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Nocebo Hypothesis Cognitive Behavioural Therapy (NH-CBT) for non-epileptic seizures: a consecutive case series

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Abstract

Background: Research has demonstrated that implementation of Nocebo Hypothesis Cognitive Behavioural Therapy (NH-CBT) achieved full symptom remission in 93% of people with Functional Neurological Symptoms Disorder (FNSD), most of them exhibiting motor symptoms. The basis for NH-CBT is consistent with a predictive coding aetiological model of FNSD. This idea is transparently shared with people with FNSD in the form of telling them that their symptoms are caused by a nocebo effect, usually followed by some physical activity that aims to change the person's belief about their body.

Aims: To demonstrate that a version of NH-CBT can also be effective in eliminating or reducing non-epileptic seizures (assumed to be a sub-type of FNSD).

Method: A consecutive case series design was employed. Participants were treated with NH-CBT over a 12-week period. The primary outcome measure was seizure frequency. Numerous secondary measures were employed, as well as a brief qualitative interview to explore participants' subjective experience of treatment.

Results: Seven out of the 10 participants became seizure free at least 2 weeks before their post-treatment assessment, and all stayed seizure-free for at least 5 months. Six of those seven remained seizure free at 6-month follow-up. There were large positive effect sizes for the majority of secondary measures assessed.

Conclusions: This case series provides evidence of feasibility and likely utility of NH-CBT in reducing the frequency of non-epileptic seizures.

Keywords: Cognitive behavioural therapy; Functional neurological symptoms disorder; Nocebo effect; Non-epileptic seizures; Predictive coding model

Introduction

Non-epileptic seizures (NES), also known as functional seizures, psychogenic non-epileptic seizures or dissociative seizures, are phenomena where individuals experience abnormal events that often have superficial similarities to epileptic seizures (e.g. convulsions or absences), but where there is evidence that the seizures are not a consequence of abnormal electrical activity in the brain (i.e. epilepsy). NES are identified in *DSM-5* as part of the broader diagnostic category of Functional Neurological Symptom Disorder (FNSD) (previously known as Conversion Disorder), which includes other symptoms that resemble those arising from other neurological conditions (e.g. motor weakness, tremor) (American Psychiatric Association, 2013).

Approximately 20% of people presenting to medical professionals with seizure-like events receive a diagnosis of NES (or similar nomenclature). Prevalence estimates range from

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2 to 50/100,000 of the general population (Hingray *et al.*, 2018). NES can substantially impact an individual's life. Levels of chronic disability and welfare dependence are high in this population (Reuber *et al.*, 2003). People with NES have a standardised mortality ratio 2.5 times higher than the general population, dying at a rate comparable to those with drug-resistant epilepsy (Nightscales *et al.*, 2020). A range of co-morbid disorders have also been identified, including other functional disorders, dissociative disorders and post-traumatic stress disorder, depressive and anxiety disorders, personality disorders, cognitive and sleep problems, epilepsy, head injury, migraine, pain, and asthma (Popkirov *et al.*, 2019). The cost to health care systems is substantial, with two studies from different countries both identifying the pre-diagnosis healthcare costs to be slightly over US\$25,000 per person with NES (Magee *et al.*, 2014; Martin *et al.*, 1998).

Research is yet to clearly establish a causal mechanism for NES. Historically, models suggesting that dissociative responses were a key mechanism in the aetiology of NES have been posited (see Nicholson *et al.*, 2011, for a summary). However, evidence for effective treatment for NES based on this type of model is limited. A large multi-centre trial of cognitive behavioural therapy (CBT) plus standardised medical care (SMC) did not achieve a significant improvement in seizure frequency (their primary measure) versus SMC alone, although did reach significance on other secondary measures (e.g. period of seizure freedom, how 'bothersome' seizures were, and quality of life) (Goldstein *et al.*, 2020). Their CBT treatment was based on the idea that NES are dissociative responses to cues that may have been associated with past traumatic experiences.

Alternative models of FNSD aetiology have been suggested in more recent years. Edwards *et al.* (2012) used a Bayesian predictive coding model to explain that perception and action arise as a result of inference based on both prior beliefs and sensory information, and that functional neurological symptoms arise due to a perception or belief that is held with undue certainty following top-down attentional modulation. It was stated that the 'overweighting of prior beliefs over sensory data' that produces FNSD symptoms also explained phenomena such as the placebo effect. Edwards *et al.* (2012) clarified that the use of the word 'beliefs' in this context is different from the use of the word by philosophers, where it refers to 'consciously held and reportable propositions'. Instead, in this context, the word refers to 'probabilistic representations (encoded by neuronal activity) in a hierarchical Bayesian network . . . whether or not one is conscious of their content'. Other reviewers have reached similar conclusions: that a 'placebo' effect was the mechanism that produced all functional neurological symptoms (including NES) (Fobian and Elliott, 2019), that the primary attentional system selects a 'rogue representation' of physical illness (Brown, 2004), or that symptoms arise when a 'seizure scaffold' is automatically activated during times of autonomic arousal (Brown and Reuber, 2016).

Nocebo Hypothesis Cognitive Behavioural Therapy (NH-CBT) intervention

NH-CBT (Richardson *et al.*, 2018) is a treatment based on the idea that FNSD symptoms are akin to a nocebo response, which could be defined as 'expectancy-induced changes in the patient's brain-body unit' (Colloca and Miller, 2011). This is consistent with the Bayesian predictive coding model described above, as beliefs are seen as influencing a person's motor output or perceptions. This definition of a 'nocebo response' is more apt in describing potential mechanisms for FNSD than a definition of a 'nocebo effect', which refers to the unintended negative consequences following the administration of an inert substance. However, as the term 'placebo effect' appears reasonably well known to laypeople, we use the term 'nocebo effect' in conversation with people with FNSD, and throughout this paper, to denote any negative effects of subconscious expectations/beliefs on a person's body.

NH-CBT starts with 60–90 minutes of psychological assessment, education and treatment, including the following components: gathering information about participants' medical history, the onset and course of their symptoms, the participant's understanding of the diagnostic evidence, their personal belief about the causes of their symptoms, and their understanding of the

terms ‘subconscious’ and ‘placebo effect’. The term ‘nocebo effect’ is carefully explained to each participant. A psychological formulation is then shared that incorporates relevant history (e.g. migraines, head injuries) within a hypothesis that their symptoms are being caused by a nocebo effect. The aim is to propose to the participant an alternative belief about the cause of their symptoms, to challenge the one initially held (e.g. something similar to ‘my brain is damaged’). Participants receive written information summarising the education received, including their personalised formulation. The subsequent treatment involves (in traditional CBT terminology) behavioural experiments. These vary between symptom types, but all have the aim of creating a visceral, lived experience (e.g. through exposure to perceived seizure triggers) that attempts to change the person’s beliefs about their bodies.

For people with NES, the next session involves collaboratively creating a graded exposure hierarchy, where antecedents that could trigger their seizures are subjectively ranked from ‘most likely’ to ‘least likely’. They are also taught some techniques that may help prevent seizures during exposure sessions (e.g. distraction, grounding).

In subsequent sessions, the person then gradually exposes themselves to those triggers (at a mutually agreed starting point on the hierarchy). Examples of exposure activities undertaken in this study include the watching of a YouTube video of a strobe effect on a mobile phone at increasing proximity, spinning around to induce dizziness with increasing velocity and duration, running, sitting in hot cars, purposely sleeping poorly, and recalling traumatic memories. Exposure to some of the triggers stated was not appropriate for a clinical setting, e.g. when it involved alcohol use. However, we found that those who stated this was a potential trigger for seizures spontaneously engaged in their own exposure work once they had some experience of exposure to other triggers.

If the exposure is successful, the lack of subsequent seizure is discussed as further evidence that they do not have epilepsy, that the trigger was actually benign, that perhaps a subconscious belief was indeed responsible for previous seizures, and that their seizures are to some extent controllable. Whilst this is an attempt to change beliefs at a more conscious and intellectual level, i.e. not at a level that the beliefs responsible for the seizures are purported to lie, this part of the intervention takes little time, and it is plausible that it may be helpful. Throughout treatment, the clinician intentionally portrays optimism about potential recovery.

In a pilot case series exploring the potential effectiveness of NH-CBT treating people with a range of presentation types (predominantly motor symptoms but also including two people with NES), 93% of FNSD patients achieved full remission of functional symptoms (Richardson *et al.*, 2018).

A treatment based on a similar aetiological conceptualisation has been shown to be effective in adolescents with NES in a small randomised controlled trial (Fobian *et al.*, 2020). This treatment, named Retraining and Control Therapy (ReACT) resulted in 100% of participants experiencing no seizures in the 7 days after the conclusion of therapy, with 82% remaining seizure-free for 60 days, with gains maintained over a year later (Stager *et al.*, 2021).

Numerous other treatments of NES described in the literature have included some therapeutic components shared with NH-CBT. For example, Cope *et al.* (2017) trialled a brief group psychoeducation intervention which appears to have taught participants that their seizures were dissociative in nature, but also taught them grounding and distraction as symptom management techniques (these latter components are shared with NH-CBT). Results saw 39% of participants seizure-free in the 4 weeks before the end of treatment, compared with 11% at baseline. Other interventions have included some form of exposure as a component of their treatment. Myers *et al.* (2017) used prolonged exposure as the main component of their intervention. They conceptualised seizures as having an emotionally traumatic origin, so this exposure was to key traumatic memories. Results saw 72% of enrolled participants seizure-free at the end of treatment, after 18–22.5 hours input, with good maintenance of gains. Goldstein *et al.*’s (2020) CBT intervention also included some exposure for the purpose of ‘reducing avoidance’ (Goldstein *et al.*, 2015). Again, this was in the context of a treatment that conceptualised seizures as dissociative in nature.

These latter exposure treatments differ from NH-CBT in that the explicit goal of exposure in NH-CBT is to create visceral, lived experiences specifically chosen for their potential to change a person's belief about their susceptibility to seizures. To our knowledge, there are no other exposure treatments for NES that target modification of health beliefs about seizures directly in this way. This primary target for treatment is consistent with predictive coding aetiological models outlined above, that state that such beliefs are a core aetiological feature of FNSD.

Research questions

This study seeks to address the following research questions:

- (1) Is NH-CBT associated with a reduced frequency of NES?
- (2) Is NH-CBT associated with the improvement of other secondary outcomes associated with NES, such as changes in illness beliefs and quality of life?
- (3) Can changes associated with NH-CBT be maintained 6 months after the end of the intervention?
- (4) Is the treatment related to any notable adverse events?
- (5) What is the nature of the therapeutic alliance in NH-CBT?
- (6) What are some common themes in the therapeutic experiences of people with NES who are treated with NH-CBT, explored in a brief qualitative interview?

It was hypothesised that NH-CBT will be associated with a reduced seizure frequency, and will be associated with positive changes in secondary outcome measures at the end of treatment, as well as at 6 months post-treatment.

If an effective treatment for adults with NES can be identified, the positive implications for public health are considerable in terms of reducing disability and distress in people with NES and their social connections, as well as increasing independence, productivity, and quality of life.

Method

Study design and participants

This study represents a preliminary investigation into the feasibility and potential utility of NH-CBT for NES, using a convergent mixed method design that combines the design of a consecutive case series (qualitative component) with self-report measures (quantitative component).

Participants were recruited via referrals from the Te Whatu Ora/Health New Zealand (Southern) Neurology Department, between 1 September 2021 and 12 April 2022. Participants met the following inclusion criteria:

- aged 18 or older;
- had been assessed by a neurologist including the appropriate medical investigation, and that assessment resulted in that neurologist diagnosing NES, or confirming a previously made diagnosis;
- having given written consent to participate in the study.

Participants were excluded from the trial if they met the following criteria:

- they had a diagnosis of Dissociative Identity Disorder (DID);
- they had a diagnosis of Post-Traumatic Stress Disorder (PTSD) with high severity and significant dissociation (i.e. severe enough that the participant would not be able to participate in sessions);

- they met diagnostic criteria for current alcohol/drug dependence;
- they required in-patient mental health treatment during the trial;
- there were concerns about their ability to participate fully in the trial, e.g. active and extensive self-harm, or frequent admissions for in-patient mental health treatment in the last 2 months;
- they had low English language proficiency;
- they did not have the capacity to consent to participating in the trial.

Ten participants were recruited in total. They were the eligible participants from 15 consecutive referrals from the local neurology department. The reasons for the five excluded referrals were as follows: (1) did not respond to repeated attempts to contact, (2) cessation of seizures immediately after delivery of diagnosis by neurologist; (3) moved away from the region; (4) low English language proficiency; (5) spontaneous recovery (not immediately after delivery of diagnosis). See Table 1 for a summary of participant characteristics.

Only one participant reported other (motor) FNSD symptoms – she considered the impact of these to be relatively mild when compared with her seizures. No functional motor symptoms were witnessed in any participant at any point during treatment.

Study procedure

Following a diagnosis of NES by a consultant neurologist (or at the most recent review appointment that generated the referral to this trial), the participant was given some standardised education about NES (Stone, 2016), which focuses on explaining that their difficulties are genuine, common and potentially reversible, and that the person is structurally intact and healthy from a neurological perspective, but that the messages being sent by their intact neurological system are abnormal. This explanation stops short of explaining potential reasons for the abnormal messages.

The lead investigator then briefly met the participant, and asked them to immediately start keeping a seizure diary. As the delivery of an NES diagnosis has been demonstrated to lead to full remission of seizures in a substantial minority of people with NES in previous studies (e.g. 14%; Hall-Patch *et al.*, 2010), newly diagnosed participants were informed of this, and told to contact the lead investigator only if they experienced any subsequent seizure activity.

Any participants still experiencing seizures then completed baseline assessment with an independent assessor. Most participants completed this assessment within 28 days of starting their seizure diary, so their 28-day pre-baseline seizure totals were partially estimated. This involved establishing the seizure frequency recorded so far, asking them if this frequency of seizures was typical for the last 4 weeks, and then attempting to deduce as accurate an estimate as possible based on this number of recorded seizures and their memory of previous weeks' seizures.

Within one working day of baseline assessment, all participants received the initial psychoeducation session of NH-CBT, delivered by the lead investigator (a clinical psychologist with 20 years experience post-qualification, and 13 years experience of treating FNSD). Treatment was then paused, and only progressed to the exposure part of the treatment if the participant experienced another seizure.

Participants received therapy over a period of up to 12 weeks, also delivered by the lead investigator, with the frequency of therapy being guided by the frequency of the seizures. If some successful exposure had taken place, participants had the option of doing more exposure work, or pausing therapy and only reconvening if there was a recurrent seizure. Total time spent in therapy sessions was monitored. If the treatment progressed well, the last session included some brief (e.g. 15–30 minutes) education about relapse prevention.

Participants underwent a post-treatment assessment with an independent assessor at the end of the 12-week treatment period. This post-treatment assessment included a qualitative interview, asking the participant about their experience of treatment. Those who declined face-to-face

Table 1. Participant characteristics at baseline assessment

Characteristic	Median (range) n (%)
Age (years)	23 (18–50)
Gender	
Female	10 (100)
Male	0 (0)
Highest education level achieved	
Secondary	6 (60)
Tertiary	4 (40)
Relationship status	
Single	5 (50)
Married	2 (20)
De facto relationship	2 (20)
Separated	1 (10)
Ethnic group	
NZ European	5 (50)
Mixed (NZ European/NZ Maori)	5 (50)
Living arrangements	
Lives with partner/spouse only	4 (40)
Lives with parents or other related adults	2 (20)
Lives with parents and siblings	1 (10)
Lives with partner/spouse and children	1 (10)
Lives with unrelated adults	1 (10)
Lives alone	1 (10)
Current employment status	
Beneficiary/unemployed	4 (40)
Student	2 (20)
Employed full-time	2 (20)
Employed part-time (<30 hours per week)	1 (10)
Self-employed	1 (10)
Time since first non-epileptic seizure (self-report)	
≤1 week ago	1 (10)
>1 and ≤3 months ago	2 (20)
>6 and ≤12 months ago	1 (10)
>1 and ≤5 years ago	4 (40)
>5 and ≤10 years ago	2 (20)
Time since first likely non-epileptic seizure (hospital records)	
>1 and ≤5 years ago	5 (40)
>5 and ≤10 years ago	4 (20)
>10 years ago	1 (10)
Lifetime mental health difficulties noted in hospital/GP records	
Anxiety	7 (70)
Depression	5 (50)
Post-traumatic stress disorder	3 (30)
Personality disorder of some type	2 (20)
Adjustment disorder	2 (20)
Bipolar disorder	1 (10)
Panic disorder	1 (10)
Hypomania	1 (10)
Bulimia nervosa	1 (10)
Dissociative disorder	1 (10)

assessment (usually due to geographical distance from our base) completed the assessment online, often but not always assisted by video calling from the assessor, depending on participant preference.

As the main wave of COVID infections experienced in New Zealand occurred during the trial, it was pre-determined that extensions could be made to the 12-week trial period if therapist or participants contracted COVID, for the duration that they were isolating. Only the final

Table 2. Outcome measures utilised

Domain	Measure	Baseline	Post-therapy	Follow-up
Primary outcome				
Seizure frequency	Seizure diary	x	x	x
Secondary outcome				
Participant perception of change	Clinical Global Impression Scale of Improvement (CGI-I) (Busner and Targum, 2007)		x	x
Somatic symptom severity	Patient Health Questionnaire-15 (PHQ-15) (Kroenke <i>et al.</i> , 2002)	x	x	x
Health care utilisation	Self-reported use of healthcare services (computerised health records where data were missing)	x		x
Illness perception	Brief Illness Perception Questionnaire* (Broadbent <i>et al.</i> , 2006)	x	x	x
Health-related quality of life	Short Form-36 Health Questionnaire (SF-36) (McHorney <i>et al.</i> , 1993)	x	x	x
Quality of life	EuroQol-5D (EQ-5D-5L) (Herdman <i>et al.</i> , 2011)	x	x	x
Fatigue	Vitality Scale of SF-36 (McHorney <i>et al.</i> , 1993)	x	x	x
Catastrophic thinking about symptoms	Symptom Catastrophising Scale (SCS) (Moore <i>et al.</i> , 2018)	x	x	x
Anxiety	Generalised Anxiety Disorder Scale-7 (GAD-7) (Spitzer <i>et al.</i> , 2006)	x	x	x
Depression	Patient Health Questionnaire-9 (PHQ-9) (Kroenke <i>et al.</i> , 2001)	x	x	x
Dissociation	Brief Dissociative Experiences Scale (DES-B) (Dalenberg and Carlson, 2010)	x	x	x
Symptom disability	Pain Disability Index (mPDI)* (Tait <i>et al.</i> , 1990)	x	x	x
Therapeutic alliance	Working Alliance Inventory-Short Form (WAI-SF) (Hatcher and Gillaspay, 2006)		x	
Adverse events in therapy	Inventory for the Balanced Assessment of Negative Effects of Psychotherapy (INEP) (Ladwig <i>et al.</i> , 2014)		x	

*Scale modified to ask the participant directly about seizures, i.e. replacing the word 'illness' or 'pain' with 'seizures'.

participant needed a treatment period extension, although she did not require any treatment sessions during that extension, due to remittance of seizures.

A follow-up assessment took place 6 months after the end of the 12-week treatment period. Participants were contacted just over 4 weeks before the end of this follow-up period, in order to restart their seizure diary.

Hospital and GP records were accessed to establish the following information: (1) any psychopharmacological medication changes that might potentially have influenced any changes in seizure frequency; (2) history of likely NES; (3) mental health diagnoses/difficulties mentioned in said records; and (4) to establish healthcare use where self-report data were missing.

Measures

The outcome measures selected largely followed the recommendations of the Functional Neurological Disorder Core Outcome Measures (FND-COM) group (Pick *et al.*, 2020).

The primary outcome measure was seizure frequency, as measured by a seizure diary. Secondary outcome measures and associated domains, including measures of adverse events and therapeutic alliance, are listed in Table 2. In terms of the modifications to previously validated measures (Pain Disability Index, Brief Illness Perception Questionnaire, Symptom Catastrophising Scale), the measures were simply modified so that the constituent questions asked specifically about NES.

Qualitative interview

A brief semi-structured qualitative interview was conducted at the end of the 12-week treatment period. The following questions were asked:

- (1) How did you find the treatment?
- (2) Which parts of the treatment worked best for you?
- (3) Which parts of the treatment were least helpful?
- (4) Has anything changed in a positive sense due to the treatment? Can you name the (up to) three most important things?
- (5) Had you heard of the placebo effect before the treatment?
- (6) Has your understanding of the placebo and nocebo effect changed?

Optional follow-up questions were included, which simply sought to prompt participants to elaborate their answers further.

As there appears to be no published literature on the influence of cultural difference on treatment of FNSD in the Aotearoa New Zealand context, additional follow-up questions were asked of participants self-identifying as Maori or part-Maori. These questions explored pre-treatment beliefs about the cause of their seizures, including beliefs expressed within their whanāu (extended family).

Data analyses

Results of the quantitative part of this study are reported using basic descriptive statistics, as well as effect size (Hedges' *g*). Qualitative interview data were analysed with an inductive thematic analysis (not conducted by the treating therapist), informed by Braun and Clarke's (2006) thematic approach. The steps were: (1) familiarisation with the data; (2) generating initial codes; (3) thematic search; (4) defining and naming themes; (5) reviewing codes in interview context to ensure thematic accuracy. After reading and re-reading the transcripts, an initial coding pass was conducted in Microsoft Word before moving data to NVivo software for a second coding pass and thematic development.

Although the analysis was informed by a series of guiding questions integral to the research objectives, a process of reflexively re-considering codes in interview context and iteratively refining themes ensured the analysis remained firmly grounded in the data.

Results

Seizure frequency: outcome at the end of treatment and 6-month follow-up

Overall, of the ten participants who began treatment, seven were seizure-free by the end of the treatment period. Five of them had been seizure-free for 7 weeks or more; the other two were seizure-free for the last 2 weeks of the treatment period. Six of the seven remained seizure-free for the next 6 months – the one person who relapsed did so after 5 months of being seizure-free.

Two of the other three participants dropped out, both completing less than 2 weeks of treatment. The other experienced nocturnal seizures only so could not participate in the exposure component of the treatment.

Table 3 illustrates seizure frequency across the course of the study for each participant, as well as the treatment times required.

Table 3. Primary outcome measure – seizures counted or estimated in the 28-day period before each assessment, per participant

Participant number	Before baseline assessment (T0)	Before post-treatment assessment (T1)	Before 6-month follow-up assessment (T2)	Longest period of seizure freedom*	Total treatment time (hours)
1	150 (estimated)	1	0	6 months	6.25
2	3	0	0	8 months	10.5
3	120 (estimated)	66***	No data [‡]	1 day	6.5 ^{‡‡}
4	11 (estimated)	0	0	8 months	4.25
5	0	0	0	10 months	5.5
6	169	1	114	5 months	9
7	100 (estimated)	92***	No data [‡]	2 days	5.25 ^{‡‡}
8	200 (estimated)	0	0	9 months	1.5
9	23**	8	No data [‡]	9 days	10.25 ^{‡‡}
10	19 (estimated)	0	0	7 months	11.5
Median (interquartile range)	61.5 (11–150)	0.5 (0–8)	0		6.4 (5.25–10.25)
Hedges' <i>g</i> (CI ^{‡‡‡}) – T0 to T1		0.99 (0.03–1.95)			

*From 1 month pre-baseline to T2 (or last data provided) – reported to the nearest day/week/month.

**Extrapolated from participant counting 21 seizures in 26 days.

***Diary results not communicated for all 12 weeks, hence this is the last 28 days of diary reporting for each case. [‡]Hospital records reported that the person was still experiencing seizures (nearest chronological entry to 6 months post-T1).

^{‡‡}Did not complete treatment offered.

^{‡‡‡}Confidence interval reported at a 95% level of confidence.

Seizure frequency: individual patient trajectories

Below is a brief description of participants' individual treatment courses, including all known adverse events, for the participants that consented to the inclusion of this more specific description. See Figure 1 for graphs illustrating seizure frequency over time for each participant.

Participant 2

Participant 2 reported experiencing NES, but also that she relied upon cannabis to prevent other seizures that she felt were imminent. She experienced three events in the pre-baseline period, although these were all experiences where she rapidly lit a pre-rolled joint as she experienced premonitory symptoms (e.g. feeling 'spaced out' and light-headed). She experienced two more of these in the following 4 weeks (week 2 and week 4). Exposure started in week 5. She completed six exposure sessions, which included running, making herself dizzy, purposeful sleep deprivation and visiting a video game arcade. She was seizure-free throughout this process.

Participant 4

Participant 4 was receiving radiotherapy to treat an oligodendroglioma alongside her seizures treatment. She had been experiencing both convulsive and non-convulsive ('blanking out') seizures, although after the sharing of the 'nocebo hypothesis', she only experienced the latter. During her treatment planning session, it became clear that her main triggers could not be reproduced in a clinic environment (alcohol use, parental stress). She lived a 1.75-hour drive away, so home visits were pragmatically difficult. Her husband was taught how to support her to do the exposure work at home. This was successful, in that she became seizure-free within 2 weeks. It should be noted that the week she started being completely seizure-free was the week her

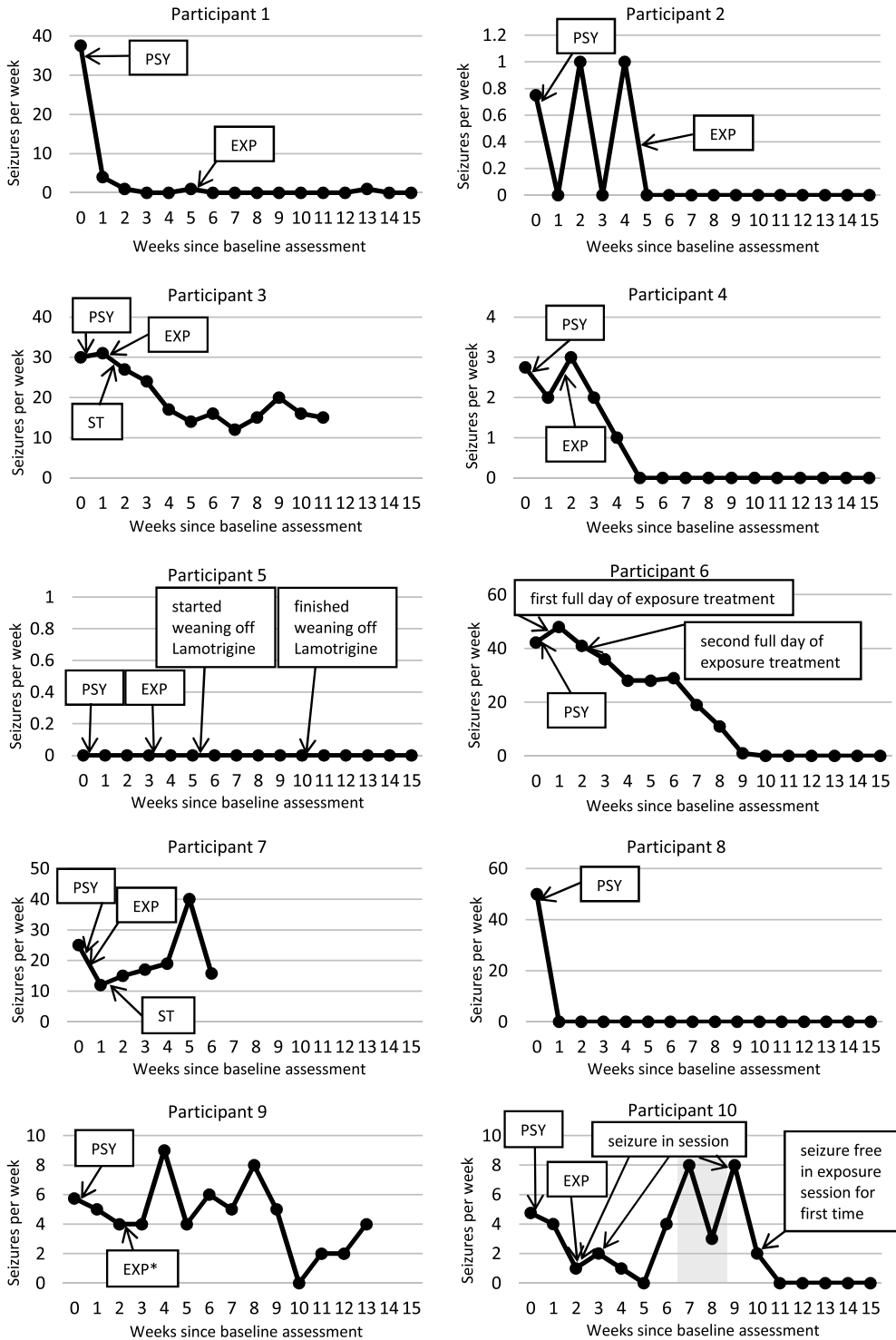


Figure 1. Clinical course of each participant. *Exposure, but only to potential daytime triggers, in someone with no daytime seizures. Week 0 value denotes mean number of seizures over the previous 4 weeks. PSY, assessment and psychoeducation session; EXP, first exposure session; ST, stopped treatment. Grey box indicates time off treatment due to COVID infection of participant and then therapist.

radiotherapy ceased, although it would be very difficult to attribute her seizures to radiotherapy, as they pre-dated the radiotherapy by a considerable period.

Participant 5

Participant 5 was first diagnosed in a different locality around 10 years previously and had been given lamotrigine as treatment. In her opinion, this had prevented her having more severe events for approximately the last 5 years, although had been having milder symptomatology (mild truncal muscle spasms, fatigue, occasional slurred speech) if she forgot to take a dose. Her treatment goal was to come off lamotrigine and remain seizure-free. She asked to engage in the large majority of the exposure treatment independently, with her partner's support, so he was educated on how to do this in an extended treatment planning session. She weaned herself gradually off lamotrigine between week 5 and week 10, remaining free of seizures and other related symptomatology.

Participant 6

This participant had never experienced a convulsive-like seizure, only events that were more akin to epileptic absences. She lived a 2.5-hour drive from our rehabilitation centre, so the assessment/psychoeducation session was completed via video call, and face-to-face exposure sessions completed intensively across two (separate) days. She had her last absence-like event around 3 weeks before the end of the treatment period, and this cessation lasted for nearly 5 months. At 6-month follow-up assessment, she reported that her absences had come back over the previous 6 weeks (approximately), although these were of reduced frequency and duration when compared with baseline.

Participant 8

Participant 8 stopped having seizures immediately after the placebo hypothesis session – she had estimated 200 in the previous 4 weeks (based on 7 days of monitoring), and had experienced seizures for over 5 years, so this was an abrupt and drastic change. She remained seizure-free at the point of 6-month follow-up assessment, nearly 9 months later.

Participant 10

This participant was the only participant who had a seizure during exposure treatment. This happened three times, all when exposing her to dizziness by getting her to spin round in a safe, controlled environment (i.e. wearing a transfer belt surrounded by crashmats). Once she managed to make herself as dizzy as possible without having a subsequent seizure, her seizures ceased from that point onwards, and she remained seizure-free at 6-month follow-up assessment.

One of the commonalities shared by most of the participants (1, 2, 4, 5 and 6) was that they had at least one moment where they experienced premonitory symptoms in the face of a trigger, but were able to prevent these progressing into a seizure, using grounding and distraction. Most expressed the idea that this experience had been very helpful, usually stating or implying (during treatment sessions) that it had showed them that they have some control over their seizures.

It should be noted that, aside from those mentioned above, there were no other changes in psychopharmacological medication for any participant where it could be argued that the change in medication might be responsible for the change in seizure frequency, i.e. in the 6 weeks preceding any such changes.

Secondary outcomes

In terms of the secondary measures assessed, descriptive statistics and effect sizes for each assessment point are summarised in Table 4 and Table 5. Table 5 shows the changes in mean scores for only the six participants (participants 2, 4, 5, 6, 8 and 10) who completed assessments at all data points, as an illustration of the degree of maintenance of gains in this small sample.

Overall, there were large inner-subject effect sizes post-treatment (>0.8 according to conventional descriptors; Cohen, 1992) for the majority of secondary measures assessed (11 out of 19), across physical health, mental health and social functioning domains.

Adverse events and negative effects of therapy

Adverse events during treatment were limited (one person having three seizures). All these events were predictable moments of higher risk, so their physical safety could be ensured (e.g. crash mats had been laid out in advance).

In terms of negative effects of therapy, the mean score on the INEP was 3.2, indicating less negative effects of therapy than in the mixed sample from the original validation study for that measure (where the sample mean can be inferred as -2.8 by adding all of the means for the constituent items; possible range of scale of -63 to 18 ; Ladwig *et al.*, 2014). It should be noted that whilst INEP scores for eight of the nine participants were above this mean from the validation study, one of the participants (#7) had an INEP score far below this, indicating a very negative therapeutic experience. Her item responses indicated that she felt worse and had some suicidal ideation after her brief treatment episode, both of which she attributed to the treatment. She also specifically commented on the therapeutic alliance within the INEP – ‘we didn’t see eye to eye’.

Therapeutic alliance

On the WAI-SF, the mean score was 52.1, with a range of 37–60 (scoring range of scale is 12–60, where higher scores indicate a better therapeutic alliance).

Qualitative interview

Seven of the ten participants completed a qualitative interview with the independent assessor. Of the three who did not, two had completed their quantitative data online after the independent assessor had to postpone the assessment, and attempts to reschedule an interview were not successful. The other participant (who had nocturnal seizures only) did not complete any post-treatment assessment at all, having ceased contact with the lead investigator.

From the thematic analysis of the qualitative data collected, five main themes emerged: reduction in seizures, improved lives, therapist communication, mixed experiences of treatment acceptability, and the nocebo effect and its relationship with symptoms. See Supplementary material for a more detailed description of these themes. However, to expand briefly on three themes that relate to treatment acceptability:

- The nocebo effect and belief change – overall, most participants indicated that their beliefs about their symptoms had changed as a result of the treatment and many felt that the concept of a nocebo effect explained the occurrence of their symptoms.
- Acceptability of the treatment – four out of seven of the participants expressed that they found the treatment challenging. For two of these participants, the discomfort experienced was acceptable given the improvements they experienced. For the other

Table 4. Descriptive summaries of secondary outcome measures, with effect sizes

Measure	Baseline (T0) Mean (SD; range)	Post-treatment (T1) Mean (SD; range)	Hedges' <i>g</i> (95% CI) T0 to T1	6-month follow-up (T2) Mean (SD; range)
SF-36				
Participants with available data, <i>n</i> (%)	9 (100%)	9 (100%)		6 (67%)
Physical Functioning	60.0 (20.6; 44.2–75.9)	78.3 (23.2; 25–100)	0.79 (–0.17–1.76)	85.8 (13.6; 70–100)
Role-Physical	22.2 (36.3; 0–50.1)	61.1 (35.6; 0–100)	1.03 (0.04–2.02)	62.5 (49.4; 0–100)
Bodily Pain	48.8 (38.9; 18.9–78.7)	59.2 (22.3; 31–84)	0.31 (–0.62–1.24)	71.2 (12.9; 51–84)
General Health	39.0 (6.5; 34.0–44.0)	45.1 (12.6; 20–60)	0.58 (–0.36–1.53)	45.2 (7.0; 35–55)
Vitality	19.4 (11.3; 10.8–28.1)	42.8 (20.8; 10–65)	1.33 (0.30–2.36)	42.5 (12.1; 25–60)
Social Functioning	34.7 (23.2; 16.9–52.6)	63.9 (22.9; 12.5–87.5)	1.21 (0.19–2.22)	58.3 (21.9; 25–75)
Role-Emotional	33.3 (50.0; 0–71.8)	63.0 (42.3; 0–100)	0.61 (–0.34–1.56)	55.6 (27.2; 33–100)
Mental Health	48.0 (26.2; 27.8–68.2)	72.0 (17.3; 44–96)	1.03 (0.04–2.02)	62.7 (17.3; 36–80)
Physical Summary	37.8 (10.2; 29.5–45.1)	42.4 (8.8; 28.0–55.3)	0.51 (–0.43–1.45)	47.2 (8.8; 37.5–57.1)
Mental Summary	34.1 (15.5; 21.4–42.4)	44.6 (9.1; 27.8–55.3)	1.05 (0.05–2.04)	39.1 (7.4; 30.3–47.0)
PHQ-15				
Participants with available data, <i>n</i> (%)	9 (100%)	9 (100%)		6 (67%)
Total	17.1 (6.5; 12.1–22.1)	12.3 (6.6; 4–27)	0.70 (–0.26–1.65)	12.0 (2.1; 9–14)
Interpretation of mean score	High severity	Medium severity		Medium severity
mPDI				
Participants with available data, <i>n</i> (%)	9 (100%)	9 (100%)		6 (67%)
Total	35.2 (16.5; 22.5–47.9)	15.3 (17.3; 0–51)	1.12 (0.12–2.12)	7.2 (17.6; 0–43)
EQ-5D-5L				
Participants with available data, <i>n</i> (%)	9 (100%)	9 (100%)		6 (67%)
EQ-5D-5L Index	0.70 (0.25; 0.50–0.89)	0.71 (0.28; 0.02–1.00)	0.04 (–0.89–0.96)	0.84 (0.16; 0.57–1.00)
Visual Analogue Scale	49.6 (24.9; 30.4–68.7)	70.8 (22.1; 30–96)	0.86 (–0.11–1.83)	68.5 (26.7; 30–100)
BIPQ				
Participants with available data, <i>n</i> (%)	9 (100%)	9 (100%)		6 (67%)
Total	54.0 (7.8; 48.0–60.0)	19.3 (17.8; 0–51)	2.40 (1.16–3.65)	7.0 (12.3; 1–32)
SCS				
Participants with available data, <i>n</i> (%)	9 (100%)	9 (100%)		6 (67%)
Total	10.0 (2.8; 7.9–12.1)	2.3 (3.2; 0–9)	2.44 (1.18–3.69)	1.2 (1.6; 0–4)
GAD-7				
Participants with available data, <i>n</i> (%)	9 (100%)	9 (100%)		6 (67%)
Total	12.7 (6.5; 7.7–17.7)	7.1 (6.2; 0–18)	0.84 (–0.13–1.81)	6.7 (6.4; 0–18)
Interpretation of mean score	Moderate	Mild		Mild
PHQ-9				
Participants with available data, <i>n</i> (%)	9 (100%)	9 (100%)		6 (67%)
Total	17.6 (5.8; 13.1–22.0)	9.0 (5.5; 5–24)	1.45 (0.40–2.50)	8.7 (4.8; 0–14)
Interpretation of mean score	Moderately severe	Mild		Mild

(Continued)

Table 4. (Continued)

Measure	Baseline (T0) Mean (SD; range)	Post-treatment (T1) Mean (SD; range)	Hedges' <i>g</i> (95% CI) T0 to T1	6-month follow-up (T2) Mean (SD; range)
DES-B				
Participants with available data, <i>n</i> (%)	9 (100%)	9 (100%)		6 (67%)
Total	1.7 (0.6; 1.2–2.2)	1.3 (1.0; 0.3–3.0)	0.46 (–0.48–1.40)	1.0 (0.5; 0.3–1.6)
CGI-I				
Participants with available data, <i>n</i> (%)	<i>n/a</i>	9 (100%)		6 (67%)
Very much improved, <i>n</i> (%)	<i>n/a</i>	4 (44%)		5 (83%)
Much improved, <i>n</i> (%)	<i>n/a</i>	3 (33%)		1 (17%)
Minimally improved, <i>n</i> (%)	<i>n/a</i>	1 (11%)		0 (0%)
No change, <i>n</i> (%)	<i>n/a</i>	1 (11%)		0 (0%)
CGI-I score*	<i>n/a</i>	1.9 (1.0; 1–4)		1.2 (0.4; 1–2)
WAI-SF				
Participants with available data, <i>n</i> (%)	<i>n/a</i>	9 (100%)		N/A
Total	<i>n/a</i>	52.1 (8.0; 37–60)		N/A
INEP				
Participants with available data, <i>n</i> (%)	<i>n/a</i>	9 (100%)		N/A
Total	<i>n/a</i>	3.2 (6.5; –13–11)		N/A
Healthcare utilisation in previous 3 months				Total for sample
Participants with available data	Total for sample			9 (100%)
GP visits	24			2
Emergency department visits	12			0
Inpatient stays	3			0**
Therapist sessions attended	14			0
Ambulances called	3			0
Days off taken by family/friends to support	32			3

Participant with only nocturnal seizures excluded throughout this table – she did not provide data at T1 or T2, and could not be treated using NH-CBT. SF-36, Short Form-36 Health Questionnaire; PHQ-15, Patient Health Questionnaire-15; mPDI, Modified Pain Disability Index; BIPQ, Brief Illness Perception Questionnaire; SCS, Symptom Catastrophising Scale; GAD-7, Generalised Anxiety Disorder Scale-7; PHQ-9, Patient Health Questionnaire-9; DES-B, Brief Dissociative Experiences Scale; CGI-I, Clinical Global Impression Scale of Improvement; WAI-SF, Working Alliance Inventory-Short Form; INEP, Inventory for the Balanced Assessment of Negative Effects of Psychotherapy.

*Measured on a 7-point scale, where 1 = very much improved, 7 = very much worse.

**Participants specifically asked about health care relating to seizures; however, one of the participants that dropped out of treatment required 29 days as an in-patient around 4 months later when she developed functional weakness in her legs.

Table 5. Descriptive summary of secondary outcome measures for participants ($n = 6$) who completed 6-month follow-up assessment, for evaluation of maintenance of treatment effects

Measure	Baseline (T0) Mean (SD; range)	Post-treatment (T1) Mean (SD; range)	6-month follow-up (T2) Mean (SD; range)	Hedges' g (95% CI) T1 to T2
SF-36				
Physical Functioning	75.0 (13.0; 65–100)	89.2 (10.7; 75–100)	85.8 (13.6; 70–100)	-0.26 (-1.39–0.88)
Role-Physical	25.0 (41.8; 0–100)	75.0 (31.6; 25–100)	62.5 (49.4; 0–100)	-0.28 (-1.42–0.86)
Bodily Pain	69.7 (29.7; 31–100)	71.5 (12.8; 52–84)	71.2 (12.9; 51–84)	-0.02 (-1.15–1.11)
General Health	41.8 (5.9; 32–47)	45.3 (14.3; 20–60)	45.2 (7.0; 35–55)	-0.01 (-1.14–1.12)
Vitality	21.7 (12.9; 10–45)	50.8 (14.6; 30–65)	42.5 (12.1; 25–60)	-0.57 (-1.73–0.59)
Social Functioning	41.7 (27.0; 0–75)	72.9 (14.6; 50–87.5)	58.3 (21.9; 25–75)	-0.72 (-1.90–0.45)
Role-Emotional	50.0 (54.8; 0–100)	83.3 (27.9; 33–100)	55.6 (27.2; 33–100)	-0.93 (-2.13–0.27)
Mental Health	52.7 (28.1; 16–88)	75.3 (17.4; 52–96)	62.7 (17.3; 36–80)	-0.67 (-1.84–0.50)
Physical Summary	42.0 (10.9; 27.8–56.0)	46.1 (6.7; 38.1–55.3)	47.2 (8.8; 37.5–57.1)	0.13 (-1.00–1.26)
Mental Summary	33.9 (16.4; 15.7–53.8)	48.1 (7.5; 37.4–55.3)	39.1 (7.4; 30.3–47.0)	-1.12 (-2.35–0.12)
PHQ-15	13.8 (4.4; 6–19)	9.0 (4.0; 4–15)	12.0 (2.1; 9–14)	-0.87 (-2.06–0.33)
Interpretation of mean score	Medium severity	Low severity	Medium severity	
mPDI	27.0 (11.3; 12–37)	6.7 (10.7; 0–30)	7.2 (17.6; 0–43)	-0.03 (-1.10–1.16)
EQ-5D-5L				
EQ-5D-5L Index	0.82 (0.16; 0.59–0.94)	0.83 (0.15; 0.52–1.00)	0.84 (0.16; 0.57–1.00)	
Visual Analogue Scale	57.5 (23.6; 25–90)	68.5 (25.5; 30–96)	68.5 (26.7; 30–100)	
BIPQ	50.8 (6.9; 42–59)	9.0 (10.3; 0–30)	7.0 (12.3; 1–32)	0.16 (-0.97–1.30)
SCS	8.5 (2.0; 6–10)	0.3 (0.7; 0–2)	1.2 (1.6; 0–4)	-0.67 (-1.84–0.50)
GAD-7	11.2 (7.1; 4–21)	6.7 (6.1; 0–18)	6.7 (6.4; 0–18)	0.00 (-1.13–1.13)
Interpretation of mean score	Moderate	Mild	Mild	
PHQ-9	15.0 (5.0; 10–21)	7.3 (1.4; 6–10)	8.7 (4.8; 0–14)	-0.36 (-1.51–0.78)
Interpretation of mean score	Moderately severe	Mild	Mild	
DES-B	1.5 (0.6; 0.6–2.4)	0.9 (0.5; 0.3–1.5)	1.0 (0.5; 0.3–1.6)	-0.18 (-1.32–0.95)
CGI-I				
Very much improved, n (%)		4 (44%)	5 (83%)	
Much improved, n (%)		2 (33%)	1 (17%)	
Minimally improved, n (%)		0 (0%)	0 (0%)	
No change, n (%)		0 (0%)	0 (0%)	
CGI-I score*		1.3 (0.5; 1–2)	1.2 (0.4; 1–2)	

This table compares data at all time points for the six participants who completed all assessments, in order to evaluate maintenance of treatment effects. SF-36, Short Form-36 Health Questionnaire; PHQ-15, Patient Health Questionnaire-15; mPDI, Modified Pain Disability Index; BIPQ, Brief Illness Perception Questionnaire; SCS, Symptom Catastrophising Scale; GAD-7, Generalised Anxiety Disorder Scale-7; PHQ-9, Patient Health Questionnaire-9; DES-B, Brief Dissociative Experiences Scale; CGI-I, Clinical Global Impression Scale of Improvement; WAI-SF, Working Alliance Inventory-Short Form; INEP, Inventory for the Balanced Assessment of Negative Effects of Psychotherapy.

*Measured on a 7-point scale, where 1 = very much improved, 7 = very much worse.

two, however, the distress they experienced from the exposure component rendered it unacceptable.

- Therapist communication – most participants praised the way the therapist instilled confidence in them about the treatment, the clear delivery of the information, and the sensitive way in which it was communicated.

Discussion

In summary, this mixed method study aimed to examine whether treatment with NH-CBT is associated with a reduced frequency of NES, and improvement on other secondary outcomes at the end of treatment, as well as at 6 months post-intervention. If these outcomes are achieved, it would represent some preliminary evidence with which to complement the results from Richardson *et al.* (2018), suggesting that a treatment with the same psychoeducational component, but using (in CBT terms) different behavioural experiments, can be delivered successfully across different FNSD symptom presentations (i.e. functional motor symptoms and NES). Additionally, the trial explored potential adverse effects of NH-CBT, the therapeutic alliance between participants and therapist, and participants' experience of the treatment.

Firstly, it appears that treatment with NH-CBT is associated with reduced frequency of NES, as it eliminated seizures in all seven participants with daytime seizures who completed the treatment (with six of them staying seizure free at 6-month follow-up), and there was a large effect size (0.99) for reduction of seizure frequency across all participants with daytime seizures (i.e. including those who dropped out of treatment). The treatment gains were achieved with a relatively short treatment duration (median = 6.4 hours), arguably because it appeared unnecessary to expose a person to every trigger on their graded exposure hierarchy. These gains were achieved in a sample who were – according to their medical records – all likely to have been experiencing NES for at least a year.

Our second finding shows that in terms of the secondary measures collected, there were large (i.e. $g > 0.8$) positive inner-subject effect sizes in the following domains – beliefs about seizures ($g = 2.40$), catastrophising about seizures ($g = 2.44$), physical limitations ($g = 1.03$), perceived disability ($g = 1.12$), fatigue ($g = 1.33$), social functioning ($g = 1.21$) and measures of mental health, including the PHQ-9 (depression) ($g = 1.45$) and the overall Mental Summary score of the SF-36 ($g = 1.05$). Whilst it could be argued that the large effect sizes on measures of beliefs about seizures and catastrophising about seizures are more predictable given that these were the therapeutic targets of this treatment, and that improvements in perceived disability and social functioning might conceivably be consequences of a reduction in seizures, the large effect size on a measure of fatigue was less expected. Here, the mean SF-36 Vitality score at baseline indicated a group of participants with severe difficulties with fatigue (mean score was 2.5 standard deviations below the mean from New Zealand normative data; Scott *et al.*, 1999), with the post-treatment mean score arguably equating to the bottom end of a normative range (1.2 SDs below the NZ mean). It is possible that similar mechanisms were responsible for both NES and subjectively experienced fatigue (or at least some elements of that fatigue) in this group, although it is also plausible that the reduction in fatigue was more related to the improvement in mood that co-occurred.

A third important finding shows that, overall, there appeared to be good maintenance of gains on the primary measure, as only one participant relapsed from a seizure perspective. In terms of secondary outcomes, whilst the small number of participants completing 6-month follow-up assessment ($n = 6$) precludes any confident conclusions, most areas of physical functioning appeared to maintain well. There did appear to be some reduced maintenance of gains made on some measures of mental health, and a measure of overall somatic symptom severity, although the scores did not return to baseline levels on any measure. It should be acknowledged that good

maintenance of gains has previously been found where interventions have led to seizure cessation in the majority of participants (e.g. Fobian *et al.*, 2020, Myers *et al.*, 2017).

Regarding adverse events during the course of treatment, they were as follows: (1) one participant who had three seizures in treatment sessions (who subsequently became seizure-free) and (2) one participant who reported on the INEP that she felt worse and had some suicidal ideation after her treatment. No participant reported an increase in seizures in their diary or reported that their overall condition was worse on the Clinical Global Impression-Improvement (CGI-I) Scale, at the post-treatment stage. This level of adverse events is comparable to that reported by Goldstein *et al.* (2020), who reported 13% of participants having adverse events, and 9% of participants reporting that their condition was worse on the CGI-I.

Regarding therapeutic alliance, it appears that there were no concerns about the acceptability of the intervention from the majority of participants. On the WAI-SF, the mean score was comparable to that seen in a recent physical therapy intervention for lower back pain (Alodaibi *et al.*, 2021).

In general, the themes emerging from the qualitative data partly corroborated the quantitative findings (e.g. reduction in seizures, with positive associated outcomes), and partly described the participant experience of the therapy. In particular, it seems that the majority of participants found the psychoeducation about nocebo effects to be acceptable. However, it was also clear that some participants found the process unhelpful, and specifically noted their discomfort with the exposure component of the treatment.

To our knowledge, this is the first study of a treatment for NES that is wholly compatible with predictive coding aetiological models of NES, i.e. primarily targets health beliefs using exposure as the key component, with promising outcomes. However, the results need to be interpreted with caution due to numerous limitations inherent in this study. These include the small sample size, the lack of a control group and randomisation, the partial estimation of baseline seizure rate in some participants, the lack of systematic processes to ensure adherence to the therapeutic model, as well as the lack of an assessment of diagnostic certainty. There was also a gender bias in this sample, in that all ten participants were women, although given the gender distribution in NES established by epidemiological review (female:male ratio = 2.94; Lesser, 1996), this was not particularly unusual. Strengths of the study include the lack of exclusion of anyone on the basis of their mental health status, increasing the probability that this is a sample representative of the overall population of people with NES.

In terms of development of the treatment approach as a result of the feedback gained from the quantitative and qualitative data, it appears that the most likely barrier to treatment success is drop-out due to low acceptability of the exposure part of the treatment. Reluctance to engage in exposure components of therapy is not unusual, and ideas to address this have previously been published, centred around the concept of collaborative empiricism (Clark, 2013). Some ways these ideas could be applied in the context of exposure to seizure triggers include identifying, evaluating and (if necessary) modifying participants' beliefs about symptom change, the exposure process and distress tolerance before engaging in behavioural exposure.

There appears to be the potential for further empirical investigation of a stepped-care model of treatment delivery. Some people with NES see their seizures cease after diagnosis and accompanying explanation of that diagnosis (Hall-Patch *et al.*, 2010). This study suggests that there is potentially extra value in giving people gaining a further understanding of NES, perhaps as the person concerned arguably goes from hearing that they have a 'software not a hardware' problem to understanding an individualised formulation for their particular 'software' problem. The rough indications from Hall-Patch *et al.* (2010) and this study suggest that around a quarter of people with NES could see a cessation of seizures with very little input post-diagnosis. Exposure therapy could represent the final step, which it appears the majority of people with NES would need, although this is still a relatively brief component (median of around 5 hours in this study).

Conclusion

In summary, this case series provides preliminary evidence of feasibility and the likely utility of NH-CBT in treating NES, with large effect sizes shown on a number of measures, including seizure reduction. The findings indicate the need for a randomised controlled trial to further investigate effectiveness.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S1352465823000565>

Data availability statement. The data that support the findings of this study are available from the corresponding author (M.R.), upon reasonable request.

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Competing interests. The authors declare none.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, and its most recent revision. Approved by Health and Disability Ethics Committee, New Zealand (reference no. 21/NTB/146).

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