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REVIEW

Isolated epileptiform activity in children and adolescents: prevalence, relevance, and implications for treatment

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Abstract

In the field of psychiatry diagnoses are primarily based on the report of symptoms from either the patient, parents, or both, and a psychiatrist's observations. A psychiatric diagnosis is currently the most widely used basis for medication selection and the brain is seldom investigated directly as a source of those symptoms. This study addresses the request from the National Institute of Mental Health (NIMH) Research Domain Criteria Project (RDoC) for scientific research into neurological abnormalities that can be linked to psychiatric symptoms for the purpose of predicting medication response. One such neurological abnormality that has been the focus of many studies over the last three decades is isolated epileptiform discharges (IEDs) in children and adolescents without seizures. We conducted a systematic review of the literature to determine prevalence rates of IEDs within diagnostic categories. We then compared the prevalence of IEDs in the selected literature to our IRB-approved data archive. Our study found a consistent high prevalence of IEDs specifically for ADHD (majority > 25%) and ASD (majority > 59%), and consistent low prevalence rates were found for Depression (3%). If children and adolescents have failed multiple medication attempts, and more than one-third of them have IEDs, then an EEG would be justified within the RDoC paradigm.

Keywords RdoC · Children · Adolescents · EEG · Isolated epileptiform discharges · Prevalence · Psychiatric symptoms · Autism spectrum disorder · Attention deficit hyperactivity disorder

Introduction

The field of psychiatry typically bases a diagnosis primarily on the patient's and parent's report of symptoms and the psychiatrist's observations. A psychiatric diagnosis is currently the most widely used basis for medication selection. Oftentimes when clinical benefit is lacking, patients have their dosage increased and if this does not work, another medication is tried until one shows more promise. This trial-and-error approach thereby results in multiple medication attempts until finding an adequate match. In this traditional model of psychiatric practice, the brain is seldom investigated directly as a source of the symptoms. The goal of this paper is to show that evaluating the brain and linking psychiatric symptom presentation with neurobiological abnormalities could result in more accurate medication selection.

In 2012 the National Institute of Mental Health (NIMH) established the Research Domain Criteria Project (RDoC), proposing biological, genetic, and imaging research to identify biomarkers and neurological abnormalities that

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could be linked to psychiatric symptoms. "The task is to identify the biomarker that predicts response—whether the treatment is a medication or a psychosocial intervention," [1].

Electroencephalography (EEG) is one such method of functional imaging that has emerged as a promising and accessible method to assist in the identification of the neurobiological abnormalities that underlie psychiatric symptoms [2]. However, a recent critical appraisal of the EEG literature concluded more systematic replication, and balanced reporting of positive and negative findings was required to evaluate the true potential of EEG as a clinical tool [3]. This personalized approach to medicine is expected to phase out the "one-size-fits-all" approach to psychiatric treatment and pave the way towards true personalized medicine.

One neurobiological abnormality that has previously been linked to psychiatric symptoms is isolated epileptiform discharges (IEDs) [4–8]. In this paper, we use the term IEDs as it refers to spike and wave or sharp and slow epileptiform activity in nonepileptic individuals. Various terms have historically been used to describe IEDs in the literature, for example, subclinical epileptiform activity, epileptiform discharges and interictal epileptiform discharges. Of the many forms of EEG abnormalities, the identification of IEDs is critical for medication selection.

Studies have found that certain classes of medication such as stimulants, antidepressants, and antipsychotics can lower the seizure threshold which can increase neuronal instability, worsening symptoms and risking the development of seizures. Evidence suggests that normalization of neuronal instability caused by IEDs has been found to be associated with symptom improvement in depression [9] and panic disorder [4], thereby demonstrating the observed psychiatric symptoms such as mood and panic attacks, and IEDs are clearly associated, albeit only for subgroups of patients. Identifying IEDs earlier in the course of treatment can prevent the use of inappropriate medications that might increase brain instability, reducing the need for multiple medication trials.

To explore the importance of identifying IEDs, this paper assesses their prevalence in the literature and compares it to a cross-sectional analysis in a large psychiatric practice. We conducted a systematic review of the literature to determine prevalence rates of IED within diagnostic categories. Then we compared the prevalence of IEDs in the selected literature to our IRB-approved data archive. The goal of this paper is to show that evaluating the brain using EEG and linking psychiatric symptom presentation with neurobiological abnormalities could result in more accurate medication selection.

Methods

Systematic literature review

Our literature search was limited to the PubMed/Medline database. Despite the multitude of literature reviews on the subject of IED prevalence, we elected to limit our search criteria to publications from 1994 -present. The major changes implemented in the DSM-IV, such as the multiaxial diagnostic system and more explicit diagnostic criteria (https://www.psychiatry.org/psychiatrists/practice/dsm/history-of-the-dsm), informed this decision. We proceeded to exclude publications not in English, with non-human subjects, and those pertaining to seizure disorders (i.e., epilepsy) and psychogenic nonepileptic seizures, as we wished to focus on the prevalence of IEDs within psychiatric diagnoses only. The following search terms were used in varying combinations: "epileptiform discharges", "paroxysms", "spikes", "spike-and-wave complex", "paroxysmal bursts", "psychiatric disorders", "anxiety", "panic (attacks/disorder)", "obsessive–compulsive disorder/OCD", "post-traumatic stress disorder/PTSD", "depression", "bipolar disorder", "psychosis", "schizophrenia", "autism/ASD", and "ADD/ADHD". Additional searches were done by author names from selected publications. Their associated reference lists were inspected for possible inclusion. To include a robust body of studies addressing our research, our systematic literature review was not age-discriminant.

Cross-sectional analysis review

In addition to the systematic literature review, we included a cross-sectional data review. The data archive database of refractory cases from a large psychiatric private practice in Houston, Texas was used for this cross-sectional review. The following data were collected: demographics, diagnostic categories, and EEG features for 722 children and adolescents ages 4–18 seeking treatment for symptoms of ADHD, anxiety disorders, autism spectrum disorder, and/or mood disorders. Electroencephalography Data Collection Equipment. Patient EEG data at the private practice were recorded using Mitsar equipment and an "Electrocap" according to the international 10–20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). A minimum of 20 min total data was recorded in both eyes open (10 min) and eyes closed (10 min) with lights off and resting conditions based upon each patient. Each of the raw EEGs were read by the same neurophysiologists who is a board certified electroencephalographer. Automatic spike detection software was employed as a

component of the EEG data analysis. Clinical correlation to any neurobiological abnormalities is established with a 296-item questionnaire sent via email directly to parents of each patient. Based on their answers, it is determined if neurological abnormalities are clinically relevant. The center's psychiatrist uses this information to assess current medications and adjust accordingly, avoid prescribing contraindicated medications, and select those that would increase neuronal stability.

Systematic review: prevalence

Isolated epileptiform discharges (IEDs): a psychiatric biomarker?

IEDs have been identified as a significant contributor to psychotropic medication failure [8, 10] and many studies have found a higher occurrence of IEDs in psychiatric populations compared to control groups [6, 7, 11]). Zimmerman and Konopka compared the clinical severity of multi-focal and single-focus IEDs, finding that psychiatric clinical severity increased as the number of foci decreased [7]. In contrast, the epilepsy literature suggests that a multi-focal distribution of epileptiform discharges is associated with greater clinical severity of seizures.

IEDs are reflective of network hyperexcitability. For patients without seizures, IEDs are referred to as "subclinical" IEDs, meaning they are not severe enough to present observable symptoms such as seizures. For patients with seizures, IEDs are considered "interictal", meaning they occur between seizures. When IEDs occur chronically for a prolonged period of time, the synapses become hyper-excited, leading to a process called epileptogenesis. Research suggests that epileptogenesis can have a genetic or congenital underpinning or be triggered by trauma, hypoxia or infection [12]. Through repetitive stimulation of the neural network, IEDs have a tendency to spread to other areas of the brain [13]. Seizures are likely to develop when this hypersynchronous activity becomes generalized. Therefore, IEDs can be considered reflective of an epileptogenetic process, even if they are considered subclinical.

The prevalence of IEDs in nonepileptic healthy populations, according to Gregory et al., should be less than 1% [14]. Shelley et al. reviewed 22 papers and found an IED prevalence of 0.8% to 18.6% in children and 0.3% to 12.3% in adults. While the research indicates that the prevalence is low in nonepileptic healthy populations, it is quite a bit higher in neuropsychiatric populations, but they vary by diagnostic category [6].

Prevalence of IEDs in ADHD

Our search identified seven studies on the prevalence of IEDs in ADHD and a review on the subject indicates that the prevalence could range from 16–35% (see Table 1). Swatzyna et al. published a study from an earlier version of the current dataset [15]. This study analyzed the prevalence of IEDs in and adolescents without epilepsy, reporting 32% prevalence in those diagnosed with ADHD. This was a replication of a study published in 2011 by Millichap and Millichap, who found a 25% prevalence in children and adolescents with ADHD. Millichap et al. has published multiple times on the topic of IEDs in children and adolescents with ADHD, consistently finding that about 26% of patients with ADHD also had IEDs [15, 16]. Kanemura et al. found a 34.8% prevalence of focal paroxysmal abnormalities in children diagnosed with ADHD [17]. Hughes et al. found that 53 of 176 children with ADHD, 30.1%, showed definite, noncontroversial epileptiform activity in their EEGs [18]. Additional studies have found similar results. A study by Kanazawa et al. found that 22.4% of children with ADHD had IEDs [19]. These children were more likely to have epileptiform activity if they did have a comorbid autism spectrum disorder (ASD) diagnosis. Lee et al. found that 16.1% of ADHD patients under the age of 18 had IEDs. Of those with IEDs, 13% of them developed epilepsy [20].

Prevalence of IEDs in anxiety disorders

Anxiety disorders have also been correlated with IEDs as this diagnostic category encompasses a wide variety of psychiatric issues. Disorders under this diagnostic category include, but are not limited to, generalized anxiety disorder (GAD), panic disorder, obsessive–compulsive disorder (OCD), post-traumatic stress disorder (PTSD), phobias, eating disorders, and oppositional defiant disorder (ODD). That being said, the search yielded one study from Hayashi et al. found that two of 17, 11.8% of patients with panic disorder had paroxysmal activity [21].

Prevalence of IEDs in autism spectrum disorder

Our investigation into the literature suggests that there is a high prevalence of IEDs in children with Autism Spectrum Disorder (ASD). Kawasaki et al. found that of 158 patients ages 1–40 with an ASD diagnosis, 60.8% of them displayed paroxysmal abnormalities in their EEG; 39% of these patients later developed epilepsy [22]. A study by Hughes and Melyn lends support to this in their finding that 58.9% of patients ages 1–21 with autism, had IEDs [23]. Studies with sleep EEGs have found IED prevalence rates of 41.3% [24] and 60.8% [25]. Swatzyna et al. found of 140 patients ages 4–25 diagnosed with ASD, 36.7% had IEDs [26]. Reinhold

Table 1 Summary table of publications on EEG IEDs in psychiatric disorders

Disorder	Study	IED prevalence	Findings
ADHD	Hughes et al. [21]	30.1%	53 of 176 children diagnosed with ADHD, 30.1%, ages 3–18, showed definite noncontroversial epileptiform activity
	Millichap et al. [18]	25.1%	157 o4 624 sleep-deprived EEGs of children with ADHD, 25.1%, have epileptiform abnormalities
	Kanemura et al. [20]	34.8%	16 of 46 children diagnosed with ADHD, 34.8%, had focal paroxysmal abnormalities
	Kanazawa et al. [19]	22.1%	32 of 145 children diagnosed with ADHD, 22.1%, showed epileptiform discharges; patients without comorbid ASD were more likely to have IEDs
	Lee et al. [15]	16.1%	29 of 180 patients diagnosed with ADHD, 16.1%, under the age of 18, had epileptiform discharges; 4 of these patients developed epilepsy later
	Zaimoğlu et al. [39]	26.4%	39 of 148 epileptiform abnormalities found in 26.4% of children, ages 6–13
	Swatzyna et al. [17, 29, 35]	32.0%	82 of 257 children diagnosed with ADHD ages 5–18, 32% had isolated epileptiform discharges
	Arns et al. [8]	4.1%	Two out of 49 children with ADHD presented with Paroxysmal EEG and two out of 49 in the control group. Low prevalence likely related to short EEG recording length of 2 min
Anxiety Disorders	Hayashi et al. [22]	11.8%	2 of 17 patients, 11.8%, ages 18–65, diagnosed with panic disorder and EEG abnormalities showed paroxysmal activity; inclusion criteria: no psychotropic medication use, no comorbid depression, personality disorder, or schizophrenia, no substance abuse, no physiological disease/conditions
Autism Spectrum Disorder	Kawasaki et al. [23]	60.8%	96 of 158 patients with a diagnosis on the autism spectrum, 60.8%, ages 1–40, displayed paroxysmal abnormalities; 39% of the autistic patients developed epilepsy
	Hashimoto et al. [27]	43%	37 of 86 sleep EEGs, 43% of autistic patients ages 2–19, had epileptic discharges
	Reinhold et al. [26]	65%	55 of 85 EEGs of children with ASD, 65%, had epileptiform discharges
	Chez et al. [28]	60.7%	540 of 889 of patients with ASD, 60.7%, showed abnormal epileptiform activity in sleep only
	Hughes and Melyn [24]	58.9%	89 out of 151 EEGs, 58.9%, of autistic patients, ages 1–21, showed epileptiform discharges; 78 patients in total, some with multiple EEGs
	Parmeggiani et al. [30]	23.5%	81 out of 345 patients, ages 2–37, displayed EEG paroxysmal abnormalities; of those, 60.5% were diagnosed with an autistic disorder and 30.9% with a pervasive developmental disorder
	Yasuhara [32]	85.8%	870 of 1014 sleep EEGs of autistic children, ages 3–20, 85.8% displayed EEG epileptic discharges (note, this did not take into account the presence of discharges without a diagnosed epileptic disorder)
	Mulligan and Trauner [25]	59.4%	60 of 101 IEDs found in 59.4% of sample with ASD; prevalence of IEDs increased as severity of ASD condition increased ("Asperger's"—20%, Autism—60%, PDD-NOS—81.3%)
	Swatzyna et al. [29]	36%	51 of 140 children with ASD, 36%, displayed epileptiform discharges
Mood Disorders	Inui et al. [30]*	3.2%	Non-psychotic mood disorder
		33%	Mood incongruent mood disorder
	Arns et al. [8]	3.6%	Patients with non-psychotic unipolar MDD versus controls did not differ significantly in IED prevalence (3.6% and 5.2% respectively), but IEDs did affect response to the antidepressants Escitalopram and Venlafaxine (but *not* to Sertraline)
Psychosis /psychotic disorders	Inui et al. [30]*	33%	Schizoaffective disorder
		30%	Schizophreniform disorder

*Denotes publications that apply to multiple diagnostic categories

et al. found the prevalence at 65%; however, the sample size was a bit smaller than the other studies [27]. Mulligan and Trauner found that 59.4% of patients with ASD had IEDs and the likelihood of IED presence increased proportionally with their clinical severity [28]. IEDs were present in 20% of those with "Aspergers", in 60% of those with autism, and in 81.3% of those with pervasive developmental disorder.

Prevalence of IEDs in mood/depressive disorders

The prevalence of IEDs in mood/depressive disorders (MDD) is lower when compared to that of ADHD, ASD, and anxiety disorders. Initial findings seem to indicate that mood disorders pertaining to mania tend to have a higher frequency of IED activity than those with depressive symptoms. In a study by Arns et al., the IED prevalence in MDD patients was actually lower than that of the healthy controls (3.6% compared to 5.3%); however, the presence of IEDs in MDD patients predicted reduced response to antidepressants [29]. Note that study also employed only 2 minutes of EEG recording, so the prevalence rates are likely underestimated. Inui et al. found a similar prevalence of IEDs in mood and psychotic disorders; only 3.2% of patients without psychotic features displayed IEDs on their EEG and none of them with mood-congruent features had IEDs. Interestingly, the highest prevalence of IEDs was identified in patients with mood-incongruent features (33%), schizoaffective disorder (33%), and schizophreniform disorder (30%). It is worth noting that patients with the highest prevalence of IEDs were those with features of both mood and psychotic disorders. There was not a high prevalence within patients with mood disorders or schizophrenia alone. This indicates a possible link between IED prevalence and patients with features within multiple diagnostic categories [30].

Results

The systematic literature review yielded 18 studies meeting the search criteria. For an overview, see Table 1 Note. * denotes publications that apply to multiple diagnostic categories. Table 2 reflects the current prevalence of IEDs per diagnosis from the cross-sectional analysis.

Discussion

Our systematic review of published articles since the introduction of the DSM-IV in 1994 and cross-sectional dataset both found high prevalence of subclinical IEDs, specifically in children and adolescents diagnosed with ADHD and ASD. The prevalence rates of IEDs in those with ADHD range from 16.1 [20] to 34.8% [17]. There is high consistency for prevalence across the literature in the 4–34.8% range (see Table 1) with a majority of studies showing a prevalence higher than 25 and with a weighted mean prevalence of 25.2%. For those with ASD, relatively high estimates are reported in the literature ranging from 23.5 [31] to 85.8% [32], with a fairly consistent prevalence rate of 59% or higher and a weighted mean prevalence of 63.3%. While yielding a limited number of studies, the prevalence rates appear relatively lower for mood disorders at approximately 3% for non-psychotic mood disorders [8, 30], 11.8% for anxiety disorders [21] and an intermediate prevalence rate for psychosis and psychotic disorders at 30–33% [30].

Table 2 Cross-sectional analysis of the occurrence of IEDs by diagnostic category in ages 4–18

Diagnostic category	Ages 4–18	Ages 4–18 with IEDs	%
ADHD	594	219	36.87
Anxiety disorders	312	122	39.10
Autism spectrum disorder	207	72	34.78
Traumatic brain injury	154	46	29.87
Mood disorders	139	54	38.85
Sleep disorders	123	49	39.84
Oppositional defiant disorder	70	35	50.00
Tourette's disorder	61	31	50.82
Seizures	52	29	55.77
Migraines/headaches	48	21	43.75
Psychosis	28	15	53.57

The numbers above represent the number of both comorbid and single diagnoses

The cross-sectional data review revealed rather similar prevalence rates for ADHD and ASD of 36.9% and 34.8%, respectively, and the rate for psychosis slightly higher relative to that obtained in the systematic review at 53.57%. On the other hand, for mood and anxiety disorders the prevalence rates from the cross-sectional dataset were much higher relative to the systematic review at 38.9% and 39.1%. These percentages may be higher as a result of a selection bias since the clinic specializes in refractory cases which can lead to an oversampling of patients with multiple medication failures.

While the literature confirming the presence of IEDs in those with an anxiety disorder is sparse, Boutros notes that subcortical structures, such as the insula and amygdala, are likely sources of panic attacks. Epileptiform activity generated subcortically is unlikely to be detected by scalp EEGs. Subcortical IEDs are typically observed with electrodes surgically implanted into the limbic structures directly, which could explain the lack of research and results on IEDs in anxiety disorders [11]. Furthermore, as Inui et al. noted, the highest prevalence of IEDs in those with mood disorders where those who also had comorbid psychotic symptoms.

Psychosis is a known predictor for poor response to many antidepressant treatments. However, it is a good predictor for the efficacy of electroconvulsive treatment (ECT), thereby suggestive of a sub-group with higher IED prevalence [30]. This requires further study.

Comorbidity was not taken into account for this review, but it is a likely contributor to the dynamic between IEDs and psychiatric issues. In a similar vein, the lack of articles relating to psychotic disorders could be due to a weaker correlation between psychosis and the presence of IEDs. A distinction between psychotic disorders and psychotic symptoms was not made in our literature search, so it is plausible that IEDs could account for psychotic symptoms, but not psychotic disorders. The link between seizures and postictal psychosis lends credence to this hypothesis; however, more research is needed.

The current review demonstrates a consistent high prevalence of IEDs in ADHD and ASD. This requires more study, specifically focused on appropriate differential diagnosis and possibly anticonvulsant treatment. Our review spanned more than 25 years of research while the sample size for ADHD and ASD combined yielded a sample of less than 700 patients. This suggests that more systematic studies are needed to understand the role of IEDs in the pathophysiology and treatment of these disorders. Table 3 reflects a comparison of prevalence data extracted from the systematic literature review and the cross-sectional data analysis for ADHD and ASD with the weighted mean prevalence for each.

Future studies

The detection of IEDs still consists of a manual review by a neurologist or neurophysiologist with board certification in electroencephalography. This subjective interpretation is a significant impediment to scientific investigation. Future studies should focus more on automated means of classification of IEDs such as Deep-Learning [33]. Grossi et al. recently published a study in 2019 using a specific machine-learning system (MLS) named MS-ROM/IFAST (Multi-Scale Ranked Organizing Map/Implicit Function as Squashing Time). This system is used to extract specific features in computerized EEG data with a high degree of accuracy [34].

Further recommendations are to use a recording length of 20 min or more (10 min eyes open and 10 min eyes closed) to meet neurology standards for a conventional EEG. A further limitation includes the lack of standard terminology in the relevant search criteria. In many cases, terms are used interchangeably. The clearest example of this is the number of ways IEDs were phrased in the search (epileptiform discharges, isolated/interictal discharges, spikes, spike-and-wave, paroxysms, transient discharges, EEG abnormalities, etc.). While many of these are used interchangeably, other

Table 3 ADHD and ASD weighted mean and cross-sectional dataset prevalence

	IED	Total	Percentage	
ADHD	53	176	30.1%	Hughes et al. [21]
	157	624	25.2%	Millichap et al. [18]
	16	46	34.8%	Kanemura et al. [20]
	32	145	22.1%	Kanazawa et al. [19]
	29	180	16.1%	Lee et al. [15]
	39	148	26.4%	Zaimoglu et al. (2017)
	82	257	31.9%	Swatzyna et al. [17, 29, 35]
	2	49	4.1%	Arns et al. [8]
ADHD weighted mean prevalence			25.2%	
AHHD cross-sectional dataset			36.9%	
ASD	96	158	60.8%	Kawasaki et al. [23]
	37	86	43.0%	Hashimoto et al. [27]
	55	85	64.7%	Reinhold et al. [26]
	540	889	60.7%	Chez et al. [28]
	89	151	58.9%	Hughes and Melyn [24]
	81	345	23.5%	Parmeggiani et al. [31]
	870	1014	85.8%	Yasuhara [32]
	60	101	59.4%	Mulligan and Trauner [25]
	51	140	36.4%	Swatzyna et al. [29]
ASD weighted mean prevalence:			63.3%	
ASD cross-sectional dataset:			34.8%	

research insists that there are distinct differences between them. Additionally, there may be terms used that we were not aware of. Future studies should make efforts to consolidate this terminology.

Treatment considerations

The data presented suggest that there is a high prevalence of IEDs across psychiatric disorders. The highest prevalence is found in children and adolescents diagnosed with ADHD and ASD. In addition, several studies suggest IEDs are likely associated with panic-attacks [4]. For those children and adolescents with ADHD, ASD and panic attacks, our research suggests that IEDs should be considered as an RDoC construct for the purpose of medication selection.

Arns et al. found that IEDs predict poor response to most antidepressant medications [8]. One antidepressant, sertraline, was found to normalize IEDs [9]. Neurology does not support the use of anticonvulsants for anything other than seizure disorders. Psychiatry commonly uses anticonvulsants for "mood disorders" without the identification of IEDs. Using the EEG to guide anticonvulsant selection has been found to be effective in psychiatric cases regardless of diagnoses [35]. Anticonvulsant neuromodulation techniques such as neurofeedback could also be an option for treatment of IEDs [36–38].

Conclusion

Regardless of diagnosis, children and adolescents are a very complex population to treat. Their rapidly evolving brains and bodies present an ever-changing target for medication selection. Our cross-sectional analysis of 772 children and adolescents identified 286 (37%) with IEDs. This high prevalence of IEDs was supported by our systematic review. Consistent high prevalence of IEDs was found specifically for ADHD (majority > 25%) and ASD (majority > 59%), and consistent low prevalence rates were found for Depression (3%). If children and adolescents have failed multiple medication attempts, and more than one-third of them have IEDs, an EEG would be justified within the RDoC paradigm.

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Author contributions RS, EB, MH, developed the original draft and started constructing the table. RS, EB, MA, NB, RT, and JT further developed the study with EB, MH, and EM compiling the relevant studies and completing the tables. RS, MA, NB, RT, and JT, expanded the scope of the study and developed the conclusions. RS, MA, NB, RT, JT, EB, MH, and EM as a group approved the final manuscript.

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Data availability The data from our cross-sectional data review can be made upon request.

Compliance with ethical standards

Conflict of interest MA is unpaid research director of the Brainclinics Foundation, a minority shareholder in neuroCare Group (Munich, Germany), reports options from Brain Resource (Sydney, Australia); and is a co-inventor on four patent applications (A61B5/0402; US2007/0299323, A1; WO2010/139361 A1) related to EEG, neuromodulation and psychophysiology, but does not own these nor receives any proceeds related to these patents; Research Institute Brainclinics received research funding from Brain Resource (Sydney, Australia), UrgoTech (Paris, France) and neuroCare Group (Munich, Germany), and equipment support from Brainsway, Deymed, neuroConn and Magventure. The author declares no conflicts of interest with respect to the research, authorship, and/or publication of this article. The other authors declare that they have no conflict of interest.

Ethical approval The manuscript does not contain clinical studies or patient data.

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