Clinical utility of the P300 wave as a biomarker for methylphenidate response in adult patients with ADHD: First phase report

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is associated with executive function deficits and neurophysiological disturbances [1]. The P300 wave is a positive electrical potential that typically appears approximately 300 milliseconds after the presentation of a relevant or infrequent stimulus. It is widely interpreted as an index of attentional resource allocation and contextual updating of working memory [2,3]. Its consistency across various cognitive paradigms has consolidated its role as a valuable tool in clinical neurophysiology, particularly in disorders characterized by attentional dysfunction, such as ADHD [3].

The P300 component of event-related potentials (ERPs) has been proposed as a promising biomarker in pediatric ADHD [4]; however, a significant gap remains between basic scientific knowledge and its translational clinical application. Recent studies have reported the utility of the P300 wave, obtained through visual event-related potentials (vERP), as a predictor of methylphenidate (MPH) treatment response in children [5], suggesting the need to explore its potential applicability in adults. In this context, we present the first phase of this study, which extends previous research through the application of a visual ERP paradigm to evaluate baseline P300 waveform characteristics in adults.

Objectives

The primary objective of this study is to evaluate the characteristics of the P300 wave in adults with ADHD prior to the initiation of treatment, with the aim of assessing its predictive value for methylphenidate (MPH) response. During the first phase, the P300 wave was acquired through visual event-related potentials (vERP) in unmedicated adult patients and compared against internal and publicly available normative data. In the ongoing second phase, the P300

wave will be recorded under MPH treatment in order to perform an intraindividual comparison with the pre-treatment P300 waveform.
As a secondary objective, we aim to evaluate the feasibility and reliability of obtaining the P300 wave through vERP in adults within a clinical context.

Methods

The study protocol —descriptive in its first phase— was reviewed prior to its initiation and approved by the Institutional Ethics Committee. A visual three-stimulus oddball event-related potential (ERP) paradigm was applied to 40 consecutive adult patients who spontaneously sought evaluation for ADHD at a specialized outpatient neurology clinic. In accordance with institutional protocol, all patients were referred for a formal neuropsychological evaluation during their initial consultation.
After providing informed consent, each participant received standardized instructions and completed two independent series of stimulus presentations. The oddball stimuli, including infrequent deviant items (Figure 1), represented 10% of the total stimuli presented (Table 1). Each session lasted approximately 18 to 20 minutes and was conducted by a trained technician.
Data acquisition was performed using a Cadwell Arc Apollo+® 32-channel EEG system, following the international 10/10 electrode placement system. The region of interest was referenced to electrode Cz, with a sampling frequency of 2000 Hz. Raw EEG files were exported in EDF+ format using Arc software version 3.0.234.0 (Cadwell Industries).
ERP analysis was conducted in JupyterLab within a Python 3.11.7 virtual environment. The signal processing pipeline utilized NumPy (v1.26.4), Matplotlib (v3.9.0), statsmodels (v0.14.2), and MNE-Python (v1.7.0). Grand averages were calculated from valid trials, and the P300 component was quantified using mean amplitude, peak latency, and area under the curve (AUC) within the 280–450 ms time window. The detailed data preparation and processing workflow is available as online supplementary material (Table 2).
Each recording was reviewed by a board-certified clinical neurophysiologist, who adjusted configuration parameters such as selection of electrodes of interest, stimulus time offset correction, independent component analysis (ICA) component rejection, and manual trial exclusion for artifact contamination, to achieve optimal visual validation. General technical recommendations from the literature were followed [6], maintaining methodological consistency with a prior pediatric study [5].

Interindividual comparisons were performed using both internal and publicly available normative data. Statistical analyses assumed normal distribution and were carried out using two-tailed independent Student's t-tests for the three quantified variables. When normality could not be assumed, Wilcoxon rank-sum tests were applied. An alpha significance threshold of $\alpha = 0.01$ was used for all statistical tests.

The final assessment of P300 waveform development was based on individual case findings, interpreted according to established literature precedents. Mean amplitude was considered the primary indicator, while AUC and peak latency served as secondary reference metrics.

Additionally, given the expected overlap between normative groups, statistical analysis was complemented by qualitative visual interpretation of waveform morphology in borderline cases.

To address potential misclassification errors identified during follow-up, a sensitivity analysis is planned for Phase 2 of the study.

Results

The mean age of the participants was 38.2 years (range: 16–68 years), with 47.5% being female (Table 3). In this initial phase, 87.5% of patients exhibited poorly developed P300 waveforms (Figure 2). Figures 3 and 4 illustrate representative examples of patients displaying this response pattern. The mean amplitude, peak latency, and area under the curve (AUC) within the 280–450 ms window are presented in Table 4.

An acceptable concordance of 96.5% was observed between the available neuropsychological evaluations (n = 29) and the degree of P300 waveform development (Table 5). A total of 51.7% of patients exhibited overall cognitive performance in the high-average or superior range (Table 6).

All participants successfully completed ERP recording sessions, and the epoch rejection rate remained below 15% across all studies.

Due to the limited recruitment of internal participants for the normative group (n = 6), publicly available datasets were used as comparative references (Figures 5 and 6).

Conclusion

A baseline P300 waveform profile was established in unmedicated adults with suspected ADHD, using a three-stimulus visual vERP paradigm feasible for

clinical application. An acceptable concordance was observed between the degree of P300 waveform development and the results of neuropsychological evaluations.

Although visual ERP paradigms are technically feasible in clinical settings, obtaining a well-defined P300 waveform in adults is more challenging than in pediatric populations. It has been demonstrated that P300 amplitude tends to decrease and latency tends to increase with age, reflecting greater neurophysiological variability [3]. These factors should be considered when evaluating the reliability of P300 as a clinical biomarker in adults with ADHD.

Among the limitations of this initial phase are the small size of the internal normative sample, which necessitated the use of external normative datasets for comparisons, and the availability of neuropsychological evaluations for only 72.5% of the participants.

To clinically validate this biomarker, the second phase of the study will include the analysis of intraindividual changes and the construction of a ROC curve, using the gold standard reference constituted by neuropsychological evaluation and clinical response to methylphenidate (MPH) treatment.

Figure 1. Diagram of the 3-Stimulus Visual Oddball Paradigm including variant or deviant stimulus.

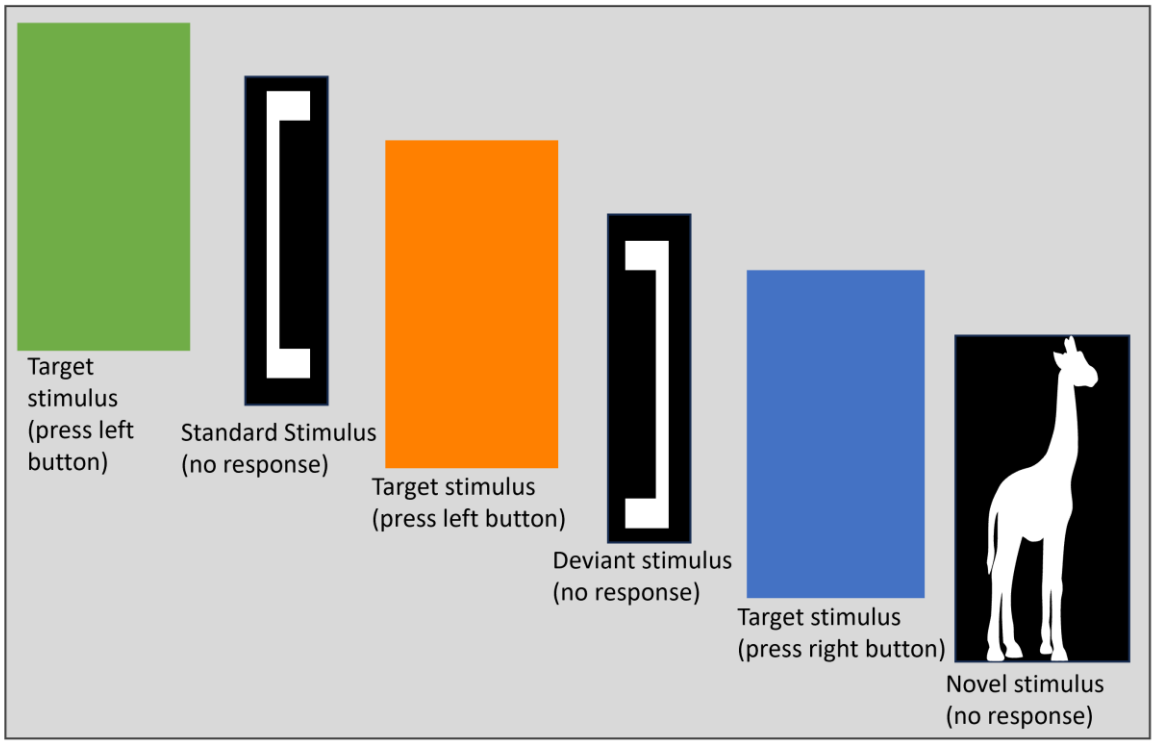


Table 1: Stimulus Distribution – Visual Three-Stimulus Oddball Paradigm

Stimulus Type	Description	Percentage (%)	Response Required
Standard	Frequent non-target stimulus used to establish a baseline expectation. **Repetitive figure** (e.g., blue circle, left button press).	80%	Yes
Target	Infrequent stimulus requiring a motor response. **Target figure** (e.g., red star, right button press).	10%	Yes
Novel	Infrequent and novel stimulus, not requiring a response, designed to elicit an orienting response. **Novel figure** (e.g., elephant).	5%	No
Deviant	Visually distinct variant of the standard stimulus, used to assess perceptual discrimination. **Altered figure** (e.g., mirrored symbol).	5%	No

Supplementary Material: Data Processing Scheme – Table 2

Step	Description
1	Import of EEG data in EDF format
2	Resampling to 250 Hz
3	Notch filtering to remove power line artifacts (45–55 Hz)
4	Channel rejection based on joint probability >3 SD from log power average (1–125 Hz), applied twice
5	Extended independent component analysis (ICA) for artifact detection and removal
6	Interpolation of rejected channels
7	Marking novelty stimulus onset using elapsed time data from a JSON file
8	Epoching the signal from −300 ms to +900 ms relative to novelty stimulus
9	Concatenation of epochs into a unified EEG file
10	Re-referencing to average reference across electrodes
11	High-frequency low-pass filtering at 40 Hz
12	Generation of a plot for visual inspection showing the P300 waveform and mean amplitude (280–450 ms)
13	Manual correction based on visual inspection using external JSON file: redefine onset, reject, or keep the novelty event
14	Calculation of the mean amplitude of the corrected P300 component

Table 3. Demographic Characteristics.

Demographic Characteristics (n=40)	
Variable	**Value**
Mean age (range), years	38.1 (16–68)
Male sex, n (%)	21 (52.5%)
Education level	
Secondary education, n (%)	9 (22.5%)
Undergraduate degree, n (%)	25 (62.5%)
Postgraduate degree, n (%)	6 (15%)

Figure 2. Baseline P300 waveform development in untreated patients with ADHD.

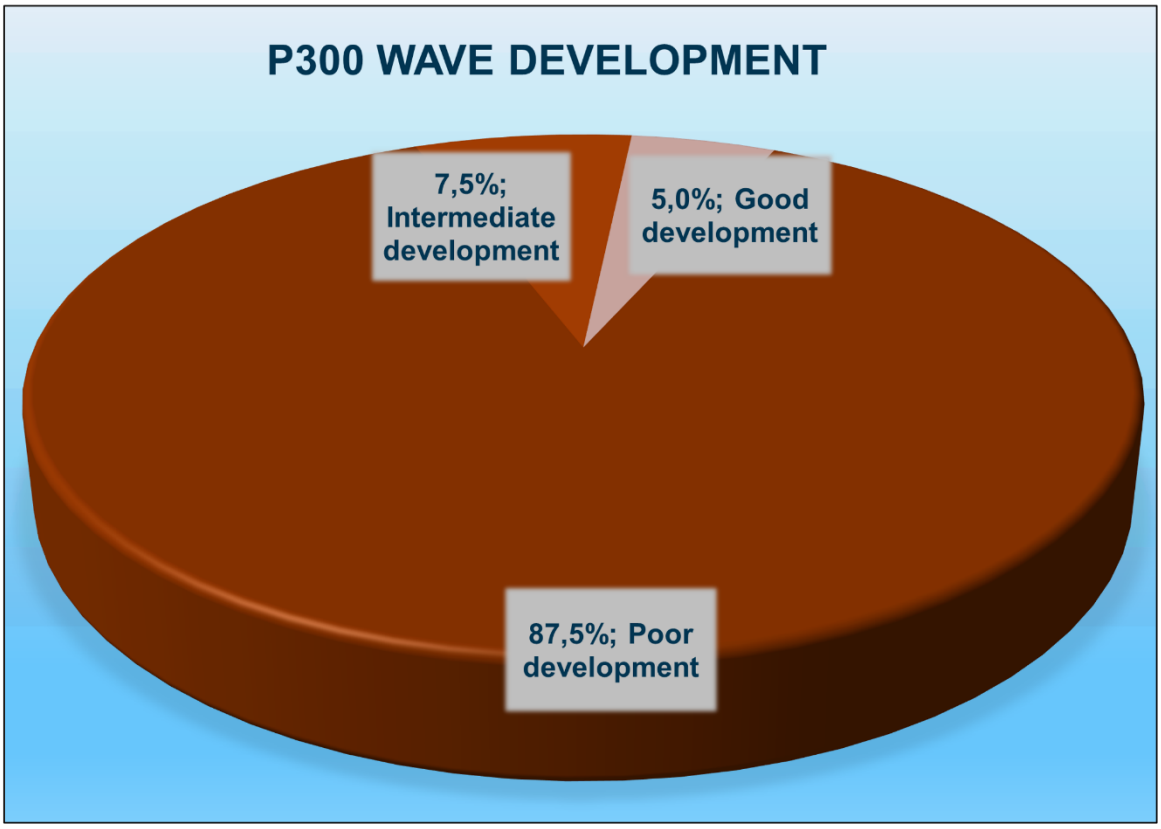
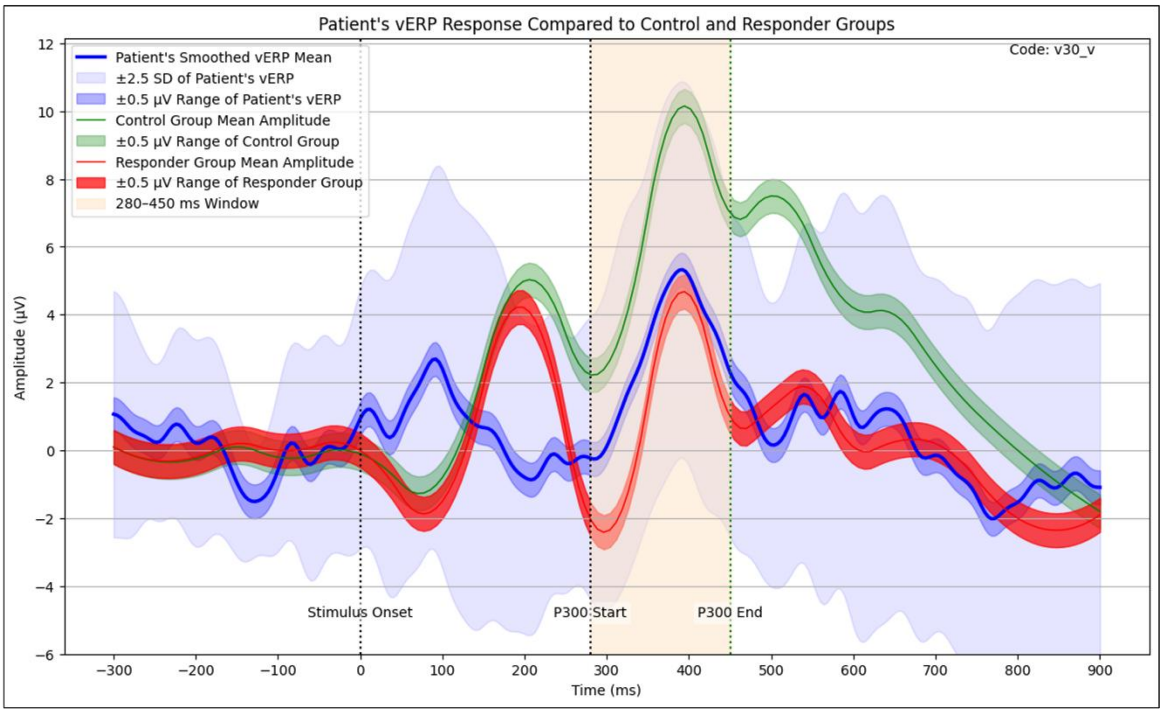
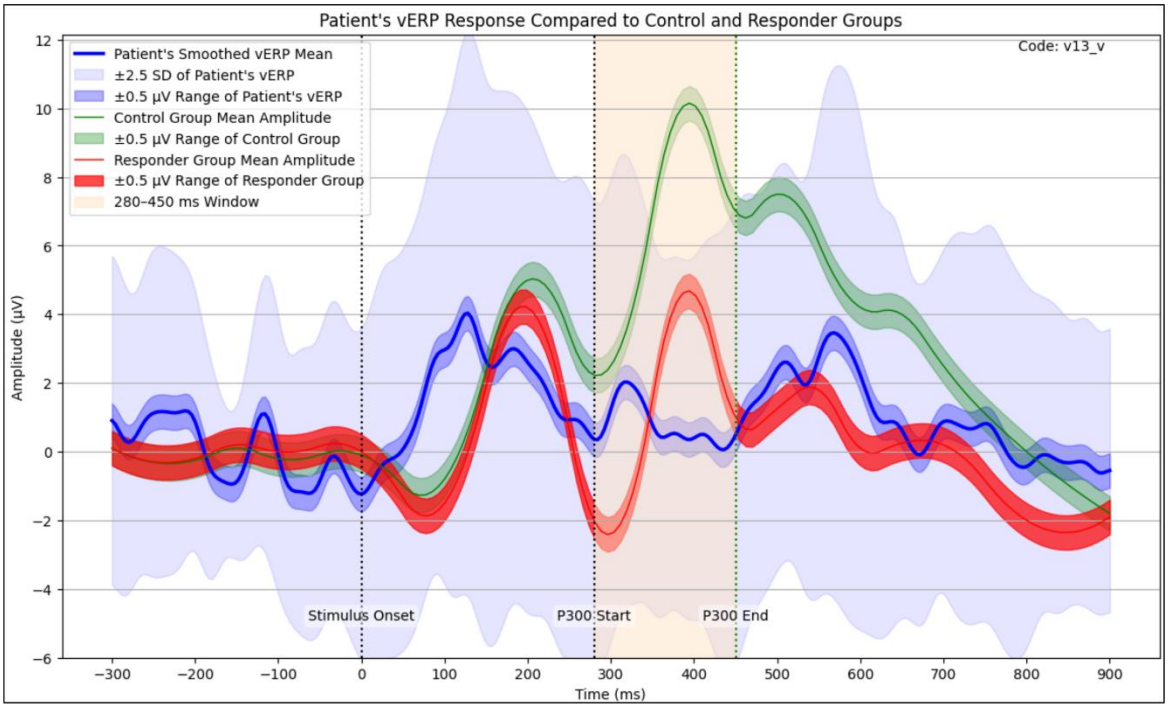


Figure 3. Amplitude vs Time vERP P300 plot for illustrative patient V30.



Male, 43y. Electrode of interest: Fz, average reference. Time window: 280-450ms. Independent components selected: 1-6.
Detailed technical steps applied available in Supplementary Material (Table 2).

Figure 4. Amplitude vs Time vERP P300 plot for illustrative patient V13.



Male, 22y. Electrode of interest: Fz, average reference. Time window: 280-450ms. Independent components selected: 1-6.
Detailed technical steps applied available in Supplementary Material (Table 2).

Table 4. Extracted vERP Parameters for Illustrative Patients (280–450 ms window).

Condition (280–450 ms window)	Mean Amplitude (µV)	Peak Latency (ms) from 0 ms	Area Under the Curve (AUC) (uV-ms)	n
Pretreatment Patient V30	2.914	396.10	504.40	42
Pretreatment Patient V13	0.777	321.46	135.66	42

Technical note: Electrode of interest: Fz, average reference. Time window: 280–450 ms. Selected independent components: 1–6. Detailed technical procedures applied are available in the Supplementary Material (Table 2).

Table 5. Concordance between Neuropsychological Assessment and P300 Waveform Development.

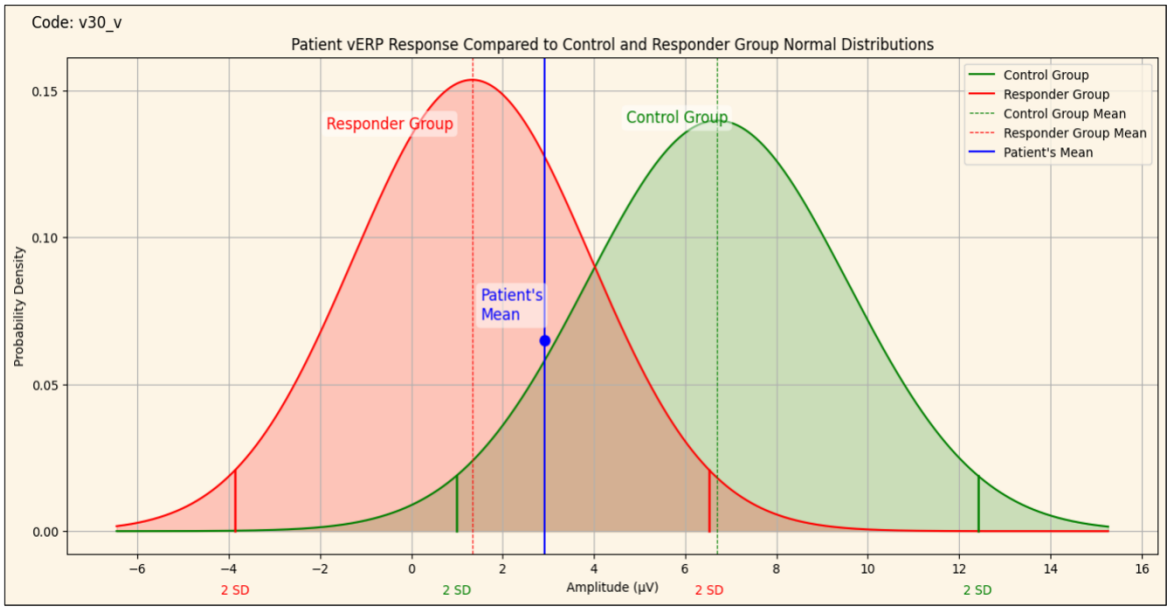
Neuropsychological Assessment (n = 29)	
Neuropsychological assessment outcome vs. P300 waveform development*	**n(%)**
Concordant	28 (96,5 %)
Discordant	1 (3,5 %)
Total	29 (100 %)

* Based on the conclusion of the formal neuropsychological assessment. Poor P300 waveform development was considered a criterion for probable good responder status.

Table 6. Global Cognitive Performance. Neuropsychological assessment of untreated patients with ADHD.

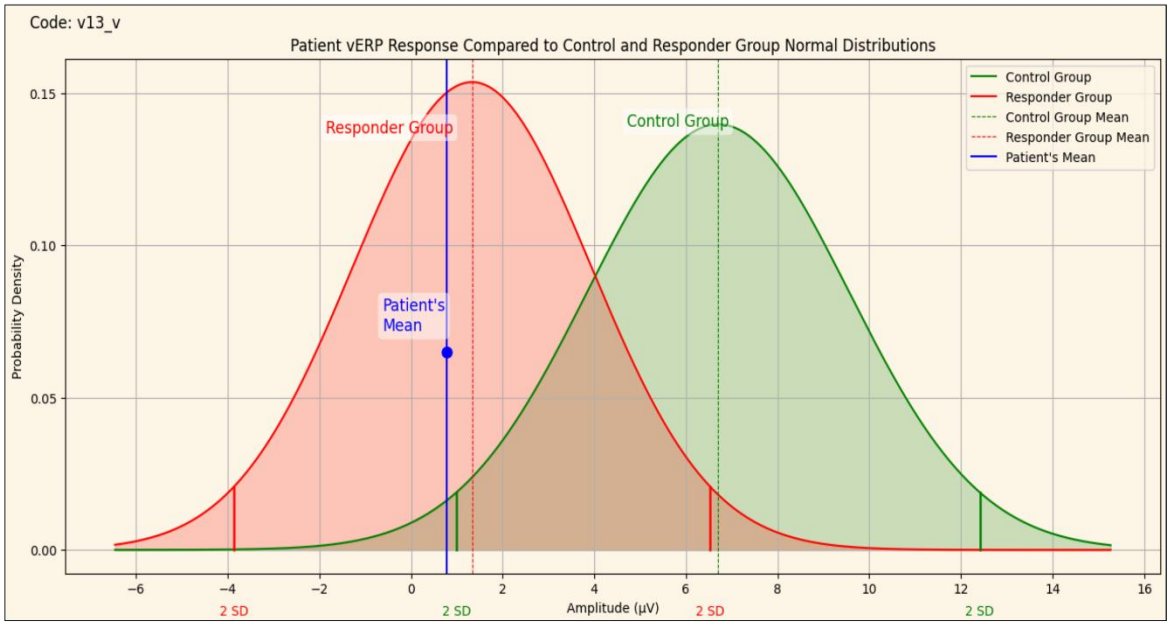
Global Cognitive Performance (n = 29)	
Range	**n (%)**
Mild deficit	1(3,4%)
Low average	1(3,4%)
Average	12(41,4%)
High average	3(10,3%)
Superior	10(34,5%)
Very superior	2(6,9%)

Figure 5. Amplitude Distribution Comparison for illustrative patient V30.



Male, 43y. Electrode of interest: Fz, average reference. Time window: 280-450ms. Independent components selected: 1-6.
Detailed technical steps applied available in Supplementary Material (Table 2).

Figure 6. Amplitude Distribution Comparison for illustrative patient V30.



Male, 22y. Electrode of interest: Fz, average reference. Time window: 280-450ms. Independent components selected: 1-6.
Detailed technical steps applied available in Supplementary Material (Table 2).

References

1. Rubia K. Cognitive neuroscience of attention deficit hyperactivity disorder (ADHD) and its clinical translation. *Front Hum Neurosci.* 2018;12:100. https://doi.org/10.3389/fnhum.2018.00100

2. Polich J. Updating P300: An integrative theory of P3a and P3b. *Clin Neurophysiol.* 2007;118(10):2128–2148. https://doi.org/10.1016/j.clinph.2007.04.019

3. Huang WJ, Chen WW, Zhang X. The neurophysiology of P300—An integrated review. *Eur Rev Med Pharmacol Sci.* 2015;19(8):1480–8.

4. Peisch V, Rutter T, Wilkinson CL, Arnett AB. Sensory processing and P300 event-related potential correlates of stimulant response in children with attention-deficit/hyperactivity disorder: A critical review. *Clin Neurophysiol.* 2021;132(4):953–966. https://doi.org/10.1016/j.clinph.2021.01.015

5. Arnett AB, Rutter TM, Stein MA. Neural markers of methylphenidate response in children with attention deficit hyperactivity disorder. *Front Behav Neurosci.* 2022;16:887622. https://doi.org/10.3389/fnbeh.2022.887622

6. Luck SJ. The design of ERP experiments. In: *An Introduction to the Event-Related Potential Technique.* 2nd ed. Cambridge (MA): MIT Press; 2014. p. 119–147.

Conflict of Interest – Management and Availability - Acknowledgments

The authors declare no conflicts of interest. The data were anonymized and are part of an ongoing study; they are available upon reasonable request. We thank the patients, assistants, and institutions.

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