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EEG markers in Emotionally Unstable Personality Disorder a possible outcome measure for neurofeedback - A Narrative Review

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Abstract:	Objectives - There is growing evidence for the use of biofeedback (BF) in affective disorders, dissocial personality disorder and in children with histories of abuse. EEG markers could be used as neurofeedback in emotionally unstable personality disorder (EUPD) management especially for those at high risk of suicide when emotionally aroused. This narrative review investigates the evidence for electroencephalogram (EEG) markers in EUPD. Methods - PRISMA guidelines were used to conduct a narrative review. A structured search method was developed and implemented in collaboration with an information specialist. Studies were identified via three electronic database searches of Medline, Embase and psychINFO. A predesigned inclusion/exclusion criterion was applied to selected papers. A thematic analysis approach with five criteria was used. Results - From an initial long list of 5250 papers, 229 studies were identified and screened, of which 44 met at least three of the predesigned inclusion criteria. No research to date investigates EEG-based neurofeedback in EUPD. A number of different EEG biomarkers are identified but there is poor consistency between studies. Conclusions - The findings heterogeneity may be due to the disorder complexity and the variable EEG related parameters studied. An alternative explanation may be that there are a number of different neuromarkers, which could be clustered together with clinical symptomatology, to give new sub-domains. Quantitative EEGs in particular may be helpful to identify more specific abnormalities. EEG standardization of neurofeedback protocols based on specific EEG abnormalities detected may facilitate targeted use of neurofeedback as an intervention in EUPD.

EEG markers in Emotionally Unstable Personality Disorder; a possible outcome measure for neurofeedback - A Narrative Review

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ABSTRACT:

Objectives -

There is growing evidence for the use of biofeedback (BF) in affective disorders, dissocial personality disorder and in children with histories of abuse. EEG markers could be used as neurofeedback in emotionally unstable personality disorder (EUPD) management especially for those at high risk of suicide when emotionally aroused. This narrative review investigates the evidence for electroencephalogram (EEG) markers in EUPD.

Methods -

PRISMA guidelines were used to conduct a narrative review. A structured search method was developed and implemented in collaboration with an information specialist. Studies were identified via three electronic database searches of Medline, Embase and psychINFO. A predesigned inclusion/exclusion criterion was applied to selected papers. A thematic analysis approach with five criteria was used.

Results -

From an initial long list of 5250 papers, 229 studies were identified and screened, of which 44 met at least three of the predesigned inclusion criteria. No research to date investigates EEG-based neurofeedback in EUPD. A number of different EEG biomarkers are identified but there is poor consistency between studies.

Conclusions -

The findings heterogeneity may be due to the disorder complexity and the variable EEG related parameters studied. An alternative explanation may be that there are a number of different neuromarkers, which could be clustered together with clinical symptomatology, to

give new sub-domains. Quantitative EEGs in particular may be helpful to identify more specific abnormalities. EEG standardization of neurofeedback protocols based on specific EEG abnormalities detected may facilitate targeted use of neurofeedback as an intervention in EUPD.

KEY WORDS:

Emotionally unstable personality disorder; Borderline personality disorder; Electroencephalogram; Neurofeedback; Neuromodulation

INTRODUCTION:

Emotionally Unstable Personality Disorder -

Emotionally unstable personality disorder (EUPD) is one of ten personality disorders defined in the ICD classification system.[1] It is a complex disorder characterised by pervasive instability of interpersonal relationships, self-image, mood and impulsive behaviour. There is a pattern of rapid fluctuation from periods of confidence to despair, with fear of abandonment and chronic feelings of emptiness. Transient psychotic symptoms including brief delusions and hallucinations may also be present. There is a strong tendency towards suicidal thinking and self-harm. People with EUPD are at high risk of suicide with 60 to 70% attempting suicide at some point and a completed suicide rate of 10%.[2,3]

Along with psychosocial and functional impairment, EUPD is associated with significant financial cost to the healthcare system, social services and wider society,[4,5] especially when in an emotional crisis or aroused state. The National Institute of Health and Clinical Excellence (NICE) guidelines for the management of EUPD advise frequent risk assessment and management, psychological treatments, medications for management of comorbidities and short-term medication use in crisis.[6] However, there are few drugs or interventions recommended specifically for EUPD or the individual symptoms or behaviour associated with the disorder. Any newer or additional treatment options would be welcome in the management of EUPD, particularly for those in the aroused state.

Electroencephalogram and psychopathology -

The relationship between changes on the electroencephalogram (EEG) and psychopathology has long been recognised (Table 1).[7-14]

There is also evidence for the impact of psychotropic medications on alpha, beta, delta and theta waves of the EEG.[11-15]

Evidence for EEG based neurofeedback in psychiatric disorders

A study examined the relationship between distribution patterns of epileptiform discharges (ED) and clinical symptoms across affective, cognitive, and somatic domains.[16] In a sample of 71 nonepileptic psychiatric patients, those with EDs appearing in homologous electrode pairs endorsed significantly fewer symptoms related to affective deregulation. Conversely, patients with isolated EDs focused to a single brain region endorsed greater affective deregulation and severe clinical symptoms. These factors suggest that a carefully recorded and analysed EEG could be used to identify neuromarkers for many non-epileptic psychiatric disorders.

Various EEG changes have been observed in psychiatric disorders. Increased slow wave activity has been demonstrated in those with depression, OCD, autism and ADHD.[17,18] Posterior sharp waves have been seen in a range of psychiatric disorders.[19] Applying modern network theory to EEG and fMRI studies of people with schizophrenia has shown loss of functional connectivity and increased randomness of the networks compared to controls.[20] Intermittent rhythmic delta and theta activity have been shown in a range of disorders,[21] and alterations in gamma synchrony have been demonstrated in schizophrenia, in particular under resting conditions and in the auditory evoked state.[22] During processing of neutral stimuli, subjects with an anxiety disorder may have a shorter latency of P300 and higher amplitude of event-related potentials compared to controls.[23]

There is growing evidence for EEG changes in dissocial personality disorder.[24-28] Gender differences in psychopathology presentation show that males under similar conditions display a higher level of externalising (including dissocial behaviour disorders) and females a higher

level of internalising (including EUPD) symptoms,[29-31] suggesting that changes evident in dissocial personality disorder may also be applicable in EUPD. Furthermore, early childhood sexual and psychological abuse and early stress have been linked to increased electrophysiological abnormalities.[32-35] Such early life experiences are associated with EUPD. Thus, electrophysiological changes may also exist in EUPD.

Researchers have been examining the possibility of using biofeedback (BF) as a treatment for affective disorders,[36,37] and in other areas of psychiatry[9,38,39]. A recent systematic review investigated various modalities of BF for psychiatric disorders.[9] Of the EEG BF articles reviewed, fourteen (70.0 %) studies reported statistically significant clinical amelioration following EEG BF exposure. Mean number of sessions per study was 23.7 (range 5–69), with BF exposure lasting 28.7 min (range 14.6–60 min) on average per session. Different types of neurofeedback therapy were utilised in the studies including alpha regulation neurofeedback, alpha-theta regulation feedback, alpha-asymmetry regulation, theta feedback, alternating theta decrease/beta increase neurofeedback, slow cortical potential neurofeedback and qEEG (quantitative EEG) guided BF. QEEG is an emerging form of neurofeedback, which applies mathematical and statistical analysis to EEG brainwaves, and compares them to age and gender controlled databases of individuals with no known brain dysfunction. Recently qEEG neurofeedback has been used therapeutically in the treatment of dissocial personality disorder.[40] QEEG guided neurofeedback has been shown to have medium size effect in improving attention and reducing behavioural, emotional and social problems of children with histories of abuse and neglect.[41] Other components of neurofeedback therapy such as the number of channels used for EEGs, number and duration of neurofeedback sessions may also represent important considerations for neurofeedback protocols.

Evidence for neurofeedback in EUPD and other psychiatric disorders using neuroimaging and neurofeedback training

More recently, evidence for neurofeedback in EUPD has emerged. A proof of concept study for fMRI-based neurofeedback in complex emotional states preliminarily validates the notion that individuals can experience powerful emotional states and recruit relevant brain networks in real time using a neurofeedback tool.[42] Furthermore, amygdala neurofeedback via fMRI has been associated with successful down-regulation of right dorsal amygdala activation in patients with EUPD.[43] There was also evidence for reduced dissociative experiences and improvements in emotion regulation in those with EUPD. Such results demonstrate that neurofeedback may improve abnormalities found on MRI and emotion regulation in patients with EUPD. However further validation is required.

Neurofeedback therapy generally utilises specific targets dependent on the disorder. A common target of EEG neurofeedback in major depressive disorder is an increased spectral power in the alpha band on the left and a decreased spectral power in the alpha band on the right fronto-central cortex.[39,44] Along with depressive disorder, EEG alpha asymmetry has also been shown in individuals with schizophrenia.[45] The theta/beta protocol where the goal is to decrease brain activity in the theta band and increase brain activity in the beta band at the vertex is the most commonly used EEG-based neurofeedback therapy in ADHD. A common goal of neurofeedback for treatment of psychiatric symptoms in children with autism is to inhibit the theta-alpha ratio while enhancing beta waves.[46] Theta neurofeedback training may also have potential benefits in treatment of generalized anxiety disorder.[47]

The growing research on EEG neurofeedback for affective disorders,[36,37,39-44] dissocial personality disorder,[40] and in children with histories of abuse,[41] raises consideration as to whether similar evidence has been explored for EUPD. The strength of any such evidence and whether such deliberations can further specific investigation and treatments in this modality for EUPD is examined in this paper.

Hypothesis -

There is evidence for fMRI neurofeedback in EUPD, but there has been no research to date which examined EEG-guided neurofeedback in EUPD. EEG-guided neurofeedback is likely to be easier to complete and can be made more widely available compared to fMRI guided neurofeedback.

Aim -

1. This review looks to appraise the evidence to date for EEG changes in EUPD and in arousal states of EUPD
2. To identify if the evidence for EEG changes in EUPD has provided any management strategies.
3. The review aims to consider if neurofeedback using EEG changes as a potential intervention for EUPD is a viable option.

METHODS:

The protocol for this review followed PRISMA guidance (appendix 3).[48]

Search strategy and selection criteria -

References for this review were identified through searching Medline, PsycInfo and Embase using the search terms "EUPD" and "arousal" and "EEG" along with associated terms as per the search terms in Appendix 1. All articles available up until the final database search in February 2018 which had an English language translation available, were included. The search was conducted by two authors and independently verified by a third author.

After removal of duplicates, articles that were not relevant to the review were removed following review by two authors i.e. not referring to electrophysiological investigation/

biological markers in personality disorder, affective disorders, general psychopathology or associated terms. Two authors then applied the following prearranged inclusion criteria to all abstracts;

1) The article refers to EUPD / Borderline Personality Disorder (BPD) as the primary diagnosis

2) Must be a case-control/ cohort/ cross sectional study or higher on the hierarchy of evidence.

3) The population under investigation were all over 18 years of age

4) EEG was the only or main investigation of the study and the article referred to EUPD.

5) The article refers to EEG changes during emotional fluctuations.

Articles fulfilling less than three of the inclusion criteria were excluded. Reference lists of potentially eligible papers were manually searched for additional citations and a grey literature search was performed. A second author confirmed included studies and a final list of included articles was developed, as per pathway 1 (see appendix 1 and 2 for full search outline).

RESULTS:

Following the database search, 5250 studies were assessed for eligibility. An additional 155 studies were included following a search of the grey literature, reference lists and checking whether eligible studies were cited elsewhere. Articles were excluded at each stage as per Pathway 1 and methods (as above). Of the 44 articles which met three or more criteria, two papers met five criteria,[49,50] 26 papers met four criteria,[51-76] and 16 papers met three criteria.[34,41,79-88,90,93]

Data on study size, population/ problem, intervention, comparisons, outcomes, setting and bias were examined. Diagnostic system used and use of sub domains of EUPD i.e. impulsive vs. borderline type were also examined. The articles were sorted according to the number of criteria fulfilled in an attempt to highlight the relative importance of individual articles to our review as per the search criteria.

Articles meeting Five Criteria -

Two articles met all five search criteria (table 2).[49,50]

Both of these studies had control groups (with depression and healthy controls) but had only female subjects and did not control for medications or comorbidities. These two papers established "greater left cortical activation" and "higher total theta power" respectively on EEG during arousal in people with EUPD compared to those with depression and healthy controls. However both studies were of small sample size, referred to specific incidences of high arousal and provided limited evidence for the above changes. The EEG parameters that were explored were different in both studies and hence cannot be combined or compared.

Articles meeting Four Criteria (Arranged into a review article, articles using standard EEGs, sleep EEGs and evoked potentials) -

One review article, which met four of our search criteria, was identified. Boutros et al. examined 26 articles on electrophysiological techniques in EUPD, including one review and 25 original research articles.[51] The authors performed MEDLINE and PsycInfo searches between 1966 to 2000 for "biological aspects" and "BPD". They also performed additional searches using the terms EEG, evoked potentials (EP), sleep and polysomnography (PSG) and a search of referenced articles.

The reviewers highlight a high prevalence of electrophysiological aberrations in EUPD (such as shortened REM latency on polysomnography and diminution of P300 amplitude in evoked potential studies). They also highlight the heterogeneity between articles due to ambiguity of

diagnostic criteria and lack of control for comorbidity and pharmacotherapy. The reviewers conclude that existing literature represents a preliminary stage in the field and suggest a need for further research combining different electrophysiological test modalities. Various types of EEG were reviewed including standard scalp EEG, sleep EEG and evoked potentials. The search used was for the period 1966 to 2000. All the studies met criteria 1,2,3 and 4, but none of the studies identified a specific EEG change due to arousal fluctuations and thus did not meet criteria five.

The following 25 papers, which met four criteria, are presented by integrating them into key themes based on the type of EEG used to aid interpretation of results.

Articles using Standard EEGs -

Eight articles, which used standard EEGs and met four search criteria, were identified (Table 3).[52-59]

The main findings include correlation of impulsiveness with EEG abnormalities (positive spikes in patients with high scores for impulsivity),[52] diffuse slowing,[53] dysrhythmias,[54] non-focal sharp waves, especially in posterior areas,[55] spike-wave discharges or a clear excess of sharp waves, increased slow wave activity,[56] less stable vigilance pattern with a tendency to drop to lower vigilance states,[57] increased prevalence of intermittent rhythmic delta (IRDA) or theta (IRTA) activity,[58] random or semi-rhythmic theta and/or delta, and abnormalities in temporal lobe areas.[59] Six of the studies had control groups and four of these discussed significant EEG abnormalities in those with EUPD. However only three of the studies adequately controlled for co-morbid conditions.[52,55,58] Two studies included a healthy control group,[57,58] one study included a control group for those with depression,[55] and one study a control group for non-EUPD personality disorders.[52] Half of the studies used clinical assessment to establish diagnosis (Table 3).[55,57-59]

Articles using sleep EEGs -

Ten articles on sleep EEGs that met four of the search criteria were identified (Table 4).[60-69] None of these articles met criteria five (i.e. refer to EEG changes between baseline and an arousal state).

The findings from sleep EEG based studies include increased REM percentage,[60] increased REM density,[60,61] shorter REM latency,[60,62-66] (much shorter in EUPD with Depression),[63] longer REM period,[60,67,68] no difference in conventional polysomnography, but increased delta power in Non-REM sleep in spectral analysis,[69] reduced slow wave, stage 3 & 4 sleep.[67,68] The most frequent abnormality found in the above studies was of reduced REM latency compared to healthy controls (six out of ten studies) and in some cases compared to other control groups. However there was no difference between the EUPD and depressed groups,[64] or the changes were more robust in those with depression.[60] Nine of the studies included healthy controls as a comparison and one study did not.[63] Three of the studies included patients with co-morbid depression in the sample with EUPD,[63,64,66] and two of the studies included patients with a history of substance misuse.[61,62] The studies discussed all had small sample sizes (8 – 24 patients with EUPD) and diagnosis was made with structured measures in 7 studies.[61,62,64,66-69] Four of these studies[64,66-68] used DIB as a diagnostic measure and clinical criteria were used in 3 studies.[60,63,65] Aside from one study,[63] all of the other studies had at least 10-14 days of prior psychotropic medication free period.

Articles using Evoked potentials -

7 articles using evoked potentials, which met at least four of the search criteria, were identified (Table 5).[70-76]

None of these studies met criteria 5 (i.e. did not refer to EEG changes between an aroused and resting state). Of the seven studies, five used structured diagnostic criteria[70,74] and two relied on clinical criteria.[75,76] All seven studies had healthy control groups and four studies had additional subjects with other psychiatric conditions.[70-72,76] There were no comorbidities

or at least no affective comorbid conditions in five studies, and two studies did not report on comorbidities.[73,76] The studies had only[70,74] or mainly[71,73,75,76] female subjects, two studies were on subjects who were medication free for at least one week[75] and 30 days[73] respectively, while others had mixed groups with either no medication or on various psychotropics. Four studies consistently highlight decreased amplitude and prolonged latency of P300 during oddball paradigms/ auditory discrimination tasks in those with EUPD compared to controls.[70-72,75] However, these changes were shown to be similar to those seen in schizophrenia[71] and schizotypal personality disorder[72] One further study illustrated differences in distinct components of P300 during an oddball paradigm/ two-tone auditory detection test between those with EUPD and healthy controls.[73] Such changes highlight a specific EEG abnormality in response to an unexpected stimulus. One study reported larger late positive potential (LPP) to unpleasant stimuli.[74] No difference in effect of facial emotion on ERP was reported in one study.[76] The studies reviewed do not investigate P300 specifically in relation to emotional fluctuations.

Articles meeting 3 Criteria

Articles meeting Criteria 1, 2 and 4

Three studies met criteria 1, 2 and 4 (Table 6).[77-79] Two of these studies used structured diagnostic criteria.[77,78] There were two studies (same authors in both) with EUPD–free adolescents in the control group.[77,78] All three studies were on medication free subjects. One study involved people with no comorbidities,[79] one had depression and conduct disorder as comorbidities,[77] while another did not report significant psychiatric comorbidity.[78] One study found no significant difference in wake and sleep EEGs between patients with EUPD, non-EUPD personality disorder, dysthymic disorder and "mixed psychiatric diagnosis".[79] Another study examining evoked potentials showed that there were no age-related changes in P300

amplitude (i.e. reduction in P300 amplitude with age) in adolescents with EUPD traits as compared to normal control subjects.[77] These findings suggest altered brain maturation in adolescents with emerging EUPD. However, a similarly designed case control study examining evoked potentials showed contrasting findings of reduction in P300 amplitude with age in adolescents with EUPD compared to controls.[78] The findings of reduced P300 amplitude in EUPD are in keeping with earlier reported findings.[70-72,75]

Articles meeting criteria 1, 2 and 3

Six studies met criteria 1, 2 and 3 (Table 7).[80-85] Of these, two studies used clinical criteria,[80,81] and four used structured instruments[82-85] to establish diagnosis. Five were case-controlled studies with four studies having healthy controls[80,82,84,85] and one was a cohort study.[83] There were no comorbidities or comorbidities were not reported. The findings in these studies include that those with EUPD have significantly higher loudness dependence of the N1/P2 component of auditory evoked potentials,[80] mean frequency on spectral analysis correlated with anxiety levels after both placebo and amphetamine challenge,[82] and that standard waking scalp EEG and TSH (thyroid stimulating hormone) influence sleep EEG, neurological soft signs and post dexamethasone cortisol levels.[83] Having an abnormal EEG increases the probability of patients with EUPD having less slow wave sleep, the opposite of which is seen in EUPD patients with a normal EEG. Five biological tests including TSH, standard waking scalp EEG, sleep EEG, post dexamethasone cortisol levels and neurological soft signs were shown to be interconnected and interdependent. Other findings include reduced P3 amplitudes during No-go responses in EUPD,[84] enhanced activation of the orbitofrontal cortex following an unexpected reward in EUPD patients with NSSI[85] and significant delay in early posterior gamma synchrony and a reduction in right hemisphere late gamma synchrony in response to salient stimuli in EUPD.[81] In the final study, the authors

conclude that EUPD is characterised by specific disturbances in neural synchrony related to core symptoms of cognitive impairment and impulsivity.

Articles meeting criteria 1, 3 and 4

One case study (Table 8) focused on QEEG changes in a patient with EUPD.[86] QEEG can provide functional information necessary to facilitate neurofeedback through engaging the brain to normalize dysfunctional brain wave patterns.[87] The article showed a mild to moderate increase in slow wave frequencies (theta, delta and slow alpha) in the orbital cortex, dorsomedial prefrontal and dorsolateral prefrontal cortices and a decrease of fast wave activities in the participant compared to normative data. The findings suggest a starting point for using QEEG as a means of investigating the potential role of neurofeedback in EUPD.

Articles meeting criteria 2, 3 and 4

Five studies met criteria 2, 3 and 4 (Table 9).[34,88-91] Of these, three studies used clinical criteria[34,88,89] and two studies used structured instruments[90,91] to make the diagnosis. All five studies were case-control studies with healthy control groups, while two studies had additional groups with other psychiatric diagnosis.[89,91] Three studies did not report on medication[34,90,91] and two studies were on those receiving antidepressants/anxiolytics.[90,91] One study had depression as a comorbidity[90] and others had no comorbidities. The findings in these studies included bimodal distribution of dominant frequencies and higher incidence of beta activity in psychoneurotic patients,[88] smaller late positive component (LPC) amplitude, P300 latency and P300 amplitudes when making incorrect responses to emotional pictures and faces;[90] there was no significant difference between groups when making correct responses to emotional cues. This article included participants who endorsed EUPD traits (i.e. endorsing a score >7 on the McLean Screening Instrument)[92] rather than meeting full diagnostic criteria. However the authors suggest that people who meet the full diagnostic criteria are likely to exhibit larger differences in evoked-potential response than those in this

study. Of note, the findings of decreased P300 amplitude are consistent with research reported earlier in this paper, but shorter P300 latencies contrast with previously reported findings.

A study found reduced P3 amplitude in those with treatment resistant depression and generalised anxiety disorder compared to healthy controls and those with EUPD.[89] A study on children with a history of abuse found greater average left hemisphere coherence and a greater number of abnormal EEGs.[34] A study found no significant difference in event-related potentials in response to a single tone between patients with EUPD, non-EUPD personality disorders and healthy controls.[91]

Articles meeting criteria 2, 4 and 5

One study met criteria 2,4 and 5 (Table 10) and showed evidence for qEEG-guided neurofeedback in children with histories of abuse and neglect.[41] This clinical trial showed a significant reduction in scores on the Childhood Behaviour Checklist[93] following qEEG-guided neurofeedback. A significant link exists between abuse and neglect in early childhood and a diagnosis of EUPD. These results point towards the potential role of qEEG-guided neurofeedback for patients with EUPD.

Of the articles which met three criteria, 11 showed EEG abnormalities in those with EUPD compared to controls. Furthermore, two articles showed EEG abnormalities in children with histories of abuse and one article demonstrated EEG abnormalities in “psychoneurosis”.

DISCUSSION:

We have conducted a comprehensive review illustrating the evidence to date for EEG markers in EUPD, especially in the aroused state. This paper reviewed 44 papers according to specific search criteria. Our findings indicate a variety of possible EEG changes present in EUPD. However, there were only two studies which referred to changes between baseline and a high arousal state.[49,50] The EEG findings of “greater left cortical activation” in EUPD in

response to rejection[49] and "higher total theta power" in response to pain in those with BPD-NP[50] are not specific to EUPD; higher alpha power in the left fronto-central cortex has been demonstrated in major depressive disorder[39,44] and increased theta activity has been utilised in neurofeedback therapy in ADHD, autism and anxiety.[45-47] Five studies consistently highlight differences in components of P300 during oddball paradigms/ auditory discrimination tasks in those with EUPD compared to controls.[70-73,75] Arousal levels have previously been shown to effect the availability of attention processes to modulate P300,[94,95] suggesting a need for further investigation of P300 in a state of high arousal in EUPD.

More than half of the studies examining standard waking EEGs in EUPD highlighted significant EEG abnormalities compared to controls (Table 11). All these findings can potentially be seen in other disorders.[17-22] Half of the sleep EEG studies identified reduced REM latency as an EEG biomarker in EUPD. However, abnormalities detected on sleep EEG cannot be used in potential EEG based neurofeedback treatments. Half of the studies on event related potentials highlight decreased amplitude and prolonged latency of P300 in those with EUPD compared to controls, similar to the potential EEG changes seen in anxiety.[23] P300 amplitude and latency may represent a neuromarker in EUPD.

It is also worth noting that the studies reviewed used varying protocols for type of EEG, number of channels and electrode placement. Three of the studies did not specify type of EEG used, site of electrode placement was not specified in 14 studies, 13 studies did not specify number of channels used and 24 studies did not specify whether artefacts were removed. Other limitations to the studies reviewed include small sample size, mainly female participants, medication use and the presence of comorbid disorders.

Although not consistent between studies, various EEG abnormalities in subgroups of patients with EUPD were identified. None of the EEG findings are specific to EUPD or any other specific disorders. However, if corroborated by further evidence, these findings may

potentially be used as neuromarkers and targets for neurofeedback in the treatment of aroused states in EUPD. One possibility is that EEG neuromarkers particular to EUPD only exist whilst in a specific state (e.g. high arousal). Alternatively there may be a number of different neuromarkers which could be clustered together with subdomains of EUPD or clinical symptomatology. This may help in identifying subdomains of patients and person-centred tailored treatments for them.

There was no study to date which investigated the potential role of EEG based neurofeedback as an intervention in EUPD. However, advances in qEEG data may improve the detection of EEG abnormalities in psychiatric disorders and thus the potential for neurofeedback therapy.[96] Use of neurofeedback therapy in EUPD based on these EEG markers may result in clinical amelioration of symptoms as in other psychiatric disorders.[9]

CONCLUSION:

Due to the limited evidence to date, specific conclusions on EEG changes during changes in arousal in EUPD or the potential mapping of EEG findings to EUPD subdomains cannot be drawn. Further study into the mapping of neuromarkers with EUPD subdomains and clinical symptomatology could define targeted use of neurofeedback as a potential intervention in this disorder. Based on the findings in this review, a checklist of EEG findings commonly found in those with EUPD has been developed (appendix 4). The mechanism of its development has been provided (appendix 5).This checklist could be used to design and conduct further studies in this area so as to confirm or rule out the identified cumulative findings as neuromarkers of EUPD. There is evidence for using neurofeedback in a number of psychiatric conditions and our review highlights a number of EEG markers in EUPD. Hence we believe that with further research verification, EEG-based neurofeedback treatment options, especially for individuals in the aroused state could be developed.

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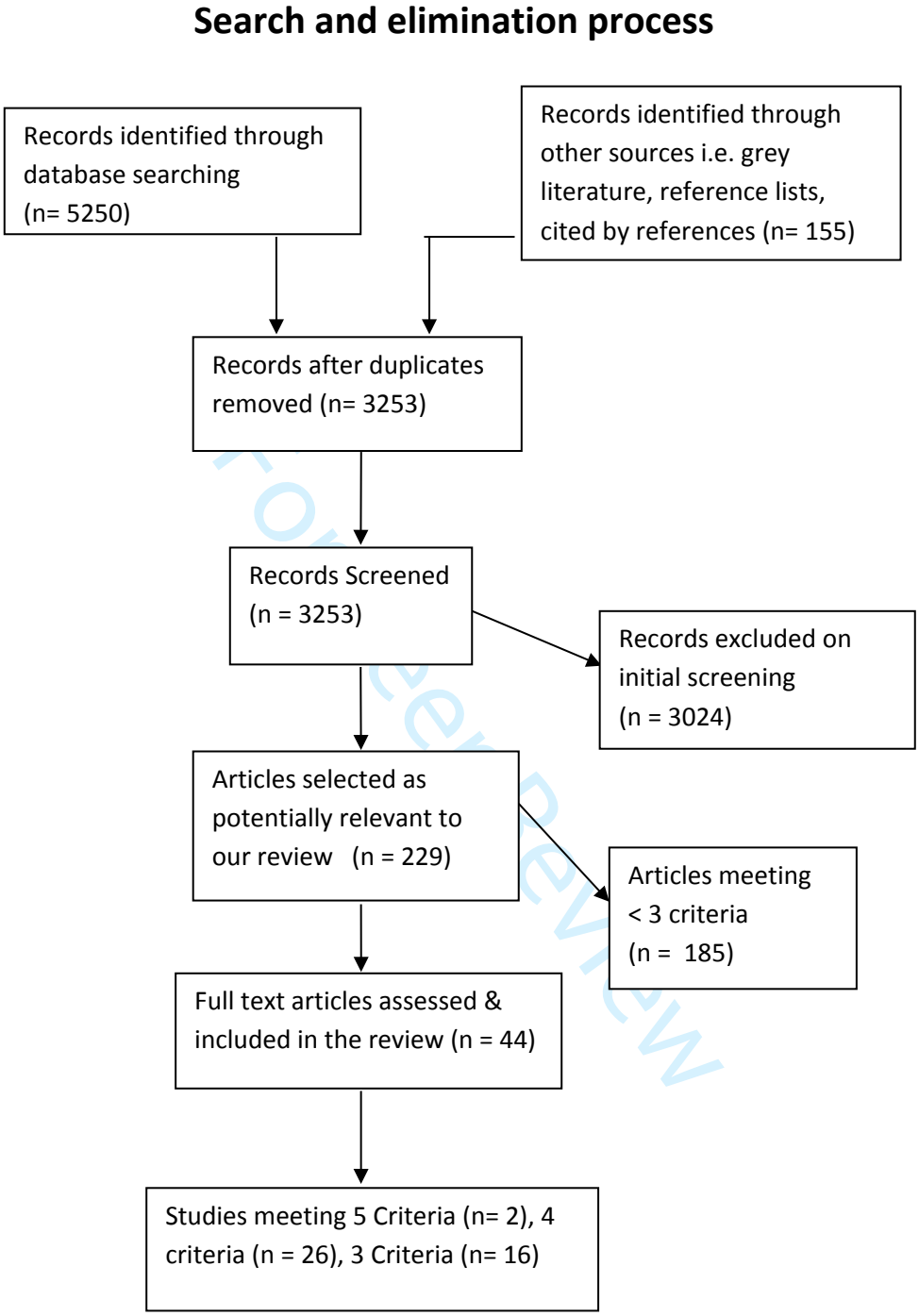
Pathway 1: Search and selection criteria



Appendix 1:

Emotionally Unstable Personality Disorder (EUPD): The diagnostic term EUPD is used throughout the article to represent both Emotionally Unstable Personality Disorder (ICD-10 F60.30 Impulsive type and F60.31 Borderline type) and Borderline Personality Disorder (DSM IV 301.83). We have retained the term EUPD throughout the article for consistency. Where the term BPD is used this is to highlight diagnostic systems used and specific terms used in the original article.

Dysrhythmia: EEG cerebral dysrhythmia denotes isolated episodic paroxysmal bursts of slow activity, controversial/anomalous spiky waveforms and/or true non-controversial epileptiform discharges

Search terms -

("eupd" OR "borderline disorder" OR "borderline patient" OR "borderline condition" OR "borderline client" OR "borderline personality" OR "borderline personalities" OR "bpd" OR "borderline state" OR "affective instability" OR "personality disorder" OR "personality disorders" OR "PERSONALITY DISORDERS" OR "ANTISOCIAL PERSONALITY DISORDER" OR "BORDERLINE PERSONALITY DISORDER" OR "antisocial personalities" OR "antisocial personality" OR "anti-social personalities" OR "anti-social personality" OR "sociopath" OR "psychopath" OR "psychoneurotic" OR "psychoneuros*" OR "impulsivity" OR "impulse control" OR "multi-impulsivity OR multi-impulsive" OR "character disorder" OR "impulsive behaviour" OR "impulsive behavior" OR "IMPULSIVE BEHAVIOR" OR "DISRUPTIVE, IMPULSE CONTROL, AND CONDUCT DISORDERS" OR "post traumatic" OR "posttraumatic" OR "ptsd" OR "STRESS DISORDERS, POST-TRAUMATIC" OR "dyssocial" OR "socio-path")

AND

(“ AROUSAL” OR “arousal” OR “arouse” OR “aroused” OR “vigilance” OR “rest state" OR "resting state” OR “rest states” OR “resting states” OR "acute phase” OR “abnormal” OR “abnormality “ OR “abnormalities” OR “crisis” OR “crises” OR “distress” OR “distressed” OR “agitated” OR “agitation” OR "PSYCHOMOTOR AGITATION” OR “panic” OR “PANIC” OR “depressed” OR “depression” OR “depressive” OR “DEPRESSION”)

AND

(“eeg” OR “electroencephalogram” OR “electroencephalograms” OR “electrograph*” OR “electrograms” OR “electrogram” OR “electroencephalograph” OR “ ELECTROENCEPHALOGRAPHY” OR "BRAIN WAVES” OR “ TELEMETRY” OR “telemetry” OR “ptsw” OR “slow wave" OR "slow waves” OR “p300” OR "EVENT-RELATED POTENTIALS” OR “P300” OR “EVOKED POTENTIALS” OR "CONTINGENT NEGATIVE VARIATION” OR “EVENT-RELATED POTENTIALS” OR “orbito-frontal” OR “orbitofrontal” OR “qeeg” OR “p3a” OR p3b” OR “evoked potential*” OR “event related potential*” OR “Bereitschaftspotential” OR "readiness potential” OR “cnv” OR "contingent negative variation”” OR “brain wave*” OR “alpha wave*” OR “beta wave*” OR “delta wave*” OR “gamma wave*” OR “theta wave*” OR “alpha rhythm*” OR “beta rhythm*” OR “delta rhythm*” OR “gamma rhythm*” OR “rhythm wave*”)

Appendix 2

Search Strategy -

1) Online database search using Medline, PsycInfo and Embase.

2) Search for grey literature.

3) Review of the references of articles meeting three or more criteria (see below)

4) Search of particularly relevant articles meeting three or more criteria for "cited by" references in Pubmed, Scopus and Google Scholar.

5) Contacting authors of relevant articles about any unpublished articles/ results.

There were no language limits in the search strategy, provided there was an English language translation of the relevant study available.

Data Sources:

Appendix 1 shows the search strategy for Medline on Healthcare Databases Advanced Search (HDAS) using a combination of text words and thesaurus terms. The same strategy was used for PsycInfo and Embase but thesaurus terms specific to the different databases were used. Other databases were searched for grey literature using an appropriately amended strategy. The number of articles from each database is indicated in Table 12.

All articles published before the final database search in February 2018 were included.

Step 1

Any articles duplicated during the collection process were removed. Articles that were not relevant to the review were removed i.e. not relevant to electrophysiological investigation/ biological markers in personality disorder, affective disorders, general psychopathology or associated terms.

Step 2

The first and final authors applied the prearranged inclusion criteria to all abstracts.

1) The article refers to EUPD / Borderline Personality Disorder (BPD) as the primary diagnosis

2) Must be a case-control/ cohort/ cross sectional study or higher on the hierarchy of evidence.

3) The population under investigation were all over 18 years of age

4) EEG was the only or main investigation of the study. Articles meeting criteria 4 must also refer to EUPD or equivalent terms.

5) The article refers to EEG changes during emotional fluctuations.

Step 3

Articles that met three or more of the above criteria were fully reviewed.

Citation searching -

Checks were made to ascertain whether particularly relevant articles (i.e. articles meeting three or more criteria) were cited elsewhere.

Reference Lists -

The reference list of each article screened as eligible was checked for additional articles not included through other search methods.

Contact with Authors -

Authors of articles meeting three or more criteria and included in this review were contacted to check if additional articles or any unpublished articles/ results were available. 11 authors of particularly relevant articles were contacted by email. Responses were received from four of these authors, none of whom were aware of additional unpublished studies/ results.

Appendix 3

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3 to 7
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	7
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	NA
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	8 -9
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Appendix 1
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Pathway 1
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	8-9 and pathway 1 and appendix 1
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	8-9 and pathway 1 and appendix 1
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Tables 2 to 10
Critical appraisal of individual	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this	9 to 16

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
sources of evidence§		information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Tables 2 to 10
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	9 to 16 and tables 2 to 10
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	9 to 16
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	9 to 16
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	9 to 16
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	9 to 16 and tables 2 to 10
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	16 -18
Limitations	20	Discuss the limitations of the scoping review process.	16 -18
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	19
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	NA

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. ;169:467–473. doi: 10.7326/M18-0850

Appendix 4:

EUPD and EEG: Checklist and Questions for EEG Findings.

Questions For Findings in QEEG/ Digital EEG.

(Examine the Z-score tables for the distribution of abnormalities)

1) Does the QEEG/Digital EEG show presence of Interhemispheric and Intrahemispheric Coherence.

(a) Greater left cortical activation (EUPD).

(b) Greater right cortical activation (Major Depression).

(c) Significant delay in early posterior gamma* synchrony & reduced right hemisphere late gamma synchrony.

(d) Delay in posterior gamma synchrony associated with cognitive symptoms

(e) Reduced right hemisphere gamma synchrony associated with impulsivity

*gamma - (37–41 Hz)

2) What is the Absolute Power in

(a) delta (<3 Hz)

(b) theta*(4-7 Hz)

(c) alpha (8-12 Hz)

(d) beta (>13 Hz)

* Total theta power higher in EUPD.

3) What is the Relative Power in

(a) delta

(b) theta

(c) alpha

(i) Less stable EEG-vigilance pattern 'A' with a tendency to drop to lower vigilance states 'B'

('A'= at least one EEG channel shows a relative alpha power >50% compared to the total power of the respective channel.

'B'=No clear alpha rhythm in any channels)

(d) beta

4) What is the Mean Frequency.

(a) Does the mean frequency on spectral analysis correlate with anxiety levels.

5) Presence of Asymmetry Values

Questions for Findings in Standard EEG.

Does the EEG indicate the following?

6) Diffuse slowing

7) Dysrhythmias (EEG cerebral dysrhythmia denotes isolated episodic paroxysmal bursts of slow activity, suppression of waveforms, controversial/anomalous spiky waveforms, sharp waves and/or true non-controversial epileptiform discharges).

8) Sharp waves, especially in posterior areas

9) Increased slow wave activity

10)

(a) Increased prevalence of intermittent rhythmic delta (IRDA) or theta (IRTA) activity.

(b) random or semi-rhythmic theta and/or delta

11) Abnormalities in Temporal lobe areas.

12) Epileptiform patterns

Questions for Findings in Sleep EEG.

Does the EEG indicate the following?

13) Increased REM percentage

14) Increased REM density

15) Shorter REM latency (much shorter in EUPD with Depression)

16) Longer REM period.

17) Increased delta power in Non-REM sleep.

18) Reduced slow wave, stage 3 & 4 sleep

Questions for Findings in Evoked Potentials.

Does the EEG indicate the following?

19) Increased P300 latency

20) Decreased P300 amplitude

21) Increased amplitude of P3a and loss of temporal synchronicity of P3a with P3b.

22) Larger late positive potentials (LPP).

23) Higher loudness dependence of the N1/P2 component of auditory evoked potentials.

24) Reduced P3 amplitudes during No-go responses in Go-No-go test.

25) Smaller LPC amplitude

26) Increase in slow wave frequencies (theta, delta and slow alpha) in the orbital cortex, dorsomedial prefrontal or dorsolateral prefrontal cortexes

27) Decreased P300 latency

Appendix 5

Generating the Checklist based on Findings in relevant articles.

Q1-Q25 indicate the question generated based on the individual article findings.

Articles	Findings	Finding based Questions:
Beeney et. al. 2014 (38)	EUPD - greater left cortical activation, MDD - greater right cortical activation. Q1	**Questions for Findings in QEEG/ Digital EEG.** (Examine the Z-score tables for the distribution of abnormalities) 1. Does the QEEG/Digital EEG show presence of Interhemispheric and Intrahemispheric Coherence. (a) Greater left cortical activation (EUPD). (b) Greater right cortical activation (Major Depression). (c) Significant delay in early posterior gamma* synchrony & reduced right hemisphere late gamma synchrony. (d) delay in posterior gamma synchrony associated with cognitive symptoms (e) Reduced right hemisphere gamma synchrony associated with impulsivity *gamma - (37–41 Hz) 2. What is the Absolute Power in (a) delta (<3Hz) (b) theta* (4-7Hz) (c) alpha (8-12 Hz) (d) beta (>13Hz) * Total theta power higher in EUPD.
Russ et. al. 1999 (39)	Total theta power significantly higher. Q2	

		3. What is the Relative Power in (a) delta (b) theta (c) alpha (i) Less stable EEG-vigilance pattern 'A' with a tendency to drop to lower vigilance states 'B' ('A'= at least one EEG channel shows a relative alpha power >50% compared to the total power of the respective channel. 'B'=No clear alpha rhythm in any channels) (d) beta 4. What is the Mean Frequency. (a) Does the mean frequency on spectral analysis correlate with anxiety levels. 5. Presence of Asymmetry Values
		Questions for Findings in Standard EEG. **Does the EEG indicate the following?** 6. Diffuse slowing 7. Dysrhythmias (EEG cerebral dysrhythmia denotes isolated episodic paroxysmal bursts of slow activity, suppression of waveforms, controversial/anomalous spiky waveforms, sharp waves and/or true non-controversial epileptiform discharges). 8. Sharp waves, especially in posterior areas 9. Increased slow wave activity 10. (a) Increased prevalence of intermittent rhythmic delta (IRDA) or theta (IRTA) activity. (b) random or semi-rhythmic theta and/or delta 11. CNS abnormalities focal to Temporal lobe areas. 12. Epileptiform patterns
Ogiso et al. 1993 (41)	NONE	
De La Fuente, 1998 (42)	EUPD -diffuse slowing on EEG Q6	
Cornelius et al. 1986 (43)	EUPD - EEG dysrhythmias Q7	
Cowdry et al. 1986 (44)	EUPD - posterior sharp waves Q8	
Synder & Pitts, 1984 (45)	EUPD -Increased slow wave activity Q9	
Hegerl et al. 2008 (46)	EUPD - less stable EEG-vigilance pattern with a tendency to drop to lower vigilance states (p=0.03). Q3ci	
Van Elst, 2016 (47)	EUPD - significantly increased prevalence of IRDAs and IRTAs (intermittent rhythmic delta or theta activity)	

	Q10a	
Yerevanian et al. 1985 (48)	EUPD - EEG abnormalities, most commonly in temporal lobe areas (abnormalities not discussed in detail) Q11,12	
		Questions for Findings in Sleep EEG. **Does the EEG indicate the following?** 13. Increased REM percentage 14. Increased REM density 15. Shorter REM latency (much shorter in EUPD with Depression) 16. Longer REM period. 17. Increased delta power in Non-REM sleep. 18. Reduced slow wave, stage 3 & 4 sleep
Assad et. al. 2002 (49)	EUPD - REM % & REM density higher, REM latency shorter, longer REM period. (Changes less robust than in those with depression) Q13, Q14, Q15, 16	
Philipsen et. al. 2005 (50)	EUPD - Higher delta power in NonREM sleep. Q17	
De La Fuente, 2004 (51)	EUPD -significantly less stage 3 sleep and slow wave sleep and a longer duration of REM sleep. Q18	
De La Fuente, 2001 (52)	EUPD - longer duration of REM sleep, significantly less stage 3, stage 4 and slow wave sleep. Q16, Q18	
Battaglia et al. 1993 (53)	EUPD - Reduced REM latency. Q15	
Battaglia et al. 1999 (54)	EUPD - Increased REM density in first REM cycle. Q14	
Bell et al. 1983 (55)	EUPD patients with depression had shorter REM latencies than non-depressed EUPD patients. Reduced REM latency both groups Q15	
Mcnamara et al. 1984 (56)	EUPD and depressive groups both had Shorter REM latency and increased REM density. Q14, Q15	
Akiskal et al. 1985 (57)	EUPD - Shorter REM latency than healthy controls and non-EUPD personality disorder patients, but similar results to those with affective disorders Q15	
Reynolds et al. 1985 (58)	EUPD - Reduced REM latency, but similar to those with depression Q15	

Blackwood et al. 1986	EUPD - Longer P300 latency and smaller amplitude. Q19, Q20	**Questions for Findings in Evoked Potentials.** **Does the EEG indicate the following?** 19. Increased P300 latency 20. Decreased P300 amplitude 21. Increased amplitude of P3a and loss of temporal synchronicity of P3a with P3b. 22. Larger late positive potentials (LPP). 23. Higher loudness dependence of the N1/P2 component of auditory evoked potentials. 24. Reduced P3 amplitudes during Nogo responses in Go-Nogo test. 25. Smaller LPC amplitude
Kutcher et al. 1987	EUPD - Longer P300 latency and decreased P300 amplitude. Q19, Q20	
Kutcher et al. 1989	EUPD (BPD) - Prolonged P300 latency and decreased P300 amplitude. Q19, Q20	
Drake et al. 1991	EUPD (BPD) Prolonged P300 latency and decreased P300 amplitude. Q19, Q20	
Meares et al. 2004	EUPD (BPD) - Enhanced amplitude of P3a and loss of temporal synchronicity of P3a with P3b. Natural age-related decline in P3a amplitude reduced in BPD. Q21	
Marissen et al. 2010	EUPD (BPD) - Larger LPP (late positive potentials) to pictures with an unpleasant valence. Q22	
He et al, 2012	NONE	No significant findings
Archer et al. 1988 (66)	NONE	No significant findings
Houston et al. 2005 (67)	NONE	No significant findings
Houston et al. 2004 (68)	EUPD - Reduced P300 amplitude. Q20	
Schaaff et al. 2007 (69)	EUPD - Significantly higher loudness dependence of the N1/P2 component of auditory evoked potentials. Q 23	
Cornelius et al. 1988 (70)	EUPD - Mean frequency on spectral analysis correlated with anxiety levels. Q4	
De La Fuente et al. 2011 (71)	TSH and standard EEG results influence sleep EEG, neurologic soft signs and post dexamethasone cortisol in patients with EUPD . Q6, Q10b	

Ruchsow et al. 2008 (72)	EUPD - reduced P3 amplitudes during Nogo responses in Go-Nogo test. Q24	
Vega et al. 2017 (73)	fMRI study, EEG not used/done	No EEG findings
Williams et al. 2006 (74)	EUPD - significant delay in early posterior gamma synchrony & reduced right hemisphere late gamma synchrony. Delay in posterior synchrony was associated with cognitive symptoms and reduced right hemisphere synchrony was associated with impulsivity. Q1c, Q1d, Q1e.	
Cohen et al. 2016 (75)	EUPD - Mild to moderate increase in slow wave frequencies (theta, delta and slow alpha) in the orbital cortex, dorsomedial prefrontal and dorsolateral prefrontal cortexes. Q26	26. Increase in slow wave frequencies (theta, delta and slow alpha) in the orbital cortex, dorsomedial prefrontal or dorsolateral prefrontal cortexes (Compare with question 9 & 18)
Brazier et al. 1945 (76)	Higher incidence of beta activity in psychoneurosis versus controls (critical ratio 6.54). No established EUPD diagnosis.	No relevant findings
Hill et al. 2005 (77)	EUPD traits - had smaller LPC amplitude, decreased P300 latency, and decreased P300 amplitudes when making incorrect responses to emotional pictures and faces. Q20, Q25, Q27	27. Decreased P300 latency
Shaofang Xu et al. 2014 (78)	TRD & GAD - Reduced P3 amplitude in those with TRD & GAD compared to healthy controls and those with EUPD. EUPD used as control group.	No relevant findings
Teicher et al. 1997 (29)	No established EUPD diagnosis	No relevant findings
Shen et al. 2008 (79)	NONE	No significant findings
Huang-Storms et al. 2006 (37)	No established diagnosis	No relevant findings

Table 1. Articles on the relationship between EEG changes and psychopathology

Paper	Type of article	Findings
Shelley et al, 2009.[7]	Review article	Higher incidence of EEG abnormalities in the nonepileptic neuropsychiatric population than the normal population in 25 out of 29 articles reviewed
Abrams et al, 1980.[8]	Cross-sectional study	Significant correlations between left-sided EEG abnormality and formal thought-disorder and emotional blunting (sample size: 159 patients with schizophrenia/ affective disorder)
Schoenberg et al, 2014.[9]	Review article	-81% of 63 articles reviewed reported clinical amelioration related to biofeedback, 65% to a statistically significant level ($p<0.05$) -EEG neurofeedback was the most investigated modality of biofeedback -Anxiety disorders were the most commonly treated with biofeedback -Multi-modal biofeedback appeared most effective in significantly ameliorating symptoms
Small et al, 1984.[10]	Cohort study	EEG abnormalities predicted diagnostic change (33% rediagnosed with affective, organic or other disorders) & relatively favourable prognosis in a sample of 759 hospitalised patients with schizophrenia
Gallinat et al, 2016.[11]	Review article	-Specific EEG changes in Alzheimers disease (increase in delta and theta activity, decrease in beta activity, slowing of the alpha basal rhythm and reduction of the topographical structure) (7 articles on Alzheimers disease reviewed) -EEG changes in delirium (slowing of delta and theta activity) (2 articles on delirium

		reviewed) - EEG changes specific to Lithium intoxication (7 articles), Clozapine (3 articles) and Benzodiazepines (1 article)
McLoughlin et al, 2013.[12]	Review article	-EEG has improved understanding of face processing (3 articles), cognitive control (2 articles) and mirror neuron activity (1 article) in the general population. - Independent component analysis of EEG can identify brain sources that correspond to distinct suggested emotions (1 article)
Balogh et al, 2010.[13]	Review article	-Patients with a diagnosis of schizophrenia, anorexia nervosa or EUPD exhibited a decrease in amplitude & those with depression and anxiety an increase in amplitude of error-negativity (an evoked potential component) (number of studies reviewed not recorded)
Hughes et al, 1999.[14]	Review article	-EEG and Quantitative EEG changes can be seen in anxiety disorder (7 articles), depression (27 articles), dementia (62 articles), obsessive-compulsive disorder (7 articles), schizophrenia (52 articles) & intellectual disabilities or attention deficit disorder (20 articles)

Table 2. Articles which met all 5 Criteria

Article	Diagnostic System	N (male /female)	Medications	Comorbid conditions	Control group	Findings	Study Design/EEG type/ Statistical Test used
Beeney et. al. 2014.[49]	IPDE[97] and LEAD standard, [98,99] SCID-1,[100]	23 (0/23)	Not discussed	No depressive episode in last 6 months. Psychotic disorders, Bipolar 1	Major depressive disorder (MDD) Healthy controls (HC)	Following rejection, individuals with EUPD showed greater left cortical activation, those with MDD greater right cortical activation and HCs a more balanced cortical profile (p<0.001).	Case-control Study. Scalp EEG using128-channel geodesic sensor net. Electrode placement not specified. Artifacts removed using independent component analysis. ANOVA and Tukey's HSD post hoc tests
Russ et. al. 1999.[50]	SCID-II,[101]	41 (0/41)	Antidepressants, antipsychotics, mood stabilizers, benzodiazepines	High rate of Axis I and II co-morbidities	Major depression Healthy controls	Total theta power significantly higher in EUPD-NP than depressive group (p=0.	Cohort Study. 16 channel scalp EEGs using 10-20 system. Artifacts removed following manual

					0074) and healthy controls (p<0.0001). Total theta power was significantly higher in the EUPD-P group compared to normal controls (p=0.016)		review. EEG data were log transformed to approximate normality. Following this, repeated measures ANCOVAs were used.

Tukeys HSD = Tukey's honestly significant difference test, EUPD-P/ EUPD-NP = patients with EUPD who are sensitive/ not sensitive to pain following self-injurious activity.

Table 3. Articles using Standard EEGs

Article	**Diagnostic System**	**N (male/female)**	**Medications**	**Comorbid conditions**	**Control group**	**Findings**	**Study Design/EEG type/ Statistical test used**
Ogiso et al. 1993.[52]	DIB[102] >7 & DSM-III.[103]	18 (0/18)	Anxiolytics, antipsychotics, antidepressants	Affective disorders, eating disorders and substance abuse	Non-EUPD in-patients (DIB <7 and without DSM-III diagnosis of BPD).	No characteristic EEG changes in EUPD vs. control group. Positive	Case control study. EEGs recorded using 10-20 technique through monopolar & bipolar leads.

						spikes appeared in patients with high scores for impulse action patterns on DIB.	Mean values of frequency and amplitude were analysed by the T-test. Fishers exact test was used for other statistical comparisons.
De La Fuente, 1998[53]	DSM-III-R,[104] & DIB.[102]	20 (6/14)	None for at least 10 days (15 days for TCAs and MAOIs, 2 months for neuroleptics)	No Axis 1 disorder or substance misuse	None	40% of patients with EUPD showed diffuse slowing on EEG	Randomized controlled trial. Scalp EEGs recorded using 17-channel equipment, according to the 10-20 system.
Cornelius et al. 1986.[54]	DIB.[102]	69 (17/52)	None for at least 7 days	None	Other Axis II disorders	18.8% EUPD patients had EEG dysrhythmias (9.1% controls), 5.8% had severe EEG abnormalities (0% controls), but not significant compared to controls	Case-control study. Scalp EEGs recorded on 16 channel instruments. Electrode placement not specified. Chi-squared test with Yates correction.

						(p>0.25).	
Cowdry et al. 1986.[55]	Clinical assessment	39 (3/36)	Antipsychotics, antidepressants, anxiolytics	No axis 1 disorder	Unipolar depression (Research diagnostic criteria).[104]	46% definite EEG abnormalities vs. 10% controls (p=0.005). 41% EUPD patients had posterior sharp waves vs. 5% controls (p=0.005).	Case-control study. Scalp EEGs using 16-electrode placements according to the 10-20 system with bipolar & monopolar leads. Fisher's exact test
Snyder & Pitts, 1984.[56]	DSM-III (> 6 criteria).[103]	37 (37/0)	None	None	Dysthmic disorder	Significantly more EEG abnormalities in those with EUPD (38% vs. 13% controls, p<0.05). Increased slow wave activity in EUPD (19% vs. 3% controls, p<0.05).	Case-control study. Scalp EEGs with 16 channels using both monopolar & bipolar leads. Electrode placement not specified. Raw Chi Square for analysis of contingency tables
Hegerl	ICD-10	20	None	None	Obsessive Compulsive	EUPD patients	Case-control study. Scalp

et al. 2008.[57]	(F60.31).[1]	(6/14)			Disorder Healthy controls	had a less stable EEG-vigilance pattern with a tendency to drop to lower vigilance states (p=0.03).	EEGs with 32 channels according to the 10-20 system. Artefacts were removed following visual inspection. ANCOVA and MANCOVA
Van Elst, 2016.[58]	SCID I and II.[100,101]	96 (3/93)	Antipsychotics, antidepressants in 57%	Affective disorders, eating disorders, ADHD, substance abuse	Healthy controls	EUPD patients had a significantly increased prevalence of IRDAs and IRTAs (14.6%) compared to HCs (3.9%) p=0.02) – intermittent rhythmic delta or theta activity	Case-control study. Scalp EEG with 25 channels according to the 10-20 system. Pearson's two-sided X^2-test
Yerevanian et al. 1985.[59]	DSM-III.[103]	29 (not recorded)	Not recorded	Not recorded	No controls	45% of EUPD patients had EEG abnormalities, most commonly in temporal lobe	Cross-sectional study. Type of EEG used and electrode placement not specified.

						areas	

TCA = Tricyclic antidepressant, MAOI = Monoamine oxidase inhibitors, IRDA/IRTA = intermittent rhythmic delta/ theta activity.

Table 4. Articles using sleep EEGs

Article	Diagnostic System	N (male/female)	Medications	Comorbid conditions	Control group	Findings	Study Design/ EEG type/ Statistical test used
Assad et. al. 2002.[60]	ICD-10, 1993.[1]	20 (8/12)	None for at least 2 weeks prior	None	Major depressive disorder Healthy controls	Higher REM % ($p<0.05$) & REM density ($p<0.01$), shorter REM latency ($p<0.001$), longer REM period ($p<0.001$) for those with EUPD than controls. Changes less robust than in those with depression	Case-control study. All-night polysomnographic assessments. Electrode placement not specified. T-test
Battaglia et al. 1999.[61]	DSM-III-R.[104] and SIDP-R.[105]	10 (4/6)	None for at least 2 weeks	Never depressed, 6 with a history of alcohol or drug abuse	Healthy controls	Increased REM density in first REM cycle in those with EUPD compared to HCs ($p<0.01$)	Case-control study. Continuous 48 hour ambulatory EEG monitoring using 3 channels.

							Electrode placement not specified. T-test
Battaglia et al. 1993.[62]	DSM-III.[103] & SIDP-R.[105]	10 (4/6)	None for at least 2 weeks	Never depressed, 6 with history of drug or alcohol abuse	Healthy controls	Reduced REM latency in those with EUPD compared to healthy controls ($p<0.003$)	Case-control study. Continuous 48 hour ambulatory EEG monitoring using 3 channels. Electrode placement not specified. T-test
Bell et al. 1983.[63]	DSM-III.[103]	8 (NR)	NR	Depression in all EUPD patients	Non-EUPD patients with depression	Reduced REM latency both groups, EUPD patients with depression had shorter REM latencies than non-depressed EUPD patients ($p<0.025$)	Case-control study. All-night polysomnographic sleep EEG. Electrode placement not specified. ANCOVA
Mcnamara et al. 1984.[64]	DIB.[102]	10 (0/10)	None for at least 2 weeks	Depression in 6/10	Depression Healthy controls	EUPD and depressive groups both had Shorter REM latency ($p=0.01$) and increased REM density	Case-control study. All night polysomnographic sleep EEG, with C3/A2 electrode

						(p=0.01) compared to HCs	placement. Analysis of variance and Kruskal-Wallis tests
Akiskal et al. 1985.[65]	DSM-III.[103]	24 (12/12)	None for at least 2 weeks	None No depression for at least 1 year	Affective disorders Non-EUPD personality disorder Healthy controls	Shorter REM latency than healthy controls and non-EUPD personality disorder patients (p<0.001), but similar results to those with affective disorders	Case-control study. Continuous overnight EEG, electrode placement not specified. ANOVA and when significant, Students t-test and the post-hoc Scheffe test
Reynolds et al. 1985.[66]	DIB.[102]	20 (3/17)	None for at least 2 weeks	Depression in 10/20	Depression Healthy controls	Reduced REM latency in those with EUPD compared to controls (p=0.02), but similar to those with depression	Case-control study. All-night EEG as per C3/A2 electrode placement. Artefacts removed following visual inspection. ANOVA
De La Fuente, 2004.[67]	DSM-III-R.[104] and DIB.[102]	20 (6/14)	None for at least 10 days, 15 days for TCAs and MAOIs and no	None	Recurrent brief depression Major depressio	EUPD patients had significantly less stage 3 sleep and slow wave sleep and a longer	Case-control study. Overnight sleep EEG using occipital, frontal and

			antipsychotics for 2 months.		n Healthy controls	duration of REM sleep.	central leads. ANOVA and post-hoc two-tailed t-tests
De La Fuente, 2001.[68]	DSM-III-R.[104] and DIB.[102]	20 (6/14)	None for at least 10 days, 15 days or TCAs and MAOIs, no antipsychotics for 2 months	None	Major Depression Healthy controls	EUPD patients had a longer duration of REM sleep, significantly less stage 3, stage 4and slow wave sleep ($p<0.001$) than all comparison groups.	Case-control study. Overnight sleep EEG using occipital, frontal and central leads. ANOVA and post-hoc two- tailed t-tests
Philipsen et. al. 2005.[69]	SCID I and II.[100,101]	20 (0/20)	None for at least 2 weeks prior	None	Healthy controls	No significant difference in polysomnographic parameters Higher delta power in Non-REM sleep for those with EUPD ($p=0.047$)	Case-control study. Continuous overnight sleep EEG using C3/A2 and C4/A1 electrode placements with spectral analysis. MANOVAs - when significant results found ANCOVAs were used

Table 5. Articles using evoked potentials

Article	Diagnostic System	N (male /female)	Medications	Comorbid conditions	Control group	Findings	Study Design/ EEG type/ Statistical test used
Blackwood et al. 1986.[70]	SADS,[106] DIB,[102] & BEFI.[107]	14 (0/14)	Lithium, antidepressant, tranquilizers	None	Non-EUPD personality disorder Healthy controls	Longer P300 latency ($p<0.05$) and smaller amplitude ($p<0.01$) in those with EUPD than in both control groups	Case-control study. Scalp EEG via electrode at Cz position. Artefacts removed using and artefact-reject circuit if voltage exceeded 45uV. Analysis of variance and Scheffe procedure
Kutcher et al. 1987.[71]	DSM-III,[103] DIB,[102] & BEFI.[107]	22 (2/20)	Antidepressants, antipsychotics, anxiolytics, Lithium carbonate	None	Paranoid schizophrenia Major depression Non-EUPD personality disorder Healthy controls	Decreased P300 amplitude ($p=0.01$) and longer P300 latency ($p<0.01$) in those with EUPD and in those with schizophrenia than in those with depressio	Case-control study. Bipolar EEG recordings using a scalp electrode at the Cz position. Artefacts removed using an artefact reject circuit if voltage exceeded 45uV. Anova and Duncan's procedure

					n, other personality disorders and healthy controls.		
Kutcher et al. 1989.[72]	DSM-III,[103] DIB,[102] & SADS.[106]	23 (5/18)	Antidepressants, tranquilizers (11 drug free, 12 medicated)	None	EUPD with schizotypal personality disorder (SPD) Schizotypal personality disorder Non-EUPD personality disorder Healthy controls (HC)	Prolonged P300 latency ($p<0.01$) and decreased P300 amplitude ($p<0.01$) in BPD and in SPD compared to other personality disorders and HCs	Case-control study. Bipolar EEG recordings using a scalp electrode at the Cz position. Artefacts removed using an artefact reject circuit if voltage exceeded 45uV. ANOVA and Duncan's procedure
Meares et al. 2004.[73]	DSM-III-R.[104] and DIB.[102]	17 (4/13)	None for at least 30 days	Not recorded	Age and sex-matched healthy controls Second control group of 50 men and 50 women at	Enhanced amplitude of P3a ($p<0.001$) and loss of temporal synchronicity of P3a with P3b in BPD compared	Case-control study. EEGs recorded from Fz, Cz & Pz electrode sites according to the 10-20 system. Artefact contaminated peaks removed below 2 &

					various ages as normative controls	to HCs ($p<0.01$). Natural age related decline in P3a amplitude reduced in BPD ($p<0.001$).	above 45uV. Parametric t-test, Non-parametric with Mann Whitney U-test. Regression analysis
Marissen et al. 2010.[74]	DSM-IV,[108] & SCID-II.[101]	60 (0/60)	Antidepressants, antipsychotics. No benzodiazepines	No major depression, anxiety, ADHD, substance abuse, psychotic symptoms or PTSD	Healthy controls	BPD patients had larger LPP (late positive potentials) to pictures with an unpleasant valence compared to controls ($p<0.01$).	Case-control study. Scalp EEGs recorded from 32 electrode sites using 10-20 system. ANOVA and T-tests
Drake et al. 1991.[75]	DSM-III.[103]	20 (2/18)	None for at least 1 week	None	Healthy controls	Prolonged P300 latency ($p<0.001$) and decreased P300 amplitude ($p<0.001$) in BPD compared to healthy controls using long-	Case-control study. Scalp EEGs recorded from electrode sites Cz, A1 & A2. Two-tailed t-test

						latency ERPs	
He et al, 2012.[76]	DSM-IV-TR.[109]	15 (2/13)	50% prescribed anxiolytics, antidepressant, mood stabilizers	Not reported	Treatment resistant depression (TRD) TRD and BPD Healthy controls	No difference in the effect of facial emotions on event related potentials in BPD compared to other groups	Case-control study. Scalp EEGs recorded at electrode sites Fz, Cz & Pz. Multiple way ANOVA

Table 6. Articles meeting 3 Criteria

Articles meeting Criteria 1, 2 and 4

Paper	Diagnostic System	N (male/ female)	Medications	Comorbid conditions	Control group	Findings	Study design/ EEG type/ Statistical test used
Houston et al. 2005.[77]	SCID-II,[101] & SSAGA.[110]	61 (0/61)	None	Depression Conduct disorder	EUPD – free adolescents	No age-related changes in P300 amplitude in adolescents with EUPD ($p<0.05$)	Case-control study. Scalp EEG recorded at 31 electrode sites. Artefacts removed using an algorithm. ANCOVA
Houston et al. 2004.[78]	SCID-II,[101] & SSAGA.[110]	88 (not reported)	None	No Schizophrenia or Bipolar Disorder, otherwise not reported	EUPD-free adolescents	Reduced P300 amplitude in those with EUPD ($p<0.05$)	Case-control study. Scalp EEG recorded at 31 electrode sites. Artefacts removed using an algorithm. Repeated measures analysis of variance

Archer et al. 1988.[79]	DSM-III.[103]	16 (not reported)	Psychotropic drug free (time without medications not reported)	None	Non-EUPD personality disorder Dysthmic Disorder Other psychiatric diagnosis	No significant difference between groups	Case-control study. Scalp EEG both waking & sleeping. Electrode placement not specified. Fisher's exact test

Table 7. Articles meeting 3 Criteria

Articles meeting criteria 1, 2 and 3

Paper	Diagnostic System	N (male /female)	Medications	Comorbid conditions	Control group	Findings	Study Design/ EEG type/ Statistical test used
Schaaff et al. 2007.[80]	DSM-III.[103]	9 (0/0)	Unmedicated & drug-naive	Not reported	Healthy controls	Significantly higher loudness dependence of the N1/P2 component of auditory evoked potentials in patients with EUPD compared to healthy controls ($p<0.05$)	Case-control study. Scalp EEGs using 32 electrodes according to the 10/10 system. Only artefact free sweeps were collected. T-tests and Mann Whitney U tests
Williams et al. 2006.[81]	ICD-10.[1]	15 (4/11)	None	None	Healthy controls	EUPD patients showed a significant delay in early posterior gamma synchrony ($p=0.02$)	Case-control study. Scalp EEG using 19 electrodes according to the 10/10 system.

						& reduced right hemisphere late gamma synchrony (p=0.02) compared with healthy controls	Artefacts removed manually following visual inspection. ANOVA
Cornelius et al. 1988.[82]	DIB,[102] & SADS.[106]	17 (7/10)	Medication free for at least one week (medications discontinued not reported)	None	None	Mean frequency on spectral analysis correlated with anxiety levels in patients with EUPD (P= 0.033 to 0.052) after placebo and amphetamine challenge	Clinical trial. Scalp EEGs with 16-channel recordings with electrodes according to the 10-20 system. Pearson correlation coefficients
De La Fuente et al. 2011.[83]	DSM III-R,[104] DIB,[102] & SADS.[106]	20 (6/14)	Medication wash-out period of at least 10 days (15 days for TCAs, benzodiazepines &MAOIs, 2 months for	None	None	TSH and standard EEG results influence sleep EEG, neurologic soft signs and post	Cohort study. Scalp wake and sleep EEGs. EEG type & electrode placement not specified. Bayesian

			neuroleptics)			dexamethasone cortisol in patients with EUPD	network model
Ruchsow et al. 2008.[84]	SCID-II.[101]	17 (1/16)	Not reported	None	Healthy controls	When performing a Go Nogo task, those with EUPD had reduced P3 amplitudes during Nogo responses compared to healthy controls ($p<0.04$)	Case-control study. Scalp EEG, 64 channels with electrodes as per 10-20 system. ANOVAs and Fisher LSD post-hoc tests
Vega et al. 2017.[85]	DSM-IV,[108] DIB,[102] & SCID-II.[101]	40 (0/40)	Antidepressants, antipsychotics, mood stabilizers, benzodiazepines	None	Healthy controls EUPD patients without a history of non-suicidal self-injury (NSSI)	EUPD patients with NSSI exhibited enhanced activation of the orbitofrontal cortex following an unexpected reward compared to healthy controls and EUPD patients	Case-control study. Functional MRI. No EEGs. Anova and F-test

						without NSSI ($p<0.05$)	

Table 8. Articles meeting 3 Criteria.

Articles meeting criteria 1, 3 and 4

Paper	Diagnostic System	N (male /female)	Medications	Comorbid conditions	Control group	Findings	Study Design/ EEG type/ Statistical test used
Cohen et al. 2016.[86]	SCID-II[101] & MCMI.[130]	1(0/1)	Not reported	Not reported	None	Mild to moderate increase in slow wave frequencies	Case study. QEEG – 19 sensor instrument

			(theta, delta and slow alpha) in the orbital cortex, dorsomedial prefrontal and dorsolateral prefrontal cortexes and a decrease of fast wave activities in the participant compared to normative data	according to 10-20 system. No statistical tests.

Table 9. Articles meeting 3 Criteria.

Articles meeting criteria 2, 3 and 4

Paper	Diagnostic System	N (male/female)	Medications	Comorbid conditions	Control group	Findings	Study design/ EEG type/ Statistical test used
Teicher et al. 1997.[34]	History of abuse	15 (7/8)	Not reported	Not reported	Healthy controls	Children with a history of abuse had greater average left hemisphere coherence than controls (p=0.007) and a greater number of abnormal EEGs (p=0.021)	Case-control study. EEG type & electrode placement not specified. Analysis of variance and two-tailed t-test
Brazier et al. 1945.[88]	Clinical examination	100 (43/57)	Not reported	None	Healthy controls	Higher incidence of beta activity in psychoneurosis versus controls (critical ratio 6.54)	Case-control study. Scalp EEG at bipolar occipital leads. Artefacts removed following visual inspection. Chi Square and critical ratio

Xu et al. 2014.[89]	DSM-IV-TR.[128]	21 (0/21)	Not reported	None	Healthy controls Treatment Resistant Depression (TRD) Generalized Anxiety Disorder (GAD)	Reduced P3 amplitude in those with TRD & GAD compared to healthy controls and those with EUPD ($p<0.05$)	Case-control study. Scalp EEGs with electrodes at midline Fz, Cz & Pz sites. Only artefact-free sweeps were included. Multivariate analysis of variance and post hoc analysis by least significant difference test
Hill et al. 2005.[90]	McLean screening instrument [92]	15 (0/15)	Antidepressants	Depression	Healthy controls	Those with EUPD traits had smaller LPC amplitude ($p<0.02$), P300 latency ($P<0.05$) and P300 amplitudes ($p=0.08$) when making incorrect responses to emotional pictures and faces	Case-control study. Scalp EEG with 16 electrodes according to the 10-20 system. ANOVAs
Shen et al. 2008.[9]	DSM-IV-TR[109] & Parker Personalit	18 (0/18)	Anxiolytics Antidepressants	None	Healthy controls Non-	No significant difference in ERPs	Case-control study. Scalp EEGs with electrodes

[1]	y Measur.[11] [1]		EUPD personality disorder	between those with EUPD and other groups	placed at midline Fz, Cz & Pz. Traces with artefact automatically rejected following visual inspection. ANOVAs and post hoc analysis by Duncan's multiple new range test

Table 10. Articles meeting 3 Criteria.

Articles meeting criteria 2, 4 and 5

Paper	Diagnostic System	N (male /female)	Medications	Comorbid conditions	Control group	Findings	Study design/ Statistical test used
Huang-Storms et al. 2006.[41]	Children with histories of abuse or neglect, many with a diagnosis of Reactive Attachment Disorder (RAD)	20 (9/11)	SSRIs Amphetamines Atomoxetine Ziprasidone Risperidone	None reported	None	Improvement in score on the Child Behaviour Checklist (95) following qEEG-guided neurofeedback ($p<0.05$)	Clinical trial. QEEG with 19 scalp electrodes as per 10-20 system. Two-tailed paired t-

test

Table 11.

Abnormalities found on standard EEGs in EUPD

1. Posterior sharp waves. [55]
2. Increased slow wave activity.[56]
3. Less stable EEG vigilance patterns.[57]
4. Increased prevalence of intermittent rhythmic delta & theta activity[58]
5. Delay in early posterior gamma synchrony & a reduction in right hemisphere late gamma synchrony in response to salient stimuli[83]

Table 12.

Embase	Final Search	2817
PsycInfo	Final Search	1123
Medline	Final Search	1310
NHS Evidence	Final Search	0
Cochrane	Final Search	0
JB	Final Search	0
Open Grey	Final Search	1
Clinical Trials	Final Search	6
UK Clinical Trials gateway	Final Search	0
EU Clinical Trials Register	Final Search	0