., 2011).

TDBRAIN+-Neurofeedback Study

The TDBRAIN+-Neurofeedback Study was an open-label, naturalistic, multi-site study, which consisted of 114 children, adolescents (< 18 years) and adults (≥ 18 years) with ADHD. Treatment data was collected from five clinics in the Netherlands, Germany and Australia, and analyses were performed post-hoc. Patients were treated with standard NFB protocols in combination with coaching and sleep hygiene advice. The choice for a particular NFB protocol was based on the individual neurophysiology of the patient, assessed by quantitative electroencephalogram (QEEG) before treatment. The Kooij and Buitelaar ADHD rating scale (Kooij & Buitelaar, 1997) was assessed at baseline, every 10th session, and at outtake.

EEG Data Collection and Preprocessing

EEG data collection and preprocessing was consistent with other studies (Dijk et al., 2022; Voetterl et al., 2022). In short, EEGs were recorded from 26 channels in agreement with the 10–20 electrode international system (Quikcap, NuAmps) and following the standardized protocol developed by Brain Resource Ltd. Measurements consisted of a resting-state measurement of 2-min eyes open (EO) and 2-min eyes closed (EC) recordings, with participants being instructed to fixate on a dot at the center of the computer screen during EO. Data were recorded with a ground at AFz, a linked-mastoids reference and a sampling rate of 500 Hz. Prior to digitization, a low-pass filter with an attenuation of 40 dB/decade above 100 Hz was applied. Horizontal eye movements were monitored using electrodes placed 1.5 cm lateral to the outer canthus of each eye, whereas vertical eye movements were recorded with electrodes placed 3 mm above the midpoint of the left eyebrow and 1.5 cm below the midpoint of the left bottom eyelid. Skin impedance was kept below 10 kΩ for all electrodes. In the preprocessing phase, data were demeaned and bandpass-filtered between 0.5 to 100 Hz and the notch-frequency of 50 Hz was removed. Custom-built Python software (Harris et al., 2020; Hunter, 2007; Virtanen et al., 2020) was used to automatically detect and remove artifacts in accordance with de-artifacting procedures described in previous studies (Dijk et al., 2022; Voetterl et al., 2022).

Brainmarker-I and Brainmarker-IV Determination

Calculation of Brainmarker-I followed the same procedure as Voetterl et al. (2022). In summary, iAF was computed by performing the fast Fourier transform (FFT) on preprocessed, artifact-free data, segmented into 5 s segments. In each individual EEG, the highest peak within the frequency range of 7 to 13 Hz was identified as the person's iAF. To determine standardized, age-independent iAF values, non-linear regression models were derived on the TDBRAIN+ data (N = 4126), separately for sex and electrode site (Fz, Pz and Oz). The models were compared to a linear model (null hypothesis) and models with the highest R^2 were identified as best fit. Divergence values, which indicate how each individual's iAF differs from the mean iAF at the individual's age and sex, were calculated based on the resulting

models by subtracting the model-derived average iAF for each individual's age from the individual's actual iAF. To ensure the elimination of the age effect, correlations between resulting divergence values and age were performed. Subsequently, divergence values were ranked from low to high and divided into deciles to improve interpretability. Brainmarker-I data from electrode Fz were used for further analysis based on prior literature (Arns et al., 2018).

Since iAF is based on the EC condition, in the present study TBR is calculated on the EC data rather than following the standard method of TBR calculation in EO, thereby ruling out differences due to recording condition. This is in line with Lansbergen et al. (2011), who calculated TBR from both EO and EC data and found a significant effect in the EC condition, but not in the EO condition.

TBR-based Brainmarker-IV was computed in line with Voetterl et al. (2022) and van Dijk et al. (2020). For TBR calculation, power spectral estimations of theta and beta were computed using the FFT on preprocessed, artifact-free segments. The theta range was defined as frequencies in the range of 4 to 8 Hz; the beta range was defined as the frequencies between 13–21 Hz (Monastra et al., 1999). As recommended by van Dijk et al. (2020), the trial-based averaging method was used for the calculation of TBR, computing the ratio between theta and beta power for each 2-s epoch. Then, the average ratio of theta to beta was computed over the complete session, allowing for correction of fluctuations in theta and beta power over time. The resulting data was strongly skewed and was, thus, log-transformed to the base of 10 to yield a normal distribution of the data. Following the biomarker development as detailed in Voetterl et al. (2022), curve fitting was conducted on the TD-BRAIN + dataset for males and females separately, to identify non-linear regression models that best fit the data for electrode Cz (Fig. 1). Further steps were in line with the Brainmarker-I development (as detailed above). Brainmarker-IV was developed in the same large heterogeneous clinical sample as Brainmarker-I, as the development of Brainmarker-I showed that the heterogenous dataset generalized better to a normative dataset than the other way around (Voetterl et al., 2022). Brainmarker-IV data was calculated on electrode Cz since this is the electrode site most commonly used in TBR research (Arns et al., 2013).

EEG Subgroups

The frequency overlap between alpha (7–13 Hz) and theta (4–8 Hz) results in interdependence of iAF and TBR. In a subject with a slow iAF, high power in the low alpha band might be misinterpreted as theta rhythm and thereby contribute to high theta power (Doppelmayr et al., 1998; Klimesch, 1999). Findings of Doppelmayr et al. (1998) and Klimesch
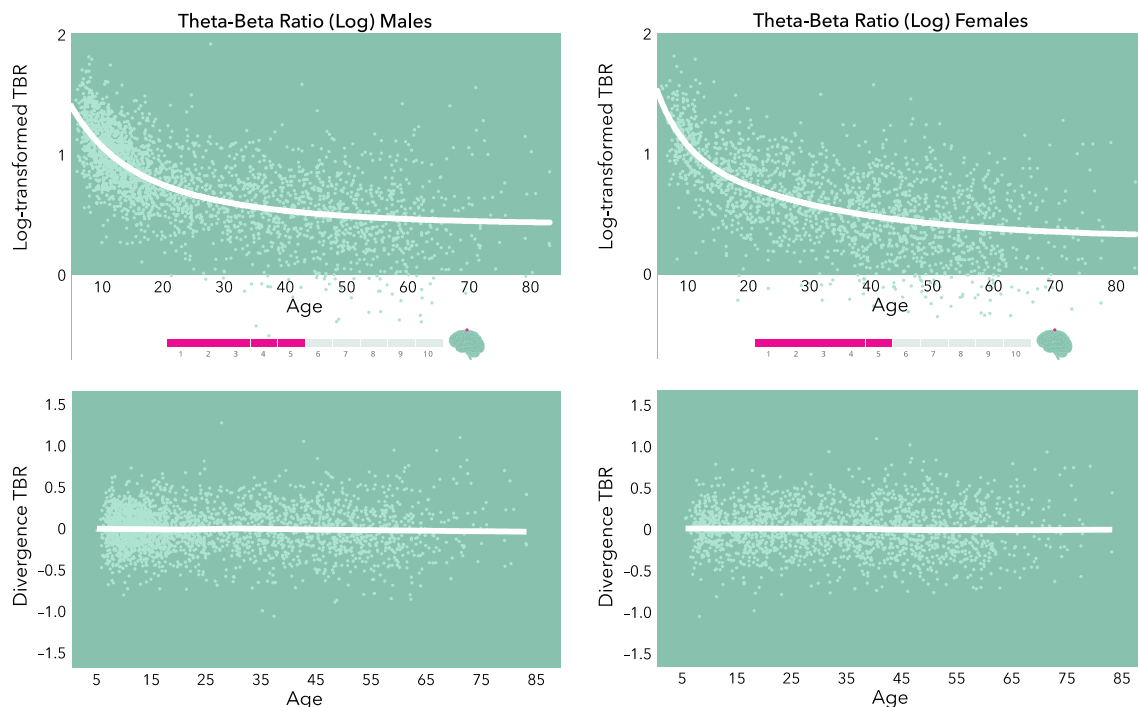
Fig. 1 Flattening the log-transformed TBR-age curve for males (left) and females (right) separately at electrode location Cz. Upper subplots depict log-transformed TBRs and the optimized two-way decay model fit. Lower subplots depict the age-standardized divergence val-

ues and a LOESS fit through the data. Examples of the derived biomarker (Brainmarker-IV) based on the final age- and sex-standardized decile scores are visualized in the middle

(1999) indicate that theta frequency varies as a function of alpha frequency and suggest using iAF as a common reference point for adjusting both alpha and theta frequency ranges.

To differentiate between slow iAF and high TBR, individuals were assigned to one of the EEG subgroups based on decile scores (Fig. 2). In line with Brainmarker-I, a decile cut-off point of 5 was chosen for Brainmarker-IV, with decile score 1 to 5 considered a low and decile score 6–10 a high value. This decision is supported by Voetterl et al.(2022), which showed that the cut-off point of decile 5 provided optimal stratification for Brainmarker-I. In brief the EEG subgroups were:

(1) SAF subgroup: individuals that have a slow alpha peak frequency, but not a high TBR. Individuals with low values on Brainmarker-I (low iAF) and Brainmarker-IV (decile 1 to 5; low-TBR) fall into this subgroup.

(2) NSAT subgroup: individuals were classified to this subtype when they had both relatively high Brainmarker-I (normal-high iAF) and Brainmarker-IV (high-TBR) values (decile 6–10). The high decile score for Brainmarker-I (i.e., a fast alpha peak outside the theta range) indicates that their elevated TBR represents real theta activity and cannot be attributed to slow alpha.

(3) NA subgroup: this subtype shows neither a slowed alpha rhythm nor excessive theta. Individuals with this subtype have decile scores between 6–10 for Brainmarker-I (normal-high iAF), and decile scores between 1–5 for Brainmarker-IV (low-TBR).

The fourth potential combination involving low Brainmarker-I and high Brainmarker-IV (other subgroup; see Fig. 2) was excluded from the subgroup analysis due to inability to dissociate between slow iAF and high TBR (iSPOT-A ADHD: 25%, ICAN Full Sample: 27% and TDBRAIN + -Neurofeedback Study: 22%).

Statistics

Curve fitting was conducted in GraphPad Prism version 9.5.1. for MacOS (GraphPad Software, La Jolla California USA, www.graphpad.com). All other analyses were performed using IBM SPSS Statistics 28.

Extra sum-of-squares F tests were performed to compare the final best model fit to a linear fit, and to test whether one curve adequately fit both the female and the male datasets compared to their respective individual curves.

For the iSPOT-A Study, Chi-square tests were conducted to examine the differences in the number of individuals for Brainmarker-I and Brainmarker-IV separately between ADHD patients and healthy controls. For this, a two-way division of decile scores (low (1–5) vs high (6–10) decile) was introduced for both Brainmarker-I and Brainmarker-IV. Next, Brainmarker-I and Brainmarker-IV were combined into the EEG subgroups specified above, and Chi-square
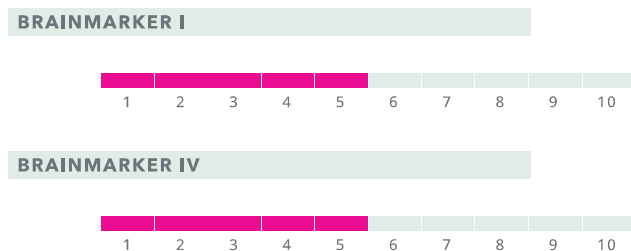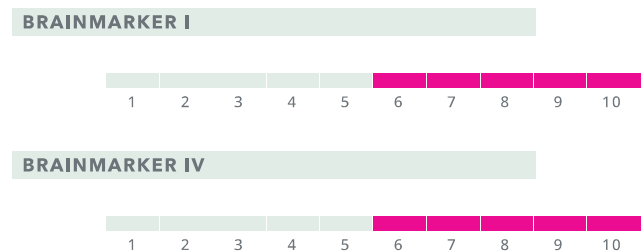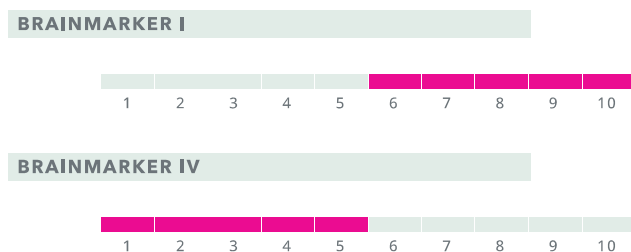
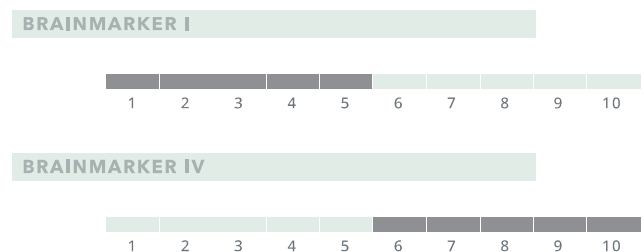Fig. 2 Visualization of the different EEG subgroups based on iAF and TBR-derived Brainmarker-I and Brainmarker-IV. Individuals were assigned to one of the subgroups based on their decile scores for Brainmarker-I and Brainmarker-IV. The other subgroup (greyed out) was excluded from the analyses

tests were conducted to determine the differences in the number of individuals between ADHD patients and healthy controls among these three subgroups.

To examine the differences in the number of individuals for Brainmarker-I and Brainmarker-IV, both separately and combined, between children (aged 6–12 years) and adolescents (aged 13–18 years), the iSPOT-A dataset was merged with the TDBRAIN + -Neurofeedback dataset and Chi-square tests were performed. The ICAN Study was excluded from this analysis, due to the limited age range.

To draw an overall conclusion and minimize type-II error, meta-analyses were conducted including iSPOT-A, ICAN and the TDBRAIN + -Neurofeedback Study. First, ESs were calculated as Cohen's d *(d)* using the pooled SD and the mean baseline difference (hyperactivity-impulsivity and inattention) for the two-way division of both Brainmarker-I and Brainmarker-IV. Second, ESs were calculated for the SAF compared to the NA subgroup and for the NSAT compared to the NA subgroup. A grand mean ES was calculated with a 95% confidence interval (CI) providing the weighted mean ES for all studies. Furthermore, heterogeneity of ESs (Q-statistic) were calculated. Sensitivity analyses were conducted for boys only, due to the limited sample size of girls.

For the ICAN Study, analyses were focused on parent-rated baseline scores, as previous research suggested that teacher-rated scores are less reliable (Arns et al., 2020;

Minder et al., 2018). Furthermore, all children with ADHD from the ICAN Study were included in the analysis of baseline effects. For the TDBRAIN + -Neurofeedback Study, analyses were focused on baseline scores in the children/adolescents (< 18 years) subsample to increase comparability.

Results

Datasets

Table 1 provides a summary of the basic demographic characteristics as well as the two-way and EEG subgroup distribution across all datasets.

Biomarker Discovery Phase

Of a number of different models tested, a two-phase decay model, i.e. a curve modelling fast initial decrease of a variable followed by a slower decrease, best explained the data (males: r2 = 4.7%; females: r2 = 4.2%), and modelled the data significantly better than a linear model (H0; $F(3,4483) = 221.3$, $p < 0.0001$). A comparison of fit showed that female and male data required distinct models and could not be appropriately described by the same curve ($F(5,4478) = 5.547$, $p < 0.0001$).

Table 1 Demographic characteristics and distribution of the different datasets

	iSPOT-A ADHD	iSPOT-A Control	ICAN Full Sample	TDBRAIN + -Neurofeedback Study
Sample size, N	278	136	90	49
Age, years, mean (SD)	12.2 (3.2)	12.2 (3.3)	8.6 (1.2)	11.2 (3.3)
Males, N (%)	196 (71%)	94 (69%)	70 (78%)	40 (82%)
Treatment	MPH	-	MM-NFB and control	MM-NFB
Two-way division, N (%)				
Low Brainmarker-I[a]	126 (45%)	64 (48%)	37 (41%)	17 (35%)
High Brainmarker-I[b]	152	71	53	32
Low Brainmarker-IV[a]	167	82	41	25
High Brainmarker-IV[b]	111 (40%)	54 (40%)	49 (54%)	24 (49%)
EEG Subgroups (%)				
SAF	57 (27%)	32 (31%)	11 (17%)	6 (16%)
NA	110 (53%)	50 (49%)	30 (45%)	19 (50%)
NSAT	42 (20%)	21 (20%)	23 (35%)	13 (34%)

Sample sizes reflect the number of people for whom both Brainmarker-I and Brainmarker-IV decile scores could be computed. All children in the ICAN study had ADHD and 90 had sufficiently clean EEG data to be included in the analysis. For the TDBRAIN + -Neurofeedback Study, the subsample of children/adolescents (< 18 years) was used

iSPOT-A = International Study to Predict Optimized Treatment in ADHD; ICAN = International Collaborative Neurofeedback Study; SD = standard deviation; MPH = methylphenidate; MM-NFB = multimodal treatment of sleep/nutrition counseling along with TBR neurofeedback; SAF = slow alpha peak frequency; NA = not applicable; NSAT = non-slow alpha TBR

[a]Decile score 1 to 5

[b]Decile score 6 to 10

Divergence values, denoting the discrepancy between each individual's TBR and the mean TBR at the individual's respective age and sex, scattered around 0 (Fig. 1), indicating that the TBR age effect is eliminated effectively for Brainmarker-IV.

ADHD Versus Healthy Controls: iSPOT-A

In line with Arns et al. (2013), in iSPOT-A no differences in number of individuals were found between ADHD and controls for the two-way division of Brainmarker-IV (Table 1; $p = 0.965$). In addition, there were no differences in number of individuals for the two-way division of Brainmarker-I ($p = 0.636$). Combining Brainmarker-I and Brainmarker-IV into EEG subgroups also yielded no differences in number of individuals between patients and controls ($p = 0.750$).

Children Versus Adolescents

In the merged iSPOT-A and TDBRAIN + -Neurofeedback Study, no differences were found in the number of children versus adolescents for the two-way division of Brainmarker-I ($p = 0.140$), the two-way division of Brainmarker-IV ($p = 0.359$) and between the EEG subgroups ($p = 0.115$).

Meta-Analysis

Table 2 provides the mean hyperactivity-impulsivity and attention scores for the EEG subgroups across the datasets. For an overview of the meta-analyses performed, see Fig. 3.

- High versus low Brainmarker-I: a random-effects model meta-analysis yielded no significant heterogeneity tests

and ESs for baseline inattention ($Q = 0.334$ $d = 0.040$, $p > 0.685$) and hyperactivity-impulsivity ($Q = 1.421$, $d = 0.105$, $p > 0.289$) scores.

- High versus low Brainmarker-IV: heterogeneity tests and ESs were not significant for baseline inattention ($Q = 2.887$ $d = -0.212$, $p > 0.099$) and hyperactivity-impulsivity ($Q = 1.403$, $d = -0.133$, $p > 0.181$).
- SAF versus NA subgroup: the heterogeneity test ($Q = 1.593$, $p = 0.451$) and ES ($d = 0.014$, $p = 0.921$) were not significant for baseline inattention. Similarly, the heterogeneity test for baseline hyperactivity-impulsivity was non-significant ($Q = 3.920$, $p = 0.141$), as was ES ($d = -0.075$, $p = 0.767$).
- NSAT versus NA subgroup: showed a non-significant ES of 0.218 ($p = 0.164$) and a non-significant heterogeneity test ($Q = 3.031$, $p = 0.220$) for baseline inattention and hyperactivity-impulsivity ($Q = 3.459$, $d = 0.019$, $p > 0.177$).

Figure 3 shows that there are some opposite effects between the datasets that might be due to heterogeneity, such as different disorder severity, different treatments, restricted age range for ICAN and participants recruited based on high TBR in ICAN. For the sensitivity analyses, random-effects model meta-analyses yielded no significant heterogeneity tests and ESs for baseline inattention and hyperactivity-impulsivity scores in boys ($-0.180 < d < 0.260$, $0.835 < Q < 3.412$, $p > 0.145$).

Discussion and Conclusions

Here, we have taken a novel approach utilizing Brainmarker-I and Brainmarker-IV-informed subtypes to investigate differences in behavioral traits including three clinical samples of ADHD patients. In the development of TBR-derived Brainmarker-IV, we obtained age- and sex-normalized values for TBR expressed in decile scores. The added value of this marker is that we could accurately normalize the strong non-linear changes across age, as visualized in Fig. 1, thereby eliminating the need to covary or otherwise statistically control for age- and sex-related differences (where assumptions of linearity would be violated). The small and non-significant ESs extracted from the meta-analyses suggest that there is no consistent association between Brainmarker-I and Brainmarker-IV, separately and combined, for baseline hyperactivity-impulsivity and inattention behavioral traits.

The lack of associations between the EEG subgroups and the baseline ADHD symptoms found in this study further confirms previous findings by Arns et al. (2013), indicating that TBR has no diagnostic value for ADHD. Whereas Arns et al. (2013) primarily focused on the EO
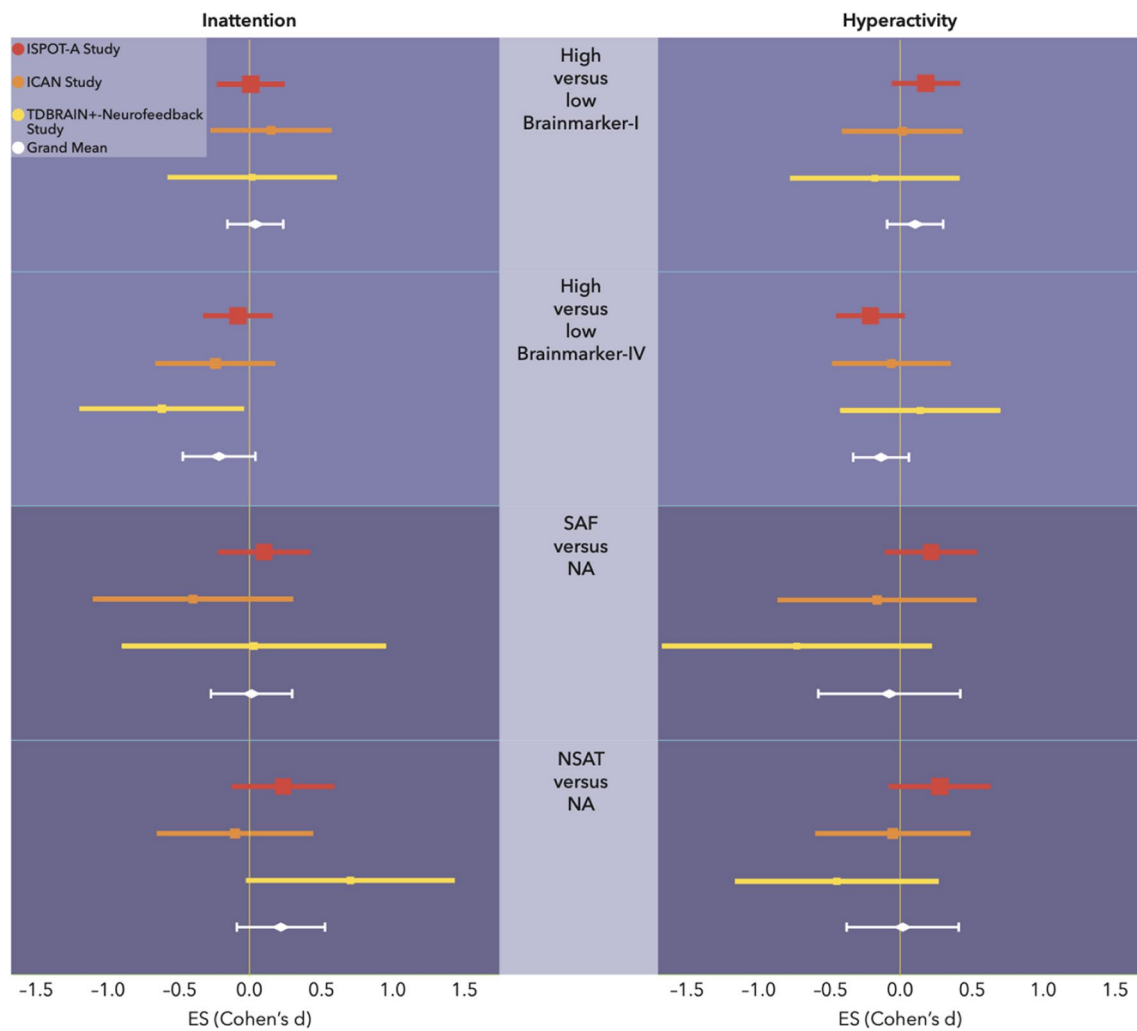
Table 2 Mean hyperactivity-impulsivity and inattention scores of the different datasets

	iSPOT-A Study	ICAN Study	TDBrain + - Neurofeedback Study
Hyperactivity-impulsivity mean (SD)			
SAF	16.21 (7.81)	1.72 (.60)	4.83 (2.64)
NA	14.46 (8.29)	1.81 (.55)	6.32 (1.89)
NSAT	16.67 (7.05)	1.78 (.63)	5.38 (2.43)
Inattention, mean (SD)			
SAF	21.18 (4.61)	1.90 (.32)	6.33 (2.16)
NA	20.72 (4.51)	2.06 (.53)	6.26 (2.33)
NSAT	21.74 (3.93)	2.04 (.45)	7.69 (1.49)

Hyperactivity-impulsivity and inattention scores of the SAF, NA and ACT groups in the three different datasets

iSPOT-A = International Study to Predict Optimized Treatment in ADHD; *ICAN* = International Collaborative Neurofeedback Study; *SD* = standard deviation; *SAF* = slow alpha peak frequency; *NA* = not applicable; *NSAT* = non-slow alpha TBR

Fig. 3 Forest plots of the different meta-analyses with the ES per study and the Grand Mean ES for all studies. The lines represent the 95% CI. Plots with a light purple background illustrate the previous two-way division of Brainmarker-I and Brainmarker-IV. Plots with a dark purple background represent the newly implemented three-way grouping approach. Abbreviations: ES = effect size; iSPOT-A = International Study to Predict Optimized Treatment in ADHD; ICAN = International Collaborative Neurofeedback Study; SAF = slow alpha peak frequency; NA = not applicable; NSAT = non-slow alpha TBR

condition, this study investigated the EC condition as a novel aspect. The concept of TBR as a diagnostic measure for ADHD was first reported by Lubar (1991), and many studies investigating this further indicated that TBR could distinguish ADHD individuals from healthy controls (Clarke et al., 1998; Monastra et al., 1999, 2001; Suffin & Emory, 1995). Findings from Snyder et al. (2015), which suggested that TBR might help improve the accuracy of ADHD diagnosis, even resulted in TBR being FDA-approved as a diagnostic marker. However, the meta-analysis by Arns et al. (2013) suggested that the TBR is not reliable in discriminating between individuals with and without ADHD for diagnostic purposes, and van Dijk et al. (2020) and Kerson et al. (2019) showed that different methods for EEG signal processing can result in

significantly different TBRs, making TBR an unreliable stand-alone tool for ADHD diagnosis.

The use of TBR as a diagnostic measure was further criticized when the FDA approved the Neuropsychiatric EEG-Based ADHD Assessment Aid (NEBA), a device that was developed to aid in the ADHD diagnosis relying on TBR (Arns et al., 2016). Arns et al. (2016) shed light on the methodological weaknesses of the clinical study (Snyder et al., 2015) that resulted in the NEBA FDA approval, making it difficult to determine the value of TBR as a diagnostic tool and the clinical value of the NEBA device. Our findings, yet another attempt to demonstrate the diagnostic value of TBR, using three datasets with a large, combined sample size (N = 417), also failed to confirm the diagnostic value of TBR regarding ADHD. In light of this criticism and our own

findings, it is clear that TBR is inadequate for diagnosing ADHD and is not recommended for clinical use.

Still, Brainmarker-IV may be useful as a prognostic tool. Several studies showed that a subgroup with high TBR responded better to MPH (Arns et al., 2008; Clarke et al., 2002; Suffin & Emory, 1995). Moreover, it has been reported that baseline excess theta was associated with a favorable response to TBR NFB (Arns et al., 2012; Holger et al., 2009; Janssen et al., 2016; Monastra et al., 2002), which suggests that TBR NFB is a preferred treatment option for the subgroup with high TBR and that TBR can be used to stratify individuals into different NFB protocols or medication. Pimenta et al. (2021) proposed that tailoring NFB parameters to individual differences was associated with superior treatment outcomes relative to randomization of individuals to standard, one-size-fits-all NFB protocols. Employing a stratification approach based on EEG is likely to improve clinical response to standard NFB protocols, likely as a result of better signal-to-noise ratio. For instance, it is expected that theta can be better down-trained in individuals that have high theta (and thus likely high TBR); conversely when TBR is low, a sensorimotor rhythm (SMR) protocol meant to target a rhythm in the low beta/high alpha range found in the sensorimotor cortex, which is known for improved sleep, focus and working memory (Pimenta et al., 2021), might yield better results. Essentially, this approach enhances the signal-to-noise ratio for NFB, thereby increasing the trainability of the signal. It would thus be valuable to assign patients to a specific NFB protocol based on Brainmarker-IV. When Brainmarker-IV is below a decile score of 5, indicating low theta activity, it is preferable to treat patients with SMR or slow cortical potential (SCP) NFB protocols. Conversely, for individuals with high Brainmarker-IV, TBR NFB is preferable as treatment. A study by Voetterl et al. (2022) already showed that Brainmarker-I is capable of differentially informing stratification to MPH and MM-NFB treatment.

Although TBR and iAF have been investigated together before, this is the first study assessing Brainmarker-I and Brainmarker-IV-informed subtypes in clinical samples of individuals with ADHD. Arns et al. (2008) and Lansbergen et al. (2011) suggested that previous findings of increased TBR in ADHD may reflect inclusion of individuals with slow iAF in addition to individuals with high theta. The Brainmarker-I and Brainmarker-IV-informed subtypes allow for the dissociation between slow iAF and high TBR. Like Brainmarker-I, Brainmarker-IV only used basic demographic information and resting-state EEG data, so it can easily be implemented in clinical practice, using an algorithm that calculates age- and sex-standardized TBR. Therefore, a free online tool has been made accessible for clinicians to calculate Brainmarker-IV by entering TBR, age and sex at www.brainclinics.com/Brainmarker-IV (Fig. 4).
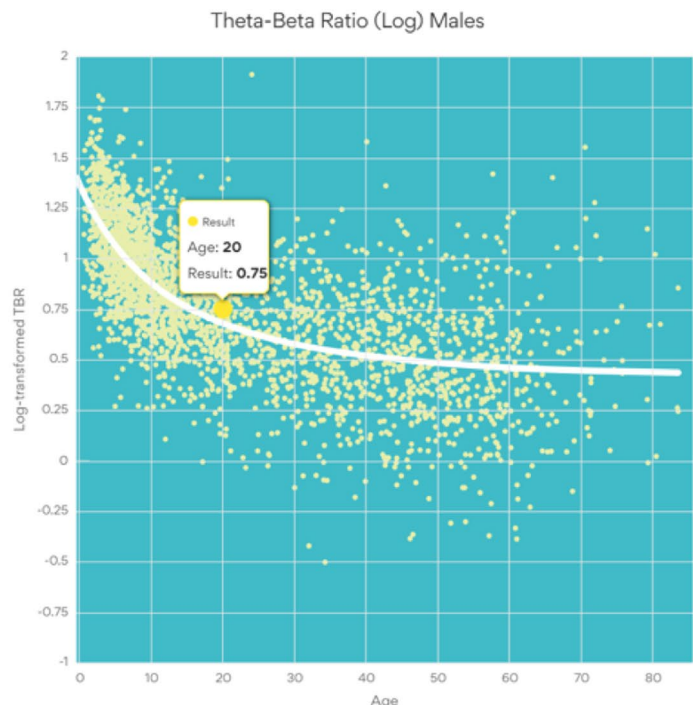

Fig. 4 The online Brainmarker-IV tool, which can be accessed at www.brainclinics.com/Brainmarker-IV, allows clinicians to input their client's sex, age, and log-transformed TBR. After clicking the 'submit' button, a graph will be displayed, comparing their client's log-transformed TBR with that of thousands of others

Across the EEG literature, EEG processing, montages and frequency range definitions vary considerably (Arns et al., 2013), which can hinder replication of findings and thereby implementation of biomarkers in clinical practice. Strong elements of this study were the use of clinical datasets processed according to the same optimized EEG processing method (Dijk et al., 2020) as well as the age- and sex-standardization of Brainmarker-I and Brainmarker-IV. It might be argued that a normative database is needed to validate the findings in ADHD patients, however Table 1 provides evidence that Brainmarker-I and Brainmarker-IV separately and combined do not differ between ADHD and healthy controls for the large clinical iSPOT-A Study. In addition, no differences were found between children and adolescents in the iSPOT-A Study merged with the TD-BRAIN + -Neurofeedback Study, indicating that we extracted the developmental trajectory by age- and sex-normalizing.

Although this study has several important strengths, it should be noted that there are several limitations. We only reported the results from ages 6 to 18 years, since the absence of adult participants for two of the datasets prevented us from investigating brain-behavior relationships for this group. Investigating the brain-behavior relationships in adults with ADHD would be valuable as 40–60% of the children continue to experience symptoms later in life (Faraone et al., 2006). Additionally, because of the restricted sample sizes for girls, we did not perform a sensitivity analysis for this subgroup. However, findings in females might be particularly important because of the male–female gap in ADHD diagnosis and treatment (Bedard & Witman, 2020), and future research should specifically focus on this subgroup.

Several studies already showed that alpha peak frequency-based Brainmarker-I can be used as a transdiagnostic biomarker predicting treatment response to medication and NFB for ADHD (Krepel et al., 2020a; Voetterl et al., 2022). Further research should focus on exploring measures beyond TBR to broaden our understanding of the prognostic capabilities of these EEG parameters in predicting response to treatment. Besides excessive theta, decreased beta activity can increase TBR, however low beta has not been broadly investigated, and might in fact represent another interesting biomarker.

While this study could not confirm consistent associations between Brainmarker-I and Brainmarker-IV-informed subtypes and behavioral traits, alpha peak correction of TBR remains important to differentially assign patients to different NFB protocols. Individual differences in TBR should be acknowledged to establish a clear dissociation between high TBR and slow iAF as these subtypes are characterized by distinct etiologies (Steriade et al., 1990). Therefore, rather than using fixed frequency ranges to estimate EEG power, future studies should focus on alpha peak correction of TBR, which could potentially lead to optimized characterization of subtypes, and subsequent implications for a stratified treatment.

Disclosures

Dr Gordon is founder and Chairman for Brain Resource Ltd. Dr DeBeus has received research funding from the National Institute of Mental Health, has served on the Board of Directors for the International Society for Neurofeedback and Research, and has a clinic in North Carolina where he performs neurofeedback, among other clinical services. Dr. Arnold has received research funding from Supernus Pharmaceuticals, Roche/Genentech Pharmaceuticals, Otsuka Pharmaceuticals, Axial, Yamo, Maplight, and YoungLiving Essential Oils and National Institute of Health (USA, R01 MH 100144), has consulted with Pfizer Pharmaceuticals, Yamo, and CHADD, and been on advisory boards for Otsuka and Roche/Genentech. Dr. Arns holds equity/stock in neurocare and Sama Therapeutics, serves as consultant to Synaeda, Sama Therapeutics and Roche and is named inventor on patents and intellectual property but receives no royalties.

All other authors report no biomedical financial interests or potential conflicts of interest.

Declarations

Competing Interests Dr Gordon is founder and Chairman for Brain Resource Ltd. Dr DeBeus has received research funding from the National Institute of Mental Health, has served on the Board of Directors for the International Society for Neurofeedback and Research, and has a clinic in North Carolina where he performs neurofeedback, among other clinical services. Dr. Arnold has received research funding from Supernus Pharmaceuticals, Roche/Genentech Pharmaceuticals, Otsuka Pharmaceuticals, Axial, Yamo, Maplight, and YoungLiving Essential Oils and National Institute of Health (USA, R01 MH 100144), has consulted with Pfizer Pharmaceuticals, Yamo, and CHADD, and been on advisory boards for Otsuka and Roche/Genentech. Dr. Arns holds equity/stock in neurocare and Sama Therapeutics, serves as consultant to Synaeda, Sama Therapeutics and Roche and is named inventor on patents and intellectual property but receives no royalties.

All other authors report no biomedical financial interests or potential conflicts of interest.

References

Arns, M., Gunkelman, J., Breteler, M., & Spronk, D. (2008). EEG Phenotypes predict treatment outcome to stimulants in children with ADHD. *Journal of Integrative Neuroscience, 07*(03), 421–438. https://doi.org/10.1142/s0219635208001897

Arns, M., Drinkenburg, W., & Kenemans, J. L. (2012). The Effects of QEEG-Informed Neurofeedback in ADHD: An Open-Label Pilot Study. *Applied Psychophysiology and Biofeedback, 37*(3), 171–180. https://doi.org/10.1007/s10484-012-9191-4

Arns, M., Conners, C. K., & Kraemer, H. C. (2013). A Decade of EEG Theta/Beta Ratio Research in ADHD. *Journal of Attention Disorders, 17*(5), 374–383. https://doi.org/10.1177/1087054712460087

Arns, M., Loo, S. K., Sterman, M. B., Heinrich, H., Kuntsi, J., Asherson, P., et al. (2016). Editorial Perspective: How should child psychologists and psychiatrists interpret FDA device approval? Caveat emptor. *Journal of Child Psychology and Psychiatry, 57*(5), 656–658. https://doi.org/10.1111/jcpp.12524

Arns, M., Vollebregt, M. A., Palmer, D., Spooner, C., Gordon, E., Kohn, M., et al. (2018). Electroencephalographic biomarkers as predictors of methylphenidate response in attention-deficit/hyperactivity disorder. *European Neuropsychopharmacology, 28*(8), 881–891. https://doi.org/10.1016/j.euroneuro.2018.06.002

Arns, M., Clark, C. R., Trullinger, M., deBeus, R., Mack, M., & Aniftos, M. (2020). Neurofeedback and Attention-Deficit/Hyperactivity-Disorder (ADHD) in Children: Rating the Evidence and Proposed Guidelines. *Applied Psychophysiology and Biofeedback, 45*(2), 39–48. https://doi.org/10.1007/s10484-020-09455-2

Barry, R. J., Clarke, A. R., & Johnstone, S. J. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and Quantitative Electroencephalography. *Clinical Neurophysiology, 114*(2), 171–183. https://doi.org/10.1016/s1388-2457(02)00362-0

Bazanova, O. M., Auer, T., & Sapina, E. A. (2018). On the Efficiency of Individualized Theta/Beta Ratio Neurofeedback Combined with Forehead EMG Training in ADHD Children. *Frontiers in Human Neuroscience, 12*, 3. https://doi.org/10.3389/fnhum.2018.00003

Bedard, K., & Witman, A. (2020). Family structure and the gender gap in ADHD. *Review of Economics of the Household, 18*(4), 1101–1129. https://doi.org/10.1007/s11150-019-09476-9

Chabot, R. J., Orgill, A. A., Crawford, G., Harris, M. J., & Serfontein, G. (1999). Behavioral and Electrophysiologic Predictors of Treatment Response to Stimulants in Children with Attention Disorders. *Journal of Child Neurology, 14*(6), 343–351. https://doi.org/10.1177/088307389901400601

Clark, C. R., Veltmeyer, M. D., Hamilton, R. J., Simms, E., Paul, R., Hermens, D., & Gordon, E. (2004). Spontaneous alpha peak frequency predicts working memory performance across the age span. *International Journal of Psychophysiology, 53*(1), 1–9. https://doi.org/10.1016/j.ijpsycho.2003.12.011

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (1998). EEG analysis in Attention-Deficit/Hyperactivity Disorder: A comparative study of two subtypes. *Psychiatry Research, 81*(1), 19–29. https://doi.org/10.1016/s0165-1781(98)00072-9

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2002). EEG differences between good and poor responders to methylphenidate and dexamphetamine in children with attention-deficit/hyperactivity disorder. *Clinical Neurophysiology, 113*(2), 194–205. https://doi.org/10.1016/s1388-2457(01)00736-2

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., Clarke, D. C., & Croft, R. J. (2003). Effects of stimulant medications on children with attention-deficit/hyperactivity disorder and excessive beta activity in their EEG. *Clinical Neurophysiology, 114*(9), 1729–1737. https://doi.org/10.1016/s1388-2457(03)00112-3

Clarke, A. R., Barry, R. J., & Johnstone, S. (2020). Resting state EEG power research in Attention-Deficit/Hyperactivity Disorder: A review update. *Clinical Neurophysiology, 131*(7), 1463–1479.

Conners, C., Pitkanen, J., & Rzepa, S. (2011). Conners 3rd Edition (Conners 3; Conners 2008). *Encyclopedia of Clinical Neuropsychology*, 675–678. https://doi.org/10.1007/978-0-387-79948-3_716

da Silva, F. L. (1991). Neural mechanisms underlying brain waves: From neural membranes to networks. *Electroencephalography and Clinical Neurophysiology, 79*(2), 81–93. https://doi.org/10.1016/0013-4694(91)90044-5

Doppelmayr, M., Klimesch, W., Pachinger, T., & Ripper, B. (1998). Individual differences in brain dynamics: Important implications for the calculation of event-related band power. *Biological Cybernetics, 79*(1), 49–57. https://doi.org/10.1007/s004220050457

Faraone, S. V., Biederman, J., & Mick, E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: A meta-analysis of follow-up studies. *Psychological Medicine, 36*(2), 159–165. https://doi.org/10.1017/s003329170500471x

Faraone, S. V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J. K., Ramos-Quiroga, J. A., et al. (2015). Attention-deficit/hyperactivity disorder. *Nature Reviews Disease Primers, 1*(1), 15020. https://doi.org/10.1038/nrdp.2015.20

Group, T. N. C., Arnold, L. E., Arns, M., Barterian, J., Bergman, R., Black, S., et al. (2021). Double-Blind Placebo-Controlled Randomized Clinical Trial of Neurofeedback for Attention-Deficit/Hyperactivity Disorder With 13-Month Follow-up. *Journal of the American Academy of Child & Adolescent Psychiatry, 60*(7), 841–855. https://doi.org/10.1016/j.jaac.2020.07.906

Harris, C. R., Millman, K. J., Van Der Walt, S. J., et al. (2020). Array programming with NumPy. *Nature, 585*, 357–362.

Hobbs, M. J., Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2007). EEG abnormalities in adolescent males with AD/HD. *Clinical Neurophysiology, 118*(2), 363–371. https://doi.org/10.1016/j.clinph.2006.10.013

Holger, G., Birgit, H., Björn, A., Dieter, S., Oliver, K., Petra, S., et al. (2009). Distinct EEG effects related to neurofeedback training in children with ADHD: A randomized controlled trial. *International Journal of Psychophysiology, 74*(2), 149–157. https://doi.org/10.1016/j.ijpsycho.2009.08.005

Hunter, J. D. (2007). Matplotlib: A 2D graphics environment. *Computing in Science & Engineering, 9*(3), 90–95. https://doi.org/10.1109/mcse.2007.55

Janssen, T. W. P., Bink, M., Geladé, K., Mourik, R., Maras, A., & Oosterlaan, J. (2016). A randomized controlled trial into the effects of neurofeedback, methylphenidate, and physical activity on EEG power spectra in children with ADHD. *Journal of Child Psychology and Psychiatry, 57*(5), 633–644. https://doi.org/10.1111/jcpp.12517

Jin, Y., Potkin, S. G., Kemp, A. S., Huerta, S. T., Alva, G., Thai, T. M., et al. (2006). Therapeutic Effects of Individualized Alpha Frequency Transcranial Magnetic Stimulation (αTMS) on the Negative Symptoms of Schizophrenia. *Schizophrenia Bulletin, 32*(3), 556–561. https://doi.org/10.1093/schbul/sbj020

Kerson, C., deBeus, R., Lightstone, H., Arnold, L. E., Barterian, J., Pan, X., & Monastra, V. J. (2019). EEG Theta/Beta Ratio Calculations Differ Between Various EEG Neurofeedback and Assessment Software Packages: Clinical Interpretation. *Clinical EEG and Neuroscience, 51*(2), 114–120. https://doi.org/10.1177/1550059419888320

Klimesch, W. (1996). Memory processes, brain oscillations and EEG synchronization. *International Journal of Psychophysiology, 24*(1–2), 61–100. https://doi.org/10.1016/s0167-8760(96)00057-8

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. *Brain*

Research Reviews, 29(2–3), 169–195. https://doi.org/10.1016/s0165-0173(98)00056-3

Kooij, J.J.S. & Buitelaar, J.K. (1997). J.J.S. Kooij, ADHD bij volwassenen. *Diagnostiek en behandeling, 3e druk*. Pearson Assessment and Information BV, 2010.

Krepel, N., Egtberts, T., Sack, A. T., Heinrich, H., Ryan, M., & Arns, M. (2020). A multicenter effectiveness trial of QEEG-informed neurofeedback in ADHD: Replication and treatment prediction. *NeuroImage: Clinical, 28*, 102399. https://doi.org/10.1016/j.nicl.2020.102399

Krepel, N., Egtberts, T., Sack, A. T., Heinrich, H., Ryan, M., & Arns, M. (2020). A multicenter effectiveness trial of QEEG-informed neurofeedback in ADHD: Replication and treatment prediction. *NeuroImage: Clinical, 28*, 102399. https://doi.org/10.1016/j.nicl.2020.102399

Lansbergen, M. M., Arns, M., van Dongen-Boomsma, M., Spronk, D., & Buitelaar, J. K. (2011). The increase in theta/beta ratio on resting-state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 35*(1), 47–52. https://doi.org/10.1016/j.pnpbp.2010.08.004

Loo, S. K., & Arns, M. (2015). Should the EEG–Based Theta to Beta Ratio Be Used to Diagnose ADHD? *The ADHD Report, 23*(8), 8–13. https://doi.org/10.1521/adhd.2015.23.8.8

Lubar, J. F. (1991). Discourse on the development of EEG diagnostics and biofeedback for attention-deficit/hyperactivity disorders. *Biofeedback and Self-Regulation, 16*(3), 201–225.

Markovska-Simoska, S., & Pop-Jordanova, N. (2017). Quantitative EEG in Children and Adults with Attention Deficit Hyperactivity Disorder. *Clinical EEG and Neuroscience*. https://doi.org/10.1177/1550059416643824

Minder, F., Zuberer, A., Brandeis, D., & Drechsler, R. (2018). Informant-related effects of neurofeedback and cognitive training in children with ADHD including a waiting control phase: A randomized-controlled trial. *European Child & Adolescent Psychiatry, 27*(8), 1055–1066. https://doi.org/10.1007/s00787-018-1116-1

Monastra, V. J., Lubar, J. F., Linden, M., VanDeusen, P., Green, G., Wing, W., et al. (1999). Assessing attention deficit hyperactivity disorder via quantitative electroencephalography: An initial validation study. *Neuropsychology, 13*(3), 424–433. https://doi.org/10.1037/0894-4105.13.3.424

Monastra, V. J., Lubar, J. F., & Linden, M. (2001). The development of a quantitative electroencephalographic scanning process for attention deficit-hyperactivity disorder: Reliability and validity studies. *Neuropsychology, 15*(1), 136–144. https://doi.org/10.1037//0894-4105.15.1.136

Monastra, V. J., Monastra, D. M., & George, S. (2002). The Effects of Stimulant Therapy, EEG Biofeedback, and Parenting Style on the Primary Symptoms of Attention-Deficit/Hyperactivity Disorder. *Applied Psychophysiology and Biofeedback, 27*(4), 231–249. https://doi.org/10.1023/a:1021018700609

Murphy, M., & Öngür, D. (2019). Decreased peak alpha frequency and impaired visual evoked potentials in first episode psychosis. *NeuroImage: Clinical, 22*, 101693. https://doi.org/10.1016/j.nicl.2019.101693

Pimenta, M. G., Brown, T., Arns, M., & Enriquez-Geppert, S. (2021). Treatment Efficacy and Clinical Effectiveness of EEG Neurofeedback as a Personalized and Multimodal Treatment in ADHD: A Critical Review. *Neuropsychiatric Disease and Treatment, 17*, 637–648. https://doi.org/10.2147/ndt.s251547

Rodriguez, G., Copello, F., Vitali, P., Perego, G., & Nobili, F. (1999). EEG spectral profile to stage Alzheimer's disease. *Clinical Neurophysiology, 110*(10), 1831–1837. https://doi.org/10.1016/s1388-2457(99)00123-6

Snyder, S. M., Quintana, H., Sexson, S. B., Knott, P., Haque, A. F. M., & Reynolds, D. A. (2008). Blinded, multi-center validation of EEG and rating scales in identifying ADHD within a clinical sample. *Psychiatry Research, 159*(3), 346–358. https://doi.org/10.1016/j.psychres.2007.05.006

Snyder, S. M., Rugino, T. A., Hornig, M., & Stein, M. A. (2015). Integration of an EEG biomarker with a clinician's ADHD evaluation. *Brain and Behavior, 5*(4), e00330. https://doi.org/10.1002/brb3.330

Steriade, M., Gloor, P., Llinás, R. R., de Silva, F. H. L., & Mesulam, M. M. (1990). Report of IFCN Committee on Basic Mechanisms. Basic mechanisms of cerebral rhythmic activities. *Electroencephalography and Clinical Neurophysiology, 76*(6), 481–508.

Stevens, J. R., Sachdev, K., & Milstein, V. (1968). Behavior Disorders of Childhood and the Electroencephalogram. *Archives of Neurology, 18*(2), 160–177. https://doi.org/10.1001/archneur.1968.00470320062007

Suffin, S. C., & Emory, W. H. (1995). Neurometric Subgroups in Attentional and Affective Disorders and Their Association with Pharmacotherapeutic Outcome. *Clinical Electroencephalography, 26*(2), 76–83. https://doi.org/10.1177/155005949502600204

Thapar, A., Cooper, M., Jefferies, R., & Stergiakouli, E. (2012). What causes attention deficit hyperactivity disorder? *Archives of Disease in Childhood, 97*(3), 260. https://doi.org/10.1136/archdischild-2011-300482

van Dijk, H., deBeus, R., Kerson, C., Roley-Roberts, M. E., Monastra, V. J., Arnold, L. E., et al. (2020). Different Spectral Analysis Methods for the Theta/Beta Ratio Calculate Different Ratios But Do Not Distinguish ADHD from Controls. *Applied Psychophysiology and Biofeedback, 45*(3), 165–173. https://doi.org/10.1007/s10484-020-09471-2

van Dijk, H., van Wingen, G., Denys, D., Olbrich, S., van Ruth, R., & Arns, M. (2022). The two decades brainclinics research archive for insights in neurophysiology (TDBRAIN) database. *Scientific Data, 9*(1), 333.

Virtanen, P., Gommers, R., Oliphant, T. E., Haberland, M., Reddy, T., Cournapeau, D., et al. (2020). SciPy 1.0: Fundamental Algorithms for Scientific Computing in Python. *Nature Methods, 17*, 261–272.

Voetterl, H., van Wingen, G., Michelini, G., Griffiths, K. R., Gordon, E., DeBeus, R., et al. (2022). Brainmarker-I differentially predicts remission to various attention-deficit/hyperactivity disorder treatments: a blinded discovery, transfer and validation study. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging., 8*(1), 52–60. https://doi.org/10.1016/j.bpsc.2022.02.007

Yeum, T.-S., & Kang, U. G. (2018). Reduction in Alpha Peak Frequency and Coherence on Quantitative Electroencephalography in Patients with Schizophrenia. *Journal of Korean Medical Science, 33*(26). https://doi.org/10.3346/jkms.2018.33.e179