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Review Article

Electrophysiological biomarkers in dual pathology

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ABSTRACT

Introduction: The co-occurrence of substance use disorder with at least one other mental disorder is called dual pathology, which in turn is characterised by heterogeneous symptoms that are difficult to diagnose and have a poor response to treatment. For this reason, the identification and validation of biomarkers is necessary. Within this group, possible electroencephalographic biomarkers have been reported to be useful in diagnosis, treatment and follow-up, both in neuropsychiatric conditions and in substance use disorders. This article aims to review the existing literature on electroencephalographic biomarkers in dual pathology.

Methods: A narrative review of the literature. A bibliographic search was performed on the PubMed, Science Direct, OVID, BIREME and Scielo databases, with the keywords: electrophysiological biomarker and substance use disorder, electrophysiological biomarker and mental disorders, biomarker and dual pathology, biomarker and substance use disorder, electroencephalography, and substance use disorder or comorbid mental disorder.

Results: Given the greater amount of literature found in relation to electroencephalography as a biomarker of mental illness and substance use disorders, and the few articles found on dual pathology, the evidence is organised as a biomarker in psychiatry for the diagnosis and prediction of risk and as a biomarker for dual pathology.

Conclusions: Although the evidence is not conclusive, it suggests the existence of a subset of sites and mechanisms where the effects of psychoactive substances and the neurobiology of some mental disorders could overlap or interact.

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Biomarcadores electrofisiológicos en patología dual

R E S U M E N

Palabras clave:

Biomarcadores
Electroencefalografía
Diagnóstico dual
Trastornos mentales
Trastornos relacionados con
sustancias

Introducción: Se denomina patología dual a la coocurrencia del trastorno por consumo de sustancias con al menos otro trastorno mental, que a su vez se caracteriza por una clínica heterogénea difícil de diagnosticar y de pobre respuesta al tratamiento. Por esto es necesario la identificación y validación de biomarcadores. Dentro de este grupo, se han reportado posibles biomarcadores electroencefalográficos útiles en el diagnóstico, el tratamiento y el seguimiento, tanto en condiciones neuropsiquiátricas como en trastornos por consumo de sustancias. Este artículo tiene como objetivo revisar la literatura existente acerca de biomarcadores electroencefalográficos en patología dual.

Métodos: Revisión narrativa de la literatura. Se realizó una búsqueda bibliográfica en las bases de datos PubMed, Science Direct, OVID, BIREME y Scielo, con las palabras clave: biomarcador electrofisiológico y trastorno por uso de sustancias, biomarcador electrofisiológico y trastornos mentales, biomarcador y patología dual, biomarcador y trastorno por uso de sustancias, electroencefalografía y trastorno por uso de sustancias o trastorno mental comórbido.

Resultados: Dado que se ha hallado mayor cantidad de literatura en relación con la electroencefalografía como biomarcador de enfermedades mentales y trastornos por consumo de sustancias y pocos artículos sobre patología dual, se organiza la evidencia como biomarcador en psiquiatría para el diagnóstico y la predicción del riesgo y como biomarcador para patología dual.

Conclusiones: Aunque la evidencia no es concluyente, indica la existencia de subconjunto de sitios y mecanismos donde los efectos de las sustancias psicoactivas y la neurobiología de algunos trastornos mentales podrían traslaparse o interactuar.

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Introduction

The co-occurrence of substance use disorders (SUD) and other mental disorders in the same individual has been an area of great interest for researchers over recent years. This co-occurrence has been called dual pathology (DP) in Spanish and *co-occurring disorders* in English, with the former term becoming increasingly popular in Latin America.^{1,2} Epidemiological studies have shown that the co-existence of both disorders can affect up to 50% of the general population and up to 80% of the clinical population.¹

According to Marín-Navarrete et al.,³ in addition to its name and the lack of consensus regarding this type of disorder, its importance lies in the fact that dual pathology has a negative impact on the lives of people who suffer from it and it is a serious public health problem. Negative impacts include severe addiction symptoms and more insidious psychiatric symptoms, high risk of suicide, increased use of health system services, more relapses, poor adherence to treatments, infectious and sexually transmitted diseases, dropping out of school, violent behaviour and social and economic marginalisation.⁴

The onset of the mental disorder before the onset of SUD in more than 80% of patients, especially at an early age, indicates that the co-existence of the two conditions may be related to common neurodevelopmental processes, in addition to homologous processes in terms of neurobiological

substrate, genetic vulnerability and precipitating environmental factors.² All of the above makes it more difficult to establish differential diagnoses in DP, since diagnostic categorisation in psychiatry depends on the criteria of the American Psychiatric Association (APA)'s Diagnostic and Statistical Manual of Mental Disorders (DSM), which has several limitations, including the internal heterogeneity of diagnoses, the lack of specificity and the absence of biological markers.³

A biomarker is defined as a biological characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention, and can involve a set of genes, proteins or other biomolecules.⁵ The search for biomarkers that can be used to obtain more objective measurements in order to clarify diagnoses more precisely, predict the prognosis, and monitor the response to treatment, is mandatory to understanding the interaction between mental disorder and SUD.⁶ Therefore, it is necessary to identify and validate biomarkers that help detect clinical symptoms and common neurobiological pathways in DP.⁷

Over the past decade, the search for biomarkers in psychiatry has focused on measures of brain structure and function through brain neuroimaging.⁸ However, electroencephalography (EEG) offers extensive advantages over neuroimaging. The main advantage is that EEG allows the electrical activity of the brain to be recorded in relation to different states of brain functioning. Its high temporal resolution makes it possible to capture brain dynamics on a millisecond timescale,

which makes it possible to evaluate brain activity at rest, during sleep, or in response to specific cognitive tasks.⁹ On the contrary, neuroimaging is expensive and, by targeting precise areas, is not as effective in understanding and following time-lines of the brain's processing of information.¹⁰ In addition, and as a result of the development of EEG techniques in the study of psychiatric disorders, it has started to be considered as a potential biomarker in psychiatry.⁹

Along these lines, and given the advantages that EEG offers for understanding the brain circuits affected in both mental disorders and SUDs, this review aims to investigate the existence of electrophysiological biomarkers in DP by reviewing their advantages and limitations.

Methods

A review of the scientific literature was performed on PubMed, Science Direct, OVID, BIREME and Scielo using the following keywords, in English and Spanish: "electrophysiological biomarker and substance use disorder", "electrophysiological biomarker and mental disorders", "biomarker and dual pathology", "biomarker and substance use disorder", "electroencephalography and substance use disorder" and "comorbid mental disorder". The selection of articles used for the review was based on the following criteria: original research articles with human participants, narrative reviews, systematic review and meta-analysis, in English or Spanish, with full text and published from 2008 to 2019. The aim was to compile the most recent findings given the huge advance in EEG over the past decade.

A matrix was constructed to compare the contents of the identified references in order to classify and compare them. The critical evaluation of the articles consisted of reading the article in its entirety, evaluating it and filling in the data collection tool. Studies published in duplicate or found in more than one database were considered only once.

Given the greater amount of literature found in relation to EEG as a biomarker of mental illnesses and SUDs, compared to the few articles found in relation to DP, and taking into account the possible common neurobiological origin,² once the sources were integrated into the matrix, it was decided to organise the evidence into the following thematic sections: a) EEG as a biomarker in psychiatry; b) EEG in the diagnosis and prediction of risks in SUDs, and c) EEG as a biomarker to characterise DP.

Results

A total of 644 references were identified and, after applying the aforementioned criteria, 68 references remained. After analysing the titles and abstracts and realising that they were relevant to the objectives of this study, 32 references remained.

EEG as a biomarker in psychiatry

Electrophysiological signals contain information about the brain's electrical activity at different frequencies, from δ (0.4–5.0 Hz) to θ (5–8 Hz), α (8–12 Hz), β (12–30 Hz) and γ (30–70 Hz). The digital processing of these signals is called

quantitative EEG (qEEG), while the analysis of the signals in response to a stimulus to evaluate a specific cognitive process is called event-related potential (ERP).⁹

Alterations in the resting EEG and in ERP have been observed in some mental disorders, especially in schizophrenia,¹¹ bipolar affective disorder,¹² major depression,¹³ attention-deficit/hyperactivity disorder,¹⁴ post-traumatic stress disorder, obsessive-compulsive disorder and anxiety disorders.¹⁵ Table 1 outlines the main findings.

In schizophrenia, no unique pattern of qEEG abnormalities has been identified. There is evidence of increased slow-wave activity (δ and θ bands), especially in frontal areas, which agrees with the report of hypoactivity in these regions in functional studies. Increased slow-wave activity in θ band has been related to more severe negative symptoms.¹¹ Abnormalities have also been reported in the resting EEG of α , β and γ bands. Of these, one compelling finding is the reduction in γ activity and the lack of lateralisation in response to various stimuli, possibly related to the alteration of perceptual processes.¹¹ With regards to connectivity studies and the hypothesis of abnormal functioning of cortical networks in schizophrenia, differences have been observed in the synchronous activity of the brain regions in these patients.¹⁶

On the other hand, there is evidence of deficits in some specific ERPs, such as those related to the sensory filtering process, and their alterations are reflected as deficits in P50 suppression, deficits in prepulse inhibition (PPI) and reduction in N100 and P200 amplitude.¹⁷ Furthermore, the increase in latency and reduction in P300 amplitude may reflect failures in attentional processes and deficits in information processing and cognitive updating resulting from the decrease in grey matter in parietal-temporal and frontal areas of the brain cortex and in relation to negative symptoms of the illness.¹¹

Likewise, an ERP with robust and highly replicated results in schizophrenia is the amplitude reduction in *mismatch negativity* (MMN), an ERP that appears between 100 and 250 ms in response to the appearance of a different stimulus within a frequent stimuli paradigm, which seems to reflect integration in the early phases of processing due to failures in auditory memory encoding.¹¹

Regarding heritability, it has been seen that P300 and MMN deficits have a heritability estimate of around 70%–80%. Therefore, they could be considered genetic markers and markers of vulnerability to the illness.¹⁸ However, P300 deficits are not specific to schizophrenia as they have been observed in bipolar affective disorder, alcohol dependence, depression and Alzheimer's disease.¹⁷

With regards to bipolar affective disorder (BAD), the resting EEG has shown a decrease in α activity in patients with BAD in the euthymic phase of the illness, and an increase in the activity of this same band has been observed in patients in the hypomanic or depressive phase, which corresponds to a decrease in thalamic metabolism that leads to attention deficits.¹⁹ Furthermore, an increase in low frequency bands and α activity has been reported in patients with BAD presenting psychotic symptoms, so the increase in slow bands is related to psychotic symptoms rather than to a specific disorder.²⁰ On the other hand, ERP studies have focused on early sensory processing and the processes of attention, inhi-

Table 1 – EEG findings/ERPs associated with mental disorders.

Mental disorder	Electrophysiological findings	Study
Schizophrenia	Increased slow-wave activity, especially θ ; decreased γ activity; P50 and PPI suppression deficits; increased latency and decreased P300 amplitude; decreased MMN amplitude	Boutros et al., 2008; Javitt et al., 2008; Light et al., 2015; Thibaut et al., 2015
BAD	Increased α activity in resting EEG; higher SL in all frequency bands; lower interhemispheric δ and θ band coherence; greater intrahemispheric α band coherence; P50, P200 and PPI suppression deficits, increased latency and decreased P300 amplitude, decreased P100 and ERN amplitude	Khaleghi et al., 2019; Barttfeld et al., 2014; Kam et al., 2013; Kim et al., 2013; Özerdem et al., 2011; Thaker, 2008; Morsel et al., 2018
MDD	Increased α and β activity; frontal α activity asymmetry; functional hyperconnectivity in frontal areas; P50 suppression deficits; increased latency and decreased P300 amplitude	Mumtaz et al., 2015; Salvatore et al., 2009; Iosifescu et al., 2009; Bruder et al., 2008
ADHD	Increased θ and δ band power; decreased β band power; higher θ/β ratio; increased latency and decreased P300 amplitude	Snyder et al., 2008; Tye et al., 2011; Soria-Claros et al., 2015
PTSD	Changes in α rhythm; frontal α band asymmetry; decreased frontal EEG connectivity; N200 and P300 deficits	Meyer et al., 2015; Lobo et al., 2015; Shu et al., 2014
OCD	α and θ band asymmetry; increased θ and δ slow-wave bands in fronto-temporal areas; decreased latency and increased P300 and N200 amplitude; increased ERN amplitude	Bandelow et al., 2017; Perera et al., 2018; Ibanez et al., 2012
Anxiety disorders	Non-specific changes in power spectra of θ , α and β bands; P100, N200, P300, LPP and ERN deficits	Buchsbaum, 2009; Clark et al., 2009; Wauthia et al., 2016

ADHD: attention-deficit/hyperactivity disorder; BAD: bipolar affective disorder; ERN: error-related negativity; LPP: late positive potential; MDD: major depressive disorder; MMN: mismatch negativity; OCD: obsessive compulsive disorder; PPI: prepulse inhibition; PTSD: post-traumatic stress disorder; SL: high degree of synchronisation.

bition and conflict monitoring in an attempt to link cognitive and behavioural changes present in BAD.²¹ Among other things, the following have been found: a decrease in suppression of P50 sensory gating in subjects with BAD and a history of psychosis, as well as PPI and P200 deficits in some individuals, a reduction in P100 amplitude, an increase in latency and a reduction in P300 amplitude, and a reduction in ERN amplitude. All of these findings are very similar to those found in subjects with psychotic disorders. In contrast, MMN has not been studied much in these patients, although there are some reports of MMN reduction in frontal regions.²²

Regarding connectivity, several authors have reported alterations.²³ These include a high degree of synchronization (SL) in all frequency bands, especially between the frontal and occipital cortex,²⁴ low interhemispheric coherence in the δ band in frontal regions and in the θ band in parietal regions,²⁵ and higher intrahemispheric coherence of the α band at parietal-temporal and central-parietal regions.²⁶

EEG changes have also been found in major depressive disorder (MDD). These include increased α activity with the eyes closed, greater suppression of this band with the eyes open, and differences in α activation between hemispheres (asymmetry) with relative hyperactivation of the right pre-frontal cortex, apparently related to decreased activation of cortical neurons in response to specific cognitive tasks.¹³ Furthermore, Mumtaz et al. also reported increased β activation, frontal functional hyperconnectivity and, less consistently, P50 suppression deficits, increased latency and reduced P300 amplitude.

It is noteworthy that qEEG has been studied particularly in MDD in order to select the best antidepressant treatment. In this regard, θ activity has been related to the response, specifi-

cally the increase in this band activity in the anterior cingulate cortex (ACC).²⁷ An increase in α activity has also been reported in patients with MDD without medication, with differences in the characteristics of this band, in subjects showing a response to selective serotonin reuptake inhibitors (SSRIs).²⁸

Attention-deficit hyperactivity disorder (ADHD) has also been studied with EEG. The findings include an increase in activity of the θ band and other low frequency bands, such as the δ band, and a decrease in the power of the β band, except for the combined attention-deficit/hyperactivity subgroup, which shows excess β activity. From these, it has been shown that the θ/β ratio is the most sensitive and specific in ADHD diagnosis. Upon treatment with stimulants, including methylphenidate, an increase in α and β activity and a decrease in δ and θ frequencies have been observed.¹⁴

Regarding ERPs, an increase in latency and reduction in P300 amplitude has been described, which is related to more time for processing information and symptoms of attention deficit. Furthermore, a wider cortical spatial distribution of P300 in right temporal, frontal, parietal and occipital areas is elicited by stimuli. This wider distribution indicates that these patients lack resources when it comes to processing information, and the changes in P300 may be related to the response to treatment.²⁹ Similarly, other ERP components associated with cognitive control and response inhibition in cue and no-go tasks (N200, contingent negative variation [CNV]), have shown an association with ADHD.³⁰

With respect to post-traumatic stress disorder (PTSD), frontal asymmetry, calculated as the mean difference of the α band between the right and left frontal cortex, has shown up on the EEG. This is the most consistent finding and is put forward as a possible biomarker, where low levels in the left

frontal region are associated with anxiety and depression in PTSD. However, it is not specific as it is also found in depression, premenstrual dysphoric disorder and schizophrenia.³¹ In addition, an association between some symptoms and α rhythm alterations, decreased frontal EEG connectivity at rest in relation to the severity of PTSD³² and N200 and P300 amplitude alteration during execution of an inhibitory control task, has also been reported.³³

Regarding obsessive-compulsive disorder (OCD), slow-wave activity has been described, among other things, as the most common abnormality, especially θ activity. On the other hand, broadband spectral measurements have verified this excess of slow-wave activity in addition to abnormalities in fast-wave bands, particularly α band. Regarding the EEG as a biomarker for drug prescription, it has been found that patients who have excess α activity in the anterior and medial regions respond better to SSRIs, which is clinically extremely useful.³⁴

Regarding ERPs, lower P300 and N200 latency and wider P300 and N200 amplitude have been described, which has been attributed to cortical hyperexcitability and hyperfocusing. Positive correlations have also been observed between N200 amplitude and the chronicity of the disorder, and between P300 amplitude and the severity of OCD symptoms.^{10,34}

It has also been found that, in patients with OCD, error-related negativity (ERN) and a negative wave around 50–150 ms after the commission of an error by the subject show an increase in the negativity of this component compared to control subjects, and it has been proposed that this could be considered a biomarker for this disorder.³⁴

In anxiety disorder, one consistent finding in qEEG studies of patients with anxiety disorders, including panic disorder, generalised anxiety disorder, social anxiety disorder, separation anxiety, and specific phobias, is corticobasal instability, which manifests itself as a change in the spectral power of θ and α frequency bands and the β band in frontal and central areas, which is more closely related to anxiety symptoms, without being specific to each disorder.³⁵ Furthermore, alterations in EEG-vigilance regulation, increased latency, decreased efficiency and decreased total sleep time have been reported in polysomnography studies.³⁶ On the other hand, deficits in the ERPs P100, N200, P300, late positive potential (LPP) and ERN have been found as a result of biases in the processing of emotional information, possibly due to failures in attentional control, which indicates decreased cognitive control, which influences mechanisms of selective attention toward threatening information.³⁷

EEG for the diagnosis and prediction of risk in SUD

In SUDs, research into EEG has focused mainly on alcohol, cocaine/crack, cannabis, heroin and methamphetamine.^{38,39} Table 2 outlines the main findings.

In individuals with alcohol use disorder (AUD), there have been reports of increased θ and δ band activity in relapsing subjects and, even after 6 months of abstinence, reversible α band changes with decreased relative power during relapse and increased β activity in frontal and central-parietal areas.⁴⁰ On the other hand, cognitive deficits in complex coordinated tasks in subjects with AUD indicate differences related

to functional brain connectivity, expressed as decreased synchronisation of α and β frequencies and increased synchronisation of θ and γ .⁹

Regarding ERPs, longitudinal studies have reported irreversible P300 wave deficits in individuals with AUD, indicating that amplitude indices represent a genetic vulnerability to alcohol abuse, rather than a brain dysfunction resulting from excessive alcohol consumption.⁴¹ Deficits in auditory P50 suppression, decreased N450 and increased N200 amplitude have also been reported, although less consistently.⁴⁰

Regarding cocaine use disorders, there is firm evidence of increased α and β bands in frontal regions and relative deficits in θ and δ bands in chronic users and this is directly related to the amount of acute consumption.³⁸ Other researchers report persistent changes in the α and δ bands after stopping consumption and outside of the abstinence period. These δ band deficits in the frontal cortex are possibly related to sensitisation of the mesocortical dopaminergic system.⁴²

On the other hand, studies of ERPs have reported decreased P300 in frontal regions, decreased amplitude of ERN and increased amplitude of late positive potential (LPP) as predictors of relapse,³⁹ decreased amplitude and deficits in P50,⁴³ N100 and P200 suppression.⁴⁴

Regarding cannabis use disorder, although the results of the effects of this substance on the EEG seem inconsistent, some have reported an association between the duration of consumption and reductions in the α and β bands at electrodes placed at posterior sites.⁴⁵

Regarding ERP studies, these show methodological differences regarding their definition of a regular user. Some studies report a decreased N160 amplitude in response to a visual stimulus, lower latency in N200 and N300 during a selective attention task and decreased P300 amplitude.³⁸ Another study reported an association between marijuana dependence and increased latency of P350 and P450, which was more marked in women, indicating a differential processing of the task.⁴⁶ Deficits in P50 suppression, increased latency and decreased amplitude of MMN have also been described in relation to heavy, long-term use.⁴³

In heroin use disorders, findings include increased β band activity and local α and β band connectivity, while distant functional connectivity decreases in subjects with chronic addiction. Changes in ERPs associated with heroin addiction include decreased P300 amplitude, increase of P300 and MMN latency, and increased N200 amplitude, all attributed to attentional bias deficit. Studies after six months of abstinence show P300 and P600 amplitudes similar to those of healthy subjects, but without complete recovery in their latency.⁴⁷

Finally, in methamphetamine use disorders, Ceballos et al.³⁸ report abnormal EEGs in 64% of cases, increased δ and θ slow-wave activity and correlation between θ activity and low scores on neuropsychological tests.

EEG as a biomarker for DP

There are very few studies that report alterations on the EEG of patients with DP. The findings of these studies describe differential effects of substance use (cannabis, methamphetamine) and alcohol use in psychotic disorders, particularly schizophrenia, with evident alterations in the

Table 2 – EEG findings/ERPs associated with substance use disorders.

SUD	Electrophysiological findings	Study
SUD due to alcohol	Increased power in θ and δ bands; increased power in β ; lower α and β SL and increased θ and gamma SL; increased latency and decreased P300 amplitude; P50 suppression deficits	Mumtaz et al., 2018; Sakkalis, 2011; Iacono et al., 2011
SUD due to cocaine	Increased α and β bands and deficits in θ and δ bands; decreased P300 and ERN amplitude; increased LPP amplitude; decreased amplitude and deficits in P50, N100 and P200 suppression	Ceballos et al., 2009; Campanella et al., 2014; Houston et al., 2018
SUD due to cannabis	Decreased α and β bands; decreased N160 amplitude; decreased latency of N200 and N300; increased latency of P350 and P450; P50 suppression deficits; increased latency and decreased amplitude of MMN	Herning et al., 2008; Ceballos et al., 2009; Ehlers et al., 2008; Campanella et al., 2014
SUD due to heroin	Increased β activity; increased local α and β connectivity and decreased remote functional connectivity; decreased P300 and P600 amplitude, increased latency of P300, MMN, and P600, and increased N200 amplitude	Ceballos et al., 2009; Motlagh et al., 2016
SUD due to methamphetamine	Increased δ and θ slow-wave activity	Ceballos et al., 2009
ERN: error-related negativity; MMN: mismatch negativity; LPP: late positive potential; SL: high degree of linear synchronisation; SUD: substance use disorder.		

frequency of δ/α activity,⁴⁸ P200 suppression⁴⁹ and P300 amplitude⁵⁰ and amplitude of the MMN component,⁵¹ indicating the central role of the alteration of thalamo-cortical connections, the endocannabinoid system and N-methyl-D-aspartate receptors (NMDA) within the pathophysiology of psychosis associated with substance use. Regarding MMN, it is worth noting that Ramlakhan et al.⁵² suggest MMN as a possible biomarker for the treatment of SUD and comorbid psychotic disorder, especially AUD, after finding a pattern of amplitude attenuation in people with both acute and chronic alcohol use disorder, which is not hereditary.

Other articles on alcohol use disorder and MDD,^{53,54} anxiety⁵⁵ and PTSD⁵⁶ indicate the possible usefulness of P3b and early emotion perception deficits (P100, N100 and N170) as a differential marker of MDD, where MDD may be the result of self-medication,⁵³ one of the theories developed to explain DP.

Regarding anxiety, PTSD and alcohol use disorder, ERN has been described as a differential marker, where its co-occurrence could indicate an endophenotype not derived from alcoholism, but rather a subpopulation with different genetic and biological characteristics.^{55,56} On the other hand, differences in P3b amplitude were also found in individuals with cocaine use disorder and comorbid PTSD.⁵⁷ A summary is presented in Table 3.

Discussion

Given the advantages that EEG offers for understanding DP, the objective of this review was to investigate possible electrophysiological biomarkers in DP. The search for biomarkers is necessary not only for risk assessment and early detection of DP, but also to determine the response to drug treatment and specific prognosis, in addition to helping to understand the

altered neurobiological bases in comorbidity, where a better knowledge of these factors, including their association with external or environmental influences, could be an effective means in clinical practice.⁵⁸

There are currently many researchers who are trying to determine biomarkers in psychiatry, although with limited results due to the heterogeneity of mental illnesses.⁵⁹ In this regard, this review, in addition to the studies on EEG/ERP in DP referenced in the results, found that both mental disorders and SUD share common EEG alterations that allow us to understand the underlying neurobiological changes, with the possibility of becoming biomarkers of DP.⁷

In this sense, it is worth mentioning the similarities of EEG findings in mental and substance use disorders, such as, for example, schizophrenia and SUD due to alcohol, cocaine, opiates (P50 suppression deficits and increased latency and decreased P300 amplitude),^{11,38,41} ADHD and SUD due to cocaine (decreased P300 amplitude),^{14,43} MDD and SUD due to alcohol (increased latency and decreased P300 amplitude, and P50 suppression deficits),^{9,28} and schizophrenia and SUD due to cannabis (decreased MMN amplitude, P50 suppression deficits).^{11,43}

Despite these similarities, there is little literature on the neurobiology of DP, with comorbidity with psychotic disorders having been studied more. Although the evidence is inconclusive, it appears that there is a small subset of sites and mechanisms where the effects of psychoactive substances and the neurobiology of some mental disorders could overlap or interact, which could result in the high degree of comorbidity between the two disorders.^{60,61}

Such observations refer especially to three major brain neurotransmitter systems: the dopaminergic, noradrenergic and serotonergic systems, where the main brain structures that seem to be involved are the prefrontal cortex, hippocampus, amygdala, thalamus and striatum, although the endocannabi-

Table 3 – Summary of EEG/ERP studies in dual pathology.

Mental disorder and SUD	EEG/ERP technique	Electrophysiological findings	Study
SCH (n = 28), BAD with psychotic symptoms (n = 28), MAP (n = 24), H (n = 29)	EEG activity δ/α with eyes closed and eyes open and visual cognitive task	EEG activity δ/α with eyes closed SCH and MAP > H and BAD < MAP; with eyes open SCH, MAP, BAD > H; with cognitive task BAD and MAP > H	Howells et al., 2018
AUD (n = 127), AUD + MDD (n = 26), H (n = 125)	P300 with visual task	P3b amplitude AUD < H and AUD + MDD = H	Fein & Cardenas, 2017
CUD (n = 45), SCH + CUD (n = 34), SCH (n = 33), H (n = 61)	P50, N100, P200 suppression with auditory paired-click task	P50 suppression without differences between groups; N100 suppression deficits in SCH; correlation between cannabis use and P200 suppression in SCH	Rentzsch et al., 2017
SCH (n = 20), CUD (n = 20), SCH + CUD (n = 20), H (n = 20)	P300 with auditory task	P300 amplitude SCH < H; correlation between cannabis use and decreased P300 in CUD but not in SCH + CUD	Rentzsch et al., 2016
PTSD (n = 25), PTSD + AUD (n = 18), H (n = 24)	ERN with visual task	ERN amplitude PTSD = H; PTSD + AUD > PTSD	Gorka et al., 2016
PS (n = 33), PS + AUD (n = 23), H (n = 17)	MMN with auditory task	Temporal MMN amplitude PS + AUD < PS or H; fronto-central MMN amplitude PS < PS + AUD < H	Chitty et al., 2011
AUD and comorbid mental disorder (n = 29), H (n = 15)	ERN with visual task	ERN amplitude AUD > H especially in comorbid anxiety	Schellekens et al., 2010
AUD (n = 12), AUD + MDD (n = 12), MDD (n = 12), H (n = 12)	P300, P100, N100, N170 with visual emotional cognitive task	Independent of MDD, AUD produced alterations in P3b, P100, N100 and N170	Maurage et al., 2008
SUD due to cocaine (n = 14), SUD due to cocaine + PTSD (n = 11), H (n = 9)	P300 with visual task	Central P3a amplitude and latency and centro-parietal P3b SUD due to cocaine + PTSD > SUD due to cocaine and H	Sokhadze et al., 2008

AUD: alcohol use disorder; BAD: bipolar affective disorder; CUD: cannabis use disorder; ERN: error-related negativity; H: healthy; MAP: methamphetamine-associated psychosis; MDD: major depressive disorder; MMN: mismatch negativity; PS: psychosis; PTSD: post-traumatic stress disorder; SCH: schizophrenia; SUD: substance use disorder.
 “A < B” means that A is significantly lower than B; “A = B” means that A and B are not significantly different; “A > B” means that A is significantly higher than B.

noid system, related to dopaminergic activity in the case of schizophrenia and other mental disorders,⁶² has been mentioned, since the interaction of the two conditions produces obvious EEG alterations that could be possible biomarkers.

However, these differential biological correlates have not been transformed into clinically useful biomarkers. Some of the reasons put forward for the absence of biomarkers⁶³ include: the current classificatory and diagnostic systems in psychiatry being primarily symptom-based; the enormous number of methodological limitations of studies on the pathophysiological bases of mental disorders; the lack of valid animal and *in vitro* models for psychiatric disorders; and issues related to pathogenetic paradigms for mental disorders.

One of the main difficulties is that current classificatory and diagnostic systems are not designed to identify biological markers, since they are not based on neurobiological parameters and have been greatly modified over time.⁶⁴ This has challenged the principle of the categorical approach to the diagnostic classification of mental disorders and has led to the proposed dimensional approach of Research Domain Criteria (RDoC) gaining ground as an alternative form of

classification.⁶⁵ Likewise, the methodological issues of existing studies, such as small sample sizes, low statistical power, frequent lack of repetition of results, and the use of unique evaluation parameters and biomarkers with small effect sizes, constitute another important difficulty in the search for biomarkers in DP.⁵⁹

However, it is important to note that all authors of the articles reviewed agree on the usefulness of EEG for establishing the cerebral pathophysiological mechanisms of DP and on the importance of taking this comorbidity into account in clinical practice, but they also recognise the lack of consistency of the findings and, therefore, the need to reproduce these results in longitudinal research. Efforts to search for biomarkers must continue as this will allow a greater understanding of the aetiology of DP and, therefore, the design of more accurate prevention and treatment programmes.

Conclusions

This article reviews the existing evidence on EEG alterations in DP. Although the evidence is inconclusive, it indicates that

there is a small subset of sites and mechanisms where the effects of psychoactive substances and the neurobiology of some mental disorders could overlap or interact. However, the lack of consistency in the findings is acknowledged. Therefore, searching for biomarkers in DP using EEG may be a new option in future research.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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