Article:
Walsh, S., Levita, L. and Reuber, M. orcid.org/0000-0002-4104-6705 (2018) Comorbid depression and associated factors in PNES versus epilepsy: systematic review and meta-analysis. Seizure, 60. pp. 44-56. ISSN 1532-2688

https://doi.org/10.1016/j.seizure.2018.05.014

Comorbid depression and associated factors in PNES or epilepsy: Systematic review and meta-analysis

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Introduction

This systematic review aims to review the current literature to compare depression patients with psychogenic non-epileptic seizures (pwPNES) with that in patients with epilepsy (PWE) in order to establish if there are differences in the prevalence and presentation of depression between these patient groups.

PWE frequently experience co-morbid psychiatric disorders. Mood disorders (including major depression) are the most common with a prevalence of 24.4%/14.1% (lifetime/past year) in PWE, as compared to 13.2%/5.2% in the general population [1]. Similarly, co-morbid psychiatric disorders are more common in pwPNES than in the general population and again, depression is the most common psychiatric disorder with an average prevalence of 31% and lifetime rates ranging from 36-80% [2].

The presence of depression is associated with worse outcomes in both patient groups. In PWE there is an association between depression and seizure frequency [3]. This relationship is one of the manifestations of the bidirectional links between depression and epilepsy [4, 5, 6, 7]. Whilst elevated levels of depression could reflect the negative impact of seizures, Lehrner et al. [8] found depression was a significant predictor of health-related quality of life (HRQoL), even after controlling for seizure frequency. It is possible a similar bidirectional relationship also exists for pwPNES as depression has been found to predict the level of dysfunction experienced by these patients [9]. Supporting a possible causative effect, one study [10] found that treating pwPNES with sertraline (an anti-depressant) reduced seizure rates compared to a placebo group which reported an increase in seizure frequency

during follow-up (although in the absence of sufficiently powered studies, it is not clear that antidepressant treatment for pwPNES can currently be recommended in the absence of evidence of co-morbid depression or anxiety)."

Several reviews have explored depression in PWE e.g. [9], however, less has been written about depression in pwPNES. Most only discuss the latter topic in passing or lack detail. For instance, Kanner et al.'s [9] review of depression in PWE, contrasted depression scores in PWE and pwPNES, with pwPNES having higher depression scores. However, the search and quality assessment method were not described and group differences were not statistically assessed. A recent systematic review [11] of depression in pwPNES found that pwPNES have higher levels of depression than PWE, although this difference was not statistically significant. However, this review focussed on clinically diagnosed depression and excluded studies using self-report measures of depression. Only seven studies met their criteria, reducing the power of the analysis and possibly explaining why the difference between the groups was not significant.

Interestingly, Kanner et al. [9] suggested that the interplay between peri-ictal symptomology and depression, along with the high co-morbidity between depression and anxiety in PWE means that depression can present atypically in this population. In a similar vein, Diprose et al. [11] suggest that pwPNES often present with somatic symptoms rather than psychological distress. Differences in the manifestation of depression could have implications for how depression is identified and treated in these patient groups, but no previous reviews have explored the phenomenology of depression in both of these common seizure disorders.

As such, this article intends to provide a systematic review of the existing literature comparing epilepsy in PWE and pwPNES in a two stage process: Stage one focuses on prevalence by conducting a meta-analysis comparing levels of self-reported and clinically diagnosed depression in patients with these two seizure disorders. Stage two explores differences in the phenomenology of depression by comparing depressive symptoms and associated factors in PWE and pwPNES.

Method

The methodology for this review was informed by the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [12].

Literature Search

To capture relevant studies, a search was run on ScienceDirect and Web of Science, on 29/01/2017. The search scanned the title-field for terms relating to PNES and all-fields for terms relating to depression, using the following terms:

TITLE: ((nonepilep) OR ({non-epilep*}) OR (pseudoseizure$) OR ({pseudo-seizure$}) OR (pseudoepilep*) OR ({pseudo-epilep*}) OR (dissociative adj seizure$) OR (dissociative adj convulsion$) OR (hysterical adj seizure$) OR (hysterical adj convulsion$) OR (hysteroepilepsy) OR ({hystero-epilep*}) OR (conversion adj seizure$) OR (psychogenic adj seizure$) OR (functional adj seizure$))*

AND

ALL FIELDS: (depress OR psychopatholog* OR psychiatric OR psycholog*)*

No time limits were used in the search. The systematic search was complemented by a search of the reference lists of identified publications.

Article Screening

Papers were required to be written in English and to describe comparative studies involving separate epilepsy and PNES samples. Abstracts were screened for key words relating to depression, psychiatric/psychological disorders or measures of depression. Because of likely differences in the aetiology of epilepsy and PNES between paediatric and adult populations as well as between patient groups with and without intellectual disabilities (ID), papers were excluded if the samples contained individuals aged 15 and under, or focussed on ID. We also excluded papers predominantly describing neurological issues, EEG or medication. During full text-analysis, studies were excluded if they did not explicitly report depression scores/prevalence for each patient group and statistically compare these (although statistical comparisons were not required for the prevalence of depression).Studies were also required to have a PNES sample ≥ 15 (i.e. > 80% power to detect a very large effect size).

Papers meeting these criteria were included in the analysis of prevalence. Papers used in the phenomenological comparison were also required to either include further analysis of depression measure subscales, or further analyses of depression scores (e.g. correlations or regression analyses).

Several papers used overlapping samples across multiple manuscripts and were excluded from the review. Whilst [13] and [14] used related samples, the level of overlap was unclear and figures from both papers were included, although [14] did not report the Beck Depression Inventory-II (BDI-II) [15] figures and so this measure was excluded. Studies [16, 17, 18 and 19] also used a shared dataset and [16] was excluded as it appeared to reflect an earlier stage of recruitment to [17]. Different sample sizes and measures in papers [17, 18 and 19] mean that all were included, although the Profile of Mood States (POMS) [20] reported by [19] was excluded as

other studies reported this using larger samples of pwPNES. The overall process is shown in Figure 1.

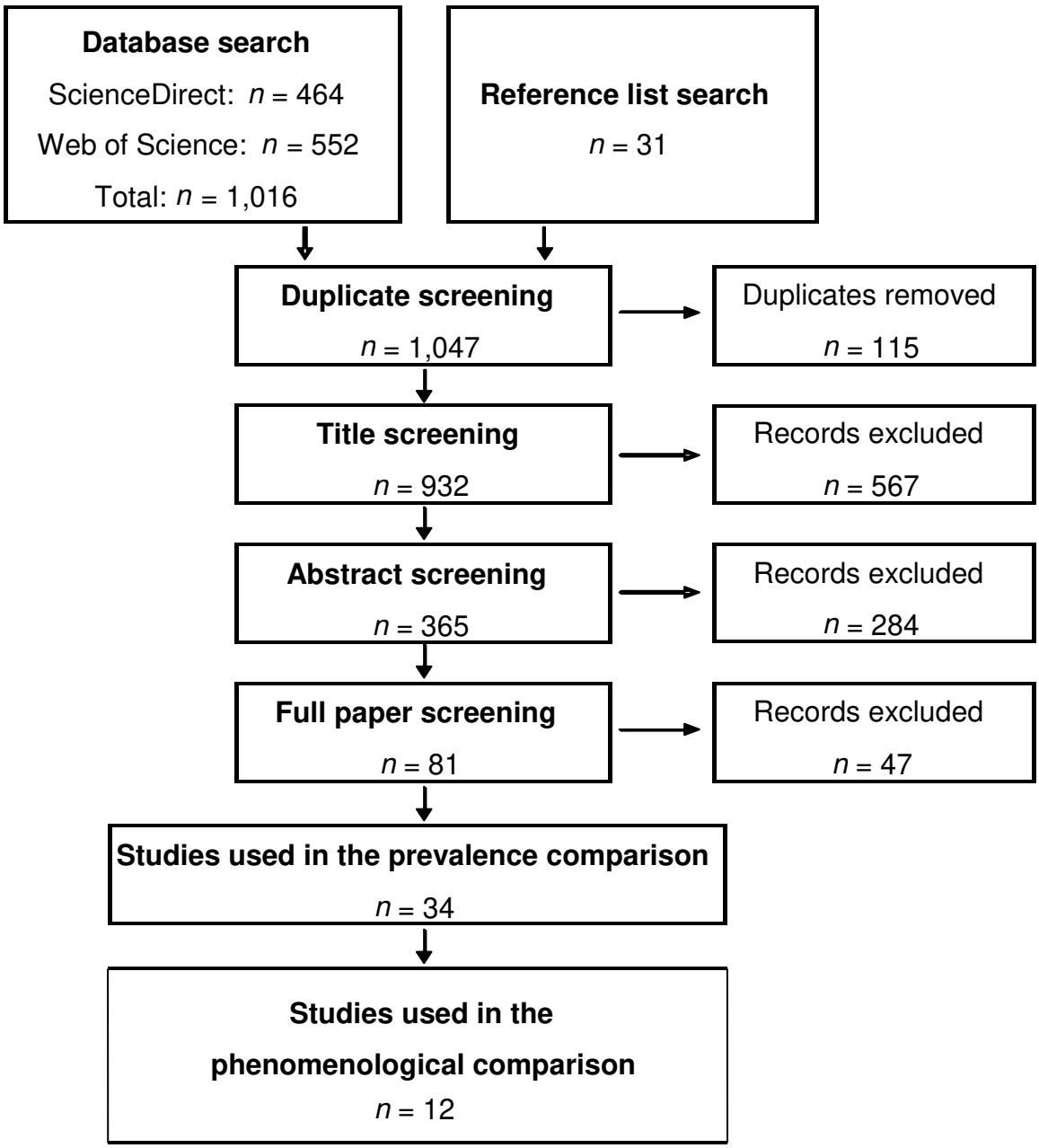

Figure 1. *PRISMA Diagram.*

Statistical Analysis

Where possible, the magnitude of the difference in depression scores between pwPNES and PWE was measured using Cohen's *d* effect size [21] and

calculated with Comprehensive Meta-Analysis (CMA; Version 3.3.070) [22]. An effect size of $d \geq .41$ was used to indicate a significant difference between the patient groups. This was based on the minimum cut-off score recommended to indicate a practical significant effect (i.e. likely to indicate a practically meaningful difference between the groups) for social science data [23].A random-effects meta-analysis was run using CMA. Publication bias was assessed using rank correlation with Kendall's tau [24], fail-safe *N* [25] and funnel plots including a trim and fill analysis [26].

Reported prevalence figures of depression were compared using a two-tailed independent t-test on the Statistics Calculator (Version 4.0) [27].

Quality Appraisal Tool

Few quality appraisals have been developed specifically for research focusing on PNES. Although generic appraisal schemes exist, these do not assess the validity of the diagnostic process used to differentiate PNES and epilepsy. One measure designed specifically to evaluate research on pwPNES [28] assesses methodology using seven criteria (Appendix A):

1. Was diagnosis based on video-EEG documentation of typical seizures?
2. Was epilepsy excluded from the PNES sample?
3. Were attacks distinguished from anxiety attacks?
4. Was recruitment consecutive?
5. Were dependent variables standardised?
6. Were comparison groups demographically comparable to the PNES sample (≤ 5 years age difference and ≤ 10% difference in the number of females)?

7. Were PNES excluded from comparison groups?

A score of 0-1 is calculated by dividing the number of achieved criteria by seven. The sample size is scored using the following criteria: good ($n \geq 64$), moderate ($n = 26$-63), or poor ($n = 15$ - 25). The methodology and sample appraisals are combined to determine the overall study quality: high (score ≥ .80 and a good sample size), medium (score ≥ .80 and a moderate sample size *or* score = 0.50 - 0.79 and a good or moderate sample size), low (score = 0.20 - 0.49, or a poor sample size), or unacceptable (score < 0.20). To determine the accuracy of the appraisals, a second researcher evaluated the papers using the same criteria.

Results

Quality Appraisal

The inter-rater agreement for the quality appraisal was 90.8%. Of the 34 papers reviewed, 22 were rated as low quality and 12 were rated medium quality (see Appendix B for a full summary). The predominant factor leading to the relatively low quality ratings was a small sample size. Most studies ($n = 29$) used a poor or moderate sample and only five had a good sample size (≥ 64 participants per group).

Excluding the sample size criteria, methodological procedures were rated more favourably, with nine rated low quality, 24 medium quality, one high quality and a mean methodological quality of 0.6. The most common shortcomings were the failure to state how PNES and anxiety were differentiated or to use samples with sufficiently similar age and gender distributions. Of these, the failure to explain how PNES were distinguished from anxiety attacks is most detrimental as anxiety is an important diagnostic confound in PNES [29]. Additionally, only 23 studies used video-EEG for all diagnoses, the gold standard diagnostic method for PNES [30].

These limitations make it more difficult to be confident that PNES had always been diagnosed correctly.

Depression Measures

A total of 46 measures of depression, including self-report measures and clinical diagnoses were used in the different studies identified. At least one well-validated measure of self-reported depression was used in 13 of the studies reviewed. The BDI-I and BDI-II have been particularly well-validated, including for use in epilepsy [31]. The Patient Health Questionnaire-9 (PHQ-9) [32] and Hospital Anxiety and Depression Scale (HADS) [33] are well-validated generic screening tools for depression [34, 35] and have been validated in PWE [31]. The Depression Anxiety Stress Scale (DASS) [36] has been validated in clinical populations [37], although it has not been validated within an epilepsy population. Finally, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) [38] was developed specifically for use in PWE and has been validated for use in pwPNES [39], although only as a categorical measure designed to identify patients likely to have current major depression, rather than a scaled measure.

However, 15 papers did not use clearly validated measures of depression. In this review, most studies of this nature used the depression scales of the Minnesota Multiphasic Personality Inventory (MMPI)-1 [40], MMPI-2 [41] or Personality Assessment Index (PAI) 426]. These measures were developed as assessments of personality. Therefore, they have significant limitations as screening tools for depression, particularly the MMPI, which was developed based on historical constructs of psychopathology that are no longer valid [43]. Whilst the PAI was designed around modern clinical diagnoses [42], only moderate evidence was found

of convergent validity between the PAI depression scale and a diagnosis of major depression [44].

Other studies used the POMS depression/dejection and Brief Symptom Inventory (BSI) [45] depression scales. It is equally unclear how valid these measures are as screening tools for depression. The factorial structure of the BSI is unclear [46], and the POMS depression/dejection scale has poor discriminant validity between depression and anxiety [47].

Of the studies reviewed, nine reported rates of clinically diagnosed depression, although two of these did not specify the diagnostic criteria used. The remaining seven studies used the diagnostic and statistical manual (DSM) criteria, either the DSM-III [48], DSM-IV [49] or DSM-IV-TR [50]. Four of these studies diagnosed depression using the Structured Clinical Interview for Axis-I Disorders for DSM-IV, Clinical Version (SCID-CV) [51], widely considered as the gold standard diagnosis tool for psychiatric disorders [52].

Comparison of Depression Levels in PwPNES Compared to PWE

The majority of measures (42 of 45, 93.3%; one measure did not report figures) reported in the studies found pwPNES had higher levels of depression than PWE, although this difference was only significant in 32.6% of analyses (see Appendix C for all results). In all comparisons where effect sizes could be calculated (n = 29), pwPNES scored higher on self-report measures of depression than PWE, with 58.6% of these exceeding d = .41 and indicating a practically significant difference (Figure 2).

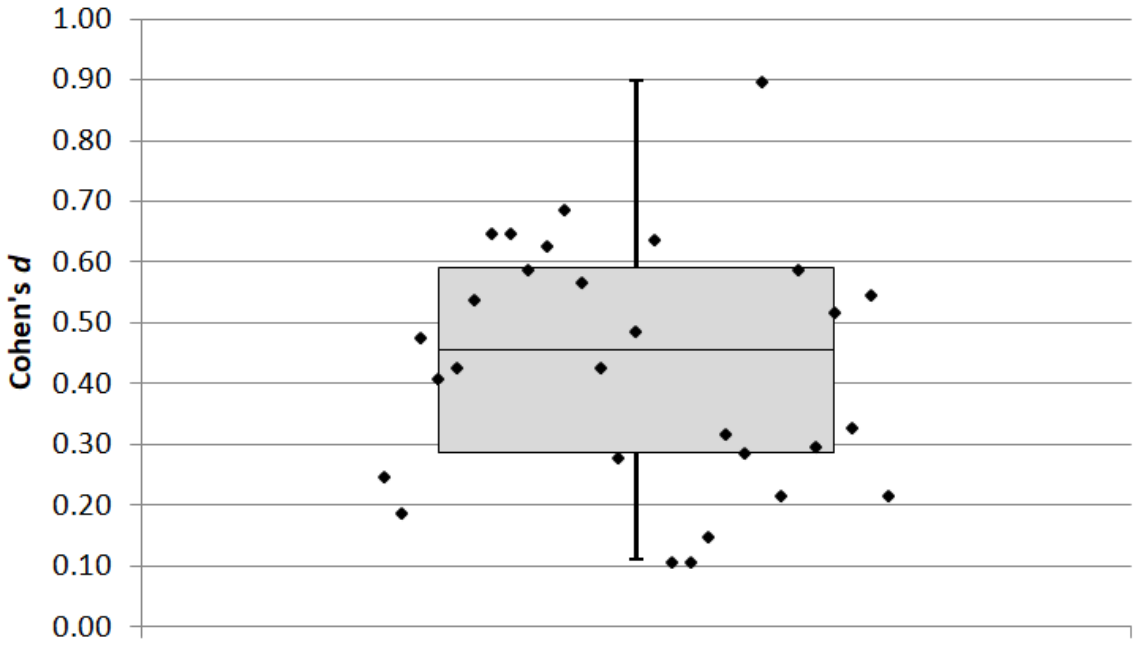

Figure 2. Box-and-whisker plot of effect sizes indicating the magnitude of difference in depression scores between PWE and pwPNES.

A meta-analysis was conducted on studies using well-validated measures (BDI-I/II, PHQ-9, HADS, DASS and NDDI-E; *N* studies = 13, *N* participants = 1,366). The median quality of these 13 studies was low (*n* = 11), with two medium quality studies. There was no correlation between the quality of the study and the effect size reported, τ (*N* = 13) = .10, *p* = .69, Effect sizes were homogenous χ^2 (12) = 10.14, *p* = .60 and a significant overall effect size was found indicating a practical difference in levels of depression between the groups, *d* = .51 (95% CI [.40 - .62]), *z* = 8.93, *p* <.001, There was no evidence of publication bias, with a fail-safe *N* = 206. The Begg and Mazumdar rank correlation was non-significant, τ (*N* = 13) = -.04, *p* = .85. The funnel plot can be seen in Figure 3, with a point estimate of .51 (95% CI [.40 - .62])

which was unchanged following the Trim and Fill analysis. These findings suggest that the finding that pwPNES report higher levels of depression than PWE is robust.

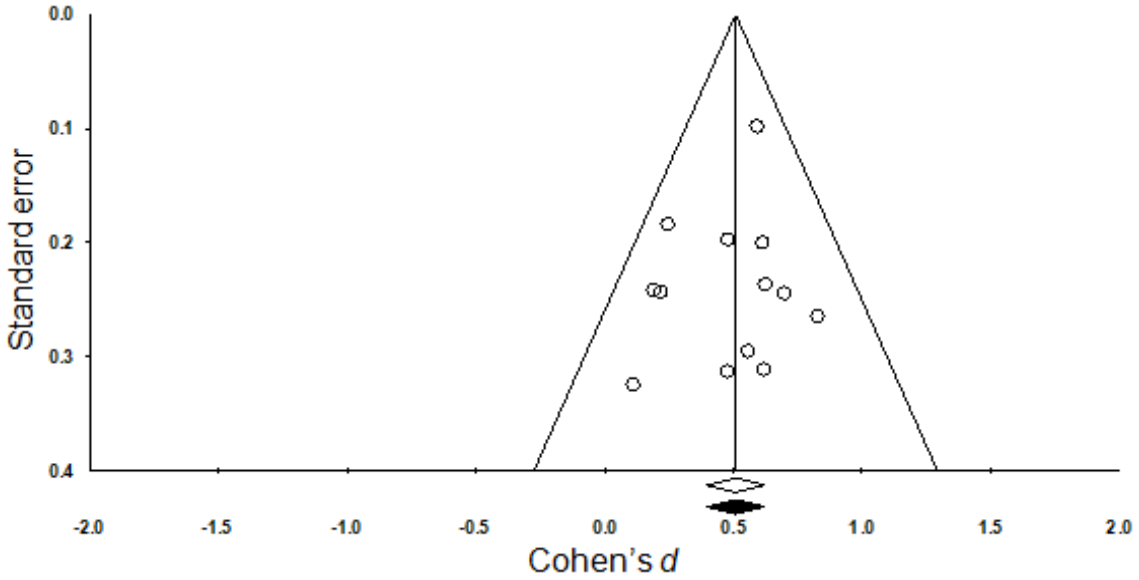

Figure 3. Funnel plot of standard error against Cohen's *d*.

This highlights an interesting discrepancy. Despite pwPNES self-reporting higher levels of depressive symptoms, only one paper reporting on clinical diagnoses found a significant difference between PWE and pwPNES. It was possible that the scores in pwPNES were still predominantly below clinical levels. To explore this, the nine studies reporting on clinically diagnosed depression were compared to the six studies which used clinical cut-off scores on self-report measures of depression. The mean prevalence rates (Figures 4a and 4b- NB [14] did not report figures, and could not be included in this figure) show that whilst rates were comparable in PWE, more pwPNES reported depressive symptoms suggesting higher rates of clinical depression than were diagnosed (or excessive symptom reporting on self-report scales). However, it is important to note that this difference was not significant, although only a small number of studies could be included in this comparison.

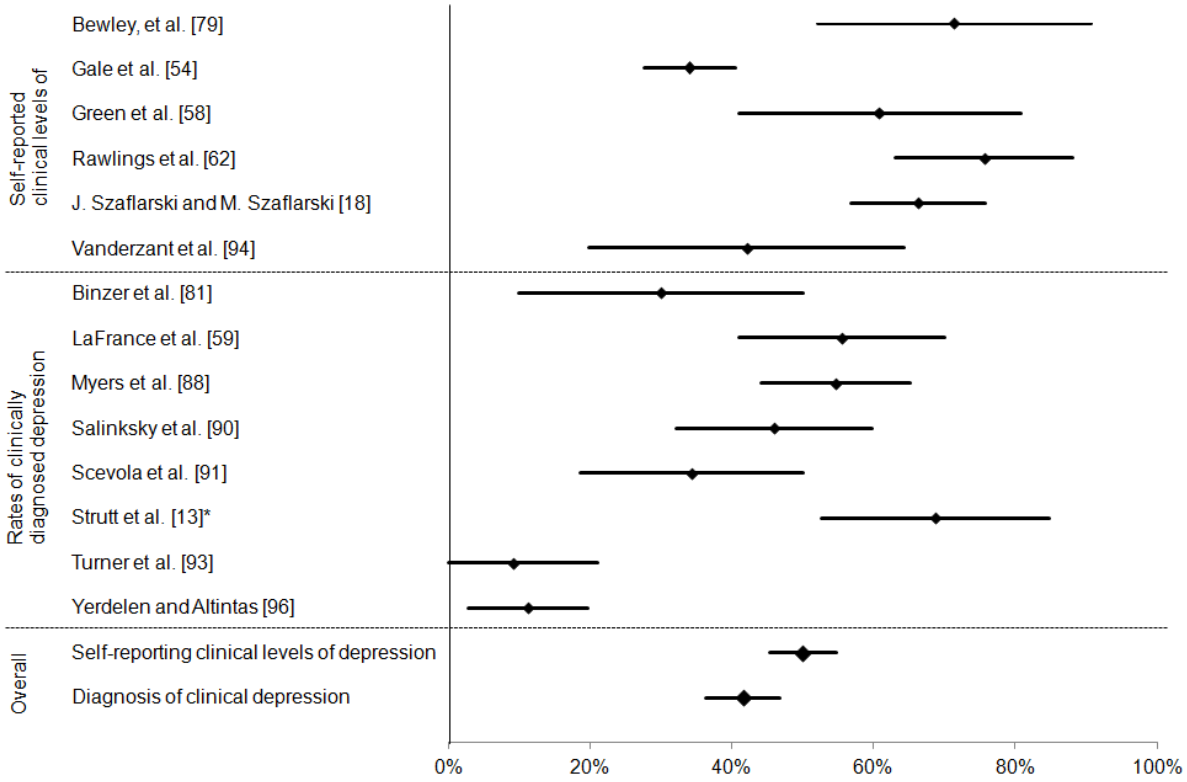

Figure 4a. Forest plot of self-reported levels of clinical depression and diagnosed clinical depression in pwPNES.

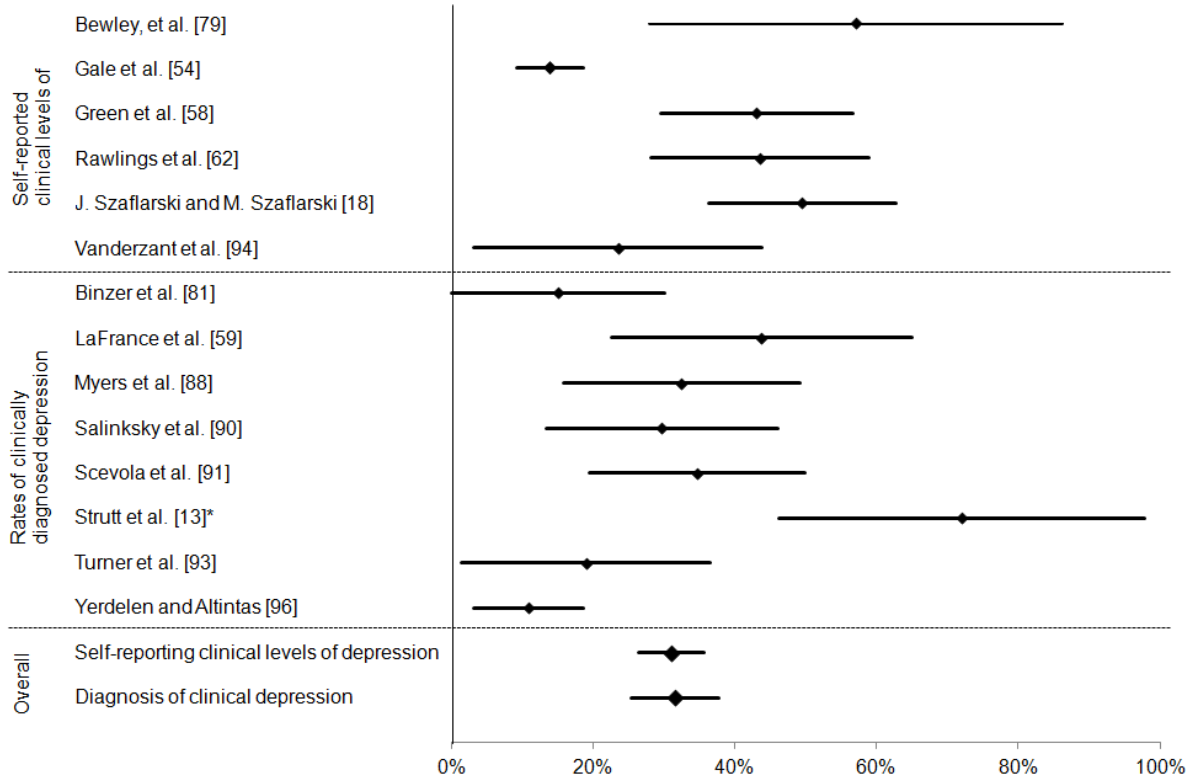

Figure 4b. Forest plot of self-reported levels of clinical depression and diagnosed clinical depression in PWE.

Comparison of Factors Associated with Depression in PwPNES and PWE

For supplementary data tables for this narrative synthesis section, please see Appendix D.

Depressive symptomology. Five studies analysed subscales of the PAI and MMPI depression scales. The PAI depression scale contains three subscales, Dep-C (cognitive symptoms e.g. poor concentration or thoughts of helplessness), Dep-A (affective symptoms e.g. sadness or loss of interest in activity) and Dep-P (physical symptoms e.g. sleep disturbance or physical functioning). PwPNES consistently

scored higher than PWE and significant differences were found on all subscales (Table 1).

Table 1

Comparisons of statistically different PWE and PNES scores on subscales of the PAI

Study		**Dep-A**	**Dep-C**	**Dep-P**
Asmussen et al. [53]	PNES / PWE mean			61.3 / 55.7
	Difference			5.6
	Effect size (*d)*			.48**
Gale et al. [54]	PNES / PWE mean	58.7 / 52.6	57.8 / 54.2	66.6 / 56.3
	Difference	6.1	3.6	10.3
	Effect size (*d)*	.49***	.28**	.88***
Thompson et al. [55]	PNES / PWE mean		61.4 / 57.7	67.7 / 59.1
	Difference		3.7	8.6
	Effect size (*d)*		.29*	.76***
Wagner et al. [56]	PNES / PWE mean			69.4 / 56.9
	Difference			12.5
	Effect size (*d)*			Unknown*

Shaded cells indicate non-significant group differences

* $p < .05$

** $p < .01$

*** $p < .001$

All studies found that pwPNES reported significantly more physical difficulties than PWE (Dep-P). In contrast, only 50% of studies found significant differences in cognitive aspects of depression (Dep-C), although the studies revealing significant differences had better sample sizes and methodological quality, and thus greater power to detect an effect. Findings on affective aspects of depression (Dep-A) were less equivocal, as only one study (with the largest sample size) found a significant result. Although pwPNES scored higher than PWE, mean scores did not indicate clinical levels of difficulty except on the Dep-P subscale which indicated a mild difficulty. Contrary to PAI findings, [57] found no significant differences on any of the depression subscales of the MMPI-2 including D3 (physical malfunctioning), although the previously discussed weakness of the MMPI-2 (e.g. outdated constructs of psychopathology) could account for these differences.

A possible explanation of the group differences on the Dep-P subscale of the PAI could be the higher proportion of females in the PNES samples. Females with PNES reported significantly higher scores on this subscale than males with PNES [53, 54]. In summary, these findings suggest that pwPNES, especially females, suffer from, or recognize, the physical symptoms of depression more than the cognitive and emotional aspects.

Attachment, relationships and depression. Several studies investigated depression in conjunction with aspects of interpersonal functioning. Green et al. [58] explored the association between attachment and depression in PWE and pwPNES, focusing on the relationship with the main caregiver. They found relationship conflict, attachment, attachment anxiety and attachment avoidance significantly correlated with depression in both patient groups. Although all these correlations were stronger for pwPNES, the only significant group difference was in attachment anxiety, where

pwPNES showed a significantly stronger positive correlation between attachment anxiety and depression. Relationship variables explained a significant proportion of depression in both patient groups, although these only accounted for 16% of the variation in PWE, compared to 45% of the variation in pwPNES. Seizure and demographic variables were more comparable between groups, explaining 26% of variation in pwPNES and 23% in PWE, although this association was only significant in PWE. Interestingly, whilst seizure severity was a significant predictor of depression in patients with PWE, this was not the case for pwPNES. These findings all suggest that depression in pwPNES is more closely related to relationship factors than illness-related factors, whilst the opposite pattern is true for PWE.

A caveat for interpreting this study is the large difference in the population sample sizes, with a PNES sample of 23 compared to a PWE sample of 72. This may explain why the proportion of depression accounted for by seizure and demographic variables was only significant in PWE, despite accounting for more variation in depression scores in pwPNES.

Another study which examined the link between depression and interpersonal factors in PWE and pwPNES was LaFrance Jr. et al. [59], who analysed the association between family functioning and depression, although the study focused on HRQoL (see next section). Family functioning was found to be unhealthy for both PWE and PNES. However, only in pwPNES was family functioning significantly correlated with depression scores, along with family affective involvement (e.g. valuing each other) and roles (the patterns of behaviour used to fulfil family functions). This suggests that family functioning may have a stronger association with depression in pwPNES, complementing the findings of Green et al. [58] and

suggesting there is a closer association between relationship variables and depression in pwPNES than in PWE.

Health status, quality of life and depression. As part of the previously described study, LaFrance Jr. et al. [59] analysed HRQoL, exploring its relationships with depression and seizure-related variables. They found a significant relationship for both patient groups, with depression explaining 46% variation in HRQoL PNES and 40% in PWE, more than that explained by seizure frequency, illness duration, or family functioning.

In contrast, Karakis et al. [60] found depression to be a significant determinant of HRQoL in pwPNES, but not in PWE. This is a surprising finding, given the strong relationship reported between HRQoL and depression in PWE [61]. This contrasting finding by LaFrance Jr. et al. [59] and Karakis et al. [60] may reflect the analyses used by Karakis et al., with only significant group differences being entered into the regression analysis.

Another study assessing HRQoL [62] found highly significant correlations between HRQoL and depression in both patient groups, with depression again explaining more variance in HRQoL scores than seizure-related variables in both patient groups. Although some participants were recruited from a hospital, this was one of the few studies which also recruited from a non-medical setting, suggesting the findings can be generalized beyond the clinical environment.

J. Szaflarski and M. Szaflarski [18] also explored the relationship between HRQoL and depression. They used the 36-item Short Form Health Survey [63] which contains 8 subscales; physical functioning, role limitation: physical, role limitation: emotional, energy/fatigue, emotional well being, social functioning, pain and general

health. Using a POMS cut-off score of >12 to indicate depression, they found depressed pwPNES reported significantly lower HRQoL across all SF-36 subscales than depressed PWE. The authors conducted further analyses on the 'role limitation: physical' subscale, comparing depressed PWE and pwPNES with clinically depressed patients. After controlling for multiple comparisons, they found that depressed pwPNES reported significantly lower scores on this subscale than clinically depressed patients, a pattern not found in PWE. This supports the earlier findings that depression in PNES is more strongly related to physical symptoms of depression. Unfortunately, the use of the POMS is a weakness as it has no standardised clinical norms.

In summary, these findings highlight a strong, positive relationship between depression and HRQoL in both pwPNES and PWE. It may be that depression has a greater influence on HRQoL for pwPNES than in PWE, but this difference is marginal. Again, the strongest relationships with depression appear to be with the physical rather than emotional aspects of HRQoL in pwPNES.

Cognitive and emotional functioning and depression. Two papers explored the links between depression and emotional or cognitive function in PWE and PNES. Prigatano and Kirlin [64] investigated subjective and objective measures of affective and cognitive functioning in PWE and PNES, using the PAI to assess psychopathology. Notably, the study found that pwPNES subjective reports of depression had significant large and medium positive correlations with subjectively reported cognitive difficulties and a standardised test of delayed memory. In contrast, the standardised measure (the PAI-depression scale) correlated with subjective memory abilities, but no other subjective or standardised cognitive measures. However, this study provided little detail about the methodology, diagnostic process,

or analytical methods used and did not adjust the significance level for the high number of correlations tested. This creates a strong likelihood of Type-I error, further compounded by the small sample size.

A more robust study of emotional functioning was completed by R. Brown et al., [65] who clustered PNES patients based on their scores on measures of emotional dysregulation and alexithymia. This identified two patient clusters, one with high emotional dysregulation and alexithymia scores (cluster one) and the other containing the remainder of the PNES sample (cluster two). Analysis of PHQ-9 scores found both clusters had significantly higher levels of depression than PWE, but no significant differences were found between the two clusters of pwPNES. Although clustering patients allowed an interesting analysis of depression in pwPNES, it reduced the sample sizes, limiting the power of analyses. This could explain why no significant difference was recorded between PHQ-9 scores in clusters one and two, despite having a larger discrepancy between means than cluster two and PWE.

Discussion

The studies identified in this review consistently found that pwPNES report higher levels of depressive symptoms than PWE. In the majority of studies, this difference was not significant; however this appears to be related to the low quality of most studies which were based on small samples and had low statistical power. Our meta-analysis confirmed the finding of higher levels of depression in pwPNES, identifying a significant and practical difference in depression levels between PWE and pwPNES. Despite pwPNES reporting higher levels of depressive symptoms than

PWE, this was not reflected by the rates of clinical diagnoses of depression. Although overall rates of diagnosed depression were higher in pwPNES than for PWE, there was a greater discrepancy between the rate of clinical diagnosis and self-reported clinical levels of depression than that seen in PWE. It was not clear from the studies reviewed what caused this discrepancy. Possible explanations include the under-diagnosis of clinical depression in pwPNES, or pwPNES catastrophising symptoms on self-report measures.

Supporting the hypothesis that depression has a specific profile in those with PNES, Wagner et al. [56] suggested that pwPNES do not show the spectrum of symptoms typically associated with clinical depression. This is supported by the consistent finding that compared to PWE; pwPNES are more likely to highlight the physical symptoms of depression than cognitive or emotional aspects. This may mean clinicians overlook patient reported symptoms of clinical depression. Additionally, many formal diagnostic methods (e.g. the SCID) are based on an etiological model which excludes symptoms that could be attributed to a known medical condition [66]. Due to the physical symptoms associated with PNES, epilepsy, or the treatment of these disorders, it is possible clinicians do not prioritise patient reports of physical symptoms of depression, potentially leading to missed diagnoses. Whilst conventional diagnostic criteria (e.g. the DSM) apply to many PWE, they may poorly reflect some of the atypical features of depression seen in this population [9]. The current findings would suggest this is even more applicable for pwPNES.

Another potential explanation for the discrepancy in rates of clinically diagnosed depression and self-reported symptoms is that pwPNES catastrophise symptoms of depression and rate these as more severe than may appear to

clinicians. Catastrophising is defined as an exaggerated set of negative cognitions which magnify anticipated or perceived threat [67]. Supporting the idea that catastrophising could explain the elevated self-reported depression symptoms seen in pwPNES, pwPNES have been found to experience emotions as more overwhelming, report more severe somatic symptoms and interpret these as more threatening than PWE [68]. Evidence of a tendency for pwPNES to catastrophise (and for PWE to normalise) potentially distressing symptoms has also been provided by a study examining how patients describe their seizures to a doctor [69].

The findings of this study add to the large evidence base that pwPNES express distress somatically and report more somatic symptoms than PWE [70, 71, 72, and 73]. Despite this finding, it is important to note that in some studies, pwPNES also reported higher scores on measures of affective and cognitive aspects of depression than PWE. Additionally, the fact that pwPNES self-report higher levels of depression than PWE suggests an awareness of emotional experience, with this awareness recorded even in pwPNES with high alexithymia scores [65].

Several factors relating to interpersonal functioning were significantly associated with depression in pwPNES. Green et al. [58] found that relationship variables explained 45% of the variation in pwPNES' depression scores, with anxious attachment scores having particularly strong positive associations with depression. This relationship was found in both pwPNES and PWE, supporting the idea that a fearful attachment style is associated with higher depression scores [74]. However, the relationship between attachment anxiety and depression was stronger in pwPNES than PWE, suggesting the link is closer in those with PNES than might typically be expected. This finding is likely to be clinically relevant as pwPNES

typically have higher levels of fearful attachment [75], suggesting this may be a key factor in the levels of depression observed.

The importance of relationship factors was supported by LaFrance Jr. et al. [59] who found that measures of family functioning, whilst unhealthy in both PWE and pwPNES, only significantly correlated with depression in pwPNES. This matches the findings of Krawetz et al. [76], who found pwPNES perceived their families as dysfunctional, particularly in areas of communication and emotional involvement. Krawetz et al. argue this suggests pwPNES may struggle to articulate their needs and feelings within the family system. Being unable to effectively resolve conflict with family members, combined with an anxious or fearful attachment style, could cause depression. Whilst it is not possible to determine cause and effect from these studies, it has been found that supporting pwPNES to address family discord lead to a subsequent reduction in depressive symptoms [77], suggesting a potential causative relationship.

Whilst seizure-related variables (e.g. seizure severity) had a stronger relationship with depression scores in PWE than pwPNES, the relationship between the impact of health status on life (as assessed by HRQoL measures) and depression was less clear cut. The findings suggest that the influence of health within a person's life has a slightly stronger relationship with depression in pwPNES than PWE. However, in both patient groups, depression explained more variation in HRQoL than seizure-related variables [59, 62] and family functioning [59]. This highlights the impact of depression in both patient groups, although again, the cross-sectional nature of the studies reviewed meant that the direction of this relationship cannot be determined. As HRQoL incorporates psychological health, it is fair to assume that depression has a causative impact on this construct, although it is likely

to be a two-way relationship. Interestingly, J. Szaflarski and M. Szaflarski [18] compared depressed pwPNES and PWE to clinically depressed patients and found that pwPNES reported significantly more physical role limitations. This again suggests that pwPNES highlight their physical symptoms and experience these as more disabling than patients with other health conditions.

Critique

This systematic review has several limitations. Whilst the abstracts of potential studies were screened for mentions of measures of depression, this was based on the author's knowledge of existing measures. It is possible that suitable papers containing depression measures unknown to the author were missed during the screening process. Another weakness of the screening process was the aim to capture all studies measuring depression. Whilst this inclusivity was a strength of the review, it meant that many of the studies reviewed did not primarily investigate depression, but simply included a measure of it. Indeed a sizable proportion of studies focused on establishing criteria for the differential diagnosis of PNES and epilepsy. This affected the critique of the studies, as the aims of the review and the studies were not always comparable, partly explaining the limitations of many of the measures of depression used. This was an important limitation as it was unclear how valid some of the measures were in measuring depression as a clinical construct, a key aim of this review. To account for this, only studies using well-validated measures of depression were included in the meta-analysis. Whilst this improved the validity of the meta-analysis in assessing levels of depression, it may have introduced other sources of bias, as the selected studies were predominantly of lower quality.

One factor which may affect the findings of this review is the demographic differences between the PNES and epilepsy samples in many of the studies reviewed. Few of these studies had demographically matched samples, and most had a higher proportion of females in the PNES samples. It has been found that females with PNES may report more symptoms of depression [53, 54] and Kerr et al. [78] found that differences in depression between pwPNES and PWE were no longer significant after controlling differences for age, sex and medical co-morbidities. As such, the demographic differences in the samples could account for the difference in levels of depression between PWE and pwPNES observed in this review. However, it is important to note that up to 80% of pwPNES are female [2] and therefore the observed differences may reflect a reliable difference between populations of pwPNES and PWE.

Finally, the majority of the studies included in this review were hospital-based. This may have allowed researchers to differentiate between epileptic and non-epileptic seizures with greater accuracy is but is likely to have skewed the samples to reflect populations with elevated levels of psychopathology. However, these weaknesses reflect the nature of the research completed with pwPNES, rather than the methodology of the review and it is hard to see how they could be overcome in a review based on the current literature.

The systematic nature of this review and the meta-analysis conducted are key strengths of this study. In particular, the absence of any publication bias suggests that the effect detected is reliable, with the fail-safe *N* suggesting 206 unpublished studies would need to exist to make the population effect size non-significant. Additionally, the use of PWE as a comparison group means that the findings are not simply due to the experience of seizures, but are likely to be specific to PNES,

identifying unique areas of difficulty and potential areas of intervention for this population.

Empirical Recommendations

The limitations highlighted in this review reflect the difficulty of conducting research in this area. PNES can be challenging to distinguish from epileptic seizures with certainty and the diagnosis is often an iterative process [30]. Researchers should aim to provide as much detail as possible about the diagnostic process and level of certainty, or clearly state the aspects for which they have no information. Additionally, recruiting large numbers of pwPNES is often beyond the timeframe and resources available to researchers, as reflected by the small sample sizes. This means many studies are prone to Type II errors, potentially missing important causal or maintaining factors for PNES. Meta-analyses can only partially address this weakness of the primary literature.

Further research should explore the potential discrepancy between levels self-reported and clinically diagnosed depression in pwPNES. Such studies could use a formal diagnostic process (e.g. the SCID) alongside self-report measures with well-defined cut-off scores (e.g. the NDDI-E or the BDI-II) to explore any identified discrepancies in diagnosis rates. It would be important that future studies comparing findings between epilepsy and PNES patient groups make appropriate adjustments of potentially relevant between-group differences, for instance in terms of gender composition, age and level of education.

Clinical Recommendations

Clinically, there is a clear need for depression to be routinely screened for in both, pwPNES and PWE. Having said that, clinicians need to be aware that

depression may not manifest in a typical manner in pwPNES. In particular, clinicians should be sensitive to complaints of physical symptoms of depression and somatic expressions of distress in this patient group. As clinical assessments may not fully reflect the level of difficulty experienced by pwPNES and may lead to under-diagnosis if used in isolation, the use of standardised self-report measures of depression should also be considered.

The elevated levels of depression in pwPNES and the strength of association with factors such as relationships and HRQoL suggest that depression should be a focus for psychological treatment, which could have beneficial effects beyond the improvement of symptoms of depression itself.

Conclusions

The findings clearly demonstrate higher levels of depression in pwPNES than PWE and suggest pwPNES particularly recognise and report physical symptoms of depression. For pwPNES, depression seems to be particularly related to relationship variables, whereas in PWE, it is more closely associated to illness-related factors.

While these findings are reasonably robust, the research available in this area has extensive limitations. Whilst depression is frequently measured in studies, it has rarely been the primary focus of research and very little information is provided about possible underlying cognitive processes.

Acknowledgements

We would like to thank Dr Georgina Rowse and Dr Tim Moss whose comments on the chapter of a DClinPsy thesis this paper is based on helped to improve the review.

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Appendix A

Study evaluation tool

Methodology Critique	**Yes/No**
All diagnoses confirmed using video-EEG	
Explicit reference to epilepsy being excluded	
Explicit reference to a procedure to distinguish from anxiety attacks (defined as the use of either diagnostic criteria for conversion disorder, psychiatric assessment more generally, or the presence of ictal loss of/alteration in consciousness	
Recruitment was consecutive	
All dependent variables standardised	
Epilepsy Controls	
Comparable to the PNES group in terms of age (≤5 years) and gender (≤10% diff. in no. of females)	
Explicit reference to PNES being excluded	
Score	
1/7 = .14 2/7 = .29 3/7 = .43 4/7 = .57 5/7 = .71 6/7 = .86 7/7 = 1	
Sample size	
Good (≥64 participants in each group)	
Moderate (26–63 participants in each group)	
Poor (<26 participants in each group)	
Very poor(<15 participants in each group)	
Overall Quality Appraisal	
High: ≥80% yes ratings and a good sample size	
Medium: ≥80%‘yes’ ratings and a moderate sample	
Medium: 50–79%‘yes’ ratings and at least a moderate sample size	
Low: 20–49%‘yes’ ratings or a poor sample size were rated as low quality	
Unacceptable: < 20%‘yes’ ratings or a very poor sample size	

Appendix B

Quality appraisal of all studies

		Methodology								Quality assessment	
Study	**Analysis group**	**Sample size**	**Video EEG**	**Epilepsy excluded**	**Anxiety excluded**	**Consecutive sampling**	**Standardised measures**	**Demographic match**	**PNES excluded**	**Score (0-1)**	**Overall rating**
Asmussen et al. [53]	Stage one & two	Moderate	Yes	No	No	No	Yes	Yes	No	0.43	Low
Bewley, et al. [79]	Stage one	Poor	No	Yes	Yes	No	Yes	Yes	Yes	0.57	Low
Binder et al. [80]	Stage one	Good	Yes	No	Yes	No	Yes	Yes	No	0.57	Medium
Binzer et al. [81]	Stage one	Poor	Yes	Yes	No	Yes	Yes	No	Yes	0.71	Low
R. Brown et al. [65]	Stage one & two	Poor	No	Yes	No	No	Yes	Yes	Yes	0.57	Low
Cragar et al. [57]	Stage one & two	Moderate	Yes	Yes	No	No	Yes	No	Yes	0.57	Medium
Gale and Hill [82]	Stage one	Poor	Yes	Yes	No	No	Yes	No	Yes	0.57	Low
Gale et al. [54]	Stage one & two	Good	Yes	Yes	No	No	Yes	Yes	Yes	0.71	Medium
Goldstein and Mellers [83]	Stage one	Poor	No	Yes	Yes	No	Yes	Yes	Yes	0.71	Low
Green et al. [58]	Stage one & two	Poor	No	Yes	No	Yes	Yes	No	Yes	0.57	Low
Hixson et al. [84]	Stage one	Poor	Yes	Yes	No	No	Yes	No	Yes	0.57	Low
Johnson et al. [85]	Stage one	Moderate	Yes	Yes	No	No	Yes	No	No	0.43	Low
Karakis et al. [60]	Stage one & two	Moderate	Yes	Yes	No	No	Yes	No	Yes	0.57	Medium
LaFrance et al. [59]	Stage one & two	Moderate	No	Yes	No	No	Yes	No	Yes	0.43	Low
Lawton et al. [86]	Stage one	Moderate	No	Yes	No	No	Yes	No	Yes	0.43	Low
Moore et al. [87]	Stage one	Poor	No	Yes	No	No	Yes	Yes	Yes	0.57	Low

Myers et al. [88]	Stage one	Moderate	Yes	Yes	No	Yes	No	No	Yes	0.57	Medium
Owczarek and Jedrzejczak [89]	Stage one	Moderate	Yes	Yes	No	No	Yes	No	Yes	0.57	Medium
Prigatano and Kirlin [64]	Stage one & two	Poor	No	Yes	No	No	No	No	Yes	0.29	Low
Rawlings et al. [62]	Stage one & two	Moderate	No	Yes	No	No	Yes	No	Yes	0.43	Low
Salinksky et al. [90]	Stage one	Moderate	No	Yes	No	No	No	No	Yes	0.29	Low
Scevola et al. [91]	Stage one	Moderate	Yes	Yes	Yes	No	Yes	No	Yes	0.71	Medium
Strutt et al. [13]*	Stage one	Poor	Yes	Yes	No	Yes	No	Yes	Yes	0.71	Low
Strutt et al. [14]*	Stage one	Moderate	Yes	Yes	No	Yes	No	Yes	Yes	0.71	Medium
J. Szaflarski et al. [17]^{y}	Stage one	Moderate	Yes	No	No	Yes	Yes	No	No	0.43	Low
J. Szaflarski and M. Szaflarski [18]^{y}	Stage one & two	Good	No	Yes	No	Yes	Yes	No	Yes	0.57	Medium
Testa et al. [19]^{y}	Stage one	Moderate	Yes	No	No	No	Yes	No	No	0.29	Low
Thompson et al. [55]	Stage one & two	Good	Yes	Yes	No	No	Yes	No	Yes	0.57	Medium
Tojek et al. [92]	Stage one	Poor	Yes	Yes	No	No	Yes	Yes	Yes	0.71	Low
Turner et al. [93]	Stage one	Poor	Yes	Yes	Yes	Yes	Yes	No	Yes	0.86	Low
Vanderzant et al. [94]	Stage one	Poor	Yes	Yes	Yes	No	Yes	No	Yes	0.71	Low
Wagner et al. [56]	Stage one & two	Poor	Yes	Yes	No	Yes	Yes	No	Yes	0.71	Low
Wolf et al. [95]	Stage one	Good	Yes	Yes	No	Yes	Yes	No	Yes	0.71	Medium
Yerdelen and Altintas [96]	Stage one	Moderate	Yes	Yes	No	No	Yes	No	Yes	0.57	Medium

*/^{y} papers using the same dataset

Appendix C

Results from all studies

Study	Study quality rating	PNES sample size	Epilepsy sample size	Depression measure (subscale)	Mean (SD) (unless otherwise indicated) PNES	Mean (SD) (unless otherwise indicated) Epilepsy	Highest scoring group	Effect size (Cohen's *d*)
Asmussen et al. [53]	Low	59	60	BDI-II	13.3 (9.6)	11.0 (9.0)	PNES	0.25
				PAI (depression)	56.46 (11.0)*	54.3 (11.2)*	PNES	0.19
Bewley, et al. [79]	Low	21	21	BDI-II	27.19 (11.37)	22.05 (10.07)	PNES	0.48
				BDI-II (moderate/severe depression)	71.4%	57.1%	PNES	-
Binder et al. [80]	Low	70	70	MMPI-2 (depression)	68.04 (12.04)*	63.24 (11.41)*	PNES	0.41
Binzer et al. [81]	Low	20	20	SCID-I (major depression)	30%	15%	PNES	-
R. Brown et al. [65]	Low	43	24	PHQ-9	13.0 (11.0)[z]	4.5 (8.75)[z]	PNES	0.83***
Cragar et al. [57]	Medium	29	58	MMPI-2 (depression)	74 (14.1)*	67 (11.7)*	PNES	0.56
Gale and Hill [82]	Low	23	17	MMPI-2 (depression)	73.04 (15.03)*	63.59 (13.99)	PNES	0.65
Gale et al. [54]	Medium	205	228	PAI (depression)	63.4 (13.2)*	55.3 (11.6)*	PNES	0.65***
				PAI (depression ≥ 70)	34.1%	14.0%	PNES	-***
Goldstein and Mellers [83]	Low	25	19	BDI-II	17.9 (11.1)	11.8 (9.5)	PNES	0.59***
				HADS	5.72 (3.64)	3.58 (3.19)	PNES	0.62*
Green et al. [58]	Low	23	72	PHQ-9	13.74 (7.52)	8.65 (7.20)	PNES	0.70**
				PHQ-9 ≥ 10 (moderate depression)	60.9%	43.1%	PNES	-

Hixson et al. [84]	Low	22	26	BDI-II	19.06 (7.68)	13.75 (10.8)	PNES	0.56
				MMPI-2 (depression)	66.58 (12.84)*	61.00 (12.93)*	PNES	0.43
Johnson et al. [85]	Low	49	49	MMPI-2 (depression)	65.9 (11.56)*	62.86 (10.21)*	PNES	0.28
Karakis et al. [60]	Medium	33	126	BDI	19 (11.55)	13.25 (12.09)	PNES	0.48*
LaFrance et al. [59]	Low	45	32	BDI-II	21.8 (14.9)	13.5 (10.5)	PNES	0.63*
				History of mood disorder	55.6%	43.0%	PNES	-
Lawton et al. [86]	Low	32	37	DASS	17.0 (20.3)[z]	13.0 (21.29)[z]	PNES	0.19
Moore et al. [87]	Low	19	19	HADS	6.2 (2.6)	5.8 (4.3)	PNES	0.11
Myers et al. [88]	Medium	86	40	Psychiatric diagnosis (mild-moderate depression)	54.7%	32.5%	PNES	-*
Owczarek and Jedrzejczak [89]	Medium	38	36	MMPI (Depression)	60.0 (11.8)*	58.1 (12.7)*	PNES	0.16
Prigatano and Kirlin [64]	Low	23	22	PAI (depression)	63.59 (15.08)*	59.42 (10.35)*	PNES	0.32
				Subjective rating	4.61 (3.33)	3.64 (3.4)	PNES	0.29
Rawlings et al. [62]	Low	45	62	NDDI-E	18 (5.75)[z]	14 (7)[z]	PNES	0.61***
				NDDI-E (> 15- major depression)	75.6%	43.5%	PNES	-**
Salinksky et al. [90]	Low	50	37	DSM-III/IV diagnosis (major depression)	46.0%	29.7%	PNES	-
Scevola et al. [91]	Medium	35	49	SCID-I (depression diagnosis)	34.3%	34.7%	PWE	-
Strutt et al. [13]*	Low	33	35	BDI-II	24.8 (13.0)	21.6 (15.9)	PNES	0.22
		32	35	DSM-IV diagnosis (depression/depression and anxiety)	68.8%	72.0%	PWE	-
Strutt et al. [14]*	Medium	30	51	DSM-IV diagnosis (depression/depression and anxiety)	63.3%	56.9%	PNES	-

				MMPI-2 (depression)	-	-	-	-
J. Szaflarski et al. [17]^{y}	Low	53	53	POMS (depression/dejection)	21.6 (15.0)	13.9 (10.7)	PNES	0.59**
J. Szaflarski and M. Szaflarski [18]^{y}	Medium	95	99	POMS (depression/dejection >12)	66.3%	49.5%	PNES	-*
Testa et al. [19]^{y}	Low	45	69	MMPI-2 (depression)	69.49 (15.69)*	65.16 (13.37)*	PNES	0.3
Thompson et al. [55]	Medium	75	109	PAI (depression)	65.7 (13.4)*	59.1 (12.1)*	PNES	0.52***
Tojek et al. [92]	Low	25	33	BSI (depression)	8.28 (6.58)	6.31 (5.39)	PNES	0.33
Turner et al. [93]	Low	22	21	SCID-I (major depression/depression and anxiety)	9.1%	19.0%	PWE	-
Vanderzant et al. [94]	Low	19	17	MMPI (depression)	67.53 (13.38)*	60.41 (12.53)*	PNES	0.55
				MMPI (depression ≥ 70)	42.1%	23.5%	PNES	-
Wagner et al. [56]	Low	26	15	PAI (depression)	67.7*	56.5*	PNES	-^{o}*
Wolf et al. [95]	Medium	85	91	PAI (depression)	61.54 (12.39)*	58.84 (12.59)*	PNES	0.22
Yerdelen and Altintas [96]	Medium	54	64	SCID-I (depressive disorder)	11.2%	10.9%	PNES	-

N.B. All figures reported to a maximum of 2dp

* $p < .05$

** $p < .01$

*** $p < .001$

**** $p < .0001$

$^{+}$ and ^{y} indicate groups of papers analysing the same dataset

^{z} median (interquartile range)

^{o} not possible to calculate

Appendix D

Supplementary data tables for narrative synthesis.

Attachment, relationships and depression

Green et al. [58]

Table A4

Correlations between depression (PHQ-9) and other variables

Category. *Subscale*	PNES	Epilepsy
Seizure characteristics		
Duration of disorder	-.05	.23
Frequency	.07	.02
Severity	.29	.36**
Relationship quality		
Support	-.26	-.06
Conflict	.52*	.28*
Depth	-.32	.09
Attachment style		
Avoidance	.58**	.47***
Anxiety	.77***	.42***

* p <.05, ** p < .01, *** p < .001

Table A5

Regression analyses between depression scores and other variables

Group	Regression step. *Measure*	*B*	*β*	ΔR^2

PNES	1- demographic/seizure variables			.26
	Age	.19	.34	
	Gender	5.61	.29	
	Duration of seizure disorder	-.21	-.21	
	Seizure severity	.03	.13	
	2- relationship/attachment variables			.45**
	Conflict	3.85	.32	
	Attachment avoidance	-.11	-.02	
	Attachment anxiety	3.82	.57*	
Epilepsy	1- demographic/seizure variables			.23**
	Age	-.02	-.05	
	Gender	3.58	.25*	
	Duration of seizure disorder	.08	.16	
	Seizure severity	.07	.31**	
	2- relationship/attachment variables			.16**
	Conflict	.31	.02	
	Attachment avoidance	3.20	.34**	
	Attachment anxiety	.80	.12	

* $p < .05$, ** $p < .01$

The LaFrance Jr. et al. [59] data is summarised under the 'Health status, quality of life and depression' heading.

Health status, quality of life and depression

LaFrance Jr. et al. [59]

Table A6

Correlations between depression (BDI-II) and other variables

Category. *Subscale*	PNES	Epilepsy
Seizure frequency (past month)	.25	-.04
Years with disorder	-.17	-.47*
FAD		
Problem solving	.17	.01
Communication	.16	.04
Roles	.41*	.30
Affective responsiveness	.11	-.05
Affective involvement	.55*	.10
Behaviour control	.17	.05
General functioning	.41*	.05
QOLIE-31	-.73*	-.75*

* $p < .01$

A regression analysis was run using HRQoL as the dependent variable. Seizure-related variables were used in step 1 and depression was entered as the sole variable in step 2: epilepsy, $\beta = .7$, $p < .01$, $\Delta R^2 = .4$; PNES, $\beta = -.7$, $p < .01$, $\Delta R^2 = .5$.

Karakis et al. [60]

Measures with significant differences between groups were entered into a regression analysis. The data for depression (BDI) was: epilepsy, not reported; PNES, $\beta = -.85$, $p < .01$, $\Delta R^2 = .55$.

Rawlings et al. [62]

Table A7

Correlations between HRQoL and other variables

Category. *Measure*	PNES	Epilepsy
Seizure characteristics		
Duration	.06	-.06
Frequency	-.22	-.38**
Severity	-.16	-.29*
Depression (NDDI-E)	-.54***	-.56***

* $p < .05$, ** $p < .01$, *** $p < .001$

J. Szaflarski and M. Szaflarski [18]

HRQoL was measured using the Short-Form-36 (SF-36).

Table A8

Mean (SD) scores on SF-36 for depressed participants

SF-36 subscale	PNES[a]	Epilepsy
Physical functioning	50.79 (24.58)	73.04 (21.94)
Role limitation: physical[b]	13.89 (26.10)	31.12 (38.71)
Role limitation: emotional	29.59 (37.45)	42.18 (39.02)
Energy/fatigue	24.78 (15.96)	38.43 (20.67)
Emotional wellbeing	39.29 (19.78)	49.43 (17.66)
Social functioning	30.89 (25.69)	48.57 (28.95)
Pain	45.05 (26.97)	58.47 (24.63)
General health	38.84 (20.85)	45.61 (19.81)

NB. A cut-off of > 12 on the POMS was used to identify participants with depression.

[a] All scores significantly different from PWE

[b] The interaction between diagnosis and depression was significant in a regression model

Table A9

Mean (SD) SF-36 scores for all participants

SF-36 subscale	Clinical depression	PNES	Epilepsy
Physical functioning	71.58 (27.17)	56.40 (25.99)*	77.67 (22.65)
Role limitation: physical	44.39 (40.26)	18.16 (28.82)*	47.47 (41.73)
Role limitation: emotional	38.90 (39.80)	43.15 (42.39)	59.83 (39.51)*
Energy/fatigue	40.12 (21.08)	28.54 (18.09)*	45.57 (21.00)
Emotional wellbeing	46.26 (20.83)	50.14 (24.18)	61.43 (20.11)*
Social functioning	57.16 (27.67)	37.60 (30.47)*	60.89 (29.03)
Pain	58.84 (26.74)	48.83 (28.39)*	65.80 (24.44)
General health	52.94 (22.98)	44.23 (22.06)*	53.48 (22.04)

NB. Higher scores = better HRQoL

Cognitive and emotional functioning and depression

R. Brown et al. [65]

PwPNES were separated into cluster one (high alexithymia and emotional dysregulation) and cluster two (the remainder of the sample).

Table A10

Mean (SD) depression scores and statistical comparisons between groups.

Group	Cluster one PNES	Cluster two PNES	Epilepsy
Cluster one PNES	-	ns	$p \leq .001$
Cluster two PNES	-	-	$p \leq .005$
Mean (SD)	16.0 (12.0)	10.0 (9.5)	4.5 (8.75)

Prigatano et al. [64]

Participants rated their memory, word finding and depression and then completed standardised measures including the PAI (depression). Memory was assessed with the Rey Auditory Verbal Learning Test (RAVLT), Brief Visuospatial Memory Test-Revised (BVMT-R), and BNI Screen for Higher Cerebral Functions Memory subscale (BNIS). Word finding was assessed using the Boston Naming Test (BNT).

Table A11

Correlations between depression and other variables

	PNES		Epilepsy	
	Patient-rated depression	PAI depression	Patient-rated depression	PAI depression
Patient rated				
Depression	-	.74**	-	.85**
Memory	.56**	.42*	.41	.49*
Word-finding difficulty	.43**	.25	.55**	.49*
Standardised measure				
PAI depression	.74**	-	.85**	-
RAVLT delayed recall	*-.42**	-.32	-.2	-.34
BVMT-R delayed recall	*-.25*	-.29	.02	.07
BNIS memory subscale	*-.05*	-.02	-.14	-.27
BNT	*.07*	-.04	-.40	-.37
BNIS affect subscale	*-.17*	-.17	-.02	-.07

* $p \leq .05$, ** $p \leq .01$