UNIVERSITY OF LIVERPOOL

Anxiety and Depression in People with Epilepsy

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Thanks to my magnificent fiancé, family and friends for your continued support. I'm looking forward to spending less time on my laptop and more time with you all.

"…Yes, you climbed on the ladder with the wind in your sails, you came like a comet, blazing your trail. Too far. Too soon. You saw the whole of the moon…" (Scott, 1985, track 2).

Reference

Scott, M. (1985). Whole of the moon. On *this is the sea* [CD]. Hastings, UK: Island Records

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Introductory Chapter

Chapter 1: Systematic Review

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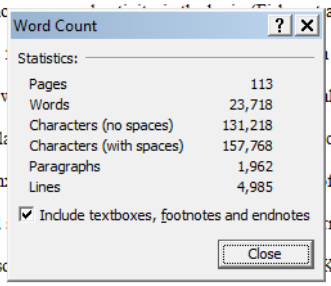
Epilepsy is a chronic neurological condition characterised by seizures from excessive or synchronc al., 2014) which affects approximately Organisation; WHO, 2017). People v lity of life (QOL) than the general popul chological difficulties, such as an f this, above that of seizure frequency and rmann, 2004) and the adverse effects assc Kwon & Park, 2011). The prevalence of anxiety and depression in PWE is significantly higher than in the general population, with up to 30% of PWE meeting diagnostic criteria for anxiety or depression (Rai et al., 2012) and several experiencing subclinical forms (Kanner, 2009). The negative effects of anxiety and depression for PWE means it is imperative that once identified, effective interventions should be implemented (Barry et al., 2008). Through offering two specific chapters, this thesis aimed to explore



Introductory chapter: Thesis overview

Epilepsy is a chronic neurological condition characterised by seizures from excessive or synchronous neuronal activity in the brain (Fisher et al., 2014) which affects approximately 50 million people worldwide (World Health Organisation; WHO, 2017). People with epilepsy (PWE) tend to have worse quality of life (QOL) than the general population (Kwon & Park, 2014). Co-morbid psychological difficulties, such as anxiety and depression are major detriments of this, above that of seizure frequency and severity (Johnson, Jones, Seidenberg & Hermann, 2004) and the adverse effects associated with anti-epileptic drugs (AED's) (Kwon & Park, 2011). The prevalence of anxiety and depression in PWE is significantly higher than in the general population, with up to 30% of PWE meeting diagnostic criteria for anxiety or depression (Rai et al., 2012) and several experiencing subclinical forms (Kanner, 2009). The negative effects of anxiety and depression for PWE means it is imperative that once identified, effective interventions should be implemented (Barry et al., 2008). Through offering two specific chapters, this thesis aimed to explore psychological interventions for anxiety and depression in PWE.

Chapter one details a systematic review of randomised controlled trials (RCT's) that had a primary aim to reduce symptoms of anxiety or depression in PWE using a psychological intervention. Through applying clinical significance criteria from Jacobsen and colleagues (Jacobson, Follette & Revenstorf, 1984; Jacobson & Truax, 1991) to individual patient data from these RCTs, it was sought to establish both the relative and absolute efficacy of psychological interventions for anxiety and depression in PWE to help inform clinical practice. To set the path for the review, the introduction offers evidence on the prevalence and detrimental effects of anxiety and depression in PWE, why psychological interventions are of particular importance for

PWE, and how previous systematic reviews have left several critical questions concerning the effectiveness of treatments unanswered.

Following this a methods section states how studies were selected for the review and how the data was analysed from the studies. The chapter then goes on to synthesise the results of the review. These showed that all studies contained methodological limitations and when their individual patient data was subjected to Jacobsen criteria (Jacobson, Follette & Revenstorf, 1984; Jacobson & Truax, 1991), the rate of participants classed as 'treatment responders' was low and the vast majority of participants made 'no reliable change' after psychological intervention. The review did not fully meet its initial aim as no calculation of the absolute efficacy of psychological interventions for anxiety was undertaken. This was due to no individual patient data on a primary outcome of anxiety being available. All studies primary aim was to reduce depression symptoms in PWE and all used a form of CBT as their intervention. As the review found limited efficacy for this intervention in PWE rationale was provided for exploring the scope of alternative psychological interventions for anxiety and depression in PWE.

Building on these findings, chapter two details an empirical study exploring the utility of an alternative psychological model in explaining anxiety and depression in PWE, the Self-Regulatory Executive Function (S-REF) model (Wells & Matthews, 1994). This is a transdiagnostic model which states maladaptive metacognitive beliefs and processes are fundamental in the development and maintenance of emotional distress, such as anxiety and depression. The model has initial support for its applicability to anxiety and depression in PWE (Fisher, Cook & Noble, 2016, Fisher & Noble, in press). This study aimed to advance evidence for using the S-REF model with PWE

through comparing its explanative ability against, illness perceptions, a well-known theoretical model for anxiety and depression in PWE.

The study was an online cross-sectional design and involved 457 participants. A detailed methods section explains the recruitment procedure, data collection and analytical process used in the study. This is followed by the results section which offered further support for the applicability of the S-REF model in anxiety and depression in PWE by showing metacognitive beliefs explained additional variance in anxiety and depression after accounting for the control variables, including illness perceptions. Also, the central principle of the S-REF model was supported regarding the mediational role of the cognitive attentional syndrome (CAS) between metacognitive beliefs and anxiety and depression. Limitations of the study are then acknowledged before the chapter finishes with a discussion of the implications of the findings.

Both chapters were written with the intention of obtaining publication in the journal 'Epilepsy and Behavior'. As such the structure and format of the chapters adheres to the specific guidelines stated by this journal (Appendix 1).

The author would like to make the reader aware that for the empirical paper in chapter two both cross-sectional and longitudinal data (three month follow-up) was collected from participants. However, only the cross-sectional data was used in the final stated analyses in the empirical paper. The original proposal for the study was to use longitudinal data to conduct a prospective test of the S-REF model. This would better establish causal inferences than a cross-sectional design. However, there was a low rate of response from participants at the second time-point which made solely using the cross-sectional data as the most justifiable option. The data collection process

highlighted the challenges of using longitudinal designs and has given the student investigator chance to reflect on how to reduce sample attrition in longitudinal designs in their future research. The unused longitudinal data will be considered by the student investigator and their supervisors for future analyses.

In summary, through adopting two contrasting methodologies detailed here in two separate chapters the thesis achieved its aims of exploring psychological interventions for anxiety and depression in PWE, and in the process, added illuminating evidence. The findings demonstrate there was limited efficacy for the psychological treatments used in RCTs. Interestingly all RCTs used cognitive behavioural therapy (CBT), which is the most frequently recommended psychological intervention for anxiety and depression in PWE (Kerr et al., 2011). This suggests it is essential to explore the potential of alternative psychological approaches. This was achieved in chapter two where further support for the applicability of the S-REF model in anxiety and depression in PWE was found.

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Are psychological interventions effective for anxiety and depression in people with epilepsy?

Chapter 1: Systematic Review

For submission to Epilepsy and Behavior (Author Guidelines in Appendix 1)

Abstract

Purpose: Psychological interventions, such as cognitive behavioural therapy are recommended for PWE experiencing clinical levels of anxiety and/or depression. However, controlled trials of psychological interventions and subsequent systematic reviews have only focused on the relative efficacy and have neglected the absolute efficacy of interventions, thus leaving many questions of efficacy unanswered. Establishing the absolute efficacy of an intervention should be an integral component of evidence-based practice. To address this limitation, an individual patient data review of the clinical significance of psychological interventions for PWE with anxiety and/or depression was conducted.

Methods: Eight eligible trials were identified, five of which supplied individual patient data (IPD) by treatment condition on the primary outcome variable. A Reliable Change Index (RCI) was calculated for each trial and used to classify if the symptom change demonstrated by each individual represented a 'reliable improvement' (treatment responders), 'no reliable change', or a 'reliable deterioration' on the primary outcome measure.

Results: The overall rate of treatment responders across studies was low, with an average of 24% for those individuals defined as treatment completers. The percentage of treatment responders between studies ranged from 6% to 37%. The majority of individuals made no reliable change after intervention, with an average of 74% across studies (range 58-94%). An average of 2% of individuals across studies made a 'reliable deterioration' post intervention (range 0%- 6%). There was a calculation of the absolute efficacy of psychological interventions for depression but not for anxiety as no individual patient data on a primary outcome of anxiety was available.

Conclusion: The findings indicate that psychological interventions are of limited efficacy for depression in PWE. The efficacy of psychological interventions for anxiety in PWE remains less clear, as it was not possible to calculate this in this study. All studies in the review used a form of cognitive behavioural therapy. Alternative psychological approaches for anxiety and depression in PWE should be explored, potentially using CBT as the control condition.

Keywords

Epilepsy, anxiety, depression, clinical significance

1. Introduction

Anxiety and depression are common co-morbid conditions for people with epilepsy (PWE). Epidemiological studies report 9-37% of PWE meet diagnostic criteria for depression and 11-25% meet diagnostic criteria for an anxiety disorder [1]. Such figures may though underestimate the scale of the problem as several PWE experience subclinical levels of anxiety and depression [2]. It is now well known that the presence of anxiety and/or depression is associated with poorer outcomes. For instance, PWE experience a poorer quality of life (QOL) [3,4], more perceived epilepsy-related stigma [5], more suicidal ideation and are at an increased risk of suicide [6,7] compared to PWE without anxiety and/or depression. Furthermore, PWE who experience anxiety and/or depression respond poorer to surgical treatments for epilepsy [8], report more side effects of antiepileptic drugs (AEDs) [9], and are almost three times less likely to achieve seizure freedom with AEDs [10].

Psychological factors are consistently associated with anxiety and depression in PWE [11,12] and may be modifiable by psychological interventions. Cognitive behavioural therapy (CBT) is endorsed by the international consensus clinical practice [13] for the treatment of anxiety and depression in PWE. The National Institute for Health and Care Excellence (NICE) recommends CBT as a psychological intervention associated with improving the quality of life in PWE [14]. However, the evidence base for CBT and other psychological interventions is questionable. Ramaratnam, Baker & Goldstein's Cochrane review [15] concluded there was insufficient evidence to support any type of psychological intervention for reducing emotional distress in PWE. Recent reviews are more optimistic and suggest psychological interventions elicit greater reductions in anxiety and depressive symptoms relative to control conditions [16-18].

A major limitation to date in terms of how interventions have been evaluated by both trials and subsequent reviews is that there has been an almost sole focus on the relative efficacy of a treatment when compared to control/comparator interventions, and a lack of consideration as to the clinical relevance of the change in symptoms. Relative efficacy is typically based on a comparison of group means and provides no information on the variability of response to interventions within a sample, such as the proportion of individuals in each condition who have deteriorated, not changed, and those who have improved or recovered [19]. A clinical significance analysis of treatments accounts for this through assessing both relative and absolute efficacy. This is essential to evidence based practice as it can provide clear evidence of treatment efficacy allowing clinicians and service users to make informed decisions about which interventions to choose [20,21].

The most established method for determining the clinical significance of interventions is that of Jacboson and colleagues [22,23]. According to such criteria, for an individual to be classed as having recovered or demonstrated a clinically significant change in the target symptoms, the individual's scores on the outcome measure of choice must meet two criteria: i) the change in symptom level from pre- to post-treatment must be 'statistically reliable', i.e. beyond that which could be accounted for by measurement error , and ii) their post treatment outcome score must be in a range that renders them indistinguishable from a 'well' population.

A cursory examination of the baseline levels of distress of PWE in some trials of psychological intervention [24,25] shows there is substantial variability. Many trials have not had explicit inclusion criteria with regards baseline distress and have included PWE who were not clinically distressed upon recruitment, as well as PWE who were. This may explain why some studies have not examined the clinical

significance of the change elicited by interventions in their trials because, as outlined above, to qualify as clinically significant Jacobson's criteria requires the change be reliable, but also be sufficient to move the persons score from a 'clinically unwell' population to that of a 'well' population.

The variability in baseline distress levels of participants in the trials limits examinations of the relevance of symptom change associated with psychological interventions for PWE. It is though possible to begin to gauge the level of change by seeing to what extent the change in symptoms is, according to Jacobson's first criteria, statistically reliably. Specifically, having obtained individual patient data (IPD) from the original trial, one can determine for which participants their change in symptoms was beyond that which could be accounted for by error associated with the outcome measure. It can then reliably calculate the proportion who can be defined as 'treatment responders' (those that demonstrated a 'reliable improvement'), those who show 'no reliable change', and those who show a 'reliable deterioration' on an outcome measure. Using these methods, this review aimed to establish the absolute efficacy of psychological interventions for anxiety and depression in PWE. This would help provide more conclusive evidence, which in turn will help inform clinical guidelines for treating anxiety and depression in PWE.

2. Method

The review followed guidance set out in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [26].

2.1. Study selection

Medline, PsycINFO, PsycARTICLES, CINAHL plus, AHMED, clinicaltrials.gov, EThOS and SIGLE were searched from inception to March 2017

using Medical Subject Headings (MeSH) terms and keywords to identify psychological intervention trials for anxiety and depression in PWE. Combinations of terms associated with psychological interventions, emotional distress, and epilepsy were used. The final search strategy used for PsycINFO (Table 1) was adapted for each electronic database. To ensure a comprehensive search, reference lists and relevant meta-analyses were hand-searched for additional studies.

Table 1: PsycINFO search terms

Order	Search term
1.	epilep*
2.	AND depress* OR anxi* OR mood OR 'quality of life'
3.	AND therap* OR interven* OR treat* OR rehab* OR psycho*OR cognitive*
4.	AND trial OR random*

To be included studies had to meet the following criteria:

1. Random assignment to two or more psychological treatments or control conditions.
2. They involved PWE aged 18 or above.
3. They used a standardised outcome measure of anxiety and/or depression as their primary outcome.

To obtain IPD the lead authors in the studies that met inclusion criteria were contacted by e-mail (Appendix 2). If no reply was received after three weeks a second e-mail was sent. After this, an attempt was made to contact the other authors in the studies by e-mail.

2.2. Data extraction

A data extraction form was developed to extract relevant characteristics and data (Appendix 3). This included sample demographics, treatment conditions,

inclusion criteria, attrition rate and an analysis of group x time interaction for the outcome measures.

2.3. Quality assessment

The PEDro-P scale [27] (Appendix 4 and 5) quality assessment tool was utilised to evaluate the methodological rigour and guide interpretation of the reliability and validity of results. The PEDro-P is a version of the PEDro scale which was modified specifically for the analysis of treatment trials for neurological disorders. The original PEDro scale is based on the Delphi list developed by Verhagen et al. [28]. It has demonstrated reliability for assessing RCT quality [29] and was used in a recent systematic review of psychological treatments in PWE [16]. The scale contains one question assessing external validity and ten assessing internal validity, all items are scored as yes (1) or no (0) to give an overall trial quality score.

A second reviewer (PHR) undertook the study selection, data extraction and quality assessment. In the study selection process, after the lead investigator had initially excluded studies through screening titles and abstracts the second reviewer independently assessed the remaining studies against the inclusion criteria. Using the same measures as the lead investigator the second reviewer performed the data extraction and quality assessment processes on a random selection of 50% of the studies that were deemed eligible. The lead investigator and second reviewer cross-checked results and inconsistencies were resolved. It was pre-agreed unresolved inconsistencies would be adjudicated by a third reviewer.

2.3. Clinical significance analysis

Jacobson's reliable change index (RCI) [22,23] was utilised. The RCI was calculated using the following formula for each study:

$$RCI = \frac{X_2 - X_1}{S_{diff}} \text{ where } S_{diff} = \sqrt{2S_E^2} \text{ and } S_E = S_1\sqrt{(1 - r_{xx})}$$

An RCI greater than ±1.96 is required for reliable change [22,23], change exceeding 1.96 times the standard error is unlikely to occur no more than 5% of the time by unreliability of the measure alone. Waitlist data were also analysed to offer baseline estimates of the degree of improvement due to factors other than therapy, such as spontaneous recovery or regression to the mean.

3. Results

3.1. Study selection

The search retrieved 1280 studies (Figure 1). An additional three papers were identified through hand search. After removal of duplicates, 580 remained for screening based on title and abstract. Of these, 564 clearly did not meet the inclusion criteria. The full text articles of the remaining 16 studies were retrieved and assessed against the inclusion criteria. Eight studies were excluded for reasons shown in Figure 1, there were no inconsistencies in the main investigator and second reviewer's study selections.

As of March 2017, eight studies were eligible for inclusion. Of these eight studies, only five studies provided individual patient data, these are described in Table 2. Individual patient data for the following studies was not made available by the original investigators:

1. Davis, Armstrong, Donovan and Temkin [30]
2. Tan and Bruni [31]
3. McLaughlin and McFarland [32]

These studies are described in Table 3.

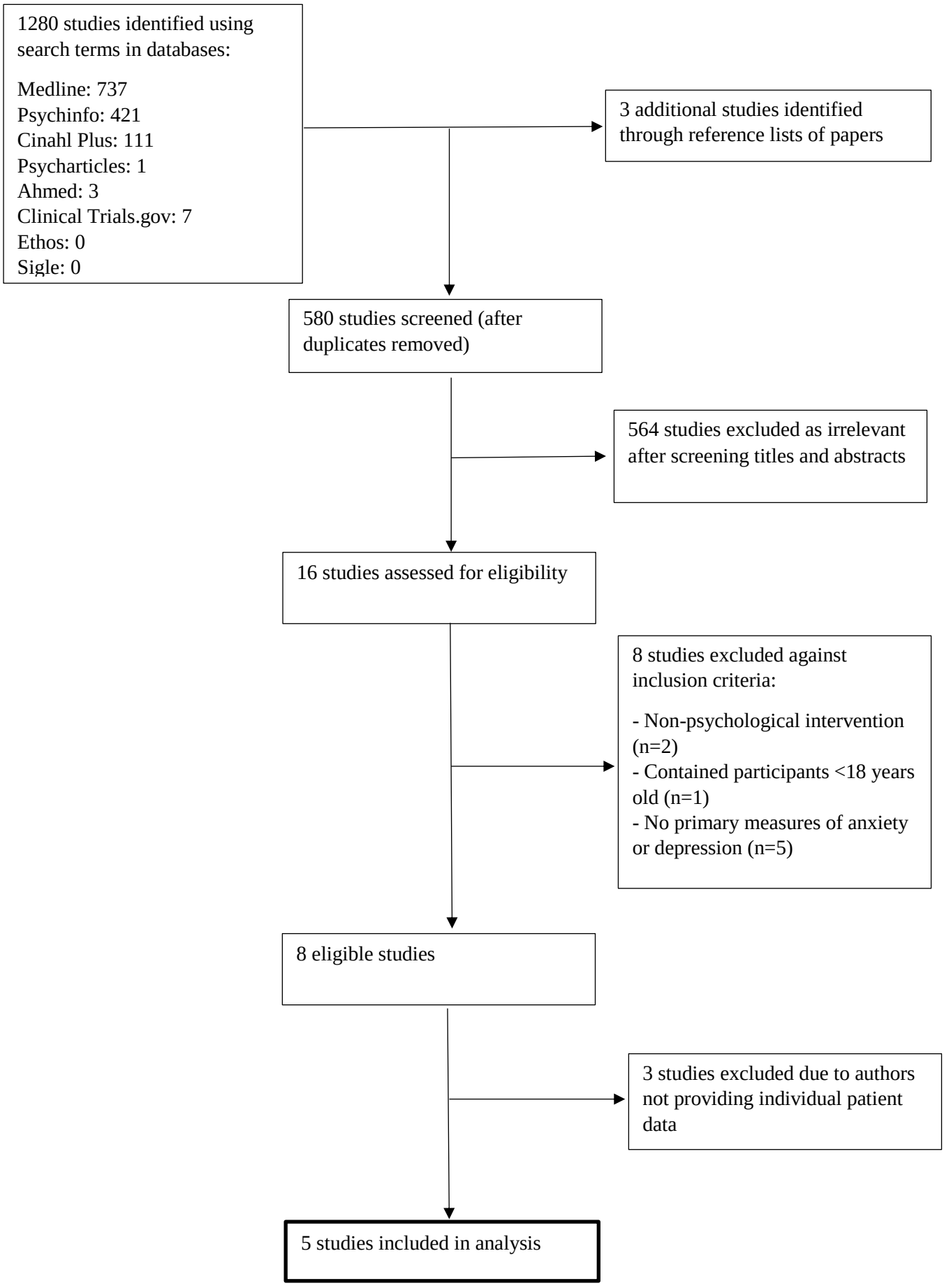

Figure 1 PRISMA diagram summarising the screening process for the included studies

Table 2
Characteristics of studies included in the review

Author (year, country),	**Conditions** (type, delivery, dosage)	**Sample**: (size), (age mean years, S.D), female %	**Inclusion criteria** (epilepsy criteria, baseline distress level, age)	**Attrition** %	**Primary measure of depression or anxiety** (when measured, group x time interaction effect size, sig)
Thompson et al.[24] (2010, U.S.A)	**CBT + M** (group therapy, phone or internet delivery by layperson with epilepsy and RA , 8x 1 hour sessions,)	CBT +M: (n=26), (36.4, 34), 77%	(One year post DX, scores on CES-D = >13 - <38, ≥21 years old	CBT +M = 25%	mBDI (baseline-post, F int = 11.99, P =0.01)
	TAU	TAU: (n= 27), (35.4, 31), 85%.		TAU =25%	
Ciechanowski et al. [25] (2010, U.S.A)	**CBT** (individualised face-to-face, home delivery by 2 SWs, 8 x 50 minute sessions)	CBT: (n= 40), (43.4, 11.0), 47.5%	(ICD-9 criteria, scores on PHQ-9 = ≥10, ≥18 years old)	CBT, post = 20%, 12 month FU = 12.5%, 18 month FU =25%	HSCL-20 (baseline-post, t =1.70, p=0.09, baseline- 12 month FU, t = 3.15, p =0.003, baseline-18 month FU, wald x^2= 4.00, P=0.046)
	TAU	TAU: (n= 40), (44.4, 11.1), 57.5%		TAU, post = 17.5%1 2 month FU = 30%, 18 month FU = 30%	
Schroeder et al. [33] (2014, Germany)	**CBT + M + ACT** (individualised, online simulated dialogue, 9 weeks)	CBT + M + ACT: (n= 40), (40, 1.85), 80%	(Self-reported epilepsy and depression symptoms on the PESOS, ≥18 years old)	CBT = 27%,	BDI (baseline-post, d = 0.46, p = 0.01)
	WLC	WLC: (n =38), (35, 9.99), 71%		WLC = 20%	

Gandy et al. [34] (2014, Australia)	**CBT** (individual face-to-face, delivered by psychology doctorate students, 9 x1 hr sessions)	CBT: (n=31), (41, 12), 50%	(ILAE criteria, scores on the NART = ≥80, ≥18- ≤65 years old)	CBT= 39%	NDDI-E (baseline-post, d = 0.6, p = 0.045, baseline- 3 month FU, d= .39, p= 0.134)
	WLC	WLC: (n=28), (38 , 13), 76%		WLC = 11%	
Thompson et al. [35](2015, U.S.A)	**CBT + M** (group therapy, phone or internet delivery by layperson with epilepsy and RA, 8x 1 hr sessions)	CBT +M: (n=64), whole sample age = (41, NR), whole sample females = 65.3 %.	(Three months post DX, scores on CES-D = >8 - <27, ≥21 years old)	CBT +M = 36%	mBDI (baseline-post, F int = 4.67, P =.036)
	TAU	TAU: = (n = 64)		TAU = 12.5%	

ACT, Acceptance and Commitment Therapy; **BDI**, Beck Depression Inventory; **CBT,** cognitive behavioural therapy, **CES-D**, Center for Epidemiological Study of Depression measure; **DX**, diagnosis **FU**, follow-up; **HSCL-20,** Hopkins Symptom Checklist-20; **ICD-9**, International Classification of Diseases Ninth Revision; **ILAE**, International League Against Epilepsy; **M,** mindfulness; **mBDI**, Modified Beck Depression Inventory; **NART**, National Adult Reading Task; **NDDI-E**, Neurological Disorders Depression Inventory for Epilepsy; **NR**, not reported; **PESOS**, Performance Sociodemographic Aspects Subjective Estimation; **PHQ-9**, Patient Health Questionnaire-9; **RA**, research assistant; **SWs**, Social Workers; **TAU**, treatment as usual; **WLC** ,waitlist control.

Table 3
Characteristics of eligible studies not supplying individual patient data

Author (year, country),	**Conditions** (type, delivery, dosage)	**Sample**: (size), (age mean years, S.D), female %	**Inclusion criteria** (epilepsy criteria, baseline distress level, age)	**Attrition** %	**Primary measure of depression or anxiety** (when measured, group x time interaction effect size, sig)
Davis et al. [30] (1984, U.S.A)	**CBT** (group therapy, delivered by 2 SWs, 6x 2 hour sessions,)	CBT: (n=8), age = (33.5,11), females = 87.5%	(NS, self-reported depression symptoms, ≥18 years old)	CBT = 0%	DACL (baseline-post, NS, 'non-significance' reported)
	WLC	WLC: (n= 5), age = (32.4, 9.5), females = 60%		WLC =10%	
Tan and Bruni [31] **(**1986, U.S.A)	**CBT** (group therapy, delivered by CP, 8 x 2 hour sessions)	CBT: (n= 8), total sample age = (33.4, 11.1), females = 62.5%	(Confirmed DX, depression symptoms on GRPA-T—GRPA-N, GRPA –P , ≥18 years old	CBT = 20%,	BDI (baseline-post, NS, 'non-significance' reported)
	AP (group supportive counselling, delivered by CP, 8 x 2 hour sessions)	AP (n= 10), females = 60%		AP = 0%	
	WLC	WLC: (n= 9), females = 67%		WLC = 10%%	
McLaughlin and McFarland [32] (2011, Australia)	**CBT** (group, delivered by CP, 6 x2 hour sessions)	CBT (n= 18), age = (67.56, 7.27), females = 56%	(Confirmed DX, self-reported depression symptoms and >24 on MMSE, age of ≥60	CBT = 0%,	GDS (baseline-post, NS, 'non-significance reported, baseline-3 month FU, NS, 'non-significance' reported)
	TAU	TAU: (n =19), age = (67.37, 7.46), females = 47%		TAU = 0%	

AP, attention placebo; **BDI**, Beck Depression Inventory; **CBT**, cognitive behavioural therapy; **CP**, Clinical Psychologist; **DACL**, Depression Adjective Checklist form E; **DX**, diagnosis; **FU**, follow-up; **GDS**, Geriatric Depression Scale; **GRPA**, Global Ratings of Psychological Adjustment; **T**—Therapist; **N**—Neurologist; **P**—Patient; **MMSE**, Mini Mental State Examination; **NS**, not stated; **SWs**, Social Workers; **TAU**, treatment as usual; **WLC** ,waitlist control.

3.1. Study characteristics

Table 2 summarises the characteristics of the five studies in the review. One study [25] had a long term follow-up published in a separate study [36]. The studies included a total of 384 participants (initially allocated to studies). The average number of participants in each study was 76.8 (SD: 32.4, range: 45-128). Most participants across the studies were female (n=257; 67%) with a mean of 68% per study (range: 53%-81%). Participants mean age was 39.4 years (SD: 3.41).

Each study's primary aim was to reduce depression symptoms using a psychological intervention. The outcome measures utilised to assess this were the Beck Depression Inventory (BDI) [37] by Schroeder et al. [33], the Hopkins Symptom Checklist-20 (HSCL-20) [38] by Ciechanowski et al. [25], the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) [39] by Gandy et al. [34] and a Modified Beck Depression Inventory (mBDI) [40] by Thompson et al. [24,35]. No study's primary aim was to reduce symptoms of anxiety, one study had a secondary outcome measuring anxiety [34]. On average, post treatment outcome measures were administered 12 weeks (range: 8-26 weeks) after administering baseline outcome measures. The average attrition rate at first 'post condition' outcome measure was 23% (SD: 9.7, range: 11%-36 %).

To meet eligibility, some studies required participants to have epilepsy conditions according to International Classification of Diseases, Ninth Revision (ICD-9) [41] criteria [25], another specified International League Against Epilepsy (ILAE) [42] criteria [34] . Other studies stated participants were at least three months [35] or at least one year post epilepsy diagnosis [24]. One study [33] required participants to have epilepsy validated by the Performance Sociodemographic Aspects Subjective Estimation (PESOS) [43] questionnaire. All studies stated baseline levels of depression required for eligibility.

Ciechanowski et al. [25] required participants to have clinically significant depression validated by the Patient Health Questionnaire-9 (PHQ-9) [44]. Thompson et al. (2010) [24] used the Center for Epidemiological Study of Depression measure (CES-D) [45] to identify those with major depressive disorder and exclude those with severe depression. The CES-D was used again by Thompson et al. in 2015 [35] to specify participants with mild-moderate symptoms and exclude those with moderate-severe symptoms of depression. Schroeder et al. [33] included participants with any self-reported depression symptoms on the PESOS questionnaire [43] and Gandy et al's [34] participants did not require any symptoms of depression to be eligible.

3.2. Interventions

All studies comprised one control and one intervention arm. Each study used a form of cognitive behavioural therapy (CBT) for depression in their intervention arm. Thompson et al in 2010 [24] and in 2015 [35] delivered CBT with mindfulness practices to a group via telephone or the internet compared against treatment as usual (TAU) group who were contacted weekly by study facilitators to control for interaction with the project staff. In the Thompson et al. 2010 [24] study TAU group, at baseline 33% of participants were undertaking psychotherapy and 37% were using antidepressants. This was not statistically significantly different to the intervention group (17% psychotherapy; 39% antidepressants). Thompson et al's. 2015 [35] TAU group also contained participants in psychotherapy and/or using anti-depressant medication. No figures reported the frequency of this, although the authors did report no statistically significant differences between intervention and TAU groups at baseline on these variables.

Ciechanowki et al. [25] compared face-to-face CBT (labelled: Program to encourage active, rewarding lives for seniors: PEARLS) delivered in the participants home against a

TAU group. At baseline this TAU group contained 40% of individuals on antidepressants and 17.5% on psychoactive drugs, this was not statistically different to the intervention group (37.5% on antidepressants, 17.5% on psychoactive drugs). However, the number of participants taking antidepressants likely increased in both groups during the study, as study protocol dictated the study's psychiatrist should contact the neurologist of any participant showing no improvement on the primary outcome measures at 4-5 weeks to recommend starting or adjusting antidepressants. There were no reported figures on this. Gandy et al. [34] compared individualised face-to-face CBT delivered in a clinic against a waitlist control (WLC) group. Here 15% (intervention) and 17% (WLC) of each group were taking antidepressants at baseline. Schroeder et al. [33] used an online simulated dialogue technique to compare CBT with mindfulness and acceptance and commitment therapy (ACT) (labelled: Deprexis) against a WLC group. Participants in both conditions were using another form of depression therapy (Intervention: 46%, WLC: 50%) and/or taking antidepressants (Intervention: 17%, WLC: 20%) at baseline.

Interventions were delivered by a research assistant and a layperson with epilepsy [24, 35], psychology doctorate students [34] and social workers [25]. These facilitators received regular supervision from either a clinical psychologist [24,34,35] or a psychiatrist [25]. One study required no direct facilitation [33]. The mean amount of treatment sessions for each trial was 8.4 (SD: 0.54, range: 8-9), with an average of 8.1 hours treatment delivery per intervention (SD: 1.1, range: 6.4-9).

3.3. Outcomes reported by studies- Relative efficacy

Four studies reported statistically significant differences in their primary outcome measures between intervention and control conditions from pre-post treatment, Thompson et al. [24] (mBDI, F int = 11.99), Gandy et al. [34] (NDDI-E, d=0.6), Schroeder et al. [33]

(BDI, d = 0.46;) and Thompson et al. [35] (mBDI, F int = 4.67). Ciechanowski et al. [25] reported statistically significant results at 12 month follow up (HSCL-20, t =3.15) which persisted to 18 month follow-up (HSCL-20, wald x^2= 4.00) [39]. These results are stated in Table 3.

3.4. Clinical significance analysis

Table 4 details the RCI calculation for each study and Table 5 contains the percentage of participants within each Jacobson treatment outcome at post treatment and follow-up. Across studies, on average 23.5% (range: 6.3%- 36.8%) of participants were treatment responders, 2.2% (range 0%-5.8%) made reliable deterioration and 74.3% (range 57.8%-93.7%) made no reliable change post-treatment.

When considering studies separately, Thompson et al. [24] achieved the highest rate of treatment responders (36.8%), followed by Schroeder et al. [33] (28%), Gandy et al. [34] (25%), Thompson et al. [35] (21.2%) and finally Ciechanowski et al. [25] (6.3%). The percentage of participants classed as making no reliable change post-treatment condition was, in descending order, Ciechanowski et al. [25] (93.7%), Gandy et al. [34] (75%), Thompson et al. [35] (73.1%), Schroeder et al. [33] (72%) and Thompson et al. [24] (57.8%).

Two studies reported follow-up data, Ciechanowski et al's. [25] rate of treatment responders in their treatment condition rose slightly at both 12 month (9.7%) and 18 month [36] (7.7%) follow-up, as did Gandy et al's [34] treatment condition at three month follow up (26.3%). Two studies contained participants who reliably deteriorated post treatment, Thompson et al. [24] (5.3%) and Thompson et al. [35] (5.8%). TAU conditions showed treatment responder rates of 28.8% [24], 5.4% [35] and 3% [25] and WLC conditions rates of 8% [34] and 6.2% [33].

Table 4
Data used to determine the RCI for each primary outcome for each study

Symbol	*Definition*	*Measure:*	*mBDI [40]*	*HSCL-20 [38]*	*BDI [37]*	*NDDI-E[39]*	*mBDI [40]*
		Author:	*Thompson et al.*	*Ciechanowski et al.*	*Schroder et al.*	*Gandy et al.*	*Thompson et al.*
			[24]	*[25]*	*[33]*	*[34]*	*[35]*
		N	*40*	*65*	*57*	*45*	*108*
S_1	*Standard deviation for sample at pre-treatment*		*12.50*	*0.6*	*10.37*	*3.58*	*9.41*
X_1	*Pre-treatment score of an individual*		-	-	-	-	-
X_2	*Post-treatment score of an individual*		-	-	-	-	-
r_{xx}	*Reliability of the scale*		*0.88*†	*0.85*††	*0.86**	*0.85***	*0.88*†
S_E	*Standard error of measurement for the scale*		*4.33*	*0.55*	*3.88*	*1.38*	*3.25*
S_{diff}	*Standard error of difference between the two test scores*		*6.12*	*0.77*	*5.48*	*1.96*	*4.60*
RCI	*Reliable change index*		*12.00*	*1.52*	*10.75*	*3.84*	*9.02*

BDI, Beck Depression Inventory; **HSCL-20,** Hopkins Symptom Checklist-20; **mBDI**, Modified Beck Depression Inventory, Mindfulness; **NDDI-E**, Neurological Disorders Depression Inventory for Epilepsy.

† Internal consistency for mBDI [40]

†† Internal consistency for HSCL-20 [38]

* Internal consistency for BDI [37]

** Internal consistency for modified NDDI-E [39]

Table 5
Participants allocated to Jacobson categories at post-treatment and follow-up

Study Treatment	Pre-post treatment*				Pre- to follow-up**				Pre- to follow-up***			
	N	No change (%)	Deteri-orated	Improved	N	No change	Deteri-orated	Improved	N	No change	Deteri-orated	Improved
Thompson et al. [24]												
CBT + M	19	57.8	5.3	36.8								
TAU	21	66.6	4.8	28.8								
Ciechanowski et al. [25]												
CBT	32	93.7	0	6.3	31	90.3	0	9.7	26	92.3	0	7.7
TAU	33	93.9	3	3	28	100	0	0	26	96.2	3.8	0
Schroeder et al. [33]												
CBT + M + A	25	72	0	28								
WLC	32	90.6	3.1	6.2								
Gandy et al. [34]												
CBT	20	75	0	25	19	73.7	0	26.3				
WLC	25	80	12	8	23	78.3	8.7	13				
Thompson et al. [35]												
CBT + M	52	73.1	5.8	21.2								
TAU	56	87.5	7.1	5.4								

***** Thompson et al. [24,35]- 8 weeks, Schroeder et al. [33]- 9 weeks, Gandy et al. [34]- 2 months, Ciechanowski et al. [25]- 6 months
****** Gandy et al. [34] - 3 months, Ciechanowski et al. [25]- 12 months
******* Chaytor et al. [36] – 18 months

3.4. Quality assessment

The results of the quality assessment are detailed in table 6. All studies scored one for external validity, as all specified eligibility criteria. The average internal validity score was 6 (range 5-7) which is classed as 'fair quality' [27]. All studies used random allocation methods and concealed treatment allocation. Only two studies used blind assessors [25,33] and none of the studies blinded participants or therapists. All studies reported a statistical comparison of interventions between groups and reported point measures and measures of variability. All of the studies had an attrition rate during treatment above 15% in at least one of their conditions. Only one study [24] did not report an intention to treat analysis.

Table 6
Quality assessment results

Study reference	Eligibility criteria specified	Subjects randomly allocated	Treatment allocation concealed	Groups similar at baseline	Blinding of subjects	Blinding of therapists	Blinding of assessors	Measures obtained from more than 85% of subjects initially allocated to groups	Subjects received treatment as allocated or data analysed by 'intention to treat'	Between-intervention group statistical comparisons reported	Point measures and measures of variability reported	Total score
Thomspon et al. (2010) (24)	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	5
Ciechanowski et al. (2010) (25)	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	7
Schroeder et al. (2014) (33)	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	7
Gandy et al. (2014) (34)	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	6
Thompson et al. (2015) (35)	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	6

4. Discussion

Although recent systematic reviews exploring the efficacy of psychological interventions for anxiety and depression in PWE suggest that psychological treatments can help alleviate emotional distress [16-18], these suggestions are based on the relative efficacy of treatment compared to control conditions. As yet, the absolute efficacy of psychological treatments for emotional distress in PWE have not been reported. In consideration of this Jacobson and colleagues [22,23] clinical significance criteria was applied to psychological interventions for anxiety and depression in PWE. Specifically, the reliable change index (RCI) was used to calculate the proportion of individuals who can be defined as i) 'treatment responders' (those that demonstrated a 'reliable improvement'), ii) showing 'no reliable change', and iii) showing a 'reliable deterioration', on each studies primary outcome measure. As most studies did not specify clinical levels of emotional distress as an inclusion criteria, it was not possible to determine if participants were more likely to have scores from a 'well' population following therapy.

Results showed the majority of PWE in psychological treatment conditions could not be classified as treatment responders. The amount of treatment responders ranged from 36.8% in a telephone/internet group delivered CBT and mindfulness intervention [24] to 6.3% in an individualised face-to-face CBT intervention [25]. Most individuals showed no reliable improvement after treatment (average 74.3% per study) and most showed no reliable deterioration following treatment (average 2.2% per study). Differences in the percentage of participants within each Jacobson category were found across studies. The two studies with most treatment responders used CBT and mindfulness [24] and CBT and mindfulness and ACT [33]. These studies adopted virtual methods of delivery, which in terms of accessibility are particularly advantageous for PWE, considering many are restricted from driving due to seizure activity. Also, virtual methods may be more cost effective for services and service

users and may reduce the fear of stigmatisation that PWE have in entering therapy [46]. In support of this, the studies using virtual methods had lower attrition rates than a clinic based face-to-face intervention [34].

An intervention delivered in a group format yielded the highest percentage of treatment responders [24]. However, when the intervention was repeated the percentage of treatment responders dropped [35]. A potential factor contributing to this was difference in group size, as this was larger in the study with higher treatment responders. The group interventions were the only studies containing participants who reliably deteriorated post treatment; Thompson et al in 2010 [24] (5.3% deteriorated) and 2015 [35] (5.8% deteriorated). Potentially, group factors such as participants feeling isolated and receiving less individual support may have contributed to this.

The one study that required participants to meet a clinical threshold for depression produced the lowest rate of treatment responders [25]. Due to only two studies supplying follow up data, where one was a short-term follow up [34] and one potentially augmented their intervention with antidepressant medication [25] it is difficult to make conclusions regarding the sustainability of therapeutic effects. Considering all studies used a form of CBT and had low rates of treatment responders, results here add little support for CBT as an intervention method for PWE. Individualised face-to-face CBT is generally the most recognised method of delivery in services, however studies using this method showed only 6.3% [25] and 25% [34] of their participants were treatment responders.

Confidently attributing the therapeutic modality factors just mentioned to the correlation of results is compromised due to several confounding variables in the studies. For instance, across studies there were different epilepsy and depression classifications, participants receiving antidepressants or alternative therapy for psychological difficulties,

varying lengths of intervention delivery and varying professions as treatment facilitators. As mentioned, none of the studies used diagnostic criteria for depression as inclusion criteria. Rather, different levels of clinical severity of symptoms were used in three studies [4,24, 25,35] one [33] only required participants to report that they had depressive symptoms and the final study [34] did not require participants to have any depressive symptoms. Therefore, it is difficult to directly compare between studies which had different thresholds based on different symptom measures. For example, participants with low levels of depression have less scope to show statistically reliable improvement, which could lead to an underestimation of treatment efficacy.

Having studies which assess the impact of psychological treatments for PWE with relatively few symptoms is important, considering having low levels of emotional distress can contribute to poor QoL in PWE [2]. However, results of such studies may lack clinical relevance and not translate to evidence based clinical services where treatment may only be provided to patients with clinical levels of emotional distress, coupled with the fact that the psychological interventions for this group of patients was only marginally better than control conditions [25].

As discussed, due to factors within the included studies in this review our analysis of absolute efficacy was restricted to reporting on the proportion of participants that made statistically reliable change based on the RCI. This is a less stringent analysis of clinical significance as solely using the RCI does not allow recovery rates to be estimated, only treatment response [21]. Also, statistically reliable change based on the RCI for those with low levels of symptoms at baseline may not be clinically meaningful as the opportunity for improvement is minimal, although it does allow deterioration over the course of treatment to be assessed [21].

The methodological quality of the included studies was somewhat limited, with an average rating of "fair" across the studies based on the PEDro-P scale [27]. The studies had large attrition rates, with a mean of 23% (range: 11%-39%) per study and only two studies systematically evaluated the characteristics of those who dropped out [33,34]. Three of the five studies did not use blind assessment [24,25,35] and none of the studies used blinded subjects or therapist, which increases the risk of bias [47]. There were also no operational definitions provided to classify participants who completed an adequate dose of therapy. The methodological quality of studies found here concords with previous reviews in the area [15-18]. Additionally, the studies were relatively small and females were over represented in all of the studies by up to 30% when compared to the wider epilepsy population [48]. Whether this higher representation of females in the studies is representative of PWE who access mental health services remains inconclusive, as no statistics were found to evidence this. Although, large-scale research exploring gender differences and anxiety and depression symptoms in PWE showed females had significantly greater depression symptoms.

The review also extracted and considered the relative efficacy of treatments. All included studies on at least one time-point, showed intervention groups with statistically significant reductions in their symptom levels when compared to a control condition. Considering this alone (discounting the analysis of clinical significance) would uphold the optimism in previous reviews and offer evidence to support psychological interventions as efficacious for depression in PWE, particularly as this review encompassed three studies undertaken subsequently to the aforementioned reviews. However, when absolute efficacy is explored through using the RCI these conclusions are contradicted. Jacobson et al. [19] argues forming conclusions based on small statistical effects of group differences is insufficient evidence of treatment efficacy and statistical effects must be supplemented with

reports of the clinical significance of treatment effects to determine if a treatment is efficacious.

The review was limited in that it included only five controlled studies, as three studies did not supply IPD, which restricts confidence in the conclusions. This highlights the limited amount of treatment outcome research conducted in this population. Including all eight studies in an analysis would have increased the generalisability of findings. This could have partially been achieved through subjecting the three studies which did not provide IPD to an analysis of their relative efficacy and their quality. Although this may have provided firmer conclusions in these areas, it was felt their inclusion within these analyses would deflect from the main focus of the review, which was to explore the clinical significance of psychological interventions using Jacobsen methodology. Including studies which did not provide IPD and were not assessed using Jacobsen methodology may have made interpretation of results more difficult and would not have allowed for a direct comparison of the absolute and relative efficacy of these studies.

The review was unable to assess the clinical significance of any psychological treatment for anxiety in PWE as none of the included studies had an anxiety measure as their primary outcome. Furthermore, the three studies where IPD was not available had no outcome measures of anxiety. This supports that there is a scarcity of research into anxiety in PWE [49] and it remains a neglected clinical issue [50].

5. Conclusion

The review found limited support for the efficacy of psychological interventions in PWE. Although previous reviews have contradicted this conclusion, their evidence was based on solely reporting relative efficacy. Evidence here suggests this is not sufficient to evidence the efficacy of a treatment, as when exploring the absolute efficacy of psychological

treatments using Jacobson's RCI a low percentage of participants could be classed as 'treatment responders'. To make more conclusive deductions on the efficacy of psychological treatments for anxiety and depression in PWE, there is a need to conduct methodologically robust clinical trials with PWE that have clinical levels of emotional distress. Specifically, large RCT's with an even gender spread are recommended with more rigorous delivery protocols. Unfortunately, the review was unable to analyse the clinical significance of psychological interventions for anxiety in PWE as there was no IPD for a primary outcome measure of anxiety available. It is essential that treatments look beyond depression and also focus on anxiety.

Overall, results imply there is substantial scope for improvements in psychological treatments for anxiety and depression in PWE. As all studies used a form of CBT, this improvement may be found through exploring alternative psychological approaches.

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Metacognitive beliefs and illness perceptions in anxiety and depression in people with epilepsy

Chapter 2: Empirical Paper

For submission to Epilepsy and Behaviour

Abstract

Purpose: Symptoms of anxiety and depression are common in people with epilepsy (PWE). However, evidence suggests the current psychological models and associated treatments for anxiety and depression for PWE are limited. It is possible that there are other psychological models of anxiety and depression with greater clinical utility for PWE. The Self-Regulatory Executive Function (S-REF) model is a transdiagnostic model of emotional disorder which states maladaptive metacognitive beliefs and processes are fundamental in the development and maintenance of anxiety and depression. There is preliminary support for the applicability of the S-REF model to emotional distress in PWE. This study aimed to provide a more stringent test of the S-REF model through comparing its explanative ability against a more established theoretical model for anxiety and depression in epilepsy, namely, illness perceptions. It was specifically explored whether metacognitive beliefs explained additional variance in anxiety and depression after accounting for demographics, epilepsy characteristics and, illness perceptions. The mediational relationships between metacognitive beliefs, the cognitive attentional syndrome (CAS) and anxiety and depression, predicted by the S-REF model were also explored.

Methods: Four hundred and fifty-seven PWE participated in an online survey and completed self-report questionnaires measuring anxiety, depression, metacognitive beliefs, illness perceptions and CAS processes. Participants also provided information on demographics, epilepsy characteristics and number of, and perceived side effects of, anti-epileptic medication.

Results: Regression analysis showed that metacognitive beliefs explained additional variance in anxiety and depression after accounting for the control variables, including illness perceptions. The central principle of the S-REF model was supported; the relationship

between negative metacognitive beliefs about uncontrollability and danger of worry and anxiety symptoms was partially mediated by the CAS.

Conclusion: Metacognitive beliefs and processes contribute to anxiety and depression in PWE more than illness perceptions, thereby providing further support for the utility of the S-REF model. Modifying negative metacognitive beliefs and the CAS using metacognitive therapy could alleviate anxiety and depression in PWE, this remains to be tested in future research.

Keywords

Epilepsy, anxiety, depression, metacognitions, S-REF model, illness perceptions

1. Introduction

Symptoms of anxiety and depression are commonly experienced by people with epilepsy (PWE). A review of epidemiological studies found 9-37% of PWE met the diagnostic criteria for depression and 11-25% met the diagnostic criteria for an anxiety disorder, and that they often co-exist [1]. Additionally, PWE frequently experience subclinical levels of anxiety and depression as evidenced by Mensah and colleague's large scale studies. Using the Hospital Anxiety and Depression Scale (HADS) [2] they reported 18.9% of their sample as having borderline anxiety and 20.5% meeting 'caseness' [3] and 11.2% as having borderline depression and 16.6% meeting 'caseness' [4]. Anxiety and depression adversely affect the quality of life (QoL) of PWE, often to a greater degree than seizure frequency and severity [5] and the adverse effects of anti-epileptic drugs (AEDs) [6]. Barry et al. [7] believe it is imperative that clinical management of PWE should include screening for the presence of anxiety and depression, and once identified as clinically significant, effective interventions should be implemented.

To best inform interventions, conceptualising which factors cause and maintain anxiety and depression in PWE is required. Age [8], gender [9], socioeconomic status [10], marital status [11], employment status [12,13], education level [14], seizure frequency [15], and AEDs side effects [16] have all been purported to have a role. However, systematic reviews have concluded psychological factors as the most robust predictors of anxiety and depression in PWE [17,18], these factors may be modifiable via psychological intervention.

Current psychological approaches to anxiety and depression in PWE focus largely on an individual's cognitive representations of their epilepsy using the framework of Leventhal's common-sense model (CSM) of self-regulation in health and illness [19]. Central to the CSM is the idea that an individual's illness perceptions, i.e. their beliefs, attitudes and ideas about their illness) influence how they make sense of their symptoms, which in turn influences

coping strategies and determines outcomes such as psychological wellbeing, i.e. anxiety and depression. Leventhal, Benyamini and Brownlee [20] describe five main illness perceptions; (i) *Identity*: beliefs about the label and symptoms that individuals associate to the condition. Individuals are likely to interpret diverse symptoms as evidence of the label [21]. (ii) *Cause*: beliefs about the cause of the condition. (iii) *Time-line*: beliefs about the course of the condition (iv) *Consequences*: beliefs about the consequences of the condition and how it affects one's life. (v) *Curability/ controllability*: beliefs about possible cures or effective management of the condition and the degree to which the individual can play a role in this. Studies with PWE have demonstrated that illness perceptions explain a greater proportion of the variance in emotional distress and an individual's ability to cope with their condition than seizure-related variables [22-24].

Illness perceptions have played an important role in influencing psychological interventions, such as CBT [25]. However, evidence for the efficacy of CBT or any other psychological therapy for emotional distress in PWE is limited. A Cochrane review concluded there was insufficient evidence to support any psychological intervention for emotional distress in PWE [26]. Subsequent systematic reviews of randomised controlled trial (RCT) evidence have offered some support for psychological interventions in PWE, showing psychological intervention conditions yield statistically greater reductions in anxiety and depression symptoms compared to control conditions [27-29]. However, each review acknowledged their conclusions were restricted as they were based on few studies which contained several methodological limitations. Also none of the reviews explored the clinical significance of the studies. Currently, insufficient evidence exists to recommend any specific psychological intervention [30].

Exploring alternative psychological models to those currently being used in PWE may identify modifiable psychological mechanisms involved in the development and maintenance

of anxiety and depression in PWE and could result in more effective interventions [31]. One candidate is the self-regulatory executive function model (S-REF) [32]. The S-REF model suggests that the presence of negative illness perceptions alone are insufficient to explain the development and maintenance of emotional distress. For example, most PWE will hold negative illness perceptions about their condition, but many of these will not experience anxiety or depression. The S-REF model proposes that it is how an individual responds to their negative illness perceptions that leads to emotional distress. The response style is termed the cognitive attentional syndrome (CAS). The CAS consists of repetitive worry/rumination and maladaptive coping strategies such as threat monitoring, avoidance and thought suppression which perpetuates emotional distress and continued negative appraisal [33].

The theory specifies that metacognitive beliefs, i.e. beliefs about the control and execution of cognition, determine whether the CAS is selected and implemented in response to the occurrence of a negative thought or illness perceptions. A broad range of metacognitive beliefs are specified in the S-REF model but they can be usefully separated into positive metacognitive beliefs and negative metacognitive beliefs about the uncontrollability and danger of worry. Positive metacognitive beliefs concern the benefits of engaging in each aspect of the CAS (e.g., 'worrying about my symptoms, means I'll cope more effectively). Negative metacognitive beliefs about the uncontrollability and danger of worry (e.g., 'I can't control my worry) maintain and increase worry and in turn increase levels of distress. In the S-REF model, negative metacognitive beliefs about the uncontrollability and danger of worry can occur anywhere in the worry process, i.e. they may occur at the start of the worry process, during worry or may be the outcome of worry. However, negative illness perceptions alone are not considered to play a causal role in the emotional distress according to the S-REF model.

As evidenced in systematic reviews CBT has been the most explored therapeutic modality for anxiety and depression in PWE [26-29]. There have been randomized controlled trials which have explored the effectiveness of alternative approaches of mindfulness [34,35] and mindfulness and acceptance and commitment therapy (ACT) [36] in combination with CBT. These showed interventions eliciting greater reductions in depressive symptoms relative to control conditions. Mindfulness and ACT encourage individuals to attend to difficult thoughts rather than avoid or attempt to suppress them. This allows the individual to link thoughts to the distress. Once an individual notices the thoughts, mindfulness and acceptance skills can be used to let them go and in the process, reduce distress. [37]. Potentially, utilizing 'third wave' approaches may be a more effective approach for PWE, as unlike CBT, they do not require individuals to engage with and test the content of negative thoughts about epilepsy, which for many PWE can be difficult as they are potentially accurate considering the threat of future seizures.

The associated therapeutic intervention of the S-REF model, metacognitive therapy (MCT) utilises the premise of mindfulness but also focuses on modifying individual's metacognitive processes. This approach was chosen as the therapeutic modality of choice for this study as it is an alternative 'third wave' approach which has been less extensively evaluated in PWE experiencing emotional distress. Also, preliminary studies have demonstrated that metacognitive beliefs are associated with anxiety and depression in PWE independently of demographic and epilepsy related variables, [38,39]. There is also extensive evidence supporting the role of metacognitive beliefs in anxiety and depression in mental health [40-42] and other physical health populations [43-45].

This study aims to provide a further test of the S-REF model and its applicability to anxiety and depression in PWE through comparing its explanative ability against illness perceptions; a more established theoretical model for anxiety and depression in PWE. The S-REF model

predicts that metacognitive beliefs should account for variation in anxiety and depression beyond the variation attributable to demographics, epilepsy related variables and illness perceptions. The following hypotheses were tested:

1) Metacognitive beliefs will explain additional variance in anxiety after controlling for demographics, epilepsy characteristics and negative illness perceptions in PWE.

2) Metacognitive beliefs will explain additional variance in depression after controlling for demographics, epilepsy characteristics and negative illness perceptions in PWE.

3) As predicted by the S-REF model, the CAS will fully mediate the relationship between positive metacognitive beliefs and anxiety and depression, and partially mediate the relationship between negative metacognitive beliefs about the uncontrollability and danger of worry and anxiety and depression.

2. Method

2.1. Study design and participants

The study was a cross-sectional design using an online survey. The University of Liverpool's Research Ethics Committee approved the study (ref: RETH00103) (Appendix 6). All participants reported a clinical diagnosis of epilepsy (all syndromes and seizures types permitted) and were currently prescribed antiepileptic medication. All were aged ≥18 years. People were excluded if they could not provide informed consent or independently complete questionnaires in English.

2.2. Procedure

The online survey was conducted between July 2016 and February 2017. Participants were recruited by advertisements (Appendix 7) placed in the newsletters and on the websites of epilepsy interest groups and organizations within England, Scotland, Wales, and the

Republic of Ireland (see acknowledgements). Individuals interested in taking part were directed to an online survey page hosted by Qualtrics. Here, participant information (Appendix 8) was given and permission for informed consent (Appendix 9) was sought. After completing the survey measures, participants were debriefed (Appendix 10) and offered the option to be entered into a 'prize draw' to win a £20 voucher.

2.3. Measures

2.3.1. Participant characteristics

Participants reported their demographics and medical history (Appendix 11). The information asked for is detailed in Table 1. Of note, participants were asked to report on the number of seizures they had experienced in the prior 12 months, whether they were on AED monotherapy or polytherapy and whether they experienced AED side effects or not.

2.3.2. Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS) [2] (Appendix 12) was developed to measure both anxiety and depression in individuals with physical illness. It comprises seven items measuring depression and seven items measuring anxiety. Each item is scored on a 4-point scale, ranging from 0-3. This produces two separate total subscale scores for anxiety (HADS-A) and depression (HADS-D) ranging from 0-21. Scores of 0-7 represent 'normal' levels of anxiety or depression, scores of 8-10 represent 'borderline' case levels, and 11-21 represent 'case' levels. The HADS has high sensitivity and specificity for anxiety and depression in PWE [36,37], and has demonstrated good internal consistency (HADS-A, α =.80, HADS-D α = .76) and stability, (test-retest intraclass correlation coefficient HADS-A = .90, HADS D = .84). Good internal consistency was found for the present sample (HADS-A, α =.80, HADS-D α = .83)

2.3.3. Metacognitive beliefs

The Metacognitions Questionnaire 30 (MCQ-30) [46] (Appendix 13) is a 30-item self-report questionnaire developed to assess participant's metacognitive beliefs. Participants are presented with statements regarding metacognitive beliefs and asked to rate using a 4-point scale (1 = do not agree, 2 = agree slightly, 3 = agree moderately, 4 = agree very much) how much they "generally agree" with that statement. Its 30 items are distributed equally onto the following five subscales: i)*'Positive beliefs about worry'* (Positive metacognitive beliefs) (e.g., Worrying helps me avoid problems in the future) ,ii) *'Negative beliefs about the uncontrollability and danger of worry'* (Negative metacognitive beliefs) (e.g., My worrying is dangerous for me), iii) *'Need to control thoughts'* (e.g., I should be in control of my thoughts all the time), iv)*'Cognitive self-consciousness'* (e.g., I pay close attention to the way my mind works) and, v) *'Cognitive confidence'* (e.g., I have a poor memory). Total scores for the subscales range from 6 to 24, with a higher score representing a stronger belief in the items encompassing that subscale. The questionnaire demonstrated good internal consistency ($\alpha = .86$) and good stability over time (test-retest intraclass correlation = .85) for assessing metacognitive beliefs in PWE [38]. Excellent internal consistency was found for the present sample ($\alpha = .90$).

2.3.4. Illness perceptions

The Illness Perception Questionnaire-Revised (IPQ-R) [47] (Appendix 14) measures illness perceptions. It is divided into three sections. The first section, 'identity' asks participants to state their experience of 15 common symptoms since their diagnosis and if these are attributed to their condition. This section was not included in the study as the symptoms were not common to epilepsy. The second section comprises of seven illness perception subscales: *'timeline (acute/chronic)', 'consequences', 'timeline cyclical', 'emotional representations', 'personal control', 'treatment control'* and *'illness coherence'*. Each subscale contains up to 6 items, where each item is a statement which participants are

asked to rate on a 5 point scale (1 = strongly disagree, 2 = disagree, 3 = neither agree or disagree, 4 = agree, 5 = strongly agree) how much they agree with that statement. This yields a total score for each illness perception subscale.

Higher scores on the *'timeline (acute/chronic)', 'consequences', 'emotional representations'* and *'timeline cyclical'* subscales signify a belief that a condition is chronic, that it has negative consequences including emotional effects and is cyclical in its nature. High scores on the *'personal control', 'treatment control'* and *'illness coherence'* subscales signify positive beliefs about the controllability of their condition and a good personal understanding of their condition. The final section of the questionnaire measures participants causal attributions of their condition and is scored on a five-point scale, this was not included in the study. Good internal consistency (α =.84) and moderate test-retest reliability (test-retest intraclass correlation coefficient =.60) have been demonstrated for the IPQ-R in epilepsy populations [48]. Moderate internal consistency was found for the present sample (α = .68).

2.3.5. Cognitive Attentional Syndrome

The Cognitive Attentional Syndrome Scale (CAS-I) [49] (Appendix 15) is a self-report measure that assesses the core aspects of the CAS, including frequency of worry and rumination, counterproductive efforts at thought control and threat focussed action. The measure used was a 10-item questionnaire adapted from the 16-item original questionnaire. In this study only the first 6 items of the questionnaire were used and the last 4 items were discarded as they assessed metacognitive beliefs, which were more specifically measured using the MCQ-30. Each of the 6 included items refers to a core aspect of the CAS. Participants are asked to rate how much time in the preceding week they have engaged in these behaviours on an 11 point Likert scale ranging from 0 (none of the time) to 10 (all of the time). A total score is yielded from adding the 6 items, with a higher score indicative of

greater use of CAS behaviours. The CAS-1 has shown good internal consistency (Cronbach's α=.78) and significant positive correlations with anxiety and depression measures in clinical populations [49]. Good internal consistency was found for the present sample (α = .81).

2.4. Analysis

Descriptive statistics examined participants' characteristics and their experience of anxiety and depression. Initially a missing value analysis was carried out revealing 35 individuals had missing data, Little's MCAR test on these values was not significant (Sig =.995), establishing these values to be missing completely at random. Subsequently, missing values were imputed in SPSS using the expectation maximization algorithm [50].

To examine the hypotheses that metacognitive beliefs will explain additional variance in anxiety and depression in PWE after having controlled for demographics, epilepsy characteristics and illness perceptions, hierarchical linear regression was used. On step 1, age, gender, marital status (married/in a relationship vs not married/not in a relationship), employment status (employed vs unemployed) and education level (left school at 'O'level/GCSE vs further education), were entered. On step 2, participants' seizure frequency in last 12 months, number of prescribed AED's (monotherapy vs polytherapy) and AED side-effects (yes vs no) were entered. On step 3; scores on the seven illness perceptions (IPQ-R) subscales were entered and on step 4; scores on the five metacognitive beliefs (MCQ-30) subscales. The associated beta values from the regression were analysed to show how strongly each predictor variable influenced either anxiety or depression. A further regression reversed steps 3 and 4 to see if illness perceptions explained additional variance when demographics, epilepsy characteristics and metacognitive beliefs were controlled for. In all regressions either anxiety (HADS-A score) or depression (HADS-D score) were the

dependent variables. As these dependent variables were not normally distributed (Shapiro Wilk, p = 0.000), bootstrapping techniques were used to ensure findings were robust [51].

To explore the predicted mediation relationships between the CAS, metacognitive beliefs and anxiety and depression, four mediation analyses were conducted. All analyses controlled for the influence of illness perceptions, the untested metacognitive beliefs and demographic and epilepsy characteristics. As the data did not meet assumptions of normality bootstrapping methods were again applied to ensure robustness. Following recommendations, 5,000 samples were used [52,53].

All analyses were undertaken using IBM SPSS Statistics v.24. [54] and the PROCESS macro [55].

3. Results

3.1. Participants

Four hundred and fifty seven participants took part, giving the study adequate power to detect an effect with a given degree of confidence (Appendix 16). Participants' demographics and characteristics are detailed in Table 1. The sample's mean age was 36.4 years (SD = 12.4; range 18 to 73), 74.2% were female and the majority (95.4 %) identified themselves as being 'white'. Fifty percent of the sample had a HADS-D score in the borderline or case range, whilst 84.5% had a HADS-A score in the borderline or case range.

Table 1
Participant characteristics (n=457)

Characteristic	Category	n (% of participants)
Gender	Male	118 (25.8%)
	Female	339 (74.2%)
Age: mean (range; SD)		36.4 (18-73; 12.4)
Ethnicity	White	437 (95.4%)
	Black or African American	1 (0.2%)
	Asian	7 (1.5%)
	Mixed ethnic origin	10 (2.2%)
	Other	2 (0.4%)
Residence	England	365 (79.9%)
	Northern Ireland	13 (2.8%)
	Republic of Ireland	17 (3.5%)
	Scotland	39 (8.5%)
	Wales	23 (5%)
Marital status	Married	167 (36.5%)
	Not married	290 (63.5%)
Highest educational qualification	Post graduate university	77 (16.8%)
	Under graduate university	158 (34.6%)
	School education	196 (44.9%)
	No qualifications	26 (5.7 %)
Employment	Full-time	141 (30.9%)
	Part-time	81 (17.7%)
	Self-employed	27 (5.9%)
	Unemployed	81 (17.7%)
	Retired	55 (20%)
	Student	44 (9.6%)
	Housewife/Househusband	28 (6.1%)
Currently driving	Yes	104 (22.8%)
Age diagnosed, mean (SD)		19.2 (11.1)
Seizure frequency past 12 months	At least daily	21 (4.6%)
	At least weekly	66 (14.4%)
	At least monthly	128 (28%)
	At least quarterly	51 (11.2%)
	Less than quarterly	62 (13.6%)
	None	129 (28.2%)
Seizure types experienced*	Single	184 (40.2%
	Multiple forms	273 (60.8%)
AED amount	Monotherapy	197 (42.7%)
	Polytherapy	260 (56.4%)
AED side-effects	Yes	342 (74.8%)
Medical history beyond epilepsy	Another medical condition	139 (30.4%)
	A psychiatric condition	52 (11.4%)
	A psychiatric and medical condition	62 (13.6%)
Anxiety (HADS-A, mean (SD)		11.7 (4.2)
	Not anxious (score: 0-7)	61 (15.5%)
	Borderline (8-10)	104 (22.8%)
	Caseness (11-21)	292 (61.7%)
Depression (HADS-D), mean (SD)		7.9 (4.5)
	Not depressed (0-7)	228 (49.9%)
	Borderline (8-10)	102 (22.8%)
	Caseness (11-21)	127 (27.2%)

Note: SD= standard deviation, *some participants reported experiencing multiple forms of seizures, the amount of participants reporting experiencing each seizures type was as follows: Simple focal seizures- 296; complex focal seizures- 278; absent seizures 230; tonic-clonic seizures 132.

3.3. Association between anxiety and depression and metacognitive beliefs

Results of the regression analysis are shown in Table 2 and the results of the regression analysis when steps 3 and 4 were reversed are shown in Table 3. After controlling for demographic variables, epilepsy variables and illness perceptions (which accounted for 21% of the variance), metacognitive beliefs explained an additional 26% of the variance in anxiety scores (F change [5, 436] = 49.26, p=0.000). Together the final model explained 73% (adjusted $R^2 = 0.51$) of variance with, in decreasing order of importance, the subscales 'negative metacognitive beliefs about the uncontrollability and danger of worry' (MCQ-30), , 'emotional representations' (IPQ-R), gender, marital status, 'consequences' (IPQ-R), and 'timeline (acute/chronic)' (IPQ-R) making significant independent contributions to the model. When metacognitive beliefs subscales were entered into the model before illness perceptions subscales, metacognitive beliefs accounted for 43% of variance in anxiety scores (F change [5, 443] = 74.8, p=0.000) and illness perceptions added an additional 4% of variance (F change [7,436] = 5.94, p = 0.000).

With depression as the dependent variable, after controlling for demographic variables, epilepsy variables and for illness perceptions (which accounted for 13% of variance), metacognitive beliefs explained an additional 13% of variance (F change [5, 436] = 16.95, p=0.000). The final model explained 58% (adjusted $R^2 = 0.31$) of the variance, with, in descending order of significance, the subscales 'negative metacognitive beliefs about the uncontrollability and danger of worry' (MCQ-30), 'need to control thoughts' (MCQ-30)','cognitive confidence' (MCQ-30), 'consequences' (IPQ-R), 'treatment control' (IPQ-R), and 'cognitive self-consciousness'(MCQ-30) making significant independent contributions to the model. When steps 3 and 4 were reversed metacognitive beliefs accounted for 22% of variance (F change [5, 443] = 27.16, p=0.000) and illness perceptions 4% of variance in depression scores (F change [7, 436] = 4.1, p = 0.000).

In both regression models there was no indication of multicollinearity as correlations were not above 0.7 (Pearson's *r*) between study variables, and collinearity statistics showed no figures greater than 1 in 'tolerance' or less than 10 in 'variance inflation factors'. Additionally, the Durbin-Watson test showed autocorrelation was not a factor with scores of 2.01 (anxiety regression) and 2.11 (depression regression).

Table 2: Final models of the variance in anxiety and depression explained by metacognitive beliefs after controlling for demographics, epilepsy characteristics, and illness perceptions

	Anxiety				Depression			
	R^2 change	**Beta**	**T**	**Sig**	**R^2 change**	**Beta**	**T**	**Sig**
Demographics	.04				.05			
Age		-.07	-1.66	.139		.08	1.75	.105
Gender		-.10	-2.93	.007		.02	.38	.728
Employment status		-.04	-1.25	.198		-.09	-2.13	.401
Education level		-.02	.48	.650		-.01	-.16	.873
Marital status		-.10	-2.54	.017		.01	-.29	.779
Epilepsy characteristics	.01				.03			
Seizure frequency 12 months		-.06	-1.43	.16		.03	-.52	.624
AED amount		-.05	-1.17	.240		-.04	-.78	.461
AED side effects		.02	.54	.602		.07	1.64	.095
Illness Perceptions	.21				.13			
IPQ-R timeline, acute/chronic		-.08	-2.01	.029		-.08	-1.78	.079
IPQ-R-consequences		.10	2.06	.036		.16	2.80	.009
IPQ-R-personal control		-.02	-.39	.653		-.01	-.08	.942
IPQ-R treatment control		-.01	-.23	.833		-.15	-2.93	.006
IPQ-R illness coherence		-.05	-1.31	.189		-.01	-.32	.770
IPQ-R timeline cyclical		.05	1.26	.212		-.04	-.77	.472
IPQ-R emotional representations		.13	2.76	.018		.02	.34	.728
Metacognitive beliefs	.26				.13			
MCQ 30; Positive beliefs		.01	.26	.781		-.08	-1.76	.085
MCQ 30; Negative beliefs		.54	11.62	.001		.23	4.07	.001
MCQ 30; Cognitive confidence		.03	.76	.432		.16	3.60	.001
MCQ 30; Need to control thoughts		.06	-.06	.951		.22	4.07	.001
MCQ 30; Cognitive self-consciousness		.06	1.49	.155		-.12	-2.50	.019
Model summary								
R^2	***.73***				***R^2***	***.58***		
Adj R^2	***.51***	***p= .000***			***Adj R^2***	***.31***	***p=.000***	

Table 3: Additional variance explained by each variable group after reversing metacognitive beliefs and illness perceptions in hierarchical regression

	Anxiety	**Depression**
	R^2 change	**R^2 change**
Demographics	.04	.05
Epilepsy characteristics	.01	.03
Metacognitive beliefs	.43	.22
Illness perceptions	.04	.04

3.3 Mediation of relationship between metacognitive beliefs, anxiety and depression

Results of the mediation analyses which examined the theoretically predicted role of the CAS in mediating the relationship between metacognitive beliefs and anxiety and depression symptoms are shown in Figures 1-4. When controlling for the influence of illness perceptions, the untested metacognitive beliefs and demographic and epilepsy characteristics the CAS had no mediational relationship between positive metacognitive beliefs and anxiety symptoms (Figure 1) (ab = -.01, BCa 95%, CI = -.03-.02) or depression symptoms (Figure 3) (ab = -.01, BCa 95%, CI = -.04-.02).

When the relationship between negative metacognitive beliefs about the uncontrollability and danger of worry and anxiety symptoms was examined the CAS partially mediated the relationship (Figure 2) as there was a significant indirect effect mediated by the CAS (ab = .09, BCa 95%, CI = .06-.13) and the direct effect remained significant. The relationship between negative metacognitive beliefs about the uncontrollability and danger of worry and depression was fully mediated by CAS (Figure 4). There was a significant indirect effect mediated by the CAS (ab = .13, BCa 95%, CI = .08-.18), but no direct effect.

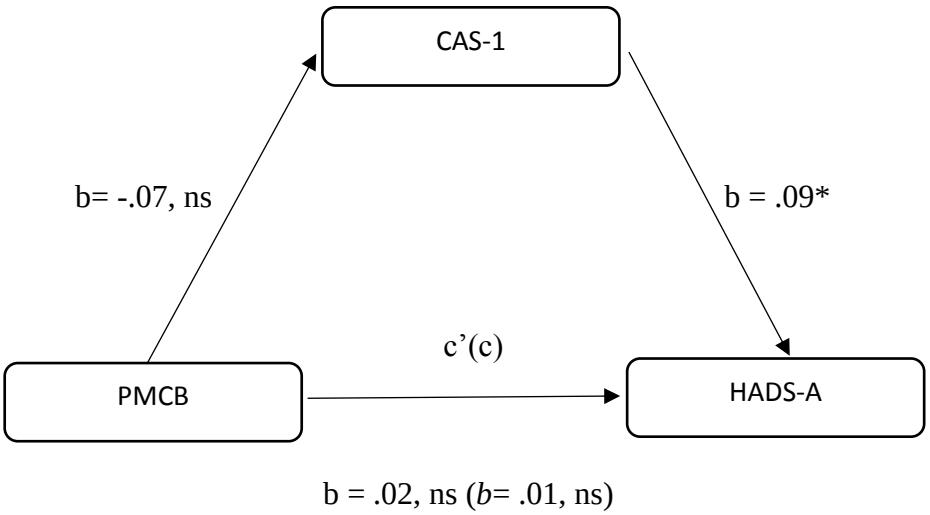

Fig 1. Mediation of positive metacognitive beliefs (PMCB) on anxiety symptoms (HADS-A), via CAS components (CAS-1).

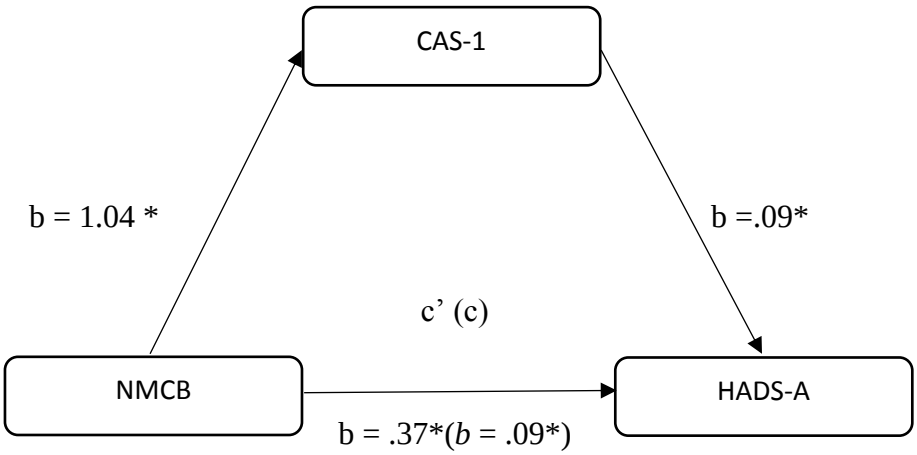

Fig 2. Mediation of negative metacognitive beliefs about the uncontrollability and danger of worry (NMCB) on anxiety symptoms (HADS-A), via CAS components (CAS-1).

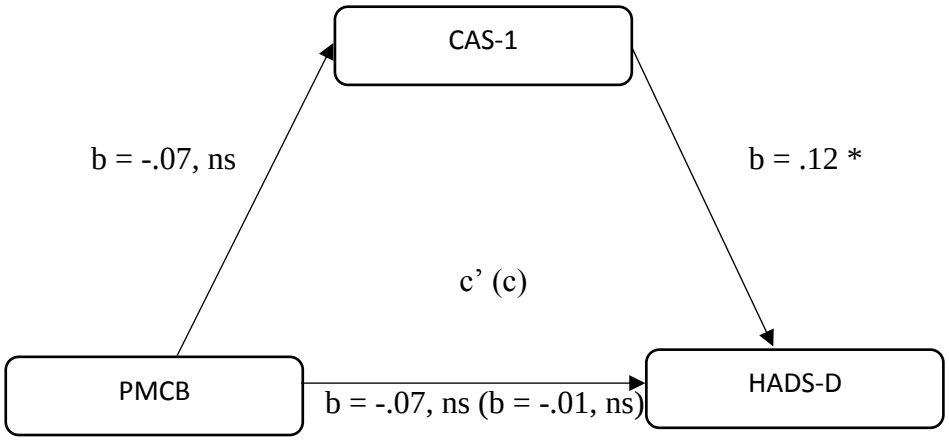

Fig 3. Mediation of positive metacognitive beliefs (PMCB) on depression symptoms (HADS-D), via CAS components (CAS-1).

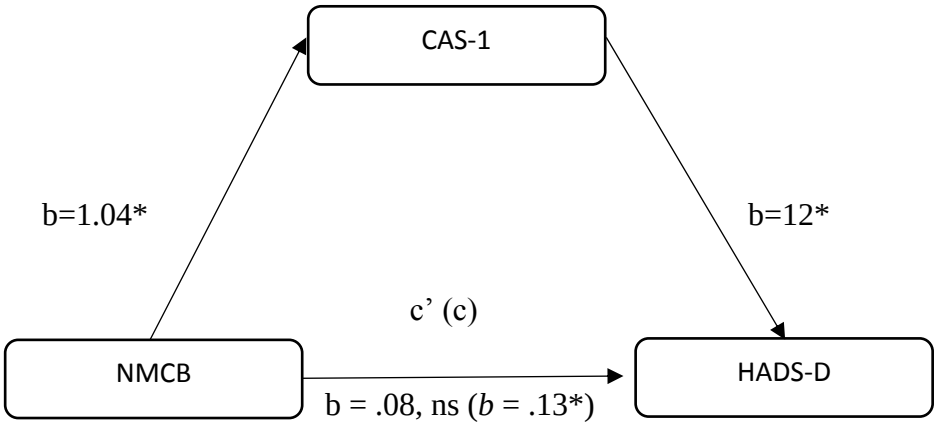

Fig 4. Mediation of negative metacognitive beliefs about the uncontrollability and danger of worry (NMCB) on depression symptoms (HADS-D), via CAS components (CAS-1).

Notes: All analyses controlled for: age, gender, education, marital status employment, seizure frequency- last 12 months, AED amount, AED side-effects, IPQ-R (all subscales), MCQ-30 (all subscales excluding the one directly tested in the mediational anlyses). N = 457 (5,000 bootstraps). *p < 0.001, ns = non–significant.

4. Discussion

This study provides further support for the S-REF model's applicability to anxiety and depression in PWE. Metacognitive beliefs explained greater variance in anxiety and depression in PWE compared to negative illness perceptions. The results also supported some of the key theoretical predictions derived from the S-REF model about the association between metacognitive beliefs, CAS and emotional distress.

When controlling for a range of variables considered to contribute to anxiety and depression in PWE; demographics (age, gender, employment status, educational status, marital status), epilepsy characteristics (seizure frequency in the past 12 months, polytherapy vs monotherapy and AED side-effects) and illness perceptions, metacognitive beliefs added significantly to the variance in symptoms of anxiety, explaining an additional 26%, and symptoms of depression explaining an additional 13%. When demographics, epilepsy characteristics and metacognitive beliefs were controlled for, illness perceptions only explained an additional 4% of the variance in both anxiety and depression symptoms.

Furthermore when controlling for participant demographics and epilepsy characteristics, metacognitive beliefs accounted for more of the remaining variance than illness perceptions in both anxiety (43% vs. 21%) and depression (22% vs. 13%).

In the anxiety regression model, 'negative metacognitive beliefs about the uncontrollability and danger of worry' made the largest single contribution. This is consistent with the predictions of the S-REF model and with previous studies in epilepsy [39], and other physical health populations including cancer [43] and Parkinson's disease [44]. No other metacognitive beliefs made independent contributions to anxiety in the final model. There were three illness perceptions that made independent contributions. 'Emotional representations' and 'consequences' had a positive relationship with anxiety outcome scores, and 'timeline (acute/chronic)' had a negative relationship with anxiety outcome scores. This suggests individuals with negative perceptions about the emotional effects of their epilepsy and individuals who strongly perceive their epilepsy has negative consequences for them are likely to have greater anxiety. Whereas individuals who perceive that their epilepsy is chronic are likely to have less anxiety. From the covariates, gender and marital status made independent contribution, with being male, and not being in a relationship associated with lower anxiety scores.

In the depression regression model, four metacognitive beliefs and two illness perceptions made independent contributions. Similarly to the anxiety model, 'negative beliefs about the uncontrollability and danger of worry' made the largest individual contribution, again supporting the theoretical predictions of the S-REF model and mirroring results exploring depression in previous epilepsy [39], and other physical health studies [43,44]. The metacognitive belief 'need to control thoughts' made the next largest contribution indicating that more conviction in the belief about the need to control thoughts was strongly associated with higher depression. Lack of 'cognitive confidence' was also strongly associated with

depression. Potentially this relationship occurs as worry and rumination may be a compensatory strategy for perceived lack of cognitive confidence which accentuates the belief that worry and rumination are uncontrollable, which leads to emotional distress[31,39]. The 'consequences' subscale on the IPQ-R was also significant suggesting those with a strong belief that their epilepsy has negative consequences are likely to have higher levels of depression.

Two subscales had a significant negative relationship with depression outcome score. Firstly, the metacognitive subscale 'cognitive self-consciousness', implying those who tend to pay close attention to the way their mind works and monitor their thoughts have fewer depression symptoms. Secondly, the illness perception 'treatment control', inferring those with a strong belief in their ability and power in controlling their epilepsy are likely to have fewer depression symptoms.

The mediational analyses found that when controlling for potentially confounding variables the CAS partially mediated the relationship between negative metacognitive beliefs about the uncontrollability and danger of worry and anxiety. This is consistent with the S-REF model which postulates negative metacognitive beliefs about the uncontrollability and danger of worry (e.g., "my worrying is uncontrollable") have a direct relationship with anxiety and additionally further increase distress through activating the CAS. Conversely, the CAS fully mediated the relationship between negative metacognitive beliefs about the uncontrollability and danger of worry and depression as there was no direct effect established. Cook et al [43] found a comparable relationship in cancer patients. They considered the absence of any direct effect between negative metacognitive beliefs about the uncontrollability and danger of worry and depression may be due to wording on the 'negative metacognitive beliefs about the uncontrollability and danger of worry' subscale on the MCQ-30, which specifically focuses on beliefs regarding worry over different forms of

perseverative thinking such as rumination, which are more closely associated to depression [43].

The prediction that the CAS would fully mediate the relationship between positive metacognitive beliefs (e.g., 'worrying helps me to avoid problems in the future') and anxiety and depression was not supported. S-REF theory would predict that, although positive metacognitive beliefs increase the likelihood that an individual will be guided towards the selecting the CAS, it is the negative metacognitive beliefs about the uncontrollability and danger of worry that are most influential in emotional distress as they intensify and maintain the processes of the CAS.

Results imply that in clinical practice it may be beneficial to considering alternatives to CBT, which is currently recommended as a psychological intervention for PWE)[56]. CBT largely focuses its approach on modifying the content of illness perceptions, which from results here, are seemingly less influential in predicting anxiety and depression than an alternative mechanism, metacognitive beliefs. Results suggest if an individual's erroneous metacognitive beliefs are accounted for, then their illness perceptions have little influence in anxiety and depression in PWE. This implies the associated treatment of the S-REF model; metacognitive therapy (MCT), may have more suitability as a psychological intervention for anxiety and depression in PWE. MCT is a 'process focused' approach which centers on modifying metacognitive beliefs, altering an individual's relationship with their thoughts , and exploring unhelpful processing styles that lead to distress. Results here show an individual's 'negative metacognitive beliefs about the uncontrollability and danger of worry' are the key influence in anxiety and depression in PWE. Exploring and attempting to modify these beliefs in therapy through MCT could be an effective approach to reduce individuals using components of the CAS which was shown to further increase distress in both anxiety and depression in this sample.

Results showed a greater explanative ability in the process and style of how people respond to their thoughts rather than the content of their thoughts in influencing anxiety and depression in PWE. This study has thus provided support for 'third wave' therapeutic approaches which encourage individuals to respond to inner thoughts in a flexible way, and has built on previous research using techniques such as mindfulness and ACT as a therapeutic approach for PWE [34-36]

There are several limitations to the study, the cross sectional design means causality cannot be inferred and it may be that maladaptive metacognitive beliefs are the consequence of emotional distress, rather than the cause. To provide more convincing evidence of causation, conducting a prospective test of the S-REF model to explore the temporal precedence of metacognitive beliefs for anxiety and depression in PWE would be necessary. The temporal precedence of metacognitive beliefs has been established in many conditions such as generalised anxiety disorder [57], depression [58], obsessive compulsive disorder [59] and anxiety and depression symptoms in cancer patients [44].

Although the mediation analyses controlled for several recognised covariates of anxiety and depression in PWE this was based on the assumption of no hidden confounders. As such the potential influence of some unmeasured common causes cannot be eliminated. Gandy, Sharpe and Perry's [17] review identified self-efficacy, stress levels, and perceived social support as variables associated with emotional distress in PWE. More robust findings may be found in future studies through controlling for these variables.

Furthermore, the study sample may be unrepresentative of the wider population of epilepsy. Our sample contained only 28% of individuals who were seizure free over the past 12 months in comparison to 51% seen in the wider population with epilepsy [60]. This may be due to recruiting through epilepsy organisations, which can be overrepresented with

people with more severe epilepsy [61]. Also the percentage of our sample meeting borderline or 'caseness' levels of anxiety and depression on the HADS was much higher than found in previous large scale studies of PWE [3,4]. In particular 'caseness' levels on the HADS-A in our sample was significantly higher (61.7%) than a previous large scale study (20.5%) [4]. Additionally, females were over represented in our sample by 24% and the average age of our sample was eight years younger in comparison to the wider epilepsy population [60]. Our samples mean age at diagnosis and mean duration of their epilepsy were though comparable to the wider epilepsy population [60].

5. Conclusion

This study demonstrated metacognitive beliefs and processes contribute to anxiety and depression in PWE more than illness perceptions, thereby providing further support for the applicability of the S-REF model. This suggests that the associated treatment of the S-REF model; metacognitive therapy (MCT) may have potential in treating anxiety and depression in PWE. To further explore the potential of MCT for anxiety and depression in PWE, preliminary tests of MCT are required using case series and open trial designs. If evidence of potential efficacy is obtained, then randomized controlled trials should follow.

Acknowledgements

We thank the people with epilepsy who generously participated in this study. We also acknowledge the invaluable help of the British Epilepsy Association (Epilepsy Action), Epilepsy Ireland, Epilepsy Scotland and the Epilepsy Society for their assistance with participant recruitment.

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Appendix 1

Author Guidelines- Epilepsy & Behaviour

For full author guidelines see:
https://www.elsevier.com/wps/find/journaldescription.cws_home/622822?generatepdf=true

Word/page limit- Not specified

Article structure- Divide article into clearly defined and numbered sections. Subsections should be numbered 1.1 (then 1.1.1, 1.1.2, ...), 1.2, etc. (the abstract is not included in section numbering). Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Abstract- A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. References non-standard or uncommon abbreviations should be avoided, but if essential, they must be defined at their first mention in the abstract itself.

Keywords- Immediately after the abstract, provide a maximum of 6 keywords, using American spelling

Footnotes: Should be used sparingly. Number them consecutively throughout the article. Please indicate the position of footnotes in the text and list the footnotes themselves separately at the end of the article.

Electronic artwork- General points:

• Make sure you use uniform lettering and sizing of your original artwork.

• Embed the used fonts if the application provides that option.

• Number the illustrations according to their sequence in the text.

• Provide captions to illustrations separately.

Tables -. Can be placed either next to the relevant text in the article, or on separate page(s) at the end. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules. If you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns.

References- In text: Indicate references by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given.

In reference list: Number the references (numbers in square brackets) in the list in the order in which they appear in the text. For more than 6 authors the first 6 should be listed followed by 'et al.'

Examples:

Reference to a journal publication: [1] Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. J Sci Commun 2010;163:51–9.

Reference to a book: [2] Strunk Jr W, White EB. The elements of style. 4th ed. New York: Longman; 2000.

Reference to a chapter in an edited book: [3] Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, editors. Introduction to the electronic age, New York: E-Publishing Inc; 2009, p. 281–304.

Reference to a website: [4] Cancer Research UK. Cancer statistics reports for the UK, http://www.cancerresearchuk.org/ aboutcancer/statistics/cancerstatsreport/; 2003 [accessed 13.03.03].

Citation of a reference as 'in press' implies that the item has been accepted for publication.

Note shortened form for last page number. e.g., 51–9. For further details you are referred to 'Uniform Requirements for Manuscripts submitted to Biomedical Journals' (J Am Med Assoc 1997;277:927–34) (see also Samples of Formatted References).

Journal abbreviations. Journal names should be abbreviated according to the List of Title Word Abbreviations.

Acknowledgements- Collate acknowledgements in a separate section at the end of the article before the references

For full author guidelines see:

https://www.elsevier.com/wps/find/journaldescription.cws_home/622822?generatepdf=true

Appendix 2

Sample e-mail to authors requesting individual patient data

Dear Dr xxxxx,

My name is James Reilly, I am a final year Trainee Clinical Psychologist working with Dr Peter Fisher at the University of Liverpool.

We are currently in the process of conducting a clinical significance review of psychological interventions for depression and anxiety in people with epilepsy. In order to review the clinical significance, we intend to apply standardized Jacobson methodology to current psychological outcome trials for depression and anxiety in epilepsy. We are currently in the process of gathering raw data in order to conduct this review, and we would be grateful if we could include the data from your study:

[*insert study reference*]

As your work provides a very valuable contribution into this field, it would be extremely important to include your study in this review. Moreover, it would be a significant limitation to the review if your work was absent. Therefore, I would be grateful if you would be willing to send me the following:

· Pre and post scores on the [*insert primary measure stated in study*] for each participant by treatment condition for all participants

· Amount of sessions attended for each participant

· Age of each participant

The data can be sent as an SPSS file, excel file or a print out, whatever form would be most convenient for you. Above is a list for all the desired data; however, if you cannot provide all of the above, anything that you do provide would be very much appreciated. I understand that this is asking a lot, and would therefore be grateful if you could let me know whether or not this is something that you would be willing to help with.

Thank you in advance for your help. If you have any queries of questions about the current research, please do not hesitate to contact me. I look forward to hearing from you.

Yours sincerely,

James Reilly

Trainee Clinical Psychologist

University of Liverpool

Appendix 3

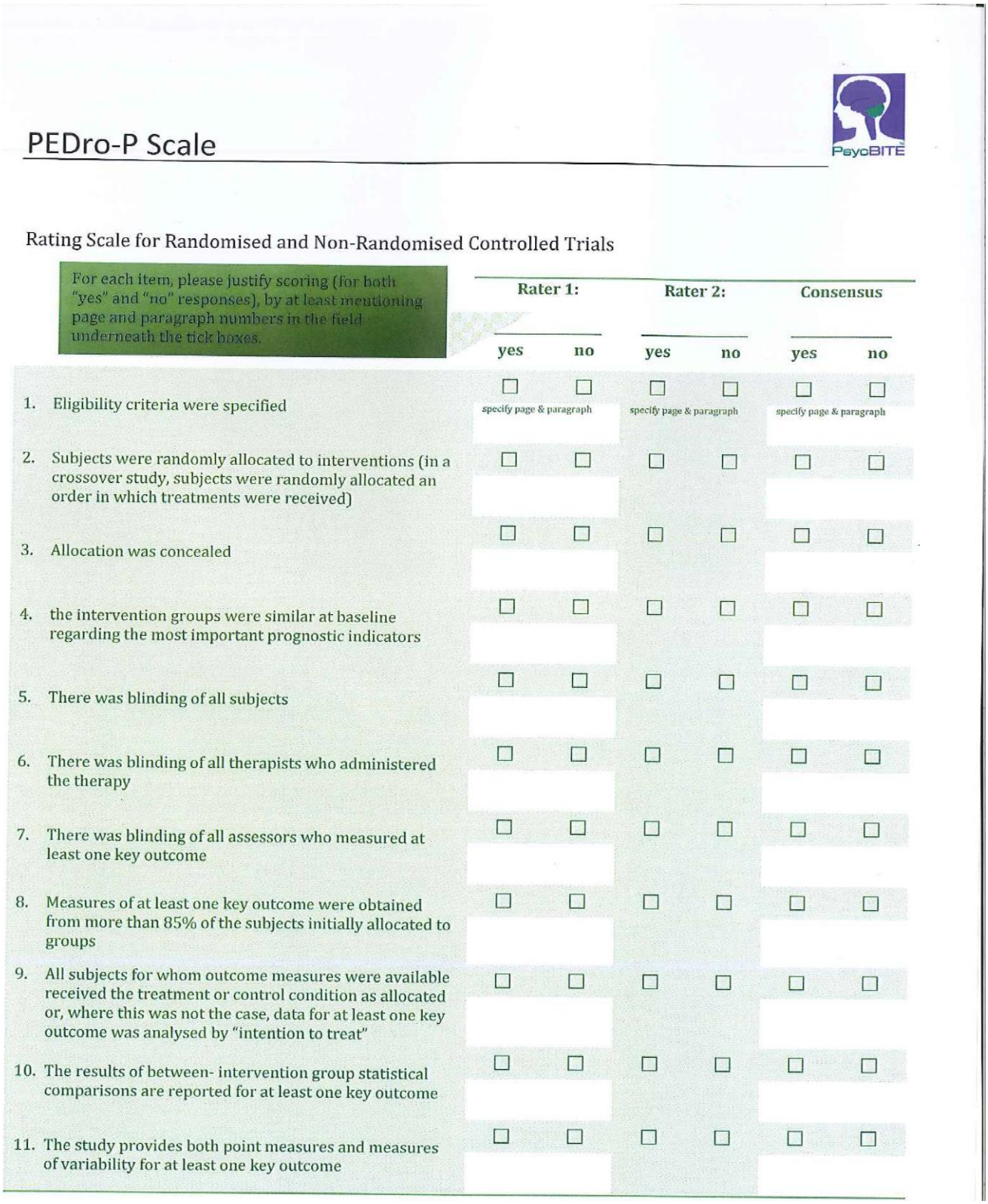
Data extraction form

	Data	Page	Paragraph
First Author:			
Year of Study:			
Country:			
Study Design:			
Sample Size:			
Mean Age (S.D):			
Female %:			
Intervention Type: (Psychological methods vs …)			
Intervention Delivery: (group/ individual/ face-to-face, facilitators:			
Intervention Duration:			
Inclusion Criteria: Epilepsy dx type:			
Emotional distress level:			
Age required:			
Other:			
Measures used:			
When measures used:			
Attrition rate %:			

Mood outcomes, group x time interaction:			

Appendix 4

PEDro-P Scale



PEDro-P Scale

PsycBITE

Rating Scale for Randomised and Non-Randomised Controlled Trials

For each item, please justify scoring (for both "yes" and "no" responses), by at least mentioning page and paragraph numbers in the field underneath the tick boxes.

	Rater 1:		Rater 2:		Consensus	
	yes	no	yes	no	yes	no
1. Eligibility criteria were specified	☐ specify page & paragraph	☐	☐ specify page & paragraph	☐	☐ specify page & paragraph	☐
2. Subjects were randomly allocated to interventions (in a crossover study, subjects were randomly allocated an order in which treatments were received)	☐	☐	☐	☐	☐	☐
3. Allocation was concealed	☐	☐	☐	☐	☐	☐
4. the intervention groups were similar at baseline regarding the most important prognostic indicators	☐	☐	☐	☐	☐	☐
5. There was blinding of all subjects	☐	☐	☐	☐	☐	☐
6. There was blinding of all therapists who administered the therapy	☐	☐	☐	☐	☐	☐
7. There was blinding of all assessors who measured at least one key outcome	☐	☐	☐	☐	☐	☐
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	☐	☐	☐	☐	☐	☐
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	☐	☐	☐	☐	☐	☐
10. The results of between- intervention group statistical comparisons are reported for at least one key outcome	☐	☐	☐	☐	☐	☐
11. The study provides both point measures and measures of variability for at least one key outcome	☐	☐	☐	☐	☐	☐

Appendix 5

PEDro-P Scale administration guidelines

The PEDro-P scale consists of 11 criteria. The first item relates to the external validity (specifically the participant selection criteria). The remaining 10 items (criteria 2 - 11) assess the internal validity of each trial and whether the trial contains sufficient statistical information to make it interpretable. Thus, the internal validity of each trial is ranked based on a total score out of 10 (i.e., excluding criterion 1).

All criteria points are only awarded when a criterion is clearly satisfied. If on a literal reading of the trial report it is possible that a criterion was not satisfied, a point should not be awarded for that criterion.

Criterion 1- Eligibility criteria were specified: This criterion is satisfied if the report describes the source of subjects and a list of criteria used to determine who was eligible to participate in the study.

Criterion 2- Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received): A study is considered to have used random allocation if the report states that allocation was random. The precise method of randomisation need not be specified. Procedures such as coin-tossing and dice-rolling should be considered random. Quasi-randomisation allocation procedures such as allocation by hospital record number or birth date, or alternation, do not satisfy this criterion.

Criterion 3- Allocation was concealed: Concealed allocation means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to. A point is awarded for this criteria, even if it is not stated that allocation was concealed, when the report states that allocation was by sealed opaque envelopes or that allocation involved contacting the holder of the allocation schedule who was “off-site”.

Criterion 4- The groups were similar at baseline regarding the most important prognostic indicators: At a minimum, in studies of therapeutic interventions, the report must describe at least one measure of the severity of the condition being treated and at least one (different) key outcome measure at baseline. The rater must be satisfied that the groups’ outcomes would not be expected to differ, on the basis of baseline differences in prognostic variables alone, by a clinically significant amount.

This criterion is satisfied even if only baseline data of study completers are presented.

Note: Criteria 4, 7-11 Key outcomes are those outcomes which provide the primary measure of the effectiveness (or lack of effectiveness) of the therapy. In most studies, more than one variable is used as an outcomemeasure.

Criterion 5- There was blinding of all subjects

Criterion 6- There was blinding of all therapists who administered the therapy

Criterion 7- There was blinding of all assessors who measured at least one key outcome.

Note: Criteria 5-7: Blinding means the person in question (subject, therapist or assessor) did not know which group the subject had been allocated to. In addition, subjects and therapists are only considered to be "blind" if it could be expected that they would have been unable to distinguish between the treatments applied to different groups. In trials in which key outcomes are self-reported (eg, visual analogue scale, pain diary), the assessor is considered to be blind if the subject was blind.

Criterion 8- Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups: This criterion is only satisfied if the report explicitly states both the number of subjects initially allocated to groups and the number of subjects from whom key outcome measures were obtained. In trials in which outcomes are measured at several points in time, a key outcome must have been measured in more than 85% of subjects at one of those points in time.

Criterion 9- All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat" : An intention to treat analysis means that, where subjects did not receive treatment (or the control condition) as allocated, and where measures of outcomes were available, the analysis was performed as if subjects received the treatment (or control condition) they were allocated to. This criterion is satisfied, even if there is no mention of analysis by intention to treat, if the report explicitly states that all subjects received treatment or control conditions as allocated.

Criterion 10- The results of between-group statistical comparisons are reported for at least one key outcome: A between-group statistical comparison involves statistical comparison of one group with another .Depending on the design of the study, this may involve comparison of two or more treatments, or comparison of treatment with a control condition. The analysis may be a simple comparison of outcomes measured after the treatment was administered, or a comparison of the change in one group with the change in another (when a factorial analysis of variance has been used to analyse the data, the latter is often reported as a group × time interaction). The comparison may be in the form hypothesis testing (which provides a "p" value, describing the probability that the groups differed only by chance) or in the form of an estimate (for example, the mean or median difference, or a difference in proportions, or number needed to treat, or a relative risk or hazard ratio) and its confidence interval.

Criterion 11- The study provides both point measures and measures of variability for at least one key outcome: A point measure is a measure of the size of the treatment effect. The treatment effect may be described as a difference in group outcomes, or as the outcome in (each of) all groups. Measures of variability include standard deviations, standard errors, confidence intervals, interquartile ranges (or other quantile ranges), and ranges. Point

measures and/or measures of variability may be provided graphically (for example, SDs may be given as error bars in a Figure) as long as it is clear what is being graphed (for example, as long as it is clear whether error bars represent SDs or SEs). Where outcomes are categorical, this criterion is considered to have been met if the number of subjects in each category is given for each group.

Appendix 6

Ethical approval letter

Dr Mantalena Sotiriadou Research Ethics and Integrity Officer
University of Liverpool
Correspondence to;
Research Support Office
University of Liverpool
Waterhouse Building
2nd Floor, Block D
3 Brownlow Street
Liverpool
L69 3GL

Email: ethics@liverpool.ac.uk

Telephone: 0151 795 8355

24 May, 2016

Dear Dr Fisher and Mr Reilly,

Re: Ethical Approval

I am pleased to inform you that your study has been approved. Details and conditions of the approval can be found below:

Ethics reference number: RETH001034

Committee name: Research Ethics Sub-committee for Physical Interventions

Review type: Full committee review

Supervisor: Dr Peter Fisher

Student Investigator: Mr James Reilly

Department: Psychological Sciences

Title: An investigation into the relative contribution of cognitive and metacognitive beliefs in anxiety and depression in people with epilepsy.

First reviewer: Professor Caroline Rowland

Date of approval: 24/05/16

Approximate end date: 30/06/17

The application was APPROVED subject to the following conditions:

Conditions

- All serious adverse events must be reported to the Subcommittee within 24 hours of their occurrence, via the Research Integrity and Governance Officer (ethics@liverpool.ac.uk).

- This approval applies for the duration of the research. If it is proposed to extend the duration of the study as specified in the application form, the Subcommittee should be notified, via the Research Integrity and Governance Officer (ethics@liverpool.ac.uk).

- If it is proposed to make an amendment to the research, you should notify the Committee by following the Notice of Amendment procedure. If the named PI / Supervisor leaves the employment of the University during the course of this approval, the approval will lapse. Therefore please contact the Research Integrity and Governance Officer at ethics@liverpool.ac.uk in order to notify them of a change in PI / Supervisor.

Yours sincerely,

Dr Mantalena Sotiriadou

Research Ethics and Integrity Office

Appendix 7

Sample advert (used online by 'Epilepsy Scotland')

Study title: Understanding anxiety and depression in people with epilepsy

Institution

University of Liverpool

About the study

We want to get a better understanding of how anxiety and depression come about in people with epilepsy. This will help tell us which psychological treatments are best suited to reducing anxiety and depression in people with epilepsy.

As a thank you for taking part you will be offered the chance to enter a prize draw to win one of ten £20 Amazon gift vouchers.

When will this study be recruiting?

Now until February 2017

What will participants be asked to do?

Complete 5 online questionnaires, this should take no longer than 45 minutes to complete, **and** complete the same questionnaires 3 months later.

Who can take part?

You can take part if you:

- Have a diagnosis of epilepsy
- Are aged 18 or over
- Are taking anti-epileptic medication
- Have a good understanding of written English.

Who is conducting the research?

The Clinical Psychology Department at the University of Liverpool

Who has reviewed this study?

The research and ethics committee at the University of Liverpool have reviewed the study and granted ethical approval for it to go ahead.

Interested…….. If you are interested in taking part please click on this link:

Appendix 8

Participant information form

PARTICIPANT INFORMATION SHEET

Title of Study: **Research to better understand anxiety and depression in people with epilepsy**

We are inviting you to participate in a research study. Before you decide whether to participate, it is important you understand why we are doing the research and what it will involve.

Please take time to read the following information carefully and feel free to ask us if you would like more information. Take time to decide if you wish to take part. We would like to say that you do not have to accept this invitation and should only agree to take part if you want to.

1. What is the purpose of the study?

The University of Liverpool is carrying out a research project, which aims to further our understanding about anxiety and depression in people with epilepsy. Unfortunately anxiety and depression are common in epilepsy but relatively little is known about the psychological factors that contribute to this. This research aims to further our understanding about how depression and anxiety is maintained in people with epilepsy. In the future this may help to develop more effective psychological treatments.

2. Why have I been chosen to take part?

We are inviting anyone with a diagnosis of epilepsy, taking anti-epileptic medication aged 18 or over to complete a set of questionnaires that ask about, how they make sense of their epilepsy, their emotional reactions, and some basic details about the nature of their epilepsy.

It is possible that some people will currently have symptoms of depression and anxiety, or have had these in the past, whereas others may never have experienced depression and anxiety. It is important to include people with different experiences so we can build a more complete picture. The invitation to take part in the study does not mean that we think you are having problems with depression and anxiety or are finding it hard to cope.

3. What will happen if I take part?

If you take part, the researchers will ask you to do the following things:

- To fill in some questionnaires online at two separate time points. The first time will be when you agree to take part and the second time will be 3 months after this. We are asking you to repeat the questionnaires so we can see if there are any changes in the anxiety or depression that you may be experiencing.
- Before you answer the questionnaires, you will see some statements about the research and your rights. Please read these and 'tick' these boxes if you agree with them. This will act as your consent to take part. After this the questionnaires will appear. These will take no longer than 45 minutes to complete all together.
- Some of the questions ask you about your epilepsy directly, some ask about how you have been feeling and some ask about how you think about your epilepsy. At the start of the survey, you will be asked to fill in some personal information (e.g., age, employment status, marital status) we ask these questions to help us better understand the results. You can choose not to answer these questions if you wish.
- If you wish to take break whilst doing the questionnaires you can as the questionnaire page will not 'time out'. Also, if you do not want to finish the

survey in one sitting you can click the 'save and continue' button. This will allow you to return to where you left off the next time you click the survey link. However, if you want to use this option you must use the same computer and the same web browser and must have not cleared your browser cookies.

- At the end of the questionnaires, we will ask you to provide an e-mail address, which we can contact you on to provide you with the webpage to complete the questionnaires 3 months later. Once we have your completed second questionnaires back this will be all you need to do for the study and your e-mail address will be destroyed.
- To thank you for taking part we will also ask if you would like to be entered into a prize draw to win a £20 amazon voucher (10 available).
- All of the information you supply will be kept confidential whilst the data is being collected. When data collection is completed, your data will be anonymised and following University Research Data Management policy will be retained for a minimum of 10 years.

4. What are the possible benefits of taking part?

Knowledge gained may lead to a better understanding of psychological factors involved in anxiety and depression in epilepsy and help decide future treatment.

5. Are there any risks in taking part?

There are no known risks of taking part and the questionnaires you will be asked to complete have been given to lots of people with epilepsy before. However, some of the questions do involve you thinking about the impact your epilepsy has on your life. For some people, this might be upsetting.

If answering the questionnaires does make you feel any discomfort, please contact the principal Investigator: Dr Peter Fisher (0151 794 4160, plfisher@liverpool.ac.uk). We also suggest that you talk to your GP if this situation arises. Detailed information about the challenges of living with epilepsy can be found on the websites of the British Epilepsy

Association (http://www.epilepsy.org.uk/old-info) and the National Society for Epilepsy (http://www.epilepsysociety.org.uk/AboutEpilepsy)"

6. Will my participation be kept confidential?

Yes. All of the information you provide will be stored securely and kept confidential. Your name and contact details will **not** appear on any of the data collected. When you complete the questionnaires online, the answers will be transferred automatically to a secure database to enable it to be analysed with data from other participants. Your e-mail addresses will only be used to contact you 3 months after the first set of questionnaires to ask you to take part in the second part of the study and if you would like to be entered into the prize draw. E-mail addresses will be destroyed after this.

7. What if I do not want to take part anymore after I agree to take part?

If you decide to take part and then want to change your mind, you can do this at any point. To do this you will just have to click the 'withdraw from study' option at the bottom of your screen and we would not collect any more information from you. Results up to the period of withdrawal may be used, if you are happy for this to be done. You may contact the primary supervisor to request that they are destroyed and no further use is made of them.

8. What if I am unhappy or if there is a problem?

If you are unhappy with the study please feel free to let us know by contacting the primary supervisor of the project Dr Peter Fisher (plfisher@liverpool.ac.uk, Tel: 0151 794 4160). If you have a complaint, which you feel you cannot come to us with then please contact the Research Governance Officer at ethics@liv.ac.uk . When contacting them, please provide details of the name or description of the study, the researcher(s) involved, and the details of the complaint you wish to make.

9. What will happen to the results of the project?

We shall report the results in scientific journals and we will not identify you in any report. A summary of the results will also be sent to the epilepsy groups who helped us recruit who

may display these for public viewing on their websites or in their newsletters. If you would like a copy of the final paper, you can contact the primary researcher and they will provide you with this.

10. Are there any reasons that would mean I could not take part?

If you have difficulty understanding written English or if you cannot understand some of the words in the questionnaires, we would kindly ask you not to take part.

12. Who can I contact if I have further questions?

Should you need further information about the project you can contact the student investigator, James Reilly, reillyj@liverpool.ac.uk or the primary supervisor of the study Dr Peter Fisher- 0151 794 4160, plfisher@liverpool.ac.uk.

Thank you for reading this.

Appendix 9

Participant consent form

PARTICIPANT CONSENT FORM

Study title: Research to better understand anxiety and depression in people with epilepsy

In order to proceed with the study please read the following statements:

- I confirm that I have read and understand the information sheet dated for the above study. I have been given the opportunity to consider the information, ask questions and have these answered satisfactorily**.**

  Yes **No**

  ☐ ☐

- I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my rights being affected. In addition, should I not wish to answer any particular question or questions, I am free to decline.

  Yes **No**

  ☐ ☐

- I give permission for members of the research team to have access to my responses. I understand I will not be identified or identifiable in the report or any publications that result from the research. I understand that my data will be anonymised upon completion of the research and following University Research Data Management policy will be retained for a minimum of 10 years.

  Yes **No**

  ☐ ☐

- I agree to take part in the study.

  Yes **No**

  ☐ ☐

Appendix 10

Participant debrief form

UNIVERSITY OF LIVERPOOL

DEBRIEF INFORMATION SHEET

Title of Study: **Research to better understand anxiety and depression in people with epilepsy**

Thank you for completing the questionnaires.

- If answering the questionnaires made you feel any discomfort, we would advise accessing information about the challenges of living with epilepsy. This can be found on several epilepsy websites such as the British Epilepsy Association (http://www.epilepsy.org.uk/) and the National Society for Epilepsy (http://www.epilepsysociety.org.uk/AboutEpilepsy). We also suggest that you talk to your GP if this situation arises. Further avenues of support can be advised by contacting the primary supervisor of the project Dr Peter Fisher (plfisher@liverpool.ac.uk, Tel: 0151 794 4160).

- If you are unhappy with the study please feel free to let us know by contacting the primary supervisor of the project Dr Peter Fisher (plfisher@liverpool.ac.uk, Tel: 0151 794 4160). If you have a complaint, which you feel you cannot come to us with then please contact the Research Governance Officer at ethics@liv.ac.uk . When contacting them, please provide details of the name or description of the study, the researcher(s) involved, and the details of the complaint you wish to make.

Appendix 11

Demographics and Medical History Questionnaire

To help us understand more about you and your epilepsy, please answer the following questions:

1. What is your date of birth?

Day:

Month:

Year:

2. What is your gender

- ❍ Female
- ❍ Male

3. In which country do you live in?

- ❍ Wales
- ❍ Scotland
- ❍ England
- ❍ Northern Ireland
- ❍ Republic of Ireland

4. What is your ethnic group?

- ❍ White
- ❍ Black or African American
- ❍ Asian
- ❍ Mixed ethnic origin
- ❍ Other

5. What is your marital status?

- ❍ Single
- ❍ Married
- ❍ Divorced
- ❍ Widowed

6. At what stage did you finish education?

- ❍ Before exam stage
- ❍ 'O' Levels, GCSE, Level 1 or 2 NVQ
- ❍ 'AS' or 'A' levels, Level 3 NVQ
- ❍ University degree, graduate certificate, Diploma
- ❍ Post graduate university degree (e.g. PGCE, MSc, MA, PHD)

7. What is your present work situation?

- ❍ Employed, full-time
- ❍ Employed, part-time
- ❍ Self-employed
- ❍ Unemployed
- ❍ Retired
- ❍ Student
- ❍ Housewife/Househusband

8. Do you regularly drive a motor vehicle?

- ❍ Yes
- ❍ No

9. How old were you when you were first diagnosed with epilepsy (this may be different to when you had your first epileptic seizure)?

10. Approximately, how many epileptic seizures (any type) have you had in the past 12 months?

11. What is the cause of your seizures?

- ❍ Head trauma/injury
- ❍ Stroke
- ❍ Brain tumor
- ❍ Unknown
- ❍ Other, please specify: _____

12. What type of seizures do you have? (You may select multiple answers). I have seizures where ...

- ❍ I am aware of what is happening (such as simple focal seizures)
- ❍ I am confused or only partly aware (such as complex focal seizures)
- ❍ I briefly lose consciousness (such as absences, tonic and atonic seizures)
- ❍ I lose consciousness and jerk or convulse (such as tonic-clonic seizures)

13. How many different anti-epileptic medications are you being prescribed (please include any emergency rescue medication you may be prescribed)?

- ❍ None
- ❍ One medication
- ❍ Two or more medications

14. Do you have any side-effects from taking your medication?

- ❍ Yes
- ❍ No

15. Who would you say is the main doctor for your epilepsy?

- ❍ G.P
- ❍ A hospital specialist (e.g., Neurologist)
- ❍ G.P and hospital specialist are equally involved

Appendix 12

The Hospital Anxiety and Depression Scale (HADS)

Please read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the **past week**.
Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

Tick only one box in each section

I feel tense or 'wound up':

Most of the time .....
A lot of the time .....
Time to time, Occasionally .....
Not at all .....

I feel as if I am slowed down:

Nearly all the time .....
Very often .....
Sometimes .....
Not at all .....

I still enjoy the things I used to enjoy:

Definitely as much .....
Not quite so much .....
Only a little .....
Hardly at all .....

I get a sort of frightened feeling like 'butterflies' in the stomach:

Not at all .....
Occasionally .....
Quite often .....
Very often .....

I get a sort of frightened feeling as if something awful is about to happen:

Very definitely and quite badly .....
Yes, but not too badly .....
A little, but it doesn't worry me .....
Not at all .....

I have lost interest in my appearance:

Definitely .....
I don't take so much care as I should
I may not take quite as much care ..
I take just as much care as ever .....

I can laugh and see the funny side of things:

As much as I always could .....
Not quite so much now .....
Definitely not so much now .....

I feel restless as if I have to be on the move:

Very much indeed .....
Quite a lot ... .
Not very much .....

Not at all .....

Not at all .....

Worrying thoughts go through my mind:

A great deal of the time .....

A lot of the time .....

From time to time but not too often .

Only occasionally .....

I look forward with enjoyment to things:

As much as ever I did .....

Rather less than I used to .....

Definitely less than I used to .....

Hardly at all .....

I feel cheerful:

Not at all .....

Not often .....

Sometimes .....

Most of the time .....

I get sudden feelings of panic:

Very often indeed .....

Quite often ...

Not very often .....

Not at all .....

I can sit at ease and feel relaxed:

Definitely .....

Usually .....

Not often .....

Not at all .....

I can enjoy a good book or radio or TV programme:

Often .....

Sometimes .....

Not often .....

Very seldom .....

Appendix 13

Metacognitions Questionnaire 30 (MCQ-30)

This questionnaire is concerned with beliefs people have about their thinking.

Listed below are a number of beliefs that people have expressed. Please read each item and say how much you generally agree with it by circling the appropriate number.

Please respond to all items, there are no right or wrong answers.

		Do not agree	Agree slightly	Agree moderately	Agree very much
1.	Worrying helps me to avoid problems in the future	1	2	3	4
2.	My worrying is dangerous for me	1	2	3	4
3.	I think a lot about my thoughts	1	2	3	4
4.	I could make myself sick with worrying	1	2	3	4
5.	I am aware of the way my mind works when I am thinking through a problem	1	2	3	4
6.	If I did not control a worrying thought, and then it happened, it would be my fault	1	2	3	4
7.	I need to worry in order to remain organised	1	2	3	4
8.	I have little confidence in my memory for words and names	1	2	3	4
9.	My worrying thoughts persist, no matter how I try and stop them	1	2	3	4
10.	Worrying helps me to get things sorted out in my mind	1	2	3	4
11.	I cannot ignore my	1	2	3	4

	worrying thoughts				
12.	I monitor my thoughts	1	2	3	4
13.	I should be in control of my thoughts all of the time	1	2	3	4

14.	My memory can misled me at times	1	2	3	4
15.	My worrying could make me go mad	1	2	3	4
16.	I am constantly aware of my thinking	1	2	3	4
17.	I have a poor memory	1	2	3	4
18.	I pay close attention to the way my mind works	1	2	3	4
19.	Worrying helps me cope	1	2	3	4
20.	Not being able to control my thoughts is a sign of weakness	1	2	3	4
21.	When I start worrying, I cannot stop	1	2	3	4
22.	I will be punished for not controlling certain thoughts	1	2	3	4
23.	Worrying helps me to solve problems	1	2	3	4
24.	I have little confidence in my memory for places	1	2	3	4
25.	It is bad to think certain thoughts	1	2	3	4
26.	I do not trust my memory	1	2	3	4
27.	If I could not control my thoughts, I would not be able to function	1	2	3	4
28.	I need to worry, in order to work well	1	2	3	4
29.	I have little confidence in my memory for actions	1	2	3	4

30.	I constantly examine my thoughts	1	2	3	4

Appendix 14

Illness Perceptions Questionnaire- Revised (IPQ-R)

YOUR VIEWS ABOUT YOUR ILLNESS Listed below are a number of symptoms that you may or may not have experienced since your illness. Please indicate by circling Yes or No, whether you have experienced any of these symptoms since your illness, and whether you believe that these symptoms are related to your illness.

	I have experienced this symptom since my illness	This symptom is related to my illness
Pain	Yes No	Yes No
Sore Throat	Yes No	Yes No
Nausea	Yes No	Yes No
Breathlessness	Yes No	Yes No
Weight Loss	Yes No	Yes No
Fatigue	Yes No	Yes No
Stiff Joints	Yes No	Yes No
Sore Eyes	Yes No	Yes No
Wheeziness	Yes No	Yes No
Headaches	Yes No	Yes No
Upset Stomach	Yes No	Yes No
Sleep Difficulties	Yes No	Yes No
Dizziness	Yes No	Yes No
Loss of Strength	Yes No	Yes No

We are interested in your own personal views of how you see your epilepsy. Please indicate how much you agree or disagree with the following statements about your epilepsy by selecting the appropriate box.

1. My epilepsy will last a short time

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree

- ❍ Agree
- ❍ Strongly agree

2. My epilepsy is likely to be permanent rather than temporary

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

3. My epilepsy will last a long time

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

4. My epilepsy will pass quickly

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

5. I expect to have epilepsy for the rest of my life

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

6. My epilepsy is a serious condition

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

7. My epilepsy has major consequences on my life

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

8. My epilepsy does not have much effect on my life

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

9. My epilepsy strongly effects the way others see me

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

10. My epilepsy has serious financial consequences

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree

- ❍ Strongly agree

11. My epilepsy causes difficulties for those who are close to me

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

12. There is a lot I can do to control my symptoms

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

13. What I do can determine whether my epilepsy gets better or worse

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

14. The course of my epilepsy depends on me

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

15. Nothing I do will affect my epilepsy

- ❍ Strongly disagree

- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

16. I have the power to influence my epilepsy

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

17. My actions will have no affect on the outcome of my epilepsy

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

18. My epilepsy will improve in time

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

19. There is very little that can be done to improve my epilepsy

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

20. My treatment will be effective in curing my epilepsy

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

21. The negative effects of my epilepsy can be prevented by my treatment

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

22. My treatment can control my epilepsy

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

23. There is nothing that can help my epilepsy

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

24. The symptoms of my epilepsy are puzzling to me

- ❍ Strongly disagree
- ❍ Disagree

- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

25. My epilepsy is a mystery to me

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

26. I don't understand my epilepsy

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

27. My epilepsy doesn't make any sense to me

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

28. I have a clear picture of understanding my epilepsy

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

29. The symptoms of my epilepsy change a great deal from day to day

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

30. My epilepsy comes and goes in cycles

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

31. My epilepsy is very unpredictable

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

32. I go through cycles in which my epilepsy gets better and worse

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

33 .I get depressed when I think about my epilepsy

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree

- ❍ Agree
- ❍ Strongly agree

34. When I think about my epilepsy I get upset

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

35. My epilepsy makes me feel angry

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

36. My epilepsy does not worry me

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

37. Having epilepsy makes me feel anxious

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

38. My epilepsy makes me feel afraid

- ❍ Strongly disagree
- ❍ Disagree
- ❍ Neither agree or disagree
- ❍ Agree
- ❍ Strongly agree

Appendix 15

The Cognitive Attentional Syndrome Scale (CAS-1)

1. How much time in the last week have you found yourself dwelling on or worrying about problems (e.g. health, family, finances)? (Circle a number below)

0	10	20	30	40	50	60	70	80	90	100

None of the time — **Half of the time** — **All of the time**

2. How much time in the last week have you found yourself analysing your feelings/symptoms or questioning why did this happen to me? (Circle a number below)

0	10	20	30	40	50	60	70	80	90	100

None of the time — **Half of the time** — **All of the time**

3. How much time in the last week have you been focusing attention on the things you find threatening (e.g. symptoms, thoughts, bodily checking)? (Circle a number below)

0	10	20	30	40	50	60	70	80	90	100

None of the time — **Half of the time** — **All of the time**

4. How much time in the last week have you avoided activity or certain situations? (Circle a number below)

0	10	20	30	40	50	60	70	80	90	100

None of the time — **Half of the time** — **All of the time**

5. How much time in the last week have you tried not to think certain thoughts? (Circle a number below)

0	10	20	30	40	50	60	70	80	90	100

None of the time — **Half of the time** — **All of the time**

6. How much time in the last week have you used alcohol to cope with thoughts/feelings? (Circle a number below)

0	10	20	30	40	50	60	70	80	90	100
None of the time					Half of the time					All of the time

7. How much do you believe that worrying or dwelling on thoughts is uncontrollable? (Circle a number below)

0	10	20	30	40	50	60	70	80	90	100
Not at all					Fifty per cent certain					Completely certain this is true

8. How much do you believe that worrying or dwelling on thoughts is harmful? (Circle a number below)

0	10	20	30	40	50	60	70	80	90	100
Not at all					Fifty per cent certain					Completely certain this is true

9. How much do you believe that worrying is helpful? (Circle a number below)

0	10	20	30	40	50	60	70	80	90	100
Not at all					Fifty per cent certain					Completely certain this is true

10. How much do you believe that anticipating problems will keep you safe? (Circle a number below)

0	10	20	30	40	50	60	70	80	90	100
Not at all					Fifty per cent certain					Completely certain this is true

Appendix 16

Power Calculation

A power analysis was undertaken to determine the sample size required to detect an effect of a given size with a given degree of confidence (Dancey & Reidy, 2002). The G*Power 3.1.9.2 (Faul, Buchner, Erdfelder & Lang, 2009) programme calculated a minimum of 127 participants would provide 80% power to identify an effect size of 0.15 with models containing up to 20 predictors at the $p<0.05$ significance.

References

Dancey,C.P., & Reidy, J. (2002). Statistics without maths for psychology. London: Pearson.

Faul, F., Erdfelder, E., Buchner, A. & Lang, A.G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behavior Research Methods, 41, 1149-1160.