Depression, Catastrophising and Repetitive Negative Thinking in Patients with Psychogenic Non-Epileptic Seizures

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This work has not been submitted for any other degree or to any other institution

Literature review word count: 7,961

Research report word count:11,712

Total word count (excluding appendices and references): 19,673

Total word count (including appendices and references): 29,611

Abstract

A systematic review identified 34 studies allowing direct comparisons of depression in patients with psychogenic non-epileptic seizures (PNES) and patients with epilepsy. A meta-analysis found patients with PNES self-reported significantly higher levels of depression than patients with epilepsy. However, group differences in rates of clinical depression were less pronounced, suggesting either under-diagnosis or over self-reporting of depression in patients with PNES. Patients with PNES reported more physical symptoms of depression than those with epilepsy. Whilst depression had a similar effect on health-related quality of life in both patient groups, it was more closely associated with seizure-related variables in patients with epilepsy and interpersonal factors in patients with PNES. A core cognitive feature of depression is repetitive negative thinking, which is a common element of many psychiatric disorders. To explore repetitive negative thinking and catastrophising of seizures in patients with PNES and patients with epilepsy, 59 participants completed a series of self-report questionnaires and 29 also completed a masked and unmasked emotional Stroop task. Patients with PNES self-reported higher levels of repetitive negative thinking, catastrophising of seizures, anxiety and depression than patients with epilepsy; although no significant group differences were found on either emotional Stroop task. This suggested a difference between self-reported catastrophising of seizures and implicit seizure phobia. A possible link between repetitive negative thinking and emotional avoidance could account for these findings. The elevated levels of repetitive negative thinking in patients with PNES suggest this could be a target for psychological intervention.

Acknowledgements

This dissertation is dedicated to my beautiful wife Melissa and son Ethan who have been incredible in keeping me motivated, smiling and well supplied with snacks throughout the three years working towards my DClinPsy. It has meant more to me than I could ever say. To Ethan (when you can read this), thank you for the perspective, giggles, smiles and drool over the last six months.

I also dedicate this dissertation to all my clinical supervisors and tutors over the years. Thank you for challenging and pushing me and helping me develop as a psychologist. Finally my thesis is dedicated to my research supervisors Markus and Liat. Without your ideas and contributions, the project would never have come to fruition. For your support and time, I am hugely grateful.

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Glossary

All sections

PNES	Psychogenic non-epileptic seizures
pwPNES	Patients with psychogenic non-epileptic seizures
PHQ	Patient Health Questionnaire
PWE	Patients with epilepsy

Literature Review

APA	American Psychiatric Association
BDI	Beck Depression Inventory
BSI	Brief Symptom Inventory
DASS	Depression Anxiety Stress Scale
DSM	Diagnostic and Statistical Manual
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health related quality of life
MMPI	Minnesota Multiphasic Personality Inventory
NDDI-E	Neurological Disorders Depression Inventory for Epilepsy
PAI	Personality Assessment Inventory
POMS	Profile of Mood States
SCID-CV	Structured Clinical Interview for Axis I Disorders for DSM-IV, Clinical Version

Research Report

CN-SI	Colour naming Stroop index
DV	Dependent variable
FDR	Benjani-Hochberg False Discovery Rate
GAD	General Anxiety Disorder
IV	Independent variable
MAR	Missing at random
MCAR	Missing completely at random
mSBCS	Modified Safety Behaviors and Catastrophizing Scale
NC	Name colour- task in the standard Stroop
NCS	Name colour Stroop- task in the standard Stroop
NW	Name word- task in the standard Stroop
NWS	Name word Stroop- task in the standard Stroop
PTQ	Perseverative Thinking Questionnaire
RNT	Repetitive negative thinking
SI	Stroop index
WN-SI	Word naming Stroop index

Section 1. Literature review

Abstract

Objectives: This systematic review aimed to contrast levels of depression and factors associated with depression in patients with epilepsy or psychogenic non-epileptic seizures (PNES). *Methods:* ScienceDirect and Web of Science were searched using terms related to PNES and depression with no time limiting criteria set. Studies were required to be quantitative experiments using separate epilepsy and PNES samples (age 16+) and to report the results of a validated measure of depression. *Results:* A total of 34 suitable studies were identified, although these were predominantly rated as low quality and had small sample sizes. Studies consistently found that patients with PNES self-reported higher levels of depression and a meta-analysis highlighting a significant medium effect size. This pattern was less pronounced in rates of clinically diagnosed depression, as although patients with PNES were more likely to have a diagnosis of depression than those with epilepsy, the difference between the groups was less pronounced. Patients with PNES were more likely to report the physical symptoms of depression than patients with epilepsy. Interpersonal factors explained more variation in depression levels in patients with PNES than those with epilepsy, for whom illness related factors were more influential, but in both patient groups, depression had a significant impact on health related quality of life. *Conclusions:* This systematic review demonstrates the higher prevalence of depression in patients with PNES compared to patients with epilepsy and suggests differences in the expression and possible causes of depression between these groups.

Practitioner points

- Patients with PNES are more likely to self-report higher levels of depression and emphasise the physical aspects of depression than patients with epilepsy.
- Whilst depression has a similar impact on health related quality of life in both patient groups, it appears more related to relationship factors in patients with PNES and seizure-related factors in patients with epilepsy.
- The majority of studies reviewed were rated as low quality due to small sample sizes.
- Many studies reviewed only reported depression as a control variable, frequently using depression measures which were not well-validated or scaled.

A Comparison of the Prevalence of Depression and Factors Associated With This in Patients With Psychogenic Non-Epileptic Seizures and Patients With Epilepsy: A Systematic Review and Meta-Analysis.

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

Epilepsy is a disease characterised by the presence of recurrent seizures caused by abnormal activity in neuronal networks in the brain (Fisher et al., 2014). Patients with this disease frequently have co-morbid psychiatric disorders. Tellez-Zenteno, Patten, Jetté, J. Williams, and Wiebe (2007) found that mental health disorders affect one third of PWE over their lifetime, as opposed to one in five of the general population. The most common psychiatric co-morbidity was mood disorder (including major depression) which had a prevalence of 24.4%/14.1% (lifetime/past year) in PWE, as compared to 13.2%/5.2% in the general population.

Psychogenic non-epileptic seizures (PNES) are one of the main differential diagnoses of epilepsy. Whilst these seizures resemble epileptic seizures, most PNES are considered a dissociative response to adverse stimuli, although due to the heterogeneity of the patient group and manifestation of PNES, it is often considered a neurological diagnosis of convenience (R. Brown & Reuber, 2016a). Co-morbid psychiatric disorders are more prevalent in pwPNES than in the general population, with reviews by Diprose, Sundram, and Menkes (2016) and Araújo Filho and Caboclo (2007) reporting estimates of psychiatric illness ranging up to 100%. Both reviews found depression to be the

most common psychiatric disorder in pwPNES. Araújo Filho's review calculated the average prevalence of depression in pwPNES to be 31%, with lifetime rates ranging from 36-80%.

The presence of depression is associated with worse outcomes in both patient groups. In PWE Jacoby, Baker, Steen, Potts, and Chadwick (1996) found a clear relationship between depression and seizure frequency. Whilst this could reflect the negative impact of seizures, Lehrner et al. (1999) found depression was a significant predictor of health-related quality of life (HRQoL), even after controlling for seizure frequency. In pwPNES, depression has been found to predict the level of dysfunction experienced (Kanner et al., 2012). Supporting a possible causative effect, LaFrance Jr. et al. (2010) found that treating pwPNES with sertraline (an anti-depressant) reduced seizure rates compared to a placebo group which reported an increase in seizure frequency.

There are several reviews evaluating depression in PWE (e.g. Kanner et al., 2012), however, few reviews focus on depression in pwPNES. Some reviews that touch on this topic lack detail (e.g. Devinsky, 2003; Kanner et al., 2012). For instance, Kanner et al.'s (2012) review of depression in PWE, contrasted depression scores in PWE and pwPNES, with pwPNES having higher depression scores. However, the search and quality assessment method were not described and group differences were not statistically assessed. Having said that, Diprose et al. (2016) completed a recent systematic review of depression in pwPNES and found that pwPNES have higher levels of depression, although this difference was not statistically significant. However, this review focussed on clinically diagnosed depression and excluded studies using self-report measures of depression. This meant only seven studies were

suitable, reducing the power of the analysis and possibly explaining why the difference between the groups was not significant.

Interestingly, Kanner et al. (2012) suggested that the interplay between peri-ictal symptomology and depression, along with the high co-morbidity between depression and anxiety in this population means that depression can present atypically in PWE. In a similar vein, Diprose et al. (2016) suggest that pwPNES often present with somatic symptoms rather than psychological distress. This suggests that the manifestations of depression may also have characteristic features in pwPNES. Differences in the manifestation of depression could have implications for how depression is diagnosed and treated in these patient groups, but no previous reviews have explored the nature of depression in both of these common seizure disorders.

As such, this article intends to provide a systematic review of the existing literature with the following aims:

1. To contrast levels of self-reported and clinically diagnosed depression in PWE and pwPNES and conduct a meta-analysis to determine if there are reliable group differences.
2. To compare the nature of depressive symptoms or experiences between PWE and pwPNES and determine if there are differences in the factors associated with depression.

Method

The methodology for this review was informed by the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement (Moher, Liberati, Tetzlaff, Altman, & the PRISMA Group, 2009).

Literature Search

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

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

AND

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

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

Article Screening

Due to differences in the nature and outcomes of epilepsy and PNES between children and adults, this review only focussed on studies in adults (or samples predominantly comprised of adults). The titles of papers were screened and were excluded if the following were indicated:

- The study was not a comparative study using separate epilepsy and PNES samples.
- Samples contained individuals' aged 15 and under.
- The study focussed on individuals with learning difficulties.

- The study describes a qualitative study or case study/series.
- The study focussed on neurological issues, EEG or medication.

Abstracts of suitable papers were then screened. In addition to those listed above, studies were required to meet the following criteria:

- The study is an English language paper.
- The study includes a full report of an experimental study (conference abstracts, reviews, etc. were excluded).
- This study refers to depression, psychiatric/psychological disorders or similar, or a measure of depression.

Following this, full-text copies of suitable identified papers were obtained. In addition to those listed above, reports had to meet the following criteria:

- Neither PNES nor epilepsy samples contained patients with mixed epilepsy and PNES.
- Reports used of a measure of depression.
- Depression figures were explicitly reported for both epilepsy and PNES groups and statistically compared between groups (unless reporting the prevalence of depression).
- Reports had a PNES sample ≥ 15 (i.e. > 80% power to detect a very large effect size).

Papers simply reporting and comparing depression figures were included in the comparison phase of the study. Papers selected for more detailed analysis were required to meet the following criteria:

- Include an analysis of subscales of depression measures.

- Have further analyses of depression scores (e.g. correlations or regression analyses)

Reference Search

The reference lists of all suitable papers were screened for additional publications not identified by the initial literature search. These were screened using the criteria and process described above.

Other Exclusions

Strutt, Hill, Scott, Uber-Zak, and Fogel (2011a) used a related sample to Strutt, Hill, Scott, Uber-Zak, and Fogel (2011b). As the level of overlap was unclear, figures from both papers were included, although the 2011b study did not report the Beck Depression Inventory-II (BDI-II; Beck, G. Brown, & Steer, 1996) figures and so this measure was excluded. J. Szaflarski et al. (2003a), J. Szaflarski et al. (2003b), J. Szaflarski and M. Szaflarski (2004) and Testa, Schefft, J. Szaflarski, Yeh, and Privitera (2007) also used a shared dataset. J. Szaflarski et al. (2003a) was excluded as it appeared to reflect an earlier stage of recruitment to J. Szaflarski et al. (2003b). Different sample sizes and measures in the remaining papers mean that all were included, although the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1992) in Testa et al. (2007) was excluded as other studies reported this using larger samples of pwPNES. The overall process is shown in Figure 1.

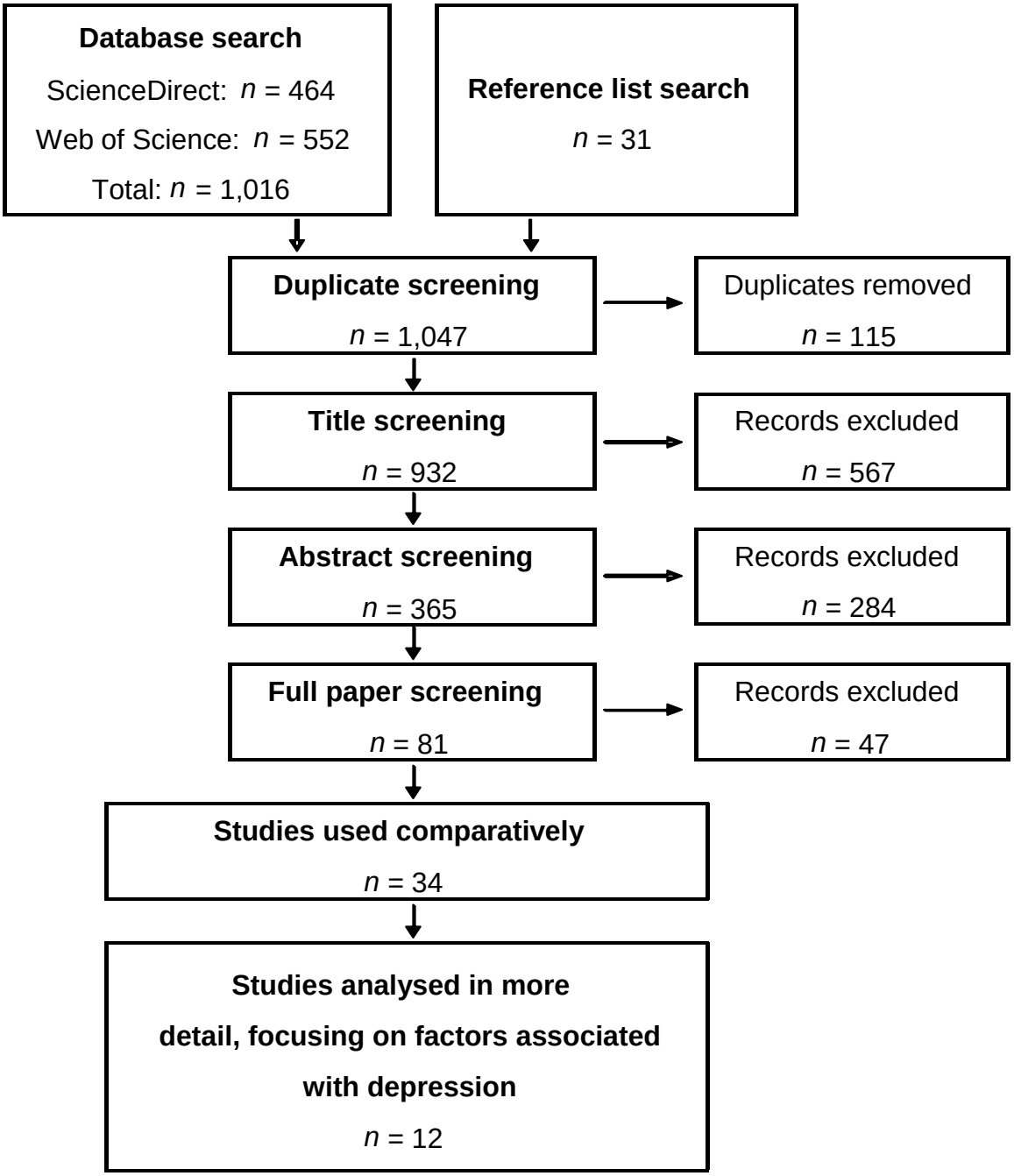

Figure 1. *PRISMA Diagram.*

Statistical Analysis

Where possible, Cohen's *d* effect size was calculated for the difference in depression scores between pwPNES and PWE using Comprehensive Meta-Analysis (CMA; Version 3.3.070; Biostat, 2014). Effect sizes were categorised as small (*d* = .2), medium (*d* = .5) or large (*d* = .8) based on Cohen (1988). A

random-effects meta-analysis was run using CMA. Publication bias was assessed using Begg and Mazumdar's (1994) rank correlation with Kendall's tau, Rosenthal's (1979) fail-safe *N* and funnel plots including a trim and fill analysis (Duval & Tweedie, 2000).

Some papers provided prevalence rates for depression, but did not statistically compare these rates between pwPNES and PWE. These comparisons were completed using a two-tailed independent t-test on the Statistics Calculator (Version 4.0; StatPac, 2017).

Quality Appraisal Tool

Few quality appraisals have been developed specifically for research focusing on PNES. Although generic appraisal schemes exist, these do not assess the validity of the diagnostic process used to differentiate PNES and epilepsy. Reuber and Elger (2003) highlight the need to correctly distinguish PNES from epileptic seizures or psychiatric disorders (e.g. anxiety), as pwPNES are often initially misdiagnosed. A measure designed to evaluate research on pwPNES was developed by R. Brown and Reuber (2016b; Appendix A). This assesses methodology using seven criteria:

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

7. Were PNES excluded from comparison groups?

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

Results

Quality Appraisal

The inter-rater agreement for the quality appraisal was 90.8%. Of the 34 papers reviewed, 22 were rated as low quality and 12 were rated medium quality (see Figure 2 for a full summary). The predominant factor leading to the relatively low quality ratings was a small sample size. Most studies (n = 29) used a poor or moderate sample and only five had a good sample size (≥ 64 participants per group).

Excluding the sample size criteria, methodological procedures were rated more favourably, with nine rated low quality, 24 medium quality, one high quality and a mean methodological quality of 0.57. The most common shortcomings were the failure to state how PNES and anxiety were differentiated or to use samples with sufficiently similar age and gender distributions. Of these, the failure to explain how PNES were distinguished from anxiety attacks is most detrimental as Alper, Devinsky, and Perrine (1995) found anxiety to be an

important diagnostic confound in PNES. Additionally, only 23 studies used video-EEG for all diagnoses, the gold standard diagnostic method for PNES (LaFrance Jr., Baker, Duncan, Goldstein, & Reuber, 2013). These limitations make it more difficult to be confident that PNES had always been diagnosed correctly.

Study	Analysis group	Methodology						Epilepsy controls		Quality assessment	
		Sample size	Video EEG	Epilepsy excluded	Anxiety excluded	Consecutive sampling	Standardised measures	Demographic match	PNES excluded	Score (0-1)	Overall rating
Asmussen, Kirlin, Gale, and Chung (2009)	A	Moderate								0.43	Low
Bewley, Murphy, Mallows, and Baker (2005)	C	Poor								0.57	Low
Binder et al. (2000)	C	Good								0.43	Low
Binzer, Stone, and Sharpe (2004)	C	Poor								0.71	Low
R. Brown et al. (2013)	A	Poor								0.57	Low
Cragar et al. (2003)	A	Moderate								0.57	Medium
Gale and Hill (2012)	C	Poor								0.57	Low
Gale, Hill, and Pearson (2015)	A	Good								0.71	Medium
Goldstein and Mellers (2006)	C	Poor								0.71	Low

Green, Norman, and Reuber (2017)	A	Poor								0.57	Low
Hixson, Balcer, Glosser, and French (2006)	C	Poor								0.57	Low
Johnson et al. (2010)	C	Moderate								0.43	Low
Karakis et al. (2014)	A	Moderate								0.57	Medium
LaFrance Jr. et al. (2011)	A	Moderate								0.43	Low
Lawton, Baker, and R. Brown (2008)	C	Moderate								0.43	Low
Moore, Baker, McDade, Chadwick, and S. Brown (1994)	C	Poor								0.57	Low
Myers, Matzner, M. Lancman, Perrine,, and M. Lancman (2013)	C	Moderate								0.57	Medium
Owczarek and Jedrzejczak (2001)	C	Moderate								0.57	Medium
Prigatano and Kirlin (2009)	A	Poor								0.29	Low
Rawlings, I. Brown, and Reuber (2017)	A	Moderate								0.43	Low

Salinksky, Evrard, Storzback, and Pugh (2012)	C	Moderate								0.43	Low
Scévola et al. (2013)	C	Moderate								0.71	Medium
Strutt et al. (2011a)[+]	C	Poor								0.71	Low
Strutt et al. (2011b)[+]	C	Moderate								0.71	Medium
J. Szaflarski et al. (2003b)[y]	C	Moderate								0.43	Low
J. Szaflarski and M. Szaflarski (2004)[y]	A	Good								0.57	Medium
Testa et al. (2007)[y]	C	Moderate								0.29	Low
Thompson, Hantke, Phatak, and Chaytor (2010)	A	Good								0.57	Medium
Tojek, Lumley, Barkley, Mahr, and Thomas (2000)	C	Poor								0.71	Low
Turner et al. (2011)	C	Poor								0.86	Low
Vanderzant, Giordani, Berent, Dreifuss, and Sackellares (1986)	C	Poor								0.71	Low

Wagner, Wymer, Topping, and Pritchard (2005)	A	Poor								0.71	Low
Wolf et al. (2015)	C	Good								0.71	Medium
Yerdelen and Altintas (2016)	C	Moderate								0.57	Medium
Total **(%)**			**23** **(67.6)**	**30** **(88.2)**	**6** **(17.6)**	**10** **(29.4)**	**29** **(85.3)**	**10** **(29.4)**	**29** **(85.3)**		

$^{+}/_{y}$ = groups of papers analysing the same dataset'; C = Comparison; A = Analysis; = Yes; = No

Figure 2. *Quality appraisal of all studies.*

Depression Measures

The 34 papers in this review used a total of 46 measures of depression, including self-report measures and clinical diagnoses. Table 1 lists the measures used and the percentage that found significant differences between PWE and pwPNES.

Table 1

A list of the measures of depression used, the number of studies that used them, and the percentage that found significant differences between PWE and pwPNES.

Measures	*N* =	% reporting significant differences
Self-report measures		
MMPI-I/ MMPI-II (depression clinical scale)*	9	0
BDI-I or II	7	42.9
PAI (depression scale)	6	50
PHQ-9	2	100
HADS	2	50
POMS (depression/dejection scale)	2	50
NDDI-E	1	100
DASS	1	0
BSI (depression scale)	1	0
Subjective rating	1	0
Diagnostic measures		
SCID-CV diagnosis	4	0
DSM (unspecified procedure)	3	0

Psychiatric diagnosis	1	100
Historical diagnosis	1	0

* All acronyms are described below

At least one validated measure of self-reported depression was used in 13 of the studies reviewed. The BDI-I and BDI-II have been particularly well-validated, including for use in epilepsy (de Oliveira et al., 2014). The Patient Health Questionnaire-9 (PHQ-9; Kroenke, Spitzer, and J. Williams, 2001) and Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) are well-validated screening tools for depression (Gilbody, Richards, Brealey, & Hewitt, 2007; Bjelland, Dahl, Haug, & Neckelmann, 2002) and have been validated in PWE (de Oliveira et al., 2014). The Depression Anxiety Stress Scale (DASS; S. Lovibond & P. Lovibond, 1995) has been validated in clinical populations (T. Brown, Chorpita, Korotitsch, & Barlow, 1997), although it has not been validated within an epilepsy population. Finally, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E; Cole, 2006) was developed specifically for use in PWE and has been validated for use in pwPNES (H. Williams & Bagary, 2012), although only as a categorical measure designed to identify patients likely to have current major depression, rather than a scaled measure.

However, 15 papers did not use clearly validated measures of depression. In this review, most studies of this nature used the depression scales of the Minnesota Multiphasic Personality Inventory (MMPI)-1 (Hathaway & McKinley, 1967), MMPI-2 (Butcher, Dahlstrom, Graham, Tellegen, & Kaemmer, 1989) or Personality Assessment Index (PAI; Morey, 1991). These

measures were developed as assessments of personality. Therefore, they have significant limitations as screening tools for depression, particularly the MMPI, which was developed based on historical constructs of psychopathology that are no longer valid (Helmes & Reddon, 1993). Whilst Morey (1991) designed the PAI around modern clinical diagnoses, Fantoni-Salvador and Rogers (1997) found only moderate evidence of convergent validity between the PAI depression scale and a diagnosis of major depression.

Other studies used the POMS depression/dejection and Brief Symptom Inventory (BSI; Derogatis, 1992) depression scales. It is equally unclear how valid these measures are as screening tools for depression. The factorial structure of the BSI is unclear (Schwannauer & Chetwynd, 2007), and the POMS depression/dejection scale has poor discriminant validity between depression and anxiety (Nyenhuis, Yamamoto, Luchetta, Terrien, & Parmentier, 1999).

Of the studies reviewed, nine reported rates of clinically diagnosed depression (three of which also used a self-report measure of depression), although two of these did not specify the diagnostic criteria used. The remaining seven studies used the diagnostic and statistical manual (DSM) criteria, either the DSM-III (American Psychiatric Association [APA], 1980), DSM-IV or DSM-IV-TR (APA, 1994; APA, 2000). Four of these studies diagnosed depression using the Structured Clinical Interview for Axis-I Disorders for DSM-IV, Clinical Version (SCID-CV; First, Spitzer, Gibbon, & J. Williams, 1996), widely considered as the gold standard diagnosis tool for psychiatric disorders (Jones et al., 2005).

Comparison of Depression Levels in PwPNES Compared to PWE

Study	Quality rating	PNES sample size	Epilepsy sample size	Depression measure (subscale)	Mean (SD) (unless otherwise specified)		Highest scoring group	Effect size (*d*)
					PNES	Epilepsy		
Asmussen et al. (2009)	Low	59	60	BDI-II	13.3 (9.6)	11.0 (9.0)	PNES	0.25
				PAI (depression)	56.46 (11.0)	54.3 (11.2)	PNES	0.19
Bewley et al. (2005)	Low	21	21	BDI-II	27.19 (11.37)	22.05 (10.07)	PNES	0.48
				BDI-II (moderate/severe depression)	71.4%	57.1%	PNES	-
Binder et al. (2000)	Low	70	70	MMPI-2 (depression clinical scale)	68.04 (12.04)	63.24 (11.41)	PNES	0.41
Binzer et al. (2004)	Low	20	20	SCID-CV for DSM-IV (major depression)	30%	15%	PNES	-
R. Brown et al. (2013)	Low	43	24	PHQ-9	13.0 (11.0)z	4.5 (8.75)z	PNES	0.83***
Cragar et al. (2003)	Medium	29	58	MMPI-2 (depression clinical scale)	74 (14.1)	67 (11.7)	PNES	0.56
Gale and Hill (2012)	Low	23	17	MMPI-2 (depression clinical scale)	73.04 (15.03)	63.59 (13.99)	PNES	0.65

Gale et al. (2015)	Medium	205	228	PAI (depression)	63.4 (13.2)	55.3 (11.6)	PNES	0.65***
				PAI (depression ≥ 70)	34.1%	14.0%	PNES	-****
				BDI-II	17.9 (11.1)	11.8 (9.5)	PNES	0.59***
Goldstein and Mellers (2006)	Low	25	19	HADS depression scale	5.72 (3.64)	3.58 (3.19)	PNES	0.62*
Green et al. (2017)	Low	23	72	PHQ-9	13.74 (7.52)	8.65 (7.20)	PNES	0.70**
				PHQ-9 ≥ 10 (moderate depression)	60.9%	43.1%	PNES	-
Hixson et al. (2006)	Low	22	26	BDI-II	19.06 (7.68)	13.75 (10.8)	PNES	0.56
				MMPI-2 (depression clinical scale)	66.58 (12.84)	61.00 (12.93)	PNES	0.43
Johnson et al. (2010)	Low	49	49	MMPI-2 (depression clinical scale)	65.9 (11.56)	62.86 (10.21)	PNES	0.28
Karakis et al. (2014)	Medium	33	126	BDI	19 (11.55)	13.25 (12.09)	PNES	0.48*
LaFrance Jr. et al. (2011)	Low	45	32	BDI-II	21.8 (14.9)	13.5 (10.5)	PNES	0.63*
				History of mood disorder	55.6%	43.8%	PNES	-
Lawton et al. (2008)	Low	32	37	DASS	17.0 (20.3)[z]	13.0 (21.29)[z]	PNES	0.19

Moore et al. (1994)	Low	19	19	HADS depression scale	6.2 (2.6)	5.8 (4.3)	PNES	0.11
Myers et al. (2013)	Medium	86	40	Psychiatric diagnosis (mild-moderate depression)	54.7%	32.5%	PNES	-*
Owczarek and Jedrzejczak (2001)	Medium	38	36	MMPI (depression clinical scale)	60.0 (11.8)	58.1 (12.7)	PNES	0.16
Prigatano and Kirlin (2009)	Low	23	22	PAI (depression)	63.59 (15.08)	59.42 (10.35)	PNES	0.32
				Subjective rating	4.61 (3.33)	3.64 (3.4)	PNES	0.29
Rawlings et al. (2017)	Low	45	62	NDDI-E	18 (5.75)z	14 (7)z	PNES	0.61***
				NDDI-E > 15 (major depression)	75.6%	43.5%	PNES	-**
Salinksky et al. (2012)	Low	50	37	DSM-III/IV diagnosis (major depression)	46.0%	29.7%	PNES	-
Scévola et al. (2013)	Medium	35	49	SCID-CV for DSM-IV (depression)	34.3%	34.7%	PWE	-
Strutt et al. (2011a)[+]	Low	33	35	BDI-II	24.8 (13.0)	21.6 (15.9)	PNES	0.22
		32	35	DSM-IV diagnosis (depression/depression and anxiety)	68.8%	72.0%	PWE	-

Strutt et al. (2011b)[+]	Medium	30	51	DSM-IV diagnosis (depression/depression and anxiety) MMPI-2 (depression clinical scale)	63.30% -	56.9% -	PNES -	- -
J. Szaflarski et al. (2003b)[y]	Low	53	53	POMS (depression/dejection)	21.6 (15.0)	13.9 (10.7)	PNES	0.59**
J. Szaflarski and M. Szaflarski (2004)[y]	Medium	95	99	POMS (depression/dejection > 12)	66.3%	49.5%	PNES	-*
Testa et al. (2007)[y]	Low	45	69	MMPI-2 (depression clinical scale)	69.49 (15.69)	65.16 (13.37)	PNES	0.30
Thompson et al. (2010)	Medium	75	109	PAI (depression)	65.7 (13.4)	59.1 (12.1)	PNES	0.52***
Tojek et al. (2000)	Low	25	33	BSI (depression)	8.28 (6.58)	6.31 (5.39)	PNES	0.33
Turner et al. (2011)	Low	22	21	SCID-CV for DSM-IV (major depression/depression and anxiety)	9.1%	19.0%	PWE	-
Vanderzant et al. (1986)	Low	19	17	MMPI (depression clinical scale) MMPI (depression ≥ 70)	67.53 (13.38) 42.1%	60.41 (12.53) 23.5%	PNES PNES	0.55 -
Wagner et al. (2005)	Low	26	15	PAI (depression)	67.7*	56.5*	PNES	-[o]*
Wolf et al. (2015)	Medium	85	91	PAI (depression)	61.54 (12.39)	58.84 (12.59)	PNES	0.22

Yerdelen and Altintas (2016)	Medium	54	64	SCID-CV for DSM-IV (depressive disorder)	11.2%	10.9%		PNES	-

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

* p < .05

** p <.01

*** p <.001

**** p < .0001

[+]/[y] papers analysing the same dataset;

[z] Median (interquartile range)

[o] Not possible to calculate

Figure 3. Results from all studies.

The majority of measures (93.3%) found pwPNES had higher levels of depression than PWE, although this difference was only significant in 32.6% of analyses (see Figure 3 for all results). In all comparisons where effect sizes could be calculated (*n* = 29), pwPNES scored higher on self-report measures of depression than PWE, with effect sizes ranging from no effect to a large effect (Figure 4).

Stem	Leaf	Frequency	Effect size
0.1	1599	4	None (13.8%)
0.2	11478	5	Small (41.4%)
0.3	023	3	
0.4	0377	4	
0.5	245599	6	Medium (41.4%)
0.6	112459	6	
0.7	-	-	
0.8	2	1	Large (3.4%)
0.9	-	-	

Figure 4. Stem-and-leaf plot of effect sizes.

A meta-analysis was conducted on studies using well validated measures (BDI-I/II, PHQ-9, HADS, DASS and NDDI-E; *N* studies = 13, *N* participants = 1,366). The median quality of these 13 studies was low (*n* =11), with only two medium quality studies included. There was no correlation between the quality of the study and the effect size reported, τ (*N* = 13) = .10, *p* = .69, Effect sizes were homogenous χ^2 (12) = 10.14, *p* = .60 and a significant medium overall effect size was found, *d* = .51 (95% CI [.40 - .62]), *z* = 8.93, *p*

<.001, There was no evidence of publication bias, with a fail-safe *N* = 206. The Begg and Mazumdar rank correlation was non-significant, *τ* (*N* = 13) = -.04, *p* = .85. The funnel plot can be seen in Figure 5, with a point estimate of .51 (95% CI [.40 - .62]) which was unchanged following the Trim and Fill analysis. These findings suggest that the finding that pwPNES report higher levels of depression than PWE is robust.

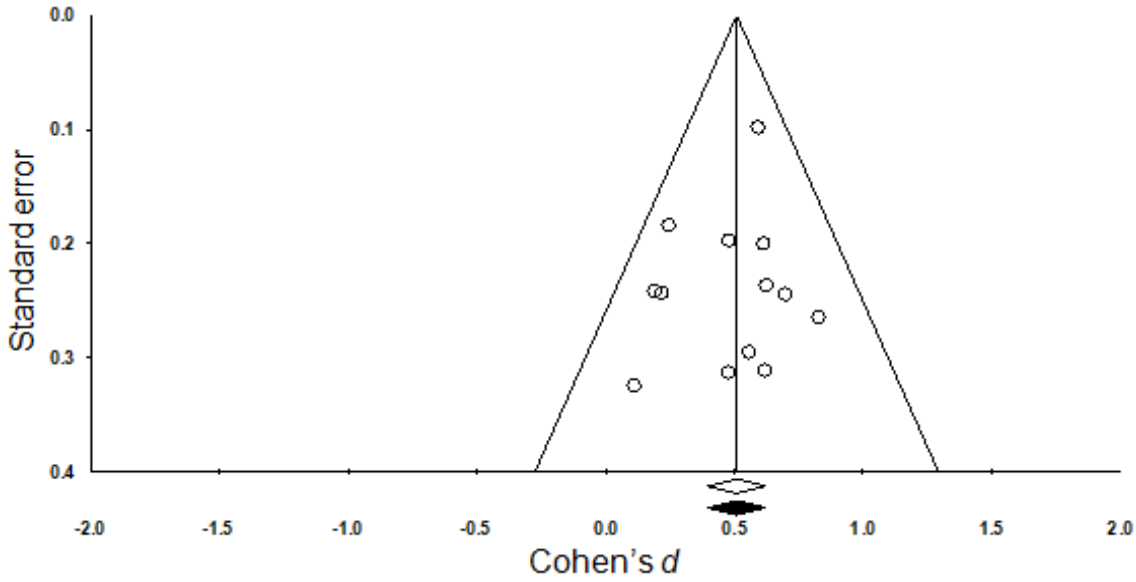

Figure 5. Funnel plot of standard error against Cohen's *d*.

This highlights an interesting discrepancy. Despite pwPNES self-reporting higher levels of depressive symptoms, only one paper reporting on clinical diagnoses found a significant difference between PWE and pwPNES. It was possible that the scores in pwPNES were still predominantly below clinical levels. To explore this, the nine studies reporting on clinically diagnosed depression were compared to the six studies which used clinical cut-off scores on self-report measures of depression. The mean prevalence rates (Figure 6) show that whilst rates were comparable in PWE, more pwPNES reported depressive symptoms suggesting higher rates of clinical depression than were diagnosed.

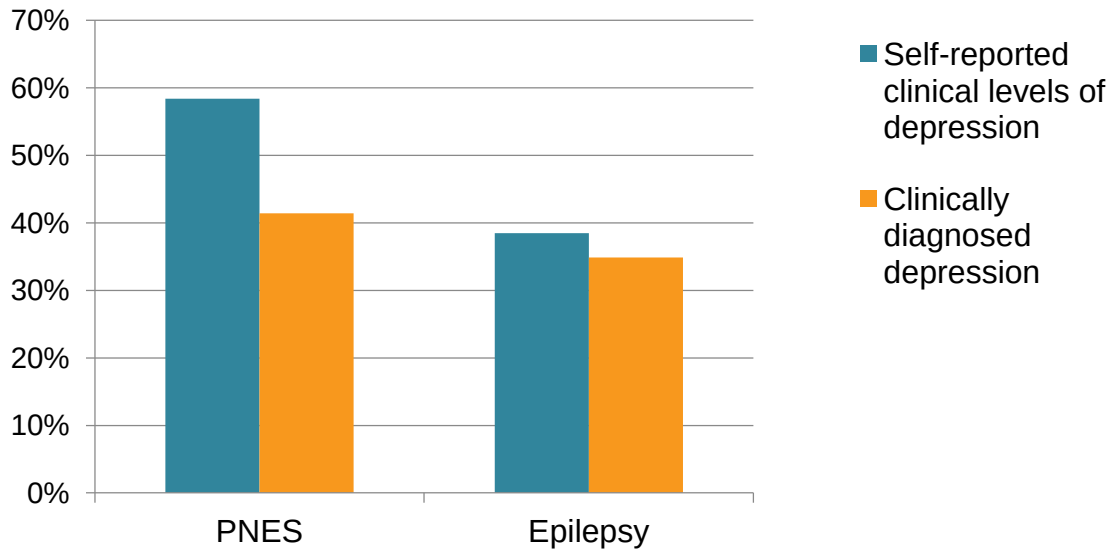

Figure 6. The mean prevalence of self-reported levels of (probable) clinical depression and clinically diagnosed depression in PWE and pwPNES.

Comparison of Factors Associated with Depression in PwPNES and PWE

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

Depressive symptomology. Five studies analysed subscales of the PAI and MMPI depression scales. The PAI depression scale contains three subscales, Dep-C (cognitive symptoms e.g. poor concentration or thoughts of helplessness), Dep-A (affective symptoms e.g. sadness or loss of interest in activity) and Dep-P (physical symptoms e.g. sleep disturbance or physical functioning). PwPNES consistently scored higher than PWE and significant differences were found on all subscales (Table 2).

Table 2

Statistical comparisons of PWE and PNES scores on subscales of the PAI

Study	Dep-A	Dep-C	Dep-P
Asmussen et al. (2009)	ns	Ns	$p < .01$, $d = .48$
Gale et al. (2015)	$p < .001$, $d = .49$	$p < .01$, $d = .28$	$p < .001$, $d = .88$
Thompson et al., 2010)	ns	$p < .05$, $d = .29$	$p < .001$, $d = .76$
Wagner et al. (2005)	ns	Ns	$p < .01$*

* effect size unobtainable

All studies found pwPNES reported significantly more physical difficulties than PWE (Dep-P). In contrast, only 50% of studies found significant differences in cognitive aspects of depression (Dep-C), although the studies finding significant differences had better sample sizes and methodological quality, and thus greater power to detect an effect. Findings on affective aspects of depression (Dep-A) were less equivocal, as only one study found a significant result, although this study had the largest sample. Although pwPNES scored higher than PWE, mean scores did not indicate clinical levels of difficulty except on the Dep-P subscale which indicated a mild difficulty. Contrary to PAI findings, Cragar et al (2003) found no significant differences on any of the depression subscales of the MMPI-2 including D3 (physical malfunctioning), although the previously discussed weakness of the MMPI-2 (e.g. outdated constructs of psychopathology) could account for these differences.

A possible explanation of the group differences on the Dep-P subscale of the PAI could be the higher proportion of females in the PNES samples. Gale et al. (2015) and Asmussen et al. (2009) found females with PNES reported

significantly higher scores on this subscale than males with PNES. In summary, these findings suggest that pwPNES, especially females, suffer from, or recognize, the physical symptoms of depression more than the cognitive and emotional aspects.

Attachment, relationships and depression. Several studies investigated depression in conjunction with aspects of interpersonal functioning. Green et al. (2017) explored the association between attachment and depression in PWE and pwPNES, focusing on the relationship with the main caregiver. They found relationship conflict, attachment, attachment anxiety and attachment avoidance significantly correlated with depression in both patient groups. Although all these correlations were stronger for pwPNES, the only significant group difference was in attachment anxiety, where pwPNES showed a significantly stronger positive correlation between attachment anxiety and depression. Relationship variables explained a significant proportion of depression in both patient groups, although these accounted for 16% of the variation in PWE, compared to 45% of the variation in pwPNES. Seizure and demographic variables were more comparable between groups, explaining 26% of variation in pwPNES and 23% in PWE, although this was only significant in PWE. Interestingly, whilst seizure severity was a significant predictor of depression in patients with PWE, this was not the case for pwPNES. These findings all suggest that depression in pwPNES is more related to relationship factors than illness-related factors, whilst the opposite pattern is true for PWE.

A caveat for interpreting this study is the large difference in the population sample sizes, with a PNES sample of 23 compared to a PWE sample of 72. This may explain why the proportion of depression accounted for

by seizure and demographic variables was only significant in PWE, despite accounting for more variation in depression scores in pwPNES.

Another study which examined the link between depression and interpersonal factors in PWE and pwPNES was LaFrance Jr. et al. (2011), who analysed the association between family functioning and depression, although the study focused on HRQoL (see next section). Family functioning was found to be unhealthy for both PWE and PNES. However, only in pwPNES was family functioning significantly correlated with depression scores, along with family affective involvement (e.g. valuing each other) and roles (the patterns of behaviour used to fulfil family functions). This suggests that family functioning may have a larger association with depression in pwPNES, complementing the findings of Green et al. (2017) and suggesting there is a stronger association between relationship variables and depression in pwPNES than in PWE.

Health status, quality of life and depression. As part of the previously described study, LaFrance Jr. et al. (2011) analysed HRQoL, exploring its relationships with depression and seizure-related variables. They found a significant relationship for both patient groups, with depression explaining 46% variation in HRQoL PNES and 40% in PWE, more than that explained by seizure frequency, illness duration, or family functioning.

In contrast, Karakis et al. (2014) found depression to be a significant determinant of HRQoL in pwPNES, but not in PWE. This is a surprising finding, given the strong relationship reported between HRQoL and depression in PWE (R. S. Taylor, Sander, R. J. Taylor, & Baker, 2011). This contrasting finding by LaFrance Jr. et al. (2011) and Karakis et al. (2014) may reflect the analysis

used by Karakis et al. (2014), with only significant group differences being entered into the regression analysis.

Another study assessing HRQoL by Rawlings et al. (2017) found highly significant correlations between HRQoL and depression in both patient groups, with depression again explaining more variance in HRQoL scores than seizure related variables in both patient groups. Although some participants were recruited from a hospital, this was one of the few studies which also recruited from a non-medical setting, suggesting the findings can be generalized beyond the clinical setting.

J. Szaflarski and M. Szaflarski (2004) also explored the relationship between HRQoL and depression. They used the 36-item Short Form Health Survey (Ware & Sherbourne, 1992) which contains 8 subscales; physical functioning, role limitation: physical, role limitation: emotional, energy/fatigue, emotional well being, social functioning, pain and general health. Using a POMS cut-off score of >12 to indicate depression, they found depressed pwPNES reported significantly lower HRQoL across all SF-36 subscales than depressed PWE. The authors conducted further analyses on the 'role limitation: physical' subscale, comparing depressed PWE and pwPNES with clinically depressed patients. After controlling for multiple comparisons, they found that depressed pwPNES reported significantly lower scores on this subscale than clinically depressed patients, a pattern not found in PWE. This supports the earlier findings that depression in PNES is more strongly related to physical symptoms of depression. Unfortunately, the use of the POMS is a weakness as it has no standardised clinical norms.

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

Cognitive and emotional functioning and depression. Two papers explored the links between depression and emotional or cognitive function in PWE and PNES. Prigatano and Kirlin (2009) investigated subjective and objective measures of affective and cognitive functioning in PWE and PNES, using the PAI to assess psychopathology. Notably, the study found that pwPNES subjective reports of depression had significant large and medium positive correlations with subjectively reported cognitive difficulties and a standardised test of delayed memory. In contrast, the standardised measure (the PAI-depression scale) correlated with subjective memory abilities, but no other subjective or standardised cognitive measures. However, this study provided little detail about the methodology, diagnostic process, or analytical methods used and did not adjust the significance level for the high number of correlations tested. This creates a strong likelihood of Type-I error, further compounded by the small sample size.

A more robust study of emotional functioning was completed by R. Brown et al., (2013) who clustered PNES patients based on their scores on measures of emotional dysregulation and alexithymia. This identified two patient clusters, one with high emotional dysregulation and alexithymia scores (cluster one) and the other containing the remainder of the PNES sample (cluster two). Analysis of PHQ-9 scores found both clusters had significantly higher levels of

depression than PWE, but no significant differences were found between the two clusters of pwPNES. Although clustering patients allowed an interesting analysis of depression in pwPNES, it reduced the sample sizes, limiting the power of analyses. This could explain why no significant difference was recorded between PHQ-9 scores in clusters one and two, despite having a larger discrepancy between means than cluster two and PWE.

Discussion

The studies identified in this review consistently found that pwPNES report higher levels of depressive symptoms than PWE. In the majority of studies, this difference was not significant; however this appears to be related to the low quality of most studies which were based on small, low-powered samples. The meta-analysis confirmed the finding of higher levels of depression in pwPNES, identifying a significant medium effect size in depression levels between PWE and pwPNES. Despite pwPNES reporting higher levels of depressive symptoms than PWE, this was not reflected by the rates of clinical diagnoses of depression. Although overall rates of diagnosed depression were higher in pwPNES than for PWE, there was a greater discrepancy between the rate of clinical diagnosis and self-reported clinical levels of depression than that seen in PWE. It was not clear from the studies reviewed what caused this discrepancy. Possible explanations include the under-diagnosis of clinical depression in pwPNES, or pwPNES catastrophising symptoms on self-report measures.

Supporting the hypothesis of under-diagnosis, Wagner et al. (2005) suggested that pwPNES do not show the spectrum of symptoms typically associated with clinical depression. This is supported by the consistent finding

that pwPNES were more likely to highlight the physical symptoms of depression than cognitive or emotional aspects compared to PWE. This may mean clinicians overlook patient reported symptoms of clinical depression. Additionally, many formal diagnostic methods (e.g. the SCID) are based on an etiological model which excludes symptoms that could be attributed to a known medical condition (A. Nezu, C, Nezu, Greenberg, & Salber, 2014). Due to the physical symptoms associated with PNES, epilepsy, or its treatment, it is possible clinicians do not prioritise patient reports of physical symptoms of depression, potentially leading to missed diagnoses. Kanner et al. (2012) reported that whilst conventional diagnostic criteria (e.g. the DSM) apply to many PWE, they poorly reflect some of the atypical features of depression seen in this population. The current findings would suggest this is even more applicable for pwPNES.

Another potential explanation for the discrepancy in rates of clinically diagnosed depression and self-reported symptoms is that pwPNES catastrophise symptoms of depression and rate these as more severe than may appear to clinicians. Catastrophising is defined as an exaggerated set of negative cognitions which magnify anticipated or perceived threat (Sullivan, Bishop, & Pivik, 1995). Supporting the idea that catastrophising could explain the elevated self-reported depression symptoms seen in pwPNES, Novakova, Howlett, Baker, and Reuber (2015) found that pwPNES experience emotions as more overwhelming, report more severe somatic symptoms and interpret these as more threatening than PWE.

The findings of this study add to the large evidence base that pwPNES express distress somatically and report more somatic symptoms than PWE

(Reuber, House, Pukrop, Bauer, & Elger, 2003). Despite this finding, it is important to note that in some studies, pwPNES also reported higher scores on measures of affective and cognitive aspects of depression than PWE. Additionally, the fact that pwPNES self-report higher levels of depression than PWE suggests an awareness of emotional experience, with R. Brown et al. (2013) finding this effect even in pwPNES with high alexithymia scores.

Several factors relating to interpersonal functioning significantly associated with depression in pwPNES. Green et al. (2017) found that relationship variables explained 45% of the variation in pwPNES' depression scores, with anxious attachment scores having particularly strong positive associations with depression. This relationship was found in both pwPNES and PWE, supporting the idea that a fearful attachment style is associated with higher depression scores (Murphy & Bates, 1997). However, the relationship between attachment anxiety and depression was stronger in pwPNES than PWE, suggesting the association is stronger than might typically be expected. This finding is significant as pwPNES typically have higher levels of fearful attachment (Holman, Kirkby, Duncan, & R. Brown, 2008), suggesting this may be a key factor in the levels of depression observed.

The importance of relationship factors was supported by LaFrance Jr. et al. (2011) who found that measures of family functioning, whilst unhealthy in both PWE and pwPNES, only significantly correlated with depression in pwPNES. This matches the findings of Krawetz et al. (2001), who found pwPNES perceived their families as dysfunctional, particularly in areas of communication and emotional involvement. Krawetz et al. (2001) argue this suggests pwPNES may struggle to articulate their needs and feelings within the

family system. Being unable to effectively resolve conflict with family members, combined with an anxious or fearful attachment style, could cause depression. Whilst it is not possible to determine cause and effect from these studies, LaFrance Jr. et al. (2009) found that supporting pwPNES to address family discord lead to a subsequent reduction in depressive symptoms, suggesting a potential causative relationship.

The association between depression and seizure-related variables was less clear-cut than the association between depression and relationship factors. Whilst seizure-related variables (e.g. seizure severity) had a stronger relationship with depression scores in PWE than pwPNES, the relationship between the impact of health status on life (as assessed by HRQoL measures) and depression was less clear cut. The findings suggest that the influence of health within a person's life has a slightly stronger relationship with depression in pwPNES than PWE. However, in both patient groups, depression explained more variation in HRQoL than seizure related variables (Rawlings et al., 2017; LaFrance Jr. et al., 2011) and family functioning (LaFrance Jr. et al., 2011). This highlights the impact of depression in both patient groups, although again, the cross-sectional nature of the studies reviewed meant that the direction of this relationship cannot be determined. As HRQoL incorporates psychological health, it is fair to assume that depression has a causative impact on this construct, although it is likely to be a two-way relationship. Interestingly, J. Szaflarski and M. Szaflarski (2004) compared depressed pwPNES and PWE to clinically depressed patients and found that pwPNES reported significantly more physical role limitations. This again suggests that pwPNES highlight their physical symptoms and experience these as more disabling than patients with other health conditions.

Critique

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

Finally, the majority of the studies included in this review were hospital-based, which increases the likelihood that the participants would be experiencing clinical difficulties. This is especially likely with diagnostic studies, as participants in these studies would have been unaware of their diagnosis and potentially experiencing a period of stress because of this. These factors are

likely to have skewed the samples to reflect populations with elevated levels of psychopathology. However, these weaknesses reflect the nature of the research completed with pwPNES, rather than the methodology of the review and it is hard to see how these could be overcome based on the current literature.

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

Empirical Recommendations

The limitations highlighted in this review reflect the difficulty of conducting research in this area. PNES are difficult to diagnose and this process is often an iterative process (LaFrance Jr. et al., 2013) and researchers will often be unaware how their participants were diagnosed. Researchers should aim to provide as much detail as possible about the diagnostic process, or clearly state the aspects for which they have no information. Additionally, recruiting large numbers of pwPNES is often beyond the timeframe and resources available to researchers, as reflected by the small sample sizes. This means many studies are prone to Type II errors, potentially missing important causal or maintaining factors for PNES. To address this, there is a need for more meta-analyses of the literature on pwPNES.

Further research should also explore the discrepancy between levels self-reported and clinically diagnosed depression in pwPNES. Such a study could use a formal diagnostic process (e.g. the SCID) alongside a self-report measure with well defined cut-off scores (e.g. the NDDI-E or the BDI-II) to explore any identified discrepancies in diagnosis rates.

Clinical Recommendations

Clinically, there is a clear need for depression to be routinely assessed. Whilst this is likely to be standard practise for most clinicians, clinicians need to be aware that depression may not manifest in a typical manner in pwPNES. In particular, clinicians should focus on the physical symptoms of depression and somatic expressions of distress. As standardised clinical assessments do not seem to reflect the level of difficulty experienced by pwPNES and may lead to under-diagnosis if used in isolation, standardised self-report measures of depression should also be considered.

The elevated levels of depression in pwPNES and the strength of association with factors such as relationships and HRQoL suggest that depression should be a focus for psychological treatment, which could have beneficial effects beyond the depression itself. In particular, the social aspects of pwPNES lives appear to have significant relationships with depression and are likely to be suitable targets for intervention. These ideas have been demonstrated by LaFrance et al. (2009), who found Cognitive Behaviour Therapy to lead to global improvements in pwPNES, including in measures of depression.

Summary

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

Despite these findings, there are extensive limitations in the available research in this area. Whilst depression is frequently measured in studies, this is not usually discussed in detail and very little information is provided about the possible underlying cognitive processes. One such cognitive bias commonly found in another chronic health condition (pain), is the propensity for depressed individuals to catastrophise (Sullivan et al., 2001), with Geisser, Robinson, Keefe, and Weiner (1994) finding that catastrophising mediated the relationship between depression and patients' experience of chronic health pain. Further research investigating this area could shed light on some of the cognitive biases experienced by pwPNES.

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Section 2. Research report

Abstract

Objectives: A growing body of evidence highlights catastrophic thinking in patients with psychogenic non-epileptic seizures (PNES). This study aimed to explore repetitive negative thinking and catastrophic thinking about seizures, comparing patients with PNES to patients with epilepsy. *Design:* The study used cross-sectional and experimental elements, with the primary analyses comparing patients with PNES and patients with epilepsy. *Methods:* The study used the Perseverative Thinking Questionnaire and a modified version of the Safety Behaviors and Catastrophizing Scale to assess levels of repetitive negative thinking and catastrophising of seizures. Participants also completed self-report measures of anxiety and depression. Questionnaires were completed by 55 participants, 29 of whom also completed an emotional Stroop task exploring fear of seizures. This consisted of a masked and unmasked emotional Stroop task using words related to seizures (threat condition) and neutral words. *Results:* Patients with PNES reported significantly higher levels of repetitive negative thinking, catastrophising of seizures, and depression and anxiety than patients with epilepsy, although no significant differences were observed on the emotional Stroop tasks. Stroop indices were not related to the levels of repetitive negative thinking, although the masked Stroop was significantly correlated with the levels of seizure catastrophising. *Conclusions:* Levels of repetitive negative thinking and catastrophising are higher in patients with PNES than PWE. Repetitive thinking has been associated with emotional avoidance, suggesting a possible function within this population.

Catastrophising and Repetitive Negative Thinking in Patients with Psychogenic Non-Epileptic Seizures Compared to Patients with Epilepsy

Epileptic seizures are characterised by recurrent seizures caused by abnormal activity across neuronal networks in the brain (Fisher et al., 2014), whilst psychogenic non-epileptic seizures (PNES) resemble epileptic seizures, but are usually considered a dissociative response to negative stimuli (R. Brown & Reuber, 2016). Moore and Baker (1997) found that 95% of patients with PNES (pwPNES) suffer from co-morbid psychological problems, which are thought to make an important contribution to the aetiology and maintenance of PNES. The aim of this study was to explore some of the psychological factors associated with PNES, comparing them to a sample of PWE to establish which factors are unique or exaggerated in pwPNES compared to PWE.

One potential psychological factor relating to PNES is the pathological processing of emotional stimuli. Roberts and Reuber (2014) argue this is an important psychological trigger for PNES, proposing that PNES are manifestations of overwhelming emotions triggered by internal processes such as cognitions which catastrophise and exacerbate their emotional experience. Sullivan, Bishop, and Pivik, (1995) define catastrophising as an exaggerated set of negative cognitions in response to anticipated or perceived threat. They propose that catastrophising cognitions have three dimensions: magnification of threat, perseverating on threat and feeling unable to cope with threat (helplessness). There is a strong link between catastrophising and anxiety. Breitholtz, Westling, and Öst (1998) found that patients with panic disorder catastrophise bodily symptoms, misinterpreting these as indicating an imminent physical disaster, a mechanism which is proposed to cause the panic attack

(Clark, 1986). There is also a well-established link between catastrophising cognitions and patients with chronic pain. Sullivan et al. (2001) found that individuals who catastrophise their pain had higher levels of anxiety and depression and reported more emotional distress. Crucially, they argue that catastrophising has a causal relation to pain. This was supported by Keefe, Brown, Wallston, and Caldwell (1989) who found that initial catastrophising in patients with rheumatoid arthritis predicted the subsequent level of perceived disability, even after controlling for other disability-related factors. There is considerable overlap in the symptomology between patients with chronic pain and pwPNES. Dixit, Popescu, Bagić, Ghearing, and Hendrickson (2013) found that pwPNES were more likely to have other functional somatic syndromes, including fibromyalgia and chronic pain syndrome. For both pain and anxiety, catastrophising is proposed to play a causative and maintaining role in the mental or physical health condition. Considering the overlap between chronic pain and PNES, it is possible that a similar mechanism exists for pwPNES.

A growing field of research is the exploration of catastrophising cognitions in pwPNES. There is evidence that pwPNES tend to magnify threat. Robson, Drew, Walker, and Reuber (2012) found that whilst PWE typically normalise the impact of their seizures when giving accounts of their seizures to doctors, pwPNES were more likely to magnify or catastrophise their seizure experiences. Novakova, Howlett, Baker, and Reuber (2015) also found that pwPNES experience emotions as more overwhelming, report more severe somatic symptoms and interpret these as more threatening than PWE, suggesting they magnify these experiences.

Evidence for the ‘helpless’ aspect of catastrophising comes from Stone, Binzer, and Sharpe (2004) who found that pwPNES had a more external locus of control than PWE and were more likely to experience events as unpredictable and out of their control. The coping responses associated with PNES also provide indirect evidence for this aspect of catastrophising. Dimaro et al. (2014) found pwPNES reported more avoidant coping strategies than PWE, particularly towards emotional responses, whilst Bakvis, Spinhoven, Zitman, and Roelofs (2011) found pwPNES show avoidant experimental responses to social threats. These avoidant coping strategies suggest a perceived inability to cope with distress more actively.

Together, these findings provide evidence for two of the three aspects of catastrophic cognition in pwPNES. However, there is little research on this patient group which explores the third aspect of catastrophising, whether or not levels of perseverative thinking are elevated. Perseverative thinking includes worry (future-focussed) and rumination (past-focussed) and maintains focus on negative stimuli (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008), often referred to as repetitive negative thinking (RNT). In the only identified study explicitly investigating RNT in pwPNES, Tojek, Lumley, Barkley, Mahr, and Thomas (2000) found that pwPNES ruminated about past stressful events more frequently than PWE. The authors argue that this demonstrates a failure for pwPNES to resolve stressful experiences. Whilst these findings suggest pwPNES may have higher levels of RNT, the study focussed on rumination on stressful events rather than RNT as a general cognitive bias. Further research would help to clarify whether pwPNES display higher levels of RNT. Whilst Nolen-Hoeksema et al. (2008) highlight differences between rumination and

worry; there is a significant degree of overlap between these measures. Ehring et al. (2011) argue that all forms of RNT share three key characteristics:

- They are repetitive, intrusive and difficult to disengage from.
- They are perceived as being unproductive.
- They place high demands on mental capacity.

McEvoy, Watson, Watkins, and Nathan (2013) argue that the high degree of overlap between different types of RNT mean it is more parsimonious to assess RNT as a unitary construct, thus reducing the patient burden during assessment. Due to these findings and the lack of previous research, this study focused on RNT as a whole, rather than assessing separate constructs of rumination and worry. As such, the primary aim of this study was to investigate whether pwPNES show higher levels of RNT than PWE.

A secondary aim of this study was to investigate the link between RNT and catastrophic thoughts, beliefs or fears relating to seizures. This phenomenon has been investigated in PWE. J. Goldstein, Seidenberg, and Peterson (1990) found that PWE who were more fearful of their seizures reported higher levels of emotional difficulty and avoidant behaviour. Considering the previously mentioned finding that PWE are more likely to normalise their seizures than pwPNES (Robson et al, 2012), it could be expected that pwPNES are more likely to catastrophise and have higher levels of fear relating to their seizures than PWE. Zeitlin, Bradburn, and Lawson-Kerr (1995) used an emotional Stroop task to investigate fear of seizures in PWE and found PWE who reported a greater fear of seizures also showed greater Stroop interference on seizure-related words. In contrast, in a similar Stroop study using pwPNES, no greater Stroop interference on seizure-related words

was observed (Novakova, 2015). Whilst this may imply that pwPNES show no attentional bias towards seizure-related words, compared to PWE, pwPNES often show a greater difference between explicit (consciously reported) and implicit (unconscious) measures (e.g. Dimaro et al., 2014), suggesting a dissociation between conscious and unconscious experiences. Whilst the Stroop task is often used as an implicit measure, it still allows the possibility for intrusion of explicit conscious processing. As such, a fully implicit measure may be more suited to detect an effect, allowing more robust conclusions to be made about whether pwPNES have a stronger response to seizure-related words than PWE. One way to isolate truly implicit processing is to use the masked Stroop task. This presents stimuli so rapidly that conscious processing is impossible and may be more sensitive to perceived threat than an unmasked Stroop (Williams, Mathews, & MacLeod (1996). Bakvis, Roelofs, Kuyk, Swinkels, and Spinhoven (2009) used a masked Stroop to investigate implicit social threat processing in pwPNES and found higher levels of pre-conscious vigilance than in control participants, demonstrating the masked Stroop can detect implicit effects in pwPNES.

In light of these findings, this study used two main methods to investigate RNT and catastrophic thoughts or fears relating to seizures. Self-report measures were used to explicitly measure levels of RNT and seizure catastrophisation and avoidant behaviours. In addition, the Stroop task was used to implicitly measure participants' fear of seizures, using seizure threat words presented in a masked and unmasked manner. To ensure that this reflects a genuine emotional Stroop effect, rather than differences in cognitive speed, a standard colour-word Stroop task (adapted from Stroop, 1935) task was used. The study compared pwPNES against PWE, as this increased the

likelihood that observed effects reflect differences between epileptic and non-epileptic seizures, rather than the experience of seizures per se.

Hypotheses

Primary hypothesis:

1. Compared to PWE, pwPNES would self-report higher levels of RNT.

Secondary hypotheses:

2. No difference would be found between pwPNES and PWE on the colour-word Stroop task (standard Stroop).
3. On the unmasked Stroop task, PWE would show greater vigilance to seizure-related words than pwPNES. However, on the masked Stroop task, pwPNES would show greater vigilance to seizure-related words than patients with PWE.
4. Self-reported RNT scores in pwPNES and PWE would significantly associate with higher masked Stroop indices.
5. Self-reported RNT would correlate with self-reported catastrophising of seizures in pwPNES and PWE.
6. In both PWE and pwPNES, self-reported RNT would be significantly associated with seizure frequency.

Pilot Study

Before commencing the main experiment, a pilot study (granted ethical approval by the University of Sheffield) was run to test the computerised Stroop tasks used in the main study.

Method

Participants. Twelve participants were recruited on a word of mouth basis.

Design. Participants were provided with an information sheet and gave their consent before completing the experiment. The task consisted of three experimental blocks:

Block one: Conscious identification task. This task was based on Wikström, Lundh, and Westerlund (2003) and established the minimum exposure time from which a participant could identify a word. This then determined how long the masked stimulus was presented in block two; ensuring participants could not consciously identify the presented stimuli.

Block two: Emotional Stroop. This contained two tasks (the emotional masked and emotional unmasked Stroop) each containing two conditions (seizure threat and neutral). In both tasks, participants were required to identify the colour of the stimulus. Words perceived as more threatening were expected to have longer reaction times than neutral words.

***Block three: Standard Stroop*.** This block contained four tasks, naming colours (NC), naming words (NW), naming colours Stroop (NCS) and naming words Stroop (NWS). The NCS and NWS tasks had congruent and incongruent stimuli creating six conditions (NC, NW, NCS-congruent, NCS-incongruent, NWS-congruent, and NWS-incongruent). This task assessed error rates and reaction times to detect any group differences that could influence the results.

At the end of the experiment, participants were given a debriefing sheet.

Apparatus. All the tasks were run on a laptop (Asus X555LA, 15.6 inch screen) using E-Prime 2.0 (Psychology Software Tools, 2012).

Stimuli. All stimuli (Appendix C) were taken from the word lists used by Novakova (2015) with each list containing ten threatening words and ten length-matched neutral words. These were presented in red, green, yellow or blue on a black background. The masked and unmasked Stroop tasks used the same neutral and threat words from the Seizure Threat list. Novakova (2015) developed this list by taking a small set of words from Zeitlin et al. (1995) and selecting additional potential words from a publication of personal accounts from PWE (Schachter, 1993). These were combined to create a list of 25 words which were rated by PWE and pwPNES for their level of threat and relevance to seizures. The ten threat words were selected based on ratings of seizure relatedness, whilst the corresponding neutral words were selected based on length and low threat ratings. To reduce semantic satiation, practice trials and the conscious identification task used stimuli from other word lists used by Novakova (2015). The conscious identification task used 20 stimuli (ten threatening and ten neutral words) which were presented in yellow as recommended by Wikström et al. (2003).

Procedure. Participants sat approximately 50cm from the laptop and completed the conscious identification task, masked emotional Stroop, unmasked emotional Stroop and then the standard Stroop task.

Conscious identification task. Participants were presented with instructions and given the chance to ask questions before viewing the experimental sequence (Figure 1). Participants verbally confirmed the stimulus to the researcher who indicated a correct or incorrect response. If incorrect, the

procedure was repeated with the stimulus presented for 17ms longer. This was repeated in increments of 17ms until the participant correctly identified the stimulus. The procedure was repeated for each word (20 trials).

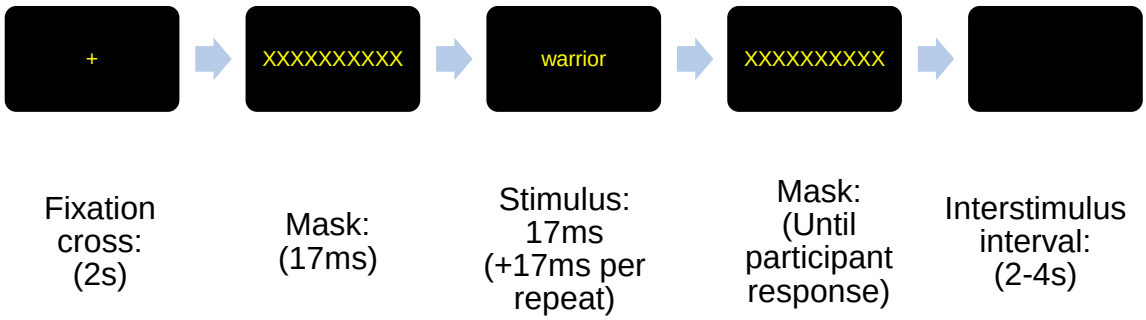

Figure 1. Conscious identification task procedure.

Emotional Stroop tasks. This block contained two tasks; the masked Stroop, followed by the unmasked Stroop task. Participants were presented with the instructions and given the opportunity to ask questions before beginning the experimental procedure (Figure 2). The exposure time for the masked stimulus was set at 17ms below the shortest exposure time a participant correctly identified a stimulus in the conscious identification task. The post-stimulus mask was shown in the same colour as the word and participants were required to indicate the colour by pressing the appropriate colour-coded key on the keyboard.

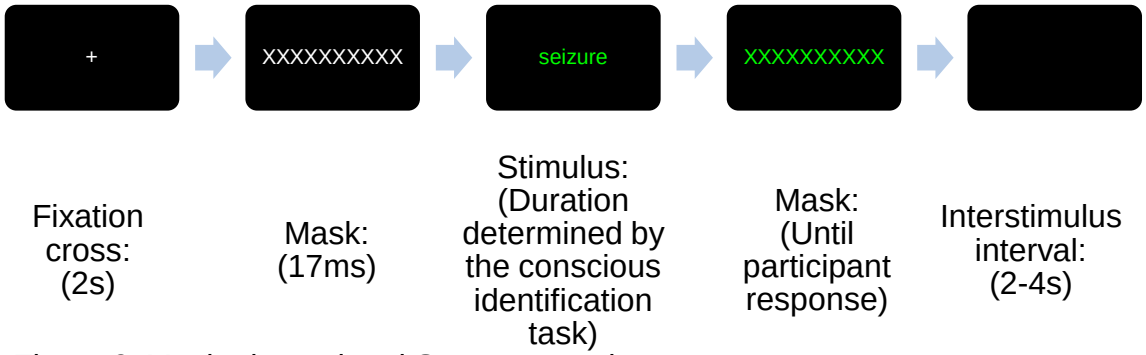

Figure 2. Masked emotional Stroop procedure.

Participants completed eight practice trials (two in each colour), which provided feedback on the accuracy of their responses. Following the practice trials, participants completed the main experimental phase. Participants viewed each of the twenty stimuli four times (once in each colour), completing 80 trials. The order of the stimuli was randomised across participants.

Participants then completed the unmasked Stroop, viewing the instructions before completing the experimental procedure (Figure 3). Participants completed eight practice trials which provided feedback, followed by 80 trials in the main experimental phase. The order of the stimuli was randomised across participants.

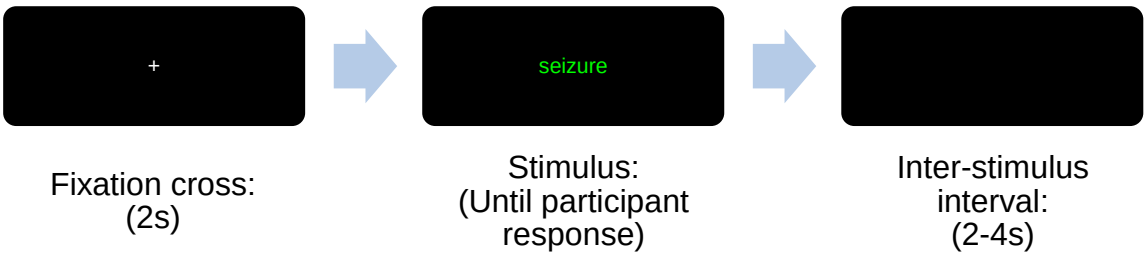

Figure 3. Unmasked emotional Stroop task procedure.

Standard Stroop task. This contained the naming colours (NC), naming words (NW), naming colours Stroop (NCS) and naming words Stroop (NWS) tasks.

The NC task used symbols (@@@@@) printed in red, green, blue and yellow. Each colour was presented three times (a total of 12 trials). Participants were required to indicate the colour of the stimuli via the appropriate colour-coded key.

The NW task used the words ‘red’, ‘green’, ‘blue’ and ‘yellow’ presented in white text. Participants were required to indicate the word by pressing the appropriate colour-coded key. Each word was presented three times (a total of 12 trials).

In the NCS and NWS, the words ‘red’, ‘green’, ‘blue’ and ‘yellow’ were presented in red, green, blue or yellow text. In the NCS, participants were required to indicate the colour the word was displayed in, whilst in the NWS, participants were required to indicate the word. Both tasks contained a congruent condition (i.e. the colour matched the word) and an incongruent condition (i.e. the word did not match the colour). Each stimuli was presented three times in the congruent condition and three times in the incongruent condition (once in each incongruent colour), resulting in 24 trials for both stages.

The order of these four stages and the order of stimuli within each task were randomised across participants. Prior to beginning, participants completed a practise of the NCS and NWS, completing two congruent and two incongruent trials for each stage and receiving feedback on their responses.

Results

Conscious identification task. Initial trials (six participants) used a list of 20 words and stimulus increments of 17ms and found the task had a long duration (around 15-20 minutes). To reduce experimental burden, the task was shortened by removing the four words in each condition with the slowest mean detection time as calculated from the data of the initial six participants.

The task was then repeated (one participant) with the reduced word list. However, a recurring problem was that the majority of participants (85.7%) recognised at least one stimulus at the minimum exposure time of 17ms, meaning the masked emotional Stroop task stimulus exposure would need to be set as 0ms. As a result, the duration was altered to use incremental intervals of 10ms. Following this change, a further five participants completed the task and were unable to identify the stimulus at the shortest exposure time (10ms).

Emotional and standard Stroop tasks. One participant made >70% errors on one of the incongruent conditions and was excluded from the standard Stroop analyses. Overall error rates (minus excluded participants) can be seen in Table 1 and individual incorrect responses were excluded from further analyses.

Table 1

Overall percentage error rates on pilot study tasks (n = 11)

Condition	Masked Stroop	Unmasked Stroop
Total	2.9	2.7
Neutral	4.2	1.5
Error	1.7	4.0

	Control Stroop (*n* = 10)
Total	3.7
NC	1.1
NW	1.5
NCS-congruent	0
NCS-incongruent	3.8
NWS-congruent	2.3
NWS-incongruent	18.2

Reaction times were filtered using a cut-off of each participant's median reaction time ±2SD within each condition (based on the procedure used by E. Chen, Wong, R. Chen & Au, 2001). This removed 4.2% of data points in the masked Stroop, 4.3% in the unmasked Stroop and 7.2% in the standard Stroop. Following data filtering, Stroop indices (SI) were calculated for all tasks. The following formula was used for the masked and unmasked Stroop tasks:

$$SI = median\ threat\ reaction\ time - median\ neutral\ reaction\ time$$

For the standard Stroop, SI's were calculated for word naming (WN) and colour naming (CN) conditions:

$$WN\ SI = NW - NWS(incongruent)$$

$$CN\ SI = NC - NCS(incongruent)$$

Table 2 shows the mean Stroop indices for each task.

Table 2

Mean Stroop indices for pilot Stroop tasks

Condition	*N*	Mean (SD)
Masked Stroop	6[1]	31.00 (29.29)
Unmasked Stroop	12	-7.13 (32.24)
Standard Stroop- colour naming	12	245.46 (224.97)
Standard Stroop- word naming	11	453.95 (351.78)

Supporting the small observed SI's in the masked and unmasked Stroop, analyses of filtered data found no significant effects on the masked Stroop, $t(5) = -2.60$, $p = .049$, $r = .76$ or unmasked Stroop, $t(11) = .77$, $p = .46$, $r = .23$. This is unsurprising given the role of the Stroop to detect seizure phobia and the use of a non-epileptic/PNES sample for piloting.

The standard Stroop was analysed using a 1x6 repeat measures analysis of variance (ANOVA). Mauchly's test indicated the assumption of sphericity was violated, $\chi^2(14) = .02$, $p = .005$, therefore degrees of freedom were corrected using the Greenhouse-Geisser estimate ($\varepsilon = .47$). This found a significant effect of task, $V = .81$, $F(2.36, 23.61) = 5.19$, $p = .001$. Three planned post-hoc analyses compared NC to NW, NCS-congruent to NCS-incongruent and NWS-congruent to NWS-incongruent. A Bonferroni correction set an adjusted $\alpha = .017$. Significant differences were observed between the NCS (congruent and incongruent) tasks, $p = .015$ and NC and NW tasks, $p = .013$, although no significant difference was recorded between the NWS (congruent and incongruent) tasks. Despite the lack of a significant difference on the NWS

[1] Participants recognising a word in 17ms on the conscious identification task were excluded from this analysis.

task, the Stroop indices indicated an overall interference effect for both NCS and NWS, with the interference effect being larger for the NWS condition than the NCS Stroop index. Unfortunately, no analysis could be completed on the Stroop indices in the pilot due to the lack of a suitable comparison group; however analyses in the main experiment were based on the Stroop index, rather than the reaction time.

Method

The experiment consisted of two parts: a series of self-report questionnaires and a three stage computerised Stroop task, including the masked and unmasked Stroop tasks assessing seizure. Two groups of participants were recruited: PWE and pwPNES.

Power Analysis

A power analysis was conducted on G*Power (Faul, Erdfelder, Lang, & Buchner, 2014) to determine the number of participants required to test the primary hypothesis using an independent t-test. As there is no current measure of the effect size of the Perseverative Thinking Questionnaire (PTQ; Ehring et al., 2011) between PWE and pwPNES, a comparable estimate was used. A. Meulders, M. Meulders, Stouten, de Bie, and Vlaeyen (2017) used the PTQ with patients with fibromyalgia and a healthy control group and found an effect size of d = 1.06 between the groups. Based on the overlap in symptomology of patients with chronic pain and pwPNES (Dixit et al., 2013), this estimate appears suitable and the power analysis for the primary hypothesis was based on a large expected effect size (d = .8; Cohen, 1988), α = .05 and $\beta\text{-}1$ = .8. This calculated that 52 participants (26 per group) would be needed. All secondary hypotheses were treated as exploratory.

Online Recruitment Details

Participants were initially recruited from an NHS hospital (described in more detail in subsequent methodology sections). To boost recruitment rates, approval for additional recruitment via on an online study was granted via the University of Sheffield Ethics Review System (Appendix D). This was conducted through www.nonepilepticattackdisorder.org.uk and Epilepsy Action who promoted the study to their members via forums, mailing lists and social media.

Participants were sent an email containing a link to the study which was run using Qualtrics (2015) software. Participants following this link were given information about the study (adapted from Appendix E) including information regarding anxiety and depression and advice to contact their GP if they have any concerns about these issues. Interested participants were required to complete a consent form (adapted from Appendix F) before beginning the study. At the end of the experiment, participants were given debriefing information (adapted from Appendix G). Unfortunately post-hoc analyses found the self-reported baseline demographic and clinical profile of the online recruits was significantly different from the NHS clinic participants and it was decided to only use the NHS sample (see the results section for a more detailed rationale). The remainder of this report will therefore focus exclusively on this sample.

Participants

Participants (N = 55, PNES n = 26, PWE n = 29) were recruited from a neurology outpatient clinic and a video telemetry ward at the Royal Hallamshire Hospital in Sheffield. Participants were required to have a clinically secure diagnosis (i.e. the patient's neurologist was confident enough in the diagnosis only to offer treatment for one condition, epilepsy or PNES) which was

retrospectively confirmed by their neurologist on the basis of all available clinical information about the patient. Participants were excluded (*n* = 4) if their diagnosis could not be confirmed, if they had any other identified neurological disorder, a learning disability, were aged under 18 or had a mixed seizure disorder (epilepsy and PNES). All participants completed the questionnaires and 20 PWE and nine pwPNES completed the Stroop task.

Measures

Perseverative Thinking Questionnaire (PTQ; Appendix H). The PTQ (Ehring et al., 2011) is a 15-item self-report measure of RNT (both rumination and worry). The total scale has excellent internal consistency and satisfactory retest reliability (α = .95, test-retest r = .69) and significant correlations with the Penn State Worry Questionnaire (Meyer, Miller, Metzger, & Borkovec, 1990; *r* = .48 - .70) and the rumination scale of the Response Style Questionnaire (Nolen-Hoeksema & Morrow, 1991; *r* = .59 - .72), suggesting it is a valid measure of RNT.

Modified Safety Behaviors and Catastrophizing Scale (mSBCS; Appendix I). The SBCS (MacDonald, Linton, & Jansson-Fröjmark, 2008) is a self-report measure containing 12 items assessing catastrophising and safety behaviours relating to pain and poor sleep. A lack of existing measures assessing these constructs make validity difficult to establish, but, MacDonald et al (2008) argue there is preliminary support for the validity of the scale based on correlations with measures of positive and negative affect.

For this study, the instructions were modified to focus on a patient's seizures and it was used as a self-report measure of a patient's fear of their seizures and safety behaviours. The total score was used in analyses. As the

SBCS was modified for this study, the internal consistency was analysed using Cronbach's alpha, which indicated excellent internal consistency (α = .91).

Patient Health Questionnaire-9 (PHQ-9; Appendix J). The PHQ-9 (Kroenke, Spitzer, & Williams, 2001) is a nine question self-report measure of depressive symptoms in the previous two weeks which is used extensively in clinical settings. It has good internal consistency and test-retest reliability (α = .89, *r* = .84) and has strong correlations with the scales of the Medical Outcomes Study Short-Form General Health Survey (Stewart, Hays, & Ware, 1988) most strongly associated with depression, suggesting it is a valid measure. As well as the 9-item scale (PHQ-9-total), the PHQ-9 contains a question assessing the difficulty associated with the problems identified (PHQ-9-difficulty).

General Anxiety Disorder-7 (GAD-7; Appendix K). The GAD-7 (Spitzer, Kroenke, Williams, & Löwe, 2006) contains seven questions measuring levels of generalised anxiety in the previous two weeks and has been used extensively in clinical settings. It has excellent internal consistency and good test-retest reliability (α = .92, test-retest r = .83) and correlates highly with the Beck Anxiety Inventory (Beck, Epstein, Brown, & Steer, 1988; *r* = .74), suggesting it is a valid measure of anxiety.

Demographic questionnaire (Appendix L). A ten-question demographic questionnaire recorded demographic information and information about patient's seizures, medication and psychological therapy.

Stroop Task

This was described in detail in the pilot study section and followed the same procedure, except for small changes to the conscious identification task as a result of the pilot study. The final version of the conscious identification task used a shortened list of 12 stimuli (Appendix C) and was presented in increments of 10ms rather than 17ms.

Analysis

All data analysis was run on SPSS Version 23 (IBM Corporation, 2015).

Missing data. Overall missing data rates for the PTQ, mSBCS, PHQ-9-total and GAD-7, were 0.4%, although the mSBCS was missing 5.6% of data due to some participants missing the second page of questions. A total of 10 participants (5 PNES, 5 epilepsy) missed >10 % of items on the mSBCS and were excluded from all further analyses involving this questionnaire. Following exclusions, missing data rates did not exceed 1% on the mSBCS, PTQ, PHQ-9-total or GAD-7. Little's Missing Completely at Random (MCAR; Little, 1988) test was run on the data from these tests. Data was MCAR except on the mSBCS (χ^2 (33, N = 537) = 48.47, p = .04). Analysis of the missing mSBCS data showed three missing data points (0.6%) spread across three different questions and three participants. This suggests it is likely the data can be assumed to be missing at random (MAR) rather than missing not at random.

Multiple imputation (Rubin, 1987) was used to calculate missing data points for the mSBCS, PTQ, PHQ-9 (excluding PHQ-9-difficulty) and GAD-7, using a Mersenne Twister random number generator, a fixed value starting point and the Markov Chain Monte Carlo imputation method (m = 5).

Constraints were used to specify the range of valid responses for the questionnaire. A mean of the imputations was calculated and used as the imputed value for each missing data point.

For demographic and seizure-related questions, 17 participants were excluded from analyses of seizure frequency (4 PNES, 13 epilepsy) due to non-response or reporting no seizures. Additionally several participants did not complete all demographic measures and were not included in comparisons of the questions with missing data. The number of eligible participants for analysis in each critical measure is shown in Table 3 in the next section ('Stroop data pre-processing').

Stroop data pre-processing. A Mann-Whitney U test was run on the fastest stimulus detection times in the conscious identification task, to determine if there were any differences between pwPNES and PWE.

Responses for the masked, unmasked and standard Stroop were analysed separately. Error rates were analysed and participants with error rates above 10% on the threat or neutral conditions in the masked or unmasked Stroop, or above 70% in the incongruent conditions of the standard Stroop, were excluded from analysis of the relevant Stroop. Table 3 shows the number of eligible participants.

Table 3

The number of eligible participants per measure

Measure	Total *N*	PNES *n*	Epilepsy *n*
PTQ/PHQ-9-total/GAD-7	55	26	29
mSBCS	45	21	24

PHQ-9-difficulty	43	20	23
Masked Stroop*	24	9	15
Unmasked Stroop*	25	9	16
Interaction analysis between masked and unmasked Stroop*	23	9	14
Standard Stroop*	16	4	12

* All Stroop *n*'s are based on the number of participants after data screening

The reaction times of eligible participants were then processed. Reaction times over 10,000ms were rescored to the highest correct reaction time below 10,000ms, responses below 200ms were excluded as anticipatory responses, and a cut-off of each participant's median reaction time ±2SD in each condition was used to remove outliers. After excluding reaction times breaching these criteria, a Stroop index (SI) was calculated for each participant using the following formula:

Masked and unmasked Stroop (MS-SI and US-SI):

$$SI = median\ threat\ reaction\ time - median\ neutral\ reaction\ time$$

Standard Stroop word naming (WN) and colour naming (CN):

$$WN\ SI = NW - NWS(incongruent)$$

$$CN\ SI = NC - NCS(incongruent)$$

A positive result demonstrates an interference effect, whilst a negative finding suggests a facilitative effect.

Comparative analyses. A total score was calculated for the PTQ, mSBCS, GAD-7 and PHQ-9. Prior to analysis all continuous measures were assessed for normal distribution using Kolgarov-Smirnov's *D* and homogeneity of variance between epilepsy and PNES samples using Levene's *F.* Measures failing these tests were analysed using non-parametric tests, or tests robust to violations of these assumptions. All measures can be assumed to meet these assumptions unless stated otherwise.

Demographic and seizure-related variables. All demographic and seizure group differences were compared using independent t-tests, Mann-Whitney U tests or chi-square as appropriate. Comparisons between demographic and seizure-related variables were uncorrected as these were exploratory analyses, aiming to highlight if there may be significant differences in group composition that would need to be considered.

Questionnaires. Group differences on the mSBCS, PTQ, PHQ-9 and GAD-7 were also compared using independent t-tests and, Mann-Whitney U tests as appropriate. These were all two-tailed analyses, with the exception of the PTQ, which used a one-tailed analysis, as *hypothesis 1* (comparing differences in RNT thinking between PWE and PNES) predicted the direction of the relationship between the groups. The Benjamini-Hochberg False Discovery Rate (FDR; Benjamini & Hochberg, 1995) was used to correct for multiple comparisons. This adjustment is less conservative than the Bonferroni correction which would allow for the lower power level of this study. The significance level was set as $Q = .05$ and the required q value will be reported for each comparison.

Stroop tasks. Error rates in the masked and unmasked Stroop tasks were analysed using a 2 (diagnosis) x 2 (condition) mixed ANOVA assessing main and interaction effects. Due to the small number of eligible participants in analyses of the standard Stroop, error rates in this task were analysed using a Mann-Whitney U test to compare error rates across the six conditions and between groups. Masked and unmasked Stroop indices were assessed for normal distribution and homogeneity of variance and t-tests were used to compare these between PWE and pwPNES. Due to the small eligible sample size in the standard Stroop, the Mann-Whitney U test was used to compare the NC, NW, WN-SI and CN-SI between groups, assessing *hypothesis 2* (no group differences would be seen on the standard Stroop). All comparisons were corrected with the FDR calculated across all Stroop comparisons.

Further analyses. In addition to the one-tailed t-test comparing group differences on the PTQ, *hypothesis 1* was further explored by using the PTQ as the dependent variable (DV) in a hierarchical multiple regression analysis. Independent variables (IV) were entered in stages: to control for anxiety and depression, GAD-7 and PHQ-9-total scores were entered into block one, MS SI was then entered as block two, before diagnosis was entered as the final block. This analysis also assessed *hypothesis 4* (comparing the relationship between RNT and the masked Stroop index), in addition to a correlation test.

A second hierarchical multiple regression analysis was used to asses *hypothesis 6* (RNT would be associated with seizure frequency) using the number of seizures as the dependent variable. To meet the assumptions of the analysis, two participants with PNES whose seizure frequency was over 3SD’s above the mean were removed from the analysis and the number of seizures

was log-transformed to correct for heteroscedascity. To control for anxiety and depression, PHQ-9(total) and GAD-7 scores were entered in the first block, before PTQ scores were entered in the second block.

Hypothesis 3 (comparing the masked and unmasked SI's) was assessed using a 2x2 mixed ANOVA looking at main and interaction effect. The Stroop index was used as the DV and diagnosis and task (masked or unmasked) were used as the IV's.

Due to the reduced number of participants in the mSBCS, it was not possible to assess *hypothesis 5* (self-reported RNT would correlate with mSCBS scores) using a multiple regression. Instead correlations were run for both patient groups and compared between groups.

Ethics

Ethical approval was obtained through the NHS Scotland East of Scotland Research Ethics (Appendix M). Participants due to attend an outpatient or video-EEG appointment were sent a letter and information sheet (Appendix E), explaining the study and requesting their participation. Participants who agreed to participate completed a consent form (Appendix F) and were provided with a debrief sheet at the end of the experiment (Appendix G). All participants' data was recorded under an anonymous code and could not be linked to their identity. If scores on the PHQ-9 and GAD-7 were ≥ 10, the participant's neurologist was notified.

Results

Comparison of NHS and Online Samples

After processing data to exclude participants with excessive levels of missing data and using multiple imputation to replace missing values, comparative analyses (t-tests, Mann Whitney U tests and chi-square tests) were used to establish if the online and NHS, epilepsy and PNES participant groups were sufficiently similar on clinical and demographic baseline measures to be combined in the data analysis. For the purposes of this study, the samples were required to be homogenous samples to increase the power of analyses comparing PWE and pwPNES. Significant differences were found between the online and NHS samples for the level of education in both PWE (Fishers exact test, p =.001) and pwPNES (Fishers exact test, p = .004), with online participants reporting higher levels of education than NHS participants in both patient groups. A significant difference was also found in gender ratios for pwPNES, with the online sample having a higher proportion of females, $\chi^2(1, N = 47) = 8.61$, p = .006. In the epilepsy sample, the online sample reported significantly higher scores than the NHS sample on all measures; PTQ, $t(42) = -2.80$, p = .008, mSBCS, $t(37) = -2.72$, p = .01, PHQ-9 (total), U = 308.50, z = 2.26, p = .02, r = .34, PHQ-9 (difficulty), U = 228.00, z = 2.22 p = .04, r = .36, GAD-7, U = 299.50, z = 2.04 p = .04, r = .31. Table 4 shows the means and frequencies for all measures where significant differences were found between the online and NHS samples.

Table 4

Comparisons of the demographic and clinical profile of the online and NHS samples of pwPNES and PWE

	PNES (*n* = 47)		Epilepsy (*n* = 44)	
	NHS (*n* = 26)	Online (*n* = 21)	NHS (*n* = 29)	Online (*n* = 15)
Questionnaires				
PTQ- mean (SD)			27.63 (13.46)**	38.53 (9.41)**
mSBCS- mean (SD)			17.61 (9.67)*	25.73 (8.01)*
PHQ-9 (total)- median (IQR)			5.00 (1.96 – 14.00)*	10.00 (7.00 – 19.00)*
PHQ-9 (difficulty)			Somewhat difficult*	Somewhat – very difficult*
GAD-7- median (IQR)			5.00 (1.50 – 10.50)*	10.00 (5.00 – 12.00)*
Demographic variables- *n* = (%)				
Gender (female)	15 (57.7)**	20 (95.2)**		

Education	**	**	**	**
No qualifications	5 (20.0)	0	1 (3.6)	0
O levels/GCSEs	9 (36.0)	5 (23.8)	11 (39.3)	0
Highers/A levels	1 (4.0)	1 (4.8)	4 (14.3)	6 (40.0)
Vocational qualification	8 (61.5)	5 (23.8)	6 (21.4)	0
HNC/HND	1 (4.0)	1 (4.8)	0	2 (13.3)
Degree	0	5 (23.8)	3 (10.7)	4 (26.7)
Postgraduate qualification	0	4 (19.0)	2 (7.1)	3 (20.0)
Professional qualification	1 (4.0)	0	1 (3.6)	0

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

For the purposes of this study, the most relevant differences were those found on the main questionnaire measures, especially the PTQ and mSBCS. A two-way ANOVA was conducted for both these measures, comparing the effect of diagnosis and recruitment source on the scores. This found a significant interaction effect between diagnosis and recruitment source on the PTQ, $F(1, 87) = 6.71$, $p = .01$) and mSBCS ($F(1, 77) = 9.86$, $p = .002$) as demonstrated in Figures 4 and 5.

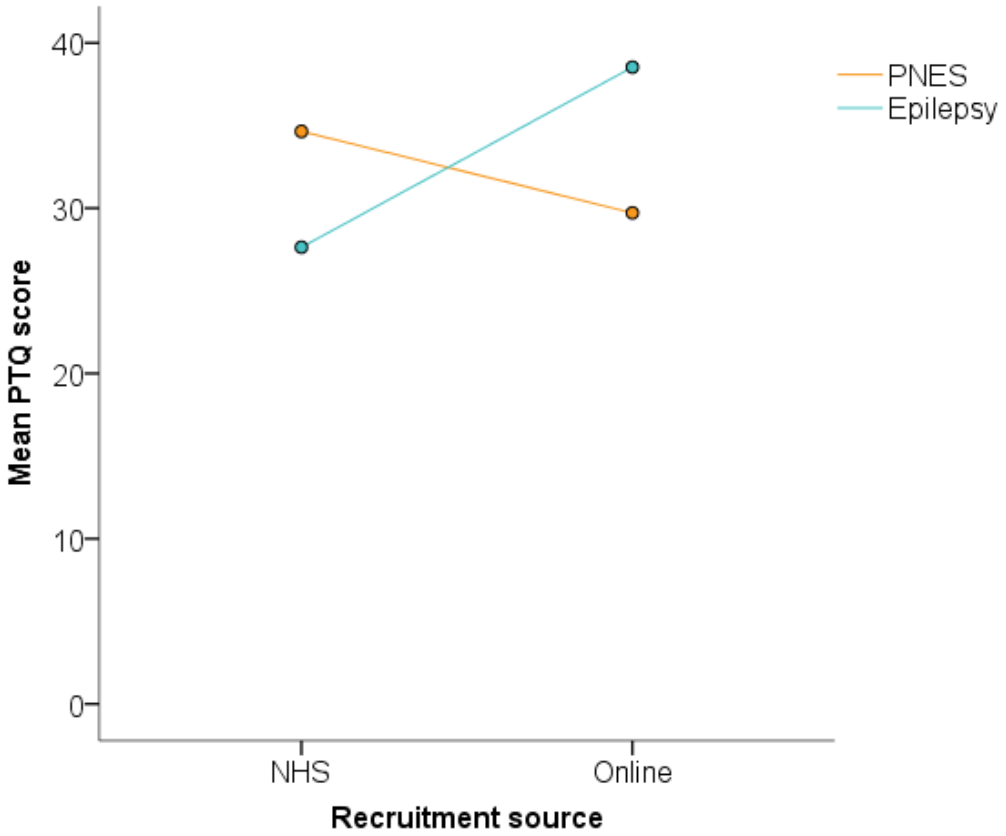

Figure 4. Mean PTQ score by diagnosis and recruitment source.

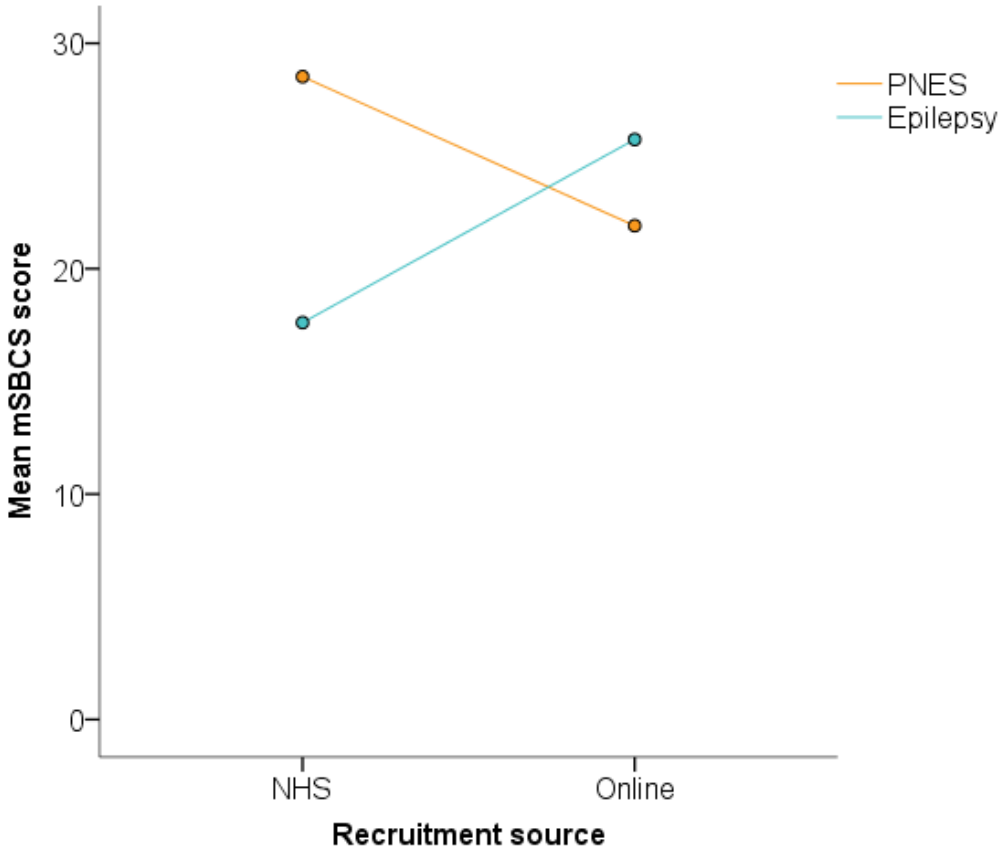

Figure 5. Mean mSBCS score by diagnosis and recruitment source.

These analyses suggest the NHS and online samples are not comparable and would need to be analysed separately, requiring more sophisticated analyses of four smaller groups as opposed to two larger groups. The current sample sizes meant such analyses would be significantly underpowered. Another weakness of the online sample is that diagnosis is based on self-report, rather than clinician confirmation. Whilst this would have been an acceptable compromise if recruitment source demographics and results had been comparable to the NHS sample, the significant differences render this a further liability. In view of these findings, it was decided to base further analyses on the NHS sample only.

Analysis of Demographic and Seizure-Related Information

All continuous variables were analysed using independent t-tests, except for '*number of seizures'* and *'time since first seizure'* which violated the assumptions of normal distribution, with *'time since first seizure'* also violating the assumption of homogeneity of variance. These variables were analysed using Mann-Whitney U tests and the remaining categorical variables were analysed using chi-square. Results are summarised in Table 5. Whilst the groups were largely comparable, pwPNES reported more seizures in the previous four weeks, $U = 79.50$, $z = -2.87$, $p = .003$, $r = -.46$ and were more likely to have had psychotherapy, $\chi^2(1, N = 52) = 5.04$, $p = .048$, whilst PWE were more likely to be on medication, Fishers exact test, $p < .001$.

Table 5

Demographic details of the PNES and epilepsy samples, including statistical comparison

	PNES (*n* = 26)	Epilepsy (*n* = 29)
Demographic variables		
Age- mean (SD)	38.19 (12.53)	43.66 (15.44)
Gender (female)	15 (57.7)	17 (58.6)
Ethnicity		
White British	25 (45.5)	24 (43.6)
Other white	0	1 (1.8)
Other mixed ethnicity	0	1 (1.8)
Indian	0	1 (1.8)
Pakistani	1 (1.8)	1 (1.8)
Black African	0	1 (1.8)

Employment		
Full-time paid work	6 (23.1)	8 (28.6)
Part-time paid work	2 (7.7)	5 (17.9)
Full-time education	1 (3.8)	3 (10.7)
Part-time education	2 (7.7)	0
Out of work due to illness/ disability	14 (53.8)	7 (25.0)
Retired	1 (3.8)	4 (14.3)
Self-employed	0	1 (3.8)
Education		
No qualifications	5 (20.0)	1 (3.6)
O levels/GCSEs	9 (36.0)	11 (39.3)
Highers/A levels	1 (4.0)	4 (14.3)
Vocational qualification	8 (32.0)	6 (21.4)
HNC/HND	1 (4.0)	0
Degree	0	3 (10.7)
Postgraduate qualification	0	2 (7.1)
Professional qualification	1 (4.0)	1 (3.6)
Taking anti-epileptic or psychiatric medication***	15 (60.0)***	26 (100)***
Psychotherapy (yes)*	15 (57.7)*	7 (26.9)*
Seizure-related variables		
Duration- years- mean (SD)	8.66 (7.70)	17.16 (16.30)
Frequency in the last four weeks- median (IQR)**	12 (4.75–88.75)**	2.5 (1.00–8.50)**
Most recent seizure		

In the last week	17 (70.8)	12 (46.2)
In the last month	5 (20.8)	5 (19.2)
In the last three months	1 (4.2)	2 (7.7)
In the last six months	1 (4.2)	3 (11.5)
In the last year	0	1 (3.8)
Over a year ago	0	3 (11.5)

All data show 'number (%)' unless otherwise specified

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

Questionnaire Data

PHQ-9-total and GAD-7 scores for PWE and the PHQ-9-difficulty scale for PWE and pwPNES were not normally distributed and were compared using Mann-Whitney U tests. All comparisons were FDR corrected (see *q* value for required significance level to reject the null-hypothesis).

Comparisons between PWE and pwPNES found significant results on all measures. PwPNES scored higher on the PTQ (see Table 6 for mean scores), one-tailed $t(53) = 1.80$, $p = .039 < q = .05$, $d = .48$. The findings for other measures were more robust with pwPNES scoring higher on the mSBCS, $t(43) = 3.32$, $p = .002 < q = .05$, $d = -.98$, PHQ-9 (total), $U = 163.00$, $z = -3.61$, $p < .001 < q = .05$, $r = -.49$) and GAD-7, $U = 173.00$, $z = -3.45$, $p = .001 < q = .05$, $r = -.46$. PwPNES also rated the difficulty associated with their depressive symptoms as higher on the PHQ-9 (difficulty) scale, $U = 111.00$, $z = -3.03$, $p = .002 < q = .05$, $r = -.46$.

Table 6

Average scores for PWE and pwPNES on questionnaires

Questionnaire	PNES	Epilepsy
PTQ	34.65 (15.51)	27.63 (13.46)
mSBCS	28.52 (12.37)	17.61 (9.67)
PHQ-9 (total)*	17.50 (12.00-20.25)	5.00 (1.96-14.00)
PHQ-9 (difficulty)	Very difficult	Somewhat difficult
GAD-7*	13.00 (8.75-18.00)	5.00 (1.50-10.50)

NB- results indicate means (SDs) unless otherwise indicated

* median (IQR)

Stroop Data

Conscious identification task. There were no differences between pwPNES and PWE for the shortest exposure time required to identify a stimulus, $U = 81.50$, $z = -.21$ $p = .85$, $r = -.04$, median = 30.00 for both groups.

Masked Stroop. Three PWE were excluded for making over 10% errors in either the threat or the neutral conditions. All further masked Stroop analyses were completed on 26 participants. A 2x2 repeat measures ANOVA did not find any significant main effects of diagnosis, $F(1, 22) = 1.80$, p = .19 or condition , $F(1, 22) = .002$, $p = .97$ and no interaction effect, $F(1, 22) = .24$, p = .63, suggesting error rates were comparable between PWE and pwPNES across conditions.

Reaction times were filtered with one response above 10,000ms adjusted and 4.2% of data points removed for exceeding ±2SD. SI's were normally distributed and met the assumption of homogeneity of variance.

Hypothesis 3 predicted a higher Stroop interference effect for pwPNES, however, a comparison of means (Figure 6) showed both groups demonstrated a facilitative effect and so a two-tailed t-test was used. This found no significant difference between the groups, $t(22) = .25$, $p = .81 > q = .04$, $g = .10$[2].

A correlation analysis between participants PTQ scores and the MS-SI found a negative correlation for both patient groups. Whilst this correlation was larger in pwPNES, $r = -.52$, $p = .15$. $R^2 = .270$ than in PWE, $r = -.10$, $p = .73$. $R^2 = .010$, neither relationship was significant.

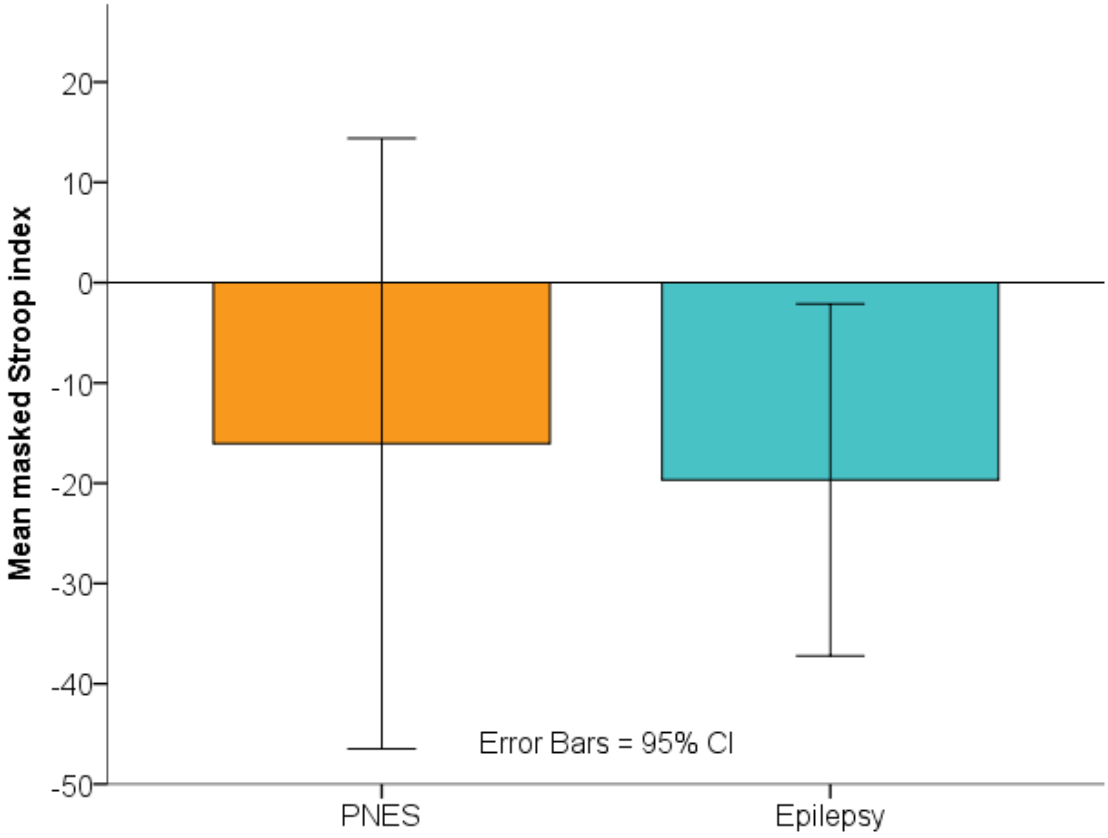

Figure 6. Mean Stroop index on the masked Stroop by diagnosis.

[2] Hedge's *g* reported due to the difference in group size.

Unmasked Stroop. Before beginning analysis, one participant was excluded as they had been observed using their phone during this task. One PWE was excluded for an error rate over 10% and all further unmasked Stroop analyses were completed on 25 participants. A 2x2 repeat measures ANOVA found no significant main effects of diagnosis, $F(1, 23) = .01$, $p = .93$ or condition, $F(1, 23) = .21$, $p = .66$ and no interaction effect, $F(1, 23) = .65$, $p = .43$, suggesting error rates were comparable across conditions and diagnosis.

Reaction times were filtered and 5.3% of data points were removed for exceeding ±2SD. *Hypothesis 3* predicted PWE to have a greater SI, however a comparison of means (Figure 7) showed the opposite effect and so a two-tailed t-test was used, which found no significant difference between the groups, $t(23) = .62$, $p = .54 > q = .03$, $g = .26$.

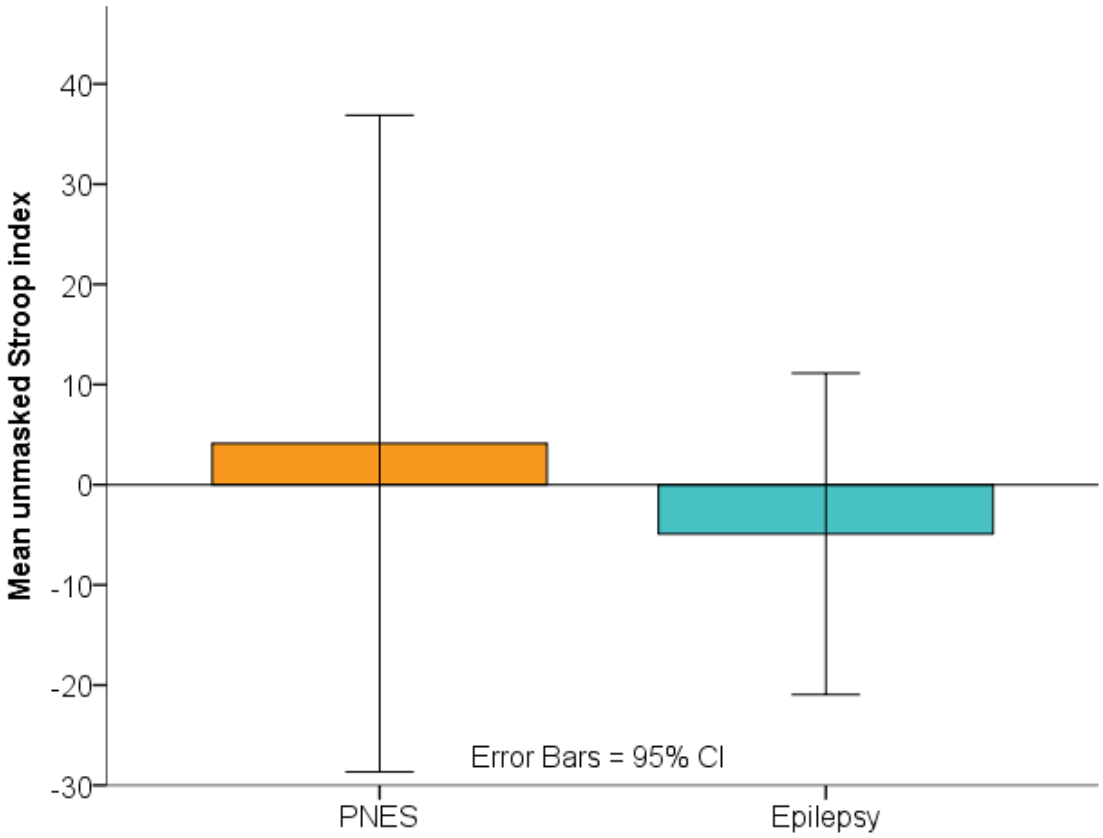

Figure 7. Mean Stroop index on the unmasked Stroop by diagnosis.

Comparison of masked and unmasked Stroop. A total of 21 participants provided eligible results for both the masked and unmasked Stroop and means can be seen in Table 7 and Figure 8.

Table 7

Mean Stroop indices (and SD's) by diagnosis and Stroop task

Condition	PNES (*n* = 9)	Epilepsy (*n* = 14)
Masked Stroop	-16.06 (39.60)	-19.67 (31.67)
Unmasked Stroop	4.11 (42.63)	-4.91 (30.09)

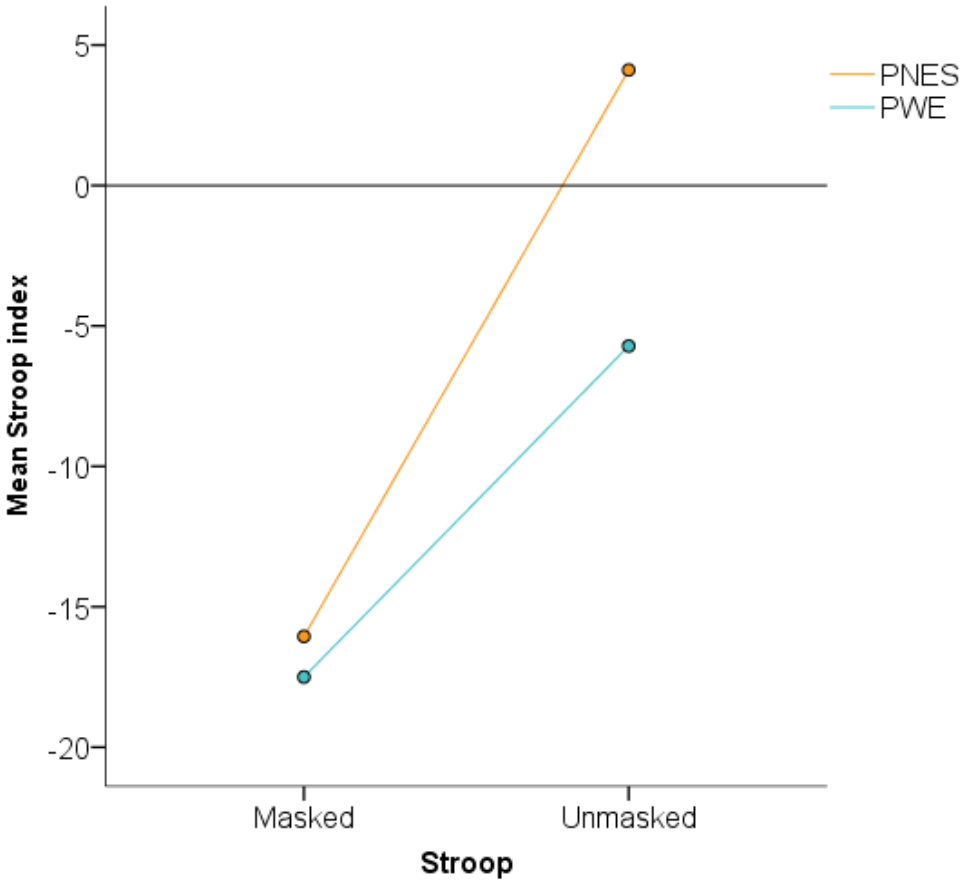

Figure 8. Mean Stroop index by diagnosis and Stroop condition.

A 2x2 mixed ANOVA found no significant effects of diagnosis, $F(1, 21) = 2.12$, $p = .16$ or Stroop task, $F(1, 21) = 2.92$, $p = .10$ and no interaction effect between these $F(1, 21) = .20$, $p = .66$.

Standard Stroop. A high number of participants exceeded the accepted error rate of ≤ 70% in the incongruent conditions and were excluded ($n = 11$, PNES = 5, epilepsy = 6). All further standard Stroop analyses were conducted on a sample of 16 participants using non-parametric tests. A comparison of overall error rates on each task using a Mann Whitney *U* Test's found no significant differences on any task.

Reaction times were filtered with one response above 10,000ms recoded and 5.6% of data points removed for exceeding ±2SD's. FDR corrected Mann-Whitney U tests found no significant differences on any task (Table 8), although WN-SI and CN-SI had differences which would have been significant using a standard α = .05, suggesting a trend towards a significant difference.

Table 8

Median reaction times and Stroop indices across the standard Stroop tasks

Condition	PNES	Epilepsy	Comparison
NC	958.50 (805.25-1081.75)	992.25 (735.75-1061.75)	$U = 22.00$, $z = -.24$, $p = .86 > q = .05$, $r = -.06$
NW	1012.75 (792.25-1175.13)	991.00 (703.63-1096.75)	$U = 19.00$, $z = -.61$, $p = .60 > q = .03$, $r = -.15$
WN-SI	1027.75 (563.50-1490.13)	278.25 (75.25-582.50)	$U = 7.00$, $z = -2.06$, $p = .04 > q = .02$, $r = -.34$
CN-SI	338.50 (294.00-428.75)	84.00 (40.38-163.25)	$U = 4.00$, $z = -2.43$, $p = .013 > q = .008$, $r = -.61$

IQR given in brackets

Analysis of Repetitive Negative Thinking Controlling for Depression and Anxiety

A hierarchical multiple regression was run to predict PTQ scores based on PHQ-9-total, GAD-7 (block one), MS-SI (block two) and diagnosis (block three). Partial regression plots and a plot of studentised residuals against predicted values suggested linearity of data and there was independence of residuals, as assessed by a Durbin-Watson statistic of 2.44. Visual inspection of a plot of studentised residuals versus unstandardised predicted values suggested homoscedasticity. Multicolinearity was not suggested as the tolerance scores were > .1 (smallest = .27). There were no residuals ±3SD and although there were some high leverage points >.2, none of these were influential (Cook's distance was not above 1). Q-Plots met the assumption of normality. The overall model significantly predicted PTQ scores, $F(4, 19) = 11.40$, $p < .001$, adjusted $R^2 = .64$, although only the GAD-7 was a significant individual predictor, $p = .003$. Indeed, the majority of variance in PTQ scores was accounted for by the first step of the model (GAD-7 and PHQ-9-total score), $F(2, 21) = 21.99$, $p < .001$, adjusted $R^2 = .646$. After accounting for PHQ-9-total, GAD-7 and MS-SI, diagnosis had a $B = 5.67$, although this was not significant. Full results of the overall regression model can be seen in Table 9.

Table 9

Summary of PTQ hierarchical multiple regression analysis

Variable	*B*	SE_B	β	*p*
Intercept	10.17	5.03		.06
PHQ-9 (total)	.17	.43	.10	.69

GAD-7	1.7	.50	.83	.003
MS-SI	.01	.06	.03	.82
Diagnosis	5.67	4.15	.19	.19

An analysis of model two (before the addition of diagnosis as an IV) also significantly predicted PTQ scores, $F(3, 20) = 13.97$, $p < .001$, adjusted $R^2 = .628$, although again, only the GAD-7 was a significant individual predictor, $p = .005$. After accounting for PHQ-9 (total) and GAD-7, MS-SI had a $B = -.003$, $p = .96$.

Analysis of the Relationship between Repetitive Negative Thinking and Seizure Frequency

Another hierarchical multiple regression was run to predict the log-transformed number of seizures based on PHQ-9-total, GAD-7 (block one) and PTQ (block two). Two participants were highlighted as outlying data points and were removed from the analysis and a log transformation was used for the number of seizures due to heteroscedasticity. Partial regression plots and a plot of studentised residuals against predicted values suggested linearity of data and there was independence of residuals, as assessed by a Durbin-Watson statistic of 1.74. Visual inspection of a plot of studentised residuals versus unstandardised predicted values suggested homoscedasticity. Multicolinearity was suggested as the tolerance scores were > .1 (smallest = .27). There were no residuals ±3SD, leverage points >.2 or influential data points (Cook's distance was not above 1). Q-Plots met the assumption of normality. The overall model did not significantly predict the number of seizures, $F(3, 31) = 1.26$, $p = .31$, adjusted $R^2 = .22$, and no individual factors reached significance

(Table 10), with PTQ scores having a non-significant negative correlation with seizure frequency, r = -.18, p = .16. R^2 = .032.

Table 10

Summary of number of seizures hierarchical multiple regression analysis

Variable	*B*	SE_B	B	*p*
Intercept	1.09	.27		<.001
PHQ-9 (total)	.02	.03	.18	.58
GAD-7	.03	.03	.29	.34
PTQ	-.02	.01	-.54	.07

Modified Safety Behaviors and Catastrophizing Scale analysis

Correlation analyses between mSBCS and PTQ scores found significant positive correlations for both patient groups; PNES n = 21, r = .67, p = .001. R^2 = .453, epilepsy n = 24, r = .61, p = .002. R^2 = .368. The PTQ accounted for slightly more variance in pwPNES (45.3% as opposed to 36.8% in PWE).

Due to the significant higher mSBCS scores in pwPNES than PWE, further exploratory correlations were run on mSBCS scores in pwPNES. No significant correlation was observed between mSBCS scores and the number of seizures suffered by an individual, n = 21, r = -.36, p = .16. R^2 = .130, or with the US-SI, n = 7, r = -.33, p = .47. R^2 = .108. However a significant correlation was found between the mSBCS and the MS-SI n = 7, r = .61, p = .002. R^2 = .368 (see Figure 9).

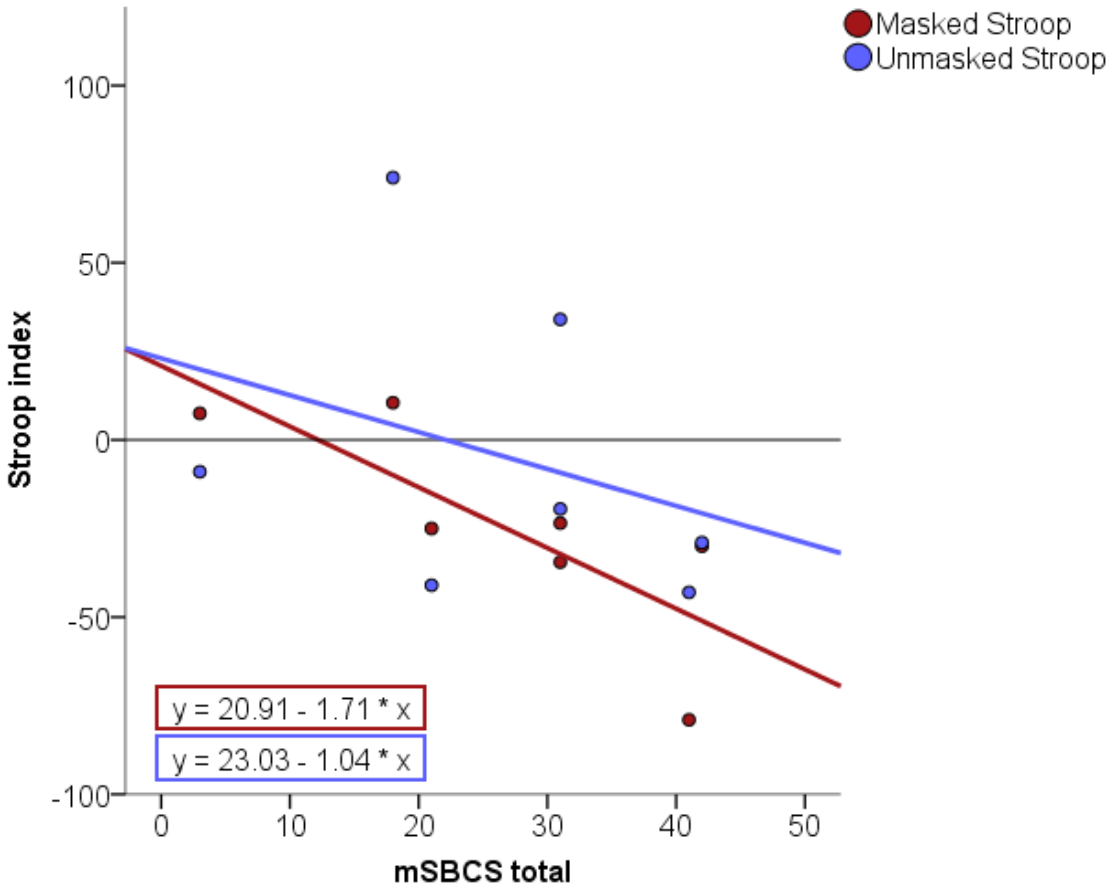

Figure 9. *Scatter plot of Stroop indices and mSCBS scores for pwPNES*.

Discussion

Repetitive Negative Thinking

This study aimed to explore RNT, catastrophising of seizures and the relationships between these factors in PWE and pwPNES, with a focus on differences in RNT between the patient groups. The primary hypothesis that pwPNES would report higher levels of RNT than PWE was supported. PwPNES had significantly higher scores on the PTQ than PWE with the effect size approaching a medium effect. PwPNES also reported significantly higher levels of depression and anxiety symptoms on the PHQ-9 and GAD-7 than PWE. Whilst median scores on the PHQ-9 and GAD-7 reflected sub-clinical levels of depression and anxiety for PWE, in pwPNES they suggested moderately

severe levels of depression and moderate levels of anxiety (based on the cut-off scores proposed by Kroenke et al., 2001 and Spitzer et al., 2006).

As depression and anxiety are strongly associated with RNT, it was possible the higher levels of RNT in pwPNES reflected the higher levels of anxiety and depression in this patient group. To assess this, a multiple hierarchical regression analysis was conducted. This found that anxiety and depression accounted for the majority (64.6%) of the overall variance in PTQ scores. After controlling for PHQ-9 and GAD-7 scores, it was found that pwPNES average PTQ score was 5.7 higher than PWE (as opposed to an uncorrected difference of 7.0), although this difference was no longer significant. These findings support the first hypothesis, demonstrating that pwPNES report higher levels of RNT than PWE, although this finding is predominantly accounted for by higher levels of anxiety and depression in the PNES group.

Catastrophising Seizures

The secondary focus of this study was to investigate whether pwPNES have a fear of their seizures and to explore the relationship between catastrophising and RNT. Patients' fear of seizures was assessed using an emotional Stroop task. Hypothesis three predicted PWE would show a greater Stroop interference effect (suggesting greater vigilance to seizure related words) than pwPNES on the unmasked Stroop, whilst the opposite pattern would be seen in the masked Stroop. The results did not support these hypotheses with an ANOVA showing no interaction effect between diagnosis and Stroop task. On the unmasked Stroop, the observed Stroop indices were small and did not show any significant differences. Surprisingly, a larger

facilitation effect was seen for both groups on the masked Stroop, although the group differences were not significant.

The lack of significant group differences on the Stroop tasks was not explained by error rate or differences in the speed of information processing between PWE and pwPNES. As predicted in hypothesis two, there were no significant differences in reaction times or filtered error rates between PWE and pwPNES on the standard Stroop. However, 55% of pwPNES were excluded for exceeding the accepted error rate, as opposed to 33% of PWE, suggesting there may have been a difference in unfiltered error rates. As such, the possibility of group differences in processing speed cannot be entirely dismissed due to the number of exclusions and the subsequent small sample used in analyses of the standard Stroop.

Whilst the lack of interference effect on the unmasked Stroop is consistent with previous research in pwPNES (Novakova, 2015), it contradicts Zeitlin et al.'s (1995) findings in PWE. Additionally, the finding of facilitation effects for both patient groups on the masked Stroop task is unexpected. One possible process is proposed by Williams et al. (1996) who suggest that facilitation effects show an adaptive avoidant response to the emotional content of stimuli, preventing it distracting from, or disrupting performance. They argued that the increased cognitive effort involved in using such a strategy would result in a faster performance across the entire task. This pattern was seen in the masked Stroop task as mean reaction times were over 90ms shorter than those in the unmasked Stroop. However, such cognitive strategies should not be possible on masked tasks which reflect automatic cognitive processes (Putman, Hermans, and van Vonk, 2004), suggesting this may not account for our

findings. This suggests that our findings reflect an unconscious facilitation effect in both PWE and pwPNES, although the mechanism for this is unclear and does not reflect existing knowledge.

Repetitive Negative Thinking and Catastrophising Seizures

Hypothesis four predicted that higher RNT would be significantly associated with higher implicit seizure phobia, as measured on the masked Stroop. This hypothesis was not supported as correlations indicated non-significant negative relationships between PTQ scores and the MS-SI for both patient groups, although these analyses were based on a small sample. After controlling for anxiety and depression, a regression analysis found no evidence of any relationships between implicit seizure phobia and RNT. RNT was also unrelated to seizure frequency in the combined patient group, only accounting for 3.2% of the variation in the number of seizures, meaning hypothesis six was not supported. The lack of relationship between RNT and seizure frequency and the absence of significant findings on the Stroop tasks could suggest RNT is not a reflection of seizure phobia. However, contrary to the non-significant results on the Stroop tasks, pwPNES report significantly higher scores on the mSBCS (assessing self-reported catastrophising of seizures and related safety behaviours) than PWE. Supporting hypothesis five, mSBCS scores were significantly positively correlated with PTQ scores for both pwPNES and PWE, suggesting a strong relationship between RNT and catastrophic thinking about seizures. This supports existing theories about the relationship between catastrophising and RNT (e.g. Flink, Boersma, & Linton, 2013; Sullivan, 1995) and the findings of Robson et al. (2012) that pwPNES were more likely to magnify or catastrophise their seizure experiences than PWE. These findings

add to the growing body of evidence that pwPNES are more likely to catastrophise than PWE. Another aspect to this is the current finding that pwPNES are more likely to display repetitive and intrusive thinking patterns than PWE. These findings support the only other study investigating this phenomenon in pwPNES. However, whilst Tojek et al. (2000) found that pwPNES ruminate about past stressful events more frequently than PWE, their study focussed solely on rumination. This study assessed RNT as a transdiagnostic cognitive process, suggesting RNT in pwPNES is likely to involve more than rumination.

It is worth considering at this point, what function RNT may serve. Nolen-Hoeksema et al. (2008) propose that the conscious purpose of RNT is to understand meanings and anticipate and prepare. However, they suggest the unconscious purpose is to avoid aversive emotions or situations. Supporting this, Segerstrom, Tsao, Alden, and Craske (2000) argue that repetitive thought inhibits emotional and information processing. A potential mechanism for this is outlined by Flink et al. (2013) who argue that catastrophising (which they conceptualise as RNT) reduces negative affect by occupying mental capacity. This is reinforced in the short-term as negative affect is avoided, but has a long-term cost as problems are not actively addressed and stress is inadequately processed. Such a role for RNT would fit with existing research on emotional avoidance in pwPNES. Dimaro et al. (2014) found that pwPNES often believe negative emotions to be damaging and have higher levels of avoidance than PWE, especially towards painful emotional experiences.

The theory that RNT functions as a form of emotional avoidance could potentially explain the difference between the null finding on the emotional

Stroop tasks and the significant differences observed on the mSBCS, which both focussed on elements of catastrophising seizures. As a core function of RNT is proposed to be to avoid negative emotions or situations, it could be that patients use RNT to manage the cognitive distress associated with their seizures (as reported on the mSBCS). This prevents processing of the emotional content of the distress, which could explain the lack of effect observed in the emotional Stroop tasks. This idea is supported by the fact that the mSBCS significantly correlated with the masked Stroop index in pwPNES. Crucially, this was a negative correlation, with higher self-reported levels of catastrophising about seizures (and thus higher levels of general RNT) being associated with lower levels of emotional interference on the Stroop suggesting lower fear of seizures. However, this conclusion must be treated with some caution, as the sample size in Stroop analyses was small and there was sizeable variability and overlap in the mean Stroop indices of the patient groups. Another possibility is that the self-report nature of the mSBCS created a degree of response bias.

The idea that pwPNES may use maladaptive strategies to suppress or avoid emotional processing is supported by Gul and Ahmad (2014) who found that pwPNES had higher scores of emotion suppression than healthy controls, but lower scores of cognitive reappraisal; a positive emotion regulation strategy to manage the psychological impact of stressful situations. Additionally, Novakova et al. (2015) found that pwPNES were more likely to experience emotions as overwhelming and had a higher tendency to suppress emotions when compared to healthy controls. These findings suggest RNT could be a form of emotional suppression in pwPNES.

Regardless of the function of RNT, there is a clear link between RNT and psychopathology (Ehring et al., 2011), including increased psychiatric co-morbidities (McEvoy et al., 2013). An experimental study by Ruscio, Seitchik, Gentes, Jones, and Hallion (2011) suggests this link is causational. They found that participants reporting higher baseline levels of RNT had stronger negative responses and showed higher levels of avoidant behaviour and negative emotions towards subsequent failure, traits that are closely linked to anxiety and depression. This was found for both healthy and clinical participants, and remained significant even after controlling for current anxiety and depression diagnoses.

Interestingly, Brosschot and van der Doef (2005) provide evidence for a causal relationship between RNT (in the form of worry) and somatic symptoms. Participants were allocated to two groups, with one control group and an experimental group instructed to limit their worry to a set 30 minute ‘worry period’ each day. Participants who limited their worry reported fewer somatic symptoms following the intervention than the control group, even after controlling for baseline levels of somatic symptoms. As PNES are characterised by somatic symptoms (Reuber, House, Pukrop, Bauer, & Elger, 2003), this suggests that interventions targeting RNT could potentially reduce some of the somatic symptoms of PNES. Although it is important to note that this study did not find a relationship between RNT and seizure frequency, pwPNES often report other physical symptoms of distress. The transdiagnostic nature of RNT means this could be a suitable target for intervention which could lead to more widespread effects.

Critique

A significant limitation of this study was the decision to exclude the online sample due to the significant differences with the NHS sample. This resulted in a small sample size and less power for analyses. Although the NHS sample was sufficiently powered for the main analysis, many secondary analyses were underpowered and thus need to be treated as exploratory. There are also several ethical concerns with the decision to exclude the online sample. There is a significant risk of introducing bias into the study. Although the online sample had been recruited on the basis it would be comparable to the NHS sample, criteria were not specified in advance for how to proceed if the groups differed, introducing potential bias into the decision making process. This was exacerbated as the main differences were on the dependent variables and had a direct influence on the results. There is the consideration of unnecessary patient burden as participants had volunteered their time to partake in the study, but were not included in analyses. In addition, the differences between the online and NHS samples are interesting in themselves, especially as most existing research focuses on participants in hospital settings. The excluded results would suggest this setting may not be representative of the wider patient populations, or fully reflect the heterogeneity in these patient groups. Although these concerns are important, the decision to exclude the data was consistent with the aim of the study to compare groups of PWE and pwPNES, rather than statistically different samples of each group. However, exclusion criteria should have been specified in advance to reduce bias and there should also have been a clear plan of what to do with any excluded data.

The Stroop analysis was significantly limited by the small sample size, especially the PNES sample, meaning the Stroop analyses must be treated with high levels of caution as variable data points would have a high level of influence on the data. Another limitation of the emotional Stroop task was that the order of the tasks was not varied. Whilst this was done to ensure that the masked Stroop stimuli remained implicit, it means that satiation or practise effects could have influenced the results of the unmasked Stroop task. Finally, whilst the Stroop task is a widely used measure of attentional biases, there is uncertainty around what is measured by the Stroop and how significantly this is affected by other factors e.g. lexical characteristics (Jończyk, 2016). Despite this, the emotional Stroop task has been extensively used to study attentional biases in numerous psychological disorders, with attentional biases found to relate to the specific disorder (Williams et al., 1996).

Whilst the focus on transdiagnostic RNT allowed a parsimonious exploration of this process, it could also be viewed as a limitation of this study. Despite the similarities of different aspects of RNT (e.g. rumination and worry), they are statistically distinguishable and fulfil different functions (Nolen-Hoeksema et al., 2008). However, a growing field of research has highlighted the validity of assessing RNT as a unitary construct. McEvoy et al. (2013) argue that elevated levels of RNT are likely to be captured across various diagnoses regardless of the measure used and that it is generally unnecessary to distinguish between worry and rumination.

Additionally, the use of the SBCS could be a weakness of this study as it has only been validated for use in patients with co-morbid pain and sleep disorder and was designed based on three subscales rather than as a unitary

measure. However, the focus on catastrophising and associated behaviours fits well with the focus of this study. Despite the limitations, the modified SBCS used in this study was found to have excellent internal consistency and no participants reported any difficulties whilst completing it.

Finally, there are limitations concerning the diagnosis of PNES. Although PNES is one of the main differential diagnoses of epilepsy, it is often a considered a neurological diagnosis of convenience (R. Brown & Reuber, 2016) due to the heterogeneity of the patient group. This imposes an inherent limitation upon research in this field as there is likely to be a lot of inter-participant variation, with different factors contributing to each individual's PNES. However, whilst acknowledging this limitation, it is only through research we will be able to develop a broader, more nuanced understanding of the different mechanisms that may be involved, or the difficulties experienced by patients. Another diagnostic consideration is not all participants were diagnosed to the highest standard of "documented PNES" as set out in the International League against Epilepsy (ILAE) guidelines on the diagnosis of PNES (LaFrance Jr., Baker, Duncan, Goldstein, & Reuber, 2013). However, all patients had their diagnoses confirmed by experienced epileptologists using all available clinical data and their own assessment of the patient. Any patients in whom there were any diagnostic doubts were excluded from this study. Limiting the study to participants with video-EEG proven diagnosis would have introduced bias, because it would have limited participation to patients with more severe seizure disorders or more frequent seizures

Clinical Implications and Further Research

The high levels of anxiety and depression observed in pwPNES support previous findings about the high level of psychiatric co-morbidity in pwPNES (Diprose, Sundram, & Menkes, 2016) and suggest that clinicians need to be aware of these disorders in pwPNES. The finding that pwPNES are prone to RNT suggests a possible mechanism for treatment of these disorders. McEvoy et al. (2013) suggest that elevated RNT should be treated regardless of the principle disorder suffered by the patient and, Ruscio et al. (2011) argue the transdiagnostic nature of RNT means it is a suitable target of intervention for patients with multiple co-morbid conditions. The potential efficacy of RNT focussed interventions was demonstrated by Brosschot and van der Doef (2004) who found that reducing the time of RNT reduced somatic symptoms. Additionally, rumination-focused Cognitive Behavioural Therapy has been shown to reduce levels of depression, with the treatment effect being mediated by the changes in rumination (Watkins et al., 2011). Such treatments have not been validated in pwPNES and it remains to be seen whether treating RNT in this population would have the same beneficial effects, a potential area for further research.

Further research on RNT could also identify more specific areas for intervention. Whilst RNT is a valid unitary construct, the significant finding suggests that further research focussing on specific forms of RNT (e.g. worrying or rumination) would be beneficial. Based on the slightly different functions of these processes, such research could provide further information about the potential function of RNT in pwPNES. Additionally, this study does not provide any information about the content of RNT. Whilst the relationship between RNT

and catastrophising and the correlations between the PTQ and mSBCS scores suggest that some RNT may relate to the impact of seizures, this is only speculative and is tempered by the lack of correlation with seizure frequency. Further research could explore the content of RNT in pwPNES to establish if there are common themes of RNT in this patient group (i.e. whether RNT focuses on specific topics e.g. interpersonal or seizure-related variables, or if it is a more general process) and also to establish if these are different to PWE.

Conclusions

This study contributes to the growing body of literature suggesting that pwPNES exhibit catastrophising cognitions. In particular, this study focused on the perseverative aspect of catastrophising, demonstrating that pwPNES report higher levels of RNT than PWE. Whilst pwPNES did not report a fear of their seizures on a Stroop task, their scores on a self-report questionnaire suggested they may catastrophise their seizures and respond in a more avoidant manner to these. As this study compared pwPNES with PWE, the findings do not simply reflect the experience of having a chronic seizure condition and instead reflect factors unique to the experience of PNES.

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Appendix A

Quality Appraisal Measure

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

Appendix B

Supplementary data for the narrative synthesis section of the literature review

Depressive symptomology

Table A1

Mean (SD) scores on MMPI-2 Harris-Lingoes subscales (Cragar et al., 2003).

Subscale	Cragar et al., (2003)	
	PNES	Epilepsy
D1 (subjective depression)	69 (15.4)	63 (13.5)
D2 (psychomotor retardation)	59 (12.5)	56 (13.5)
D3 (physical malfunctioning)	73 (13.9)	71 (8.9)
D4 (mental dullness)	72 (16.3)*	65 (9.7)*
D5 (brooding)	63 (14.1)	58 (13.9)

Group differences: * p <.05,

Table A2

PwPNES Mean (SD) scores on PAI subscales broken down by gender.

Subscale	Asmussen et al. (2009)		Gale et al. (2015)	
	Females	Males	Females	Males
PAI (Dep-A)	52.3 (11.4)	52.5 (11.6)	58.0 (13.7)	60.4 (14.5)
PAI (Dep-C)	53.0 (11.1)	51.0 (10.0)	57.1 (13.5)	59.6 (14.6)
PAI (Dep-P)	64.9 (11.5)**	05.9 (8.5)**	67.6 (11.4)*	63.8 (11.9)*

Gender group differences: * p <.05, ** p < .01

Table A3

Mean (SD) scores on PAI subscales.

Subscale	Asmussen et al. (2008)		Gale et al. (2015)		Thompson et al. (2010)		Wagner et al. (2005)	
	PNES	Epilepsy	PNES	Epilepsy	PNES	Epilepsy	PNES	Epilepsy
PAI (Dep-A)	52.8 (11.4)	51.5 (10.4)	58.7 (14.0)***	52.6 (10.9)***	59.7 (13.5)	56.3 (11.7)	-	-
PAI (Dep-C)	51.7 (10.3)	53.5 (11.5)	57.8 (13.8)**	54.2 (11.8)**	61.4 (12.7)*	57.7 (12.7)*	-	-
PAI (Dep-P)	61.3 (11.6)**	55.7 (12.6)**	66.6 (11.6)***	56.3 (11.8)***	67.7 (12.1)***	59.1 (10.7)***	69.4**	56.9**

Group differences: * p <.05, ** p < .01, *** p < .001

Attachment, relationships and depression

Green et al. (2017)

Table A4

Correlations between depression (PHQ-9) and other variables

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

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

Table A5

Regression analyses between depression scores and other variables

Group	Regression step. *Measure*	*B*	*β*	ΔR^2
PNES	1- demographic/seizure variables			.26
	Age	.19	.34	
	Gender	5.61	.29	

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

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

The LaFrance Jr. et al. (2011) data is summarised under the ‘Health status, quality of life and depression’ heading.

Health status, quality of life and depression

LaFrance Jr. et al. (2011)

Table A6

Correlations between depression (BDI-II) and other variables

Category. *Subscale*	PNES	Epilepsy

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

* $p < .01$

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

Karakis et al. (2014)

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

Rawlings et al.

Table A7

Correlations between HRQoL and other variables

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

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

J. Szaflarski and M. Szaflarski (2004)

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

Table A8

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

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

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

[a] All scores significantly different from PWE

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

Table A9

Mean (SD) SF-36 scores for all participants

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

NB. Higher scores = better HRQoL

Cognitive and emotional functioning and depression

R. Brown et al. (2013)

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

Table A10

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

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

Prigatano et al. (2009)

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

Table A11

Correlations between depression and other variables

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

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

Appendix C

Stroop Task Word Lists

Conscious Identification Task

Threatening	**Neutral**
RAPE	TALE**
MASSACRE**	MUSICIAN
MURDER	DETAIL**
TERROR	BUTTER
BOMB	BOWL
RAGE	KNEE
KILL**	SEAT
HOSTAGE	HAIRCUT**
HOSTILE**	FORESTS**
ASSASSIN**	SCISSORS

**** only used in the pilot study**

Experimental Stroop: Practice Phase

EQUATIONS	STREAMS
BILLBOARD	FLOWERS
BOTTLES	ORBITAL
CAPTAIN	LANDSCAPES
PAVEMENT	LUGGAGE
PROGRAMMED	ADJACENT
SILKY	HOUSEHOLDS
PARK	BANANA

Experimental Stroop: Main Phase

Seizure threat	**Neutral**
SEIZURE	PEANUTS
EPILEPSY	PLATYPUS
BLACKOUT	LANTERNS
HEADACHE	NOTEBOOK
CONFUSION	DOCUMENTS
FORGETFUL	READERSHIP
MEDICATION	STATIONERY
FALL	CENT
FATIGUE	DRAWERS
COLLAPSE	CATEGORY

Appendix D

Ethical Approval for Online Recruitment

The University Of Sheffield.

Downloaded: 21/03/2017
Approved: 21/03/2017

Sean Walsh
Registration number: 140149605
Psychology
Programme: Doctorate in Clinical Psychology

Dear Sean

PROJECT TITLE: The Effects of Repetitive Thoughts and Feelings in People with Chronic Seizure Disorders
APPLICATION: Reference Number 013163

On behalf of the University ethics reviewers who reviewed your project, I am pleased to inform you that on 21/03/2017 the above-named project was **approved** on ethics grounds, on the basis that you will adhere to the following documentation that you submitted for ethics review:

- University research ethics application form 013163 (dated 20/03/2017).
- Participant information sheet 1028058 version 1 (03/03/2017).
- Participant consent form 1028059 version 1 (03/03/2017).

If during the course of the project you need to deviate significantly from the above-approved documentation please inform me since written approval will be required.

Yours sincerely

Thomas Webb
Ethics Administrator
Psychology

Appendix E

Information Sheet

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Royal Hallamshire Hospital
Glossop Road
Sheffield
S10 2JF
Tel 0114 271 1900 Fax 0114 271 1901

Title of the project: 'The Effects of Repetitive Thoughts, and Feelings in People with Chronic Seizure Disorders'.

Thank you for thinking about taking part in this research project.

Before you decide to take part it is important for you to understand why this research is being done and what it will involve.

This information sheet tells you about the project. Please read this sheet carefully and take time to decide whether or not you wish to take part. Please feel free to ask us if there is anything that is not clear or if you would like more information. This research is confidential and your anonymity will be protected at all times. Thank you for reading this.

What is the purpose of this study?

This study aims to explore two different areas.

1. People who suffer seizures often worry about these and have fears about the effects upon their health. People will often adapt their behaviour because of these fears (e.g. not leaving the house very often, or avoiding social situations) which can affect their quality of life.

2. When people worry about things, they can often spend a lot of time thinking about them, or other bad things that have happened in the past. This may also affect people's quality of life and can be linked to anxiety and depression.

We will explore whether the questionnaires or tests used in this study will show up any differences between people with epilepsy or people with nonepileptic seizures. Learning more about the different ways people think about their seizures will allow us to help people adapt to their seizures more effectively and

maintain as high a quality of life as possible.

This study will contribute to a doctoral degree in Clinical Psychology (DClinPsy) which will be awarded by the University of Sheffield.

What would I be asked to do?

There are two parts to to this study. In the first part, we will ask participants to complete a computer-based task which will present them with words or symbols. Participants will be required to identify the colour of these words and symbols.

In the second part, we would ask participants to complete several short questionnaires focussing on:

- their thoughts about their seizures,
- whether they think about the same things repeatedly,
- their mood and anxiety,
- their seizures.

It should take around 60 minutes to complete all tasks and will take no longer than 75 minutes.

Why have I been chosen to take part?

You have been asked to take part because you are attending a neurology clinic or EEG appointment at the Royal Hallamshire Hospital, or because you have previously indicated a willingness to participate in clinical research.

Do I have to take part?

No, the decision to participate is entirely up to you. This information sheet is to help you decide, and we are happy to answer any questions you may have. If you do decide to take part you will be asked to sign a consent form and will be able to leave the study at any time without having to give a reason. Any decision to leave the study or to not take part will not affect your standard of care.

The consultation with your neurologist will be no different whether or not you take part in the study.

What do I have to do if I want to take part?

At the moment, simply consider whether you would like to take part in the study. This information sheet gives you the opportunity to think about this before you meet your doctor. A member of the research team will be present in the waiting area and if you have any questions about the study, you will be able to ask them when you go for your appointment. If you want to take part, we would ask

you to speak to your consultant or the research team member after your appointment.

As the study looks at epileptic and non-epileptic seizures, we will ask for your permission to contact your neurologist to confirm your epilepsy diagnosis. This consent would be required for you to be eligible to take part.

What are the possible benefits of taking part?

The information from this research will be used to help improve future health services for people with non-epileptic seizures. It will help us understand the difficulties that sufferers of non-epileptic seizures face and help offer more appropriate support for these.

What are the possible inconveniences or disadvantages of taking part?

If you are a patient participant, your clinical care will not be affected in any way by your participation in this study and the only inconvenience is the time it will take to complete the study.

We will ask some questions about depression and anxiety in this study (because these problems can affect our ways of thinking). If your scores on these questionnaires indicate a difficulty with anxiety or depression, we would ask your permission to contact your neurologist about this. If you have any concerns about these issues, information can be found on the NHS Choices website (http://www.nhs.uk/pages/home.aspx), or you can arrange to speak to your GP.

Would I be reimbursed for participating?

Participants who attend the Royal Hallamshire solely to participate in this study can claim £5 to cover their travel expenses.

What happens when the study ends?

Unfortunately, we will be unable to tell you about your individual results, although you can request a summary of the project results. This would be sent when the project is finished and is likely to take up to one year. The results of the study will be published in scientific journals. It usually takes one or two years before the results of a study like this will be published.

What will happen if I don’t carry on with the study?

You can withdraw from the study at any time. This will not affect your standard of care in any way.

Will my taking part in this study be kept confidential?

YES, all information that is collected about you during the course of the research will be kept strictly confidential.

1) We comply with the Data Protection Act 1998 in handling, processing, storage and destruction of the information that we collect from you.

2) Your data will be stored under a code number and will not contain your name. This means that information collected for the study can be kept strictly confidential. Consent forms will be kept separately from other data collected.

3) All patient-identifiable data will be kept in the Royal Hallamshire Hospital and stored securely in locked cabinets. Other non-identifiable data will be stored securely in locked cabinets at the Clinical Psychology Unit at the University of Sheffield. All electronic data will be anonymised and kept on secure servers/computers

4) Access to data is restricted to research staff from the University of Sheffield and Sheffield Teaching Hospitals NHS Foundation Trust and named team membersfrom the research team conducting this project. The research team has access to the coded information for the purpose of analysis, writing reports and presentations.

5) Data will be stored for up to ten years and will then be disposed of securely.

What if something goes wrong?

It is extremely unlikely that anything will go wrong during the study, as it only uses questionnaires and a simple computer task. If you have a concern about any aspect of this study, you should ask to speak to the study coordinator in the first instance who will do their best to answer your questions (Sean Walsh; swalsh1@sheffield.ac.uk or Markus Reuber, 0114 226 8763).

If you have any concerns or complaints about the study or about the way you've been approached and treated during it, the normal National Health Service complaints procedure is available to you. You may contact the Sheffield Patient Service Team (previously known as PALS), who can assist you if you have any concerns about your care in the NHS; (tel.: 0114 271 2400; email: PST@sth.nhs.uk; address: Patient Services Team, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF. If you remain unhappy and wish to complain formally, you can contact the Research Director at Sheffield Teaching Hospitals (Professor Simon Heller, Research and Development, Room G11, 6 Claremont Place, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF.

Who is organising and funding the research?

The research is being conducted by a Trainee Clinical Psychologist, a Neurologist and Researcher at Sheffield Teaching Hospitals NHS Foundation Trust (at the Royal Hallamshire Hospital) and the University of Sheffield. It is funded by the University of Sheffield.

Who has reviewed the study?

The East of Scotland Research Ethics Service REC 2, which has responsibility for scrutinising all proposals for medical research on humans, has examined the proposal and has raised no objections from the point of view of research ethics. It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from the University of Sheffield and Sheffield Teaching Hospitals NHS Foundation Trust, whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

Contact details:

Sean Walsh, swalsh1@sheffield.ac.uk or Markus Reuber, Academic Neurology Unit, University of Sheffield, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF. Telephone: 0114 2268763 Email: markus.reuber@sth.nhs.uk Fax: 0114 2713158.

Appendix F

Consent form

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Royal Hallamshire Hospital
Glossop Road
Sheffield
S10 2JF
Tel 0114 271 1900 Fax 0114 271 1901

Title of the project: The Effects of Repetitive Thoughts, and Feelings in People with Chronic Seizure Disorders.

Please, write your initials in box:

I confirm that I have read and understand the Information Sheet for the above study and had the opportunity to ask questions	☐
I understand my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or rights being affected.	☐
I agree to take part in the study.	☐
I agree to complete questionnaires on my thoughts about my seizures, repetitive thinking, my mood, anxiety, quality of life and seizures.	☐
I agree to complete the computer task which will require me to name the colours of words and stimuli.	☐
I agree for you to contact my neurologist if you have concerns about my scores on the depression or anxiety questionnaires	☐
I agree for you to contact my neurologist to obtain confirmation of my epilepsy diagnosis	☐

Date:

Name:

Signature:

Person taking Consent:

Signature:

Appendix G

Debriefing Sheet

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Royal Hallamshire Hospital
Glossop Road
Sheffield
S10 2JF
Tel 0114 271 1900 Fax 0114 271 1901

Title of the project: 'The Effects of Repetitive Thoughts, and Feelings in People with Chronic Seizure Disorders'.

Thank you for thinking about taking part in this research project.

This study was investigating whether patients with non-epileptic seizures were prone to repetitive thinking, and whether they feel a high level of fear of their seizures. These factors have both been shown to associate with avoidant behaviours (e.g. not leaving the house or avoiding social situations) and impact upon a person's quality of life.

How was this tested?

In this study, you were asked to complete numerous questionnaires assessing fear of seizures, avoidant behaviour, repetitive thinking, anxiety and depression.

The computerised part of the task asked you to name the colour of a word or symbol. When a symbol was presented, a word had flashed up very quickly beforehand. This was presented so fast that you would be unable to see it, but your brain would pick up on it at an unconscious level. The words used were either related to seizures or were neutral words. It is thought that if a word grabs people's attention (e.g. if it is threatening), then they will take longer to name the colour. The goal of this task was to see if participants found the seizure words more threatening than the neutral words, suggesting a fear of seizures, even if they are unaware of this.

Why is this important and what do you expect to find?

We expect to find that participants with non-epileptic seizures will show a fear of seizures and will also think more repetitively about things. If this is the case, it

will help us to develop better support for patients experiencing these difficulties and help to improve patients' quality of life.

What if I want to know more?

If you wish to know the results of the study, know more, or wish to withdraw from the study, please contact the researcher (Sean Walsh; swalsh1@sheffield.ac.uk). It will be possible to withdraw until the project is submitted around April 2017. For further information about non-epileptic seizures or epilepsy, please visit:

http://www.nhs.uk/pages/home.aspx

If you have any concerns or complaints about the study or about the study has been conducted, the normal National Health Service complaints procedure is available to you. You may contact the Sheffield Patient Service Team (previously known as PALS), who can assist you if you have any concerns about your care in the NHS (tel: 0114 271 2400; email: PST@sth.nhs.uk; address: Patient Services Team, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF). If you remain unhappy and wish to complain formally, you can contact the Research Director at Sheffield Teaching Hospitals (Professor Simon Heller, Research and Development, Room G11, 6 Claremont Place, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF.

Appendix H

The Perseverative Thinking Questionnaire

In this questionnaire, you will be asked to describe how you typically think about negative experiences or problems. Please read the following statements and rate the extent to which they apply to you when you think about negative experiences or problems.

		Never	Rarely	Sometimes	Often	Almost always
1	The same thoughts keep going through my mind again and again.	0	1	2	3	4
2	Thoughts intrude into my mind	0	1	2	3	4
3	I can't stop dwelling on them.	0	1	2	3	4
4	I think about many problems without solving any of them.	0	1	2	3	4
5	I can't do anything else while thinking about my problems.	0	1	2	3	4
6	My thoughts repeat themselves.	0	1	2	3	4
7	Thoughts come to my mind without me wanting them to.	0	1	2	3	4
8	I get stuck on certain issues and can't move on.	0	1	2	3	4
9	I keep asking myself questions without finding an answer.	0	1	2	3	4
10	My thoughts prevent me from focusing on other things.	0	1	2	3	4
11	I keep thinking about the same issue all the time.	0	1	2	3	4
12	Thoughts just pop into my mind.	0	1	2	3	4
13	I feel driven to continue dwelling on the same issue.	0	1	2	3	4
14	My thoughts are not much help to me.	0	1	2	3	4
15	My thoughts take up all my attention.	0	1	2	3	4

Appendix I

The Modified Safety Behaviour and Catastrophising Scale

How many seizures have you experienced during the past four weeks?___

We are interested in your thoughts and feelings about your seizures. Please indicate the extent to which you agree with the statements below.

	Not at all true for me	Somewhat true for me	Moderately true for me	Very much true for me	Extremely true for me
I should not do my usual work because of my seizures	0	1	2	3	4
I should avoid activities that create strain	0	1	2	3	4
I should avoid emotionally charged situations	0	1	2	3	4
It is best for me to avoid complicated problems as much as possible	0	1	2	3	4
I should avoid work that requires a lot of thought	0	1	2	3	4
It is best that I avoid situations that demand prolonged and intensive focus	0	1	2	3	4
I cannot stop thinking about them	0	1	2	3	4
I think about how much I would like to be rid of the problem	0	1	2	3	4

I worry that my seizures may get worse	0	1	2	3	4
I wonder if there is something seriously wrong with me	0	1	2	3	4
There is nothing I can do to alleviate the seizures	0	1	2	3	4
I believe I will never be rid of the seizures	0	1	2	3	4

Appendix J

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use "✔" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
Trouble falling or staying asleep, or sleeping too much	0	1	2	3
Feeling tired or having little energy	0	1	2	3
Poor appetite or overeating	0	1	2	3
Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
☐	☐	☐	☐

Appendix K

GAD-7

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use "✔" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
Feeling nervous, anxious or on edge	0	1	2	3
Not being able to stop or control worrying	0	1	2	3
Worrying too much about different things	0	1	2	3
Trouble relaxing	0	1	2	3
Being so restless that it is hard to sit still	0	1	2	3
Becoming easily annoyed or irritable	0	1	2	3
Feeling afraid as if something awful might happen	0	1	2	3

Appendix L

Demographic Questionnaire

Personal Information

Please answer the following questions about yourself. The information you are giving us will be treated as confidential and will be anonymised. Do not put your name on the questionnaire.

1. Date of birth:

2. Gender: *(please tick the correct option)*

   Male ☐ Female ☐ Other please specify:

3. How would you describe your ethnic background? (Please tick the box that applies to you, or write an answer in the space provided)

   White – English/Welsh/Scottish/Northern Irish/British ☐

   White – Irish ☐

   White – Gypsy or Irish Traveller ☐

   White - Any Other White background ☐

   Mixed/Multiple ethnic group - White and Black Caribbean ☐

   Mixed/Multiple ethnic group - White and Black African ☐

   Mixed/Multiple ethnic group - White and Asian ☐

   Mixed/Multiple ethnic group - Any Other Mixed/multiple ethnic background ☐

   Mixed/Multiple ethnic group - Any Other Mixed/multiple ethnic background ☐

   Asian/Asian British – Indian ☐

   Asian/Asian British – Pakistani ☐

   Asian/Asian British – Bangladeshi ☐

   Asian/Asian British – Chinese ☐

   Asian/Asian British - Any other Asian background ☐

Black/African/Caribbean/Black British – African ☐

Black /African/Caribbean/Black British – Caribbean ☐

Black/African/Caribbean/Black British – Any other Black / African / Caribbean background ☐

Other ethnic group – Arab ☐

Any other ethnic group; Please specify:

5. How would you describe your current employment status? (Please tick the box/(es) that applies/(apply) to you or write an answer in the space provided)

In full-time paid work ☐

In part-time paid work ☐

In full-time education ☐

In part-time education ☐

Full-time carer/homemaker ☐

On leave/out of work due to illness or disability ☐

Retired ☐

Other; Please specify:

6. What is your highest educational qualification? (Please tick the box/(es) that applies/(apply) to you or write an answer in the space provided)

No educational qualifications ☐

Standard grades, O grades, O levels, GCE/GCSEs ☐

Highers, advanced highers, A levels ☐

Vocational qualification (e.g. SVQ, NVQ, SCOTVEC) ☐

HNC/HND ☐

Degree (e.g., BA, BSc) ☐

Postgraduate qualification (e.g. MSc, PhD) ☐

Professional qualification (e.g. CAEW, CIIA) ☐

Other; Please specify:

7. When did you first have a seizure?
   (For example, 6 months ago or 3 years ago)

   _____months ago

   _____years ago

8. When did you have your last seizure? *(e.g., 1 day ago or 3 months ago)*_____

9. Are you currently on any medication? *(please tick as appropriate)*

   ☐ YES

   ☐ NO

   If yes, please list your medication below:

10. Have you received or are receiving any form of psychological therapy

    ☐ YES

    ☐ NO

Appendix M

NHS Ethical Approval for the Main Study.

NHS SCOTLAND
Research Ethics Service

East of Scotland Research Ethics Service (EoSRES)

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

TAyside medical Science Centre
Residency Block Level 3
George Pirie Way
Ninewells Hospital and Medical School
Dundee DD1 9SY

Professor Markus Reuber
Professor of Clinical Neurology and Honorary Consultant Neurologist
Sheffield Teaching Hospitals NHS Foundation Trust
Academic Neurology Unit, Royal Hallamshire Hospital
Glossop Road
Sheffield
S10 2JF

Date: **18 May 2016**
Your Ref:
Our Ref: AG/16/Es/0060
Enquiries to: Arlene Grubb
Direct Line: 01382 383848

Dear Professor Reuber

Study title:	**The effects of repetitive thoughts, and feelings in people with chronic seizure disorders**
REC reference:	**16/ES/0060**
Protocol number:	**STH19428**
IRAS project ID:	**203578**

Thank you for your letter of 16 May 2016, responding to the Proportionate Review, Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the Assistant Co-ordinator Mrs Arlene Grubb, eosres.tayside@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

The chair as asked that the footer on PTQ questionnaire V2 dated 12/5/16 be added.

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).
Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.
There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites