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RESEARCH ARTICLE

Anterior prefrontal EEG theta activities indicate memory and executive functions in patients with epilepsy

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Abstract

Objective: Cognitive deficits are one of the most debilitating comorbidities in epilepsy and other neurodegenerative, neuropsychiatric, and neurodevelopmental brain disorders. Current diagnostic and therapeutic options are limited and lack objective measures of the underlying neural activities. In this study, electrophysiological biomarkers that reflect cognitive functions in clinically validated batteries were determined to aid diagnosis and treatment in specific brain regions.

Methods: We employed the Cambridge Neuropsychological Test Automated Battery (CANTAB) tasks to probe memory and executive functions in 86 patients with epilepsy undergoing clinical electroencephalography (EEG) monitoring. EEG electrode signals during performance of particular battery tasks were decomposed to identify specific frequency bands and cortical areas that differentiated patients with impaired, normal, and good standardized performance according to their age and gender.

Results: The anterior prefrontal cortical EEG power in the theta frequency band was consistently lower in patients with impaired memory and executive function performance (z-score < -1). This effect was evident in all four behavioral measures of executive, visual, spatial, and working memory functions and was confined to the cortical area of all four frontal pole electrodes (Nz, Fpz, Fp1, and Fp2).

Significance: Theta EEG power in the anterior prefrontal cortex provides simple, accessible, and objective electrophysiological measure of memory and executive functions in epilepsy. Our results suggest a feasible clinical biomarker for diagnosis, monitoring, and treatment of cognitive deficits with emerging targeted neuromodulation approaches.

KEYWORDS
cognition, neural oscillations, neurofeedback, neurophysiology, neuropsychology

1 | INTRODUCTION

Cognitive functions encompass a broad range of domains, including memory, perception, learning, attention, language abilities, problem solving, and decision-making, which are impaired in a range of neurological and psychiatric diseases. Such impairments affect general performance and quality of life.[1,2] Hence, individuals with brain disorders often seek treatments to address cognitive impairments as much as other primary disease symptoms, such as seizures, in the case of epilepsy.[3] Limited treatment options for cognitive deficits, such as systemic drugs, have driven the development of more focused and innovative interventions for therapy, targeting specific brain regions and neural activities. Multiple neuroimaging, electrophysiological, and behavioral methods can be used to target new therapy, among which electroencephalography (EEG) offers non-invasive localization of neural activities involved in cognitive functions.

As the demand for safe and effective neuromodulation therapy rises, there is an increasing need for objective functional metrics to assess cognitive and other brain functions. Such physiological and behavioral measures would play a fundamental role in diagnosing and treating cognitive deficits.[4,5] Specific frequency ranges within the EEG spectrum can serve as biomarkers of cognitive abilities. For instance, enhancing resting spectral power in the upper alpha frequency range through neurofeedback training was associated with improved cognitive performance.[6] Other studies have associated specific EEG features, such as spectral power in the delta, theta, and alpha frequency range, with particular cognitive functions.[7–9] Moreover, neural activities in theta and gamma EEG frequencies have been proposed to play critical roles in various aspects of memory and executive functions,[10–16] suggesting their potential use as biomarkers for therapeutic interventions. Despite these advancements, biomarker integration into the clinical practice of diagnosing and treating cognitive impairments remains limited[17] due to inconsistent EEG frequency bands and brain regions engaged in various—often clinically unvalidated—tasks.

Previous studies have shown that different cognitive tasks induced EEG activities in multiple frequency bands and cortical regions,[18–20] indicating the demand for a more comprehensive approach to determine consistent EEG biomarker in the EEG frequency spectrum and anatomic space. An ideal biomarker would target a given neuromodulation therapy or diagnosis in one frequency band and cortical region for a spectrum of cognitive functions.

Here, we conducted EEG recordings during performance of a battery of tasks probing memory and executive functions. Given the results of our previous study with intracranial brain recordings,[21,22] we hypothesized that theta activities in the anterior prefrontal cortical regions will reflect patient performance in the tasks. Theta frequency activities[7,11,23–25] in frontal cortical regions[23–25] have been shown to play essential roles in memory and executive functions, but only during specific tasks. Our goal was to identify a consistent EEG activity across multiple frequency bands and cortical regions that can discriminate between patients with epilepsy with impaired and healthy cognitive performance.

Key points

- Clinically validated battery of touch screen tasks effectively identified epilepsy patients with impaired memory and executive functions.
- Patients with memory and executive function deficits showed significantly decreased electroencephalography (EEG) theta power in the anterior prefrontal cortex.
- Theta power from all four frontal pole EEG electrodes correlated with the behavioral measures of memory and executive functions.
- Anterior prefrontal theta power provides a feasible electrophysiological biomarker for the diagnosis and treatment of cognitive deficits in epilepsy and potentially other brain disorders.

2 | MATERIALS AND METHODS

2.1 | Participants

Eighty-six epilepsy patients with confirmed electrographic seizures in the epilepsy monitoring unit (EMU) at Mayo Clinic were recruited for this study. All participants were recruited and tested under a standardized protocol to ensure consistent experimental conditions throughout their EMU stay. Patients were enrolled in the study within 24 h from their first clinically confirmed electrographic seizure recorded during the monitoring. The cohort consisted of 45 male and 41 female participants with an average age of 36 years (±12.8). These patients experienced their first seizure on average at the age of 21.4 years (±15.6), with a mean epilepsy duration of 14 years (±12.3). Participants reported ~476 mean seizures annually. During an EEG and video examination in the EMU, the patients were asked to complete a series of Cambridge Neuropsychological Test Automated Battery (CANTAB) tasks.[26] The data were collected at the Mayo Clinic (Rochester, MN, USA). The research protocol was approved by the respective

institutional review board (IRB), and written informed consent was obtained from each participant.

2.2 | Experimental paradigm

The data consists of EEG signals and behavioral performance on the CANTAB battery of selected cognitive tasks. We selected CANTAB tasks that assess three primary cognitive domains: attention, memory, and executive function. The attention domain probed by CANTAB involves the capacity to focus selectively on pertinent information while disregarding irrelevant stimuli. Memory tasks probed the patients' capacity to hold information during short and long delays. Executive functions assessed strategic problem-solving and decision-making. The three selected battery tasks that probed these cognitive domains are summarized as follows and visualized in Figure 1A with the average task duration under each schematic (mean ± standard deviation [SD]).

Delayed match to sample (*DMS*): The participants were presented with a complex, abstract, non-verbal visual pattern (sample), followed by a brief delay, and then the presentation of four similar patterns to choose (test). The task required the participants to identify and touch the test pattern that exactly matched the sample. Occasionally the sample and choice patterns were presented simultaneously, whereas in all other trials, a delay of 0, 4, or 12 s was applied before the four choices appeared. The first trial type assessed visual matching ability, whereas the others tested short-term visual recognition memory for patterns that were difficult to describe verbally. Subject performance in this task was quantified as percentage of correct responses, defined as "visual memory" performance.

Spatial span (*SSP*): White squares were displayed on a touchscreen, changing color in a variable order sequence (sample phase). Following the presentation of the entire sequence, the patients were required to touch the boxes in the exact order in which they changed their color in the sample phase (test phase). The sequence begins with two boxes and gradually increases to nine

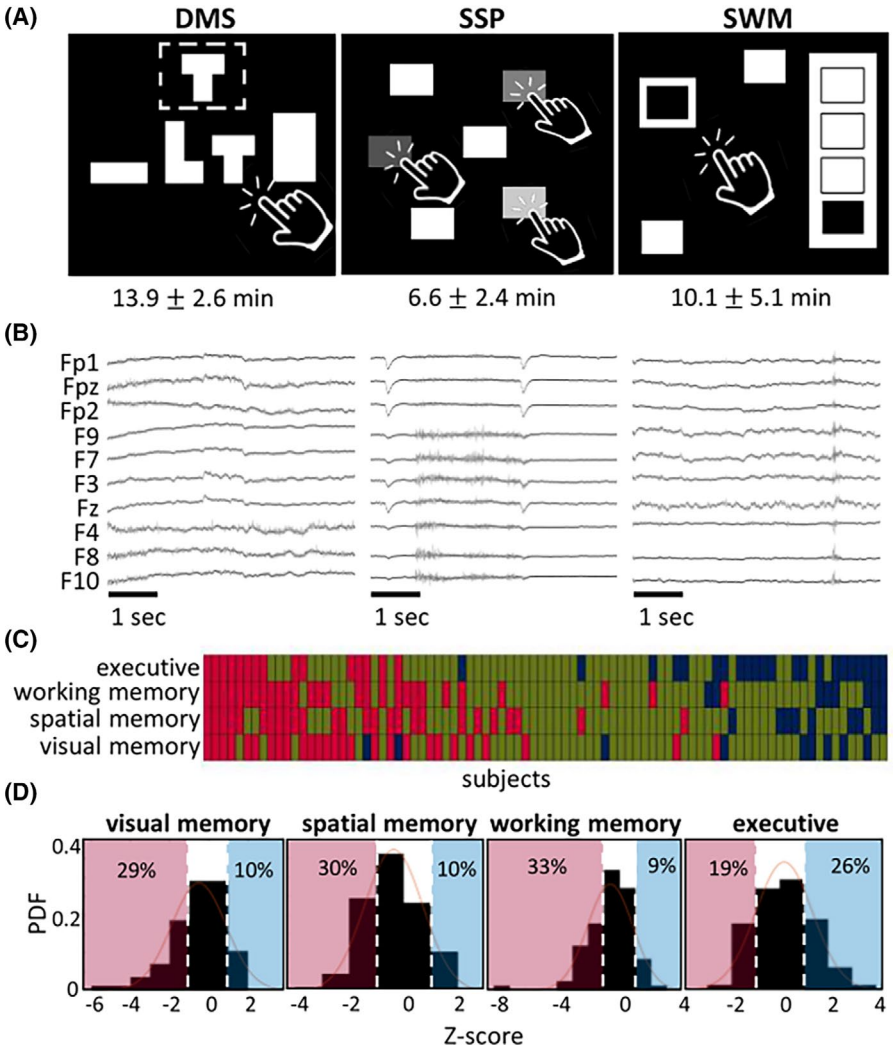

FIGURE 1 EEG recordings during performance of CANTAB tasks were used to identify epilepsy patients with poor, normal, and good memory and executive functions. (A) Selected CANTAB tasks were performed on a touch-screen tablet with a range of time frames during video-EEG monitoring. Under each task's schematic, the average time taken to complete the task among all participants is provided. (B) Example signals recorded from frontal EEG electrodes were taken from entire segments of performing a given task. (C) Participants were arranged in ascending order from the poorest to the best performance across the four measures (poor performers in red, normal performers in green, and good performers in blue) based on their overall scores. (D) Age- and gender-normalized behavioral scores of task performance identified patients with good (blue) and poor (red) memory and executive functions. CANTAB, Cambridge Neuropsychological Test Automated Battery; EEG, electroencephalography.

as the test progresses, with variations in both sequence order and color. Once a sample sequence is successfully replicated in the test phase, the patient advances to the next stage with an additional box in the sequence. In the case of a mistake in the test, the patient has two more attempts at that stage until the task is finished with a score of 1–9 corresponding to the maximum number of boxes in a sequence remembered. This test assesses visuospatial working memory capacity. The final score of the longest sequence recalled was defined as the "spatial memory" performance.

Spatial working memory (*SWM*): The participants were presented with squares randomly located on the screen. The objective was to find which one of them contained a hidden colored "token" by pressing a square and then collecting the found tokens in a column on the right hand side of the screen. The difficulty level of the test gradually increased from three to nine squares. The colors and positions of the boxes on the screen changed in each trial to discourage the use of the same search strategy. However, using a consistent search strategy, for example, from the left to the right side or from top to bottom, to avoid visiting the same box twice, was assessed as a measure of executive planning. This task assesses both the retention and capacity to hold visuospatial information, placing notable demands on executive functions, and providing a metric for both strategy and working memory errors. Two measures were used to evaluate the participants' performance. The former tracked the number of times a participant reopens a box where the token was previously found, to indicate "working memory" performance. The second tracked the search strategy, as explained above, to indicate "executive" task performance.

Moreover, each subject started with completing a control motor screening task (MOT), which tested basic sensorimotor performance by requiring subjects to touch a cross appearing at random locations on the screen. This task, included in the CANTAB and administered at the start of each session, did not engage memory or executive functions, while maintaining a baseline level of attention.

2.3 | EEG data

Data were acquired using the Quantum system (Natus, Middleton WI, USA) at the Mayo Clinic (Rochester, MN, USA). The system utilized a 31-channel setup following the 10-20 electrode placement system. The reference electrode was placed close to the "CPz" lead, and a referential montage was used in all cases. The data were sampled at a rate of 256 Hz, and a hardware-based high-pass filter with a cutoff frequency of 0.1 Hz was applied to the data (see Figure 1B for an illustrative 5-s segment of the signal recorded from frontal EEG electrodes). Data were recorded continuously during the entire experiment but only the EEG epochs related to the tasks were extracted, and periods around the battery performance were removed. Some patients had additional electrode leads recording electrocardiography (ECG) and electrooculography (EOG) signals; these electrodes were not included in the analysis to maintain a standardized process.

2.4 | Behavioral analysis

Each task of the battery was performed once by each subject, and four behavioral measures were computed (visual memory, spatial memory, working memory, and executive function), and expressed as *z*-scores normalized to the age and gender (see Table S1 for a summary of the patients' scores). This allowed us to group each task score into "good," "normal," or "poor" performance based on the z-score distribution (good: $z\text{-score} > +1$; normal: $-1 < z\text{-score} < +1$; poor: $z\text{-score} < -1$). Since each task was evaluated independently; a subject could be labeled as a good or poor performer in different tasks (Figure 1C). The number of patients ($n = 86$) in the study was sufficient to ensure more than eight patients in any group (poor, normal, and good) to power the statistical comparisons. Figure 1D shows the probability density function (PDF) of the *z*-scores for all four behavioral measures.

2.5 | EEG analysis

EEG signal processing was conducted using the MATLAB academic version R2022b software package (MathWorks Inc.). The following pre-processing was applied to the entire signal using the EEGLAB toolbox.[27] The first step involved applying a band-pass finite impulse response (FIR) filter within the frequency range of 1–57 Hz to eliminate power-line noise (at 60 Hz) and non-neural signal artifacts. Independent component analysis (ICA) was employed to remove physiological artifacts, such as eye blinks and heartbeats, using both an automated approach[28] and visual examination of the components.

Subsequently, the signals were segmented with the complete duration of each task considered, and the frequency domain features of the signal were extracted by computing the spectral power within seven distinct frequency bands: δ (1–4 Hz), θ (4–8 Hz), α (8–12 Hz), β_1 (12–20 Hz), β_2 (20–30 Hz), γ_1 (30–40 Hz), and γ_2 (40–55 Hz). The signal power acquired from the 31 electrodes was estimated across seven frequency bands and then normalized

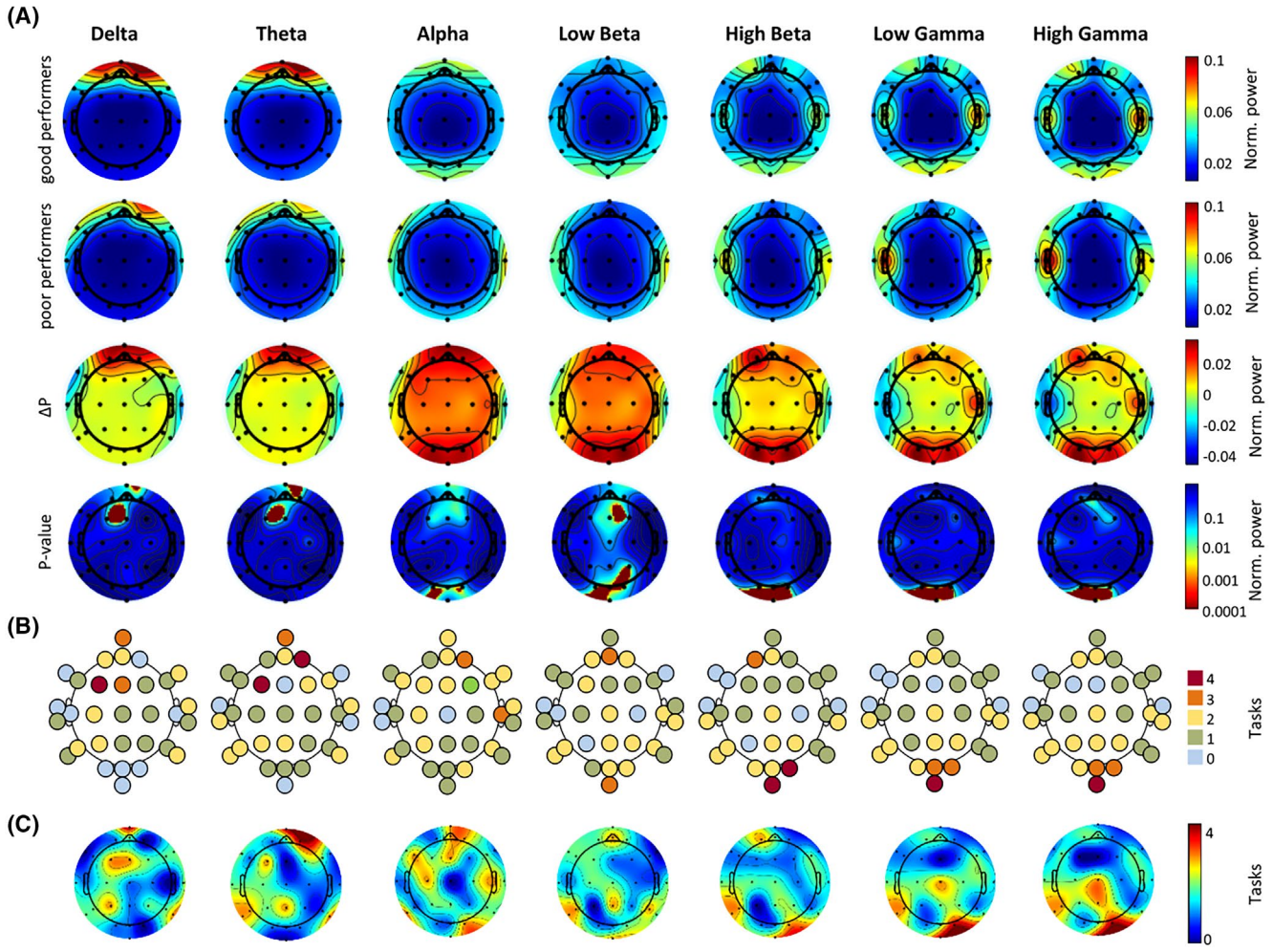

FIGURE 2 The increased spectral power of low-frequency frontal and high-frequency occipital EEG activities differentiates between patients with good and poor task performance. (A) Patients with a good visual memory task performance (see Figure S1 for the other measures) showed significantly greater power in the anterior low-frequency bands and posterior high-frequency bands. (B) EEG electrodes with significantly greater low- and high-frequency powers in up to four memory and executive performance measures were localized in the anterior prefrontal and posterior occipital cortical areas. (C) Electrodes with significant power-in-band differences (ANOVA, $p \leq .05$) in up to four tasks, as displayed in "b", revealed the low- and high-frequency "hotspots" in the corresponding anterior prefrontal and the occipital cortical areas on the interpolated heatmaps. ANOVA, analysis of variance; EEG, electroencephalography.

using an ℓ_1-normalization.[29] Having the normalized power for all patients, the final feature was determined as the average spectral power for a given behavioral measure, which can be seen as a grand average of the spectral power across subjects (Figure 2A, Figure S1).

In addition, we derived the difference in spectral power (ΔP), which serves as a metric of neural processing, defined as the difference in the magnitude of activation in a specific brain region between the good and poor patient performance from the task measure. This was calculated by subtracting the normalized signal power in the poor condition from that in the good condition. ΔP was first computed at the resolution of each electrode within specific frequency bands, as illustrated in Figure 3C, and then averaged among the electrodes within a particular cortical region, as shown in Figure 3D.

2.6 | Statistics

All statistical tests were conducted using the MATLAB academic version R2022b software (MathWorks Inc.). A two-way analysis of variance (ANOVA) was conducted to compare spectral features across all good and poor performers in each task, examining the effects of performance type (1 df) and channel location (30 df) on the normalized signal power. One-way and two-tailed ANOVA with Tukey–Kramer post hoc testing of median and confidence intervals (CIs) was employed to test differences in variance across frequency bands and brain regions and to identify significantly different groups. The spectral features in specific brain regions and frequency bands during the performance of a given cognitive task were compared between groups of patients showing good and poor performance.

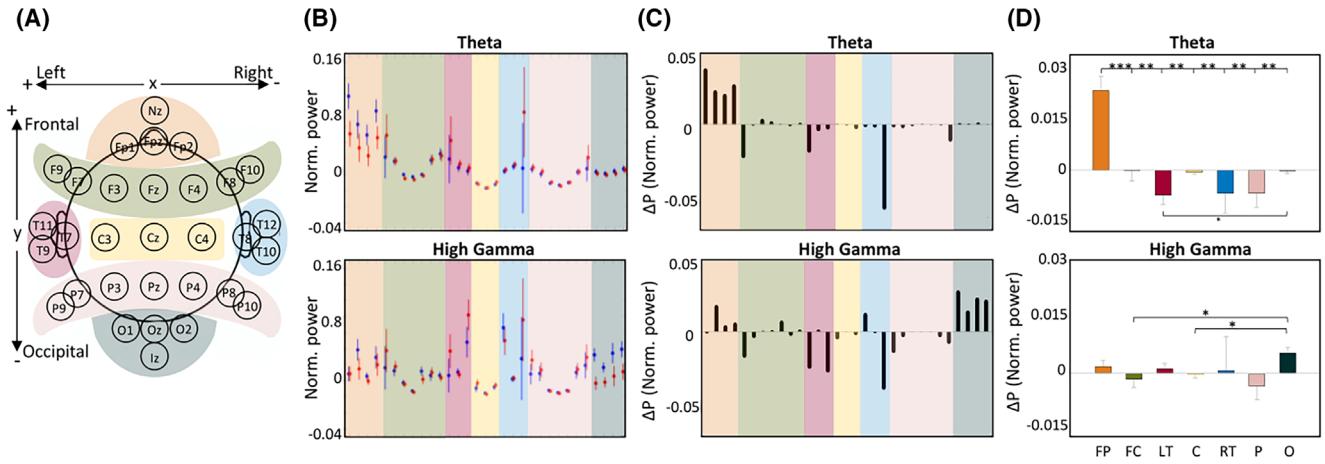

FIGURE 3 Anterior prefrontal EEG theta activities show the greatest spectral power and differences in poor and good memory and executive function performance. (A) EEG electrodes were anatomically grouped into seven color-coded cortical areas of interest in a normalized 2D Cartesian system, derived from spherical coordinates, with "Cz" marking the origin. (B) Average spectral power of the theta band activities in the anterior prefrontal cortex was greater than in any other area, including the gamma band activities in the occipital cortex (bars indicate 95% confidence interval). Notice that the theta power was greater both in case of the good (blue) and the poor (red) patient performance, which was higher than the background range of increasing power away from the "Cz" center of the 2D plane (see Figure S3 for the other three task measures). (C) Spectral power difference (ΔP) between the good and poor patient performance from the task measure plotted in (B) was consistently positive (good > poor) for all four anterior prefrontal electrodes in the theta band (upper panel) and all occipital electrodes in the gamma band (lower panel). Note: the anterior theta was consistent across all four task measures. (D) Mean Δ*p*-values from all the task measures reveal significantly greater anterior prefrontal theta power differences (Tukey–Kramer post hoc, error bars indicate SEM; * $p < .05$, ** $p < .01$, *** $p < .001$) than in any other area (top panel) with fewer significant differences in the gamma band (lower panel). 2D, two-dimensional; EEG, electroencephalography; SEM, standard error of the mean.

ANOVA was used to compare these groups using ΔP magnitude averaged for each cortical region, with a specific focus on the theta and high gamma frequency bands (Figure 3D). Finally, prefrontal theta power was analyzed across the three performance groups (good, normal, and poor) in each task using an analysis of variance (Figure 5C and Figure 5D).

3 | RESULTS

To identify the specific cortical areas and EEG frequency bands that indicate behavioral differences between good and poor performers we used the EEG data of 86 patients with epilepsy performing the CANTAB tasks with standardized behavioral measures of four cognitive domains: visual memory, spatial memory, working memory, and executive functions (Figure 1). Within each domain, patients were stratified into three groups (good, normal, and poor performers) normalized by age and gender according to the CANTAB database. Behavioral results effectively separated the good and poor performance groups (below and above 1 SD from the average) in each of the four domains tested. Most participants belonged to either the good performers or the poor performers group, with only 10% performing both well and poorly across any of the four behavioral measures (Figure 1C). There were consistently more patients with poor (29%–33%) than with good (9%–10%) memory performance (Figure 1D). Executive function performance was more evenly distributed, with 19% poor performers and 26% good performers (Figure 1D). These CANTAB results confirm the profile of cognitive impairments observed in epilepsy, which is focused on memory more than executive functions. A significant correlation was found between all these measures (Spearman, $r > .28$, $N = 86$, $p \leq .01$) and was particularly strong between the executive and working memory scores, as well as between working memory and spatial memory scores (Spearman, $r > .6$). Visual memory scores showed the weakest correlation with the other three measures, which likely include a stronger executive function component in both working and spatial memory functions (Table 1).

We compared spectral EEG power features to examine the effects of the performance group (good and poor; 1 *df*) and the channel location (31 standard scalp EEG leads; 30 *df*). Analysis of variance showed significant effects of the group, channel location, and their interaction across all frequency bands and in each task (ANOVA, *p*-value ≤ .01). The average spectral power in the seven EEG frequency bands was mapped across the neocortex (Figure 2). We found that the most prominent disparities between good and poor cognitive performers were localized in the frontal and occipital regions in the low- and high-frequency

TABLE 1 Summary of the correlation coefficients across all cognitive measures.

	Visual memory	Spatial memory	Working memory	Executive
Visual memory	1	.3773	.3013	.3269
Spatial memory	.3773	1	**.6093***	.4746
Working memory	.3013	**.6093***	1	**.6678***
Executive	.3269	.4746	**.6678***	1

Note: Values marked with asterisks indicate strong correlations ($r > .5$).

bands, respectively (Figure 2A, Figure S1). We identified the specific electrodes that contributed the most to these differences by assigning the number of behavioral task measures (from 0 to 4) for which a given electrode's power-in-band exhibited a significant difference (Figure 2B). Based on our grouping of EEG electrodes into anatomic regions (Figure 3A)—prefrontal [N, Fp], frontal [F], central [C], temporal [T], parietal [P], and occipital [O, I]—we found that prefrontal theta and occipital gamma spectral powers effectively distinguished between good and poor performance across most of the cognitive domains studied. The occipital gamma contribution explains the visual aspect of the CANTAB tasks performed, whereas the prefrontal theta activities point to the memory and executive functions engaged in the tasks. We focused our subsequent analyses on these two spectral activities. We also compared the EEG spectral estimates obtained during the MOT task between good and poor performers in the memory and executive function measures (Figure S2). The results indicate that some statistical differences between patients impaired in memory and executive functions can be detected even using a simple sensorimotor task. However, these differences were less consistent than those observed during the memory and executive function tasks.

The prefrontal theta power values stood out from the other areas, more than the occipital high-gamma activities (Figure 3B, Figure S2). There was a consistent pattern of gradually greater power on the lateral electrodes and lower power on the medial electrodes within each anatomic area (Figure 3B). This pattern shows that the lowest power is observed on the central electrodes and increases away from these reference electrode locations. The prefrontal theta power stood above this background trend across the cortical areas. It is important to note that the elevated theta power showed consistent differences between good and poor performers across nearly all prefrontal electrodes, whereas gamma power differences were observed in the occipital electrodes (Figure 3B, Figure S3). The most reliable trends were seen in the theta and high gamma bands, with consistent effects across subjects and electrode locations, underscoring the robustness of these findings. We compared the magnitude of the theta and gamma spectral power differences between good and poor performers (ΔP) for a given behavioral measure. ΔP across all four measures of memory and executive functions showed high positive ΔP theta values for all prefrontal electrodes (Figure 3C, Figure S4), indicating a greater signal power in the good than in the poor performance condition. The grand average of ΔP from all electrodes in a given area differed significantly across the seven areas (ANOVA, $F = 11.27$, 6 *df*, $p \leq .001$). The prefrontal theta ΔP was significantly greater than that in any other area (Tukey–Kramer post hoc test, $p \leq .001$) (Figure 3D). These grand average values were not significantly different for the high gamma ΔP.

To visualize the spatial distribution of these spectral patterns across the brain, we generated surface plots of the averaged theta and gamma power for the poor and good performers and their ΔP difference across the four behavioral measures (Figure 4A, Figure S5 for each individual measure). These plots confirm a central low-power valley with peaks rising proportionally to the distance from the "CPz" electrode in both the lateral and anterior-posterior directions. The highest and most consistent peaks are concentrated in the theta activities of the anterior prefrontal cortex. These theta power peaks in the anterior prefrontal cortex, also known as the frontal pole, were greater than would be expected from the background pattern of gradually increasing power away from the central "CPz" electrode. However, we did not see a similar pattern in the high-gamma activity. As shown in Figure 3A, although there is a significant difference in high-gamma power between good and poor performers in the occipital brain region, the power magnitudes are not distinctly higher compared to those in electrodes from the other brain regions.

The logarithmic distribution of theta and high gamma powers plotted against the Euclidian distance from the "CPz" reference area exhibited an approximately linear correlation (Figure 4B). However, some electrodes showed their distribution away from this background linear power trend, including all four prefrontal ones, with notably greater power values compared even to those positioned farther away from the reference point. It is notable that the four anterior prefrontal electrodes consistently showed a large difference between the good and the poor

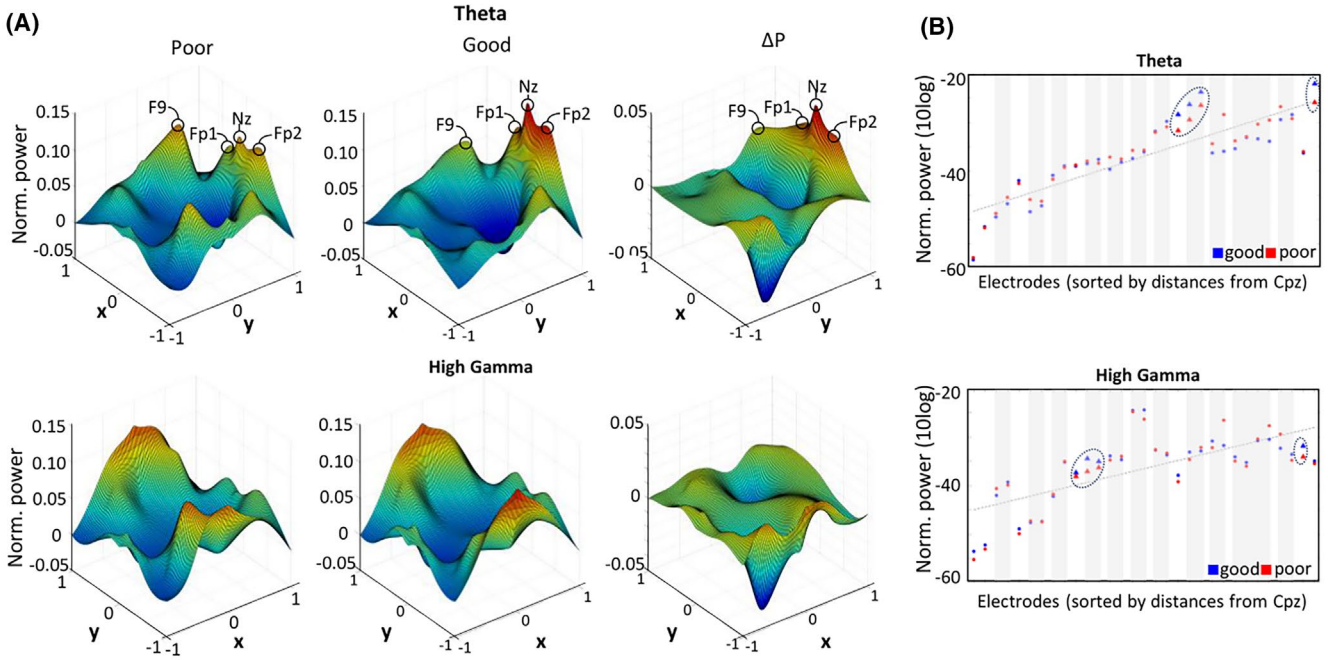

FIGURE 4 Memory and executive function performance are indicated by the anterior prefrontal EEG theta power. (A) 3D surface plots identify global peaks (warmer colors indicate greater magnitudes) of the average spectral power (left and middle column) and the power difference (right column) in the anterior prefrontal theta (upper row) and not in the occipital high-gamma (lower row) band. Notice the characteristic "red hot" peaks at the anterior EEG electrodes rising above the "deep blue" valley around the center of the 3D plane. (B) Logarithmic distribution of the average theta and high gamma power plotted against the Euclidean distance from the reference point "Cpz" confirms the trend of gradually increasing power away from the reference point. Note that the anterior prefrontal and occipital electrodes in the theta and high-gamma bands, respectively, are outlined by a black dotted oval. Only the anterior prefrontal electrodes in the theta band show a rise above this background trend. 3D, three-dimensional; EEG, electroencephalography.

performance conditions (Figure 4B upper panel). This was not the case for the high gamma activities at the occipital electrodes (Figure 4B lower panel).

Finally, focusing on the prefrontal theta band activities, we tested this candidate biomarker activity across the four behavioral measures and among all three performance groups (good, poor, and normal performers) of the 86 participating patients with epilepsy. The results are summarized in Figure 5A, showing that the four prefrontal electrodes (Nz, Fp2, Fp1, and Fpz) have proportionally increased theta power, going from poor to good performance conditions in the four behavioral measures. This pattern is especially evident for the most anterior "Nz" electrode across all four behavioral measures (Figure 5B; see Figure S6A for the other prefrontal electrodes). The theta power recorded from that electrode during individual patient performance in a given task (Figure 5B) revealed a continuous linear ascending trend—the greater the theta power, the better the performance. This analysis was conducted at the level of the entire group of subjects. There was a significant effect of the performance groups on the theta power (ANOVA, $F = 48.14$, 2 *df*, $p \leq .001$) and a significant difference between good and poor (Tukey–Kramer post hoc test, $p \leq .001$) as well as between good and normal (Tukey–Kramer post hoc test, $p \leq .001$) performers (Figure 5C; see Figure S6B for the analysis of other prefrontal electrodes).

Breaking down this analysis into individual task measures for the same "Nz" electrode lead confirmed the significant effect of higher theta power with better task performance (Figure 5D; ANOVA, 2 *df*, $p < .05$; refer to Figure S7 for the analysis of other prefrontal leads). A significant difference was observed between good and poor groups across all four measures (Tukey–Kramer post hoc test, $p \leq .05$). Between good and normal groups, a significant difference was found across all measures except visual memory (Tukey–Kramer post hoc test, $p \leq .001$; Table 2 for detailed Tukey–Kramer post hoc test results). Altogether, our results show that increased theta power is associated consistently with improved performance across the individual memory and executive function measures.

Given the consistent correlation between behavioral performance in the task measures and prefrontal theta power on specific electrodes, we predicted that the average theta power across all four electrodes would also correlate with the behavioral measures. Figure 5E shows the

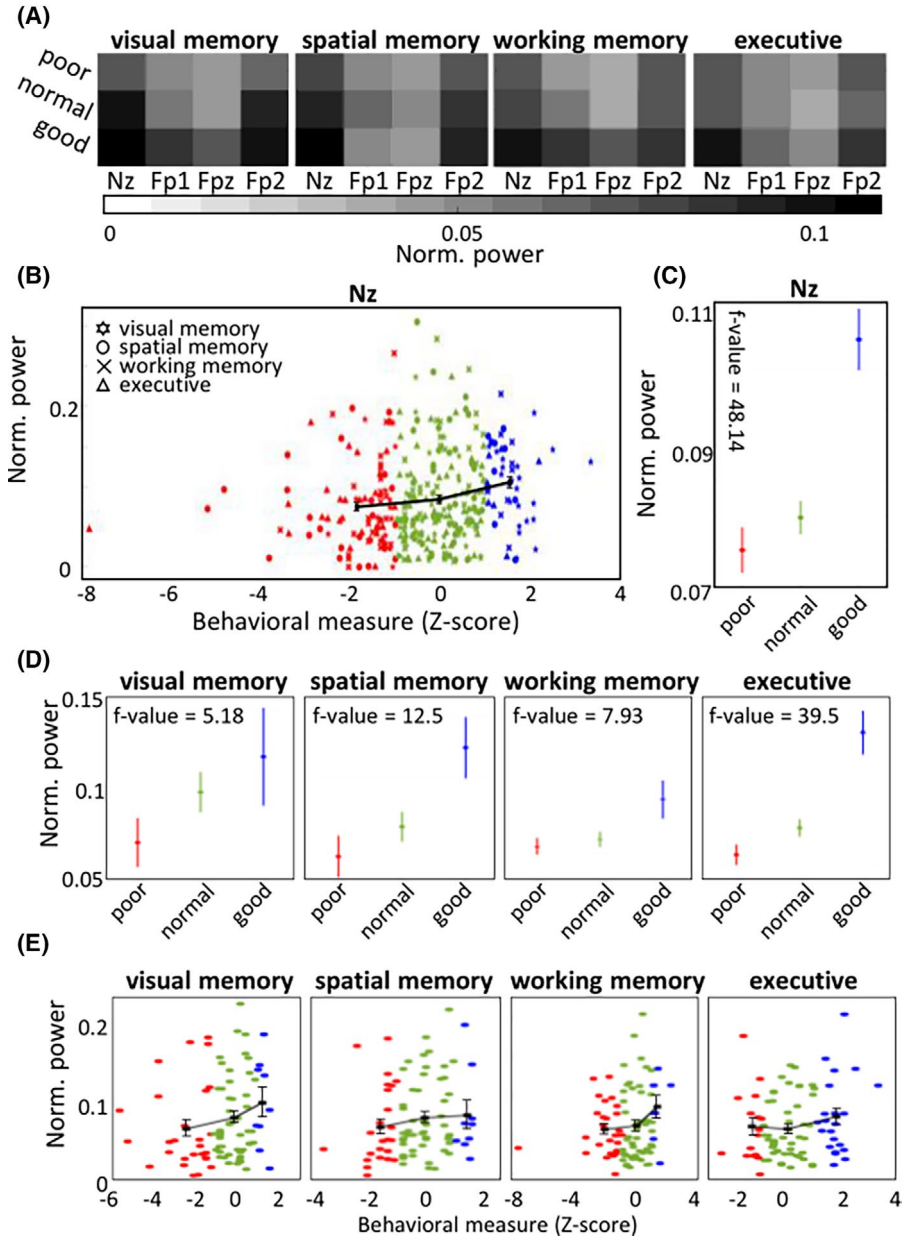

FIGURE 5 Memory and executive function performance are indicated by the anterior prefrontal EEG theta power. (A) Summary of the average theta power across the four anterior prefrontal electrodes and all four task measures shows a consistent pattern of gradually higher power (dark shades) going from poor to good patient performance. (B) Scatterplot of all patient performance scores across the four task measures (shapes) confirms the ascending trend of the grand-average means (black square plot with SEM) with significantly greater theta power on the "Nz" electrode (see Figure S6A for the other frontal pole electrodes) in case of the good (blue) vs normal (green) and poor (red) populations (Tukey–Kramer post hoc *test*, $p < .001$). (C) The average theta power across the four task measures is evaluated as the test statistic (F value) with post hoc group comparisons (95% confidence intervals). (Refer to Figure S6B for the other three electrodes.) (D) The average spectral power of theta band activities on the "Nz" electrode confirms the ascending trend in the grand-average means (bars indicate 95% confidence interval), with effect sizes indicated inside each plot (ANOVA, $df = 2$, $p < .01$); (see Figure S7 for the other three electrodes). (E) Grand-average theta power from all four frontal pole electrodes, plotted as in "B", shows the persistent ascending trend in each task measure of the studied memory and executive functions. ANOVA, analysis of variance; EEG, electroencephalography.

ascending pattern of this averaged prefrontal theta power increasing from poor to normal and good performer conditions. We conclude that theta activity across the entire anterior prefrontal cortical area is indicative of memory and executive functions in patients with epilepsy.

4 | DISCUSSION AND CONCLUSIONS

The goal of this study was to determine the neural activities that would match the behavioral assessment of memory

TABLE 2 Summary of patient group effects on the anterior theta power.

	Nz				Fp1		Fpz		Fp2			
	Visual memory	**Spatial memory**	**Working memory**	**Executive**	**Visual memory**	**Executive**	**Visual memory**	**Executive**	**Visual memory**	**Spatial memory**	**Working memory**	**Executive**
Good versus poor	.4520	**.0001**	**.0014**	$<10^{-5}$	$<10^{-5}$	**.0358**	$<10^{-5}$	$<10^{-5}$	.9969	.3752	**.0188**	$<10^{-5}$
Good versus normal	**.0170**	$<10^{-5}$	**.0002**	$<10^{-5}$	$<10^{-5}$	.1765	$<10^{-5}$	.0791	.1680	**.0057**	**.0051**	**.0252**
Normal vs poor	**.0221**	.1225	.5193	.8016	.0715	.9816	.6289	.3304	**.0120**	**.0160**	.6112	.2574

Note: Tukey–Kramer post hoc test results for each electrode and task measure are summarized only for instances of a significant result of the analysis of variance (ANOVA) for any given measure (bold text indicates significant effects).

and executive functions to identify potential electrophysiological biomarkers for cognitive impairments in epilepsy and other brain disorders. Using a clinically-validated CANTAB of cognitive tasks[30–34] we successfully identified patients with impaired, normal, and good performance in visual, spatial, working memory, and executive functions compared to age- and gender-matched healthy populations. These normalized behavioral measures confirmed a predominant impairment of memory functions observed in this patient population.[35] Approximately one-third of the patients tested were impaired across the three memory domains, whereas one fifth of these patients, on average, was also impaired in the executive function measure. Thus, our behavioral results support the use of CANTAB for the assessment and diagnosis of cognitive deficits in epilepsy. However, even this standardized battery is limited to human behavioral performance, which is prone to multiple factors affecting cognition, such as medication, sleep mood, alertness, and other factors related to neurological and psychiatric disorders. Neuropsychological assessment tools are limited not only in terms of the accurate detection of cognitive impairments but also in targeting and monitoring therapeutic interventions. Therefore, there is a need for complementary, more objective, biomarkers of cognitive function that reflect neural activity in specific brain areas.

Our study showed that a relatively simple EEG measure of spectral power in the theta frequency range from four electrodes in the anterior prefrontal cortex correlated with the CANTAB behavioral measures. This is remarkable given that theta power was averaged over the entire period of task performance when patients were likely to be distracted and engaged in other cognitive activities such as mind-wandering. The EEG and behavioral measures were affected by these internal and external factors in the hospital setting; yet they remained closely associated in the three separate tasks, probing four different cognitive measures. The identified EEG biomarker was consistent across all three tasks and cognitive measures and was limited to only one cortical region and frequency band, which stood above the background trend of increasing power away from the reference electrode area. Correlation analyses in individual patients further suggest that, although distinct brain regions support specific memory and executive functions, a shared neural network likely underlies all these processes, with the frontal pole area emerging as a potential region integrating these task-related functions.

This suggests that anterior prefrontal theta activities have the versatility and robustness that would be required for a clinically used biomarker, which suggests that they would not be limited to only a specific task or a cognitive function in the background of other patient-specific "internal" and environment-specific "external" factors.

Although our results show these necessary properties of a potential neural biomarker of memory and executive functions, they are not yet sufficient for clinical use. Likely due to the above-mentioned confounding factors, theta activity was not perfectly correlated with behavioral performance measures. For instance, the poor performance group was differed significantly only from the good performance group, but not from the normal patients in the entire cohort studied (Figure 5). For these reasons, we could not successfully use theta activities to classify patient groups using a machine-learning approach to separate the patient groups (data not shown). A recent study attempted to identify neural biomarkers of chronic pain[36] with similar results in terms of identifying brain areas and a range of intracranial EEG activities but without a clear classification. New studies using intracranial EEG have likewise proposed potential biomarkers of movement impairments[37] or depression.[38] Memory and cognitive functions are arguably more widely spread across networks of brain areas and are thus more challenging to target. Nevertheless, our previous studies with intracranial EEG took advantage of large cohorts of patients[21,22,39] or chronic continuous recordings[40] to identify the theta activities in the anterior cortico-thalamic circuits as a hub for memory functions and a target for therapeutic interventions such as direct electrical brain stimulation.[41] In this study, we demonstrated that the prefrontal theta activities sampled non-invasively with scalp EEG present an accessible, versatile, and robust biomarker for further studies of clinical utility and applications.

Previous studies have confirmed that non-invasive EEG can be used to predict cognitive function performance. Measures as simple as amplitude and latency of particular components of the event-related potential can differentiate good and poor memory performance as subjectively rated by young and old adults.[42] Spectral power in the alpha frequency band during rest is correlated with executive function performance and has been proposed as a biomarker of cognitive training in Parkinson's disease.[43] Theta activity has recently been proposed for diagnosing cognitive impairment in epilepsy.[44] However, most of these EEG studies did not use a clinically validated battery of tasks for a range of memory and cognitive functions, such as CANTAB. The anterior theta activities reported in our study were tested on a range of tasks and behavioral measures that were normalized in a large subject population. Other studies have also shown relevance of the anterior theta activities in particular cognitive functions impaired in various brain disorders.[7,24,44] Hence, they are likely to generalize to other memory and executive functions and extend to other patient populations.

Both theta and gamma frequency bands were associated with memory and executive functions.[2,10,12,13] It has been proposed that these two rhythms play critical roles in coordinating memory representations.[45] In our visual touch-screen cognitive tasks, we consistently showed that better performance is generally related to greater prefrontal theta and occipital gamma activity. Both visual gamma and prefrontal theta are required to coordinate memory representations in all the cognitive tasks that we used. However, in our case, the prefrontal theta signal was even more pronounced than the occipital gamma signal and was solely effective in indicating patient performance (Figures 3 and 4). CANTAB tasks require maintaining increased levels of attention and higher cognitive functions, which may explain greater prefrontal engagement. A greater prefrontal theta signal is promising as a more general biomarker of memory and executive functions that could now be tested in non-visual tasks involving auditory, olfactory, or tactile stimuli.

A study involving adults with self-reported everyday executive function complaints compared two groups: one with attention-deficit/hyperactivity disorder (ADHD) and one without any diagnosis, to a control group using EEG-based cognitive tasks. The analysis focused on the power and functional connectivity in four regions of interest (frontal-midline, fronto-lateral left and right, and parietal regions). Across all executive function domains, dynamic increases in theta power and functional theta connectivity were observed over time in both groups, with notable group differences, especially in conflict monitoring, evident in the frontal-midline and fronto-lateral right regions.[24] Another study was conducted to compare EEG spectral power and theta phase coherence during rest and while performing a working memory task in pediatric individuals with common genetic neurodevelopmental disorders linked to cognitive impairment in a control group of typically developing children matched for age and sex. The findings revealed that the group with cognitive impairment displayed higher resting-state slow-wave power, a lower peak alpha frequency, and elevated theta power, along with increased frontoparietal theta phase coherence during the working memory task. However, these differences disappeared when controlling for the baseline resting-state activity.[25]

Our results revealed a distinct single brain area with significantly greater signal activity than other areas associated with human memory and cognitive function. These functions are widely distributed in the brain between multiple frontal, temporal, and parietal association areas. Single biomarker localization is an attractive target for therapeutic interventions—a hub or a hotspot for memory processing.[21] Other hotspot targets may

exist within the memory and executive function networks, such as the anterior nucleus of the thalamus,[40,41] which could be more suitable in terms of therapeutic efficacy. Nonetheless, anterior prefrontal EEG theta activities provide an accessible biomarker signal in the neocortex, which is more feasible even for non-invasive neuromodulation interventions than the deep thalamic or mesial temporal lobe targets. They also provide an accessible objective biomarker for diagnosing cognitive deficits; suppressed prefrontal theta band power could be a general indicator of memory and executive function impairments.

The accuracy of estimating the reported anterior theta biomarker could be further improved by overcoming several limitations in our study. One is the lack of hemisphere-specific data, which restricted our ability to investigate potential hemispheric lateralization in the studied verbal functions. Due to this constraint, we were limited to identifying a general biomarker for memory and executive functions by averaging measures across all frontal pole electrode leads. Although this approach offers insights into overall frontal activity, it may overlook more precise biomarkers associated with specific functions that could be isolated by focusing on particular leads within the left or right hemisphere. For example, we have found that only the "Fp2" lead in the right hemisphere was showing a significant effect of the patient performance in spatial memory on the anterior theta activities but not the central "Fpz" or "Fp1" leads (see Figure S7). Future studies with hemisphere-specific data may provide more accurate localization of these cognitive biomarkers.

In addition, our analysis was not restricted to specific periods of memory performance, such as encoding or recall, when movement and other artifacts are minimized. Limiting analysis to these artifact-free intervals could improve signal quality and provide more accurate indicators of performance levels (poor, normal, or good), as well as reduce noise contamination, potentially affecting the spectral power estimates. However, implementing this approach in clinical practice poses technical challenges, as it would require precise synchronization between the task tablet and the EEG system. Another possible approach is to segment the task epochs into smaller intervals (e.g., 10 s), estimate power within each segment, and exclude any segments showing abnormally high power levels that could indicate artifacts.

This study was limited to a specific population of patients with epilepsy and may therefore be affected by epileptogenic EEG activities. Although we cannot fully exclude the effects of seizures, epileptiform activities, anti-epileptic medication dosages, or sleep deprivation without complex statistical adjustments—which remain challenging even with this substantial sample size—we at least provided consistent testing conditions for all participants. These potential confounding factors underscore the robustness of the anterior theta biomarker effects that we found. Further research is necessary to assess the generalizability of these results to other brain disorders.

Finally, a comprehensive clinical biomarker of memory and executive functions in brain disorders can be employed to develop new treatments. For example, neurofeedback training to enhance alpha spectral power during rest was shown to improve cognitive performance.[4] Similarly, training to enhance frontal-midline theta activity resulted in improved performance in a memory task testing attention and working memory functions.[46] Therefore, modulating the identified biomarker activities through the neurofeedback of brain stimulation would likely modulate memory and executive functions, leading to new therapy. Future studies will test these predictions for particular clinical applications and patient populations. Building upon recent investigations into memory enhancement through direct brain stimulation,[47–50] we understand that electrical stimulation in specific brain areas can enhance human cognitive performance. Therefore, we anticipate that our findings will represent a promising step toward modulating cognitive functions in the brain.

AUTHOR CONTRIBUTIONS

Nastaran Hamedi drafted the manuscript, directly accessed and verified the underlying data, conducted data analysis, interpreted the results, and revised and approved the manuscript. Jesús S. García-Salinas contributed to data analysis and revised and approved the manuscript. Brent M. Berry contributed to data collection. Gregory A. Worrell designed the study and contributed to data collection. Michal T. Kucewicz designed the study, drafted the manuscript, contributed to data collection, directly accessed and verified the underlying data, contributed to data analysis, interpreted the results, and revised and approved the manuscript. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

All recorded data and metadata are available on DOI: 10.17632/3bt248ppv5.1

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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