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NEW RESEARCH

Methylphenidate, Guanfacine, and Combined Treatment Effects on Electroencephalography Correlates of Spatial Working Memory in Attention-Deficit/Hyperactivity Disorder

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Objective: The combination of d-methylphenidate and guanfacine (an α-2A adrenergic agonist) may be an effective alternative to either agent as monotherapy in children with attention-deficit/hyperactivity disorder (ADHD). This study investigated the neural mechanisms underlying medication effects using cortical source analysis of electroencephalography (EEG) data.

Method: A total of 172 children with ADHD (aged 7-14; 118 boys) completed an 8-week randomized, double-blind, comparative study with 3 treatment arms: d-methylphenidate, guanfacine, or their combination. EEG modulations of brain oscillations at baseline and end point were measured during a spatial working memory task from cortical sources localized within the anterior cingulate (midfrontal) and primary visual cortex (midoccipital), based on previously reported ADHD and control differences. Linear mixed models examined treatment effects on EEG and performance measures.

Results: Combined treatment decreased midoccipital EEG power across most frequency bands and task phases. Several midoccipital EEG measures also showed significantly greater changes with combined treatment than with monotherapies. D-methylphenidate significantly increased midoccipital theta during retrieval, while guanfacine produced only trend-level reductions in midoccipital alpha during maintenance and retrieval. Task accuracy improved with combined treatment, was unchanged with d-methylphenidate, and worsened with guanfacine. Treatment-related changes in midoccipital power correlated with improvement in ADHD severity.

Conclusion: These findings show that combined treatment ameliorates midoccipital neural activity associated with treatment-related behavioral improvements and previously implicated in visuo-attentional deficits in ADHD. Both monotherapies had limited effects on EEG measures, with guanfacine further showing detrimental effects on performance. The identified midoccipital EEG profile may aid future treatment monitoring for children with ADHD.

Clinical trial registration information: Single Versus Combination Medication Treatment for Children With Attention Deficit Hyperactivity Disorder (Project1); https://clinicaltrials.gov/; NCT00429273.

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

Key words: attention-deficit/hyperactivity disorder; electroencephalography; guanfacine; methylphenidate; treatment effect

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Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder, affecting 5%-10% of children and youth worldwide.[1] Substantial heterogeneity exists among patients with ADHD in clinical presentations, persistence into adulthood, functional outcomes, and response to pharmacotherapy,[2] likely owing to multiple etiological pathways.[3,4] Elucidating the differential mechanisms of action of available medications and identifying objective measures (ie, biomarkers) that track treatment response hold promise for improving long-term outcomes in children with ADHD.[5]

Neurobiological models of ADHD and its treatment highlight the role of poor dopaminergic and noradrenergic modulation primarily in neural pathways that involve the prefrontal cortex.[6] Stimulant medications (eg, methylphenidate), the first-line treatment for ADHD, typically

produce medium-to-large short-term effects on ADHD symptoms[7] and related cognitive functions[8,9] by increasing dopamine stimulation, mainly at D_1 receptors, and norepinephrine at α-2 adrenergic receptors.[6] Functional magnetic resonance imaging studies, largely conducted on small samples (n = ~20 per group), show that methylphenidate broadly attenuates functional alterations found in unmedicated children with ADHD relative to controls, including activity of the anterior cingulate cortex, inferior frontal cortex, striatum, insula, parietal cortex, and cerebellum during executive functioning tasks.[10-12] Other studies have investigated the neural mechanisms of methylphenidate effects using electroencephalography (EEG), which compared with functional magnetic resonance imaging provides a more direct measure of brain activity with superior temporal resolution.[5] EEG is also more suitable for conducting larger-scale studies of children with ADHD thanks to its practical advantages (low cost, noninvasiveness, tolerance of participant's movement, lack of contraindications).[13] Available EEG studies of methylphenidate effects have shown that stimulants improve many of the atypical EEG patterns shown by children with ADHD, including increased frontocentral theta power (4-7 Hz) during resting state[14-16] and reduced event-related potential components (eg, P3) during cognitive paradigms.[17,18]

Despite their robust short-term effects, stimulants are ineffective, not tolerated, or not suitable in approximately 25%-35% of children with ADHD.[19,20] Nonstimulant medication can be beneficial in these cases, either as an alternative treatment or in combination with stimulants.[20] In particular, guanfacine, one of the available nonstimulant options, has been shown to ameliorate ADHD symptoms (with response rates of 50%-70%)[20,21] and improve prefrontal function and associated cognitive processes through selective agonism of postsynaptic α-2A adrenergic receptors.[6,22] In a recent randomized, double-blind, comparative trial of d-methylphenidate (DMPH), guanfacine (GUAN), and their combination (COMB) in children with ADHD, COMB showed superior effects in reducing symptom severity compared with either monotherapy.[20] COMB also had greater effects on working memory (WM) deficits than GUAN, although it did not differ from DMPH, whereas other cognitive domains did not improve with any treatment.[8]

Although stimulant, nonstimulant, and combination treatments may show differential effects, very few studies have directly compared the effects of different medications on brain functioning. The only available study has shown that GUAN, DMPH, and COMB produce distinct medication-related changes in resting-state EEG spectral power, suggesting different neural mechanisms of action.[15] Furthermore, available EEG studies of ADHD medications have typically relied on measures from individual electrodes, such as event-related potentials and resting-state power. Owing to volume conduction between brain and scalp, these measures represent spatially blurred scalp projections of activities from numerous underlying cortical sources that carry limited ability to pinpoint and localize medication-related neural mechanisms. Advanced EEG analysis techniques (ie, source-resolved EEG imaging) can overcome this limitation by decomposing the mixture of signals recorded at the scalp into temporally independent brain sources with improved signal-to-noise ratio and spatial localization.[5,23-25] As a result, source-resolved EEG approaches may allow for more precise and accurate investigation of neural mechanisms associated with psychiatric conditions and their treatment effects.[5] Previous studies have shown that attenuated event-related power modulations from occipital (visual) cortical sources, especially in the alpha band, reliably distinguish children with ADHD from controls.[23,26,27] This EEG power profile is thought to index visuo-attention deficits and is associated with frontoparieto-occipital hypoconnectivity.[28] However, no study to date has examined ADHD medication effects on source-resolved neural mechanisms.

Using data from the aforementioned trial of DMPH, GUAN, and COMB treatment,[20] the current study is the first to our knowledge to investigate the neural mechanisms of action of each treatment in children with ADHD using source-resolved EEG measures. Given previous findings showing that COMB had beneficial effects on WM,[8] we focused on EEG modulations of event-related spectral power during a spatial WM task with encoding (ie, visual attention), maintenance (ie, memory retention), and retrieval (ie, recall and response) phases.[23] We focused a priori on EEG oscillations in the theta, alpha, and beta bands from midfrontal and midoccipital cortical regions, based on their role in supporting coordinated activity between visual and cognitive systems[28-30] and their association with attentional and WM performance in ADHD[23,26,27,31-34] and neurotypical samples.[25,29,30,35] We hypothesized that COMB would have greater effects compared with either monotherapy on source-resolved EEG activity and performance markers previously found to be impaired in children with ADHD.

METHOD

Sample

The sample comprised 172 children diagnosed with ADHD (118 boys; mean [SD] age = 10.14 [2.09] years) enrolled in the Translational Research to Enhance Cognitive Control

(TRECC) project[20] (ClinicalTrials.gov Identifier: NCT00429273). Participants were recruited from clinic referrals, radio and newspaper advertisements, community organizations (Children and Adults With Attention-Deficit/Hyperactivity Disorder [CHADD]; https://chadd.org/), local schools, and primary care physicians. Inclusion criteria were 1) male or female 7-14 years of age; 2) *DSM-IV* ADHD (any subtype) diagnosis made by semistructured diagnostic interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version [K-SADS-PL])[36] and clinical interview; and 3) Clinical Global Impressions–Severity (CGI-S) score $\geq$4 for ADHD. Participants were excluded if they had a 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; or estimated Full Scale IQ <80.[37] After receiving verbal and written explanations of study requirements, all parents and participants enrolled in the study provided written informed permission and assent, respectively. All procedures were approved by the UCLA Institutional Review Board and overseen by a data safety and monitoring board.

Procedures

Eligible participants were enrolled in an 8-week, double-blind, randomized controlled trial with 3 arms: DMPH extended-release (5-20 mg/day; treatment from baseline to week 4 with placebo, followed by treatment from week 4 to week 8 with DMPH); immediate-release GUAN (1-3 mg/day for 8 weeks); or COMB (treatment from baseline to week 4 with GUAN, followed by treatment from week 4 to week 8 with GUAN and DMPH). Participants were titrated to the optimal GUAN and/or DMPH dose, determined by Clinical Global Impressions–Improvement (CGI-I) ratings, ADHD Rating Scale–IV (ADHD-RS-IV)[38] scores, and side effects. Although the total time on medication differed across groups, all participants reached optimal GUAN and/or DMPH doses by week 7 and remained on optimal dose before week 8 assessments. For full details on the study design, see Supplement 1, available online. Participants underwent clinical, cognitive, and EEG assessments at baseline and during follow-up assessments.[8,15,20] Only participants who were medication-naïve (84%) or not optimally treated with prior medication (7% medicated at first contact, 9% with past treatment) were included. Participants who were taking medication before the trial were off medication for at least 1 week for short-acting agents, or 5 half-lives for all other medications, before baseline assessments.

Clinical Measures

Participants were evaluated based on the K-SADS-PL[36] conducted with the primary caretaker (usually mother) and with children if >8 years of age. Teacher reports (Conners Teacher Questionnaire)[39] were solicited at baseline and used to supplement clinical interview data and gain a more complete picture of the child's behavior. Psychiatric disorders were considered present if the participant met full *DSM-IV* diagnostic criteria at the time of the assessment. All interviews were conducted by clinical interviewers with extensive experience in psychiatric diagnoses and using the K-SADS. Best-estimate diagnoses were determined after individual review of diagnoses, symptoms, and impairment by a senior clinician. The ADHD-RS-IV,[38] which served as the primary clinical outcome in the current study, was completed by a clinician blinded to medication status at baseline and week 8 based on all available data. This measure was used to examine associations with treatment-related effects on cognitive and EEG measures (see "Statistical Analyses").

Spatial WM Task

We used a computerized version of a spatial WM task[40,41] to assess components of WM (Figure S1, available online). Trials began with a fixation cross presented for 0.5 second (fixation period), followed by 1, 3, 5, or 7 yellow dots presented for 2 seconds whose locations were to be remembered (encoding phase). The number of dots is a manipulation of load, with greater load expected to demand more WM. The screen then turned blank for 3 seconds (maintenance phase). On presentation of a single dot (displayed 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). A 2-second intertrial interval followed the retrieval phase. Task performance variables included accuracy, mean reaction time, and standard deviation of reaction time (RTV) as an index of intraindividual variability (Table S1, available online).

A training block preceded the testing session. In the first 8 trials, encoding and probe stimuli appeared side by side; in the next 8 trials, the probe followed encoding without the maintenance interval; finally, 8 full trials were presented. Accuracy >60% during practice was required to continue to the 2 testing blocks, each containing 48 trials. In each block, there were equal numbers of trials for each load and match/no-match response type, the order of which was randomized within block. The total testing time was approximately 17 minutes, including practice.

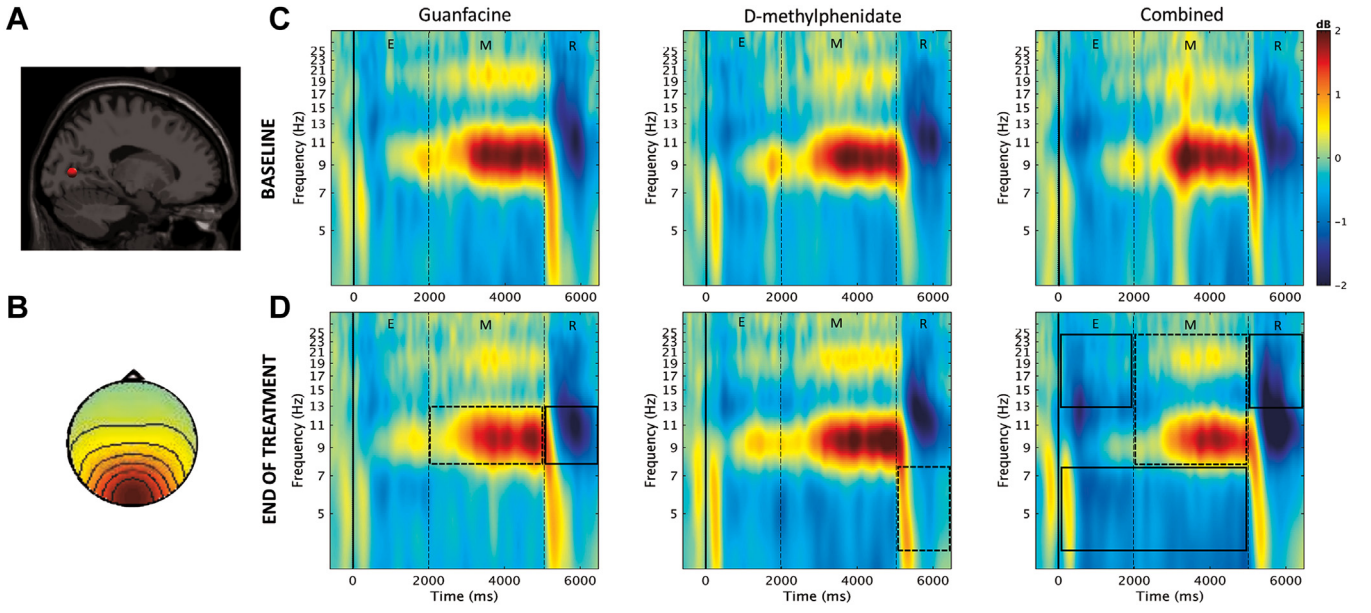
EEG Recordings and Analysis

EEG recordings were collected during the spatial WM task using a 40-Ag/AgCl electrode cap (extended 10/20 configuration) (Electro-Cap International, Inc., Eaton, Ohio). Electrode impedances were kept below 10 kOhms, and EEG signal was recorded using MANSCAN hardware and software (SAM Technology, Inc., San Francisco, California) at 256 Hz with linked-ears reference. Eye movements were monitored by electrodes placed on the outer canthus of each eye and above the eye. Physical electrode locations were recorded by measuring the pairwise distances between electrodes and landmarks (preauricular points and nasion) using Fowler calipers and transformed to three-dimensional spherical coordinates.

EEG processing was performed using EEGLAB[42] and custom MATLAB scripts (The Mathworks, Inc., Natick, Massachusetts), following the approach in previous publications on the baseline data of this sample[23,26] (Supplement 2, available online). Briefly, the EEG data from correct trials were filtered using a high-pass filter (>1 Hz) and inspected for noisy electrodes (excluded from further analysis). Sections of gross movements and muscle artifact were rejected if signal power in that epoch exceeded the 85th percentile for >60% of the channels. Each participant's data were then decomposed into source signals by independent component (IC) analysis[43] (extended infomax algorithm). Each IC time course is thought to reflect the activity of a putative cortical source generator. After removing artifactual ICs, we localized ICs corresponding to brain sources within the cortex by fitting single-equivalent current dipole source models and gathered them into functionally common source clusters across participants using k-means clustering.[23,25] IC activities were analyzed in lieu of electrode data, as they show better spatial resolution, higher signal-to-noise ratio, higher reliability, and stronger associations with clinical phenotypes.[5,13,23] IC time courses were segmented into epochs time-locked to the encoding stimulus, from −1.2 to 6.5 seconds. Clusters corresponding to midoccipital and midfrontal sources were included in analyses, as they were sensitive to differences between children with ADHD and controls at baseline in this sample[23,26] and reflect prominent cortical sources related to the frontoparietal network.[28] Montreal Neurological Institute[44] coordinates were used to identify the anatomical locations for both cluster centroids.

Stimulus-related modulations of power were computed from ICs in these midoccipital and midfrontal clusters with the event-related spectral perturbation index by dividing power for each frequency and time point by the prefixation baseline period (−1.2 to −0.6 seconds) and log-transforming it (10log10) to decibel units. 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). Averaging all event-related spectral perturbations across trials produced a time-

FIGURE 1 Occipital Power Modulations by Treatment Group at Baseline and End of Treatment



Note: *Event-related spectral power was measured from a cortical source localized in the primary visual cortex (V1, Brodmann area 17) (A) with midoccipital topography (B). Time-frequency modulations during the encoding (E), maintenance (M), and retrieval (R) task phases are shown at baseline (C) and end of treatment (D) by medication group. Rectangles with solid line depict measures that showed treatment-specific time by medication interactions, whereas boxes with dashed line depict measures that showed significant post hoc treatment-specific effects following main time effects. Please note color figures are available online.*

frequency representation in decibel units of event-related power increases (in red) and decreases (in blue) in the spectral power at a given frequency and latency with respect to prestimulus activity (Figure 1; Figure S2, available online).

Power modulations, especially event-related decreases (ie, reductions in power on stimulus presentation),[23,26,32] during encoding reflect attentional processes to inhibit irrelevant information and support coordinated activity between visual and memory storage systems.[23,26,28] In this context, stronger decreases (ie, lower power) are associated with greater allocation of cognitive resources, resulting in better task performance,[23,45] and are typically observed in individuals without ADHD.[23,26,32] Power modulations during maintenance are interpreted as processes to facilitate WM storage operations.[25,26,33] Power modulations during retrieval are consistent with joint attentional allocation and motor response processes.[26,32,33]

Statistical Analyses

Random-intercept linear mixed models (ie, multilevel repeated measures regressions) tested for effects of medication, WM load, time, and their interaction (medication by load by time) as well as age as a covariate of no interest on each EEG and task performance measure. When the 3-way interaction was not statistically significant, indicating that treatment effects did not vary across groups as a function of load, analyses were run across loads, with the primary effects of interest being the main effect of time and medication by time interactions. A significant time effect indicates an effect across medication groups, while a significant medication by time interaction suggests differential time effects by treatment. Post hoc tests examined within-group change between pre- and posttreatment and compared the degree of change between groups. 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 and will require replication. Standardized β coefficients are also reported to provide an indication of effect size. Finally, to understand the functional relationships of the EEG changes, we examined the association between treatment-related change and end-of-treatment measures of EEG, ADHD severity, and WM accuracy using only the EEG metrics sensitive to effects of treatment. Pearson partial correlations controlling for age were run between EEG measures, ADHD-RS-IV scores, and WM accuracy at end point and on change from baseline to end point (week 8 – baseline scores) in these measures. All analyses were run in Stata 14 (StataCorp LLC, College Station, Texas).

RESULTS

Participants' Characteristics

Of the 207 randomized participants (Table 1), 182 completed the 8-week trial.[20] Of these, 172 participants (60

TABLE 1 Sample Characteristics by Treatment Group

	GUAN (n = 68)		DMPH (n = 69)		COMB (n = 70)			
	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	F/χ^{2a}	p
Age, y	10.1	(2.1)	10.1	(2.0)	9.9	(2.2)	0.11	.89
Sex, male	45	(66.2)	46	(66.7)	51	(72.9)	1.67	.43
Race							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	16	(23.5)	10	(14.5)	18	(25.6)	1.50	.47
Full Scale IQ	102.6	(14.2)	101.5	(13.3)	102.9	(13.0)	0.10	.90
ADHD subtype							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-IV baseline	36.8	(9.1)	35.6	(8.1)	35.6	(9.8)	0.37	.69
ADHD-RS-IV week 8	18.7	(11.2)	20.4	(8.1)	17.9	(9.8)	0.97	.38

Note: ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-IV = ADHD Rating Scale IV total score; COMB = combined treatment; DMPH = d-methylphenidate; GUAN = guanfacine.

[a]*F statistics from analysis of variance are reported for continuous measures (age, Full Scale IQ, ADHD-RS scores); χ^2 from χ^2 tests are reported for the remaining categorical measures.*

COMB, 56 GUAN, 56 DMPH) completed the spatial WM task at baseline and week 8 and were included in this study (Tables S1, S2, available online). Participants with extremely noisy data owing to movement and other artifacts were excluded from EEG analyses, leaving 145 participants (80% of those who completed the trial) with complete EEG data both at baseline and at week 8, of which 134 and 125 had ICs in the midoccipital and midfrontal clusters at both time points, respectively. Participants who completed the 3 treatments showed no significant differences on baseline demographic characteristics, IQ, ADHD severity, EEG, and performance measures used in this study (Table S2, available online).

Treatment Effect on EEG and Performance Measures

No measure showed a significant 3-way interaction between treatment group, time, and load (all $p > .05$), indicating that treatment effects did not significantly vary across groups as a function of load. Thus, all analyses were run across load.

Task Performance. Main time effects emerged for all task performance measures, with accuracy and RTV further showing significant medication by time interactions (Table 2). Reaction time and RTV significantly improved with all treatments (reaction time: β between -0.52 and -0.51, $p < .01$; RTV: β between -0.74 and -0.32, $p < .01$) (Figure 2A; Table S3, available online). Accuracy significantly improved with COMB ($\beta = 0.39$, $p < .01$), while it significantly worsened with GUAN ($\beta = -0.20$, $p < .01$) and did not change with DMPH ($\beta = 0.09$, $p = .23$). The COMB and DMPH effects on accuracy and RTV were significantly greater than the GUAN effect, and the COMB effect on accuracy was also greater than the DMPH effect (Figure 2A; Table S3, available online).

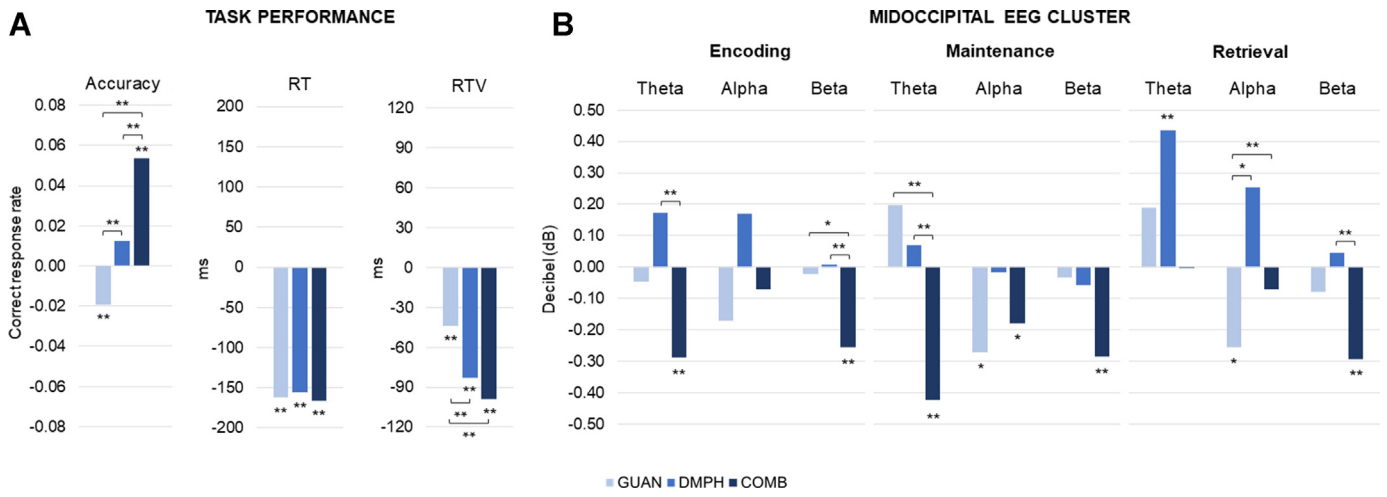
Midoccipital EEG Cluster. The cluster centroid was localized to the primary visual cortex (Brodmann area 17) (Figure 1). A main effect of time emerged at trend level ($p < .05$) for beta during encoding, alpha and beta during maintenance, and theta and beta during retrieval (Table 2), suggesting that power modulations with medication, regardless of type, were generally in the direction of lower power, either stronger power decrease (ie, beta) or attenuated power increase (ie, alpha). Significant ($p \leq .01$) medication by time interactions emerged for theta power during encoding and maintenance and for alpha during retrieval, with additional trend-level interaction effects for beta during encoding and retrieval (Table 2). Post hoc tests (Figure 2B; Table S3, available online) revealed that the majority of group-level effects were driven primarily by the COMB group, which showed significant decreases in theta power during encoding ($\beta = -0.39$, $p < .01$) and maintenance ($\beta = -0.47$, $p < .01$) and in beta power across task phases (β between -0.42 and -0.36, $p < .01$), as opposed to a lack of significant effects in these measures with DMPH and GUAN (Table S1, available online). Trend-level power decreases in alpha power during later phases of the task (maintenance and retrieval) were the primary effect of GUAN ($\beta = -0.19$, $p = .05$ and $\beta = -0.22$, $p = .03$, respectively). The exception to the broad treatment-related power decreases was a significant theta power increase during retrieval in the DMPH group, which was driven by a burst of theta power with onset of the probe ($\beta = 0.42$, $p < .01$) (Figures 1, 2B).

TABLE 2 Main Effects of Time and Medication by Time Interaction Effects for All Electroencephalography and Performance Measures

	Time		Medication by time	
	F	p	F	p
Midoccipital cluster				
Encoding theta	1.68	.20	4.55	.01**
Encoding alpha	1.67	.20	2.78	.06
Encoding beta	5.58	.02*	3.84	.02*
Maintenance theta	1.07	.30	6.60	< .01**
Maintenance alpha	4.58	.03*	1.93	.15
Maintenance beta	5.79	.02*	2.74	.07
Retrieval theta	5.46	.02*	2.88	.06
Retrieval alpha	1.61	.21	4.58	.01**
Retrieval beta	5.84	.02*	4.10	.02*
Midfrontal cluster				
Encoding theta	1.29	.26	0.62	.54
Encoding alpha	<0.01	.95	1.13	.32
Encoding beta	0.42	.52	< 0.01	1.00
Maintenance theta	4.35	.04*	0.41	.66
Maintenance alpha	5.98	.02*	0.25	.78
Maintenance beta	0.13	.72	0.53	.59
Retrieval theta	< 0.01	.95	0.28	.76
Retrieval alpha	0.51	.47	2.21	.11
Retrieval beta	1.53	.22	0.98	.38
Task performance				
Accuracy	4.29	.04*	13.50	< .01**
RT	106.00	< .01**	< 0.01	1.00
RTV	143.00	< .01**	7.12	< .01**

Note: All models controlled for age. RT = mean reaction time; RTV = reaction time variability.
*$p \leq .05$; **$p \leq .01$.

FIGURE 2 Change in Performance Measures and Electroencephalography (EEG) Measures From the Midoccipital Cluster Between Baseline and End of Treatment



Note: *Bars represent change from baseline to end of treatment in performance measures (A) and event-related EEG power (B) in each treatment group. Asterisks over horizontal square brackets represent differences between groups for measures showing significant medication by time interactions. Asterisks over individual bars represent within-group effects for measures showing significant main time effects. COMB = combined treatment; DMPH = d-methylphenidate; GUAN = guanfacine; RT = mean reaction time; RTV = reaction time variability. *p ≤. 05; **p ≤ .01. Please note color figures are available online.*

Midfrontal EEG Cluster. This cluster centroid was localized to the dorsal anterior cingulate cortex (Brodmann area 32) (Figure S2, available online). Theta and alpha power during maintenance showed trend-level main effects of time (Table 2), potentially reflecting decreased power between baseline and week 8 across all medication groups (Figure S2, available online). Although there were no significant medication by time interaction effects (Table 2), the DMPH group showed a trend-level reduction in theta power ($\beta = -0.27$, $p = .05$) that was not evident in the other groups (Table S1, Figure S2, available online).

Dimensional Associations Between Treatment-Related Change in EEG, Clinical, and Cognitive Measures

Several small to medium-size correlations indicated associations between the EEG measures sensitive to medication effects and ADHD-RS-IV at the end of treatment (week 8) or between their treatment-related degrees of change from baseline to week 8 (Table 3). ADHD improvements were associated with midoccipital theta and alpha during retrieval, as both lower ADHD-RS-IV scores and greater treatment-related symptom reductions correlated with lower week 8 power and greater power reductions in these EEG measures. Lower ADHD-RS-IV at week 8 and greater ADHD-RS-IV reductions were further associated, respectively, with lower power (encoding) and greater power reductions (maintenance) of midoccipital theta.

Higher WM accuracy at week 8 was significantly associated with lower midoccipital power during encoding (theta, beta power), maintenance (theta power), and retrieval (theta, beta power) in the midoccipital cluster (Table 3). Additionally, treatment-related increases in midfrontal theta power during maintenance correlated with improvements in WM accuracy. There were nonsignificant correlations between ADHD severity and WM accuracy in treatment-related change ($r = 0.07$, $p = .40$) and at week 8 ($r = 0.01$, $p = .95$).

DISCUSSION

This is the first study testing the comparative effects of an α-2A agonist (GUAN), a psychostimulant (DMPH), and their combination (COMB) on cortical source–resolved neural oscillations and cognitive markers of spatial WM in children with ADHD. We found widespread effects of COMB on event-related power modulations in EEG sources localized within the midoccipital visual cortex and previously implicated in visuo-attention impairments in children with ADHD[23,26,46] as well as on cognitive performance. Monotherapies produced more limited effects on the investigated brain activity measures. DMPH significantly enhanced theta activity from midoccipital sources during retrieval and showed a trend-level reduction on theta from a midfrontal source localized to the dorsal anterior

TABLE 3 Association of Electroencephalography (EEG) Measures With Attention-Deficit/Hyperactivity Disorder (ADHD) Symptom Scores and Working Memory (WM) Accuracy at the End of Treatment and of Treatment-Related Change in EEG Measures With Treatment-Related Change in ADHD Symptom Scores and WM Accuracy

	End of treatment (week 8)		Treatment change	
	ADHD-RS-IV ↓	WM accuracy ↑	ADHD-RS-IV ↓	WM accuracy ↑
Midoccipital cluster				
Encoding theta ↓	0.18*	−0.22*	0.15	0.13
Encoding beta ↓	0.09	−0.29*	0.02	0.13
Maintenance theta ↓	0.15	−0.17*	0.18*	0.09
Maintenance alpha ↓	−0.05	−0.06	0.01	−0.03
Maintenance beta ↓	0.00	−0.11	0.03	0.05
Retrieval theta ↑	0.25*	−0.17*	0.19*	0.08
Retrieval alpha ↓	0.20*	−0.11	0.19*	−0.17
Retrieval beta ↓	0.13	−0.20*	0.07	0.02
Midfrontal cluster				
Maintenance theta ↓	0.10	0.07	−0.13	−0.24*
Maintenance alpha ↓	0.02	0.07	−0.04	−0.18

Note: Partial correlations (controlling for age) were run between EEG measures showing treatment effects (Table 2), ADHD severity, and task accuracy at the end of treatment (left side) and across treatment-related changes (right side). All change scores were calculated as week 8 − baseline. The direction of a treatment effect on ADHD-RS-IV, WM accuracy, and EEG measures (Table S3, available online) is indicated with arrows. As more negative change scores in both ADHD-RS-IV and most EEG power measures indicate improvements with treatment, a positive correlation between these change scores indicates that improvement in ADHD severity and EEG power are related to one another. ADHD-RS-IV = ADHD Rating Scale–IV total score; WM = working memory.

*$^{*}p < .05$.

cingulate cortex during maintenance. GUAN showed trend-level reductions on midoccipital alpha during maintenance and retrieval, but also significantly decreased WM accuracy. At the end of treatment, most of the midoccipital EEG measures that were sensitive to medication effects, seen especially in the COMB group, were associated with lower ADHD severity and/or better WM accuracy. These results point to an EEG profile reflecting changes in midoccipital brain activity that, in the future, may serve as a promising biomarker to monitor improvements in ADHD severity, cognitive performance, and brain networks supporting visual attention and WM in children with ADHD.

Our results extend previous findings in this sample indicating greater clinical effects of COMB relative to monotherapies, despite significant clinical improvements across treatments.[20] The broad positive effects of COMB on brain activity from midoccipital visual regions emerged across all task phases, starting during encoding, a key phase of this task that enables successful memory storage and retrieval.[23,26] Occipital event-related decreases in theta, alpha, and beta power have been suggested to reflect suppression of visual regions in support of coordinated activity between visual and cognitive systems (eg, frontoparietal network) implicated in optimal WM storage and performance.[28-30,47] Modulations in both theta and beta power have been proposed as a top-down mechanism to preserve objects in WM[25,48] and facilitate interaction between frontoposterior regions.[49] Conversely, higher power (ie, attenuated power decrease), especially during stimulus encoding, characterizes individuals with ADHD, correlates with attentional and WM deficits,[23,26,46] and has been linked with hypoconnectivity between the frontoparietal network and visual cortex in concurrent EEG and functional magnetic resonance imaging studies.[28] This pattern suggests that COMB ameliorates ADHD-related impairments in midoccipital activity implicated in the visual attention network. The additional COMB effect on midoccipital alpha during maintenance is further consistent with this pattern, given previous evidence of higher power in children with ADHD relative to controls.[23,26] As this finding was interpreted as compensatory activity to retain the weak memory trace during encoding,[23,26] a COMB-related reduction of alpha power during maintenance coupled with improvements in encoding might reflect that this compensatory process was no longer needed. Of note, COMB showed nonsignificant effects on midfrontal activity, despite the known role of midfrontal power (especially theta) in WM.[25,30] In this sample at baseline, the ADHD-related impairments in midfrontal theta power identified in a portion of participants[23] did not replicate in the rest of the sample.[26] This suggests that midfrontal power in ADHD may be more heterogeneous than midoccipital power

and less robustly associated with the disorder. Midoccipital activity may thus be a more promising biomarker to monitor treatment effects.

In contrast to the broad effects of COMB, DMPH and GUAN had more limited effects on brain oscillations and did not improve WM accuracy. This indicates that the combined effects of DMPH and GUAN are not simply additive. Rather, the more pronounced effects of COMB may result from a complex interplay between psychostimulant and α-2A agonism. This is consistent with treatment models emphasizing the importance of optimized dopaminergic and noradrenergic effects in ADHD therapy[6] and with evidence that both catecholaminergic systems are implicated in WM.[6,8,20-22] The potentially unexpected lack of DMPH effects on WM accuracy, consistent with previous findings using this task,[50] may be explained by the direction of the significant DMPH effects on midoccipital theta during retrieval. Previous evidence showed higher theta power from occipital visual regions in children with ADHD relative to controls.[27] The increase in midoccipital theta power with DMPH may thus indicate a suboptimal effect of this drug, which warrants further investigation in future studies. Similarly, GUAN produced limited trend-level effects on brain oscillatory measures (alpha power during maintenance and retrieval) and a significant worsening of WM accuracy. As GUAN did not show effects during encoding, in contrast to COMB, the reduction of alpha power during maintenance, previously interpreted as a compensatory mechanism,[23,26] might suggest detrimental effects. This possible explanation is in keeping with the worsening in WM accuracy and the sedative effects commonly observed in children with ADHD treated with GUAN.[20] These negative effects of GUAN on WM, despite its positive effects on ADHD severity,[20] may be explained by the lack of association between treatment-related changes in ADHD severity and WM, suggesting a possible dissociation of treatment effects on clinical and WM profiles. Taken together, these findings suggest that GUAN may be more indicated for children with ADHD not showing marked executive dysfunction. Future research should confirm this hypothesis in larger-scale studies of GUAN treatment for ADHD.

These medication-specific effects are supported by our dimensional analyses, broadly showing that treatment-related midoccipital power decreases correlated with behavioral improvements. Specifically, the association of lower ADHD severity with lower midoccipital theta power during encoding and maintenance is consistent with the positive COMB-related effects on these measures. The majority of midoccipital power measures sensitive to COMB effects were also dimensionally associated with higher WM accuracy at week 8, consistent with strong COMB effects on WM. Furthermore, ADHD symptom improvement was dimensionally associated with greater alpha decrease during retrieval, consistent with the trend-level effects of GUAN on this EEG measure. A similar dimensional association during retrieval also emerged for theta power, as lower power correlated with lower ADHD severity and higher WM accuracy at week 8. Greater treatment-related power reductions also correlated with greater ADHD improvement. However, these associations contrast with the significant DMPH-related increase in midoccipital theta power during retrieval. Together, these results suggest that this DMPH-related effect on theta power was not reflected in clinical and cognitive improvements, supporting our interpretation that this finding may represent a suboptimal effect of DMPH.

Although this is the first study to report different effects of GUAN, DMPH, and COMB on brain activity during a cognitive task, the following limitations should be considered. First, the 8-week period examined in this study does not inform on long-term effects. Future studies are needed to investigate whether these differential treatment effects are maintained over a longer period. Second, common to most medication trials, this sample comprises a selected group of children with few psychiatric comorbidities; thus, results may not generalize to more heterogeneous populations of children with ADHD. Finally, as our a priori approach focused on EEG measures from midoccipital and midfrontal regions that have previously been associated with WM deficits in ADHD,[23,26,28] we did not investigate possible medication effects in other cortical regions. This may explain the limited effects of monotherapies on the investigated EEG measures, despite their effects on ADHD severity and other brain measures in previous studies.[14,16,20] Future studies should replicate these findings in larger independent samples and investigate effects on EEG activity from other cortical regions or on connectivity between cortical regions. Larger samples may also examine potential differences in treatment effects at different loads, which could not be tested in the current study owing to a lack of significant 3-way interactions between treatment group, time, and load.

In conclusion, our findings suggest that COMB treatment ameliorates atypical profiles of midoccipital brain oscillations that have been implicated in impaired visual attention and WM in children with ADHD. Improvements in these neural patterns over the course of treatment were associated with improved clinical and cognitive functioning, suggesting shared mechanisms of treatment effects at the neural and behavioral level. Conversely, the effects of both monotherapies were limited to fewer EEG power measures and did not yield improvements in WM accuracy. Taken together, the current findings point to different brain

mechanisms of action of DMPH, GUAN, and their combination, highlighting the role of midoccipital regions involved in top-down–controlled cognitive processes. Future studies should investigate the clinical utility of the identified midoccipital EEG profile to objectively monitor response to combined stimulant and nonstimulant treatment in children with ADHD.

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