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Review article

A systematic review of quantitative EEG as a possible biomarker in child psychiatric disorders

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ABSTRACT

Quantitative EEG (qEEG) has emerged as a potential intermediate biomarker for diagnostic clarification in mental illness. This systematic review examines published studies that used qEEG in youth with psychiatric illness between 1996 and 2017. We conducted a comprehensive database search of CINAHL, PubMed, and Cochrane using the following keywords: "quantitative EEG" and depression (MDD), anxiety, attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), eating disorder, conduct, substance use, schizophrenia, post-traumatic stress disorder, and panic disorder. Our search yielded 516 titles; 33 met final inclusion criteria, producing a total of 2268 youth aged 4–18. qEEG was most frequently studied as a potential diagnostic tool in pediatric mental illness; few studies assessed treatment response. Studies show higher theta/beta ratio in ADHD vs healthy controls (HC). The most consistent finding in ASD was decreased coherence in ASD vs HC. Studies show MDD has lower temporal coherence and interhemispheric coherence in sleep EEGs than HC. Further research is needed in the areas of mood, anxiety, ASD, and relationship to treatment. It remains unknown if abnormalities in qEEG are nonspecific markers of pediatric psychiatric illness or if they have the potential to differentiate types of psychopathology.

1. Introduction

Mental illness often first presents in childhood and adolescence, with up to 1 in 5 adolescents having a psychiatric illness that will persist into adulthood (Lee et al., 2014). Accurate diagnosis and early intervention in these early stages of psychiatric illness can mitigate sequelae into adulthood (Belcher, 2014; Yap, 2010). Although significant advances have been made in the last several decades in the treatment of childhood psychiatric disorders, diagnostic certainty remains challenging, and imprecise nosology and overlapping presentations are particularly difficult in childhood (Mendelson and Tandon, 2016). Biomarkers have the potential to clarify and aid in diagnosis. Many biomarkers are being investigated, ranging from genetic markers to active markers of disease (Kim et al., 2014).

Electroencephalography (EEG) has emerged as a promising biomarker for a wide range of psychiatric illnesses (Dharmadhikari et al., 2018; Verrusio et al., 2015). When studying EEG as a biomarker for psychiatric illness, the bulk of the research has been on quantitative EEG (qEEG)- the mathematical analysis of EEG through standardized algorithms (Jackson and Bolger, 2014). qEEG is appealing as a potential biomarker because of its ease of use, relatively low cost and wide availability (David Soltysik, 2018). Research is expanding regarding the use of qEEG as both a possible biomarker aiding in diagnosis and a possible predictor of response to treatment for individuals with psychiatric disorders (Olbrich et al., 2015; Widge et al., 2018).

In contrast to the adult psychiatric literature, qEEG research is only recently expanding in pediatrics (Simkin et al., 2014; Swatzyna et al., 2015). To date, O'Reilly and colleagues have systematically reviewed the literature regarding autism spectrum disorder (ASD) and the use of qEEG, but no systematic review of the full body of research in qEEG regarding childhood mental illness exists (O'Reilly et al., 2017). qEEG is a quick and relatively inexpensive process that uses existing and widely available technology. Given the need for biomarkers in pediatric psychiatric disorders and some evidence of promising utility in adults with psychiatric disorders, this systematic review examined the existing data on use of qEEG in psychiatrically impaired, with the goal of determining whether qEEG is useful in identifying and characterizing children with psychiatric disorders.

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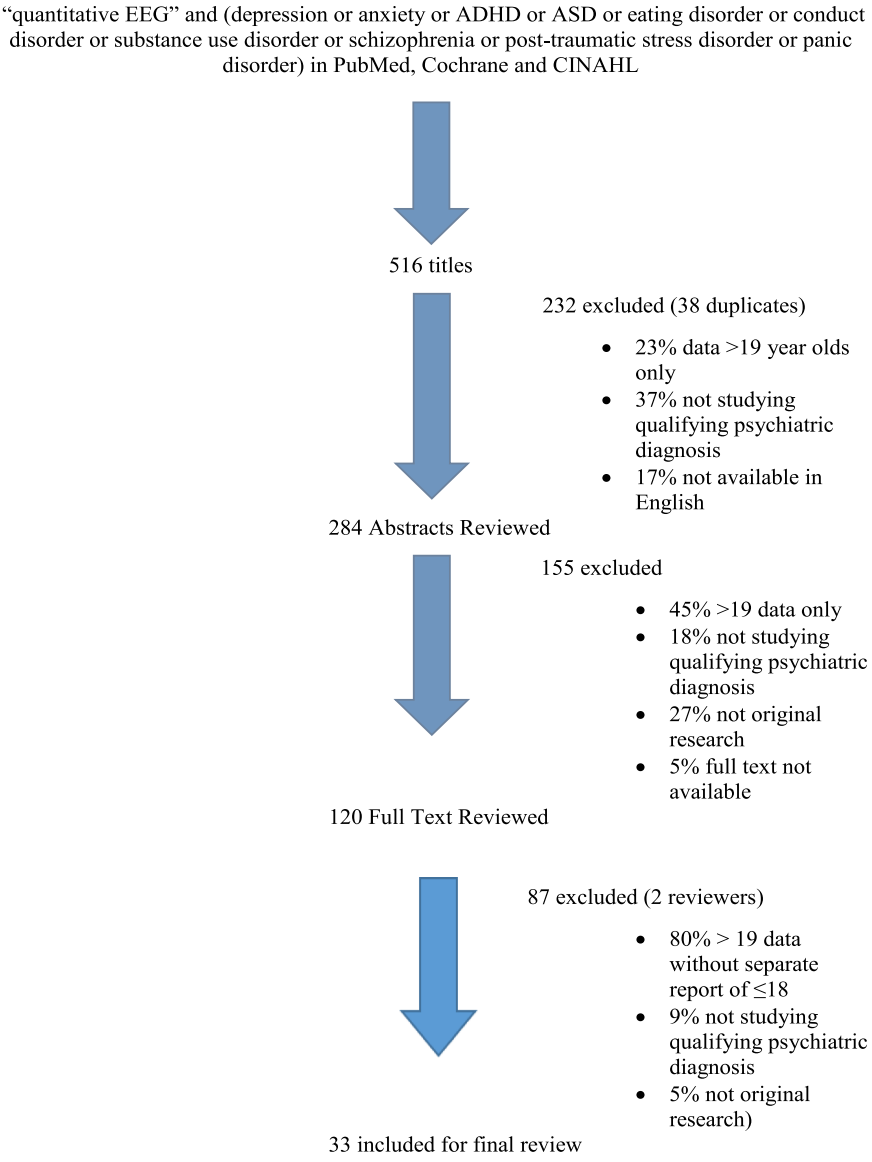

Fig. 1. Systematic review search diagram.

2. Methods

We performed a systematic review to examine existing data on qEEG in children and adolescents with psychiatric disorders. Because of the limited research available, we cast a broad net, searching published reports up to 2017 and included the top ten most frequently diagnosed disorders in children and adolescents, listed in search terms below (Merikangas et al., 2010; Michaud and Fombonne, 2005). As the review strategy was to include studies published up until 2017, any studies after 2017 are not included in the formal results, though they are briefly discussed.

The following search strategy was used in PubMed, CINAHL and Cochrane databases: "quantitative EEG" and (depression or anxiety or attention-deficit/hyperactivity disorder (ADHD) or ASD or eating disorder or conduct disorder or substance use disorder or schizophrenia or post-traumatic stress disorder or panic disorder). Our initial search yielded 516 titles, of which 33 articles met final inclusion criteria; see Fig. 1.

One author identified duplicates and titles to be excluded, with feedback from the review team (SL, MS). Two authors reviewed abstracts and full text for inclusion in final review. The review was an iterative process (Fig. 1), with the core review team giving input weekly. Inclusion criteria were: new research studying qEEG in children and adolescents (including data ages 1–18 (inclusive of 18)) with psychiatric illness (DSM-IV or -5) commonly seen in children (as defined by the 10 most common psychiatric illness in youth (Merikangas et al., 2010; Michaud and Fombonne, 2005)).

Exclusion criteria were: 1) data on age 19 and older only; 2) neonatal or infant data; 3) non-psychiatric diagnoses; 4) diagnosis not within previously defined top 10 illnesses; 5) healthy controls only; 6) case reports, review articles or meeting presentations; 7) not written in English; 8) studying non-humans; 9) full text not available; and 9) studying EEG, but not qEEG. If the article stated "children" but did not define an age range, the article was included. If article made no mention of age range of participants, it was excluded.

3. Results

3.1. Studies and sample

Thirty-three studies of qEEG met inclusion criteria, with a total sample of 2268 children and adolescents, ages 4–18. Males outnumbered females in the sample (M:1295 (66%), F:649 (34%)); two studies (N = 324) did not report gender; see Table 1 for details of the

Table 1
Summary of data collected in included studies.

Variable	Number (%) of studies
Sample size	33 (100)
Demographic	
Age	33 (100)
Sex	31 (93.9)
Race or ethnicity	1 (3.0)
Education	6 (13.1)
Handedness	7 (21.2)
Medical/Neurologic Comorbidity Excluded	21 (63.6)
EEG measures	
Power	29 (87.9)
Power Ratio	14 (42.4)
Coherence	4 (12.1)
EEG methodology	
Eye position	29 (87.9)
Task	33 (100)
Awake	31 (93.9)
Asleep	3 (9.0)
Length of EEG	26 (78.8)
System	33 (100)
Standard	32 (97.0)
LORETA	1 (3.0)
Number of electrodes	33 (100)
Symptom or illness severity/diagnostic measures	
ADHD	
DSM-V criteria	1 (3.0)
DSM-IV criteria	4 (12.1)
DSM-IV-TR criteria	2 (9.7)
DSM-III-R criteria	1 (3.0)
Achenbach scales	1 (3.0)
BRIEF	1 (3.0)
Conners' Rating Scales	7 (21.2)
Child Behavioral Checklist	1 (3.0)
CPNI	1 (3.0)
DISC-IV	1 (3.0)
Disruptive Disorder Behavior Checklist	1 (3.0)
Wender Utah Rating Scale	1 (3.0)
Other clinical interview/questionnaire	3 (9.0)
ASD	
DSM-V criteria	4 (12.1)
DSM-IV criteria	4 (12.1)
DSM-IV-TR criteria	1 (3.0)
ADI-R	1 (3.0)
ADOS-2	1 (3.0)
ASDS	1 (3.0)
CARS	3 (9.0)
VAB-S	1 (3.0)
Other clinical interview/questionnaire	3 (9.0)
Bipolar Disorder II	
DSM-IV	1 (3.0)
BDI-II	1 (3.0)
Edinburgh	1 (3.0)
K-SADS-PL	1 (3.0)
YMRS	1 (3.0)
Conduct Disorder	
DSM-IV-TR	1 (3.0)
APSD	1 (3.0)
Generalized Anxiety Disorder	
ICD-10	1 (3.0)
Other clinical interview/questionnaire	1 (3.0)
Intermittent Explosive Disorder	
Other clinical interview/questionnaire	1 (3.0)
Major Depressive Disorder/Depression	
DSM-III-R criteria	3 (9.0)
Brief Psychiatric Rating Scale-Children's	1 (3.0)
Beck Depression Inventory	3 (9.0)
Bellevue Index of Depression	1 (3.0)
Children's Depression Rating Scale-Revised	2 (9.7)
CGAS	2 (9.7)
K-SADS	2 (9.7)
Weinberg Screening Affective Scale	3 (9.0)
Medication use reported	
Unreported	13 (39.4)
No use during testing	12 (36.4)
Use reported	
Antipsychotics	3 (9.0)
Antidepressants	3 (9.0)
Stimulants	4 (12.1)
Type of study	
Interventional	11 (33.3)
Diagnostic	22

Fig. 2. Study distribution.

type of data collected in the included studies. Geographically, there was a wide distribution of studies; see Fig. 2. As noted in Fig. 3, diagnostic categories targeted by studies in decreasing frequency were ADHD ($N = 16$, 46%), ASD ($N = 9$, 27%), Mood Disorders ($N = 4$, 14%), Disruptive and Impulse Control Disorders ($N = 2$, 5%) and one studied multiple diagnoses. Twenty-one studied qEEG as a tool to aid in diagnosis, and the remaining 12 studies investigated qEEG's use as a marker of medication or biofeedback treatment effect.

3.2. Summary of findings by diagnostic category

See Figs. 4 and 5 for common terms and definitions used in reviewed studies.

3.2.1. ADHD

In ADHD, qEEG was reported as a diagnostic aid in 10/16 (62.5%) of the studies, as a part of biofeedback in 3/16 (18.8%) of the studies, and as a measure of stimulant response in 3/16 (18.8%) of the studies.

When used as a diagnostic aid in ADHD, three studies collected qEEG readings with the subjects' eyes open (EO) (Bresnahan et al., 1999; Kuperman et al., 1996; Markovska-Simoska and Pop-Jordanova, 2017), three studies collected qEEG with eyes closed (EC) (Clarke et al., 2006; Fonseca et al., 2008; Hermens et al., 2005), three studies had both EO and EC conditions (Coolidge et al., 2007; Fonseca et al., 2013; Ogrim et al., 2012) and one study provided no information (Kim et al., 2015). While the majority of diagnostic studies compared qEEG variables in children with ADHD to healthy controls (HC) (Bresnahan et al., 1999; Clarke et al., 2006; Fonseca et al., 2013, 2008; Hermens et al., 2005; Kim et al., 2015; Kuperman et al., 1996; Markovska-Simoska and Pop-Jordanova, 2017; Ogrim et al., 2012), one studied qEEG variables as a tool to differentiate ADHD from other psychiatric disorders (Coolidge et al., 2007). Half of the diagnostic studies reported the participants were medication free (Clarke et al., 2006; Fonseca et al., 2013, 2008; Hermens et al., 2005; Markovska-Simoska and Pop-Jordanova, 2017); the other half did not specify if participants were

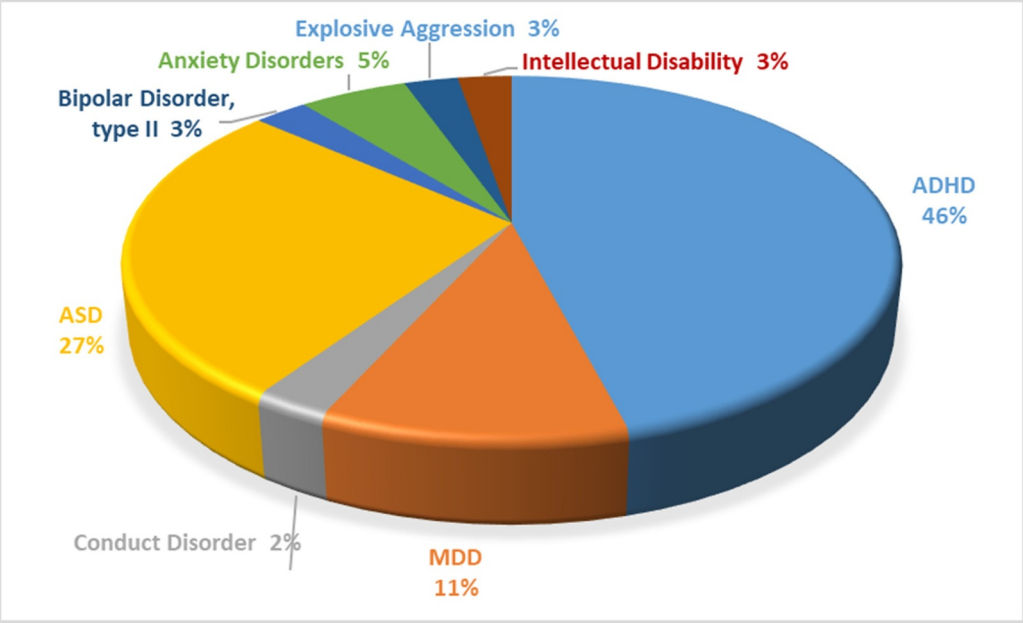

Fig. 3. Diagnoses studied with qEEG .

taking any psychoactive medications (Bresnahan et al., 1999; Coolidge et al., 2007; Kim et al., 2015; Kuperman et al., 1996; Ogrim et al., 2012).

When studying qEEG as a diagnostic aid for ADHD, the most common qEEG variables collected in studies were absolute and relative theta power, beta power, delta power and the ratio of theta power/beta power. Findings were mixed regarding differences between ADHD participants and healthy controls; see Table 2 for details.

Several studies reported on the ability of qEEG measures to differentiate between a participant with ADHD and HC (Fonseca et al., 2008; Kim et al., 2015; Markovska-Simoska and Pop-Jordanova, 2017). Markovska-Simoska and colleagues reported that when using the ratio of theta power/beta power (theta/beta ratio) qEEG was 81% accurate

Absolute Power – voltage of a frequency band

Relative Power – percentage of power in any band compared with the total power in the patient's EEG

Coherence – similarity or correlation of 2 EEG signals in a frequency band (measured from 0-1 with 1 representing the most similarity)

Amplitude – square root of power

ERP- Event Related Potential; measure of qEEG response to a specific external stimulus

Fig. 5. Common terms in qEEG.

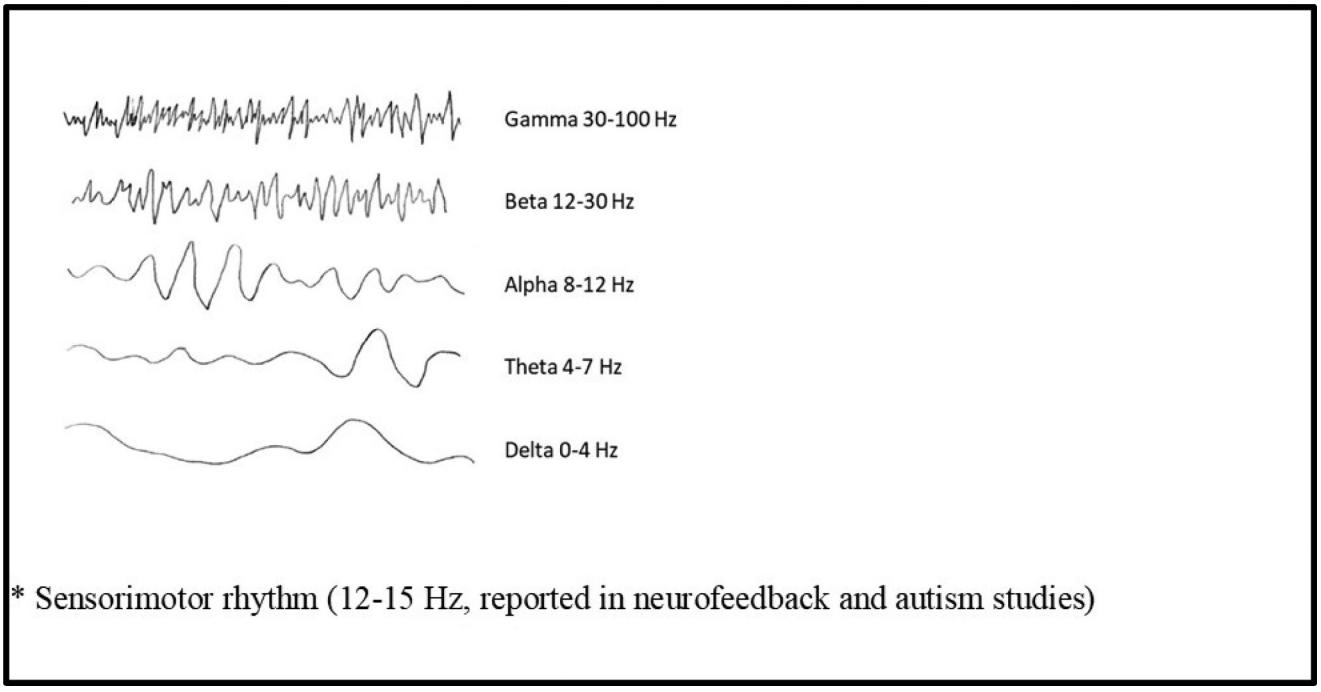

Fig. 4. Common frequencies in qEEG studies.

Table 2
Summary of key findings.

Author(s)	Year	Age (yrs)	N	M:F[a]	Title	I or D[b]	Primary outcome measure	Main results	Limitations
Attention-Deficit/Hyperactivity Disorder									
Isiten et al.	2017	8–16	43	3:1	Medication Effects on EEG Biomarkers in Attention-Deficit/ Hyperactivity Disorder.	I	Power (theta/beta ratio)	Theta/beta power ↓ after treatment; change was largely due to an ↑ in beta power.	No standardization of medication choice, duration or dosage
Markovska-Simoska et al.	2017	6–14	60	All M	Quantitative EEG in Children and Adults With Attention Deficit Hyperactivity Disorder: Comparison of Absolute and Relative Power Spectra and Theta/Beta Ratio.	D	Power (absolute power across frequencies; theta/ beta ratio)	↑ absolute delta, TBR in patients with ADHD. No differences in adults.	Male patients only
Kim et al.	2015	8–12	97	3:1	Theta-phase gamma-amplitude coupling as a neurophysiological marker of attention deficit/ hyperactivity disorder in children.	D	Power (theta/beta ratio, theta/ gamma coupling)	↑ delta power and theta/beta ratio in ADHD	No confirmation of clinical implication of TGC; multiple confounders
Hillard et al.	2013	10–17	18	2:1	Neurofeedback training aimed to improve focused attention and alertness in children with ADHD: a study of relative power of EEG rhythms using custom-made software application.	I	Power (relative power across frequency bands)	Theta/beta ratio and theta/alpha ratios ↓ throughout neurofeedback; improvement in the behavioral measures and functional outcomes	Absence of post-neurofeedback parent and teacher ratings; variability in stimulant usage
Fonseca et al.	2013	8–11	76	2.8:1	Electroencephalographic alpha reactivity on opening the eyes in children with attention-deficit hyperactivity disorder.	D	Power (absolute alpha power, alpha reactivity)	No difference in absolute alpha power between groups on eye opening; difference in frontal region alpha reactivity between ADHD and controls.	Unclear clinical correlation
Ogrim et al.	2012	7–16	101	1.9:1	The quantitative EEG theta/beta ratio in attention deficit/hyperactivity disorder and normal controls: sensitivity, specificity, and behavioral correlates.	D	Power (absolute power across frequencies, theta/ beta ratio);	Power spectral data did not discriminate patients and controls	No correction for multiple statistical analyses
Breteler et al.	2012	10–16	10	1:1	Neurofeedback in Residential Children and Adolescents with Mild Mental Retardation (MMR) and ADHD Behavior.	I	Power (absolute power across frequencies)	Open eye EEGs showed ↑ amplitudes in lower frequencies in children with MMR. Attention and concentration improved following NFB.	Small sample size, lack of randomized control group

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Table 2 (*continued*)

Author(s)	Year	Age (yrs)	N	M:F[a]	Title	I or D[b]	Primary outcome measure	Main results	Limitations
Fonseca et al.	2008	8–11	60	4:1	Epileptiform abnormalities and quantitative EEG in children with attention-deficit/hyperactivity disorder.	D	Power (relative and absolute power across all frequency bands); epileptiform activity	ADHD group showed ↑ absolute delta and theta powers diffusely; model "differentiated" ADHD from control with 83% sensitivity and specificity.	Homogeneity of sample; No correction for multiple statistical analyses
Doehnert et al.	2008	9–12	26	5.5:1	Slow cortical potential neurofeedback in attention deficit hyperactivity disorder- is there neurophysiological evidence for specific effects.	I	Power (absolute power across frequency bands, theta/beta ratio)	There were no significant differences between NFB and group therapy arms	Non-randomization; participant fatigue impact
Coolidge et al.	2007	6–18	188	1.5:1	Comparison of a parent-rated DSM-IV measure of attention-deficit/hyperactivity disorder and quantitative EEG parameters in an outpatient sample of children.	D	Power (relative power across all frequencies and location, theta/beta ratio)	No correlation between ADHD rating scales and qEEG measures	No control group, no diagnostic specificity, no clinical evaluations
Clarke et al.	2006	8–13	40	9:1	Quantitative EEG in low-IQ children with attention-deficit/hyperactivity disorder.	D	Power (absolute and relative power across all frequencies and location)	ADHD youth had increased theta activity with ↓ levels of alpha and beta activity compared to control subjects. IQ was not found to impact on the EEG.	Small sample size, difficult to generalize
Hermens et al.	2005	11–17	140	2:1	Sex differences in adolescent ADHD: findings from concurrent EEG and EDA.	D	Power (absolute power across frequencies and location, theta/beta ratio)	ADHD males showed ↑ theta (widespread); ADHD females showed a localized frontal enhancement of theta with reduced rate of EDA decrement.	Non-generalizable ratios of males to females
Song et al.	2005	6–12	20	All M	Effects of methylphenidate on quantitative EEG of boys with attention-deficit hyperactivity disorder in continuous performance test.	I	Power (absolute power across frequencies and location, theta/beta ratio)	Post- MPH administration: ↑ alpha and beta power in frontal region, ↓ delta and theta in occipital and parieto-occipital; ↑ in theta/beta ratio in right frontal and	Absence of placebo/control group; one-time MPH dosing

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Table 2 (*continued*)

Author(s) Year	Age (yrs)	N	M:F[a]	Title	I or D[b]	Primary outcome measure	Main results	Limitations
							parieto-occipital and L temporal.	
Bresnahan et al. 1999	6–17	100	[c]	Age-related changes in quantitative EEG in attention-deficit/hyperactivity disorder.	D	Power (absolute and relative power across all frequencies and location, theta/beta ratio)	Theta activity was ↑ in the ADHD groups across age groups compared with the normal controls. Abnormal fronto-central beta activity diminishes with age.	Unclear diagnostic process and no report of patient gender
Chabot et al. 1999	6–16	130	3:1	Behavioral and electrophysiologic predictors of treatment response to stimulants in children with attention disorders.	I	Power and Coherence (absolute and relative power across all frequencies and location)	Reported correspondence between behavioral and quantitative EEG changes at 78.5%. EEG "predicted" treatment response with a sensitivity of 83.1% and a specificity of 88.2%	Poorly defined model; No correction for multiple statistical analyses
Kuperman et al. 1996	7–13	40	2:1	Quantitative EEG differences in a nonclinical sample of children with ADHD and undifferentiated ADD.	D	Power (relative power across all frequency bands, evoked response potential)	ADHD and UADD ↓ delta band relative percent power, ↑ beta band relative percent power compared to control	No mention of medication status
Autism Spectrum Disorders								
Paula et al. 2017	5–12	16	7:1	High-Frequency EEG Variations in Children with Autism Spectrum Disorder during Human FacesVisualization.	D	Power	There were ↑ activation in higher frequencies (primarily gamma) in frontal, central, parietal and occipital in the ASD group.	Very small sample size
Billleci et al. 2016	6–8	5	All M	An Integrated Approach for the Monitoring of Brain and Autonomic Response of Children with Autism Spectrum Disorders during Treatment by Wearable Technologies.	I	Power and Coherence (relative power all frequencies and intrahemispheric coherence)	Suggested feasibility of this platform.	Very small sample size, absence of a control group, no control for effects of physical movement
Khadem et al. 2016	9–17	31	All M	Long- Range Reduced Predictive Information Transfers of Autistic Youths in EEG Sensor-Space During Face Processing.	D	ERP, PIT (predicitive information tranfers); differential	Long-range ↓ of PITs in ASD during face processing; nearly similar binary patterns for	All male, small sample, no control group

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Table 2 (*continued*)

Author(s) Year	Age (yrs)	N	M:F[a]	Title	I or D[b]	Primary outcome measure	Main results	Limitations
						connectivity graph (dDCGs)	changes of PITs in ASD while changing facial image orientation.	
Wang et al 2015	13.2 ± 4.3	18	3.5:1	Relative Power of Specific EEG Bands and Their Ratios during Neurofeedback Training in Children with Autism Spectrum Disorder.	I	Power (power across frequencies; theta/beta ratio)	↓ in Lethargy/ Social Withdrawal subscale. Linear ↓ theta/beta ratio and linear ↑ of relative power of gamma activity over 18 weeks in children with ASD.	Small sample size, no control group, not focused on clinical or diagnostic outcomes
Machado et al. 2015	5.8 ± 2.4	25	1.8:1	QEEG spectral and coherence assessment of autistic children in three different experimental conditions.	I	Power and Coherence	No significant effect of medication status and no significant interaction between medication status and other variables.	No control group, small sample
Chan et al. 2009	5–9	32	4:1	Seven-star needle stimulation improves language and social interaction of children with autistic spectrum disorders.	I	Behavioral report, Power (absolute power across all frequencies)	Improvement in language and social interaction with treatment. Spectral amplitudes in the treatment, but not in the control group, ↓ with treatment.	Unclear clinical correlation; no healthy controls
Coben et al. 2008	6–11	40	2.3:1	EEG power and coherence in autistic spectrum disorder.	D	Power	relative theta power ASD > control (posterior); delta power ASD < control (frontal); Coherence ASD < control	Small sample size
Chan et al. 2006	7.5 ± 2	122	1:1	Differentiating autistic children with quantitative encephalography: a 3-month longitudinal study.	D	Power (relative and absolute power across all frequencies and location, theta/ beta ratio)	Absolute sensorimotor rhythm and beta amplitudes were the best predictors differentiating autistic children from normal children, with a reported accuracy rate of 95.2%	Small sample size; no correction for multiple statistical analysis
Scolnick, B 2005	12–16	5	All M	Effects of electroencephalogram biofeedback with Asperger's syndrome.	I	Coherence, Power (theta/beta ratio, coherence across	No improvement in theta/beta ratios but improvement in	Very small sample size, poorly-defined

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Table 2 (*continued*)

Author(s)	Year	Age (yrs)	N	M:F[a]	Title	I or D[b]	Primary outcome measure	Main results	Limitations
							frequencies and location)	coherence in theta, alpha, beta.	outcome measure
Major Depressive Disorder									
Armitage et al.	2002	8–18	47	1:1	Sleep microarchitecture as a predictor of recurrence in children and adolescents with depression.	D	Coherence (during sleep); sleep macroarchitecture	Depressed adolescent females ↓delta amplitude and power in the first NREM period than controls, despite similar sleep macroarchitecture.	Small sample size
Armitage et al.	2001	13–16	16	All F	Delta sleep EEG in depressed adolescent females and healthy controls.	D	Power (during sleep, absolute delta power), sleep macroarchitecture	Interhemispheric coherence ↓ in depressed adolescents vs. controls.	Very small sample size.
Armitage et al.	2000	8–17	65	1:1	Ultradian rhythms and temporal coherence in sleep EEG in depressed children and adolescents.	D	Power and Coherence (during sleep)	↓ interhemispheric coherence in depressed adolescents; no differences in sleep architecture MDD vs. HC	No control for multiple analysis; small control group
Conduct Disorders, Explosive Aggression									
Calzada-Reyes et al.	2017	14–17	42	All M	QEEG and LORETA in Teenagers With Conduct Disorder and Psychopathic Traits.	D	Power (absolute power across frequencies and brain regions)	↑ beta power bilateral fronto-temporal regions CD with psychopathy; ↓ alpha in right fronto-temporal-central and parietal-central in CD with psychopathy	No control group, all male sample
Bars et al.	2001	10–16	326	2:1	Use of visual evoked-potential studies and EEG data to classify aggressive, explosive behavior of youths.	D	Power (amplitude of visual evoked potential)	Patients with explosive behaviors more likely to produce high-amplitude P100 wave forms in the ERP than patients without explosive behaviors.	Poorly defined diagnostic category
Miscellaneous									
Demerdzieva et al.	2011	7–18	26	1.9:1	Alpha asymmetry in QEEG recordings in young patients with anxiety.	D	Power (absolute alpha power)	Statistically significant difference of alpha power between left and right	No control or comparison groups; small sample size

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Table 2 (*continued*)

Author(s)	Year	Age (yrs)	N	M:F[a]	Title	I or D[b]	Primary outcome measure	Main results	Limitations
								hemispheres in children with anxiety.	
Swatzyna et al.	2015	5–17	224	[c]	Pharmaco-EEG: A Study of Individualized Medicine in Clinical Practice.	I	Beta-Spindles, transient-discharges, focal slowing, encephalopathy	Significant relationship between beta-spindles and MDD in adolescents; no relationship between anxiety and encephalopathy	Subject medication variability; poor procedural standardization
Moeini et al.	2015	12–18	39	1:1	Characteristics of Alpha Band Frequency in Adolescents with Bipolar II Disorder: A Resting-State QEEG Study.	D	Power (absolute alpha power across brain regions)	Alpha power ↑ in the fronto-central region and right parietal lobe in BP II vs. HC	Hypomanic and depressed patients were grouped together; small sample size

[a] M (male) F (female).
[b] I (Interventional) or D (Diagnostic).
[c] No report of gender.

in differentiating un-medicated ADHD subjects from HC, using a diagnostic assessment from a clinician as the gold-standard comparator (Markovska-Simoska and Pop-Jordanova, 2017). Kim and colleagues investigated how in sync or "lock step" the gamma amplitude is relative to the theta phase as a possible marker of ADHD. Using theta-gamma coupling as the marker, Kim et al. reported qEEG was 71.7% accurate in differentiating ADHD from HC, again using a clinical evaluation as a reference (Kim et al., 2015). Kim et al. did not report if participants were taking any psychoactive medications at the time of qEEG reading (Kim et al., 2015). Fonseca et al. reported on a qEEG model using absolute delta power and absolute theta power that was 83.3% sensitive and 83.3% specific in differentiating un-medicated ADHD youth from HC, with a clinical evaluation as a reference (Fonseca et al., 2008).

Coolidge et al. analyzed qEEG as an ADHD diagnostic tool in a mixed clinical sample of a group of clinically-referred children with a wide range of behavioral and mood issues (Coolidge et al., 2007). Using the theta/beta ratio as the qEEG parameter, Coolidge et al. reported qEEG had a sensitivity of 50% and a specificity of 36% differentiating ADHD (as measured by parent report) from other non-ADHD psychiatric disorders (Coolidge et al., 2007).

Two open-label studies and one active treatment comparison study reported on the use of qEEG as a part of neurofeedback, a type of biofeedback, for the treatment of ADHD (Breteler et al., 2012; Doehnert et al., 2008; Hillard et al., 2013). Hillard et al. reported on a study of 18 children and adolescents age 10–17 (male:12, female:6) with ADHD that completed 12 sessions of neurofeedback. The authors reported a decrease in the theta/beta ratio and theta/alpha ratio, as well as a decrease in measures of irritability, lethargy, stereotypy, hyperactivity, and inappropriate speech as measured by the Aberrant Behavior Checklist (ABC) from session one to 12 (Hillard et al., 2013). Breteler and colleagues studied neurofeedback in youth with intellectual disability and ADHD living in a residential facility. Ten youth, age 10–16 (M:5, F:5), with ADHD and IQs ranging from 50 to 70 completed 30 sessions of neurofeedback. The authors reported improvement in measures of attention and concentration, but no change in impulsivity. They also reported a decrease in absolute delta and beta power after the completion of neurofeedback (Breteler et al., 2012). Doehnert et al. completed an active treatment trial comparing neurofeedback with group therapy in youth, age 9–12 (n = 26) with ADHD. Youth were assigned to treatment group based on parental preference, and both groups reported improvement in measures of ADHD by the end of treatment (Doehnert et al., 2008). No difference between treatment groups was noted in qEEG changes over time, specifically theta/beta ratio and amplitude of several event-related potentials (ERP) (Doehnert et al., 2008).

Three studies investigated medication effects with qEEG (Chabot et al., 1999; Isiten et al., 2017; Song et al., 2005). Two of these studies examined the effects of methylphenidate (MPH) on qEEG markers in ADHD (Isiten et al., 2017; Song et al., 2005). One study used qEEG measures as possible markers for response to stimulant medication (Chabot et al., 1999). Both Isiten et al. and Song et al. studied how qEEG changed from pre-MPH treatment to post-treatment. Isiten (N = 43 youth with ADHD) reported lower theta/beta ratio, increased relative beta power on a resting qEEG after MPH treatment (Isiten et al., 2017). Song (N = 20) reported no difference between the theta/beta ratio with a resting qEEG and after MPH treatment (Song et al., 2005). However, they reported increased theta/beta ratios on qEEG after MPH treatment during continuous performance tests in multiple brain regions. They also reported increased frontal alpha and beta power, and a decrease in theta and delta power in occipital regions with MPH treatment during continuous performance testing qEEG (Song et al., 2005). Neither study reported a control group (Isiten et al., 2017; Song et al., 2005).

Chabot et al. reported on youth with ADHD treated with MPH, dexamphetamine, or thioridazine (N = 130) and associated qEEG findings (Chabot et al., 1999). The participants' initial medication

treatment was non-randomized, based on the child's clinical presentation. If participants experienced negative effects or did not respond to the initial treatment, they were switched to another treatment. Resting EC qEEGs were obtained prior to treatment initiation and ten months after initiation of treatment. These were compared to a database of 31 HC youth. The authors reported that predominately inattentive symptoms and elevated theta power were associated with lower response to both stimulant medications and more negative effects. Youth with elevated alpha and beta power were more likely to respond to either stimulant medication (Chabot et al., 1999).

Ultimately, in ADHD, the most common finding in the reviewed studies was a higher theta/beta ratio in youth with ADHD vs. HC. Treatment with either medication or biofeedback showed a wide range of changes in qEEG over time.

3.2.2. Anxiety

One study investigated the use of qEEG in adolescent anxiety disorders specifically (Demerdzieva and Pop-Jordanova, 2011), while one additional study looked at a wide variety of diagnoses, including anxiety disorders (Swatzyna et al., 2015). Demerdzieva and colleagues studied 26 youth (M:17, F:9), ages 7–18 with GAD, per ICD-10 criteria; no diagnostic procedure was described. The participants were not on medication, and the EEG was recorded for five minutes with EO and five minutes with EC. The authors reported asymmetry in the absolute power in the alpha wave length. The authors reported only finding statistically significant asymmetry in the EC condition. There was no HC group in this study.

Swatznya and colleagues analyzed a clinical database containing diagnostic, demographic, and qEEG records of 224 youth, aged 5–17, with a wide variety of psychiatric disorders who were reported to have failed two trials of medications and were defined as “refractory” by the authors. No diagnoses were specifically targeted and no gender information was available. Four non-specific abnormalities (encephalopathy (EN), focal slowing (FS), beta spindles (BS), and transient discharges (TD)) were identified in the participants’ EEGs and several statistical models were developed to explore the relationship between diagnosis, medication trials, and qEEG abnormality. The authors reported that there was a statistically significant association between the presence of BS and the diagnosis of MDD, although only 35% of subjects with BS on the qEEG carried a diagnosis of MDD. In addition, the authors reported that the presence of EN was negatively associated with the diagnosis of an anxiety disorder. Participants were on a wide variety of medication; the specific medications and durations were not documented or reported in the manuscript.

3.2.3. ASD

Nine studies reported the use of qEEG in children with ASD; five used qEEG as a diagnostic biomarker and four used qEEG in the course of ASD treatment. (Billeci et al., 2016; Chan et al., 2009; Chan and Leung, 2006; Coben et al., 2008; Khadem et al., 2016; Machado et al., 2015; Paula et al., 2017; Scolnick, 2005; Wang et al., 2015). When used as a diagnostic aid in children with ASD, qEEG was collected during the task of visualizing human faces in two studies, at rest in two studies and with video input in one study (Chan and Leung, 2006; Coben et al., 2008; Khadem et al., 2016; Machado et al., 2015; Paula et al., 2017).

Khadem et al. reported on a measure of effective connectivity, predictive information transfers (PITs) in youth with ASD during a task of visualizing human faces (Khadem et al., 2016). The authors found reduction of long range PITs in children with ASD ($N = 12$), particularly from frontal to right temporal channels in comparison to HC ($N = 19$) (Khadem et al., 2016). Paula and colleagues studied the power spectrum during facial processing in children with ASD ($N = 8$) compared to HC during the same task ($N = 8$) (Paula et al., 2017). During the visualization of human faces, youth in the ASD group demonstrated higher absolute power in beta and gamma frequencies compared to HC, particularly in the frontal, occipital, and centerparietal areas (Paula et al., 2017).

Coben et al. and Chan et al. compared qEEG measures of youth with ASD to HC while at rest (Chan and Leung, 2006; Coben et al., 2008). Coben et al. reported on power and coherence in 20 ASD youth and 20 HC while at rest with EC (Coben et al., 2008). The authors reported that relative delta was reduced globally in children with ASD compared with controls, seen most predominantly in the left frontal and vertex regions. They also reported higher relative theta in ASD youth vs. HC at frontal and posterior regions, and lower absolute beta in the posterior region. Regarding coherence, Coben et al. reported reduced coherence across multiple electrodes and across hemispheres when compared to HC. They reported lower delta and theta coherence with short-medium inter-electrode distances and lower delta coherence with the long inter-electrode distances. Interhemispheric coherence was also lower in delta, theta and beta bands in youth with ASD vs. HC (Coben et al., 2008).

Chan et al. compared 17 ASD youth to a database of 105 HC. Two qEEGs were taken three months apart with EO at rest (Chan and Leung, 2006). The authors report higher absolute amplitude in all frequency bands in youth with ASD vs. HC, and a higher theta/beta ratio in youth with ASD. The authors reported higher variability within session in amplitudes of all frequency in youth with ASD vs. HC but reported that differences between youth with ASD and HC remained stable over three months (Chan and Leung, 2006). The authors reported a sensitivity of 87.5% and a specificity of 96.2% when using a combination of amplitude of the sensorimotor frequency and the beta frequency to differentiate youth with ASD from HC. Using variability within the alpha frequency alone to differentiate the two groups, they report a sensitivity of 62.5% and specificity of 94.2% (Chan and Leung, 2006).

Machado et al. studied youth with ASD with qEEG while they watched a cartoon. In this experimental condition, the authors reported lower absolute delta and theta power in central brain regions, and lower absolute beta power in posterior brain regions in ASD youth ($N = 11$) when compared to HC ($N = 14$). Machado et al. also reported higher intra-hemispheric coherence in youth with ASD compared to HC (Machado et al., 2015).

Three studies described small, pilot studies which investigated the use of qEEG as part of biofeedback or behavioral interventions with ASD youth ($N = 28$) without a comparator group (Billeci et al., 2016; Scolnick, 2005; Wang et al., 2015). Billeci et al. described a feasibility study where five children with ASD used a wearable qEEG device during a therapeutic interaction with a behavioral therapist (Billeci et al., 2016). Authors reported that when the children were engaged with the therapist, there was an overall increase in power in the occipital areas in the theta, alpha, beta, and gamma bands compared to when they were not engaged. They also found increased interhemispheric coherence at the central and posterior beta frequency bands (Billeci et al., 2016). Wang et al. reported on 18 ASD youth that participated in 18 sessions of neurofeedback. There was an overall increase in the relative power of the gamma frequency and a decrease in the theta/beta ratio at the end of the 18 neurofeedback sessions (Wang et al., 2015). Scolnick et al. described a pilot study of five participants with Asperger's disorder who completed 24 sessions of neurofeedback in which participants were rewarded for increased qEEG activity in the 12–15 Hz, or “sensorimotor frequency”. The authors reported that 2 of the 5 participants’ qEEG showed an increase in power in the 12–15 Hz range, but 3 of the 5 did not (Scolnick, 2005).

Chan et al. used qEEG as an outcome measure in a randomized, controlled trial of a seven-start needle stimulation (a form of acupressure) compared to treatment as usual (control group) ($N = 32$) (Chan et al., 2009). Sixteen of the participants completed qEEG pre- and post-treatment. The authors reported a decrease in amplitude of whole brain delta, theta, and beta frequencies in the treatment group when compared to the control group (Chan et al., 2009).

In summary in ASD, studies reported a wide range of findings

comparing ASD youth to HC; the most consistent finding was decreased coherence in ASD youth vs. HC. Treatment studies showed that qEEG technology was tolerated by youth with ASD but did not report consistent changes in qEEG after intervention.

3.2.4. Mood disorders

Swatzyna et al.'s study included a wide range of clinical diagnoses, including MDD (see above) (Swatzyna et al., 2015). In addition, Moeini et al. described the only investigation found on qEEG in youth with bipolar (BP) spectrum illness (Moeini et al., 2015).

Armitage and colleagues published three studies reporting that qEEG recorded during sleep is related to depressive disorders in youth (Armitage et al., 2001; Armitage et al., 2000, 2002). In their 2000 study, they compared 25 children (age 8–12) with MDD to five HC children, and compared 25 adolescents (age 13–17) with MDD to ten HC adolescents. The MDD diagnosis was obtained by clinical interview, structured diagnostic interview, and children's depression rating scale (CDRS). Youth with MDD showed lower coherence between beta/delta waves between right and left hemisphere vs. HC in both adolescents and female children with MDD. In addition, lower interhemispheric coherence in the beta and theta frequencies were measured in adolescents with MDD vs. HC while asleep, most notably in adolescent females. These results were not found in children with MDD, only adolescents (Armitage et al., 2000).

Armitage et al. (2001) studied delta power during NREM sleep in adolescent females (ages 13–16) with MDD (n = 8) vs. HC (n = 8). As above, MDD was diagnosed with a clinical interview, a structured DSM interview, and the CDRS. The authors reported MDD adolescents have lower delta power than HC during sleep (Armitage et al., 2001). Armitage et al. (2002) investigated if qEEG variables during sleep could predict treatment response in MDD youth, age 8–18 (n = 47). A sleep qEEG was recorded at baseline and measured temporal (over time) coherence of beta, theta, and delta frequencies. Youth were part of a larger treatment study, and were assessed for treatment response at six months one year. Authors reported that lower temporal coherence was associated with a longer time to recovery from MDD. For males with MDD, low temporal coherence was associated with shorter time to recurrence; in females, lower coherence was associated with a longer time to recovery (Armitage et al., 2002).

Moeini et al. reported on the only included study of youth with bipolar disorder (Moeini et al., 2015). The authors studied 21 youth, ages 12–18, with BP type II compared with 18 HC using qEEG with EO at rest as a possible diagnostic marker. Eleven of the participants were reportedly hypomanic and ten were actively depressed during the study (Moeini et al., 2015). Moeini et al. reported increased alpha power in the front-central, temporal, and right parietal regions in BP youth when compared to HC.

Overall in mood disorders, studies of youth with MDD were reported to have lower temporal coherence and interhemispheric coherence in sleep EEG when compared to HC.

3.2.5. Disruptive behavior disorders

Two studies reported on the use of qEEG in aggressive and disruptive behavior in youth (Bars et al., 2001; Calzada-Reyes et al., 2017). Calzada-Reyes et al. reported on the use of qEEG in youth with conduct disorder (CD) (n = 42) (Calzada-Reyes et al., 2017). They dichotomized the youth with CD into those with and without callous and unemotional traits. Their qEEGs were recorded while subjects were awake with EC. Results showed increases in both non-specific paroxysmal activity and beta activity in the frontal lobe when compared to those without callous and unemotional traits (Calzada-Reyes et al., 2017). Bars et al. reported on the evaluation of a clinical database of 267 youth with qEEG data and explosive aggression compared with a clinically referred group of 59 youth without explosive aggression. Explosive aggression was defined as "any mention of rage, out-of control anger, out-of-control aggression, verbal or physical attacks, intermittent explosive disorder, or episodic dyscontrol syndrome"(Bars et al., 2001). qEEG was obtained with EO. Resting and visual EP were measured after the youth were shown a series of patterns and flashing lights. The authors reported higher amplitude of the P100 evoked potential and higher absolute delta power in youth with explosive aggression compared to youth without explosive aggression. No diagnostic or medication information was reported (Bars et al., 2001).

Ultimately, youth with aggression and disruptive behavior disorders were studied with a wide range of tools and a non-specific definition of diagnoses. No control groups were included to make comparisons to.

4. Discussion

This systematic literature review of the qEEG literature in pediatric psychiatric disorders identified 33 studies with a combined sample of 2268 children and adolescents. qEEG was most frequently studied as a potential diagnostic tool, with only a handful assessing the use of qEEG related to treatment response. The majority studies focused on ADHD (N = 16, 46%), on ASD (N = 9, 27%) and MDD (N = 3, 11%).

In youth with ADHD, the most common qEEG finding was a higher theta/beta ratio vs. HC. However, several studies found no qEEG differences between ADHD and HC. As an ADHD diagnostic aid vs. HC, studies reported sensitivity of qEEG ranging from 83 to 93% and specificity from 83 to 88%. However, none of these studies corrected for multiple statistical analyses and may have overestimated sensitivity and specificity. As a specific biomarker differentiating ADHD from other psychiatric disorders, qEEG appears more limited with a sensitivity of 50% and specificity of 36%. Behavior rating scales, as a diagnostic aid for comparison show sensitivity ranging from 75 to 98% and specificity ranging from 33 to 83% differentiating ADHD from other psychiatric disorders in youth (Tripp et al., 2006). ADHD treatment, both with medication and with neurofeedback, demonstrated changes on qEEG, with wide variation in what qEEG variables were measured across studies. Ogrim et al. published a 2019 study showing possible differences between stimulant responders and non-responders regarding posterior theta/alpha ratio, where excess theta in ADHD is related to a positive medication response (Ogrim and Kropotov, 2019). Overall, qEEG findings in ADHD indicate an increase in slow-wave cortical activity, possibly related to frontal hypo-activity (Fernandez et al., 2009). qEEG markers were non-specific in ASD vs. HC. The most consistent finding was decreased inter- and intra-hemispheric coherence; researchers have hypothesized that decreased connectivity, particularly in response to social stimuli, is a neurobiological feature of autism. Consistent with this hypothesis, the included studies show decreased coherence, one measure of connectivity, in ASD subjects compared to HC. Measures of power spectra were less consistent; several studies showed increased fast-wave activity and decreased slow-wave activity, yet several other showed increased amplitude across all frequencies in youth with ASD. All of the included studies regarding qEEG and treatment modalities were pilot studies testing feasibility of using qEEG as a marker of treatment response. In 2018, Sysoeva et al. published a well-designed study that compared youth with ASD, relatives of ASD youth and HC and assessed previously reported changes in amplitude of ERPs in these populations. This study showed modest evidence for difference in ERP amplitude in ASD and highlighted the importance of the way the EEG data is collected and analyzed and the variability in how this is reported across studies (Sysoeva et al., 2018). Overall, however, no consistent conclusions regarding treatment response can be drawn from these preliminary studies in ASD.

In youth with MDD, lower coherence was found in three studies in sleep EEGs when compared to HC. Preliminary data suggested that lower coherence may be associated with a longer time to recovery and shorter time before relapse. This decreased coherence was only found in adolescents, not younger children, and was particularly pronounced in adolescent females with MDD. This may indicate that MDD disrupts a sensitive developmental period in adolescence when normal

connectivity and cortical coordination develops.

The studies that reported on aggression in youth did not have control groups to compare to and attempted to characterize types of aggression within a larger group of disruptive and aggressive youth. The authors reported higher levels of non-specific, atypical qEEG patterns in youth with callous and unemotional traits and in youth with explosive aggression compared to those without.

5. Conclusions

This systematic literature review suggests that qEEG may separate psychiatrically ill children from HC, however, further studies with larger sample sizes are needed to reach a solid conclusion regarding ability to differentiate psychiatrically ill youth from healthy controls. Beyond this, it remains a bigger question if abnormalities in qEEG are nonspecific markers of pediatric psychiatric illness or if qEEG has the potential to differentiate one type of psychopathology from another.

Significant limitations remain in the current literature regarding youth with psychiatric illness and qEEG as a biomarker. Most studies lacked a control group, sample sizes were small and a wide range of age groups were often compared. Many of the studies failed to control for multiple comparisons in the statistical analysis, increasing likelihood of false positive conclusions and potentially inflating effect size.

In addition, there is significant inconsistency in the process of qEEG acquisition, even within diagnostic categories. Consistency of acquisition with EC, when possible, may mitigate some of the confounding variables of qEEG measures “at rest,” and standardized visual stimuli for qEEGs obtained with EO may make comparison across studies more feasible. In addition, there was wide variety in number of EEG channels and how the EEG data was processed.

Finally, it appears that psychotropic medication has an impact on qEEG outcomes, although non-specific at this point. However, studies were inconsistent in the reporting of medication use and types of medication given during qEEG administration. Consistent reporting of medication use and monitoring of medication effects will also improve the ability to distinguish effects of underlying psychopathology, treatment, and medication.

Although promising, there is a clear need for further research on qEEG in youth with psychiatric illness, especially in the areas of mood, anxiety and in relationship to treatment. Overall, the literature would benefit from researchers adopting a more consistent methodology when it comes to using qEEG. Ideally, future research will analyze previous qEEG methodology and determine if it is methodologically appropriate. If it is, it is recommended that the researchers replicate the study using as many similar criteria as possible, such as: type of machine, number of channels used, having patients open or close their eyes during the qEEG, and analyzing the data similarly. If the researchers do not choose not replicate a past study, it would be helpful if it was clearly articulated why they decided the study wasn't methodologically sound for replication. By doing this, qEEG collection will become more uniform and will allow for better comparison and conclusions to be drawn from a larger pool of data.

6. Limitations

This systematic review has limitations that need to be considered. Because of the broad net cast to review all of the most common disorders of childhood, it is possible that, within a specific diagnosis, qEEG literature were missed. In particular, studies of ASD often included both youth and adults but did not report youth data separately. Consequently, this review does not address the full breadth of qEEG literature in autism.

In addition, neurofeedback studies may not have specifically mentioned qEEG in the abstract and consequently may have been missed in this broad review of the literature. Future reviews, as the research expands, may want to focus on qEEG as a diagnostic marker alone or as aid to treatment alone.

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