## Title

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NEW RESEARCH

# Electrophysiological and Clinical Predictors of Methylphenidate, Guanfacine, and Combined Treatment Outcomes in Children With Attention-Deficit/Hyperactivity Disorder

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**Objective:** The combination of d-methylphenidate and guanfacine (an α-2A agonist) has emerged as a potential alternative to either monotherapy in children with attention-deficit/hyperactivity disorder (ADHD), but it is unclear what predicts response to these treatments. This study is the first to investigate pretreatment clinical and electroencephalography (EEG) profiles as predictors of treatment outcome in children randomized to these different medications.

**Method:** A total of 181 children with ADHD (aged 7-14 years; 123 boys) completed an 8-week randomized, double-blind, comparative study with d-methylphenidate, guanfacine, or combined treatments. Pretreatment assessments included ratings on ADHD, anxiety, and oppositional behavior. EEG activity from cortical sources localized within midfrontal and midoccipital regions was measured during a spatial working memory task with encoding, maintenance, and retrieval phases. Analyses tested whether pretreatment clinical and EEG measures predicted treatment-related change in ADHD severity.

**Results:** Higher pretreatment hyperactivity-impulsivity and oppositional symptoms and lower anxiety predicted greater ADHD improvements across all medication groups. Pretreatment event-related midfrontal beta power predicted treatment outcome with combined and monotherapy treatments, albeit in different directions. Weaker beta modulations predicted improvements with combined treatment, whereas stronger modulation during encoding and retrieval predicted improvements with d-methylphenidate and guanfacine, respectively. A multivariate model including EEG and clinical measures explained twice as much variance in ADHD improvement with guanfacine and combined treatment ($R^2$= 0.34-0.41) as clinical measures alone ($R^2$ = 0.14-.21).

**Conclusion:** We identified treatment-specific and shared predictors of response to different pharmacotherapies in children with ADHD. If replicated, these findings would suggest that aggregating information from clinical and brain measures may aid personalized treatment decisions in ADHD.

**Clinical trial registration information:** Single Versus Combination Medication Treatment for Children With Attention Deficit Hyperactivity Disorder; https://clinicaltrials.gov; NCT00429273

**Diversity & Inclusion Statement:** We worked to ensure sex and gender balance in the recruitment of human participants. We worked to ensure race, ethnic, and/or other types of diversity in the recruitment of human participants. One or more of the authors of this paper self-identifies as a member of one or more historically underrepresented racial and/or ethnic groups in science. We actively worked to promote sex and gender balance in our author group. We actively worked to promote inclusion of historically underrepresented racial and/or ethnic groups in science in our author group. While citing references scientifically relevant for this work, we also actively worked to promote sex and gender balance in our reference list.

**Key words:** attention-deficit/hyperactivity disorder; methylphenidate; guanfacine; electroencephalography; predictor

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Predicting which treatment will be most effective for each individual patient remains one of the greatest challenges in child (as well as adult) psychiatry. This is a particularly acute problem for treating disorders characterized by high clinical and etiological heterogeneity, such as attention-deficit/hyperactivity disorder (ADHD). Psychostimulants are the first-line treatment for ADHD and show acute medium-to-large effects at the group level,[1] but are ineffective or not tolerated in ~30% of patients.[2,3] Nonstimulant medications (eg, guanfacine) may

be a suitable alternative when stimulants are ineffective, but typically show lower response rates[3,4] and can produce significant side effects (eg, somnolence in 50% of cases).[5] In some studies, combined stimulant and nonstimulant treatment has shown superior efficacy compared to monotherapy, for example in global response and inattentive symptoms,[3,6,7] and has proved useful in stimulant-refractory cases.[8] However, combination therapy is not efficacious for every child with ADHD[3] and is more costly, suggesting that careful consideration of individual benefits is required. This wide variability in efficacy of various treatments means that it may take considerable time before an effective treatment is found through a trial-and-error process, with prolonged negative impact on children. Identifying individual characteristics that predict whether a child will show improvements with a given ADHD medication would allow personalized treatment decisions,[9,10] which may substantially reduce the time between diagnosis and beneficial treatment effects.

Previous efforts to predict treatment outcomes have mostly focused on clinical predictors. Research shows that higher pretreatment ADHD symptomatology is associated with better psychostimulant treatment outcomes,[11,12] although opposite[13,14] or no[15] effects have also been observed. Evidence is also mixed with regard to comorbidities, with some studies reporting that low co-occurring anxiety and oppositionality predict greater effectiveness of psychostimulants[13,14] and other data indicating no effects on treatment outcomes.[16,17] These inconsistencies may be explained by methodological differences, the scarcity of large rigorous treatment trials,[16] and the high clinical heterogeneity within ADHD.[18] Moreover, most studies have investigated predictors of psychostimulant monotherapy response and have not considered other treatments.

Besides clinical predictors, objective tests and biomarkers informed by pathophysiological mechanisms may help to predict what works best for each patient (ie, predictive biomarkers), as emphasized by personalized and precision medicine approaches.[9,10] Yet, only a few studies consistent with these principles have been conducted in child psychiatry.[19] Efforts to identify predictive biomarkers using electroencephalography (EEG), which is cost-effective, noninvasive, and tolerant of participants' movement, may be particularly useful to facilitate future applications in clinical settings.[20] The majority of available EEG studies found that better psychostimulant treatment outcome (ie, reduction in ADHD symptomatology) is predicted by atypical EEG patterns that commonly distinguish children with ADHD from controls, for example higher theta and lower beta resting-state power.[21-24]

Despite these promising findings, it remains unclear which EEG measures predict improvements with other medications. Identifying EEG measures that predict response to different treatments (ie, moderators) would be especially useful for treatment stratification, which is a particularly promising way to inform personalized treatment decisions in psychiatry given its less stringent specificity and sensitivity requirements.[25] This is because a predictive biomarker informing the choice between different established treatments, as opposed to treatment vs no treatment, is more likely to yield some benefit even if a suboptimal treatment is used.[25] Another methodological limitation of prior EEG studies is that they used measures from individual scalp electrodes that reflect a mixture of scalp projections of activities from several underlying sources across the cortex, thus providing limited information on pathophysiological mechanisms.[20] Modern EEG signal-processing methods (ie, source-resolved EEG) allow a more direct estimation of cortical activities, yielding more precise spatial localization, improved signal-to-noise ratio, and excellent reliability.[20,26] These properties make source-resolved EEG measures promising predictive biomarkers to aid future treatment decisions.

The current study examined whether pretreatment source-resolved EEG predictors, alone or combined with clinical characteristics, could help predict improvements in ADHD severity with different medications. We used data from a large 8-week randomized, double-blind, comparative trial of d-methylphenidate (DMPH), guanfacine (GUAN), and their combination (COMB) in children with ADHD. In previous analyses on this sample at baseline, EEG measures from midoccipital and midfrontal cortical regions during a spatial working memory (WM) task were sensitive to ADHD-control differences[26,27] and to differential effects of medications.[28] Simultaneous EEG−functional magnetic resonance imaging (fMRI) studies during WM tasks linked these midoccipital EEG alterations with hypo-connectivity between the fronto-parietal network and visual cortex[29] and midfrontal EEG alterations with greater pre-stimulus activity in anterior cingulate cortex (ACC) and default model network.[30] Here we build on these findings to examine whether pretreatment EEG markers and clinical ratings predict treatment-related ADHD improvement. We focused on ADHD severity, oppositionality, and anxiety measures as clinical predictors based on the aforementioned literature[13,14,16,17] and because oppositionality and anxiety are the most commonly co-occurring symptoms in children with ADHD.[31] Based on studies on psychostimulants, we hypothesized that greater alterations in midoccipital and midfrontal activities and higher levels of ADHD, but lower levels of anxiety and oppositional behaviors, would predict improvements with DMPH. Specific hypotheses for GUAN and COMB could not be formulated, as this is the first study of predictors of outcome with these treatments. We

further hypothesized that EEG measures would predict ADHD improvements over and above clinical measures.

## METHOD

### Sample

The sample consists of 207 children with ADHD aged 7 to 14 years who took part in the UCLA Translational Research to Enhance Cognitive Control (TRECC) project[3,6,7] (ClinicalTrials.gov Identifier: NCT00429273). Sources of recruitment were clinic referrals, radio and newspaper advertisements, community organizations (CHADD; www.chadd.org), local schools, and primary care physicians. All parents and participants enrolled in the study provided written informed permission and assent, respectively, after receiving verbal and written explanations of study requirements. All procedures were approved by the University of California, Los Angeles Institutional Review Board and overseen by a data safety and monitoring board.

### Procedures

Male and female participants were included if they met criteria for *DSM-IV* ADHD (any subtype) based on the Kiddie-Schedule for Affective Disorders and Schizophrenia—Present and Lifetime version[32] and clinical interview, and whether they had Clinical Global Impression—Severity (CGI-S) score of $\geq$4 for ADHD. Exclusion criteria were as follows: lifetime history of any neurological disorder, head injury resulting in concussion, autism, chronic tic disorder, bipolar disorder or psychosis, medical conditions contraindicating stimulant or α-agonist medication; current major depression or panic disorder; and IQ < 80.[33] Eligible participants were enrolled in an 8-week, double-blind, randomized controlled trial (RCT) with 3 arms: (1) DMPH extended-release (5–20 mg/d; treated from pretreatment to 4 weeks with placebo, and from week 4 to week 8 with DMPH); (2) GUAN (1–3 mg/d for 8 weeks); or (3) COMB, treated from pretreatment to week 4 with GUAN, and from week 4 to week 8 with both GUAN and DMPH. Participants were titrated to the optimal GUAN and/or DMPH dose based on clinical profiles and side effects. All participants reached optimal doses for GUAN and/or DMPH by week 7 and remained on the following optimal mean daily doses during week 8: DMPH doses were 16.0 (± 3.9) mg for DMPH-only and 15.1 (± 4.8) mg for COMB; GUAN doses were 2.2 (± 0.7) mg for GUAN-only and 2.4 (± 0.6) mg for COMB. All participants were off medication for pretreatment assessments. Full details are provided in Supplement 1, available online.

### Measures

*Pretreatment Clinical Predictors.* Pretreatment severity in ADHD and oppositional symptoms was measured with the parent-rated Strengths and Weaknesses of ADHD symptoms and Normal (SWAN) Behavior scales.[34] The Multidimensional Anxiety Scale for Children (MASC) scales[35] was used to assess anxiety problems.

*Pretreatment EEG Predictors.* EEG data were collected and processed following the approach in previous publications on the pretreatment data of this sample[26,27] while participants completed a spatial WM task. Trials began with a fixation cross presented for 0.5 seconds, followed by 1, 3, 5, or 7 yellow dots presented for 2 seconds the locations of which were to be remembered (encoding phase). The number of dots is a manipulation of load, with greater load expected to engage more WM. The screen then turned blank for 3 seconds (maintenance phase). Upon presentation of a single dot (for up to 3 seconds), children indicated with a button press (left or right arrow key) whether this probe was in a location previously shown (match) or not (nonmatch) (retrieval phase). Accuracy of >60% during a training block was required to continue to the 2 testing blocks, each containing 48 trials. Task performance variables included accuracy, mean reaction time (RT), and SD of reaction time, as an index of intraindividual reaction time variability (RTV) (Table S1, available online).

Full details regarding EEG processing and analysis are provided in Supplement 2, available online. Briefly, after standard pre-processing procedures, independent component analysis decomposed the data from EEG electrodes into source signals from independent components (ICs) reflecting the activity of putative cortical generators. ICs corresponding to cortical brain sources were localized through source localization and grouped into functionally common source clusters across participants.[20,26] We focused a priori on IC activities from sources localized to mid-occipital and midfrontal regions (primary visual area and dorsal ACC [dACC], respectively), following previous work showing that these cortical sources are sensitive to ADHD−control differences[26,27] and to medication effects in this sample.[28] Event-related modulations of power were computed by dividing post-stimulus power by a pre-stimulus window and log-transforming it (10log10) to decibel (dB) units. Averaging these values across trials allows the examination of stimulus-related power increases and decreases with respect to pre-stimulus activity. These values were then averaged across theta (4-7 Hz), alpha (8-12 Hz), and beta (13-25 Hz) ranges during encoding (0–2 seconds), maintenance (2–5 seconds), and retrieval (5-6 seconds).

Event-related power modulations during encoding (especially decreases) are thought to reflect allocation of attention-related resources to facilitate coordinated activity between visual and WM memory storage systems.[26,27,36] Power modulations during maintenance represent activity to support maintenance of the encoded stimulus in WM,[27] whereas modulations during retrieval index interaction between visual and WM systems (similar to encoding) combined with motor response processes.[27,36]

*Treatment Outcome.* The ADHD Rating Scale IV (ADHD-RS-IV)[37] was completed at pretreatment and end-of-treatment (week 8) by a clinician blinded to group assignment, based on clinical interviews and parent and teacher ratings. The difference between scores at the end-of-treatment and pretreatment was used as the primary treatment outcome, with higher difference scores reflecting greater improvements. We used this dimensional measure of improvement as the primary outcome, rather than a binary definition of treatment response, to maximize power because all 3 medication groups showed high response rates based on standard thresholds,[3] resulting in small nonresponder groups. (Note: Two different measures of ADHD symptoms are used as predictor [SWAN] and clinical outcome [ADHD-RS] in this study. The clinician-rated ADHD-RS was used as outcome for consistency with our previous work reporting clinical outcomes in this RCT.[3] The SWAN was used as a predictor because it was completed by a different rater [parent] and because it was developed to measure the full distribution of ADHD symptoms.)

### Statistical Analyses

To investigate predictors of ADHD-RS improvement, we ran linear regression models with each pretreatment clinical, EEG, and WM performance measure as independent variables to predict change in ADHD-RS. EEG and WM performance measures were averaged across load to reduce the number of predictors. A significant main effect indicated predictors of change across treatments. Analyses were run with an interaction term between predictor and medication group, with significant interactions indicating that the predictive effect significantly differed between treatments, consistent with requirements to identify candidate predictive biomarkers for future treatment stratification.[38]

Multivariate analyses evaluated the proportion of variance jointly explained by combining predictors that individually showed main or interaction effects on change in ADHD-RS. We examined models with clinical predictors alone, EEG/performance predictors alone, and combining all clinical and EEG/performance. All models included age as a covariate.

Models predicting treatment outcome were validated using *k*-folds cross-validation in R, a statistical method to evaluate predictive models by partitioning the original dataset into *k* subsets of roughly equal size. Each model was first trained in *k*-1 subsets and then tested on the remaining subset. This was repeated *k* times with each subset used as a test-dataset once. The average root mean squared error (RMSE) and the RMSE SD were used to evaluate fit.

Analyses were restricted to participants who completed the RCT. Missing data in EEG variables (eg, due to participants not completing EEG assessments, technical issues, or very noisy data) were imputed using model-based imputation.[39] Sensitivity analyses were performed only on participants with complete data. For analyses testing individual predictors, multiple testing was minimized by using a hypothesis-driven approach restricting the number of measures based on previous literature and using a conservative significance threshold of $p \leq .01$. Effects between $p > .01$ and $p \leq .05$ are presented as trend-level effects that may provoke further research. Standardized $\beta$ coefficients ($\beta$) are reported to provide an indication of effect size. For multivariate models, which were restricted to measures showing effects in analyses of individual predictors, we used a $p < .05$ threshold.

## RESULTS

### Participant Characteristics

The 8-week trial was completed by 181 (123 boys, mean age = 10.09 years, SD = 2.10 years) of the 207 randomized participants (Table 1). Participants in the 3 groups (61 COMB, 59 GUAN, 61 DMPH) showed no significant differences on pretreatment demographic, clinical, EEG, and WM performance measures (Table S2, available online). EEG variables for participants who completed the RCT but had noisy data and missing ICs in midoccipital (n = 47, 26%) or midfrontal (n = 56, 31%) clusters were imputed. There were no significant differences between participants with imputed and complete data on sociodemographic, clinical, or cognitive characteristics (Table S3, available online).

### Pretreatment Predictors of Treatment Outcome

Greater improvements in ADHD-RS across medication groups were predicted by higher pretreatment hyperactivity-impulsivity ($\beta = 0.21$, 95% CI = 0.01-0.39, $p = .02$) and oppositional behaviors ($\beta = -0.21$; 95% CI = 0.05-0.36, $p < .01$). Lower anxiety also predicted greater ADHD

**TABLE 1** Sample Characteristics by Treatment Group

| | GUAN (n = 68) | DMPH (n = 69) | COMB (n = 70) | $F/\chi^2$ | p |
|---|---|---|---|---|---|
| Age, y, mean (SD) | 10.1 (2.1) | 10.1 (2.0) | 9.9 (2.2) | 0.11 | .89 |
| Male sex, n (%) | 45 (66.2) | 46 (66.7) | 51 (72.9) | 1.67 | .43 |
| Race, n (%) | | | | 7.63 | .47 |
| White | 51 (75.0) | 51 (73.9) | 41 (58.6) | | |
| African American | 7 (10.3) | 10 (14.5) | 19 (27.1) | | |
| Asian/Pacific Islander | 7 (10.3) | 4 (5.8) | 5 (7.1) | | |
| Other | 3 (4.4) | 4 (5.8) | 5 (7.1) | | |
| Ethnicity, Hispanic, n (%) | 16 (23.5) | 10 (14.5) | 18 (25.6) | 1.50 | .47 |
| Full Scale IQ, mean (SD) | 102.6 (14.2) | 101.5 (13.3) | 102.9 (13.0) | 0.10 | .90 |
| ADHD subtype, n (%) | | | | 0.86 | .93 |
| Inattentive | 28 (41) | 33 (48) | 31 (44) | | |
| Hyperactive-impulsive | 1 (2) | 2 (3) | 2 (3) | | |
| Combined | 38 (56) | 32 (46) | 35 (50) | | |
| ADHD-RS baseline, mean (SD) | 36.8 (9.1) | 35.6 (8.1) | 35.6 (9.8) | 0.37 | .69 |
| ADHD-RS week 8, mean (SD) | 18.7 (11.2) | 20.4 (8.1) | 17.9 (9.8) | 0.97 | .38 |

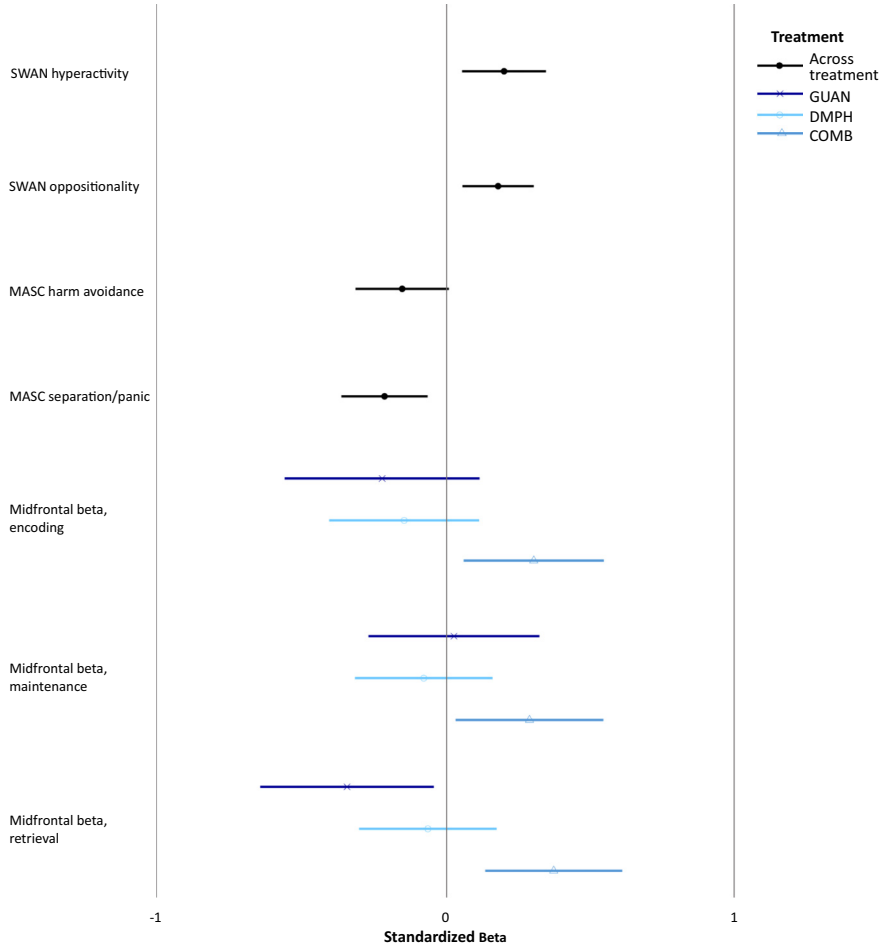
*Note*: F *statistics from analysis of variance are reported for continuous measures (age, Full Scale IQ, ADHD-RS scores);* $\chi^2$ *values from* $\chi^2$ *tests are reported for the remaining categorical measures. ADHD-RS = Attention Deficit Hyperactivity Disorder Rating Scale IV total score; COMB = combined treatment; DMPH = d-methylphenidate; GUAN = guanfacine; n = number of participants.*

improvement across treatments (separation/panic: $\beta = -0.23$, 95% CI = −0.39 to −0.07, $p < .01$; harm avoidance: $\beta = -0.17$, 95% CI = −0.33 to −0.00, $p = .05$) (Figure 1). These effects did not differ across medications, as indicated by nonsignificant interactions (Table S4, available online).

Differential treatment effects emerged for EEG measures in midfrontal regions localized in the dACC. Event-related beta power showed significant ($p < .01$) interactions with medication group during encoding and retrieval, and a trend-level ($p = .05$) interaction during maintenance (Table S4, available online). In the COMB group, greater ADHD-RS improvement was predicted by higher beta power (ie, weaker power decreases) during encoding ($\beta = 0.30$, 95% CI = 0.06-0.44, $p < .01$), maintenance ($\beta = 0.29$, 95% CI = 0.03-0.54, $p = .03$), and retrieval ($\beta = 0.37$, 95% CI = 0.14-0.62, $p < .01$) (Figure 1). An opposite pattern emerged in the GUAN group during the retrieval phase, as lower beta power (ie, stronger power decreases) predicted ADHD-RS improvement ($\beta = -0.34$, 95% CI = −0.64 to −0.04, $p = .03$). The effects in the GUAN group were not significant during encoding ($\beta = -0.22$, 95% CI = −0.56 to 0.12, $p = .20$) and maintenance ($\beta = 0.03$, 95% CI = −0.27 to 0.32, $p = .86$). No significant effects in these beta power measures emerged in the DMPH group (encoding: $\beta = -0.14$, 95% CI = −0.40 to 0.11, $p = .27$; maintenance: $\beta = -0.08$, 95% CI = −0.31 to 0.16, $p = .52$; retrieval: $\beta = -0.06$, 95% CI = −0.30 to 0.17, $p = .60$). Consistent with these significant interactions and the opposite direction in which beta power predicted ADHD improvement in COMB vs GUAN groups, post hoc tests showed that the predictive effect in the COMB group significantly differed from the effect in the GUAN and DMPH groups during encoding and retrieval (Table S5, available online). Other EEG measures and WM performance measures did not predict ADHD improvements across medications or in interaction with medication group (Table S4, available online).

To help the interpretation of predictor-by-treatment interactions in analyses of continuous treatment outcome, we ran follow-up logistic regressions testing whether midfrontal beta power predicted binary treatment response (≥30% ADHD-RS improvement) vs nonresponse. Consistent with the analyses of continuous improvement, the direction of the effects differed by group, as depicted in Figure 2. In the COMB group, treatment response was predicted by weaker power decreases during encoding (odds ratio [OR] = 13.34, 95% CI = 2.28-135.99, $p = .01$) and retrieval (OR = 7.75, 95% CI = 1.84-45.18, $p = .01$), with no significant effect during maintenance (OR = 1.97, 95% CI = 0.59-7.79, $p = .29$). Conversely, in the GUAN group, treatment response was predicted, at trend level, by stronger power decreases during retrieval (OR = 0.19, 95% CI = 0.03-0.82, $p = .04$), with nonsignificant effects during encoding (OR = 0.40, 95% CI = 0.05-2.42, $p = .34$) and maintenance (OR = 1.26, 95% CI = 0.32-4.69, $p = .72$). In the DMPH group, there were no effects of beta power during maintenance (OR = 0.43, 95% CI = 0.14-

**FIGURE 1** Pretreatment Predictors of Change in Attention-Deficit/Hyperactivity Disorder (ADHD) Severity Between Pretreatment and End of Treatment




*Note:* *This graph shows predictors of significant (p ≤ .01) or trend-level (p ≤ .05) effects across treatments or interaction effects with treatment group. Higher scores of the treatment outcome measure reflect greater improvement, so positive values of beta coefficients indicate that higher values of the parameter are associated with greater improvement. Full results are presented in Table S1, available online. SWAN scores were reverse coded, such that higher scores represent higher ADHD severity. 95% CI not including 0 indicate p < .05. COMB = combined treatment group; DMPH = d-methylphenidate monotherapy group; GUAN = guanfacine monotherapy group; MASC = Multidimensional Anxiety Scale for Children scales; SWAN = Strengths and Weaknesses of ADHD symptoms and Normal Behavior scales. Please note color figures are available online.*

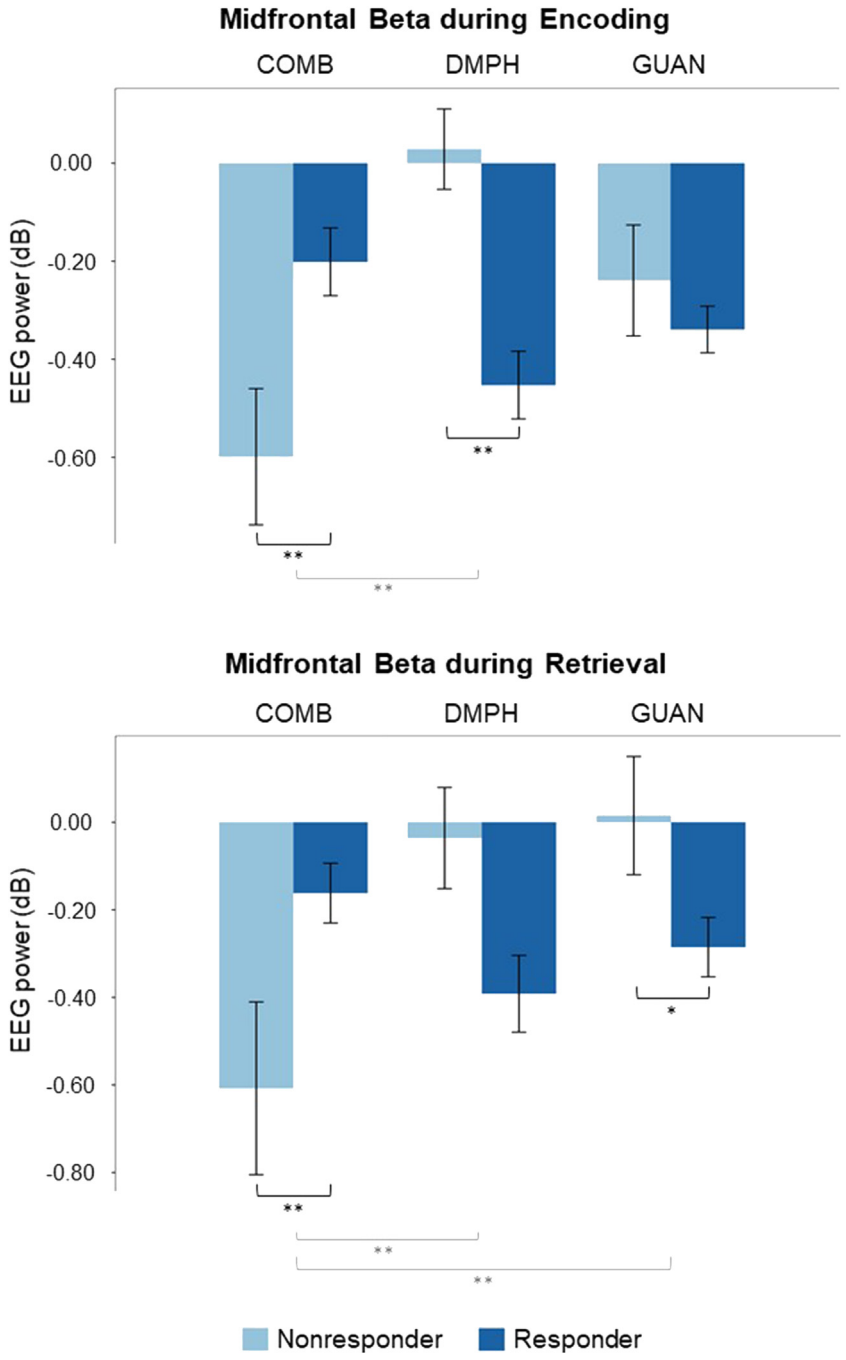
1.28, $p = .14$) and retrieval (OR = 0.33, 95% CI = 0.10-0.99, $p = .06$), but a significant effect emerged during encoding (OR = 0.04, 95% CI = 0.01-0.26, $p < .01$), indicating that stronger power decreases predicted treatment response. Results of post hoc tests comparing predictive effects across groups were similar to those examining continuous outcomes (Table S5, available online, Figure 2).

Finally, we ran exploratory analyses to map the identified beta power profiles onto heterogeneity in WM performance at baseline. Higher beta (ie, weaker midfrontal power decreases) correlated with worse WM accuracy (encoding: $r = -0.25$, $p < .01$) and higher RTV (encoding: $r = 0.27$, maintenance: $r = 0.19$, retrieval: $r = 0.16$, all $p < .05$), suggesting that the EEG profiles predictive of clinical improvements with COMB were related to cognitive markers of executive dysfunction and attentional lapses in ADHD.

## Multivariate Predictive Models

Because EEG predictors had different predictive effects on treatment outcome in the 3 groups, we ran multivariate models for each medication group separately, including age as a covariate in all models (Figure 3). In the COMB group, a multivariate model including all clinical measures individually predicting continuous treatment outcome yielded $R^2 = 0.21$ ($p = .03$). A

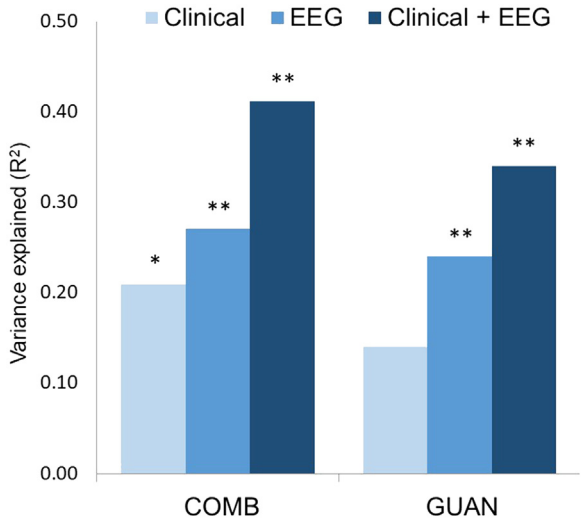
**FIGURE 2** Bar Graphs Showing the Mean and Standard Error of Pretreatment Beta Power Measures Divided by Binary Treatment Response (≥30% ADHD-RS Improvement) in Each Treatment Group




*Note:* *Asterisks refer to significant (**p ≤ .01) or trend-level (*p < .05) predictive effects within each group based on results of logistic regressions. Black square brackets and arrows reflect differences between responders and nonresponders within each treatment group. Gray square brackets and arrows reflect differences in the predictive effects between treatment groups. ADHD-RS = Attention Deficit Hyperactivity Disorder Rating Scale; COMB = combined treatment group; DMPH = d-methylphenidate monotherapy group; GUAN = guanfacine monotherapy group. Please note color figures are available online.*

model including EEG measures that individually predicted improvements with COMB (midfrontal beta power during encoding, maintenance, and retrieval) yielded $R^2 = 0.27$ ($p < .01$). Combining clinical and EEG predictors in a multivariate model explained the greatest proportion of variance in continuous ADHD improvement ($R^2 = 0.41$, $p < .01$). In the GUAN group, multivariate models aggregating EEG (midfrontal beta

**FIGURE 3** Variance Explained ($R^2$) in Multivariate Prediction Models of Continuous Treatment Improvement in ADHD-RS by Medication Group




*Note:* *All models also included age as a covariate. Results for DMPH are not shown, as there were no significant electroencephalographic predictors of continuous change in ADHD severity with this treatment. ADHD-RS = Attention Deficit Hyperactivity Disorder Rating Scale IV total score; COMB = combined treatment group; DMPH = d-methylphenidate monotherapy group; GUAN = guanfacine monotherapy group. Please note color figures are available online.*
**p < .05; **p ≤ .01.*

power during retrieval) and clinical predictors, as well as a model with EEG alone, significantly predicted ADHD improvement (respectively, $R^2 = 0.34$, $p < .01$; $R^2 = 0.24$, $p < .01$). Conversely, a model including only clinical predictors was not statistically significant ($R^2 = 0.14$, $p = .18$). For DMPH, we additionally tested a multivariate model aggregating clinical predictors and beta power during encoding, which predicted binary response. None of the multivariate models were statistically significant (clinical: $R^2 = 0.11$, $p = .27$; EEG: $R^2 = 0.05$, $p = .23$; clinical and EEG: $R^2 = 0.12$, $p = .32$).

### Cross-Validation and Sensitivity Analyses

Cross-validation analyses testing predictors of continuous treatment outcome individually in the whole sample used $k = 5$ folds, balanced in terms of ADHD treatment, age, and sex. A 3-fold cross-validation was used in multivariate analyses run in each group separately. All models had consistent fit across test data for every fold, indicating that the identified clinical and EEG predictors showed good validity within this sample (Table S6, available online).

Results of sensitivity analyses on participants with complete data were largely consistent with results using imputed data (Supplement 3, Tables S7 and S8, available online).

## DISCUSSION

The current study represents the first investigation of clinical and EEG predictors of treatment outcome following DMPH, GUAN, and COMB treatments in children with ADHD. Event-related EEG beta activity from midfrontal cortical sources in the dACC differentially predicted (ie, moderated) improvements in ADHD severity with COMB and monotherapies, pointing to distinct EEG profiles associated with better clinical outcomes with each treatment. Specifically, greater reductions in ADHD severity were predicted by weaker beta power modulations across task phases in children randomized to COMB, but by stronger modulations during retrieval in children taking GUAN. Stronger beta power modulation during encoding further predicted binary treatment response in children taking DMPH, although this effect was not significant in analyses of continuous treatment outcome and thus warrants further research. Pretreatment hyperactivity-impulsivity, oppositional behavior, and anxiety emerged as clinical predictors across treatments, meaning that they could not forecast better improvement with each specific treatment. In children treated with COMB and GUAN, aggregating EEG and clinical predictors in multivariate analyses predicted ADHD improvements to a greater extent than using clinical or EEG measures alone. The identified EEG predictors in the beta band may represent promising predictive biomarkers that could be used alongside clinical information to aid treatment stratification and personalized treatment decisions for children with ADHD.

Our study provides novel evidence that event-related midfrontal beta power at pretreatment represents a moderator of treatment outcome, differentially predicting treatment improvement with COMB and monotherapies. Beta oscillations during cognitive tasks have been interpreted as a possible neural mechanism of top-down–controlled processing,[40] as indicated by frontal event–related power decreases during memory performance,[41,42] attentional processing,[40,43] and preparation and execution of motor responses.[40] Beta power decreases have, in some contexts, been reported in tandem with alpha power decreases,[36,40] which have similarly been implicated in visual attention and top-down inhibition of task-irrelevant brain functions.[26,29] In individuals with ADHD, weaker beta and alpha power decreases in comparison to those in neurotypical controls have been found during WM and cognitive control tasks,[41,44] consistent with studies reporting associations between weaker power modulations in these frequencies and worse task performance.[27,42] The current findings extend this literature by showing that atypical beta patterns implicated in top-down executive dysfunction are predictive of response to different ADHD pharmacotherapies.

A clinical implication is that distinct groups of children with ADHD may benefit to a different extent from the treatments investigated in this study. Children displaying attenuated midfrontal beta power modulations in the ACC, which potentially represent a subpopulation of children with ADHD showing broader top-down attentional impairments during stimulus encoding/retrieval and WM storage functions,[18] may benefit from more intensive treatment with combined stimulant and nonstimulant medication. Conversely, children displaying attenuated pretreatment beta power modulations may show worse treatment outcome with GUAN alone, consistent with previous findings in this sample that GUAN did not have positive effects on cognitive functioning at the group level.[7,28] A possible explanation for this pattern may be found in the functional role of the ACC, which, aside from its role in the salience network supporting attention and goal-directed behavior, is also a key region of cortico-limbic circuitry. Specifically, both the dorsal and ventral ACC have been involved in multiple emotional processes[45] and in pathological anxiety.[46] Because GUAN has positive effects on disorders characterized by emotional difficulties,[5,47,48] it is possible that children with ADHD displaying these ACC-mediated emotional difficulties may show greater clinical improvements with GUAN monotherapy. Future studies are needed to further test this hypothesis and to confirm the localization of this midfrontal component (eg, with simultaneous EEG and fMRI), which our EEG source modeling localized within the dACC. Of note, whereas pretreatment EEG power was associated with treatment outcome, WM performance did not show significant predictive effects, suggesting that the identified EEG profiles may be more powerful predictors of treatment response than behavioral performance indices. Taken together, our findings suggest that midfrontal beta power during WM represents a brain profile that may help to delineate distinct subpopulations of children with ADHD who are likely to benefit from different treatments, consistent with requirements for predictive biomarkers.[38]

Interestingly, previous studies showed that attenuated frontal beta modulations during WM performance were not ameliorated by stimulant monotherapy.[41] Similarly, in another publication on this sample,[28] none of the midfrontal EEG measures, including beta power, were sensitive to the effect of DMPH, GUAN, or COMB; rather, significant treatment effects, which were especially widespread in the COMB group, were found in EEG measures from midoccipital regions.[28] A possible explanation is that, whereas midfrontal power emerged as a moderator of treatment outcome (ie, candidate predictive biomarker), midoccipital measures may reflect mediators potentially pointing to mechanisms by which treatments achieved their effects (ie, candidate monitoring biomarkers).[49] This distinction between moderators and mediators of ADHD treatment outcome mirrors previous theoretical accounts and empirical evidence on developmental outcomes in children with ADHD.[31,50] For example, a prominent developmental model posits a separation between neurocognitive processes predicting developmental courses from neurocognitive processes that parallel developmental changes in ADHD symptoms.[50] Future studies examining the relationship between different cortical regions in treatment trials, for example with functional connectivity analyses, may provide further insights into the neural moderators and mediators of treatment outcomes in children with ADHD.

Unlike midfrontal EEG measures, which predicted opposite effects with COMB and GUAN treatments, higher levels of hyperactivity-impulsivity and oppositional symptoms and lower levels of anxiety predicted improvements in ADHD severity across treatment, as indicated by nonsignificant interactions with treatment group. Pretreatment inattention did not predict treatment outcome, possibly because of the restricted variance in this symptom dimension, as most participants had inattentive or combined ADHD subtype (ie, 6-9 inattentive symptoms). These findings on clinical predictions suggests that children showing greater behavioral difficulties, coupled with low anxiety, may be in greater need of treatment and more likely to show some ADHD improvement irrespective of which treatment they receive. However, these clinical characteristics were nonspecific predictors of treatment outcome, and may thus not be useful for forecasting which treatment might work for a given child. Conversely, the differential predictive effects that we observed for midfrontal EEG power suggest that using brain biomarkers may add specificity in forecasting treatment outcome on an individual basis. Our multivariate analyses are consistent with this possibility, as a model aggregating the identified EEG predictors with clinical predictors roughly doubled the amount of variance explained in treatment improvement relative to using clinical measures alone. In contrast, multivariate models including only clinical predictors explained a relatively small proportion of variance and were not statistically significant in the GUAN and DMPH groups, indicating limited clinical utility for predicting treatment outcome. Together, these findings provide novel proof-of-concept evidence that considering objective brain biomarkers alongside clinical characteristics may improve treatment decision making for children with ADHD.

The current study has multiple limitations. First, although this is one of the largest EEG studies of multiple ADHD medications and we used a cross-validation

approach, our study did not include an independent validation sample, as no other study with similar assessments and medication groups exists to date. Thus, our results, especially those of the multivariate models, which may be prone to overfitting, await replication in an independent sample. Second, the current analyses examined predictors of acute improvements over 8 weeks, and thus do not inform predictors of long-term effects. Third, as is common in medication trials, this sample comprises a selected group of children with relatively few psychiatric comorbidities. Future clinical trials in more diverse ADHD populations are required to generalize these findings. Fourth, the limited predictive effects in the DMPH group might be partly because this group received 4 weeks of active treatments, whereas the GUAN and COMB groups received 8 weeks of treatments. However, all 3 groups reached optimal doses before week 8 and showed clinically significant improvements,[3] in line with prior research showing maximal benefit from GUAN and DMPH within 3 to 4 weeks.[2,4] It is thus unlikely that that this difference had an impact on our findings, although replication will be required. Finally, as our hypothesis-driven study focused a priori on clinical and EEG markers suggested by previous literature,[26,27] we cannot rule out the possibility that treatment-related improvements may be further predicted by EEG and other measures not included in this study.[15,23,24] This is consistent with our multivariate results, in which the majority of the variance in treatment outcome remained unexplained even in models combining clinical and EEG predictors. Future studies should investigate whether EEG measures from other cortical sources or functional connectivity measures between sources predict treatment outcomes in children with ADHD. Given these limitations, it is important to note that our findings should not be used for clinical purposes before a full replication with more stringent statistical correction is carried out.

In conclusion, we report initial evidence that EEG cortical source activity may predict clinical improvements in response to combination treatment and monotherapy in children with ADHD. The identified midfrontal EEG profiles represent candidate brain biomarkers that, if replicated in future studies, may be used alongside clinical measures to assist in personalized treatment decision making for ADHD pharmacotherapy.

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