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EDITED BY
Giovanni Luca Romano,
Kore University of Enna, Italy

REVIEWED BY
Enrique Germany Morrison,
Université Catholique de Louvain, Belgium
Matthew Bergosh,
University of Southern California,
United States

*CORRESPONDENCE
Leonardo Jose Trejo,
ltrejo@pacdel.com

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Quantitative electroencephalograms and event-related potentials as biomarkers in central nervous system drug development

Leonardo Jose Trejo[1*], Simon Titone[1,2], Kevin M. Spencer[1], Gé S. F. Ruigt[1], Larry Ereshefsky[3,4,5], Roman Rosipal[1,6], Brett A. English[7], John E. Donello[8] and Brianna Killion[9]

[1]Pacific Development and Technology, LLC, Capitola, CA, United States, [2]Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University, Clayton, VIC, Australia, [3]CenExel Research, Draper, UT, United States, [4]The University of Texas Health Science Center at San Antonio, San Antonio, TX, United States, [5]Follow the Molecule, LLC, Marina del Rey, CA, United States, [6]Institute of Measurement Science, Slovak Academy of Sciences, Bratislava, Slovakia, [7]Worldwide Clinical Trials, Durham, NC, United States, [8]Syndeio Biosciences, Inc., Indianapolis, IN, United States, [9]Q-Metrx, Inc., Glendale, CA, United States

Quantitative electroencephalography and event-related potentials are scalable translational biomarkers of the pharmacodynamic effects of drugs acting in the central nervous system. This review synthesizes evidence for resting-state quantitative electroencephalography, sensory-evoked responses, and endogenous event-related potentials across major central nervous system drug classes, including antidepressants, antiseizure medications, antipsychotics, cannabinoids, cholinergic modulators, N-methyl-D-aspartate (NMDA) receptor modulators, psychedelics, sedatives, stimulants, and selected mixed-mechanism agents. Across classes, drug effects are most interpretable when spectral power is separated into periodic and aperiodic activity, and when resting-state measures are integrated with event-related biomarkers such as mismatch negativity, auditory steady-state response, sensory gating, and P300. The evidence supports several mechanistic principles: γ- and δ-subunit-containing $GABA_A$ modulation generate distinct electrophysiological profiles; NMDA receptor antagonism dissociates spontaneous from evoked gamma band activity; cholinergic tone produces bidirectional and pharmacologically transparent effects on cortical desynchronization and sensory gating; and catecholaminergic, serotonergic, sedative, and antiseizure agents converge on several non-specific band-power changes. These convergences limit the interpretability of biomarkers and support the use of prespecified multi-feature panels that combine spectral, aperiodic, connectivity, and event-related measures. We conclude with practical recommendations for early-phase clinical trials, including time-matched baselines, control of vigilance and eye condition, pharmacokinetic-pharmacodynamic sampling, standardized acquisition, and statistical analysis plans suitable for biomarker qualification.

KEYWORDS

pharmaco-electroencephalography, event-related potentials, quantitative electroencephalography, central nervous system drug development, pharmacodynamic biomarkers, target engagement, aperiodic activity, translational pharmacology

Introduction

Central nervous system (CNS) disorders are among the leading causes of disability-adjusted life years worldwide and carry a substantial economic burden in both direct healthcare costs and lost productivity (GBD 2019 Mental Disorders Collaborators, 2022; Olesen et al., 2012). CNS drug development is especially challenging, with attrition exceeding 80% and costs often above $1 billion per approved compound, largely reflecting difficulty in demonstrating target engagement and efficacy amid uncertain disease mechanisms and patient heterogeneity. These challenges underscore the need for reliable translational biomarkers to support early-phase trials and dose selection (Etkin et al., 2025).

Electroencephalography (EEG) directly and non-invasively measures large-scale neural activity, reflecting the summed postsynaptic potentials of cortical pyramidal neurons. Quantitative EEG (qEEG) and event-related potentials (ERP) have become powerful translational biomarkers of CNS drug action, sensitive to changes in neurotransmission, circuit engagement, and cognitive processing (Cecchi et al., 2023; Hua et al., 2022; Javitt et al., 2008). They are well suited to early-phase trials, where objective markers of target engagement and dose response are needed, and are readily scalable to multi-site studies.

Pharmaco-EEG (pEEG) is the study of how drugs affect brain electrical activity. The field has been shaped by seminal reviews and consensus guidelines, most notably those of the International Pharmaco-EEG Society (IPEG), which set standards for using qEEG to assess CNS drug effects. These guidelines aim to bridge the translational gap between preclinical models and human trials (Jobert et al., 2012). Several reviews update or extend the guidelines (Arns et al., 2011; Herrmann & Demiralp, 2005; Herrmann et al., 1991; Jobert & Arns, 2016; Jobert & Wilson, 2016; Newson & Thiagarajan, 2019; Pagel, 1993; Pogarell et al., 2006; Saletu et al., 2005; Wilson et al., 2014; Wilson & Danjou, 2015).

Across drug classes, CNS-active compounds produce characteristic, mechanism-linked changes in EEGs and ERPs. Sedatives and other GABAergic drugs enhance frontal beta activity and slow background rhythms; cholinergic and other pro-cognitive agents shift the balance between slow-wave and faster activity and modulate sensory gating; NMDA-receptor antagonists such as ketamine increase spontaneous gamma while degrading evoked responses; and stimulants raise cortical arousal, reducing slow-wave power. Evoked and event-related responses, including mismatch negativity, the auditory steady-state response, and P300, track drug effects on sensory processing, cortical inhibition, and cognitive control. These reproducible "electrophysiological signatures" allow qEEG and ERP measures to serve as objective indices of central target engagement, dose–response, and, in some cases, treatment response, an organizing theme this review develops class by class.

The development and application of qEEG and ERP biomarkers of CNS drug effects rely on several fundamental principles of measurement and analysis.

Spectral power, frequency, and ratio-based qEEG measures

The EEG primarily reflects the summed postsynaptic potentials of cortical pyramidal neurons at the scalp level (Nunez & Srinivasan, 2006). Quantitative EEG and ERP methods offer promising biomarkers for assessing drug-induced changes in brain function. Resting-state qEEG typically quantifies ongoing periodic oscillations across canonical bands and, increasingly, aperiodic activity.

Pharmaco-EEG methods using qEEG have demonstrated sensitivity to drug-specific effects on cortical excitability and neurotransmission (Jobert et al., 2012; Lombardi et al., 2017). Analysis typically begins with spectral decomposition of resting-state EEG into canonical bands (δ, θ, α, β, γ), quantifying band-limited power and peak frequencies across scalp regions. Derived frequency ratios are also widely used to index brain states and drug effects, including the θ/β ratio or TBR (Clarke et al., 2019), commonly interpreted as a marker of attentional control; the θ/γ ratio or TGR (Moretti et al., 2009), linked to cognitive integration and memory processes; and the β/α ratio or BAR (Kislov et al., 2023), often associated with arousal or cortical activation, but also with some forms of sedation such as with sedative doses of benzodiazepines (Herrmann & Schaerer, 1986). Measures of dominant frequency or individual α frequency (IAF) provide subject-specific markers of cortical speed and integrity, with slowing frequently observed in aging, sedative states, neurodegeneration, and antiseizure medication exposure (Assenza et al., 2025; Kang et al., 2024; Voetterl et al., 2023). Finer subdivision of bands (e.g., α_1/α_2, $\beta_1/\beta_2/\beta_3$) improves sensitivity to drug effects that differentially modulate low- versus high-frequency components within a band (Jobert et al., 2012).

Regional asymmetry measures, most notably frontal α asymmetry, capture lateralized differences in cortical activity that have been linked to affective state, antidepressant response, and motivational processes. For example, the iSPOT-D study found that baseline α asymmetry could predict response to specific selective serotonin reuptake inhibitors (SSRIs) in a gender-dependent manner (Arns et al., 2016) and is a stable trait whose baseline levels can predict therapeutic outcomes (van der Vinne et al., 2019).

Separating periodic and aperiodic parts of the EEG spectrum

Recent developments in qEEG analysis emphasize the importance of separating periodic (synchronized oscillatory) and aperiodic (fractal or 1/f-like) components in EEG signals (Donoghue et al., 2020; Rosipal et al., 2022; Wen & Liu, 2016). The aperiodic (or fractal) component, quantified by the power spectral density (PSD) slope, reflects the bal-

ance of excitatory and inhibitory synaptic input. Analyses focused solely on band power can conflate these sources and obscure drug effects. Two teams (Donoghue et al., 2020; Wen & Liu, 2016) introduced practical parameterization methods to dissociate these elements, enabling clearer interpretation of neurophysiological changes. Gerster et al. (2022) and Pani et al. (2022) have reviewed best practices for spectral decomposition for clinical biomarker development. The aperiodic (1/f) slope is increasingly used as a proxy for cortical excitation/inhibition (E:I) balance (Lombardi et al., 2017). A steeper slope indicates increased inhibition and a flatter slope increased excitation or neural noise, whereas the slope flattens with age (Kang et al., 2024). Drugs that modulate neurotransmitter systems, particularly GABA and glutamate, predictably shift this slope. Drugs that increase inhibitory neurotransmission (e.g. $GABA_A$ receptor agonists) typically steepen the aperiodic slope whereas stimulants that increase catecholamine levels (like dopamine and norepinephrine) generally flatten the aperiodic slope.

State dependence and recording conditions

Quantitative EEG measures are strongly state-dependent, making eyes-closed versus eyes-open recording a critical distinction. Eyes-closed recordings emphasize posterior alpha activity and intrinsic dynamics, whereas eyes-open recordings reduce alpha power and increase sensitivity to attention- and arousal-related drug effects. Because sedative slowing and stimulant beta enhancement are state-dependent, standardized acquisition protocols are essential when comparing compounds, doses, or time points.

Functional connectivity and network-level measures

Beyond spectral power, functional connectivity metrics serve to characterize drug effects on large-scale networks. Linear measures such as coherence and nonlinear measures such as mutual information quantify coupling between channels (Chiarion et al., 2023; Nunez et al., 1999; Srinivasan et al., 2007). Cross-frequency coupling (CFC), especially θ-γ coupling, tracks coordination across distributed cortical areas during cognition (Canolty et al., 2006). Changes in coherence and phase synchrony often reflect altered network integration or segregation under pharmacological manipulation (Alonso et al., 2012).

Time–frequency and event-related measures

ERPs are voltage deflections in the EEG time-locked to sensory, motor, or cognitive events. They are extracted by averaging EEG epochs over multiple stimulus trials to reveal consistent neural responses. These components have been linked to specific perceptual, motor, and cognitive processes and have been widely used in clinical research (Luck & Kappenman, 2012).

Standard ERP techniques isolate stimulus- or task-locked responses, namely components such as mismatch negativity (MMN), auditory steady-state response (ASSR) and P300, which index sensory processing, cortical inhibition, and cognitive control. Complementing amplitude and latency measures, event-related spectral perturbation (ERSP) analysis captures task-induced changes in oscillatory power, including induced (non-phase-locked) activity not evident in averaged waveforms (Grandchamp & Delorme, 2011; Tallon-Baudry et al., 1999). Discrete wavelet decomposition of ERP signals can serve to optimally represent transient responses as needed for precise estimation and accurate classification of components (Trejo & Shensa, 1999) and complex wavelets can serve for functional measurement of evoked oscillations and phase locking of responses (Farnes et al., 2020; Spencer et al., 2008).

Signal complexity, entropy, and asymmetry metrics

Lempel–Ziv complexity, sample entropy, and multiscale entropy quantify the regularity of EEG signals and may index sedation, anesthesia, and excitation–inhibition balance (Lau et al., 2022).

Tensor decomposition methods

Tensor (multi-way) decomposition, for example PARAFAC, preserves the multidimensional structure of qEEG data (space × frequency × time × subjects) and extracts EEG atoms that are stable across domains (Miwakeichi et al., 2004; Rosipal et al., 2022). These atoms can track mental states such as cognitive fatigue (Trejo et al., 2009, 2015) and have also served to track EEG source responses to treatment with a novel mTORC1 modulator (Trejo et al., 2021).

Toward mechanistically informed biomarkers

Together, these qEEG and ERP measures give complementary views of brain function, spanning local oscillatory dynamics, network connectivity, evoked responses, and global signal organization. Interpreted against pharmacological mechanisms, they form a physiologically grounded framework for biomarker development, which the following sections apply across major CNS drug classes.

Evidence synthesis approach

This article is a narrative scoping review. It is not a systematic review, and no pooled effect sizes were estimated. It addresses one question: which qEEG and ERP measures

change reproducibly in response to CNS-active drugs, in which direction for each major drug class and mechanism, and how well do those changes serve as pharmacodynamic biomarkers of target engagement, dose response, and treatment response in drug development?

Sources and search

The starting point was an author archive of 1,547 unique pEEG and ERP publications. A further 43 publications came from targeted searches of PubMed and Google Scholar and from co-author contributions, giving 1,590 records published between 1967 and 2026 (Figure 1). The last search was run on August 19, 2026.

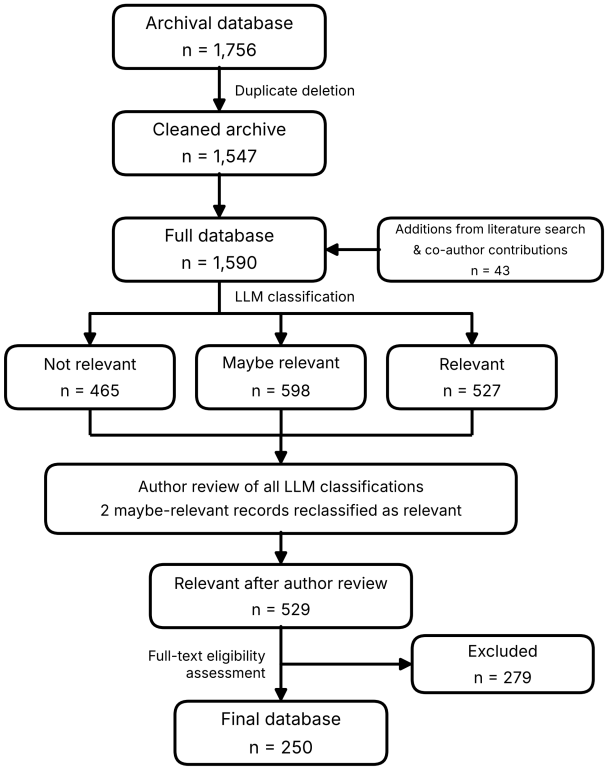


FIGURE 1
Selection of the evidence base. Records from the author archive and from targeted searches were classified by large language models (LLMs) as not relevant, maybe relevant, or relevant, using the prompt in Supplementary Note 2. Authors reviewed every LLM classification in all three classes, and two maybe-relevant records were reclassified as relevant. The 529 relevant records were then assessed in full text against the eligibility criteria, leaving 250 publications.

LLM-assisted classification

Full-text PDFs were submitted in batches of 10 to large language models (LLMs), initially to ChatGPT-4o (OpenAI, 2025) and later to Gemini 3.1 Pro (Google, 2026), with a fixed prompt (Supplementary Note 2). For each paper the model wrote a short summary of aims, methods, and findings and assigned a relevance score. A paper was scored relevant if it presented direct data on, or substantial discussion of, drug effects on EEG or ERP measures. It was scored maybe-relevant if it studied a medicated population, reviewed links between drug mechanisms and EEG or ERP measures, or reported pharmacological imaging results that could inform EEG-based models. All other papers were scored not relevant. The model also recorded the modality, drug class, compounds named in the body text, and species. It was instructed to take medications and species from the methods section without assumption, and to place borderline papers in the maybe-relevant class with a stated reason. This step classified 527 papers as relevant, 598 as maybe-relevant, and 465 as not relevant.

Human screening

Two authors (ST, BK) reviewed every LLM classification in all three classes, and a third author (LJT) performed the final screening and resolved disagreements. The LLM score was used to organize this review and never to exclude a paper without an author's check. Two papers scored maybe-relevant were moved to the relevant class, giving 529 relevant papers.

Eligibility

The relevant papers were then read in full (authors LJT, ST, KMS). A paper was included if it (i) reported a pharmacological manipulation or a clinically relevant drug exposure, (ii) recorded EEG, ERPs, or magnetoencephalography with adequately described methods, and (iii) reported quantitative results for at least one qEEG or ERP measure, or was a review or mechanistic paper needed to interpret such results. Of the 529 papers, 279 did not meet these criteria and were excluded for one of three reasons: no qEEG/ERP outcome, no drug-specific result, or redundant with another included report. The final evidence base comprised 250 publications: 233 research articles, 13 reviews, 2 conference posters, and 2 commentaries. Of these, 231 reported human data, 9 animal data, and 9 both. All entries in Supplementary Table 1 and Supplementary Table 2 and all mechanistic interpretations were checked by the authors (ST, BK, LJT) against the source publications.

Subjects and conditions testing

Many pEEG studies have assessed psychoactive drugs in patients with a targeted CNS disorder (e.g., Arns et al., 2011; Fink, 2010; Pogarell et al., 2006; Ulrich, 2002; Ulrich & Fürstenberg, 1999). This contrasts with the use of pEEG in early phase clinical trials, which mostly use healthy volunteers, focusing on safety and tolerability of novel treatments, with secondary goals of assessing target engagement and potential efficacy (Cecchi et al., 2023; de la Salle et al., 2025; Önnestam et al., 2023; Preskorn et al., 2008; Trejo et al., 2021). Patient studies may not span wide dose ranges or examine pharmacodynamic–pharmacokinetic (PK-PD) relationships. Healthy volunteer trials often use single- and multiple-ascending-dose (SAD/MAD) designs to

identify doses that signal CNS target engagement, evidenced by EEG changes relative to placebo or baseline (Modi et al., 2025). The literature mixes both study types, with dose-response and PK-PD studies in the minority, mainly because much early-phase pEEG data remains unpublished. Analysts have data from many double-blind, placebo-controlled early-phase trials but are often restrained by confidentiality agreements and commercial interests resulting in very limited sponsor-approved publication (e.g., Cecchi et al., 2023; English et al., 2014; Modi et al., 2025; Trejo et al., 2021). This is an area in which academia and industry could benefit greatly from increased transparency in publication of clinical trial results, but attempts to set up large open pEEG databases have failed thus far.

Pharmacodynamic signatures by drug class

Studies in the evidence base were grouped by compound, primary pharmacological mechanism, indication, subject type, sample size when available, and reported electroencephalography or event-related potential effects, detailed in Figure 1 and in Supplementary Table 1. The resulting synthesis is organized by drug class, with additional compound-level detail in Supplementary Table 2.

The final 250 articles met inclusion criteria for relevance, qEEG/ERP methodology, and quantitative results (Figure 2), showing that growth of relevant publications was initially slow for nearly 30 years but rose markedly across successive decades, with the steepest increases in more recent periods.

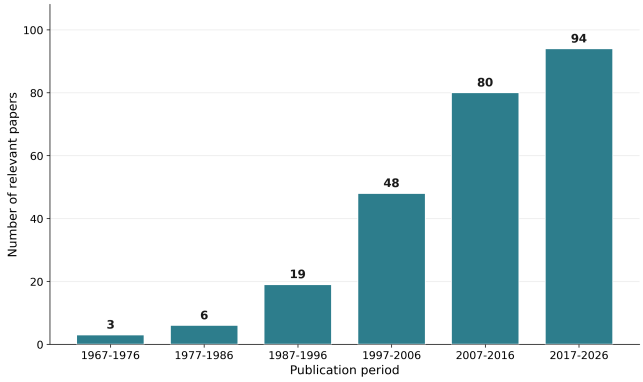


FIGURE 2
Number of relevant papers grouped into ten-year publication periods from 1967 to 2026. The number of relevant papers increased steadily across successive decades, with the steepest growth occurring in recent periods. The partial period 2017–2026 covers publications through the last search on August 19, 2026.

The review organizes these classes into two groups. The first comprises classes defined primarily by clinical indication: antidepressants, antipsychotics, stimulants, sedatives (including anxiolytic and hypnotic agents), antiseizure medications, and psychedelics. The second comprises classes defined primarily by pharmacological mechanism: NMDA receptor modulators, cholinergic modulators, cannabinoids, and miscellaneous compounds. This hybrid scheme reflects an unavoidable feature of CNS pharmacology: many compounds have multiple clinical indications and multiple molecular targets, so neither a purely clinical nor a purely mechanistic taxonomy is fully satisfactory. Each compound is discussed under a single class. A compound is placed by its primary pharmacological mechanism when that mechanism defines one of our classes, and otherwise by its principal clinical indication; its other uses are cross-referenced. Benzodiazepines and barbiturates are therefore covered under Sedatives, as a named subgroup of $GABA_A$ receptor positive allosteric modulators, although they are also used as antiseizure medications and anxiolytics. Ketamine and esketamine are covered under NMDA receptor modulators although they are used as antidepressants and anesthetics, nicotine under Cholinergic modulators although it is often called a stimulant, and gabapentin and pregabalin under Antiseizure medications although they are also used for pain and anxiety. Studies that span two classes carry both labels in Supplementary Table 1.

The sections below summarize mechanisms and predominant qEEG/ERP findings for each class, emphasizing target engagement, dose-response interpretation, and biomarker specificity. We present the clinically defined classes first, followed by the mechanistically defined classes, reflecting how compounds are most often encountered in early-phase drug development; although neuroscience-based nomenclature has been proposed, this review retains conventional classes to support practical use. Unless stated otherwise, findings are from human studies. Where reports disagree, we state the species, the population (healthy volunteers or patients), the dosing regimen (acute or repeated), and the recording condition (resting or task) of each, because many apparent disagreements reflect differences in design. These attributes are listed for every study in Supplementary Table 1.

Drug classes defined by clinical indication

Antidepressants

Most antidepressants act by modulating monoaminergic neurotransmission: serotonin (5-HT), norepinephrine (NE), and/or dopamine (DA). SSRIs such as fluoxetine block the serotonin transporter (SERT), raising extracellular 5-HT. Serotonin–norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine inhibit both SERT and the norepinephrine transporter (NET) (Meyer et al., 2004). Norepinephrine–dopamine reuptake inhibitors (NDRI), such as bupropion and its active metabolites (i.e. hydroxybupropion), weakly inhibit the neuronal reuptake of the neurotransmitters NE and DA (Foley et al., 2006; Stahl et al., 2004). By prolonging exposure of pre- and post-synaptic receptors to endogenous agonists across multiple monoamine receptor subtypes, reuptake inhibitors act as

non-selective functional agonists, and many also bind off-target receptors directly (fluoxetine, for example, antagonizes 5-HT_{2C}). Chronic treatment can further up- or down-regulate monoaminergic receptors (chronic fluoxetine downregulates 5-HT_{1A} and upregulates 5-HT_{2C}), so acute and chronic pEEG effects must be distinguished.

Tricyclic antidepressants (TCAs) inhibit SERT and NET but also bind histaminergic, cholinergic, and adrenergic receptors, contributing to both therapeutic and adverse effects. Monoamine oxidase inhibitors (MAOIs) block monoamine breakdown via MAO-A and/or MAO-B. Chronic treatment produces neuroadaptive changes in receptor sensitivity and plasticity such as increased brain-derived neurotrophic factor (BDNF) (Stahl, 2021).

Attempts to use a drug's EEG profile as a biomarker for its putative antidepressant effects go back to the early work of Max Fink and Turan Itil (Fink, 2010; Itil et al., 1972), who predicted the antidepressant efficacy of mianserin, a tetracyclic antidepressant, from the overlap of its EEG effects with imipramine. Later attempts by Herrmann to build an antidepressant pEEG profile from discriminant analyses across drug classes were less successful (Filip et al., 1993; Herrmann et al., 1979). Other approaches targeted disease EEG biomarkers such as the loudness dependence of the auditory evoked potential (LDAEP) (Linka et al., 2007), or frontal EEG α asymmetry (Luo et al., 2025). Yet another approach, which has surfaced over the last two decades, is the use of qEEG parameters as prognostic response prediction biomarkers, such as rostral anterior cingulate cortex θ power (Korb et al., 2009) and θ cordance (Hunter et al., 2006; Leuchter et al., 1994). Cordance combines the normalized absolute power and the normalized relative power in a frequency band at each electrode into a single value and was introduced as a surface EEG index of regional brain activity (Leuchter et al., 1994).

In patients treated with SSRIs, SNRIs, or mixed antidepressant regimens, an early decrease in prefrontal θ cordance in the waking resting EEG, measured within the first 1–2 weeks of treatment, is a replicated qEEG predictor of later clinical response (Bares et al., 2008; Cook et al., 2002). This is a change from baseline and is distinct from baseline predictors such as higher pretreatment θ activity in the rostral anterior cingulate (Korb et al., 2009). The direction depends on state: when cordance was measured during rapid-eye movement (REM) sleep, higher prefrontal θ cordance after one week of treatment predicted response (Adamczyk et al., 2015). Most of these studies were small and open-label, and not every later sample replicated prediction from early EEG change (Baskaran et al., 2018), so these markers remain candidates and not validated predictors.

In healthy male volunteers, bupropion (50 mg t.i.d. then 100 mg t.i.d., 7 days each) reduced α and θ power without affecting δ or β, suggesting a subtle psychostimulant effect (Siepmann et al., 2005). In a study of non-depressed smokers, 14 days of bupropion treatment significantly reduced visuospatial task-related parietal EEG α power asymmetry (driven by decreased right parietal α power) compared to a placebo group (Zhu et al., 2017). The authors interpreted the bupropion-induced reduction in parietal EEG asymmetry as a potential biomarker of reduced depressive states and traits.

Other common antidepressant EEG effects include reduced frontal α asymmetry, elevated δ/θ activity, and reduced global power, especially in responders (Baskaran et al., 2012; Knott, 2000). Tricyclic antidepressants and lithium may induce diffuse δ and θ activity at higher doses (Blume, 2006).

A notable study applied a latent-space machine-learning approach to resting-state EEG to predict sertraline response (Wu et al., 2020). Lower baseline prefrontal α power was associated with greater clinical improvement, interpreted as greater prefrontal excitability in responders, consistent with α power reflecting regional inhibitory tone.

Single or infrequent ketamine and esketamine infusions can provide rapid and durable antidepressant effects. Esketamine is indicated in treatment-resistant depression (TRD) and requires administration along with oral antidepressants. EEG and ERP effects of these compounds are discussed in the section on NMDAR modulators below.

Antipsychotics

Antipsychotics primarily target dopamine D_2 receptors to reduce psychotic symptoms. First-generation (typical) agents such as chlorpromazine and haloperidol are potent D_2 antagonists, especially in the mesolimbic pathway. Second-generation (atypical) agents such as risperidone and clozapine also block D_2 but have higher 5-HT_{2A} affinity, contributing to fewer extrapyramidal symptoms and better efficacy for negative symptoms. Clozapine, the most effective atypical antipsychotic (Erlianti et al., 2025), also has affinity for histaminergic, noradrenergic, and muscarinic receptors (Nucifora et al., 2017). Achieving balance between dopaminergic and serotonergic modulation is important in treating schizophrenia and related disorders (Miyamoto et al., 2012; Stahl, 2021).

Assessing antipsychotic effects on EEG is difficult, given the ethics of testing unmedicated patients. In schizophrenia, EEG studies of first-episode patients can predict antipsychotic treatment response (Ambrosen et al., 2023; Dominicus et al., 2023) and provide insight into the effects of long-term antipsychotic administration, while studies of non-medicated individuals with a high risk for psychosis can provide clues as to possible antipsychotic EEG effects. To date, however, prominent EEG abnormalities observed in chronic schizophrenia patients (e.g., P50 sensory gating, P300, MMN, and 40 Hz ASSR deficits) have also been found in first episode patients, and high psychosis risk individuals, so it is difficult to separate existing abnormalities from effects of antipsychotic treatment.

With or without medication, schizophrenia patients typically show EEG "slowing" and ERP abnormalities: elevated frontal δ and θ power, reduced α and β power, and reduced P300 amplitude (Jeon & Polich, 2003; Newson & Thiagarajan, 2019; Qiu et al., 2014; Turetsky et al., 2006). In

healthy volunteers, acute exposure to most antipsychotics (chlorpromazine, haloperidol, clozapine, thiothixene, molindone) increases δ and θ power and decreases β power (Herrmann et al., 1979). For example, chlorpromazine shows a progressive increase in δ and θ power, accompanied by a decrease in α power that appears 1 h after dosing and increases further at 3 h (Herrmann et al., 1991). β bands are relatively unaffected with only a slight decrease in the β_3 range (21–30 Hz). Similar effects are seen in patients with schizophrenia-spectrum disorders (Hyun et al., 2011).

γ-band oscillations are of key interest in schizophrenia research as potential efficacy biomarkers for new antipsychotics. Spencer's critical review (Spencer, 2024) explains a dichotomy between decreased evoked γ and increased spontaneous γ in schizophrenia patients. A key biomarker is the 40-Hz ASSR, which is impaired in patients and first-degree relatives. However, unlike the stimulus-locked γ band response of ASSR, spontaneous γ activity (SGA) power can be elevated in schizophrenia patients. There is also evidence of increased resting state SGA connectivity in first-episode schizophrenia patients as compared to healthy controls, which is lateralized to left frontal, temporal, and inferior parietal areas (Andreou et al., 2015).

Distinct mechanisms underlie the ASSR and SGA anomalies in schizophrenia. SGA reflects ongoing background activity and indexes excitation/inhibition (E/I) balance; disrupting that balance by blocking NMDARs raises SGA in humans and animals. Parvalbumin-positive interneurons (PVIs) act as rhythmic brakes on the pyramidal cells that generate EEG oscillations. Under the NMDAR/PVI hypofunction hypothesis, PVIs in schizophrenia receive insufficient NMDAR-mediated excitation and the weakened PVI braking prevents a strong synchronized response to a 40-Hz stimulus (reduced evoked γ and ASSR) while leaving unstimulated pyramidal cells to fire noisily, raising background SGA. The same mechanism may underlie the ASSR and SGA effects of NMDAR antagonists such as ketamine, considered below.

Sensory gating is a normal function of the auditory system, which can be assessed with the P50 component of the auditory evoked potential (Cromwell et al., 2008). Gating efficiency is the amplitude reduction of the second of two successive stimuli (the S2/S1 ratio). This ratio is markedly higher in schizophrenia patients and first-degree relatives than controls (patients S2/S1>0.85, controls <0.20), indicating a deficit in filtering afferent sensory input (Siegel, 1984). Patients on first-generation antipsychotics (haloperidol, chlorpromazine) showed deficient P50 gating (S2/S1=0.44), whereas those on second-generation (clozapine, olanzapine, risperidone) had normal ratios (S2/S1=0.26); clozapine's benefit may reflect its nicotinic and muscarinic activity. Because the P50 deficit is linked to the α-7 nicotinic receptor, nicotine can temporarily normalize gating in patients and relatives (Martin & Freedman, 2007), perhaps explaining the high smoking rates (>80%) in schizophrenia as self-medication to restore the sensory filter. P50 gating is thus a well-documented biomarker for testing antipsychotic candidates, though its utility is largely limited to patient trials, since healthy volunteers show no gating deficit.

While not often used in pEEG studies, EEG microstates, stable spatial EEG patterns, lasting about 60-120 ms (Lehmann et al., 1987), appear to be altered in schizophrenia and may be relevant as a response prediction biomarker for antipsychotics (De Pieri et al., 2025; Kim et al., 2021; Koenig et al., 1999). Patients with schizophrenia often show increased duration of microstate Class C (linked to the salience and default-mode networks) and decreased Class D (linked to attention and executive function). Antipsychotic treatment can shift these dynamics back toward a healthy profile (Kikuchi et al., 2007). One hypothesis is that antipsychotics stabilize the duration of functional brain networks, smoothing the fragmented thoughts associated with psychosis.

Stimulants

Most stimulants, including amphetamines and methylphenidate, raise synaptic dopamine and norepinephrine by blocking and reversing the dopamine transporter (DAT) and NET; amphetamines also promote vesicular monoamine release via vesicular monoamine transporter 2 (VMAT2). These actions enhance cortical arousal, attention, and executive function, notably in attention-deficit/hyperactivity disorder (ADHD). Cocaine blocks DAT, NET, and SERT comparably but is faster acting with higher abuse liability. Modafinil, a wake-promoting agent, likely raises catecholamines and modulates orexin and glutamate systems (Heal et al., 2013; Volkow et al., 2012). Orexin receptor modulators act on hypothalamic orexin 1 and 2 receptors (OX1R and OX2R) as antagonists to promote sleep (e.g., suvorexant) or agonists to enhance wakefulness in narcolepsy (Gotter et al., 2012; Scammell & Winrow, 2011).

Amphetamine, methylphenidate, and cocaine are associated with increased frontal β activity, consistently observed across resting-state and task-related EEG studies. Other stimulants reduce δ and θ power shortly after dosing, though patterns vary by agent, e.g., amphetamine and modafinil, both wake-promoting, differ. In a placebo-controlled trial in healthy volunteers, Chapotot et al. (2003) reported that a 20 mg dose of d-amphetamine produced a sustained suppression of sleep deprivation-related increases in δ and θ_1 power, regardless of dosing time. It also reduced α_1 activity, limited γ power increases, and largely abolished circadian EEG rhythms observed under placebo. In contrast, 300 mg of modafinil caused a shorter-lived (3–6 h) reduction in γ_2 and θ_1 power, countered γ increases, and delayed θ_2 circadian rhythms. Notably, in contrast to d-amphetamine, modafinil preserved frontal α_1 power; this preservation of the wake-EEG α_1 signature, rather than an absence of effect, distinguishes the modafinil spectral profile.

Orexin receptor agonists such as the non-peptide alixorexton (ALKS 2680) and oveporexton (TAK-861; Lammers et al., 2026) are being explored as wake-promot-

ing therapies for narcolepsy. Modi et al. (2025) reported that ALKS 2680 dose-dependently reduced low-frequency (δ, θ) and increased high-frequency (β, γ) oscillations. These spectral changes correlated with wakefulness measures (Karolinska Sleepiness Scale, Maintenance of Wakefulness Test), highlighting the utility of spectral biomarkers for tracking orexinergic engagement in hypersomnia disorders. These findings come from a conference presentation and have not yet been peer reviewed; two of the authors (LJT, RR) analyzed these data.

Stimulant effects on ERPs are heterogeneous and dissociate by agent. Caffeine has been associated with enhanced P3b amplitude and shortened P300 latency (Barry et al., 2014; Camaz Deslandes et al., 2004), alongside faster brainstem and middle-latency auditory-evoked components (Dixit et al., 2006), consistent with accelerated central processing. By contrast, dexamphetamine reduces auditory P3a and P3b amplitude in healthy volunteers, resembling the P300 deficit seen in schizophrenia (Albrecht et al., 2011), while the broader amphetamine literature reports conflicting directions of effect. Stimulant-class membership alone therefore does not predict a uniform ERP signature, with outcomes depending on the specific agent, dose, and task.

Sedatives

GABA and glycine are the major inhibitory neurotransmitters in the CNS, suppressing neuronal activity in the brain and spinal cord. GABA receptors come in two very different varieties ($GABA_A$-ionotropic and $GABA_B$-metabotropic). $GABA_A$ receptors are heteropentameric ligand-gated ionophores channeling chloride ions into the cell leading to hyperpolarization and reduction of excitability, while $GABA_B$ receptors are G-protein-coupled receptors which by activation through agonists like baclofen inhibit calcium channels and activate potassium channels, decreasing neuronal firing (Olsen & Sieghart, 2009). The five subunits that make up the $GABA_A$ receptor complex have 19 subunit varieties, yielding combinations that differ in cellular location (synaptic/extrasynaptic), distribution, and pharmacology. Beyond the GABA site, separate binding sites exist for positive and negative allosteric modulators: benzodiazepines, barbiturates, neuroactive steroids, alcohol, inhaled anesthetics, and picrotoxin. Benzodiazepines increase channel opening frequency; barbiturates increase opening duration.

Benzodiazepines and other $GABA_A$ receptor positive allosteric modulators

Most $GABA_A$ receptor positive allosteric modulators (PAMs), including benzodiazepines, barbiturates, some anesthetics, alcohol, and propofol, enhance inhibitory neurotransmission by increasing chloride conductance through the $GABA_A$ ion channel (Macdonald & Olsen, 1994; Olsen & Sieghart, 2009). This hyperpolarizes neurons, lengthens and amplifies inhibitory postsynaptic potentials, and reduces pyramidal firing, shifting the network excitation/inhibition balance toward inhibition and reshaping both periodic and aperiodic spectral components (Gao et al., 2017). Because these agents raise the gain of PVIs and other inhibitory interneurons that pace frontal and central networks in the β range, they paradoxically and robustly increase frontal β power (~15–25 Hz), consistently observed after benzodiazepines, barbiturates, and ethanol (Blume, 2006; Wang et al., 1997). This excess β reflects synchronous inhibition and reduced cortical responsiveness and is widely read as a biomarker of sedation (Gunkelman, 2010). The same agents also produce background slowing: reduced individual alpha frequency (IAF) and increased θ power. Gaboxadol is an instructive exception: a $GABA_A$ agonist that binds δ-subunit-containing extrasynaptic receptors rather than the γ-subunit-containing synaptic receptors targeted by benzodiazepines, it produces a large increase in δ and θ power across sleep and waking with concomitant decreases in α and slow β. Its EEG signature is abolished in rodents by knockout of the $GABA_A$ δ-subunit, confirming the receptor basis of the effect (Winsky-Sommerer et al., 2007).

Beyond their spectral signature, $GABA_A$ PAMs produce a consistent effect on ERPs: acute benzodiazepines reduce P300 (P3b) amplitude and prolong its latency, paralleling the slowing of information processing they induce. This has been demonstrated across structurally diverse compounds, including diazepam (Ray et al., 1992), alprazolam (Semlitsch et al., 1995), triazolam (Urata et al., 1996), and clonazepam, which also reduces the earlier auditory N1 (Rockstroh et al., 1991). Because the P300 indexes attention allocation and working memory updating, its amplitude reduction is interpreted as a direct electrophysiological correlate of benzodiazepine-induced cognitive slowing, complementing the frontal-β sedation marker. Notably, this ERP sensitivity is component-specific: unlike the P300, the pre-attentive mismatch negativity is largely spared by benzodiazepines (Kasai et al., 2002), a dissociation that reinforces the principle that ERP components track distinct, mechanism-linked processes rather than global drug effect. Evidence for the frontocentral novelty subcomponent (P3a) is comparatively sparse, marking a gap for future work on GABAergic modulation of involuntary attention.

GABA antagonists such as bicuculline (competing at the GABA site) and picrotoxin (blocking the channel pore) are convulsants. At high doses, some GABA agonists, including baclofen and pentobarbital, have been associated with triphasic waves. Muscle relaxants such as baclofen (a selective $GABA_B$ receptor agonist**)** have been reported to reduce γ-band excess and are associated with attenuation of abnormal oscillatory synchrony in schizophrenia models (Featherstone et al., 2015).

Salvatore et al. (2024) demonstrated that PAMs of $GABA_A$ receptors increased the aperiodic exponent in EEG power spectra. This effect is consistent with the interpretation that a steeper exponent reflects enhanced inhibitory tone. Importantly, this study exemplifies the utility of sepa-

rating periodic and aperiodic spectral components to isolate drug-specific mechanisms. The aperiodic exponent thus emerges as a candidate biomarker of GABAergic modulation.

Antiseizure medications

Antiseizure medications (ASMs; also termed antiepileptic drugs, AEDs) commonly produce diffuse EEG slowing: reduced posterior α, increased δ and θ, and a lowered median frequency (Clemens et al., 2006; Drake et al., 1990; Salinsky et al., 2002). These effects reflect a generalized reduction in cortical excitability arising from distinct pharmacodynamic mechanisms. Benzodiazepines and barbiturates, which are also used to control seizures and are covered under Sedatives, enhance inhibitory transmission by acting as PAMs of $GABA_A$ receptors, increasing chloride conductance and neuronal hyperpolarization (Macdonald & Olsen, 1994). Carbamazepine, phenytoin, and lamotrigine inhibit voltage-gated sodium channels, reducing repetitive firing, while ethosuximide blocks thalamic T-type calcium channels to suppress absence seizures (Rogawski & Löscher, 2004). Gabapentin and pregabalin bind to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, reducing excitatory neurotransmitter release, whereas valproate has multiple actions, including enhancement of GABA synthesis, inhibition of sodium currents, and histone deacetylase inhibition that may promote neuroprotection (Löscher et al., 2013). Comparative pEEG data indicate that carbamazepine and gabapentin produce particularly prominent EEG slowing, consistent with their membrane-stabilizing and GABAergic mechanisms (Brienza et al., 2019; Meador et al., 2016).

Quantitative EEG effects of ASMs vary according to their distinct mechanisms of action. In newly diagnosed, unmedicated young epilepsy patients, valproic acid reduced θ band power without significantly affecting alpha mean frequency (Clemens et al., 2006). In the same study, carbamazepine increased absolute θ power and significantly decreased α mean frequency. While carbamazepine primarily targets voltage-gated sodium channels, valproic acid has multiple targets (GABA systems, T-type Ca^{2+}, histone deacetylases (HDACs)). Like valproic acid, lamotrigine also reduced power across δ and θ bands but significantly increased alpha mean frequency (Clemens et al., 2007). A possible reason for the different effect on α is that lamotrigine increases α frequency by enhancing I_h pacemaker currents through hyperpolarization-activated cyclic nucleotide-gated (HCN) channel activation (Poolos et al., 2002), whereas valproic acid lacks this mechanism. Thus, lamotrigine's qEEG pattern of reduced slow-wave power and increased α frequency resembles that of a mild stimulant.

Rare findings include generalized burst suppression (high-voltage activity alternating with electrical silence) at neurotoxic ASM levels, e.g., carbamazepine overdose (Blume, 2006).

Impaired ERPs are generally found in epilepsy patients; for example, P300 amplitude decreases and latency increases with seizure activity (Hasan et al., 2023; Zhong et al., 2019). ASM effects on ERPs vary by drug, dose, duration, and mono- versus polytherapy. In one study, patients on valproic acid, carbamazepine, or levetiracetam had lower P300 amplitudes and longer latencies than controls (Tumay et al., 2013), with levetiracetam having less impact than the other two. In another study, ERP metrics worsened two months after starting ASMs (carbamazepine, zonisamide, valproate, or topiramate) but improved by six months, suggesting a time-course effect (Karadaş et al., 2025). Another study found longer latency and lower N200–P300 amplitude in epilepsy patients on polytherapy versus monotherapy, implying that simplifying regimens may help reduce the adverse effects of ASMs on ERP indices (Šarić Jurić et al., 2021).

Psychedelics

Classic psychedelics (lysergic acid diethylamide (LSD), psilocybin, dimethyltryptamine (DMT), mescaline) act at multiple targets, but their partial agonism at serotonin 5-HT_{2A} receptors, especially in cortical layer V pyramidal neurons (McClure-Begley & Roth, 2022) is critical for their psychedelic effects (Moliner et al., 2023). This activation leads to altered thalamocortical signaling and increased cortical entropy, underlying profound changes in perception, mood, and cognition. Psychedelics may also promote neuroplasticity via increased BDNF and synaptogenesis, potentially explaining their emerging antidepressant and anxiolytic effects. Their therapeutic mechanisms, including the enhancement of the effectiveness of psychotherapy, are still under investigation but involve both acute and long-lasting changes in brain connectivity (Carhart-Harris & Friston, 2019; Vollenweider & Preller, 2020).

Classic psychedelics consistently induce broadband EEG desynchronization, with reduced oscillatory power across all frequency bands (δ to γ) during both eyes-open and eyes-closed conditions (Murray et al., 2022; Vejmola et al., 2021). These effects appear dose-dependent and are most pronounced at peak subjective intensity. These studies are small, and functional unblinding is nearly unavoidable, so expectancy effects on state-dependent measures such as α power cannot be excluded.

DMT produces widespread α suppression and δ increases that track subjective intensity at the experiential peak, whereas γ increases appear only in time-averaged analyses of the post-injection period (Timmermann et al., 2023).

The serotonergic system also underlies the psychedelic action of 3,4-methylenedioxymethamphetamine (MDMA; ecstasy), which shares EEG features with classic psychedelics: increased IAF and decreased θ and α power after acute administration (Frei et al., 2001; Lansbergen et al., 2011). However, in cross-sectional studies of regular users, MDMA use is associated with increased α power

(Dafters et al., 2004; Gamma et al., 2000), although Herning et al. (2005) found increased δ instead.

ERP data on psychedelics are relatively scarce. Psilocybin has been shown to decrease 40 Hz ASSR phase-locking, with the extent of disruption correlating to subjective ratings of cognition and affect (Viktorin et al., 2022). Notably, acute 5-HT_{2A} agonism leaves the MMN largely intact: psilocybin and DMT spare the response that ketamine reliably degrades (Heekeren et al., 2008; Umbricht et al., 2003). The MMN therefore appears to be insensitive as an acute target-engagement marker for 5-HT_{2A} agonists.

Drug classes defined by pharmacological mechanism

NMDA receptor modulators

NMDA receptor modulators act on glutamatergic neurotransmission, which is critical for synaptic plasticity, learning, and memory. NMDA receptors are ligand- and voltage-gated heterotetrameric channels requiring glutamate plus a co-agonist (glycine or D-serine); the resulting calcium influx is central to synaptic signaling, though excessive activation causes calcium-mediated excitotoxicity implicated in neurodegeneration (Traynelis et al., 2010; W. L. Wu et al., 2025). Uncompetitive antagonists, including ketamine, phencyclidine (PCP), memantine, and dizocilpine (MK-801), act as open-channel blockers of the NMDA receptor. Ketamine provides rapid antidepressant effects, while memantine is prescribed for cognition in Alzheimer's disease and has been investigated for pro-cognitive effects in schizophrenia. Direct (D-serine) or indirect (glycine transporter inhibitor) agonists may improve cognition in schizophrenia (Krystal et al., 2019; Parsons et al., 1999).

The collective psychiatric, cognitive, and neurophysiological effects of subanesthetic doses of ketamine in humans resemble those of schizophrenia (Krystal et al., 1994) and have led to the glutamate hypothesis of schizophrenia (Javitt & Zukin, 1991). The most prominent qEEG effect of subanesthetic ketamine is increased spontaneous γ power; decreases in δ and α are also reported (de la Salle et al., 2016; Muthukumaraswamy et al., 2015; Rivolta et al., 2015). This frontal γ increase was the best EEG predictor of sustained antidepressant response in TRD (de la Salle et al., 2022). Ketamine is not a selective antagonist, however. It also blocks HCN channels (Chen et al., 2009), and blocking hyperpolarization-activated current (I_h) through HCN channels also raises γ power. Animal studies suggest that ketamine-induced spontaneous γ increase may also reflect NMDAR blockade on PVIs (Guyon et al., 2021). Subanesthetic NMDAR antagonist doses further disrupt frontoparietal functional connectivity and cause transient cognitive dissociation (de la Salle et al., 2016; Grent-'t-Jong et al., 2018; Muthukumaraswamy et al., 2015), through the disruption of NMDAR-dependent cortico-cortical feedback projections that operate in the α/β range (Grent-'t-Jong et al., 2023; Self et al., 2012).

ERP abnormalities are reliably reported after NMDAR antagonist exposure in humans, including decreased MMN amplitude (Cecchi et al., 2026; Javitt et al., 1996), decreased P300 amplitude (Gunduz-Bruce et al., 2012), reduced auditory evoked γ (Curic et al., 2019) and 40 Hz ASSR power, and phase-locking (Roach et al., 2025). These effects support the hypothesis that NMDAR hypofunction impairs sensory and cognitive integration. However, increased evoked γ power has also been reported after acute ketamine in both humans (Hong et al., 2010) and animals (e.g., Sullivan et al., 2015). This discrepancy may reflect differences in species, population, paradigm, and in the time of recording after dosing, since receptor occupancy changes rapidly after administration (Sivarao et al., 2016). Baseline physiology also matters: in pooled data from three placebo-controlled ketamine challenge studies in healthy volunteers, ketamine reduced duration-deviant MMN amplitude in individuals with large baseline MMN but enhanced it in those with small baseline MMN, a disordinal effect that exceeded regression to the mean (Cecchi et al., 2026).

Molina et al. (2020) studied memantine effects on EEG markers of E/I balance in schizophrenia. Patients showed a steeper resting aperiodic slope than controls, suggesting increased inhibition; 20 mg memantine normalized this slope, indicating the aperiodic slope as a biomarker of glutamatergic modulation. A single 20 mg dose of memantine also enhanced 40 Hz ASSR power and phase-locking and MMN amplitude in both patients and healthy controls (Light et al., 2017; Swerdlow et al., 2016).

Other NMDA channel blockers may have more favorable therapeutic windows than ketamine. Using dose titration to match ketamine's spontaneous γ (SGA) increases, the low-trapping blocker lanicemine was shown to produce antidepressant effects without psychotomimetic or dissociative side effects (Sanacora et al., 2014). This novel approach shows how a qEEG measure can be used to match the electrophysiological effects of two drugs while other measures distinguish behavioral or symptomatic effects (however, lanicemine subsequently failed to show efficacy in a larger multi-center trial).

NR2B-selective negative allosteric modulators (NAMs) were developed to retain ketamine's rapid antidepressant action while avoiding its dissociative and psychotomimetic liabilities, and they illustrate why pharmacodynamic biomarkers must be matched to the molecular target rather than the therapeutic class. Traxoprodil (CP-101,606) showed ketamine-like efficacy in treatment-resistant depression with fewer adverse effects (Preskorn et al., 2008), and several agents have followed, including onfasprodil (MIJ821), BI 1569912, and the orally active NBI-1070770 (Gomez-Mancilla et al., 2023; McIntyre et al., 2025). Critically, NR2B NAMs do not reproduce ketamine's spectral signature. In cynomolgus monkeys, ketamine and lanicemine increased relative gamma power, whereas traxoprodil and BMT-108908 had no gamma effect; instead, ke-

tamine, traxoprodil and BMT-108908 robustly decreased beta (13–30 Hz) and alpha power and increased delta (Keavy et al., 2016). This subunit specificity aligns with rodent work attributing antagonist-induced aberrant gamma primarily to NR2A- rather than NR2B-containing receptors (Kocsis, 2012), although deviance detection remains NR2B-dependent, as CP-101,606 abolishes MMN-like responses in awake rats (Sivarao et al., 2014). In the first-in-human study, MIJ821 produced dose-dependent resting qEEG changes at one hour post-infusion, supporting central target engagement (Gomez-Mancilla et al., 2023). The implication is direct: gamma power, the standard readout for NMDA channel blockers, would falsely indicate absent target engagement for an NR2B NAM, whereas beta reduction and delta increase provide the appropriate translational biomarker for target engagement, although its biomarker value for therapeutic efficacy of these compounds is still unknown.

NV-5138/SPN-820 is a novel mTORC1 activator that directly engages the mTORC1 pathway, a key downstream mediator of the synaptic and antidepressant effects of NMDAR antagonists such as ketamine (Harraz et al., 2016; Sengupta et al., 2019; Zanos & Gould, 2018). NV-5138/SPN-820 is believed to enhance synaptic protein synthesis and plasticity, and was tested as a potentially rapid-acting antidepressant for TRD. It produced a robust, rapid, and reproducible shift in EEG activity consistent with increased cortical activation and arousal (Trejo et al., 2021). At ~1-hour post-dose (Tmax), low-frequency power (δ, θ) and α amplitude decreased while high-frequency activity (high β, γ) and high-band coherence increased and the θ/β ratio fell, indicating increased cognitive and perceptual processing. At later timepoints (≈4–23 h), α power and the α slow-wave index rose. These effects were consistent across dosing days and largely absent under placebo, supporting central target engagement. The profile is biphasic (early high-frequency activation followed by later α enhancement), consistent with an antidepressant-like increase in synaptic activity and network efficiency.

Cholinergic modulators

Neuronal acetylcholine receptors fall into two classes: ionotropic nicotinic receptors (nAChRs), pentameric ligand-gated channels, and metabotropic muscarinic receptors (mAChRs), G protein-coupled receptors with five CNS subtypes (M_1–M_5) (Picciotto et al., 2012; Wess, 2004). Acetylcholine signaling plays a critical role in cognition, attention, and motor control (Hasselmo & Sarter, 2011; Sarter et al., 2009). Nicotinic receptor agonists enhance alertness, cognition and reward processing and are implicated in addiction (Dani & Bertrand, 2007; Gilbert et al., 2000; Preskorn et al., 2014), whereas muscarinic receptor modulation (e.g., via scopolamine) disrupts memory and arousal (Ebert & Kirch, 1998). Nicotine is the prototypical nAChR agonist: although often categorized as a stimulant because it activates the CNS, its primary molecular action is agonism at neuronal nicotinic receptors, triggering a rapid dopamine surge in the nucleus accumbens shell and, peripherally, adrenal catecholamine release (Benowitz, 2009; Tiwari et al., 2020). Acetylcholinesterase inhibitors such as donepezil increase synaptic acetylcholine availability and are widely used in Alzheimer's disease, a condition characterized by degeneration of basal forebrain cholinergic neurons (Birks, 2006; Ferreira-Vieira et al., 2016).

High cholinergic tone (wakefulness, focused attention) supports desynchronized, high-frequency EEG, while low tone (drowsiness, sedation, receptor blockade) promotes synchronized slow-wave activity, making the cholinergic system a key regulator of the EEG activation–synchronization balance. The dominant posterior alpha rhythm and its frequency are set by recurrent thalamocortical loops, which depend on the membrane potential of thalamocortical relay neurons. This is set by ascending neuromodulatory drive (cholinergic from basal forebrain and brainstem, plus noradrenergic and orexinergic input). When that drive is high, relay cells are depolarized in a tonic firing mode and the cortex desynchronizes: fast, low-amplitude activity, fast alpha or alpha suppression (Steriade et al., 1993).

Muscarinic antagonists such as scopolamine and atropine block mAChRs on cortical pyramidal cells and interneurons, reducing ACh-mediated depolarization and suppressing cortical activation (Hasselmo & Sarter, 2011). Reduced ACh lowers thalamocortical excitability and intracortical coupling, so neurons fire more synchronously at slower rhythms, reducing α power, increasing δ and θ power, and decreasing interhemispheric coherence, particularly posteriorly (Sannita et al., 1987). These changes correspond to cognitive slowing and sedation and have been used to model transient cognitive impairment (Sannita et al., 1987; Soufflet et al., 2011).

Conversely, cholinergic enhancement by acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine) or direct nAChR stimulation increases cortical and thalamic excitability (Simpraga et al., 2018). Higher cholinergic tone promotes desynchronization, suppressing δ/θ and facilitating α and γ (30–80 Hz), consistent with increased sensory gating, arousal, and attention. M_1-selective agents include both orthosteric agonists and PAMs, the latter enhancing responses to endogenous acetylcholine without global overstimulation. In primates, the M_1 PAM TAK-071 decreased scopolamine-induced δ/θ power, increased posterior α, and reduced β-band connectivity, especially in combination with donepezil (Kurimoto et al., 2019; Yin et al., 2021). In humans, TAK-071 alone increased upper-θ/lower-α and lower-β power while reducing δ power (Yin et al., 2021). Human evidence for M_1-targeted agents is emerging. In a multiple-ascending-dose study in healthy volunteers, the selective M_1 orthosteric partial agonist HTL0018318 produced dose-related qEEG changes consistent with central cholinergic engagement (Bakker et al., 2021). In a single-ascending-dose study in healthy volunteers, the M_1 PAM VU0467319 (VU319) produced dose-related effects on ERPs, including enhanced parietal P300/P600 amplitudes

in oddball and incidental-memory tasks, supporting functional M_1 target engagement (Conley et al., 2025). Human EEG and ERP evidence for M_1-selective agents rests on a single study per compound and awaits replication.

Consistent with this activating profile, nicotine produces a characteristic qEEG signature: increased low-β power, reduced θ activity, and an upward shift in spectral edge frequency (Knott, 1988; Pickworth et al., 1997), changes that index enhanced cortical arousal and have served as reference signatures for pro-attentional compounds. Its effects on event-related potentials are more limited; despite this arousal-enhancing spectral profile, nicotine has shown no reliable effect on the auditory P300 (Lindgren et al., 1999). In contrast, pre-attentive and sensory measures are sensitive to nicotine. It augmented MMN amplitude by increasing positivity to standards without affecting deviant negativity (Baldeweg et al., 2006). Nicotine also transiently normalizes P50 gating in patients with schizophrenia and their relatives, although this effect diminishes with repeated dosing (Martin & Freedman, 2007). This dissociation between clear spectral activation and absent P300 modulation reinforces that resting-state and event-related measures capture distinct aspects of cholinergic drug action.

Muscarinic receptors (mAChRs) have re-emerged as therapeutic targets, aided by subtype-selective ligands and allosteric modulators with better tolerability than earlier non-selective agents (Johnson et al., 2022). M_1 receptors are implicated in cognitive processes and synaptic plasticity, whereas M_4 receptors modulate dopaminergic signaling and are associated with antipsychotic effects. These developments have renewed interest in mAChR-targeted therapies for neurological and psychiatric disorders, including Alzheimer's disease and schizophrenia. Together, these advances mark a shift toward more precise cholinergic modulation in CNS drug development (Tobin, 2024).

Selective M_4 muscarinic modulators act on $G_{i/o}$-coupled G-protein-coupled receptors (GPCRs). Activation inhibits adenylyl cyclase, lowers cyclic adenosine monophosphate (cAMP), and modulates neurotransmitter signaling, particularly dopaminergic transmission, in the striatum and cortex (Tobin, 2024). M_4 modulators are in clinical development (e.g., emraclidine, a selective M_4 PAM, for schizophrenia), expected to affect cognition and attention via cholinergic/dopaminergic networks (Konis et al., 2024). While M_4 mAChR modulators have shown synaptic/neurotransmitter effects in animal models (Leach et al., 2010), their impact on human EEG/ERP biomarkers (e.g., power spectra, coherence) has not yet been published. As a potential antipsychotic, emraclidine might normalize ERP deficits of schizophrenia. By increasing M_4 activity, emraclidine might improve the signal-to-noise ratio of signaling in cognitive and attentional networks, thereby normalizing ERP biomarkers such as P50 sensory gating and ASSR.

In summary, the cholinergic system tunes neuronal gain and oscillatory synchrony: high ACh yields desynchronized EEG and efficient information transfer, low ACh yields synchronized slow-wave EEG and impaired cognition. Cholinergic modulators act by controlling the precision and excitability of cortical neurons in thalamocortical and hippocampal circuits.

Cannabinoids

Cannabis exerts its psychoactive effects mainly through Δ^9-tetrahydrocannabinol (THC), a partial agonist at cannabinoid CB_1 receptors (CB1R), densely expressed in the hippocampus, cerebellum, and cortex (Iversen, 2003). Anandamide is an endogenous CB1R ligand. CB1R, a Gi/o-coupled receptor, inhibits presynaptic release of glutamate and GABA by suppressing adenylyl cyclase, lowering cAMP, and inhibiting voltage-gated calcium channels (Howlett et al., 2010; Lu & Mackie, 2021; Zou & Kumar, 2018). Other approaches to modulating endocannabinoid tone, such as fatty-acid amide hydrolase (FAAH) inhibitors, which elevate anandamide by blocking its degradation, are of growing therapeutic interest, but no publicly available qEEG/ERP data currently characterize their electrophysiological effects, suggesting potential for future biomarker work.

Many earlier EEG cannabis studies used variable or poorly controlled conditions, variably linking cannabis to increased or decreased α power, reduced α peak frequency, and increased or decreased β power. Delivery, dose, timing relative to exposure, and mood effects are all potential confounds, and the relaxed setting itself can raise α power independently of the drug. Well-controlled qEEG studies of acute and chronic THC remain scarce. We focus here on studies with adequate methods.

In the resting EEG, an often-cited acute effect of exposure to cannabis/THC during subjective states of altered mood is that of increased α power (Lukas et al., 1995; Volavka et al., 1973). In a placebo-controlled study of healthy young adults (Fink, 1976), exposure to inhaled THC (~20 mg Δ^9 THC) increased α_1 (9–10 Hz), and decreased both α_2 (11–12 Hz) and β_1 (13.5–18.5 Hz) power within 10 minutes. Peak α frequency decreased and heart rate increased over the same interval. Comparison with weaker preparations showed dose dependence of these effects.

Acute THC also dose-dependently decreases θ power during mental tasks, correlating with reduced working memory performance (Böcker et al., 2009; Ilan et al., 2005).

Chronic and acute THC effects may differ. In a cross-sectional comparison of chronic users with non-users, a design that cannot separate drug effects from pre-existing differences, α power was unrelated to chronic use, but users showed decreased δ, increased θ, β, and γ power, and increased inter- and intrahemispheric coherence (Prashad et al., 2018). However, at least one study reported that chronic cannabis use reduced γ in healthy adults, using magnetoencephalography (Schantell et al., 2024).

A few studies have examined THC-related EEG complexity using the Lempel-Ziv Complexity (LZC) measure. One acute-administration study (Cortes-Briones, Cahill, et al., 2015) found THC dose-dependently increased LZC, re-

flecting elevated neural noise correlated with psychosis-like effects. Another study (Laprevote et al., 2017) found greater LZC in dependent than in non-dependent cannabis users (neither group differing from controls). In contrast, Murray et al. (2024) did not find any effect of acute THC administration on LZC (and α power was reduced).

For ERP biomarkers, THC has been reported to weaken sensory gating (higher S2/S1 ratios) in auditory and somatosensory modalities (Edwards et al., 2009; Skosnik et al., 2018). ASSR studies of cannabis users compared to controls found decreased 40 Hz ASSRs (Cortes-Briones, Skosnik, et al., 2015; Skosnik et al., 2006, 2012). In a double-blind, placebo-controlled crossover study of 20 healthy adults (24 h abstinence), an acute intravenous dose of THC (0.03 mg/kg) dose-dependently disrupted evoked γ oscillations, measured by inter-trial coherence (ITC) of the 40 Hz ASSR (Cortes-Briones, Skosnik, et al., 2015). The authors suggested that CB1R activation on cholecystokinin (CCK)-positive interneurons may interfere with the fine-tuning of network oscillations.

THC and cannabis use are generally associated with reduced cognitive task performance, with parallel EEG and ERP impairments. Inhaled THC reduces P300 amplitude in a working memory task and N400 in word recognition (Ilan et al., 2005). Both THC and a cannabis extract also reduced P300 amplitude in a choice reaction task as compared to a placebo (Roser et al., 2008). In a randomized, placebo-controlled study, THC reduced P300a and P300b amplitudes dose-dependently while early sensory ERPs were unaffected, suggesting cannabinoids impair novelty detection and working-memory updating (D'Souza et al., 2012). Chronic use of cannabis has also been shown to affect ERP components. For example, in a study of healthy young adults, as compared to nonuser controls, chronic users had increased N200 latency and reduced P300 amplitude for target tones in an auditory oddball task (Kempel et al., 2003), with 24 h abstinence before testing, suggesting chronic exposure altered stimulus evaluation, though residual fat-stored THC cannot be fully excluded.

Acute THC effects on frequency-deviant MMN were studied in one placebo-controlled study of 22 healthy adults, using oral Δ^9-THC and a standardized cannabis extract containing Δ^9-THC and cannabidiol (CBD) (Juckel et al., 2007). Oral THC did not affect MMN but, surprisingly, the cannabis extract with CBD increased central MMN amplitudes, suggesting a contributory effect of the CBD.

In another study of 30 chronic heavy cannabis users and 30 controls, no long-term THC effect on frequency- or duration-deviant MMN was evident between groups (Roser et al., 2010). However, among cannabis users, reduced frontal MMN amplitudes were found in long-term and heavy users as compared to short-term and light users for the frequency-deviant MMN only.

CBD, a non-intoxicating cannabinoid, has complex pharmacology (weak CB1/CB2 antagonism, positive allosteric modulation of glycine receptors, and 5-HT_{1A} and $TRPV_1$ interactions), contributing to anxiolytic and anticonvulsant effects (Ibeas Bih et al., 2015; Pertwee, 2008). Cannabidiol as a monotherapy shows limited EEG modulation and may have a stabilizing effect when combined with THC (Skosnik et al., 2018).

By engaging CB1R, THC mimics retrograde endocannabinoid suppression of synaptic release, reducing both excitatory and inhibitory neurotransmission and dampening overall network excitability, consistent with the observed EEG changes (increased α, decreased β) and MMN/ASSR/sensory-gating alterations. Because CB1R sits on both excitatory and inhibitory terminals, THC's net effect depends on their relative distribution, network state, and dose.

Miscellaneous

Lithium, used in bipolar disorder, reduces excitatory (dopamine, glutamate) and enhances inhibitory (GABA) neurotransmission via intracellular signaling pathways (adenylyl cyclase, phosphoinositide cascades, protein kinase C (PKC), glycogen synthase kinase-3 (GSK-3)). Through these mechanisms and neuroprotective effects (reduced oxidative stress, increased BDNF and Bcl-2), lithium stabilizes mood and supports neuronal resilience (Malhi et al., 2013; Malhi & Outhred, 2016). Lithium produces a plasma level related increase in relative power in both δ and θ bands, a decrease in relative occipital α power and a decrease in the peak α frequency (Hyun et al., 2011; Schulz et al., 2000).

Clinically available antihistamines that cross the blood–brain barrier (e.g., diphenhydramine) antagonize central H_1 receptors, reducing histaminergic arousal and producing sedation (Simons & Simons, 2011). First-generation H_1 antagonists (diphenhydramine, hydroxyzine) are sedating, shown in EEG by increased δ and θ power and reduced α, consistent with decreased arousal (Simons & Simons, 2011). These alterations resemble patterns observed during drowsiness or early sleep stages. In contrast, second-generation antihistamines (e.g., loratadine, fexofenadine) have limited CNS penetration, are less sedating and generally show minimal effects on EEG spectral power, aligning with their nonsedating clinical profile (Church & Church, 2011). ERP studies provide complementary evidence. Sedating antihistamines have been associated with delayed latencies and reduced amplitudes of attention-related ERP components such as the P300, reflecting impaired cognitive processing speed and vigilance (Theunissen et al., 2004).

Opioid analgesics act primarily through μ-opioid receptors, Gi/o-coupled GPCRs that inhibit adenylyl cyclase, lower cAMP, and reduce neuronal excitability by enhancing potassium efflux and reducing calcium influx, diminishing pain transmission (Stein, 2016). Opioid analgesics increase spontaneous δ band activity and may affect higher frequencies depending on dose and chronicity (Malver et al., 2014).

Synthesis: mechanistic principles linking drug action to EEG/ERP signatures

A cross-class review of the evidence reveals that qEEG and ERP signatures do not map one-to-one onto pharmacological mechanisms. Rather, they reflect the emergent consequences of various receptor-level perturbations on large-scale cortical dynamics. Several organizing principles emerge, which are described here and summarized in a matrix of pharmacodynamic EEG/ERP signatures by drug class and mechanism of action (Table 1, see also Supplementary Table 1 for a list of all articles reviewed and Supplementary Table 2 for a list of all compounds and associated EEG or ERP effects).

Excitation/inhibition balance and arousal as a unifying framework

The aperiodic (1/f) exponent of the EEG power spectrum, which reflects the balance of inhibitory versus excitatory synaptic drive, provides a transdiagnostic biomarker spanning drug classes (Gao et al., 2017) (Figure 3, Table 2). Agents that enhance GABAergic inhibition (benzodiazepines, barbiturates, propofol) reliably steepen the aperiodic exponent, consistent with increased inhibitory tone. Stimulants that boost catecholamines flatten it, consistent with increased excitatory drive and cortical noise. NMDA antagonists at subanesthetic doses also flatten the exponent, reflecting disinhibition-driven cortical noise despite a nominally excitation-blocking mechanism. The aperiodic exponent is therefore a mechanistically interpretable, cross-class biomarker of the E/I balance shift, and its routine dissociation from periodic spectral components should be considered standard practice in pEEG analysis.

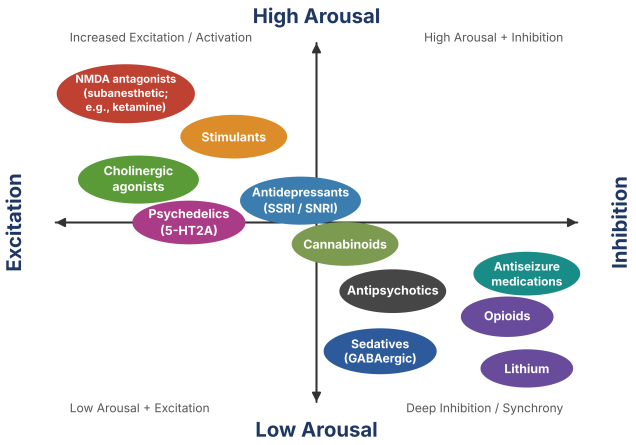


FIGURE 3
Conceptual mapping of CNS drug classes along excitation–inhibition and arousal axes. Drug classes are positioned according to their predominant acute pharmacodynamic effects on large-scale neural activity as measured by qEEG and ERP. The horizontal axis reflects net excitation/inhibition (E/I) balance (increased excitation, left; increased inhibition, right); the vertical axis reflects behavioral and electrophysiological arousal (low/sedation, bottom; high/activation, top). Quadrants: Upper-left (Increased Excitation / Activation): agents that shift the E/I balance toward excitation or disinhibition with high arousal, flattening the aperiodic slope and raising high-frequency power (NMDA antagonists at subanesthetic doses (e.g., ketamine), stimulants, and cholinergic agonists, the last promoting cortical desynchronization and alertness; psychedelics sit at the excitation edge via broadband desynchronization). Lower-right (Deep Inhibition / Synchrony): agents that enhance inhibition with reduced arousal, slowing the EEG, increasing low-frequency power, and steepening the aperiodic slope (sedatives/GABAergic drugs, antipsychotics, antiseizure medications, opioids, and lithium). The upper-right (heightened arousal with net inhibition) and lower-left (excitation with low arousal) quadrants are not populated by the classes reviewed here, reflecting the general coupling of cortical excitation with arousal and of inhibition with sedation. Antidepressants sit near the origin, reflecting modest acute effects. Cannabinoids occupy a central position, reflecting mixed effects that do not localize cleanly to one quadrant. NMDA antagonists are placed according to the effects of channel blockers such as ketamine at subanesthetic doses, at which participants remain awake and the EEG shows increased spontaneous γ power, reduced δ and α power, and a flatter aperiodic slope. This position does not describe anesthetic doses of ketamine, which abolish responsiveness, or memantine at therapeutic doses, which does not raise spontaneous γ. Positions are qualitative and indicate the predominant direction of acute effects, not measured coordinates. Table 2 lists how each qEEG and ERP measure is read on the two axes.

The level of arousal or vigilance is a separate dimension that may independently modulate EEG/ERP signatures in the absence of drug exposure but may also be a consequence of it (Figure 3). For example, low arousal, reduced vigilance, or mental fatigue promote cortical synchronization, with increased δ and θ power and reduced α frequency (Barry et al., 2007; Clarke et al., 2019; Sander et al., 2016; Trejo et al., 2015). ERPs are likewise affected: P300 and MMN amplitudes are reduced under low arousal or attention and enhanced under high arousal (Kawamura et al., 1996; Kramer et al., 1995; Trejo et al., 1995). However, some auditory ERPs may actually have greater amplitudes during low-arousal than high-arousal conditions, including P50, middle latency responses and ASSR (Griskova-Bulanova, Paskevic, et al., 2011; Griskova-Bulanova, Ruksenas, et al., 2011; Pockett & Tan, 2002).

Across the framework shown in Figure 3, consistent relationships emerge between drug mechanism and

TABLE 1 Summary matrix of pharmacodynamic EEG/ERP signatures by drug class and primary mechanism. Rows are grouped by neurotransmitter system; columns represent spectral measures (delta through gamma, individual alpha frequency, aperiodic slope) and ERP components. Cell color and symbol encode the direction and strength of the predominant effect across reviewed studies.

		qEEG SPECTRAL MEASURES							ERP COMPONENTS			
Drug class / mechanism		Delta 1–4 Hz	Theta 4–8 Hz	Alpha power	IAF	Beta 13–30 Hz	Gamma >30 Hz	Aperiodic slope	P50 gating	MMN	40 Hz ASSR	P300 amplitude
GABAergic	**$GABA_A$ γ-subunit PAMs** *Benzodiazepines, barbiturates, propofol, alcohol*	↑	↑	↓	↓	↑↑	—	↑	—	—	—	↓[+]
	$GABA_A$ δ-subunit agonist *Gaboxadol*	↑↑	↑↑	↓	?	↓	—	↑	—	—	—	—
Glutamatergic	**NMDA antagonists – subanesthetic** *Ketamine, PCP (high dose)*	↓	↑	↓	?	—	↑↑	↓	—	↓↓	↓	↓
	NMDA antagonists – therapeutic *Memantine (low occupancy)*	—	—	—	?	—	—	↓[b]	—	↑	↑	—
	NMDA co-agonists *Glycine, D-cycloserine*	—	↓	↑	?	—	—	?	—	—	—	—
Cholinergic	**nAChR agonists** *Nicotine*	↓	↓	↑	↑	↑	—	—	↑[a]	↑	—	—
	mAChR antagonists *Scopolamine, atropine*	↑↑	↑	↓↓	?	↑	—	—	—	—	—	↓
	AChE inhibitors *Donepezil, rivastigmine, galantamine*	↓	↓	↑	?	—	↑	—	↑	—	—	—
	M_1 mAChR PAMs *TAK-071*	↓	↑	↑	?	↓	—	?	?	?	?	?
Monoaminergic	**Catecholamine stimulants** *Amphetamine, methylphenidate, cocaine*	↓	↓	—	?	↑↑	—	↓	—	—	—	—
	SSRI / SNRI antidepressants *Fluoxetine, venlafaxine, escitalopram*	↓	↑	↓	?	—	—	—	—	↑	—	—
	D_2/5-HT_{2A} antagonists *Antipsychotics (haloperidol, clozapine, risperidone)*	↑	↑	—	↓	—	—	—	—	—	—	—
Serotonergic	**5-HT_{2A} agonists (psychedelics)** *LSD, psilocybin, DMT*	—	↓	↓↓	?	↓	↓	↓	—	—	↓	↓
Orexinergic	**Orexin receptor agonists** *ALKS 2680, oveporexton (TAK-861)*	↓↓	↓↓	—	?	↑↑	↑	—	?	?	?	?

		qEEG SPECTRAL MEASURES							ERP COMPONENTS			
Drug class / mechanism		Delta 1–4 Hz	Theta 4–8 Hz	Alpha power	IAF	Beta 13–30 Hz	Gamma >30 Hz	Aperiodic slope	P50 gating	MMN	40 Hz ASSR	P300 amplitude
Other / mixed	**Na^+/Ca^{2+} channel blockers (ASMs)** *Carbamazepine, phenytoin*	↑	↑	↓	↓	—	—	—	—	—	—	↓†
	Lamotrigine *Na^+ channel blocker (ASM)*	↓	↓	↓	↑	—	—	—	—	—	—	↓
	CB1R agonists *Δ^9-THC / cannabis*	—	—	↑	↓	↓	↓	—	↓	—	↓	↓
	H_1 antagonists (sedating) *Diphenhydramine, hydroxyzine*	↑	↑	↓	?	—	—	—	—	—	—	↓†
	μ-Opioid agonists *Morphine, oxycodone, fentanyl*	↑	—	—	?	—	—	—	—	—	—	—

↑↑ Strong increase | ↑ Moderate increase | — No consistent effect / mixed | ↓ Moderate decrease | ↓↓ Strong decrease | ? Insufficient data

Notes: Aperiodic slope: ↑ = steeper (more inhibition); ↓ = flatter (more excitation). IAF: ↑ = faster; ↓ = slower. P50 gating: ↑ = stronger gating (lower S2/S1 amplitude ratio); ↓ = weaker gating (higher S2/S1 ratio). MMN and P300: direction refers to amplitude; † = latency also prolonged. 40 Hz ASSR: direction refers to evoked power and phase-locking. a = shown in patients with schizophrenia and their relatives who have a gating deficit. b = normalization of an abnormally steep slope in patients with schizophrenia; minimal effect in controls. Effects represent the predominant direction in the reviewed literature; individual studies vary by dose, population, and recording context.

electrophysiological signatures. Increased inhibitory tone is associated with EEG slowing and increased aperiodic slope, whereas increased excitation or disinhibition is associated with enhanced γ activity and reduced low-frequency power. Similarly, arousal level tracks with the balance between synchronized low-frequency rhythms (sedation) and desynchronized high-frequency activity (alertness). ERP measures provide complementary information, with reduced amplitudes and prolonged latencies indicating impaired cognitive processing, and enhanced amplitudes reflecting improved attentional engagement. Table 2 summarizes how each measure is read on the two axes.

TABLE 2 Interpretation of qEEG and ERP measures on the excitation/inhibition and arousal axes of Figure 3. Entries give the direction of change in each measure. "Not directional" means that the measure does not by itself indicate position on that axis.

Measure	Shift toward inhibition	Shift toward excitation or disinhibition	Lower arousal	Higher arousal	Caution
Aperiodic slope (exponent)	Steeper	Flatter	Not established in this review	Not established in this review	Flattens with age; depends on fitting method and range
δ and θ power	Increase	Decrease	Increase	Decrease	Produced by at least six unrelated mechanisms
α power	Not directional	Not directional	Decrease with drowsiness (eyes closed)	Decrease with activation (eyes open)	Depends strongly on eye condition
Individual α frequency	Slower	Faster	Slower	Faster	Also slows with age and neurodegeneration
Frontal β power	Increase (interneuron pacing; $GABA_A$ modulators)	Increase (catecholaminergic drive)	Not directional	Increase	Ambiguous alone; read with the aperiodic slope
Spontaneous γ power	Decrease	Increase (NMDA antagonist disinhibition)	Decrease	Increase	Moves opposite to evoked γ under NMDA blockade
40 Hz ASSR (power, phase-locking)	Not directional	Decrease under NMDA blockade	May increase	May decrease	Indexes integrity of interneuron-pyramidal synchrony more than the direction of the shift
MMN amplitude	Largely unchanged (benzodiazepines)	Decrease under NMDA blockade	Decrease	Increase	Spared by 5-HT_{2A} agonists
P50 gating	Not directional	Not directional	P50 amplitude may increase	Not directional	Stronger with nicotinic agonism, weaker with THC; informative mainly in patients with a gating deficit
P300 amplitude and latency	Smaller, later ($GABA_A$ modulators)	Variable by agent	Smaller, later	Larger, earlier	General marker of cognitive disruption; not mechanism-specific
Signal complexity (Lempel-Ziv, entropy)	Decrease	Increase (psychedelics, THC)	Decrease	Increase	Few controlled drug studies

Three mechanisms map directly onto EEG signatures

As described in the class sections above, γ- and δ-subunit-containing $GABA_A$ receptor modulation produces distinct profiles (a frontal β increase with slowing versus δ and θ enhancement without the β increase); subanesthetic NMDA antagonism raises spontaneous γ while reducing evoked γ, MMN, and P300; and cholinergic tone shifts cortical desynchronization and sensory gating in both directions, which anchors the scopolamine challenge model (Simpraga et al., 2018).

Monoaminergic stimulation: mechanistically distinct pathways converging on a similar EEG profile

Catecholaminergic stimulants (amphetamine, methylphenidate, cocaine) increase frontal β and reduce θ, an activation profile superficially resembling that of GABAergic drugs. The mechanisms are opposite, however: stimulant β reflects increased excitatory drive, whereas benzodiazepine β reflects inhibitory interneuron pacing. The aperiodic slope dissociates them: stimulants flatten it, GABA PAMs steepen it. ERPs discriminate poorly here. Stimulant P300 effects are heterogeneous and agent-dependent (e.g., caffeine enhances P3b and shortens latency; dexamphetamine reduces auditory P3b), unlike the consistent P300 degradation with GABA PAMs. Two opposite

mechanisms converging on similar spectral patterns cautions against reading individual bands as mechanism-specific.

Serotonergic psychedelics: a uniquely recognizable broadband signature

5-HT_{2A} agonists (LSD, psilocybin, DMT) produce an electrophysiological profile distinct from other major neurotropic drug classes: broad α/β desynchronization, increased signal complexity (LZC), and altered sensory gating and evoked dynamics. Mechanistically, this pattern is driven by 5-HT_{2A} activation on layer V cortical pyramidal neurons, which dysregulates top-down predictive processing and normal thalamocortical rhythms. Unlike NMDA antagonists, which robustly drive SGA, psychedelics generally suppress broad SGA and β oscillations. However, effects can vary temporally and across compounds; for instance, IV DMT acutely increases both average δ and SGA power across the overall post-injection period (Timmermann et al., 2023). Unlike sedatives that produce widespread hypnotic slow-wave activity, psychedelics increase signal entropy alongside δ shifts without loss of wakefulness. Unlike stimulants, they reduce rather than increase β rhythms. This unique direction of change across multiple spectral and complexity parameters makes the broadband desynchronization signature a selective indicator of 5-HT_{2A} receptor engagement, suggesting utility as a translational biomarker.

Antidepressants: response prediction outperforms acute drug signatures

SSRIs and SNRIs produce modest, inconsistent acute EEG changes relative to the mechanistically direct classes above. The most reproducible finding is not an acute signature but a response-predictive biomarker: reduced prefrontal θ cordance within 1–2 weeks predicts clinical response at 4–8 weeks. This temporal dissociation (receptor occupancy in hours versus meaningful EEG change over days to weeks) implies the relevant events are neuroadaptation and circuit reorganization, not acute perturbation. Frontal α asymmetry normalization and rostral anterior cingulate cortex (rACC) θ current density are similarly predictive. The implication for drug development is that later-stage pEEG designs should include both acute post-dose and longitudinal timepoints. The rapid antidepressant effects of ketamine in TRD correlate best with the increase in γ power.

Where mechanism-to-signature mapping breaks down

Several classes produce EEG patterns poorly differentiated by mechanism. Antipsychotics (D_2 and 5-HT_{2A} antagonists) generate δ/θ increases and IAF slowing resembling ASM and sedative patterns, especially H_1-blocking compounds such as clozapine. Neither typical nor atypical antipsychotics reliably normalize the core schizophrenia markers (P300, MMN, 40 Hz ASSR) despite clinical efficacy, consistent with these deficits being trait rather than state markers. Sodium-channel-blocking ASMs likewise produce non-specific slowing that poorly distinguishes their mechanism from GABAergic or other slowing, with lamotrigine a partial exception (reduced power without δ/θ slowing; Table 1).

Cross-class convergences limit single-biomarker specificity

Several EEG phenomena recur across unrelated drug classes: frontal β increase arises from both GABA PAMs (interneuron pacing) and catecholamine stimulants (cortical arousal); δ/θ increase spans antipsychotics, ASMs, anticholinergics, opioids, sedating antihistamines, and lithium, at least six distinct mechanisms; α suppression follows anticholinergics, psychedelics, and some antidepressants via different targets; and P300 degradation occurs with sedatives, anticholinergics, ASMs, THC, and antipsychotics as a general marker of cognitive disruption. Individual bands or single ERP components therefore cannot be read as mechanism-specific in isolation; multi-feature profiles combining periodic bands, the aperiodic exponent, and ERP components are needed for adequate pharmacological specificity.

Discussion: implications for translational pharmacology

The evidence synthesized across drug classes, and summarized in Table 1 and Figure 3, provides an overall picture of how receptor-level pharmacological perturbations translate into reproducible electrophysiological signatures. Several themes with direct implications for CNS drug development emerge from this review.

Mechanistic specificity varies substantially across drug classes

Where the receptor-to-oscillation mapping is clear, as in the cholinergic and GABAergic systems, qEEG can confirm target engagement and even receptor-subtype selectivity, as formalized for nicotinic agents by the nAChR composite index (Simpraga et al., 2018). Where it is not, as with antipsychotics and most ASMs, its realistic uses are tracking central exposure, quantifying cognitive burden (e.g., P300 degradation and IAF slowing with ASM load) and predicting response. It is not yet known whether subtype-specific profiles extend to newer compounds such as M_4 modulators, for which no human EEG data are published.

The spontaneous versus evoked γ dissociation under NMDA antagonism has important implications for biomarker selection in glutamatergic drug development

Because resting-state and evoked γ move in opposite directions under NMDA receptor blockade, and because NR2B-selective modulators do not raise γ at all, the primary endpoint must be chosen for the molecular target, and trials should include both measures, interpreted against dose and occupancy. The occupancy at which the EEG phenotype changes has not been defined in humans.

The aperiodic slope provides a transdiagnostic, mechanism-sensitive E/I balance biomarker that is underutilized in current pEEG practice

As shown in Figure 3, the aperiodic exponent distinguishes the direction of E/I perturbation across classes with superficially similar periodic profiles. Stimulants and GABA PAMs both raise frontal β power, yet their aperiodic slopes move oppositely, flattening with stimulants, steepening with GABAergic compounds (Gao et al., 2017). This dissociation, shown empirically by Salvatore et al. (2024) and Gao et al. (2024), means that studies relying solely on band-limited power will conflate mechanistically opposite effects. The routine separation of periodic and aperiodic components using IRASA (Wen & Liu, 2016) or FOOOF (Donoghue et al., 2020) should be considered standard practice for pEEG analyses. Dose-response data for the slope are still scarce, and its reproducibility across parameterization methods and fitting ranges needs study.

Cross-class EEG convergences are the primary threat to single-biomarker specificity and must inform study design

Early-phase trials should pre-specify multi-feature qEEG/ERP panels, including resting-state spectral measures, aperiodic slope, and at least one ERP component matched to the target circuit, rather than single endpoints. The discriminant validity of such panels, shown in precompetitive initiatives such as the ERP Biomarker Qualification Consortium (Cecchi et al., 2023; Hua et al., 2022; Javitt et al., 2008), substantially exceeds that of any individual measure, but it has been shown mainly in schizophrenia and remains to be tested in other indications.

The temporal dimension of EEG biomarkers is underappreciated and design-critical for antidepressant trials

Predictive EEG changes may arise over weeks of treatment, so a single post-dose session misses them; designs need sessions at baseline, in early treatment (weeks 1 to 2), and near the clinical endpoint. Growing evidence for machine-learning analysis of resting-state EEG connectivity as a baseline predictor of antidepressant response (Li et al., 2025; Wu et al., 2020) extends this principle but requires prospective validation.

Quantitative EEG also serves as a pharmacodynamic measure of central drug exposure, independent of its mechanistic signature

Because the EEG responds to a drug that reaches and acts within the brain, the magnitude and time course of any drug-induced EEG changes directly index central target-site exposure, confirming central penetration, quantifying the onset, peak, and offset of central activity, and providing the pharmacodynamic input for PK-PD modeling that informs dose and regimen selection in early-phase development. Critically, the central pharmacodynamic time course need not parallel the plasma concentration profile: a compound with rapidly cleared plasma levels can produce persistent EEG effects when it is retained in the brain compartment (for example, through slow receptor dissociation or trapping in neurons), a dissociation that plasma pharmacokinetics alone would miss. Used this way, qEEG contributes to translational decision-making not through the class-specific signatures emphasized throughout this review, but simply as a sensitive, continuous readout that a centrally active drug is present and acting. This is a role that complements, and is analytically separable from, its use as a mechanism-specific biomarker.

Emerging drug classes are beginning to yield characteristic electrophysiological signatures that warrant standardization

Orexin receptor agonists (ALKS 2680, oveporexton) produce a dose-dependent spectral shift from sleepiness-associated low-frequency bands to wakefulness-associated high-frequency bands that parallels and correlates with behavioral wakefulness measures (Modi et al., 2025). This profile is conceptually analogous to the catecholamine stimulant activation signature but arises via a mechanistically distinct hypothalamic orexinergic projection. Establishing consensus EEG/ERP normative profiles for this emerging class would substantially strengthen pharmacodynamic characterization in ongoing and planned trials.

Recommendations for early-phase trial design

Table 3 lists six design choices that recur in trials that yield interpretable EEG and ERP endpoints, with the measures each one protects and the setting in which it applies (further detail in Supplementary Note 1).

TABLE 3 Recommendations for early-phase trial design using qEEG and ERP endpoints, with the measures each recommendation protects and the study setting in which it applies. Further practical detail is given in Supplementary Note 1.

Design choice	Recommendation	Measures protected	Study setting
Redundant baselines	Record a second predose baseline on the day before dosing, so that one unusable baseline does not remove a participant from baseline-adjusted analyses.	All baseline-adjusted endpoints	Single- and multiple-ascending-dose cohorts in healthy volunteers, which may have as few as six active and two placebo participants
Time-matched baselines	Adjust each post-dose time point to a baseline taken at the same clock time on the previous day. Placebo adjustment alone does not remove circadian effects, because a drug may interact with the circadian rhythm.	δ, θ, and α power, which show large circadian and postprandial changes in the afternoon and evening	Any design with several post-dose time points in one day
Eye condition and vigilance	Record at least five minutes each with eyes closed and eyes open. Monitor for drowsiness, which raises δ and θ power, slows α, and reduces ERP amplitudes, and so mimics a sedative drug signature.	α power and individual α frequency; δ and θ power; P300 and MMN amplitude	All resting-state recordings
Pharmacokinetic sampling	Place EEG and ERP time points around the expected time of maximum concentration, with plasma samples (and cerebrospinal fluid samples where feasible) taken close to each. Model EEG measures against concentration to account for individual exposure and for delays between plasma and brain.	All measures used for PK-PD modeling and dose selection	Early-phase dose-ranging studies
Acquisition quality	Use trained EEG technologists and standardized equipment; where turn-key systems are operated by site staff, provide expert training and periodic monitoring.	Low-amplitude measures: γ power, the 40 Hz ASSR, MMN, and P50. Control of subject attention and arousal states.	Multi-site studies and long recording days with repeated sessions
Prespecified analysis	Write the statistical analysis plan before data collection. Name a multi-feature panel (band power, aperiodic slope, and at least one ERP component matched to the target circuit), the handling of missing data, and the pooling of placebo participants across cohorts. In antidepressant studies, schedule sessions at baseline, at weeks 1 to 2, and near the clinical endpoint.	The full endpoint panel; longitudinal response predictors such as θ cordance	All trials; repeated sessions apply to patient studies of antidepressants

Limitations of the evidence base

Several limitations temper strong mechanistic conclusions. First, the literature is heavily weighted toward healthy-volunteer studies with single acute doses, with far fewer examining dose–response and PK–PD relationships in patients or the evolution of signatures with repeated dosing. Second, most studies predate rigorous periodic/aperiodic decomposition, so earlier band-power findings may conflate the two. Third, electrode density varies widely, limiting comparability of topographic and connectivity findings. Fourth, sample sizes are often small (median n ≈ 20), limiting power to detect effects at low doses or to quantify individual differences. Fifth, the proprietary nature of much early-phase data creates a publication bias toward positive findings, potentially overstating the reproducibility of some signatures. Sixth, many of the comparisons drawn in this review are between studies that differ in species, population, dosing regimen, and recording state, so some apparent disagreements, and some apparent agreements, may reflect study design more than pharmacology. Seventh, in studies of medicated patients the effects of the drug cannot always be separated from those of the illness, of prior treatment, or of concomitant medication. Eighth, this is a narrative review built on an author archive; the selection of studies was not exhaustive, and study quality was not formally scored. An open-source standardized pEEG (pre)clinical database with qEEG/ERP effects of reference compounds in animals, healthy volunteers and patients is direly needed.

Toward regulatory qualification

The FDA Biomarker Qualification Program and the European Medicines Agency (EMA) Qualification of Novel Methodologies procedure provide formal pathways for validating qEEG and ERP measures as drug development tools

(Amur et al., 2015). Progress has been slow relative to imaging biomarkers, partly due to heterogeneous recording and analysis methods. The field would benefit from harmonized data standards such as the EEG extension of the Brain Imaging Data Structure (EEG-BIDS; Pernet et al., 2019), combined with data-sharing initiatives that enable pooled analyses across trials. The pre-competitive ERP Biomarker Qualification Consortium represents an important model for the kind of cross-industry collaboration needed to generate the evidentiary base required for formal biomarker qualification in schizophrenia and related indications.

Conclusion and implications for drug development

This review demonstrates that qEEG and ERP biomarkers provide reproducible, mechanistically grounded pharmacodynamic signatures across all major CNS drug classes. Class-specific electrophysiological profiles, such as benzodiazepine-induced frontal β enhancement, ketamine-associated γ increases, and cholinergic modulation of α desynchronization, are sufficiently consistent to serve as objective indicators of target engagement and central drug activity in both healthy volunteers and patient populations.

The progressive separation of periodic and aperiodic EEG components, combined with advances in functional connectivity and signal complexity metrics, is expanding the specificity and translational value of these measures. Practical adoption in clinical trials requires standardized acquisition protocols, time-matched baseline designs, and rigorous statistical analysis planning, considerations addressed in the Discussion and in Supplementary Note 1.

As CNS drug development continues to demand earlier and more reliable evidence of target engagement, qEEG and ERP methods are well positioned to reduce attrition, inform dose selection, and support regulatory biomarker qualification across a broad range of neurological and psychiatric indications. Greater transparency in the publication of clinical trial pharmaco-EEG and ERP data would further accelerate the field.

Author contributions

LJT: conceptualization, data curation, methodology, project administration, resources, software, supervision, visualization, writing – original draft, and writing – review & editing. ST: investigation, methodology, software, data curation, visualization, writing – original draft, and writing – review & editing. KMS: data curation, methodology, writing – original draft, and writing – review & editing. GSFR: data curation, methodology, resources, and writing – review & editing. LE: visualization and writing – review & editing. RR: writing – review & editing. BAE: writing – review & editing. JED: writing – review & editing. BK: data curation, methodology, and writing – review & editing. All authors contributed to manuscript revision and approved the submitted version.

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Conflict of interest

Authors LJT, ST, KMS, GSFR, and RR were employed by Pacific Development and Technology, LLC. ST was additionally affiliated with Monash University and is currently employed by Beacon Biosignals, Inc.; ST also declares a relationship with Q-Metrx, Inc. KMS was additionally affiliated with the VA Boston Healthcare System and Harvard Medical School. GSFR declares relationships with the Netherlands Organisation for Health Research and Development (ZonMW) and Consultancy CNS Drug Development (CCNDD). RR was additionally affiliated with the Slovak Academy of Sciences. BAE is employed by Worldwide Clinical Trials and was previously employed by Boehringer Ingelheim. JED is employed by Syndeio Biosciences, Inc. BK is employed by Q-Metrx, Inc. LE provides consulting services through Follow the Molecule LLC and declares consulting income, via Follow the Molecule, from CenExel, Inc., Q-Metrx, Inc., Vandria, AbbVie, ProScience Research Group, and SureAdhere. LE also serves as an Associate Editor of Frontiers in Pharmacology; he recommended the journal as a suitable venue and has been excluded from all editorial handling, reviewer selection, and editorial decisions concerning this manuscript.

Generative AI statement

ChatGPT (OpenAI, 2025) and Gemini 3.1 Pro (Google, 2026) were used to assign preliminary relevance scores to candidate publications and to extract candidate study characteristics, using the prompt in Supplementary Note 2. Claude Opus 5.5 (Anthropic, 2026) was used to assist with revising the manuscript (including checking formatting, citations, references and shortening text to meet journal

word count limitations). All classifications, extracted data, interpretations, and manuscript text were reviewed and verified by the authors, who remain responsible for the scientific content.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2026.1982607/full#supplementary-material

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