








CRITICAL REVIEW

A meta-analytic review of the effectiveness of psychological treatment of functional/dissociative seizures on non-seizure outcomes in adults

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Abstract

Psychological therapies are considered the treatment of choice for functional/dissociative seizures (FDSs). Although most previous studies have focused on seizure persistence or frequency, it has been argued that well-being or health-related quality of life outcomes may actually be more meaningful. This study contributes by summarizing and meta-analyzing non-seizure outcomes to quantify the effectiveness of psychological treatment in this patient group. A pre-registered systematic search identified treatment studies (e.g., cohort studies, controlled trials) in FDSs. Data from these studies were synthesized using multivariate random-effects meta-analysis. Moderators of treatment effect were examined using treatment characteristics, sample characteristics, and risk of bias. A total of 171 non-seizure outcomes across 32 studies with a pooled sample size of $N = 898$ yielded a pooled effect-size of $d = .51$ (moderate effect size). The outcome domain assessed and the type of psychological treatment were significant moderators of reported outcomes. Greater rates of improvement were demonstrated for outcomes assessing general functioning. Behavioral treatments emerged as particularly effective interventions. Psychological interventions are associated with clinical improvements across a broad array of non-seizure outcomes, over and above seizure frequency, in adults with FDSs.

KEYWORDS

functional dissociative seizures, meta-analysis, non-epileptic attack disorder, psychogenic non-epileptic seizures, treatment effectiveness

1 | INTRODUCTION

Functional/dissociative seizures (FDSs) are events characterized by alterations of awareness, self-control, and perception.¹⁻³ Although FDSs superficially resemble

epileptic seizures, or in some cases syncope, they are not associated with epileptiform activity. FDSs are understood as an automatic response to internal or external triggers involving dysfunctional emotion regulation often occurring in the absence of conscious perception of adverse,

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distressing, or threatening seizure precipitants.³ The prevalence of FDSs has been estimated as 50/100 000 per year.⁴ Together with syncope and epilepsy, they are one of the three common causes of transient loss of consciousness.⁵

There are currently no international treatment guidelines for FDSs, but most experts consider psychological therapy the intervention of choice.^{6,7} However, many uncertainties remain regarding the effectiveness, efficacy, acceptability of psychotherapy, or mechanisms of psychotherapeutic change, as well as the optimal therapeutic modality, dose, and outcome measurement.⁸

Over the last two decades an increasing number of studies have reported psychological treatment outcomes from routine clinical practice settings and randomized controlled trials (RCTs). A recent meta-analysis of psychological interventions focusing on seizure cessation or treatment-associated seizure frequency change in FDSs based on 13 studies found that 47% of included patients became seizure-free by the end of treatment, and 82% had a >50% reduction in seizure frequency.⁹ The authors concluded that their findings were “suggestive” of a favorable outcome but noted the limited availability of relevant evidence, the heterogeneity of study designs, and the dearth of RCTs, which limited confidence in reported findings. Similar observations had led the authors of a Cochrane review 3 years prior to conclude that they could not carry out a meaningful meta-analysis of psychological and behavioral therapies for adults with FDSs.¹⁰

However, the research landscape in this area has shifted significantly since then. First, the results of the CODES (cognitive behavioural therapy for adults with dissociative seizures) study were published in 2020. This landmark study was a pragmatic, multi-center RCT investigating the addition of cognitive behavioral therapy (CBT) to standardized medical care. It involved 368 patients with FDSs who were recruited in the United Kingdom (UK).⁶ This single study, therefore, involved more patients with FDSs than the 228 individuals whose data had been included in the previous meta-analysis.⁹

Second, there has been much debate regarding the most pertinent outcomes to target in treatment (for a review see Nicholson et al.¹¹). It has been argued that broader self-report measures of distress and functioning are as clinically meaningful in individuals with functional neurological disorders (FNDs) as measures focusing exclusively on the core neurological symptoms themselves (including FDSs). Indeed, psychological factors, such as depression and anxiety, as well as psychological mechanisms such as illness perceptions have been found to be stronger predictors of health-related quality of life (HR-QoL) in people with FDSs^{12,13} and may also be more amenable to treatment-associated change.¹⁴ Such findings also recognize that individuals with FDSs are at a higher

Key Points

- Non-seizure outcome measures are sensitive to the effects of psychological treatment of functional/dissociative seizures (FDSs).
- This is the first meta-analysis examining psychological therapy on outcomes that are not limited to FDS frequency.
- Outcome measures of distress/health-related quality of life demonstrate a moderate effect of psychological therapy.
- The type of therapy delivered, and the focus of measures had moderating effects on reported outcomes.
- Findings support the commissioning of psychological services for FDSs and the adoption of broader outcome measures in this group.

risk of experiencing comorbid axis I and axis II disorders, which may also mediate treatment outcomes.^{3,15} The uncertainty about what outcomes should be measured is reflected in studies evaluating FDS treatments in which a host of different non-seizure measures have been employed. In addition to concerns about the relevance of seizure-frequency-derived measures, the reliability of self-reported FDS frequency data is questionable: The accuracy of self-reported seizure frequency has been shown to be poor in individuals with epilepsy and has not been proven to be any better in patients with FDS.¹⁶ Cutoff points such as a reduction of seizure frequency by $\geq 50\%$ appear arbitrary. Although the challenges associated with establishing reliable seizure frequency data do not mean that they should be disregarded, they have prompted researchers to consider other outcomes that may change during treatment. HR-QoL, psychosocial or occupational functioning, disability, and distress have been identified as clinically relevant supplementary outcomes to capture when evaluating psychological treatments of patients with FNDs, including FDSs.¹⁷

Although non-seizure outcomes are widely implemented in FDS treatment studies, they have not been previously systematically reviewed. The current review set out to systematically identify and evaluate all psychological interventions for adults with FDSs. Due to the inherent difficulties associated with synthesizing proportional outcomes (i.e., seizure improvement, seizure frequency) and conventional effect sizes (e.g., standardized mean difference), and the focus of this review on non-seizure outcomes, we decided that seizure-specific outcomes would not be included in this review. To be comprehensive and to ensure that the results are translatable to clinical practice,

we included both RCTs (i.e., examining efficacy of psychological FDS interventions) and observational cohort studies (i.e., examining the effectiveness of psychological FDS interventions). First, we investigated pooled effect sizes by comparing pre- and post-treatment scores across non-seizure outcome measures. Second, differences in the amount of change between different outcome domains were assessed. Finally, we examined whether patient characteristics, treatment characteristics, and 'risk of bias' ratings moderated treatment effects.

2 | METHODS

2.1 | Systematic search

The systematic search of primary literature for this meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The protocol was pre-registered at Open Science Framework (<https://osf.io/sk6xm>). Studies were identified using four electronic databases (CINAHL, PsycINFO, MEDLINE, Cochrane Reviews). A comprehensive search was performed in February 2022 by two study authors (GHR and BN) using pre-identified search terms (Table 1). Following removal of duplicates, the titles and

abstracts were screened using a pre-developed screening tool. Full-text articles were retrieved and re-assessed for inclusion. To identify studies not captured by the electronic databases, we performed forward and backward citation searches using the R package *citation chaser*¹⁸ and scanned reference lists from relevant prior review papers.^{9,10}

Inclusion and exclusion criteria are reported in Table 1. Studies describing adults (≥ 16 years) accessing psychological therapy with FDSs were eligible. This is often the age at which patients transition or access adult services, reflecting differences in the provision of health care between adult and child samples. Studies were required to have used a validated outcome measure of therapeutic effectiveness. Studies that reported that a majority ($\geq 50\%$) of patients were (1) ≤ 16 years *and/or* (2) did not describe patients with FDSs (e.g., patients with epilepsy or a dual seizure diagnosis) were excluded. This step was taken to reduce the clinical heterogeneity of samples reported previously.¹⁰ All publication types were included to reduce upward bias of peer-reviewed journals (and therefore inflated effect-sizes^{19,20}).

2.2 | Data extraction

Relevant data (author details, year of publication, study characteristics, sample characteristics, treatment

TABLE 1 Systematic review key terms and inclusion/exclusion criteria using the PICOS framework (population, intervention, comparison, outcome, and study design).

	Concept 1	AND	Concept 2
	Functional seizures		Treatment
Key words	Functional seizure* OR hysterical seizure* OR psychogenic non\$epileptic seizure* OR dissociative seizure* OR pseudoseizure* OR non\$epileptic attack disorder OR non\$epileptic seizure* OR psychogenic seizure* OR nonepileptic OR PNES OR NES OR NEAD		Psychotherapy OR psychological therapy OR psychological treatment OR psychological intervention
	Inclusion		Exclusion
Population	Adults (≥ 16 years) with a diagnosis of FDSs		Samples with a majority proportion of patients who are (i) under the age of 16; or (ii) have a mixed seizure disorder (FDSs and epilepsy)
Intervention	Psychological treatment such as CBT, psychodynamic psychotherapy, psychoeducation, including behavioral interventions. Delivered on a 1:1 or group basis with patients; in person or remotely		Solely focusing on non-psychological treatment, which was not the aim of this study
Comparison	Any comparison group		–
Outcome	Outcome measure utilizing a standardized tool assessing psychological, emotional, or behavioral functioning		Objective outcome measures (i.e. non-subjective measures) or solely examining seizure frequency
Study design	Published after the year 2000		Case study, single-case experimental studies. Not published in English

Abbreviations: FDSs, functional/dissociative seizures; CBT, cognitive behavioral therapy.

characteristics, design, outcome domain, and effect-sizes) were extracted from study manuscripts by two study authors (CG and NP). To ensure reliability, all details relevant to effect-size computation were extracted in duplicate (disagreements were resolved through project team consensus). Effect sizes were extracted for the acute treatment phase (i.e., pre- and post-treatment; or, in the absence of immediate post-treatment data, the closest time point to treatment completion). When multiple independent samples were reported (e.g., treatment comparison) both samples were extracted. In cases in which a manuscript reported overlapping samples (e.g., both completers and intention-to-treat) the preference to be given to one analysis or other was decided during research meetings using a preference hierarchy, favoring robustness (i.e., intention-to-treat), sample size, and recency.

A codebook was developed to support the extraction process. Treatment variables included delivery format, treatment setting, modality, and treatment length. Delivery formats included individual, group, or a combination of both. Treatment settings included outpatient, inpatient and tele-therapy. For treatment modalities, treatment samples were coded into six categories: behavioral, cognitive-behavioral, relational (psychodynamic/psychoanalytic), body-focused, psychoeducation, and other (including eclectic treatments). Coding was based on the treatment description reported by authors. In situations when the treatment modality was ambiguous, decisions were made in research meetings. Treatment duration/dose was coded as short (≤ 6 sessions), medium (7–13 sessions) and long (≥ 14 sessions). The six session cutoff was selected as this duration has been reported as characteristic of “low intensity” interventions in UK primary care health settings.^{21,22} The 13-session upper threshold for medium-duration treatments was selected based on the tendency for protocol delivered treatments within included trials to include 12–13 sessions.^{6,23,24,25,26,27,28,29,30} Outcome domains were classified into five categories: mental health (e.g., anxiety, depression), HR-QoL, functioning (global functioning ratings, work/social adjustment scales), dissociation and somatoform symptoms, and finally non-specific psychological outcomes (e.g., interoceptive awareness, anger). Assignment of each outcome measure to outcome domain group was based upon available descriptions of the included scales. A decision was made to have a “non-specific” psychological outcomes domain to avoid the likely scenario of an unmanageable number of outcome domains, each being represented by only one or very few studies. Dissociation and somatoform questionnaires were collapsed due to the small number of outcomes identified for each domain (dissociation $k=10$, somatoform $k=3$). However, in addition to providing pooled effect sizes for the collapsed group (i.e., dissociation and somatoform

outcomes combined) we also report dissociation and somatoform outcomes separately.

2.3 | Risk of bias

All studies were evaluated using the Cochrane Collaboration's tool for assessing risk of bias (ROB-2).³¹ This included seven items, covering selection bias, more specifically (1) random sequence generation and (2) allocation; performance bias examining (3) blinding of participants and personal; detection bias exploring (4) blinding of outcome assessment; attrition bias investigating (5) incomplete outcome data; reporting bias via (6) selective reporting; and (7) other sources of bias. Ratings included “high,” “low” and “unclear” risk of bias, with all studies receiving an overall quality score based on how the study scored on each of the seven items (“low,” “medium” or “high”). In order for studies to be classed as “low” they needed to be an RCT and score low on the majority (i.e., $>50\%$) of risk of bias item; “high” studies had the majority of “unclear” or “high” ratings (i.e., no high rated study had more than one low rating); and “medium” studies were more mixed with no study scoring the majority ($>50\%$) of items as “high” risk. All risk of bias ratings were performed in duplicate by two study authors (GHR and BN) with 100% consensus achieved (see Table S2).

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE)³² approach was used to rate the quality of the evidence included in the meta-analysis. The quality of evidence base was assessed on five domains: (1) risk of bias in the individual included studies, (2) publication bias, (3) inconsistency, (4) imprecision, and (5) indirectness of treatment estimate effects. The body of evidence included in the meta-analysis was graded by two study authors (SK and MSB) during a consensus review meeting (rated as high, moderate, low, or very low quality).

2.4 | Data analysis

All analyses were conducted using R.³³ Standardized mean change (i.e., Cohen's d) was calculated for each extracted outcome.³⁴ This approach divides the mean change score by the pre-treatment standard deviation before adjusting the standard error using the pre-post correlation (Pearson's r).³⁵ The distribution of effect sizes was visualized and suggestive of positive outliers. Tukey's definition of outliers (effect sizes below the first quartile [-3 times the interquartile range] or above the third quartile [$+3$ times the interquartile range]) isolated seven positive outliers. Each outlier was recoded (winsorized) to the upper fence

value ($d = 2.51$). This approach has been followed in a comparable meta-analytic investigation using robust-variance estimation.³⁶ The role of highly influential studies was examined using leave-one-out sensitivity analyses.³⁷

The meta-analysis utilized a random-effects model, as effects were anticipated to show heterogeneity, and as results were intended to be generalizable beyond the current pool of studies.³⁸ To address the statistical dependency inherent when extracting multiple outcomes/effects per sample (i.e., correlational dependencies)^{38–40} we utilized a multi-variate meta-analysis. This allowed us to examine variation in outcomes both within and between studies. Robust variance estimation was performed to increase precision of estimates. In this approach n denotes participants, k denotes number of included effect sizes, and c denotes numbers of clusters (i.e., studies). Meta-analytic procedures were conducted using the *Metafor*⁴¹ package. To explore under what conditions effect sizes vary significantly, heterogeneity was explored using categorical (i.e., subgroup) and continuous moderator variables (i.e., meta-regression). For subgroup moderators, the QM test (i.e., Wald-type test of the model coefficients)⁴¹ was used to examine differences between moderator levels and a designated reference level. A significant QM test infers that there are significant differences between moderator levels. Moderator output was reported in absolute terms (i.e., not relevant to an intercept) to support reader interpretation. Correction for multiple moderators (i.e., Bonferroni) was not employed due to the low statistical power within moderator analyses. A forest plot was generated using the *ggplot2*⁴² package to visualize subgroup moderator analyses. The Q statistic,⁴³ and the proportion of variance not attributable to sample error (I^2), was reported⁴⁴ to assess heterogeneity (low = 25%–49%, moderate = 50%–74%, high 75%–100%). The impact of publication bias on treatment estimates has been visualized using funnel plots and assessed statistically using Egger's regression test for funnel plot asymmetry.

3 | RESULTS

3.1 | Systematic search

The PRISMA diagram (Figure 1) presents a summary of the systematic search process. Overall, 3064 records were identified, of which 43 were suitable according to inclusion and exclusion criteria. These articles were then screened to determine that a non-seizure outcome was reported (for extraction) and that there was sufficient reporting of data for effect-size computation. Twelve authors were contacted to request additional information around primary data, three of whom responded. In total, 32 studies were eligible for inclusion. A full list of outcomes included in the review is available in Table 2.

3.2 | Study characteristics

Across the 32 studies (c), there were 36 unique patient cohorts, 171 non-seizure-related outcomes (k) representing 898 patients (N) treated with a psychological therapy for their FDSs (patients in control conditions not included in the review). Studies were conducted across 11 countries, although the majority came from the United States ($c = 14$) or UK ($c = 9$). There was a female preponderance across participants (78.9%) whose mean age was 36.1 years. Most studies were conducted in routine outpatient settings ($c = 27$, $k = 137$), using a cognitive-behavioral treatment modality ($c = 18$, $k = 106$). In terms of delivery format, 21 studies used one-to-one treatment ($k = 94$), 9 studies used group treatment ($k = 60$), and 2 studies used a combination ($k = 2$). Treatment duration was 7–16 sessions (i.e., of medium duration [$m = 17$, $k = 117$]), whereas a smaller number of studies used “brief” ($c = 8$, $k = 19$) or long treatments ($c = 3$, $k = 5$) (Table 3).

3.3 | Meta-analysis

A median of three (range $k = 1$ –30) outcomes were reported per study. Due to the inclusion of observational/cohort studies, the starting grade of evidence was determined to be “low” according to the GRADE assessment. Assessment across the five domains indicated concerns regarding the inconsistency of results, imprecision, and publication bias, but concerns about the directness of the evidence were minimal. The quality of the meta-analytic evidence was downgraded specifically due to significant variation not attributable to sampling error (i.e., I^2), imprecise effects based on wide lower and upper bounds of confidence intervals (CIs), indication of potential impacts from reporting biases, and the small number of studies including moderator analyses. The overall GRADE quality of the evidence across the included studies was, therefore, “low,” indicating there are limits to our confidence in the synthesized effect and acknowledging that it may not be an accurate representation of the true effect.

The multi-variate random-effects meta-analysis was statistically significant ($p < .001$). The mean effect size for psychological interventions for non-seizure outcomes was moderate ($d = .51$ [95% CI = .39–.64 GRADE = low]). Heterogeneity was significant based on the Q statistic ($Q[df = 170]$, = 655.7826, $p < .0001$). The variance components were $\tau^2_{\text{Level 3}} = .051$ (between study) and $\tau^2_{\text{Level 3}} = .067$ (within study). Subsequently, the proportion of variation in effect size that could not be attributed to sampling error (i.e., I^2) was 73.97% overall (31.85% between studies, 42.12% within studies).

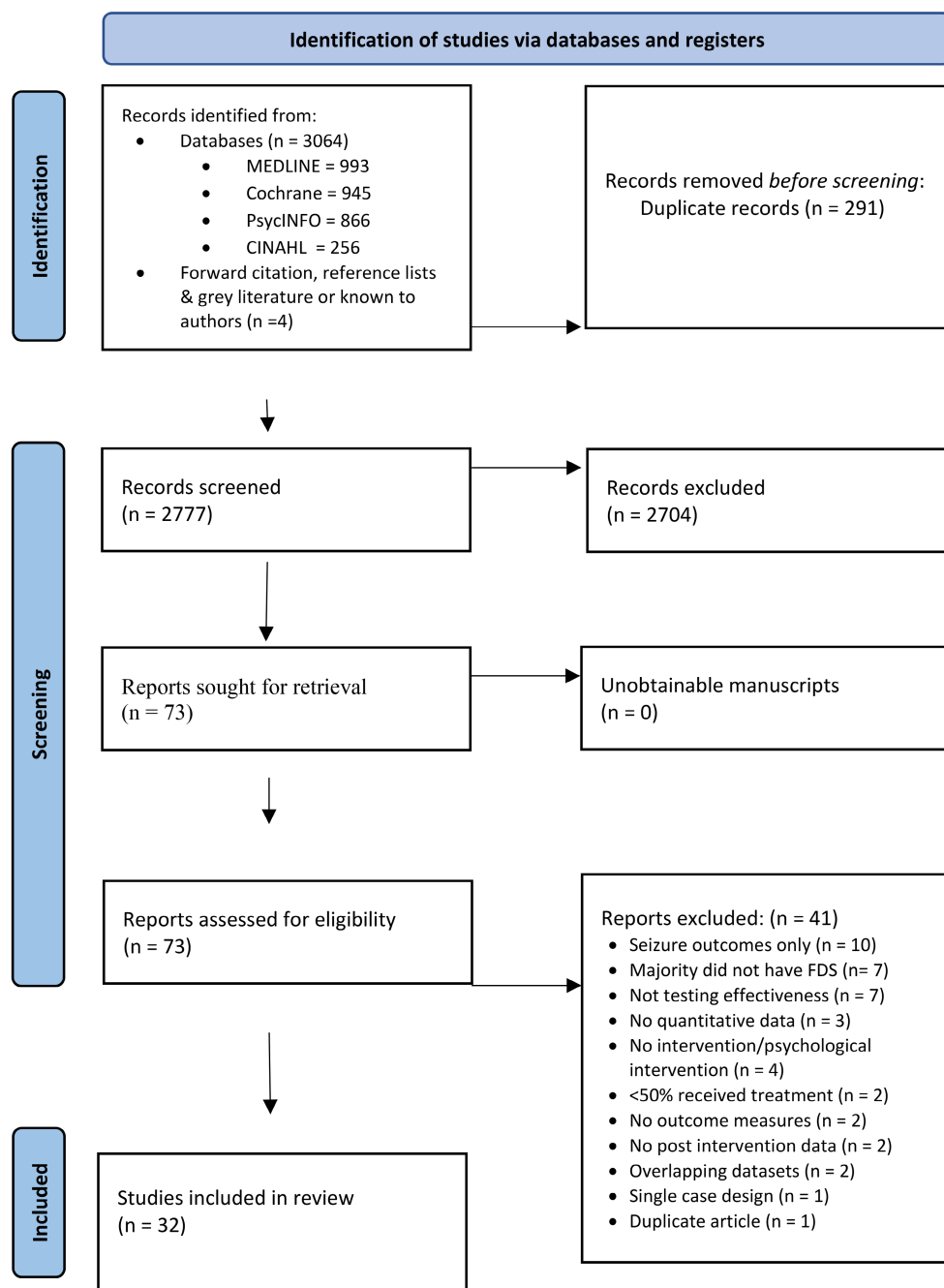


FIGURE 1 PRISMA flow diagram of studies throughout the review.

3.4 | Moderator analysis

Table 4 reports the model statistics for each moderator included in the meta-analysis and the average effect sizes. A reference level (denoted in Table 4 by *) is allocated as the intercept for each moderator analysis. A significant model, therefore, indicates significant differences between the intercept and at least one of the remaining levels of the moderator. It is important to note that a null finding does not rule out the possibility that there are significant differences between other pairwise contrasts not

captured by this approach. Running all possible contrasts would inflate the risk of type 1 error. Therefore, the additional post hoc contrasts included were conducted on a theory-driven basis. Moderator level summary effect sizes are also illustrated in the forest plot (Figure 2).

There were significant differences between outcome domains assessed ($F(4)=21.55$, $p<.001$), with mental health outcome effect sizes (intercept) being on average greater ($d=.52$) than quality of life ($d=.36$) outcomes, but smaller than functioning outcomes ($d=.78$). The post hoc contrasts demonstrated that effect sizes of functioning

TABLE 2 List of outcome measures included in the meta-analysis, grouped by outcome domain.

Domain	Measure	k
Mental health	Beck Depression Inventory (BDI) I/II	10
	Symptom Checklist-90 - Global Severity Index (SCL-90)	7
	Physical Health Questionnaire (PHQ-9)	6
	Hospital Anxiety and Depression Scale (HADS) – Anxiety; Hospital Anxiety and Depression Scale (HADS) – Depression	5
	Generalized Anxiety Disorder 7 (GAD-7); Spielberger State-Trait Anxiety Inventory - State	4
	Spielberger State-Trait Anxiety Inventory - Trait; Beck Anxiety Inventory (BAI); Hamilton Rating Scale for Depression (HRSD)	3
	Clinical Outcomes in Routine Evaluation (CORE-10)	2
	Depression Anxiety & Distress Scale (DASS-21); Depression Anxiety & Distress Scale - Anxiety (DASS-A); Clinical Outcomes Routine Evaluation (CORE-OM); Brief Symptom Inventory (BSI); Davidson Trauma Scale; PTSD Checklist (PCL); Post-traumatic Disorder Scale (PDS); PTSD checklist (PCL-C) civilian version; Hamilton Rating Scale for Anxiety	1
Health related quality of life	Short Form-36 (SF-36 -all versions, including subscales)	33
	Quality of Life in Epilepsy-31 (QOLIE-31); Quality of Life in Epilepsy-10 (QOLIE-10)	6
	Family Burden Scale	2
	European Quality of Life5 Dimensions (EQ-5D)	2
	Quality of Life - Six Dimensions (QOL-6D)	1
Non-specific psychological change	State-Trait Anger Expression Inventory (STAXI-2, all subscales)	12
	Brief Illness Perceptions Questionnaire (BIPQ)	3
	Barratt Impulsivity Scale; Davidson Trauma Scale	2
	Acceptance & Alliance Questionnaire (AAQ); Comprehensive Assessment of Acceptance and Commitment Processes (CompACT); Emotional Thermometer 7; Fear Questionnaire; Health Locus of Control; Toronto Alexithymia Scale; Coping Inventory for Stressful Situations (CISS): Task; Coping Inventory for Stressful Situations (CISS): Emotion; Coping Inventory for Stressful Situations (CISS): Avoidance	1
Functioning	Work & Social Adjustment Scale (WSAS)	7
	Global Assessment of Functioning (GAF); Clinical Global Impression Scale (CGI)	4
	Side Effects Profile; Range of Impaired Functioning Scale; Oxford Handicap Scale	2
Dissociation	Dissociative Experiences Scale (DES)	10
	Physical Health Questionnaire (PHQ-15)	3
	The Dissociation Questionnaire (DISQ); Curious Experiences Survey	2

Abbreviations: BSI, Brief Symptom Inventory; DASS-21, Depression, Anxiety & Stress Scale; EQ-5D-5L, Euro Quality of Life-5 dimensions; QOLIE-31, Quality of Life in Epilepsy; SCL-90 (GSI), Symptom Checklist 90 Global Severity Index; STAXI2, State-Trait Anger Expression Inventory 2.

outcomes ($d = .78$) were greater than dissociative and somatoform ($d = .41, p = .003$), non-specific ($d = .41, p = .001$), and quality of life outcomes ($d = .36, p < .001$). When separating out dissociative and somatoform outcomes, the pooled effect size was $d = .39$ for dissociative outcomes and $d = .55$ for somatoform outcomes.

The moderator model examining the effects of intervention characteristics was not significant for delivery format ($F(2) = 1.18, p = .555$), intervention delivery setting ($F(2) = .87, p = .555$), or treatment length (as measured by number of sessions) ($F(2) = 5.19, p = .075$). Although the overall model for treatment length was null, a post hoc contrast demonstrated a significantly higher ($p = .026$) average effect size for longer treatments (≥ 14 sessions, $d = 1.36$) over medium-length treatments (7–13 sessions, $d = .57$).

The type of psychological intervention delivered was the only significant moderator for treatment characteristics ($F(2) = 13.78, p = .017$). Behavioral interventions ($d = 1.30$) outperformed cognitive-behavioral interventions ($d = .42$). Post hoc contrasts revealed no significant difference between CBT ($d = .42$) and relational interventions ($d = .42, p = .937$).

It should be noted that due to the size of error bars we cannot say with confidence that long treatments or treatments coded as eclectic/various are effective because the lower fence of the 95% CI fell below 0. This may be an artifact of the small number of outcomes and studies within these moderator levels (i.e., an underpowered finding). For meta-regression variables, the intercept (* in Table 4) denotes the average effect size when variable matches

TABLE 3 Studies included in the meta-analysis.

Study	Country	N (female)	Age M (SD/ range)	Design	Modality
Aamir (2011) ⁴⁵	Pakistan	18 (15, 83.3%)	22.2 (2.7)	RCT	Behavioral
Ataoglu (2003) ⁴⁶	Korea	15 (15, 100.0%)	23 (16–30)	RCT	Behavioral
Barrett-Naylor (2018) ⁴⁷	UK	6 (5, 83.3%)	NR	Non-concurrent case series	C-B
Barry (2008) ⁴⁸	USA	7 (7, 100.0%)	45.4 (7.9)	Pilot study	Relational
Baslet (2015) ²⁶	USA	6 (6, 100.0%)	NR	Case series	C-B
Baslet (2020) ²³	USA	26 (23, 88.5%)	46.4 (16.2)	Prospective uncontrolled trial	C-B
BenNaim (2020) ⁴⁹	Israel	22 (15, 68.2%)	31.3 (13.8)	Pre-post evaluation	Eclectic-various
Castillo (2022) ⁵⁰	UK	18 (17, 94.4%)	37.7 (11.9)	Pilot study/case series	Relational
Chen (2014) ⁵¹	USA	20 (NR)	50.8 (12.3)	Pilot RCT	Psycho-education
Conwill (2014) ⁵²	UK	10 (7, 70.0%)	33.1 (11.6)	Pilot study/service evaluation	C-B
Cope (2017) ⁵³	UK	25 (21, 84.0%)	NR	Pre-post evaluation	C-B
DeLeuran (2019) ⁵⁴	Denmark	42 (36, 61.9%)	36 (18)	Pre-post evaluation	C-B
Goldstein (2004) ²⁷	UK	16 (14, 87.5%)	34.9 (13.4)	Open, prospective trial	C-B
Goldstein (2010) ²⁴	UK	31 (24, 77.4%)	37.4 (12.6)	RCT	C-B
Goldstein (2020) ⁶	UK	185 (140, 75.7%)	37.3 (14.2)	Pragmatic, parallel-arm, multi-center RCT	C-B
Khattak (2006) ⁵⁵	Pakistan	50 (NR)	24.3 (8.8)	RCT	Behavioral
Kuyk (2008) ⁵⁶	Netherlands	22 (NR)	30.6 (10.8)	Uncontrolled, prospective inpatient treatment program	C-B
Labudda (2020) ⁵⁷	Germany	80 (60, 75.0%)	33.8 (13.6)	Prospective, naturalistic evaluation	C-B
LaFrance (2009) ²⁸	USA	20 (17, 85.0%)	36 (10.4)	Prospective non-randomized clinical trial	C-B
LaFrance (2014) ²⁹	USA	9 (7, 77.8%)	37.9 (11.5)	Multi-site pilot RCT	C-B
LaFrance (2014) ²²⁹	USA	9 (9, 100.0%)	39.1 (13.2)	Multi-site pilot RCT	C-B
LaFrance (2020) ³⁰	USA	32 (5, 15.6%)	49.1 (NR)	Single-arm, prospective, observational, cohort study	C-B
Mayor (2013) ⁵⁸	UK	29 (NR)	37 (23–38)	Prospective, multi-center, feasibility study	Psycho-education
Metin (2013) ⁵⁹	Turkey	9 (8, 88.9%)	22.5 (NR)	Pre-post evaluation	Eclectic-various
Myers (2017) ⁶⁰	USA	16 (13, 81.3%)	42.8 (NR)	Case series	Behavioral
Santiago-Trevino (2017) ⁶¹	Mexico	9 (NR)	NR	RCT	C-B
Santiago-Trevino (2017) ²⁶	Mexico	7 (NR)	NR	RCT	Relational
Sarudiansky (2020) ⁶²	Argentina	12 (10, 83.3%)	30.8 (14.1)	Case series	Psycho-education
Senf-Beckenbach (2022) ⁶³	Germany	22 (18, 81.8%)	36.6 (12.1)	Pilot RCT	Body focused
Senf-Beckenbach (2022) ⁶³	Germany	20 (12, 60%)	32.8 (13.2)	Pilot RCT	GSH
Streltsov (2022) ⁶⁴	USA	6 (6, 100%)	36.2 (9.0)	Pilot study	C-B
Tilhaun (2021) ⁶⁵	USA	64 (47, 73.4%)	36.3 (11.3)	Pre-post evaluation	C-B
Tolchin (2019) ²⁵	USA	31 (26, 83.9%)	40.7 (14.3)	RCT	C-B
Tolchin (2019) ²⁵	USA	29 (23, 79.3%)	39.6 (16.8)	RCT	C-B + MI
Wiseman (2016) ⁶⁶	UK	25 (13, 52%)	41.8 (18.1)	Multi-center evaluation/service evaluation	Psycho-education
Zaroff (2004) ⁶⁷	USA	10 (6, 60.0%)	35.7 (12.9)	Pre-post evaluation	Psycho-education

Abbreviations: C-B, cognitive behavioral; GSH, guided self-help; M, mean; MI, motivational interviewing; NR, not reported; RCT, randomized controlled trial; SD, standard deviation; UK, United Kingdom; USA, United States of America.

the pooled mean. Neither mean sample age nor proportion of participants identifying as female were significant moderators of effect size (age [$\beta = -.013$, $p = .252$], gender [$\beta = .004$, $p = .151$]).

3.5 | Risk of bias

Based on the overall risk of bias ratings, most studies were categorized as being subject to medium risk

Duration/dose	Delivery	Setting	Overall risk of bias	ComparisonAssessment period
15 sessions	Individual	Outpatient	Medium	Baseline to last follow up session
3 weeks inpatient treatment. 2×sessions per day	Individual	Inpatient	Low	Start of treatment to 3 weeks post discharge
6 weeks	GSH (telephone)	Outpatient	Medium	Start of treatment to end of treatment
32×90 min group sessions	Individual	Outpatient	High	Start of treatment to end of treatment
12 sessions	Individual	Outpatient	High	Start of treatment to end of treatment
12 sessions	Individual	Outpatient	Medium	Post diagnosis to last appointment
Months=(M=15.77, SD=10.96, range=2 and 48)	Individual	Outpatient	High	Start of treatment to end of treatment
3 session course	Individual	Outpatient	Medium	Start of treatment to end of treatment
3×1.5 h sessions	Group	Outpatient	Medium	Start of treatment to end of treatment
4 group sessions	Group	Outpatient	Medium	Start of treatment to end of treatment
3 sessions	Group	Outpatient	Medium	Start of treatment to end of final group session
10–15 sessions (mean=12; SD=5.7)	Individual	Outpatient	High	Start of treatment to end of treatment
12 sessions	Individual	Outpatient	Medium	Start of treatment to end of treatment
12 sessions	Individual	Outpatient	Low	Start of treatment to end of treatment
12+1 (median=13)	Individual	Outpatient	Low	Start of treatment to end of treatment
NA	Individual	Inpatient	High	Baseline to discharge
Mean=4.8 months	Individual + Group	Inpatient	High	Start of treatment to end of treatment
Mean=64.5 days	Individual + Group	Inpatient	High	Start of treatment to end of treatment
12 sessions	Individual	Outpatient	Medium	Start of treatment to end of treatment
12 sessions	Individual	Outpatient	Low	Start of treatment to end of treatment
12 sessions	Individual	Outpatient	Low	Start of treatment to end of treatment
12 sessions	Remote	Teletherapy	Medium	Start of treatment to 16-week follow-up (i.e., end of treatment)
4×1 h sessions	Individual	Outpatient	Medium	Start of treatment to 1-month following treatment completion
Weekly 90-min sessions for 12 weeks	Group	Outpatient	High	Start of treatment to third month of follow-up (i.e., completion of therapy)
12–15 sessions	Individual	Outpatient	Medium	Start of treatment to end of treatment
36 weekly sessions	Individual	Outpatient	Medium	Start of treatment to end of treatment
36 weekly sessions	Individual	Outpatient	Medium	Start of treatment to end of treatment
3 bi-monthly sessions each 2 h long	Group	Outpatient	Medium	Start of treatment to end of treatment
10×90 min sessions	Group	Outpatient	Low	Start of treatment to end of treatment
10×90 min sessions	Group	Outpatient	Low	Start of treatment to end of treatment
8 sessions	Group telephone	Outpatient	Medium	Start of treatment to 1-month follow up
7–12 sessions	Individual	Outpatient	Medium	Initial visit to 3-month follow-up
12 sessions	Individual	Outpatient	Low	Assessment to 16-week follow-up
13 sessions	Individual	Outpatient	Low	Assessment to 16-week follow-up
4×1 h sessions	Group	Outpatient	Medium	Start of treatment to end of treatment
10 group sessions	Group	Outpatient	High	Start of treatment to end of treatment

of bias ($m = 18$, $k = 65$), whereas there was a smaller number of high- ($m = 6$, $k = 50$) and low- ($m = 9$, $k = 56$) risk studies. Low-risk studies demonstrated a smaller average effect size ($d = .40$); however, this trend was

not significant when entering risk of bias rating as a sub-group moderator ($F(2) = 1.07$, $p = .586$) (see supplementary Table S1 for individual study risk of bias ratings). To assess publication bias, we examined a

TABLE 4 Moderator analysis outcomes.

Level	c	k	d	SE	95% CI	p
Delivery: $F(2)=1.18$, $p=.555$, [$\tau^{3/3}=.092$, $\tau^{2/3}=.064$], $I^2=78.81\%$ [$L^2=32.46$, $L^3=46.36$]						
Individual*	21	94	.60	.11	.37 to .83	
Group	9	60	.42	.09	.22 to .61	.284
Individual and group	2	17	.50	.05	.39 to .61	.707
Outcome domain: $F(4)=21.55$, $p<.001$, [$\tau^{3/3}=.025$, $\tau^{2/3}=.059$], $I^2=65.23\%$ [$L^2=45.79$, $L^3=19.44$]						
Mental health*	26	62	.52	.06	.39 to .65	
HR-QoL	15	47	.36	.09	.17 to .55	.022
Non-specific psychological	9	28	.41	.16	.08 to .73	.227
Functioning	10	21	.78	.14	.5 to 1.07	.004
Dissociation and somatoform	9	13	.41	.06	.28 to .54	.278
Overall risk of bias: $F(2)=1.07$, $p=.586$ [$\tau^{3/3}=.064$, $\tau^{2/3}=.067$], $I^2=75.33\%$ [$L^2=38.52$, $L^3=36.81$]						
Low	6	50	.40	.14	.11 to .69	.304
Medium*	17	65	.59	.09	.39 to .78	
High	9	56	.51	.13	.24 to .78	.646
Treatment length: $F(2)=5.19$, $p=.075$ [$\tau^{3/3}=.120$, $\tau^{2/3}=.021$], $I^2=76.79\%$ [$L^2=11.4$, $L^3=65.39$]						
Short*	8	29	.55	.11	.34 to .77	
Medium	17	117	.57	.09	.38 to .76	.913
Long	3	5	1.36	.74	-.16 to 2.88	.028
Treatment modality: $F(5)=13.78$, $p=.017$, [$\tau^{3/3}=.067$, $\tau^{2/3}=.064$], $I^2=76.04\%$ [$L^2=37.19$, $L^3=38.85$]						
Cognitive-behavioral*	18	106	.42	.05	.31 to .54	
Behavioral	4	7	1.30	.46	.35 to 2.25	.001
Relational	3	5	.45	.11	.24 to .67	.937
Eclectic-various	2	14	.87	.82	-.82 to 2.56	.170
Psychoeducation	5	33	.47	.13	.21 to .73	.802
Body Focused	1	6	.29	.00	.29 to .29	.701
Treatment setting: $F(2)=.87$, $p=.646$, [$\tau^{3/3}=.76$, $\tau^{2/3}=.65$], $I^2=77.02\%$ [$L^2=35.55$, $L^3=41.47$]						
Outpatient*	27	137	.63	.09	.46 to .81	
Inpatient	4	20	.76	.25	.25 to 1.26	.359
Tele-therapy	3	21	.49	.24	0 to .98	.955
Age (mean = 36.1): $F(1)=1.31$, $p=.252$, [$\tau^{3/3}=.070$, $\tau^{2/3}=.071$], $I^2=78.82\%$ [$L^2=39.60$, $L^3=38.63$]						
Intercept	30	158	.52	.07	.37 to .68	
Age	30	158	-.01	.01	-.04 to .02	.381
Female (mean = 78.9%): $F(1)=2.06$, $p=.051$ [$\tau^{3/3}=.018$, $\tau^{2/3}=.064$], $I^2=67.81\%$ [$L^2=52.67$, $L^3=15.14$]						
Intercept	21	146	.46	.06	.34 to .58	
Female	21	146	.00	.00	0 to .01	.067

Note: p values in bold indicate a statistically significant finding (i.e., $p < 0.05$).

Abbreviations: * = model intercept; c = number of clusters (studies); CI, % confidence intervals; d, Cohen's d effect size; I^2 , within study I^2 ; L^2 , between study I^2 ; k, number of effect estimates (outcomes); p, alpha level; SE, standard error; $\tau^{2/3}$, tau² within study; $\tau^{3/3}$, tau² between study.

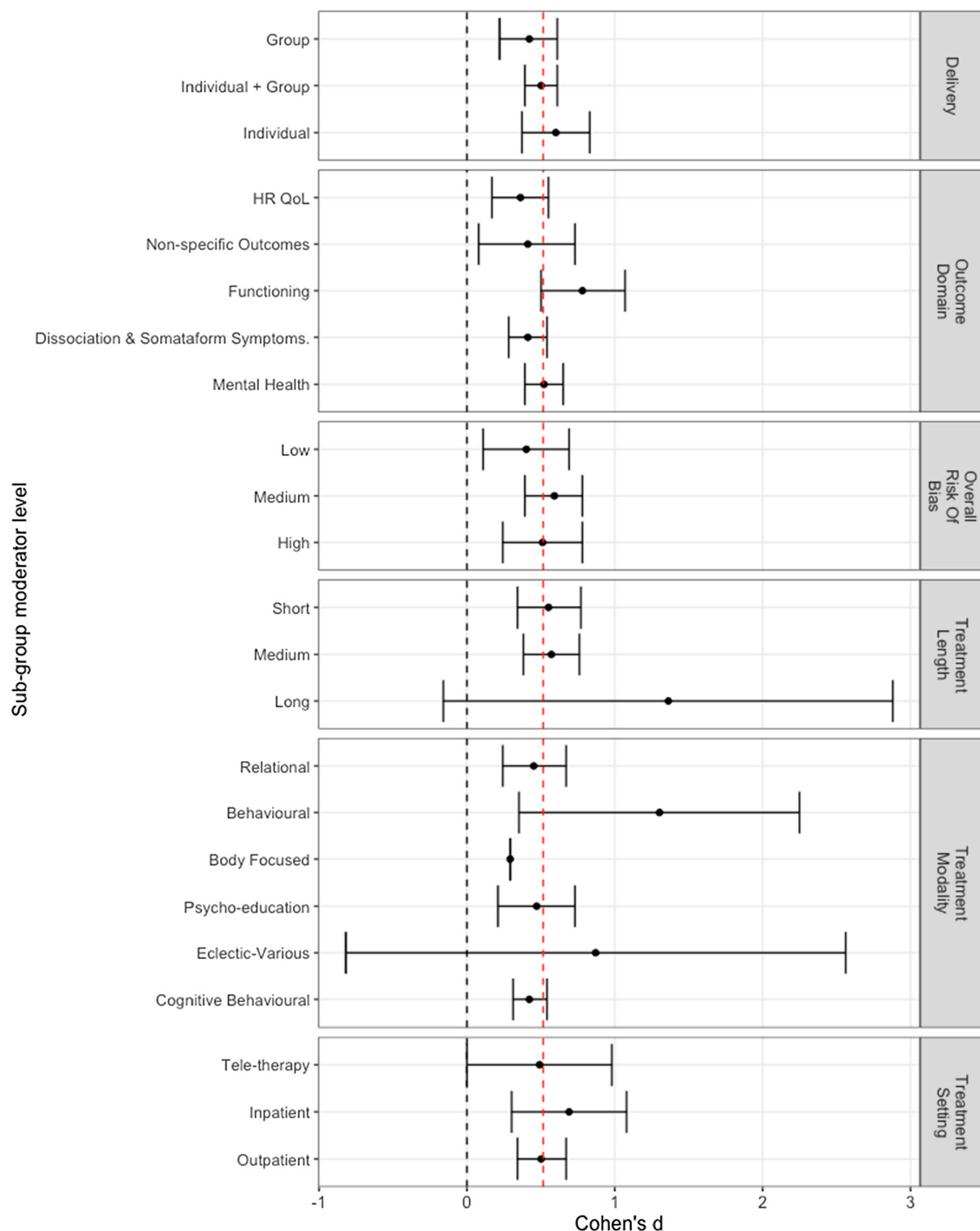


FIGURE 2 Forest plots of subgroup moderators included in the meta-analysis (black, dashed line denotes 0 [i.e., no effect], red line denotes the pooled average across all samples [i.e., $d = .51$]). HR-QoL = health-related quality of life.

funnel plot of effect sizes (Figure S1) and conducted an Egger's regression test for funnel plot asymmetry. The Egger's test was statistically significant ($\beta = .584$ [CI = .45–.72], $p = <.001$) indicating the potential for reporting biases of small-study null effects. The funnel plot shows a greater skew of outcomes to the right-hand side of the plot.

4 | DISCUSSION

Our analysis revealed that psychological treatment was associated with significant improvements across a wide range of outcomes, with a moderate mean effect size ($d = .51$). By accounting for statistical dependency through multi-variate meta-analytic exploration, this review is the

first systematic examination of variation in effectiveness between different outcome domains. It is difficult to compare our observed effect size with the results from the previous quantitative synthesis that specifically examined seizure frequency as an outcome of psychological therapy in this clinical group.⁹ That review focused on proportional change (commonly reported for seizure-frequency studies), which is a fundamentally different metric from the approach utilized here (standardized mean difference). An important next step for meta-analytic research in FDSs is to explore ways of synthesizing different forms of outcomes, including standardized mean differences (as is the convention for continuous outcomes such as questionnaires) and proportional change metrics (as is the convention for seizure frequency). However, although there is still value in examining reductions in seizure frequency, duration, and intensity, our meta-analysis reveals the sensitivity of broader markers of well-being to a range of different psychological interventions. The observed CIs did not demonstrate a negative value for the pooled effect size or the outcome domain subgroups, suggesting that psychological treatments are effective across a broad range of non-seizure outcome domains. The fact that these measures proved capable of demonstrating psychological treatment effects and that they are more closely related to patients' functioning and HR-QoL than seizure-related parameters suggests that they could be suitable as primary outcome measures.

Although the findings of this review are encouraging, it is noteworthy that the observed pooled effect size was smaller than that previously reported in meta-analyses of psychological treatment effects for other common mental health conditions (e.g., $d = .8-1.01$, 67). One explanation for this could be that the outcome measures captured in this meta-analysis are simply less sensitive to change in patients with FDSs. This may in part be due to confounds around baseline severity, chronicity, and limits to our current understanding around treatment mechanisms for FDSs. Because indices of FDS severity (e.g., frequency, duration, intensity) were not included in this meta-analysis (and could not be compared directly for methodological reasons), it is not possible to say to what degree changes in seizure-severity measures might explain the heterogeneity shown in individual effects observed on other measures. Moreover, none of the measures used were developed specifically for people with FDSs and generic measures may be less sensitive than those that are disorder specific. An alternative explanation is that the multivariate analysis, although highly inclusive of outcomes, produced a diluted result by virtue of including outcomes that are less salient across all patients. The decision for a clinical service to benchmark effectiveness using any given outcome measure is often based on an assumption that the construct

being measured is relevant to the population under study. This decision is more straightforward in conditions with less clinical heterogeneity. However, for FDSs it is much less clear which outcome is most salient. Clinically, not all patients with FDSs present with elevated rates of depression, anxiety, or dissociation at baseline, and, therefore, measuring change in these constructs at the group level may serve to miss changes at the individual level.³ Future research needs to explore the development of purposefully validated measures that can capture meaningful change across this highly heterogeneous condition.¹⁷ Indeed, one approach could be to develop a measure that triangulates the outcome of several measures, which reflects an overview of functioning while being specific to FDSs. Future work also needs to explore ways of including routine evaluation of change at the individual level, as opposed to simply the group level. An idiosyncratic approach to treatment evaluation is likely to offer novel insights into what changes during psychological interventions for FDSs when considered alongside the evidence generated by RCTs. Future research is also needed to establish more reliable methods of measuring seizure frequency as seizures are a core symptom of the disorder.

The moderator analysis indicated that psychological treatments were associated with greater improvements in overall functioning than in mental health outcomes, HR-QoL, dissociation and somatoform symptoms, and non-specific psychological outcomes. In other words, although psychological treatment was effective across all examined outcomes, it showed the greatest levels of effectiveness in allowing patients to engage with social, leisure, and occupational activities. Such behavioral engagement is likely to form a positive feedback loop regarding seizure-specific outcomes and could contribute to the improvements in seizure frequency previously shown to be associated with psychological treatments during the treatment phase.⁹

The moderator analysis revealed that behavioral treatments were associated with the greatest improvement effect sizes; however, these interventions represented the least commonly studied treatment modality (11% of the whole sample, $c = 4$). Furthermore, the studies were small and were, therefore, associated with the risk of small-study effects. The most assessed treatment was cognitive-behavioral interventions ($c = 18$, 73.3% of the total sample). This is consistent with the evidence base for psychological interventions for other conditions (including FNDs) and may reflect the relative ease with which such treatments can be operationalized, manualized, and delivered in the context of the demands of RCTs.⁶⁸ However, our examination of the effects of treatment modality did not appear to demonstrate any advantages of cognitive-behavioral treatments over the smaller number of relational ($k = 3$) and psychoeducation ($k = 5$)

interventions in terms of effectiveness, with small to medium effect sizes being observed across these therapeutic approaches. Of surprise to the authors was the absence of representation of several well-established models of psychological therapy (e.g., cognitive-analytic therapy [CAT], schema-focused therapy, mentalization-based therapy [MBT], systemic family therapy, and eye movement desensitization and reprocessing [EMDR]) that have been shown to be effective in complex trauma-related and dissociative disorders, which are frequently comorbid with FDSs. It is striking that practice-based evidence is yet to emerge for the use of these treatments. This is perhaps an artifact of the relatively small (albeit growing) community of psychological therapists providing services for patients with FDSs. Future research should explore the preference for, feasibility and patient acceptability, and effectiveness of non-cognitive-behavioral approaches in particular as additional treatments for patients who do not respond to first-line psychological interventions. There are useful frameworks to help explore acceptability of health interventions, such as the one proposed by Sekhon et al.,⁶⁹ which has seven domains: affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, and self-efficacy. However, the therapists delivering the intervention also need to view it as acceptable. Acceptability is both static and dynamic, as patient's and therapist's thoughts and feelings change with the actual experience of receiving or delivery treatment.

There is ongoing debate about the benefits and drawbacks of the delivery of psychological treatments in a stepped-care model, starting with the least intensive intervention.^{22,70,71} In such models, patients progress to more individualized and lengthier psychological interventions when their problems have proven unresponsive to lower intensity interventions or treatments requiring less provider expertise. The current findings support the delivery of relatively simple psychoeducational approaches initially to patients with FDSs; however, more research is needed to examine their efficacy. Our assessment identified no significant difference between individual and group therapy for FDSs. This supports the utility and organizational efficiency of group treatment programs in treatment pathway for FDSs.

The reliability of our findings in relation to the relative impact of treatment modality is reduced by the fact very few studies used a measure of treatment fidelity. Indeed, although authors defined treatments under investigation, descriptions of their content were often limited, and details of the delivering clinician, experience, and qualifications were often absent. This is unsurprising, given that fidelity measures tend to be routinely used only in definitive RCTs, of which there were only nine. Fidelity in psychological therapy has been shown to be an important

moderator of treatment outcomes.⁷² Although this limitation was partly considered in the assessment of the risk of bias (which did not moderate outcome), this is unlikely to be a sufficient replacement for a formal assessment of fidelity. Going forward, FDS outcome studies need to routinely index treatment fidelity so that there can be more certainty that the intervention delivered matched the treatment intended.

Some insights can be gleaned from other treatment characteristics, including duration/dose and service setting. Outcomes for treatments delivered over short (≤ 6 sessions) and medium (7–13 sessions) terms were comparable. The overall effect size was largest for longer treatments (≥ 14 sessions), but caution should be applied when interpreting this finding given the large variation in session length and outcomes. This has clear implications for service commissioning, as longer psychological treatments may be required in this clinical group due to challenges regarding symptom chronicity (treatment is often only provided several years after the diagnosis⁷³), acceptability of the diagnosis,⁷⁴ the need for trust to develop and for patients to overcome negative care experiences,⁷⁵ and high rates of interpersonal trauma characterizing this patient group.⁷⁶ This may help to explain the positive outcome we found for relational therapies, which tended to be longer.

Most interventions studied were delivered in outpatient settings ($c = 27$). Although this appeared more effective than tele-therapy ($c = 3$), more research is needed into the acceptability and efficacy of remote treatments. Inpatient settings were associated with the largest effects, perhaps reflecting the intensity of treatment delivered by specialized, multi-disciplinary teams. Although we did not investigate FDS severity or pre-treatment functioning as a moderator, it is possible that those who received inpatient treatment were the most unwell and, therefore, had the greatest potential to demonstrate change.

4.1 | Limitations

The key critique of this review is its reliance on effects sizes from uncontrolled studies. The decision to do so was informed by our aim to include cohort studies in order to maximize statistical power and generalisability. Because of this critique, we are unable to rule out alternative explanations for observed effect sizes (e.g., placebo effects, regression to the mean).⁷⁷ Although we would argue that regression to the mean is unlikely in this scenario given that symptoms have often persisted for long periods (typically for several years⁷⁸) between symptom onset, diagnosis, and psychological treatment.

Efforts to assess for systematic differences in effect sizes between studies showing different levels of risk of bias revealed no significant differences, which helps to mitigate, but not totally discount, this limitation. Furthermore, pooled uncontrolled effect sizes from observational studies serve as a valuable data source for benchmarking of routine care.^{79,80}

The GRADE approach highlighted issues with inconsistency across results, treatment comparisons, and some imprecision resulting in a meta-analytic comparison of moderate-to-low quality. The current review did not examine durability of treatment effects at follow-up. This is especially pertinent for inpatient treatments, where discharge to the home environment at the end of treatment is likely to be associated with particular challenges. Further research is needed to investigate the long-term effectiveness of psychological therapy for FDSs, particularly considering some evidence suggesting that outcomes may become more pronounced after therapy has ended.⁸¹ Indeed, it must be recognized that given that the end points of treatment varied across studies and were not always immediately at the end of therapy, the results may be an under- or overestimation of treatment effects due to delays in obtaining the post-treatment outcomes. Although we attempted to categorize treatment length and outcome domain pragmatically (recognizing there will be some degree of overlap), we acknowledge the arbitrary nature of this process and that it may be inconsistent with the description of treatment length in other conditions. Variables included in the meta-regression (i.e., continuous) were entered into the meta-analysis as mean study level averages. A problem with this approach is that it is inherently difficult to make inferences about individuals (i.e., variation in how they change) when based upon statistics that describe the group in which they belong to (i.e., ecological fallacy). The analysis of subgroup moderators may be underpowered. Future replications of this review will benefit from a larger pool of studies and also employing Bonferroni adjustments to account for the number of included moderator variables. Future research should seek to synthesize findings about how patients respond at the individual level (e.g., individual participant data meta-analysis). This was partly due to lack of reporting of this information in manuscripts, as well as the need to be selective of the number of moderator variables. Although we recognize the clinical and psychopathological heterogeneity of the patient group as a whole (and suspect that there may have been relevant differences between different study cohorts) we made no allowances for such differences (such as chronicity or complexity) in our analysis. Finally, we may have missed relevant articles as we did not include the word “therapy” alone in our search.

5 | CONCLUSION

Combined with the results of a previous meta-analysis focusing on seizure frequency, this meta-analysis provides further evidence that psychological therapy for FDSs is associated with modest improvements across a broad range of treatment outcomes. Further research is needed to explore treatment acceptability, durability (i.e., beyond the acute treatment phase), other psychotherapies, and development of tailored outcome measures for capturing change in this highly heterogeneous patient group.

AUTHOR CONTRIBUTIONS

CG: Review coordination, protocol and manuscript development, data analysis; he approved the final manuscript for submission. NP: protocol and manuscript development, coding support, and data analysis; he approved the final manuscript for submission. BN: protocol and manuscript development, systematic search, and data analysis; she approved the final manuscript for submission. MS-B: protocol and manuscript development, and data analysis; she approved the final manuscript for submission. MR: protocol and manuscript development; he approved the final manuscript for submission. SK: protocol and manuscript development; he approved the final manuscript for submission. GHR: systematic search and coding support, data analysis, and protocol and manuscript development; he approved the final manuscript for submission.

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CONFLICT OF INTEREST STATEMENT


The authors declare no conflicts of interest.

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*Denotes inclusion in the meta-analysis.

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