

Archival Report

Brainmarker-I Differentially Predicts Remission to Various Attention-Deficit/Hyperactivity Disorder Treatments: A Discovery, Transfer, and Blinded Validation Study

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ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder is characterized by neurobiological heterogeneity, possibly explaining why not all patients benefit from a given treatment. As a means to select the right treatment (stratification), biomarkers may aid in personalizing treatment prescription, thereby increasing remission rates.

METHODS: The biomarker in this study was developed in a heterogeneous clinical sample ($N = 4249$) and first applied to two large transfer datasets, a priori stratifying young males (<18 years) with a higher individual alpha peak frequency (iAPF) to methylphenidate ($N = 336$) and those with a lower iAPF to multimodal neurofeedback complemented with sleep coaching ($N = 136$). Blinded, out-of-sample validations were conducted in two independent samples. In addition, the association between iAPF and response to guanfacine and atomoxetine was explored.

RESULTS: Retrospective stratification in the transfer datasets resulted in a predicted gain in normalized remission of 17% to 30%. Blinded out-of-sample validations for methylphenidate ($n = 41$) and multimodal neurofeedback ($n = 71$) corroborated these findings, yielding a predicted gain in stratified normalized remission of 36% and 29%, respectively.

CONCLUSIONS: This study introduces a clinically interpretable and actionable biomarker based on the iAPF assessed during resting-state electroencephalography. Our findings suggest that acknowledging neurobiological heterogeneity can inform stratification of patients to their individual best treatment and enhance remission rates.

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Attention-deficit/hyperactivity disorder (ADHD) is arguably the most common neurodevelopmental disorder and is characterized by highly heterogeneous impairment profiles and etiology (1,2). Because of this heterogeneity and differential modes of treatment action (e.g., psychostimulant vs. non-stimulant medication vs. nonpharmacological treatments), even the most common interventions, although generally effective in the treatment of ADHD, only work in part of the ADHD population, as shown by a large meta-analysis by Cortese *et al.* (3) on the efficacy of various commonly prescribed ADHD medications (3,4), with real-life remission rates of 31% to 57% (reflecting the effectiveness of treatments in the clinical setting rather than treatment efficacy as assessed in randomized clinical trials) (5).

Therefore, individualized treatment recommendation based on biomarkers that predict clinical response to specific therapeutic interventions is desirable, one example being specific activity patterns measured by electroencephalography (EEG) (6).

Ideally, treatment should be individually adapted to a given patient as envisioned in precision psychiatry. However, the multidimensionality of psychiatric disorders, in contrast to such clearly delineated problems as tumor tissue, complicates tailoring treatment to a single person (7). An implementable intermediate step is treatment stratification, which aims to select a treatment from a range of effective treatments for a given disorder, informed by a biomarker [for review, see (8)].

As an example, EEG biomarker studies for treatment prediction in major depressive disorder (MDD) have shown that specific EEG patterns or abnormalities are differentially associated with drug-specific or drug class-specific antidepressant treatment effects, as well as repetitive transcranial magnetic stimulation outcome (9–13). Many such studies yielded sex-specific EEG predictors of MDD treatment response (10,14,15) and methylphenidate (MPH) response in ADHD (16). Treatment stratification has already been implemented in the treatment of different cancer types (17–19) and recently also MDD, where stratification to different antidepressant medications was

informed by pretreatment EEG biomarkers, resulting in improved remission rates relative to treatment as usual (20).

EEG is one of the most cost-effective and easily deployable methods to measure brain activity and is, thus, suitable for broad usage in clinical practice. Although several EEG patterns have been proposed for predicting treatment success in different mental disorders (7,21), in ADHD most biomarker studies have focused on diagnostic biomarkers, while studies investigating prognostic ADHD biomarkers are still scarce (22,23).

The individual alpha peak frequency (iAPF) is the modal frequency at which an individual's alpha activity oscillates and is known to index brain maturation (24,25). This EEG pattern has been extensively investigated and shows promise in predicting outcome to various treatments across different disorders (11,26). A higher mean frequency or a faster alpha peak is often associated with better cognitive performance, possibly reflective of faster information processing in thalamocortical pathways (22,23,27,28). Conversely, many mental disorders, such as Alzheimer's disease, mild cognitive impairment (29), psychosis/schizophrenia (30,31), and ADHD (32), are characterized by a slowed iAPF, potentially reflective of reduced or slowed information flow between the thalamus and the cortex (22). Furthermore, slow iAPF has been associated with worse clinical outcome to different treatments such as psychostimulants in ADHD (16,33) and antidepressant medication in MDD (34), whereas it was found to be related to better clinical outcome to multimodal (MM) EEG neurofeedback (NFB) treatment in ADHD (35) and sertraline in MDD (9).

This study therefore investigated whether iAPF is able to differentially predict clinical outcome for two disparate ADHD treatments, MPH and a multimodal behavioral intervention including NFB, sleep hygiene, and coaching (MM-NFB).

Given the opposite implications reported for these treatments, we hypothesized that iAPF can help subdivide a heterogeneous population into more homogeneous subpopulations with relevance to clinical outcome and thus serve as a biomarker informing treatment stratification between medications (e.g., MPH) and MM-NFB. While there has been controversy regarding the specificity of EEG-NFB in the treatment of ADHD (36,37), this manuscript focuses on EEG-NFB as part of a broader multimodal treatment including sleep hygiene and coaching, for which remission rates of 32% to 57% have been reported (5) and lasting clinical benefit has been demonstrated (36,38), although this is likely not solely attributable to EEG-NFB alone. Given the stratification approach investigated here, being able to prescribe MM-NFB to people for whom psychostimulants are unlikely to work would nonetheless be advantageous.

Across the EEG literature, EEG (pre-)processing, EEG montages, and frequency band definitions vary considerably, which diminishes comparability and reproducibility that might at worst result in different findings (39) (see the Supplement for more details). We therefore first developed Brainmarker-I in a biomarker discovery phase, where the most precise iAPF algorithm, i.e., the algorithm yielding the most biologically plausible iAPF, was determined. This algorithm was validated against a ground truth scenario, in this case relying on the well-established finding that iAPF indices brain

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maturation (24,25). The resulting biomarker was subsequently used to predict treatment outcome in the previously mentioned MPH and MM-NFB datasets based on previous findings (16,35). These predictions were then corroborated in blinded, out-of-sample validations in an MPH and an MM-NFB dataset, which—to our knowledge—had not been attempted in EEG biomarker studies before. Furthermore, we tested the biomarker's capacity to predict remission to two other pharmacological treatments, guanfacine (GUAN) and atomoxetine (ATX). To maximize clinical utility of this stratification biomarker, we focused on remission as the primary outcome, representing the most clinically relevant measure (40,41).

METHODS AND MATERIALS

Datasets—Biomarker Discovery Phase

Because the goal was to explain variance in clinical data, the large TD-BRAIN+ (Two Decades—Brainclinics Research Archive for Insights in Neuroscience) dataset (see Table 1 for overview), composed of patients with various psychiatric disorders, was used to determine the optimal parameters of iAPF calculation. The resulting optimized iAPF EEG processing pipeline was used to develop an age-standardized biomarker for males and females separately in accordance with previous reports of sex differences (10,42), which was subsequently divided into deciles for enhanced interpretability.

The open access TD-BRAIN dataset ($n = 1274$), a subset of the data used for the discovery phase, is freely available at <http://www.brainclinics.com/resources> (43), with all data recorded at Research Institute Brainclinics (Brainclinics Foundation, Nijmegen, The Netherlands). In the TD-BRAIN+ dataset, this was complemented with data from additional clinics (EPI-PIT clinics [Eindhoven and Tilburg; author JJ], EEG Resource [Nijmegen; author RB], Neuroscan [Dordrecht; author PdJ], and neuroCare clinics [Hengelo, Groningen, Munich, and Sydney; author RvR]), for which the laboratory setup, including EEG caps, amplifiers, instructions, and other details, was identical to the iSPOT-A (International Study to Predict Optimised Treatment in Attention Deficit/Hyperactivity Disorder) trial (16).

Datasets—Biomarker Transfer Phase

The biomarker determined in the discovery phase was used to find the best way to stratify patients to MPH (iSPOT-A: $n = 257$) (16) and MM-NFB ($n = 50$) (35) according to the previously demonstrated directionality of effects (16,35). NFB protocols were composed of standard protocols such as sensorimotor rhythm, theta/beta ratio, and slow cortical potential NFB.

This step focused on boys only, owing to a limited sample size of girls and no robust a priori knowledge regarding directionality of effect [e.g., Arns *et al.* (16) only found effects for boys].

Datasets—Biomarker Validation Phase

For independent out-of-sample replication analysis, we conducted a blinded prediction of remission in the MPH/GUAN dataset (44) (Table 1) and the ICAN (International Collaborative

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Table 1. Baseline Demographics

	Datasets					
	TD-BRAIN+	iSPOT-A	NFB	MPH/GUAN	ICAN	ACTION
Full Datasets						
Sample size, <i>N</i>	4249	336	136	141	142	56
Age range, years	6–88	6–18	6–68	7–15	7–11	6–16
Included in Analysis						
Sample size, <i>n</i>	4126	184	41	76	71	39
Males, <i>n</i> (%)	2528 (60%)	184 (100%)	41 (100%)	76 (100%)	71 (100%)	39 (100%)
Age, years, mean (SD)	29.3 (18.3)	11.8 (3.1)	11.1 (3.1)	10 (2.0)	8.6 (1.2)	11.5 (2.5)
Treatment	NA	MPH	NFB multimodal treatment ^a	MPH/GUAN	NFB/multimodal treatment	ATX

Full datasets sample size reflects the number of people who were enrolled. Sample size included in analysis reflects the number of people with complete baseline data who finished treatment (except for TD-BRAIN+, where only baseline data but no clinical data were used). In the TD-BRAIN+ dataset the full age range was used for age standardization, while an age range of 6–18 years was used for the correlation analyses. Sample size of this age range was 1715 (1253 male); mean age was 11.8 (SD = 3.1) years.

ACTION, Attention Deficit Hyperactivity Disorder Controlled Trial Investigation Of a Non-stimulant; ATX, atomoxetine; GUAN, guanfacine; ICAN, International Collaborative ADHD Neurofeedback; iSPOT-A, International Study to Predict Optimised Treatment in Attention Deficit/Hyperactivity Disorder; MPH, methylphenidate; NA, not applicable; NFB, neurofeedback; TD-BRAIN, Two Decades–Brainclinics Research Archive for Insights in Neuroscience.

^aNFB treatment augmented with advice on sleep hygiene and coaching.

ADHD Neurofeedback) study (36), with accuracy verified by a third person not involved in the EEG analysis.

In the former trial, subjects were blindly randomized to either MPH (*n* = 58) or GUAN (*n* = 55) treatment. In the ICAN study (*n* = 96), subjects were blindly randomized to a multimodal treatment of sleep and nutrition counseling and either theta/beta ratio NFB (MM-NFB) or a control treatment (NFB administered based on a prerecorded EEG to facilitate blinding of all).

Datasets—Biomarker Exploration Phase

In the exploratory phase to test performance of the biomarker to another commonly prescribed form of pharmacotherapy for ADHD (i.e., noradrenergic medications), the predictive value of the biomarker to ATX (*n* = 47) and GUAN (*n* = 55) was examined in the ACTION (Attention Deficit Hyperactivity Disorder Controlled Trial Investigation Of a Non-stimulant) dataset (45) and in the MPH/GUAN dataset that had already been used in the validation phase for MPH replication (44). All participants (or their parents or caretakers) gave written informed consent prior to testing.

EEG Data Collection and Preprocessing

All EEGs were recorded in a standardized manner as developed by Brain Resource Ltd [for more details, see (10)] apart from the independent MPH/GUAN validation dataset (44).

In short, EEGs were recorded from 26 channels according to the 10–20 electrode international system (FP1, FP2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz, O2; Quikcap, NuAmps). Measurements consisted of 2-minute eyes-open and 2-minute eyes-closed recordings. During eyes-open recordings, participants were asked to fixate on a dot in the middle of the computer screen.

Data were recorded with the ground at AFz, and a sampling rate of 500 Hz and a low-pass filter with an attenuation of 40 dB/decade above 100 Hz was used prior to digitization. Horizontal eye movements were recorded with electrodes placed

1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid. Skin resistance was <10 kΩ for all electrodes.

Automatic artifact detection and removal were performed using a custom-built Python package (46–49) and were in accordance with de-artifacting as described in (10) and van Dijk *et al.* (43), with full code available online (<http://www.brainclinics.com/resources>).

For the MPH/GUAN validation dataset (44), eyes-closed EEGs were recorded from 40 channels (AF3, AF4, AFz, C3, C4, CPz, Cz, F10, F3, F4, F7, F8, F9, FCz, FP1, FP2, FPz, FT10, FT7, FT8, FT9, Fz, Iz, O1, O2, Oz, P10, P3, P4, P7, P8, P9, POz, Pz, T7, T8, TP10, TP7, TP8, TP9) for 5 minutes with a sampling rate of 256 Hz and referenced to linked ears [for further details, see (44,50)]. Recordings were subsequently matched to the other data, i.e., the 40 channels were reduced to 22 channels matching the TD-BRAIN+ setup (with FC3, FC4, CP3, and CP4 missing). Artifact rejection for the independent validation dataset was performed in BrainVision Analyzer version 2.2.0 (Brain Products GmbH) by semi-automatic removal of epochs with signal amplitudes >150 mV.

iAPF Determination

iAPF was determined by computing the fast Fourier transform of the preprocessed, artifact-free data. Subsequently, each individual's iAPF was determined by identifying the highest peak within the frequency range of 7 to 13 Hz.

Biomarker Discovery Phase

Biomarker discovery a priori focused on males and females separately owing to previously reported qualitative sex differences (10,42). In short, data with low-voltage alpha were identified and excluded from further analysis (for more details, see the Supplement). To optimize EEG processing, iAPFs determined with different processing parameters (e.g.,

segment length, reference montage) were correlated with age (<18 years). The parameter combination with the highest correlation and retention of subjects was used for further prospective testing. Subsequently, the data were age- and sex-standardized and resulting values divided into 10 equal-sized bins (deciles) to improve interpretability. For more information, see the [Supplement](#).

Biomarker Transfer Phase

We first aimed to align previous findings, which differed with regard to primary outcome measure (response vs. remission) and subsample (boys aged 6–18 vs. boys aged 12–18) (16,35). To increase comparability and clinical impact, we focused our analyses on males in the age range of 6 to 18 years and on remission, defined as an item mean of ≤ 1.00 on the ADHD Rating Scale-IV, as primary clinical outcome (40).

Biomarker Validation Phase

Finally, the biomarker was prospectively validated on the same subsample (boys aged 6–18 years) for MPH and MM-NFB treatment by a blinded prediction of remission status, solely based on age, sex, and baseline EEG in two independent datasets.

Biomarker Exploration Phase

Analyses for the exploration phase were similar to those in the transfer phase but without a guided hypothesis.

Statistics

First, Spearman correlations between the various iAPFs resulting from different EEG processing combinations and age in subjects below 18 years ($n = 1671$) were calculated. To determine standardized iAPF values independent of age, we derived nonlinear regression models based on the full TD-BRAIN+ dataset that most closely fit the given data for each electrode (Fz, Pz, Oz). Different mathematical models following the developmental trajectory of the iAPF [such as a Log Gaussian model, in line with (51)] were contrasted against a linear model (null hypothesis) and individually adjusted for females and males and for each site (channel). Divergence values representing where the individual's iAPF lies in relation to other people's iAPFs were calculated from the resulting models by subtracting the model-derived average iAPF for each subject's age from the person's actual iAPF. Correlations between divergence values and age were conducted to confirm that the age effect had been eliminated from the data. The resulting divergence values were ranked from low to high and divided into 10 equal-sized bins (deciles) to improve interpretability by clinicians.

The final stratification outcome for the transfer phase and stratification decision for the exploration phase were based on the positive predictive values (PPVs) at different decile cutoff points, indicating remission rate within the subsample of patients that the biomarker would have stratified to the respective treatment. Because PPVs are dependent on prevalence (here, observed remission) and remission rates differed between treatment datasets, we normalized PPVs for better comparability across datasets by dividing the PPV by the observed remission and subtracting 1.

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Curve fitting models were developed in GraphPad Prism version 8.4.0 for MacOS. Spearman correlations were conducted with Python modules "scipy" and "numpy." All other statistical analyses were performed in IBM SPSS Statistics for Macintosh, version 27.0.

RESULTS

Datasets

[Table 1](#) provides a summary of the basic demographic information of all datasets.

Biomarker Discovery Phase

[Figure 1](#) visualizes the individual steps of the biomarker development. In short, a total of 108 algorithm permutations were tested ([Figure 1A](#)). The resulting best permutation (linked-mastoid reference/eyes closed/5-second segments) was selected for further prospective testing of the biomarker ([Figure 1B](#)). A linear regression of the resulting age-standardized divergence values and age yielded a model with a slope of 0 ($\beta = 0.000$), demonstrating that the curve-fitting procedure successfully removed the age effect seen previously (e.g., Fz: $R^2 = 0.000$). For an overview of all correlation and secondary analyses, see the [Supplement](#).

Biomarker Transfer Phase: Stratification With Biomarker Results in Higher Likelihood of Remission

To account for possible confounding effects of symptom severity, we first conducted a partial correlation between baseline ADHD Rating Scale scores and iAPF, controlling for age, which was not significant ($r = -0.064$, $n = 253$, $p = .311$).

[Figure 2](#) summarizes the outcome of the transfer phase. The direction of stratification was informed by the previously reported directionality of effects [higher iAPF indicating stratification to MPH (16), lower iAPF indicating stratification to MM-NFB (35)] and was based on the Fz electrode as primary site based on prior literature (16) (see the [Supplement](#) for a post hoc analysis examining stratification based on Fz and Oz). A decile cutoff point of 1 to 5 for MM-NFB and 6 to 10 for MPH was chosen a priori, stratifying approximately half of the patients to each treatment. To test this a priori decision, PPVs, indicating remission rates in the patient subsample that would have been stratified according to our biomarker, were determined for different decile cutoff points. The chosen cutoff point of decile 5 indeed led to the highest combined PPV ([Table S1](#)). Therefore, the presented biomarker (Brainmarker-I) was based on this cutoff point, recommending MM-NFB treatment to boys with a relatively lower iAPF in the decile range 1 to 5 and MPH to boys with a relatively higher iAPF in deciles 6 to 10 ([Table S2](#) for additional accuracy measures).

The normalized PPV indicated a predicted increase in remission rate of 17% compared with the observed remission rate if patients had received MPH (PPV = 41%) and 30% if patients had received MM-NFB (PPV = 62%) as treatment recommendation based on Brainmarker-I.

In a post hoc analysis predicting remission with Brainmarker-I calculated at the occipital site (Oz), no improvement could be seen for MPH (normalized

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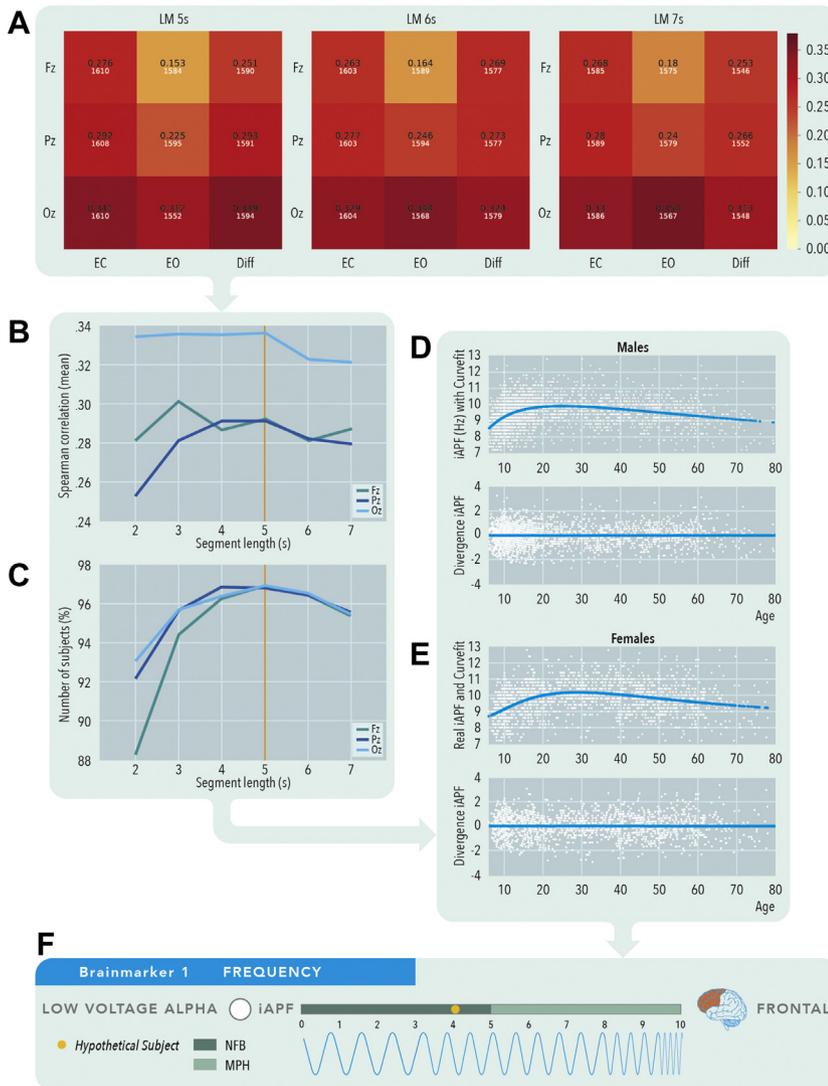


Figure 1. Biomarker discovery phase. **(A)** Excerpt from heatmaps of the total of 108 algorithm permutations (27 depicted) that were tested and selected based on the highest correlation between age and individual alpha peak frequency (iAPF) in subjects <18 years (Spearman correlation ρ ; black digits) and the highest retention of data (number of subjects N ; white digits). **(B, C)** Spearman correlation ρ between age (6–18 years) and iAPF **(B)** and number of subjects **(C)** for each electrode and segment length (2–7 seconds) for condition eyes-closed (EC) averaged across reference montages ($n = 1715$). **(D, E)** Flattening the iAPF-age curve for males **(D)** and females **(E)** separately at electrode location Oz. Upper subplots depict nonstandardized iAPFs and the optimized Log Gaussian model fit. Lower subplots depict the age-standardized divergence values and a linear fit through the data. **(F)** Example of the derived biomarker (Brainmarker-I) based on the final age- and sex-standardized scores, with deciles 1–5 yielding a recommendation for neurofeedback (NFB) treatment and deciles 6–10 yielding a recommendation for methylphenidate (MPH). EO, eyes-open; LM, linked-mastoid.

PPV = +1.7%); however, for MM-NFB, the PPV increased to 71.4% (normalized PPV = +51% as compared with +30% in Fz). Despite this improvement for MM-NFB treatment, Fz remained the primary stratification site, because prediction for MPH was only possible with the iAPF recorded at this location. For the results of stratification based on both Fz and Oz locations, we direct the reader to the [Supplement](#).

Out-of-Sample Validation Phase: Stratification Biomarker Predicts Remission in Prospective Validation Analysis

Next, the biomarker was validated by predicting remission to MPH and multimodal treatment including MM-NFB (ICAN) in two independent datasets (36,44), blinded to clinical outcome, and based solely on the subjects’ age, sex, and baseline iAPF. Accuracy was verified by a third person not involved in the EEG

analysis (for MPH, authors GM and SKL; for MM-NFB, author MA). Results are visualized in [Figure 2](#).

In line with the previous analyses, we normalized PPVs to improve comparability with the transfer datasets. The normalized PPV predicted an increase in remission rate of 36% (PPV = 50%) compared with the observed remission rate if patients had received MPH and 29% (PPV = 29%) if patients had received the multimodal treatment based on Brainmarker-I.

Biomarker Exploration Phase

In a final step, we explored the predictive potential of Brainmarker-I for ATX and GUAN treatment. When testing different decile ranges for ATX, a cutoff point of ≤ 6 resulted in the highest normalized PPV of +27% (PPV = 40%). This seems to point to a similar directionality of effect as was observed for MM-NFB treatment, while using the cutoff point

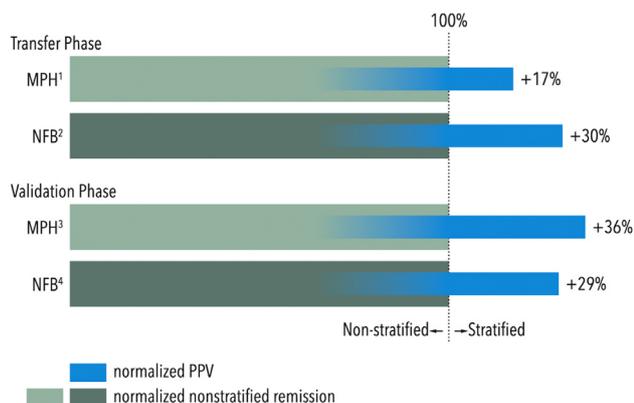


Figure 2. Predicted remission rate after stratification. Normalized positive predictive values (PPVs) (in blue) for each treatment group depict predicted gain in remission if patients had been stratified according to Brainmarker-I. Light vs. darker green implicates opposite direction for Brainmarker-I, i.e., light green indicates decile 6–10 (MPH) and dark green deciles 1–5 (e.g., NFB). Note that the predicted remission in the blinded validation is highest. ¹iSPOT-A dataset ($n = 184$); ²NFB dataset ($n = 41$); ³MPH/GUAN dataset (MPH: $n = 41$, GUAN: $n = 35$); ⁴ICAN dataset ($n = 71$). GUAN, guanfacine; ICAN, International Collaborative ADHD Neurofeedback; iSPOT-A, International Study to Predict Optimised Treatment in Attention Deficit/Hyperactivity Disorder; MPH, methylphenidate; NFB, neurofeedback.

that was also used for MPH (deciles ≥ 6) results in a decline in remission rate (improvement: -8%). However, when the same decision process as for MM-NFB was applied, i.e., predicting remission to ATX in individuals with decile scores ≤ 5 , the resulting improvement was marginal (PPV = 33% , improvement = $+6\%$).

For GUAN treatment, a prediction of remission for deciles 6 to 10, the same that was used for MPH prediction, resulted in the highest PPV (53%) and normalized PPV ($+26\%$).

DISCUSSION

In this study, an iAPF algorithm indexing brain maturation was developed in the biomarker discovery phase in a large clinical sample. Subsequently, this iAPF was used to develop an iAPF-based, age- and sex-standardized, treatment stratification biomarker (Brainmarker-I), which was found to be capable of differentially informing stratification to MPH and MM-NFB treatment. The results from the biomarker transfer phase indicate that a neurobiologically heterogeneous sample of patients with ADHD can be successfully divided into two more homogeneous subsamples characterized by a relatively faster or slower iAPF and a differential response to MPH and MM-NFB.

Given that both MPH and MM-NFB can be considered effective interventions for the treatment of ADHD, with remission rates between 31% and 51% (3,52), using EEG to stratify to one of these treatments effectively increases predicted remission rates in the stratified group by 17% to 30% compared with nonstratified remission rates. Crucially, the biomarker validation phase substantiated Brainmarker-I through a blinded out-of-sample prediction of remission in two external datasets, based solely on age, sex, and baseline iAPF. Because Brainmarker-I uses only basic demographic information and resting-state EEG data, it can easily be

implemented in clinical practice, using an algorithm that calculates age- and sex-standardized iAPF and decile score and yields a treatment recommendation.

Most importantly, the directionality of iAPF and its association with remission to MPH/GUAN is opposite that of MM-NFB/ATX. This is imperative for the concept of treatment stratification, because its aim is to use a biomarker to inform the best treatment option for each patient, choosing from a range of effective treatments for that disorder instead of merely discouraging a particular intervention.

This differential association of iAPF with remission in response to different treatments might be related to the branches of the autonomous nervous system (ANS). ADHD has been associated with hypoarousal of the ANS or hyperactivity of the parasympathetic nervous system (PSNS) (53,54), which is supported by the finding that heart rate is generally lower in children with ADHD, suggestive of higher vagal tone (33). However, there have also been studies that found an elevated sympathetic nervous system (SNS) response (42,55) or a hyperactivation of both PSNS and SNS (56), pointing to a general ANS imbalance. Similarly, iAPF has been hypothesized to index fight or flight response, with iAPF acutely speeding up in the presence of an acute threat, such as pain (57), or slowing down with chronic stress, such as chronic pain (58,59) or burnout syndrome (60), possibly reflecting a thalamocortical gating mechanism, counter-regulating the surplus of pain- or stress-induced innervation (57,58). Moreover, it has been shown that people with posttraumatic stress disorder, a disorder characterized by an overactive SNS, have a generally faster iAPF (61). A slower iAPF could thus point to a hyperactive PSNS, while a faster iAPF could reflect relatively normal PSNS or increased SNS activation.

While MPH also acts on noradrenaline, its main working mechanism seems to be an increase of synaptic dopamine by inhibiting dopamine reuptake through inhibition of the dopamine transporter. It might, thus, be possible that the mechanism of action of MPH is relatively unrelated to ANS imbalances and instead brings about its effect by acting on a number of different neurotransmitters simultaneously (62). This is in line with a recent meta-analysis that reports null effects of ANS imbalances in ADHD as the most common finding (53), suggesting a more diverse pathophysiology that goes beyond ANS abnormalities.

In contrast, ATX, a selective noradrenaline reuptake inhibitor, might normalize PSNS hyperactivity in people with a slower iAPF by increasing noradrenaline, the major neurotransmitter in the SNS. Although the relation with iAPF is unclear, one difference in the working mechanism between MPH and ATX is the location of their dopaminergic and noradrenergic effects, with both increasing noradrenaline and dopamine in the prefrontal cortex but only MPH leading to an increase in the striatum and nucleus accumbens (63).

Our findings suggest that the effect of GUAN is similar to that of MPH. While both drugs act on noradrenaline, GUAN, an α_{2A} adrenergic receptor agonist, inhibits noradrenaline, thereby dampening sympathetic arousal, which might explain its effect in people with a higher iAPF (64).

Our biomarker findings thus suggest that there might be relevant functional differences between ATX, MPH, and GUAN, requiring further investigation.

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The precise working mechanism of EEG-NFB is unknown at present. However, speculatively, it has been hypothesized that sensorimotor rhythm NFB might affect sleep-regulating mechanisms (65–67). Because ADHD has been associated with increased daytime sleepiness (68) and sleepiness is correlated with increased parasympathetic activity (69), EEG-NFB might work by improving sleep and thereby normalizing parasympathetic activity. In contrast, Garcia Pimenta *et al.* (5) recently emphasized the multimodal nature and importance of nonspecific effects of this treatment, also evident from the absence of group effects in the double-blind placebo-controlled ICAN study (36) that was used here in the validation phase. Long-term effects of up to 1-year follow-up in the ICAN study demonstrated clinical benefits on the group level similar to the MPH arm of the Multimodal Treatment Study of Children with Attention Deficit and Hyperactivity Disorder (National Institute of Mental Health) (36). This further suggests that for the multimodal approach, frequent reinforcement and sleep coaching are important factors.

While we demonstrated the prognostic value of Brainmarker-I in two independent and blinded out-of-sample validations, this study also had some limitations. Brainmarker-I presently only pertains to males and ages 6 to 18 years. The reason for this is limited sample size for females in the treatment studies and clear qualitative sex-specific effects (16), as well as a lack of adult participants for most of the datasets, which prevented us from investigating stratification for these groups. Findings in females might be particularly important because they are usually underrepresented in ADHD research (70), and future research should specifically focus on this subgroup. Likewise, investigating treatment stratification in adults with ADHD would be valuable.

Because this study examined multiple treatment datasets from different test locations with different designs, rating scales, methods, and EEG methodology, testing was not standardized. However, the fact that the out-of-sample validation was successful demonstrates the strength of the developed biomarker in spite of those differences.

Moreover, the transfer MM-NFB sample received EEG-NFB treatment augmented with sleep hygiene and coaching while the MM-NFB validation dataset received an MM-NFB or control treatment and sleep hygiene, coaching, and nutrition counseling. Findings might, therefore, not be directly comparable to standard EEG-NFB monotherapy (35).

While this study already successfully validated MPH and MM-NFB prediction by means of Brainmarker-I, a validation study that prospectively stratifies patients between the interventions based on baseline iAPF would be valuable, similar to the feasibility study of van der Vinne *et al.* (20). Because the relationship between iAPF and MDD treatment outcome has already been established (9,13,71), a next step will involve incorporating different pharmacological and non-pharmacological interventions for MDD making the here-presented Brainmarker-I a transdiagnostic biomarker.

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