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A cognitive behavioural approach to functional neurological disorder: a systematic review, meta-analysis and grounded theory study

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Abstract

Introduction: Functional neurological symptoms are commonly reported by people presenting to neurology services. Symptoms are diverse, and there is little published evidence to inform treatment guidelines. Idiopathic drop attacks are also seen within neurology services, but literature about them is sparse and it is unclear whether they should be considered within the spectrum of functional neurological disorder.

Aims: The aim of this thesis was to assess cognitive behavioural therapy (CBT) as an intervention for functional neurological disorder (FND), through a systematic review and meta-analysis. A second aim was to look at idiopathic drop attacks and determine whether a psychological understanding of these would help to inform formulation and treatment.

Methods: A systematic review identified 28 studies of CBT for FND, nine of which were included in meta-analysis. In addition, a grounded theory study of idiopathic drop attacks was conducted through the coding and synthesis of data from interviews and diaries of seven individuals with FND, with the aim of identifying predisposing, precipitating and maintaining factors.

Results: In the systematic review and meta-analysis, random effects models revealed a significant advantage of CBT over control on daily functioning, and a significant improvement within CBT groups over time. CBT also had a significantly positive effect on anxiety, depression and functional neurological symptoms, both compared to control groups, and within CBT groups over time. Positive effects of CBT were maintained over six months.

In the grounded theory study, themes relating to predisposing and precipitating factors for drop attacks, along with thoughts, emotions and behaviour both before and after a fall, were identified. A cognitive behavioural model was proposed, with a traumatic first fall and life stressors as predisposing factors, situational triggers and increased worry as precipitating factors, and a maintaining cycle of thoughts, emotion and behaviour.

Conclusions: Meta-analysis suggests that CBT may be effective for FND, and that the positive impact of this persists over time. However, as the evidence base is currently small, larger trials are required. The grounded theory study proposed a cognitive behavioural understanding of the onset and maintenance of idiopathic drop attacks and noted considerable overlap between drop attacks and non-epileptic seizures. This understanding could help to guide formulation, and suggests a CBT treatment approach would be worth exploring in this population.

Lay summary

Functional neurological disorder is a term used to describe symptoms which are similar to those seen in neurological illnesses, but which are not due to disease. They are common in people who go to neurology clinics. Symptoms vary, and there is little published evidence to inform the best course of treatment. Idiopathic drop attacks are unexplained falls to the floor, and are also seen within neurology services, but it is unclear whether they should be considered a functional neurological disorder.

This thesis contains two papers. The aim of the first was to assess whether cognitive behavioural therapy (CBT; a psychological intervention which focuses on thoughts and behaviour) was an effective treatment for functional neurological disorder (FND), through reviewing the evidence. The second paper aimed to look at idiopathic drop attacks and determine whether a psychological understanding of these would help to inform treatment.

In our review, we found 28 studies of CBT for FND. Results from nine high-quality studies were synthesised and we found that CBT improved everyday functioning, anxiety, low mood and functional neurological symptoms.

For the second paper, we interviewed seven people who were experiencing drop attacks, and asked them to keep diaries of their falls. We found that participants had experienced a traumatic first fall and noted that stressful life experiences may have made the falls more likely to happen. People were more likely to fall in certain places, and when they were feeling more stressed or worried. We also found that people were more likely to cope with their falls by avoiding certain situations.

Overall, the first study concluded that CBT seems to be an effective treatment for FND, but we need more high-quality research to determine this. The second study found that drop attacks are very similar to other functional neurological symptoms and that a CBT treatment approach could be helpful.

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1 Cognitive behavioural therapy for functional neurological symptoms: a systematic review and meta-analysis

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1.1 Abstract

Functional neurological symptoms are common in those who present to neurology services. However, currently there is a sparse evidence base to inform treatment. Cognitive behavioural therapy (CBT) is an intervention which has been trialled with different functional neurological disorder (FND) presentations. We systematically reviewed CBT trials for FND to investigate its efficacy on daily functioning, functional neurological symptoms, and anxiety and depression symptoms.

Electronic databases were systematically searched for studies investigating CBT for FND, and 28 studies with a total of 1010 participants were identified. Nine of these, including seven controlled trials, were of a methodological quality that allowed them to be combined in meta-analysis.

Random effects models revealed a significant advantage of CBT over control on daily functioning (g=-0.44, 95% CI -0.66, -0.22, p<0.0001), and a similar effect size was seen within CBT groups over time (d=-0.50, CI -0.76, -0.24, p=0.0002). CBT also had a significantly positive effect on anxiety, depression and functional neurological symptoms, both compared to control and over time. At six- to twelve-month follow-up, positive effects of CBT had been maintained.

CBT improved daily functioning, anxiety, depression and functional neurological symptoms for those with FND, and these persisted once treatment had ended. However, the generalisability of the estimates of effect produced here are limited due to the small number of small heterogeneous trials. CBT is a promising intervention for FND, and further large-scale trials would help to determine its efficacy.

Keywords: Cognitive behavioural therapy; functional neurological disorder; functional neurological symptoms

1.2 Introduction

Functional neurological disorder (FND) is a term which describes neurological symptoms which do not have an identified organic cause. DSM-5 (APA 2013) criteria for FND state that there must be A) One or more symptoms of altered voluntary motor or sensory function, B) Clinical findings that provide evidence of incompatibility between the symptom and recognised neurological or medical conditions, C) Symptoms or deficits that are not better explained by another medical or mental disorder, and D) Symptoms or deficits that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, or warrants medical evaluation.

The prevalence of FND has been estimated at 9-30% of those presenting to neurology inpatient and outpatient settings (Stone et al. 2009; Lempert et al. 1990) with follow-up at 18 months showing this initial diagnosis to be accurate in all but 0.4% of cases (Stone et al. 2009). A large study in Scotland estimated that neurologists were diagnosing around 5000 cases of FND per year (Stone et al. 2010a).

Functional symptoms often persist over time, leading to increased costs to the health service and to the wider economy, due to reduced capacity for work (M Reuber et al. 2005). Direct healthcare costs alone in Scotland have been estimated to be £11.3 million, with 27% of patients also receiving benefits, and 50% unable to work (Stone et al. 2010a; Carson et al. 2011). Therefore it is important that research highlights effective and acceptable treatments.

1.2.1 Symptoms and comorbidity

A wide variety of symptoms are included under the FND classification. These include paralysis, weakness, seizures, visual problems and speech problems. Other functional symptoms are often co-morbid with FND, such as chronic pain, headache and chronic fatigue (Carson et al. 2000). Although these have separate evidence bases, there are increasing calls for a transdiagnostic approach to functional symptoms, given the similarities and comorbidity between them (Chalder and Willis 2017). However, for the purposes of this review, the focus will be on functional neurological symptoms, as included in previous reviews of this population (Ludwig et al. 2018; Hopp and LaFrance 2012).

The pattern of functional neurological symptoms can vary widely between individuals, with some having a single symptom and some multiple. The frequency and persistence of these symptoms also varies, and people may experience a single acute episode, intermittent symptoms or a more chronic course. This has raised questions about whether FND should have a single classification or whether certain presentations, such as specific clusters of symptoms, should be categorised separately (Stone et al. 2011; Carson and Lehn 2016).

One of the most researched functional neurological presentations is non-epileptic seizures (NES), also termed ‘psychogenic seizures’, ‘dissociative seizures’, ‘functional seizures’ and

‘non-epileptic attack disorder’. These are ‘episodes of altered movement, sensation, or experience resembling epileptic seizures, but not associated with ictal electrical discharges in the brain’ (M Reuber 2009). Functional motor disorders (FMD), which is a term that covers several presentations such as weakness, gait disorders and tremor, have also been widely studied (Ricciardi and Edwards 2014). Less research has been conducted with other presentations, such as functional dizziness (Popkirov et al. 2018).

Comorbidity between functional neurological symptoms is common. A six-year follow-up of 73 patients with functional motor symptoms found that 44% had experienced other unexplained neurological symptoms (Crimlisk et al. 1998). A more recent study of functional weakness compared 107 patients with functional weakness to 46 patients with a neurological weakness. Those with functional weakness were significantly more likely to also experience other functional symptoms, such as non-epileptic seizures, functional tremor and functional dystonia (Stone et al. 2010b).

Stone et al. (2010b) also found those with functional weakness to be significantly more likely to meet diagnostic criteria for other psychiatric disorders, including major depression, panic, generalised anxiety disorder and somatisation disorder. Seventy-five percent of the sample in Crimlisk and colleagues’ (1998) study also met the criteria for other psychiatric disorders.

1.2.2 Mechanism

There are a number of theoretical understandings of functional neurological disorders. Originally, functional symptoms were conceptualised as ‘hysterical conversion’ by Breuer and Freud (2009). The functional symptom was seen as a physical representation of repressed thoughts and emotions. More recently, the main model of functional symptoms has been the somatosensory amplification model (Barsky and Wyshak 2018), which states that stress related physical arousal and attention on physical symptoms leads to the misattribution of normal physical sensations to disease. Over time, with increased attention on physical symptoms, tolerance decreases and arousal increases, further exacerbating physical arousal symptoms (Nakao and Barsky 2007). Until recently, this has been the central basis of cognitive behavioural models of functional symptoms. However, it has not fully explained how subjective and measured stress levels can be lower in those with functional symptoms (Tak et al. 2011).

The predominant current understanding of functional symptoms is a Bayesian predictive coding framework. A comprehensive model of functional symptoms was outlined by Van den Bergh and colleagues (2017), based on a review of the functional symptom literature. The authors suggest that functional symptoms are a set of perceptions, based on the brain’s interpretation of information from the body, which is guided by past experience. A cognitive representation of a symptom, which is preconscious in nature, is activated when certain triggers are present, such as physiological stress, or contextual triggers. This helps to

explain symptoms which occur in the absence of subjective stress, and highlights the importance of the individual's interpretation of symptoms, and the context in which they occur.

1.2.3 Intervention

At present there are no official treatment guidelines, due to limited randomised controlled trial evidence, however various approaches have been trialled, including antidepressant use (Voon and Lang 2005), hypnotherapy (Moene et al. 2002), and physical therapy (Nielsen et al. 2013). Psychological therapies have also been investigated, including CBT, psychodynamic therapy, paradoxical intention therapy, mindfulness, psychoeducation, and eclectic interventions. A meta-analysis of these interventions for NES found them to reduce seizure frequency by at least 50% in 82% of participants, and psychological intervention led to seizure freedom in 47% of the participants in the review (Carlson and Perry 2017).

A stepped care approach to FND was developed by a group of healthcare professionals, as part of an NHS Scotland healthcare improvement project (2012). The treatment approach outlined in the NHS Scotland report recommended that, following diagnosis, a brief, guided cognitive behavioural self-help programme should be delivered if required, following positive results from a randomised controlled trial (RCT) of such an intervention (Sharpe et al. 2011). However, this type of intervention may not be suitable for all patients with FND, as a degree of self-motivation is required for guided self-help to be an effective intervention (Coull and Morris 2011).

CBT interventions have been trialled with the most common FND presentations, including non-epileptic seizures (LaFrance et al. 2014), functional motor disorder (Dallocchio et al. 2016) and functional dizziness (Schmid et al. 2018). The approaches tend to have the same basic elements, which involve trying to interrupt current patterns of thoughts and behaviour through identifying negative thoughts and illness beliefs, and engaging in avoided activities in order to reduce any anxiety associated with them. Coping strategies such as relaxation exercises and distraction techniques are also developed as part of these interventions.

CBT has been trialled with non-neurological functional symptoms, with positive results. A recent systematic review and meta-analysis identified 15 RCTs of CBT for 'somatic' or 'medically unexplained' symptoms. They found CBT to significantly reduce somatic symptoms, anxiety symptoms and depression symptoms, and to improve physical functioning (Jing et al. 2019). However, this review did not include trials of common functional symptom presentations, such as irritable bowel syndrome (IBS) and chronic fatigue syndrome (CFS), and significant heterogeneity within meta-analyses was not taken into account. An earlier meta-analysis of 20 CBT RCTs found the intervention to be effective in reducing physical symptoms of IBS (d=0.73; Laird et al. 2016). An additional meta-

analysis of 13 studies of CBT for CFS also found CBT to be effective in reducing fatigue compared to controls (d=0.48; Malouff et al. 2008).

Although a previous narrative review of CBT for FND has been completed (Hopp & LaFrance, 2012), this is the first systematic review in this area, as far as we are aware. As CBT is starting to be recommended within treatment guidelines, it is important to assess the expanding evidence base to determine the impact of CBT on different functional neurological symptoms. Given ongoing debates on whether different clusters of symptoms should be treated as separate disorders, or different manifestations of the same underlying process (Carson and Lehn 2016; Stone et al. 2011), this review aimed to give an overall picture of the evidence base of CBT for all functional neurological symptoms.

Our aim was to review the literature on CBT as a treatment for functional neurological symptoms, investigating everyday social and occupational functioning as a primary outcome, along with secondary outcomes of functional neurological symptoms, and symptoms of anxiety and depression.

1.3 Methods

The systematic review was conducted following PRISMA guidelines and a checklist is included in Appendix B. The protocol was registered on PROSPERO with reference number CRD42018093988 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=93988).

1.3.1 Data sources

The Cochrane Register, PsycINFO, EMBASE, MEDLINE and Web of Science were searched, up to November 2018, using the following phrases:

(“functional sympto*” OR unexplained OR somati* OR conversion OR hysteri* OR psychogenic OR “dissociative seizure*” OR “non-epilepti*” OR nonepilepti* OR pseudoseizure* OR “functional motor” OR “functional weakness*” OR “functional dystonia” OR “postur*-perceptual” OR PPPD OR "chronic subjective dizziness" or "phobic postural vertigo" or "somatoform vertigo" OR (functional and (dysphagi* or dysphoni* or dysarthri*)) AND (“cognitive therap*” OR “cognitive behav*” OR “behav* therap*” OR “behav* treatment*” OR “cognitive treatment*” OR CBT OR “acceptanc* and commitment” OR "dialectical behav*" OR DBT OR CBASP OR "function* analyt*" OR FAP OR "relation* frame" OR mindfu* OR "mind-fu*" OR compassio* OR CFT OR "3rd wave" OR "third wave" OR "third-wave")

The reference lists of all included studies were searched for other relevant studies. Papers which cited included studies were also checked. Corresponding authors of included studies and other known research groups working in the field were contacted for information regarding unpublished or ongoing trials.

1.3.2 Study inclusion

Studies had to meet the following inclusion criteria:

1) Participants had to be adults who had been diagnosed with functional neurological symptoms, which would fit with diagnostic criteria for functional neurological disorder (FND). That is, clusters of symptoms which present as a neurological condition but for which there has been no identified organic basis for the symptoms experienced. This included a range of disorders which included functional motor disorders, non-epileptic seizures, functional speech disorders and functional dizziness. Although there are similarities between functional neurological disorders and other conditions with medically unexplained symptoms, such as chronic fatigue syndrome, headache and chronic pain, this review focused on conditions defined by clusters of functional neurological symptoms only, as included in pervious reviews (Hopp and LaFrance 2012; Ludwig et al. 2018). Therefore studies of more general 'medically unexplained symptoms' were excluded. Studies with subgroups of patients who met the criteria for FND were, however, included if separate data on FND participants could be obtained.

2) The studies had to be intervention studies where the treatment used was based on CBT, including studies of what have been termed 'third-wave' CBT interventions (Öst 2008). Interventions were assessed to identify whether they contained key components of CBT, specifically both cognitive and behavioural elements. Studies where participants received additional treatment alongside CBT were included but were highlighted as such within the review.

3) Studies had to have a sample size of five or more to be included. Single-case studies were excluded.

4) As the primary outcome being investigated are daily functioning (defined as general functioning across social, occupational and practical tasks), and secondary outcomes are functional neurological symptoms, anxiety and depression symptoms, studies had to report on a structured assessment of one or more of these areas.

Figure 1.1 shows the flow of study inclusion. Screening was completed by the lead author and any studies where it was unclear whether inclusion criteria were met were discussed within the research team.

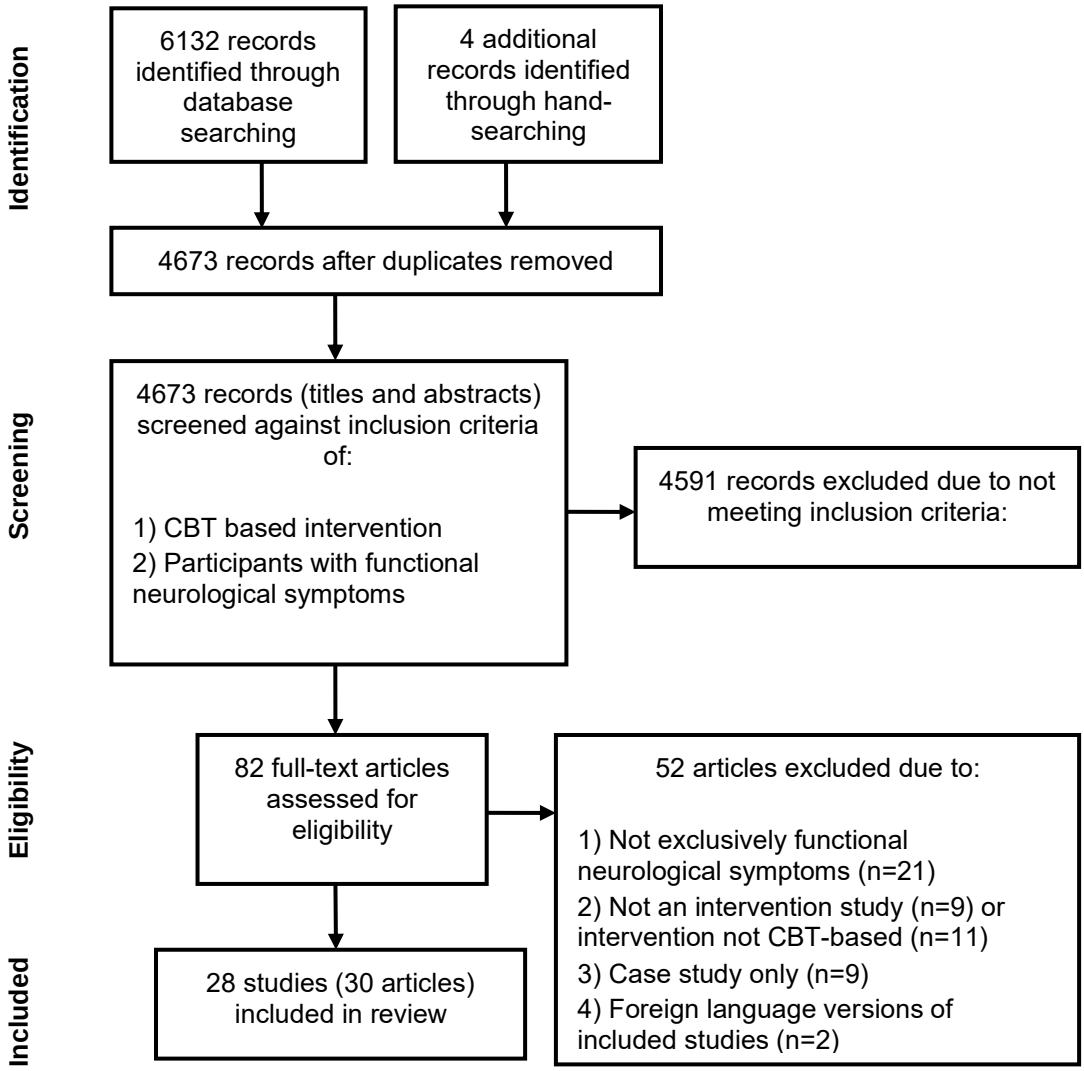

Figure 1.1 *Flow diagram of study identification and inclusion*

1.3.3 Data extraction

The lead author extracted data from all studies which met inclusion criteria, and data from a random 25% sample of these were extracted by an independent researcher to ensure reliability (Kappa=0.91, indicating strong agreement). Data were extracted onto standard forms. Extracted information included study design; intervention design, setting and duration; information for quality assessment; sample size and attrition rates; number of intervention

groups and intervention/control details; outcome measures used; time points for data collection; and main findings.

The Effective Public Health Practice Project (EPHPP) quality assessment tool (Thomas et al. 2004) was used to assess the methodological quality of each study. Studies were not excluded from the review on the basis of methodological quality. However, only studies deemed to be of 'moderate' or 'strong' methodological quality were included in the meta-analysis, in order to reduce the potential effects of bias. This is covered further in section 1.4.4.

1.3.4 Meta-analysis

Where data were available, means and standard deviations were used to calculate both independent groups and repeated measures effect sizes in order to conduct random effects meta-analyses using the Cochrane Collaboration's RevMan software (v5.3). Effect sizes as reported in papers were not included in meta-analysis. Consistency was measured using the I^2 statistic and publication bias was assessed using funnel plots (Appendix I). As the number of studies included in each meta-analysis was fewer than ten, a formal Egger's test (Egger et al. 1997) was not used (Higgins and Green 2011).

For independent groups, Hedge's g was calculated for each measure relating to primary or secondary outcomes, along with an estimate of standard error, using the following equations:

$$\text{Effect size (g)} = (M_t – M_c)/SD^*_{pooled}$$

M_t and M_c refer to the means of the treatment and control groups respectively and SD pooled is the pooled SD of both the treatment and control groups using the following equation where n_t and n_c are the sample size of the treatment and control groups and sd_t and sd_c are the SDs of each group.

$$SD^*_{pooled} = \text{sqrt}([n_t\text{-}1*sd_t^2]+[n_c\text{-}1*sd_c^2]/n_t+n_c\text{-}2)$$

The standard error of the effect size was calculated using the following equation where n_t and n_c are the sample sizes of the treatment and the control groups.

$$SE(g) = \text{sqrt}([n_t+n_c]/[n_t \times n_c])]+(g*g/[2\times(n_t+n_c\text{-}2)])$$

For repeated measures, Cohen's d was calculated using the equation:

$$\text{Effect size (d)} = Mpost_t\text{-}Mpre_t/SDpre_t$$

$Mpost_t$ is the post-treatment mean, $Mpre_t$ is the pre-treatment mean, and $SDpre_t$ is the pre-treatment SD. As r statistics were not available, standard error was calculated using the equation above, as described in a recent meta-analysis (Hirst et al. 2018). In this equation, n_t and n_c were replaced by the number of observations of the treatment group, giving:

$$SE(d) = \text{sqrt}([n_t+n_t]/[n_t \times n_t])]+(d*d/[2\times(n_t+n_t\text{-}2)])$$

Different measures were included within each overall outcome effect size. However, where possible, sensitivity analyses were performed with a single measure, in order to determine the validity of this approach.

1.4 Results

1.4.1 Corpus of studies

Table 1.1 shows summary characteristics of the 28 studies included in the review. Nine were described as randomised controlled trials, two were controlled trials, 11 were uncontrolled cohort studies (two retrospective), one was a case-control study and five were case series (two retrospective). A total of 1010 participants were included across the 28 studies, with a sample size range of 6-127, and a mean of 37 (SD=28).

1.4.2 Target of intervention

As shown in Table 1.1, ten studies only included people with non-epileptic seizures (NES), whereas one included a split sample with 63% NES and 37% other functional neurological symptoms, such as limb weakness (Conwill et al. 2014). Three studies included only those with functional motor disorder (FMD), such as limb weakness, paralysis or stiffness. Eight studies included those with functional dizziness, and two included participants with functional dysphonia. A further six studies included participants with a range of functional neurological symptoms.

1.4.3 Type of intervention

The design, content, setting and timescale of interventions varied widely between the studies. CBT interventions are described in Table 1.1, with the main treatment groups including manualised CBT, CBT enhanced with other therapies, CBT-based psychoeducation, CBT-based guided self-help, and CBT-based multidisciplinary inpatient programs, which included input from physiotherapists, occupational therapists and psychiatrists, as well as psychologists. Five studies used so called “third-wave” interventions based on a cognitive behavioural approach; one used dialectical behaviour therapy, two used Acceptance and Commitment Therapy (ACT), one used Mindfulness-Based Psychotherapy (MBPT), and another used a combination of Mindfulness-Based Stress Reduction (MBSR) and Mindfulness-Based Cognitive Therapy (MBCT).

Eight of the interventions were delivered in a group format, whereas 14 were delivered on an individual outpatient basis. Six interventions were delivered in an inpatient setting, as a CBT-based multidisciplinary approach. Two of these inpatient programs were for FMD, three for any FND and one for NES. Therapist contact time ranged from a total of two hours over

three months, as part of a guided self-help program (Sharpe et al. 2011) to an intensive inpatient program with a median length of 101 days (McCormack et al. 2014). Timescales and therapeutic contact time for each study is summarised in Table 1.1.

Table 1.1 *Summary characteristics of included studies*

Author	Design	Target disorder [a]	Description of Intervention	Control Group	Sample size and attrition rate	Outcome measures and timepoints [a]	Main Findings
Andersson et al. (2006)	RCT	Dizziness (mixed functional and organic)	Group combined CBT and vestibular rehabilitation: Five sessions of 60-120 minutes over seven weeks.	Waitlist control group	n=29 (of which 14 had functional dizziness): CBT group=14, control group=15	Baseline and post-treatment: DHI, VSS, CEA, STAI, BDI, PSS, balance measures, symptom diary	Significant benefit of CBT over control on post-treatment on DHI (Cohen's d=.40) and VSS (d=.44). Differences between functional and organic disorder not explored.
Barrett-Naylor et al. (2018)	Case series	NES	Guided self-help ACT intervention over six weeks, with weekly telephone support.	None	n=7 (6 completers)	Baseline, post-treatment, 1-week and 1-month follow-ups: DASS-21, QOLIE-10, CompACT, AAQ-II, seizure frequency	Reliable and clinically significant positive change on compACT, DASS, QOLIE and seizure frequency for four participants.
Baslet et al. (2015)	Case series	NES	Individual mindfulness-based psychotherapy: Twelve weekly or biweekly sessions.	None	n=6	Baseline and post-treatment: BDI, DASS, NES frequency	No significant differences. Mean diff in NES frequency per week = 14.98 (18 at baseline to 2.67 at follow-up)
Best et al. (2015)	Case-control	Somatoform vertigo and dizziness	Group CBT-based intervention: Weekly 90-minute sessions over 10 weeks.	Age and gender matched healthy controls	n=45: 17 cases (13 completers) and 28 matched controls	Baseline and post-treatment: Static posturography, VHQ	Statistically significant improvements in postural control at post-treatment compared to baseline.
Bullock et al. (2015)	Cohort	NES	Group DBT-skills training: 3 modules, each 8-10 weeks long, comprising weekly 90-minute sessions.	None	n=21 (19 completers)	Baseline and post-treatment: NES frequency, skills diary cards. Baseline only: demographics	No significant differences. Mean diff in frequency per week = 9.1 (13.8 at baseline to 4.7 at 20/5 weeks (average intervention duration))

Author	Design	Target disorder [a]	Description of Intervention	Control Group	Sample size and attrition rate	Outcome measures and timepoints [a]	Main Findings
Chen et al. (2014)	Pilot RCT	NES	Group CBT-based psychoeducation: One 90-minute session per month, over three months following diagnosis of NES.	Treatment as usual control group	n=64: Intervention group=34 (20 completers), Control group=30 (23 completers)	3 months post-diagnosis (post-treatment; T1) and 6 months post-diagnosis (T2): WSAS, NES frequency, NES intensity	Significantly better scores on WSAS in intervention group compared to control at T1 (d=0.81, 95% CI=0.19-1.43; p=0.013) and T2 (d=0.69, 95% CI=0.06-1.32; p=0.038)
Conwill et al. (2014)	Cohort	NES and other FNS	Group CBT-based therapy: 1 hour per week over 4-5 weeks.	None	n=16: 10 NES, 6 other FNS	Baseline and post-treatment: HADS, SF-36, CGI, NES frequency	Significant improvements in the 'emotional well-being' (p=0.04) and 'role limitation due to emotional well-being' (p=0.04) sub scores of SF-36.
Cope et al. (2017)	Cohort	NES	Group CBT-based psychoeducation: One 90-minute session per week over three weeks.	None	n=25 (19 completers)	Baseline and post-treatment: frequency of NES, intensity of NES, attitudes, ET7, PHQ-9, GAD-7, WSAS, B-IPQ, DES-II	Significant improvements in time on ET7 (t = 2.42, p=0.028; d=0.38) and BIPQ (t=4.43, p<0.001; d=0.54)
Dallocchio et al. (2016)	Pilot RCT	FMD	3 arms: Twelve-week intervention of CBT (90-minute session once a week) vs CBT plus APA (60-minute session twice a week) vs control	Waitlist treatment as usual (TAU) control group	n=37: CBT group=14 (11 completers), CBT & APA group=15 (10 completers), TAU control = 8	Baseline and post-treatment: PMDRS, HDS, BAI, PHQ-15	Significant improvement on all outcomes over time for both active groups (all p < 0.001) but not for the control group. Significant differences between CBT and TAU and CBT+APA and TAU at follow-up on all measures (p<0.001).

Author	Design	Target disorder [a]	Description of Intervention	Control Group	Sample size and attrition rate	Outcome measures and timepoints [a]	Main Findings
Daniilidou et al. (2007)	Consecutive cohort	Functional dysphonia	Individual CBT-enhanced voice therapy: Six weekly 60-minute sessions.	Voice therapy	n=32: CBT-enhanced group=16 (13 completers), control group=16 (15 completers)	Baseline and post-treatment: GRBAS, VPQ, VoiSS, HADS, GHQ	Significant benefit of CBT over control at post-treatment on GHQ (p=.022). Both groups improved significantly over time on VoiSS, VPQ and GHQ. CBT group significantly improved over time on GRBAS and HADS depression.
Deary et al. (2018)	Pilot RCT	Functional dysphonia	Individual CBT-enhanced voice therapy: 6-8 fortnightly sessions lasting 60-minutes each.	Voice therapy	n=74: CBT group=37 (33 completers), control group=37 (33 completers)	Baseline and follow-up: GRBAS, HADS, VPQ, GHQ	CBT found to be feasible and acceptable. Both interventions had clinical benefits, but trial was not designed to assess between-group effects.
Demartini et al. (2014)	Cohort	FND	Multidisciplinary CBT-based inpatient program: 5 days per week over an average of 4 weeks.	None	n=66 (all completed post-treatment, 36 completed 1-year follow-up)	Baseline, post-treatment and 1-year follow-up: HoNOS, COPM, HADS, FQ, PHQ-15, CNSQ, IPQ-R	Clinically significant improvement on COPM and statistically significant improvement on CNSQ (p<0.001), HoNOS (p<0.001), HADS (p=0.004) and PHQ-15 (p<0.001). Improvements maintained at 1-year follow-up.
Detert & Douglass(2014)	Cohort	Neurological disorders with FND subgroup	Group MBSR/MBCT: 8 weekly 2.5 hour sessions.	None	n=182 enrolled, n=147 completed, n=98 followed-up (FND subgroup n=16)	Baseline and post-treatment: BSI (GSI), PSS	Small significant positive effect of MBSR/MBCT on psychiatric symptoms (d=0.2, p<0.05), and large positive effect on perceived stress (d=1.41, p<0.001).

Author	Design	Target disorder [a]	Description of Intervention	Control Group	Sample size and attrition rate	Outcome measures and timepoints [a]	Main Findings
Edelman et al. (2012); Mahoney et al. (2013)	RCT	Chronic subjective dizziness	Individual CBT: weekly sessions over three weeks	Waitlist control group	n=41: 20 in initial treatment group (all completed)	Baseline, post-treatment and 6-month follow-up: DHI, DSI, SBI, DASS-21	Significant benefit of CBT over waitlist on DHI and SBI (both $p<0.001$), but not on DASS. Positive changes maintained at 6-month follow-up.
Goldstein et al. (2004)	Cohort	NES	Individual CBT over 12 weeks: Two-hour session in week one, followed by hour-long weekly or fortnightly session. Carer involvement in 3 sessions.	None	n=20 (16 completers)	Baseline, post-treatment and 6-months: NES frequency, WSAS, fear questionnaire, HADS, employment status, MHLC, IPQ, beliefs	Significant improvement on seizure frequency, WSAS, and control and consequences subscales of IPQ ($p\leq0.01$), as well as fear questionnaire, HADS and physical causes IPQ subscale ($p<0.05$). Changes maintained at 6-months.
Goldstein et al. (2010)	Pilot RCT	NES	Individual CBT over 12 weeks, with one hour-long weekly or fortnightly session.	Treatment as usual control group	n=66: CBT group=33 (30 completers), SMC control group=33 (29 completers)	Baseline, post-treatment and 6-months: NES frequency, NES freedom, WSAS, HADS, CSRI	Significant differences in seizure frequency, favouring CBT, at post-treatment ($d=0.75$). Both groups improved in some health service use measures and on the WSAS
Graham et al. (2018)	Case series	FNS	Individual ACT: one hour per week or fortnight, for up to 8 sessions.	None	n=8	Baseline and post-treatment: WSAS, CORE-10, AAQ-II	Post-treatment improvements on WSAS ($d=1.02$), CORE-10 ($d=1.70$) and to a lesser degree on AAQ-II ($d=0.77$).

Author	Design	Target disorder [a]	Description of Intervention	Control Group	Sample size and attrition rate	Outcome measures and timepoints [a]	Main Findings
Holmberg et al. (2006); Holmberg et al. (2007)	Controlled trial	Phobic postural vertigo	Individual CBT: 8-12 sessions, each lasting between 45 and 120 minutes.	Self-administered treatment (dizziness exposure)	n=36: CBT group=18 (16 completers), control group=18 (15 completers)	Baseline, post-treatment and 12-month follow-up: VSS, VHQ, DHI, HADS	Significant benefit of CBT over control on VHQ and HADS at post-treatment (both $p<0.01$). Significant improvements over time in CBT group on DHI, VHQ and HADS. No significant treatment effects remained after 12 months.
Jacob et al. (2018)	Retrospective cohort	FMD	Inpatient motor retraining rehabilitation programme: One-week MDT intervention, consisting of CBT sessions alongside physiotherapy, occupational therapy and speech therapy.	None	n=25	Baseline: anxiety and depression symptoms. Post-treatment: CGI	88% of participants rated symptoms as improved on CGI at post-treatment.
Kuyk et al. (2008)	Cohort	NES	CBT-based inpatient program: 2-6 months of individual therapy, psychomotor and creative therapy, family therapy and a variety of groups.	None	n=25 (22 completers)	Baseline, post-treatment, 6-month follow-up: NES frequency, SCL-90, BDI, STAI, UCL, SF-36, DISQ	Significant reduction in seizure frequency ($d=0.37$, $p=0.02$), maintained at follow-up. Significant improvements also seen on BDI, STAI-trait, UCL-active and DISQ scores (all $p<0.05$).

Author	Design	Target disorder [a]	Description of Intervention	Control Group	Sample size and attrition rate	Outcome measures and timepoints [a]	Main Findings
LaFrance et al. (2009)	Cohort	NES	Individual CBT: one hour per week, for 12 weeks.	None	n=21 (17 completers)	Baseline, and fortnightly thereafter: NES frequency, CGI, BDI, MHRSD, DTS, DES, BIS, FAD, SCL-90, GAF, OHS, LIFE-RIFT, WoC, QOLIE	Significant reduction in seizure frequency from 17.2-7.1 per week (d=0.44, p=0.001). Significant improvement (p<0.05) on BDI, DTS, BIS, FAD, SCL-90, GAF, OHS, LIFE-RIFT, CGI, QOLIE
LaFrance et al. (2014)	RCT	NES	Individual CBT: one hour per week, for 12 weeks. 4 arms: CBT vs Sertraline vs CBT and Sertraline vs control	Treatment as usual control group	n=38: CBT=9 (8 completers), Sertraline=9 (9 completers), CBT+Sertraline=10 (10 completers), TAU=10 (7 completers)	Baseline, week 2, week 8, week 16 (post-treatment): NES frequency, BDI, BAI, BIS, DTS, DES, SEP, SCL-90, QOLIE, QOL-BFS, ES, WoC, GAF, HDRS, CGI, LIFE-RIFT	Significant reduction in seizure frequency in CBT group (p=0.01) and CBT+Sertraline group (p=0.008). Significantly greater improvement in CBT group, compared to TAU, on GAF (p=0.03), CGI (p=0.01) and OHF (p=0.002). Significantly greater improvement on OHF in CBT group compared to Sertraline group (p=0.01) and CBT+Sertraline Group (p=0.02).
McCormack et al. (2014)	Retrospective cohort	FMD	CBT-based inpatient program, with psychology, psychiatry, physiotherapy and occupational therapy. Median length of treatment was 101 days.	None	n=33	Baseline and post-treatment: Mobility, ADLs, MRS	Significant improvement in mobility (p<0.001), ADLs (p=0.002) and MRS (p<0.001) at post-treatment.

Author	Design	Target disorder [a]	Description of Intervention	Control Group	Sample size and attrition rate	Outcome measures and timepoints [a]	Main Findings
Richardson et al. (2018)	Retrospective case-series	FND	Nocebo Hypothesis CBT delivered in an inpatient setting: 2-4 hours of therapy per day, over an average of 14 days.	None	n=13 (12 completers)	Baseline, post-treatment, 12-26 months follow-up: FIM	10 patients in full remission following treatment. 58% had reliable, significant change on FIM. 67% full remission at follow-up.
Saifee et al. (2012)	Retrospective case series	FND	Multidisciplinary CBT-based inpatient program: 5 days per week over an average of 4 weeks.	None	n=26	Baseline and post-treatment (retrospectively scored), and current (average 7 years post-treatment): Impact of symptoms, IPQ and WSAS	Significant decrease in 'time bothered by symptoms' between baseline and post-treatment (p=0.019). 58% thought symptoms had improved. Significant improvement on WSAS between baseline and follow-up (p=0.01).
Schmid et al. (2018)	Controlled trial	Functional dizziness	Group CBT (plus vestibular rehabilitation and psychoeducation): 8 90-minute sessions.	Balance disorder control group	n=32: normal balance=16, balance disorder=16	Baseline and post-treatment: DHI, EuroQol questionnaire, BSI, BCI	Significant improvement in normal balance group on DHI (p<0.001) and BSI (p<0.05), but not in balance disorder group.
Sharpe et al. (2011)	RCT	FNS	Guided self-help (GSH): CBT self-help manual, plus 4 30-minute guidance sessions over 3 months.	Treatment as usual (TAU) control group	n=127: GSH group=64 (62 completers), TAU group=63 (63 completers)	Baseline, post-treatment and 6-month follow-up: PHQ-15, SF-12, HADS, WI, IPQ (and additionally CGI and CPS at post-treatment only)	Significant improvement in GSH group at post-treatment, compared to TAU, on CGI (p=0.016), CPS (p=0.014), PHQ (p=0.009), WI (p<0.05). Significant benefit of GSH group over TAU at 6-month follow-up on CPS (p=0.014), SF-12 (p=0.008) and HADS anxiety (p=0.028).

Author	Design	Target disorder [a]	Description of Intervention	Control Group	Sample size and attrition rate	Outcome measures and timepoints [a]	Main Findings
Yu et al. (2018)	RCT	Functional dizziness	CBT plus Sertraline vs Sertraline alone. 2 one-hour CBT sessions per week, over 8 weeks.	Sertraline control group	n=91: CBT group=46, Sertraline group=45	Baseline, week 2, week 4, week 8 (post-treatment): DHI, HARS, HDRS	DHI, HDRS and HARS scores significantly improved in both groups following treatment ($p<0.001$). Significantly greater improvements seen in CBT group, compared to control group, on PHI ($p<0.001$), HDRS ($p=0.005$) and HARS ($p<0.001$).

[a]*Abbreviations:*

AAQ-II: Acceptance and Action Questionnaire
ADLs: Activities of Daily Living
BAI: Beck Anxiety Inventory
BCI: Balance Control Index
BDI: Beck Depression Inventory
B-IPQ: Brief Illness Perceptions Questionnaire
BIS: Barrett Impulsivity Scale
BSI: Brief Symptom Inventory
CEA: Confidence in Everyday Activities Questionnaire
CGI: Clinical Global Impressions
CNSQ: The Common Neurological Symptom Questionnaire
CompACT: The Comprehensive Assessment of Acceptance and Commitment Processes
COPM: Canadian Occupational Performance Measure
CORE-10: Clinical Outcomes in Routine Evaluation (10 item)
CPS: Change in Presenting Symptoms Scale
CSRI: Client Service Receipt Inventory
DASS: Depression Anxiety Stress Scales
DES: Dissociative Experiences Scale
DHI: Dizziness Handicap Inventory
DISQ: Dissociation questionnaire
DSI: Dizziness Symptom Inventory
DTS: Davidson Trauma Scale
ET7: Emotional Thermometer Scale
ES: Expectations Scale
FAD: Family Assessment Device
FIM: Functional Independence Measure
FMD: Functional Motor Disorder
FMS: Functional mobility scale
FND: Functional Neurological Disorder
FNS: Functional Neurological Symptoms
FQ: Fear Questionnaire
GAD-7: Generalised Anxiety Disorder Assessment
GAF: Global Assessment of Functioning
GHQ: General Health Questionnaire
GRBAS: Perceptual Rating of Voice Quality
HADS: Hospital Anxiety and Depression Scale
HARS: Hamilton Anxiety Rating Scale
HDRS: Hamilton Depression Rating Scale
HoNOS: Health of the Nation Outcome Scale
IPQ: Illness Perceptions Questionnaire
LIFE-RIFT: Longitudinal Interval Follow-Up Evaluation Range of Impaired Functioning
MHLC: Multidimensional Health Locus of Control Scales
MRS: Modified Rankin Scale
MHRSD: Modified Hamilton Rating Scale for Depression
NES: Non-epileptic seizures
OHS: Oxford Handicapped Scale
PHQ-9: Patient Health Questionnaire
PMDRS: Psychogenic Movement Disorder Rating Scale
PRIME-MD: Primary Care Evaluation of Mental Disorders
PSS: Perceived Stress Scale
QOL-BFS: Quality of Life Burden to Family Scale
QOLIE: Quality of Life in Epilepsy-31
SBI: Safety Behaviours Inventory
SCL-90: Symptom checklist-90
SEP: Side Effects Profile
SF-12: Short form health survey (12 item)
STAI: State Trait Inventory
UCL: Utrecht coping list
VHQ: Vertigo Handicap Questionnaire
VPQ: Voice Performance Questionnaire
VoiSS: Voice Symptoms Scale
VSS: Vertigo Symptom Scale
WSAS: Work and Social Adjustment Scale
WI: Whitely Index
WoC: Ways of Coping

1.4.4 Quality assessment

Using the EPHPP quality assessment tool (Thomas et al. 2004), global ratings of quality were calculated based on the number of areas of bias which received a ‘weak’ rating, with no weak ratings indicating a strong study, one weak rating indicating a moderate study, and two or more indicating a weak study (Table 1.2). As well as using the tool, each study was assessed to determine any aspects of bias which would likely impact on the results if included within meta-analysis, as well as looking at any areas where the tool may not have accurately reflected the quality of studies in this particular population.

One aspect of the tool which had potential to over-state bias was the blinding component. As most studies were using interventions with the aim of improving symptoms, and as patients had to be aware of this in order to consent and participate, blinding was impossible in many cases. Some studies also used participant-rated measures where, although some bias may have been present due to participants being aware of the intervention, this was not outcome assessor bias on the part of the research team. In these cases, the blinding component did not contribute to overall ratings, as noted in Table 1.2, where ratings have been put in parentheses. Overall, six studies were deemed to be of strong quality, six were of moderate quality and 16 were classed as weak.

Table 1.2 *Quality assessment ratings, using the EPHPP quality assessment tool (Thomas et al., 2004)*

Study	Selection Bias	Design	Confounders	Blinding	Data Collection Methods	Withdrawals and drop-outs	Global Rating
Andersson et al. (2006)	weak	strong	strong	(weak)	strong	weak	weak
Barrett-Naylor et al. (2018)	moderate	weak	strong	moderate	weak	strong	weak
Baslet et al. (2015)	moderate	weak	weak	weak	strong	strong	weak
Best et al. (2015)	weak	moderate	weak	moderate	weak	moderate	weak
Bullock et al. (2015)	strong	moderate	moderate	(weak)	weak	strong	moderate
Chen et al. (2014)	strong	strong	strong	weak	strong	moderate	moderate
Conwill et al. (2014)	moderate	moderate	weak	weak	strong	weak	weak
Cope et al. (2017)	strong	moderate	strong	(weak)	strong	moderate	strong
Dallocchio et al. (2016)	moderate	strong	strong	moderate	strong	moderate	strong
Daniilidou et al. (2007)	weak	moderate	strong	moderate	weak	strong	weak
Deary et al. (2018)	moderate	strong	strong	weak	weak	strong	weak
Demartini et al. (2014)	strong	moderate	strong	weak	strong	weak	weak
Detert & Douglass (2014)	strong	moderate	strong	(weak)	strong	weak	moderate
Edelman et al. (2012)	moderate	strong	strong	(weak)	moderate	weak	moderate
Goldstein et al. (2004)	strong	moderate	strong	moderate	strong	strong	strong
Goldstein et al. (2010)	moderate	strong	strong	(weak)	strong	strong	strong
Graham et al. (2018)	moderate	weak	weak	(weak)	strong	strong	weak
Holmberg et al. (2006)	moderate	strong	strong	moderate	moderate	strong	strong
Jacob et al. (2018)	strong	moderate	weak	(weak)	strong	strong	moderate
Kuyk et al. (2008)	strong	moderate	weak	weak	weak	strong	weak
LaFrance et al. (2009)	weak	moderate	strong	moderate	strong	weak	weak
LaFrance et al. (2014)	weak	strong	strong	moderate	strong	strong	moderate
McCormack et al. (2014)	weak	moderate	strong	weak	weak	n/a	weak
Richardson et al. (2018)	weak	weak	weak	weak	moderate	strong	weak
Saifee et al. (2012)	strong	weak	strong	(weak)	weak	n/a	weak
Schmid et al. (2018)	weak	strong	weak	moderate	strong	weak	weak
Sharpe et al. (2011)	moderate	strong	strong	(weak)	strong	strong	strong
Yu et al. (2018)	strong	strong	strong	weak	strong	weak	weak

1.4.5 Outcomes

A summary of main findings is included in Table 1.1. Most studies used outcome measures at baseline and post-treatment, with ten studies additionally following-up participants between six months and seven years post-treatment.

Twelve of the 28 studies were rated as being of 'moderate' or 'strong' quality and were therefore eligible to be included in meta-analysis. However, suitable data were not available in three of the twelve studies. Nine studies (Chen et al. 2014; Cope et al. 2017; Dallocchio et al. 2016; Edelman et al. 2012; Goldstein et al. 2010; Goldstein et al. 2004; Holmberg et al. 2006; LaFrance et al. 2014; Sharpe et al. 2011) were therefore included in meta-analyses, and pre-post effect sizes for the intervention group were calculated for each. Seven of the included studies had a control group, allowing post-intervention effect sizes to be calculated between treatment and control groups, excluding any measures with baseline differences between groups. Funnel plots did not show any evidence of publication bias.

1.4.5.1 Daily functioning

Twenty-one of the 28 studies used a measure of daily functioning or functional impairment. The Work and Social Adjustment Scale (WSAS) was the most commonly used measure of functioning, used in six studies.

Between-group analysis

Effect sizes between CBT and control groups at post-treatment were calculated for the seven controlled studies. Significant heterogeneity was seen (I^2=55%), with two studies reporting larger effect sizes. Even after these were removed in a sensitivity analysis (reducing I^2 to 0%), a significant positive effect of CBT was seen over control (g=-0.44, 95% CI -0.66, -0.22, p<0.0001; Figure 1.2).

A sensitivity analysis looked at the two studies which used the WSAS as the measure of functioning (Chen et al. 2014; Goldstein et al. 2010), and the significant effect remained (g=-0.68, CI -1.03, -0.33, p=0.0002). However, an additional sensitivity analysis combined the two studies which used the Dizziness Handicap Inventory (DHI; Edelman et al. 2012; Holmberg et al. 2006), and no significant overall positive effect was seen, although the effect size was still in the small-medium range (g=-0.34).

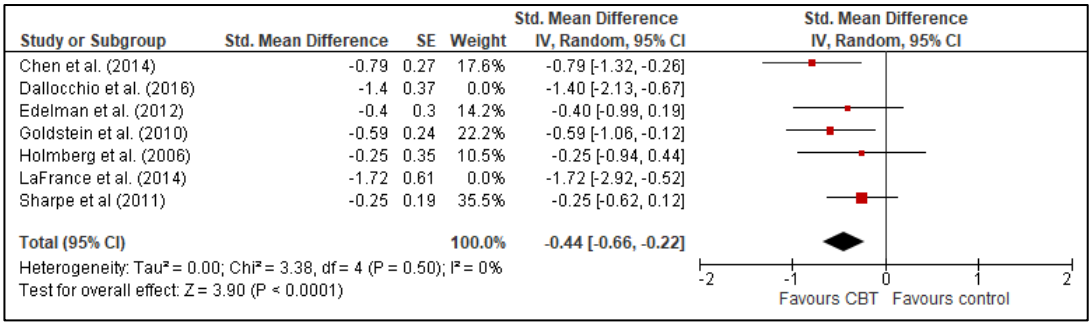

Figure 1.2 *Forest plot of the post-intervention effect of CBT on daily functioning, compared to control*

Within-group analysis

In all nine studies included in meta-analysis, repeated measures effect sizes were calculated for daily functioning. However, significant heterogeneity was found (I^2=66%). Three outliers were identified, all with larger effect sizes, and removed from the analysis. A significant effect of CBT over time was seen on measures of functioning (d=-0.50, CI -0.76, -0.24, p=0.0002; Figure 1.3), a similar sized effect as that seen in the between-groups comparison. A sensitivity analysis including studies which used the WSAS again showed a significant benefit of CBT over time (d=-0.64, CI -0.90, -0.37, p<0.00001), as did the two studies which used the DHI (d=-0.99, CI -1.69, -0.29, p=0.006).

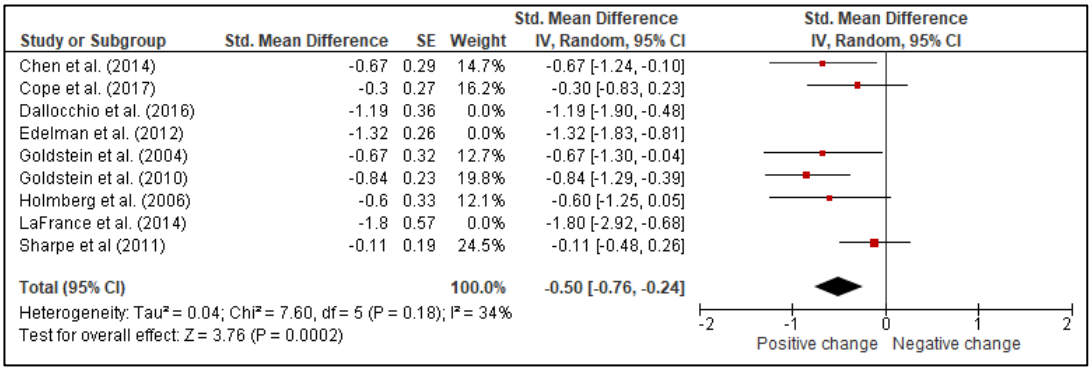

Figure 1.3 *Forest plot of the pre-post effect sizes of CBT on daily functioning*

1.4.5.2 Functional neurological symptoms

Functional neurological symptoms were measured as an outcome in all studies. The ten NES studies used frequency of attacks as a key outcome. In FMD studies, measures of movement disorder type (tremor, dystonia etc.), mobility, and use of aids were used. In functional dizziness studies, dizziness symptoms and balance measures were used. Of the nine studies of good methodological quality, four reported data on functional neurological symptoms which could be used in meta-analysis, all of which had control groups. As the

other five studies reported NES frequency as an outcome, these were not included due to the data not having normal distribution.

Between-group analysis

The four controlled studies had significant heterogeneity when combined (I^2=92%). However, when an outlier with a large effect size was removed, a significant effect of CBT over control remained (g=-0.30, CI -0.56, -0.03, p=0.03; Figure 1.4).

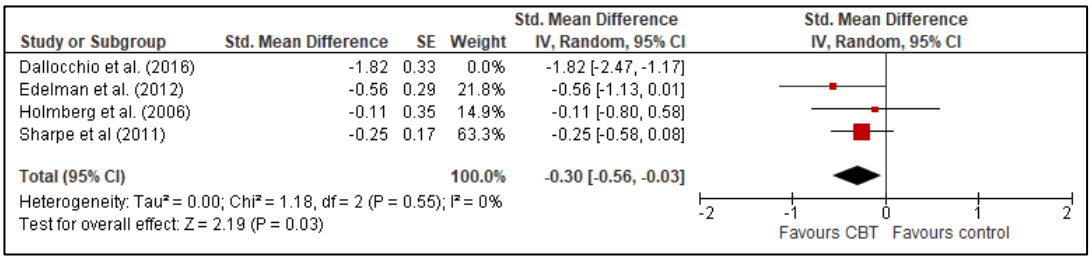

Figure 1.4 *Forest plot of the post-intervention effect of CBT on functional neurological symptoms, compared to control*

Within-group analysis

Data from four studies were used to calculate within-groups effect sizes. Significant heterogeneity was again present (I^2=94%), and when an outlier with a larger effect size was removed, an overall significant positive effect of CBT over time was found (g=-0.56, CI -0.98, -0.13, p=0.01; Figure 1.5).

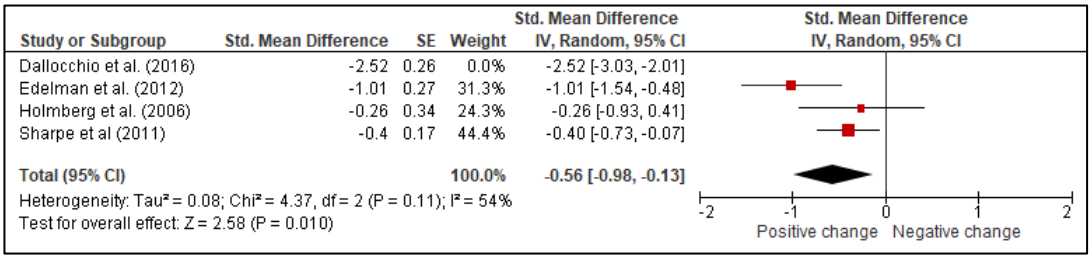

Figure 1.5 *Forest plot of the pre-post effect sizes of CBT on functional neurological symptoms*

1.4.5.3 Anxiety and depression symptoms

Measures of mood and anxiety were used in 13 studies. These varied between studies, with the Hospital Anxiety and Depression Scale (HADS), Hamilton depression rating scale (HDRS), patient health questionnaire (PHQ-9) and Beck Depression Inventory (BDI) used in three or more studies.

Between-group analysis

Five controlled studies reported data which could be used to calculate independent groups effect sizes. An additional study (LaFrance et al. 2014) collected data but effect sizes was not calculated for meta-analysis due to baseline differences between groups. Heterogeneity caused by an outlier with large positive effect sizes was seen in both depression (I^2=69%) and anxiety (I^2=51%) comparisons. After this study was excluded, a significant small positive effect of CBT compared to control was seen on both anxiety symptoms (g=-0.25, CI -0.50, -0.01, p=0.04; Figure 1.6) and depression symptoms (g=-0.26, CI -0.50, -0.02, p=0.03; Figure 1.7).

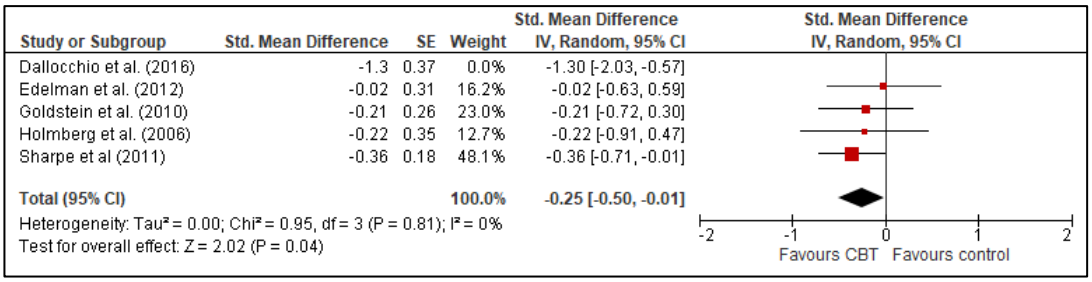

Figure 1.6 *Forest plot of the post-intervention effect of CBT on anxiety symptoms, compared to control*

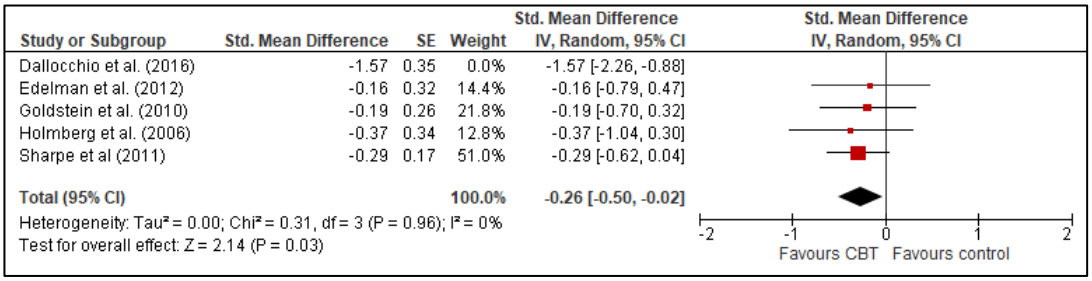

Figure 1.7 *Forest plot of the post-intervention effect of CBT on depression symptoms, compared to control*

Within-group analysis

Eight studies reported repeated-measures data on anxiety and depression symptoms. High but not significant heterogeneity was seen in the anxiety analysis (I^2=47%), but an overall significantly positive effect of CBT over time was seen on anxiety symptoms (d=-0.59, CI -0.87, -0.31, p<0.0001; Figure 1.8). When two outliers with larger effect sizes were removed in a sensitivity analysis, the significant effect remained (d=-0.41, CI -0.62, -0.19, p=0.0002). In analysis of depression symptoms, significant heterogeneity was observed due to one outlier with a large effect size (I^2=83%). When this as removed, a significantly positive effect of CBT over time was seen (d=-0.37, CI -0.61, -0.13, p=0.002; Figure 1.9). Effects remained

in a sensitivity analysis when only the four studies which had used the most common measure of anxiety and depression symptoms, the HADS, were included.

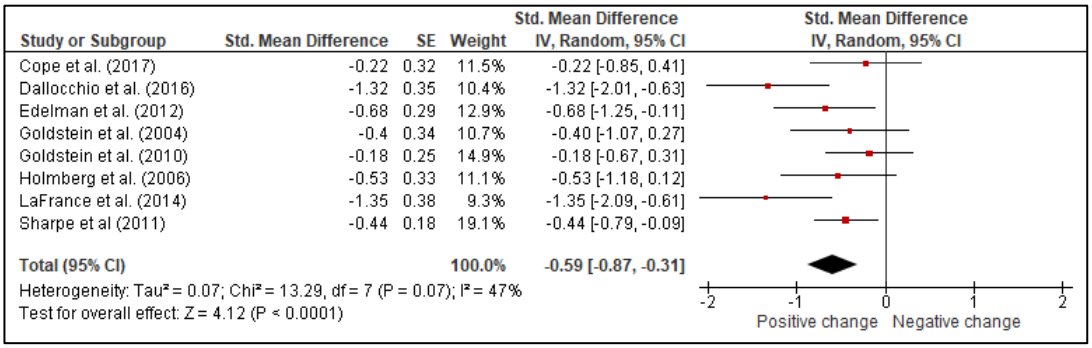

Figure 1.8 *Forest plot of the pre-post effect sizes of CBT on anxiety symptoms*

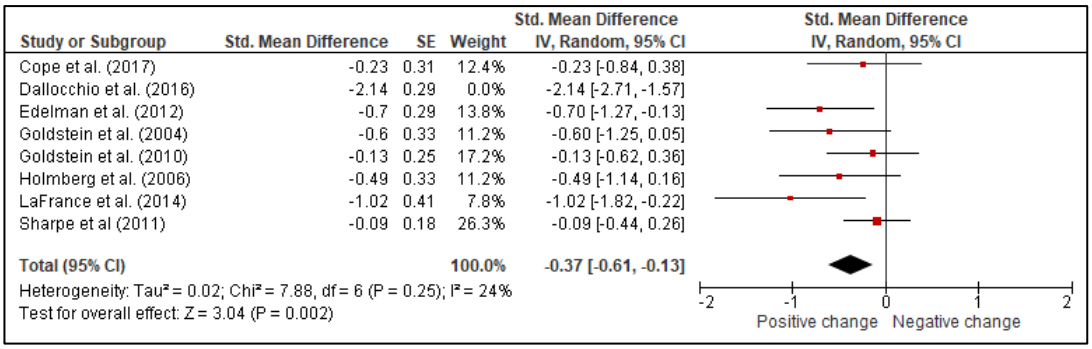

Figure 1.9 *Forest plot of the pre-post effect sizes of CBT on depression symptoms*

1.4.5.4 Outcomes at follow-up

Six of the studies included in meta-analysis reported six- or twelve-month follow-up data (Chen et al. 2014; Goldstein et al. 2010; Goldstein et al. 2004; Sharpe et al. 2011; Holmberg et al. 2007; Mahoney et al. 2013). Meta-analysis of three controlled studies showed that CBT's significantly positive effect on functioning, compared to control was strengthened at six-month follow-up (g=-0.57, CI -0.84, -0.30, p<0.0001). A similar effect size was seen in the CBT groups in five of the six studies between baseline and follow-up, after one outlier was removed due to heterogeneity (d=-0.53, CI -0.84, -0.21, p=0.001).

Only one study (Sharpe et al. 2011) reported data to calculate an independent groups effect size for functional neurological symptoms at six-month follow-up, which was not significant. However, the significantly positive effect of CBT on functional symptoms over time seen at post-treatment, in meta-analysis of three studies, was strengthened at follow-up (d=-0.61, CI -1.00, -0.21, p=0.003).

A meta-analysis of effect sizes between CBT and control groups at follow-up for two studies, with non-significant individual effect sizes, found an overall significantly positive effect of CBT for both anxiety symptoms (g=-0.35, CI -0.64, -0.06, p=0.02) and depression symptoms (g=-0.32, C I-0.61, -0.03, p=0.03), larger than immediately following treatment. The effect of CBT at follow-up compared to baseline was calculated for four studies, showing significantly positive change from baseline in both anxiety (d=-0.34, CI -0.58, -0.10, p=0.006) and depression symptoms (d=-0.27, CI -0.51, -0.03, p=0.03).

1.5 Discussion

This systematic review and meta-analysis is the first to explore CBT as an intervention for a wide range of functional neurological symptoms. Overall, based on a small number of high-quality studies, CBT was found to significantly improve daily functioning outcomes, both compared to control groups, and in repeated measures comparisons. CBT also significantly improved functional neurological symptoms, as well as depression and anxiety symptoms. Our findings build on previous reviews which have suggested that psychological interventions are effective for non-epileptic seizures (NES; Gaynor et al. 2014; Carlson and Perry 2017), and that CBT is effective for reducing anxiety, depression and functional symptoms, and improving daily functioning, in those with non-neurological functional symptoms (Jing et al. 2019).

CBT had a significantly positive effect on social and occupational functioning, with effect sizes in the medium range. Effects of this size were seen in both within- and between-groups comparisons, and had slightly increased at follow-up. The effects of CBT on both functional neurological symptoms, and anxiety and depression symptoms were also statistically significant, within the small-medium range. Significantly positive change in anxiety, depression and functional neurological symptoms was maintained at follow-up.

One study was an outlier in most comparisons. This was a pilot RCT with a small sample size investigating CBT as a treatment for functional movement disorders, compared to standard medical care (Dallocchio et al. 2016). The effect sizes calculated from this study were far larger than those seen in other studies, although overall effect sizes were still significant when this study was removed from meta-analyses. This was the only study included in meta-analysis which looked specifically at movement disorders, whereas the rest looked at NES (five studies), functional dizziness (two studies), and mixed functional symptoms (one study). This raises the question of whether CBT for movement disorders may have different effects than in other functional neurological disorders. However, as Dallocchio et al. (2016) is currently the only published RCT of CBT in this population, further research is required to determine whether this is indeed the case.

1.5.1 Limitations

Overall, the methodological quality of studies in this area is mixed, with only nine of the 28 studies included in this review rated as having moderate or strong methodological quality. The main issues across studies were small samples and lack of outcome assessor blinding, leading to considerable risk of bias, and limiting the number of studies which could be combined in meta-analysis. Therefore, only a small number of studies were used to inform estimates of effect, potentially limiting the generalisability of the results.

A limitation was the use of a structured assessment of quality which produced a global rating of bias. In order to ensure that areas of bias were successfully identified, and that overall ratings were accurate, areas of identified bias were assessed further to determine whether they would have an impact on the results if included in meta-analysis. Areas where the tool may not have accurately reflected the quality of studies in this particular population were also investigated further. The tool was adjusted to reflect this, although global ratings were still produced.

In this review, ratings of bias were used to exclude studies from meta-analysis. This in itself may have biased the findings, although he steps outlined above sought to minimise this. Although best practice would be to have included all studies in meta-regression, the high number of poor quality studies would have introduced considerable error into the results and it was decided to exclude these for the purpose of this meta-analysis. However, all studies were included in the review, and a summary of results from these studies were highlighted in Table 1.1.

It should also be noted that there was heterogeneity within study methods. Due to this, different outcome measures were combined within meta-analysis. However, where possible combined effect sizes were compared to specific outcome measures analysed separately, in order to check the validity of this method, and effect sizes were found to be comparable.

1.5.2 Clinical implications

CBT had a significantly positive impact on functioning, functional neurological symptoms, and anxiety and depression symptoms. These differences remained, and were strengthened, at six-month follow-up. This suggests that positive change was maintained, despite participants receiving no further active intervention. Given the high costs associated with healthcare and inability to work in those with FND (Carson et al. 2011), an effective 12-week CBT intervention (such as were those included in this meta-analysis) with lasting positive effects would be an attractive treatment option. However, further research is required to determine whether positive effects persist for longer than six months.

Due to the small number of studies, it was not possible to compare different symptom presentations or types of intervention. However, the aim of this systematic review was

primarily to look at the overall quality of the literature in this area, and assess whether CBT for FND was an intervention that warranted further exploration. There are several studies of CBT for NES with good methodological quality, but further trials for other functional symptoms are required. Overall, all studies identified reported positive outcomes from a CBT-based intervention, suggesting that it is a promising intervention, but further high-quality trials are required.

Future trials would benefit from comparing CBT to treatment as usual, with a long follow-up period in order to assess change over time without intervention. A six- to twelve-month follow-up would also help to determine the lasting effects of any positive change following CBT. Collecting data on social and occupational functioning, and overall emotional wellbeing, would help to determine the impact of CBT on quality of life and disability for those with FND. This is arguable more important as an outcome, for both individuals and services, than a reduction in functional neurological symptoms alone.

1.5.3 Conclusions

CBT is a promising intervention which can improve social and occupational functioning, functional neurological symptoms, and anxiety and depression symptoms in those with FND. These effects persist over time, suggesting CBT could have lasting benefits. However, further high quality and adequately powered trials are required to explore the effectiveness of this intervention further, and to explore any differences between the various FND presentations.

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2 Developing a cognitive behavioural understanding of idiopathic drop attacks in the context of functional neurological disorder: a grounded theory study

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2.1 Abstract

Idiopathic drop attacks are falls to the floor, without warning, and without loss of consciousness, for which the cause is uncertain. They are poorly studied but recent research suggests that some drop attacks may be usefully considered as within the spectrum of functional neurological disorder (FND).

The aim of this study was to develop a psychological understanding of idiopathic drop attacks, in order to inform formulation and treatment. Interviews and diaries were completed by seven individuals experiencing drop attacks, and the content of these was analysed using a grounded theory approach.

Predisposing and precipitating factors for idiopathic drop attacks, along with thoughts, emotions and behaviour both before and after a fall, were identified through the coding and synthesis of data into themes. A proposed cognitive behavioural model was identified, with a traumatic first fall and life stressors as predisposing factors. Precipitating factors identified included situational triggers and increased worry. A maintaining cycle of thoughts, emotion and behaviour is outlined.

Our proposed theory overlaps with cognitive behavioural models of functional symptoms, in particular those of non-epileptic seizures. A cognitive behavioural understanding of drop attacks could aid formulation in clinical practice, and suggests that cognitive behavioural therapy interventions for non-epileptic seizures may also be applicable in this population.

Keywords: Functional neurological disorder; cognitive behavioural; idiopathic drop attacks; cryptogenic drop attacks; formulation

2.2 Introduction

Idiopathic drop attacks have been defined as falls to the floor without warning, where there is no identified cause, despite comprehensive diagnostic testing to rule out other conditions which can cause drop attacks, such as cardiac, cerebrovascular, vestibular or seizure disorders [e.g. 1, 2]. They are also not caused by malfunction of the lower limbs, or changes in body or head posture [3]. Little research has investigated idiopathic drop attacks, with only two studies exploring them in detail [3, 4], although case studies have also been published [5, 6]. Idiopathic drop attacks have previously been referred to as 'cryptogenic drop attacks' [3] or 'La maladie des genoux bleus' [5]. In this paper, the term 'drop attacks' will be used synonymously with idiopathic or cryptogenic drop attacks.

2.2.1 Prevalence

A recent study surveyed patients with drop attacks presenting to a single neurology clinic over a ten-year period [4]. Eighty-three patients were identified, 89% of whom were female, with a mean age of 44 (range 12-78 years). In a previous study of drop attacks, Stevens and Matthews [3] retrospectively identified 33 patients with drop attacks who had presented to a neurology clinic over a twelve year period, all of whom were female. In their study, onset occurred on average at age 44. The age-range of onset spanned from 19 to 69, but in two thirds of the sample onset was between the ages of 40 and 59. Both studies were conducted within adult services, so it is possible that children are also affected by drop attacks, but no published studies are available to determine this.

Many more women than men present with drop attacks, with women comprising 89-100% of the samples mentioned above. In order to investigate this prospectively in those not presenting specifically to neurology services, Stevens and Matthews [3] approached 100 consecutive male surgery patients to ask if they had ever experienced 'attacks of unexplained falling', none of whom had. The authors also asked the same question of 200 consecutive women attending a gynaecological clinic, and found that 3.5% met the criteria for drop attacks. This suggests that this phenomenon could account for a significant number of falls in women in the general population, who may not present to neurology clinics. However, a survey within a general setting attended by both men and women would be required to determine this further, as those presenting to specialist clinics may not be representative of the general population.

2.2.2 Frequency

The frequency of drop attacks varies greatly between individuals. In Hoeritzauer and colleagues' [4] study, three patterns of attacks were noted: of the 57 patients for whom frequency was reported, 60% experienced regular attacks, which varied between ten per day and one per month, 30% reported single or less frequent attacks, and 10% had clusters

of attacks with periods of freedom from drop attacks between these. However, for 32% of the overall sample, the frequency was not reported. When first seen in clinic, the mean duration of drop attacks was 56 months (range 2-388 months). A similar frequency pattern was seen in the earlier study [3], with 28% having between three and 12 drop attacks per year, 15% having more than 12 falls per year, 45% having two falls or fewer per year, and 12% having clusters of attacks with freedom in between.

2.2.3 Associations

Stevens and Matthews [3] reported that falls usually happened while walking (96%), and usually occurred outside of the house, although 43% also had drop attacks inside the house. In Hoeritzaeur et al's [4] sample, 34% of patients could identify triggers for their drop attacks, such as specific places, times or situations where falls would be more likely to occur. Upon direct questioning, 43% of patients described a brief period prior to a drop attack where they would experience feelings of dissociation or depersonalisation.

Hormonal changes were also investigated by Stevens and Matthews [3] as a potential association, given that the age of onset in females frequently coincides with when menopause could be likely to start, and due to the fact that 60% of the younger patients in their sample had onset of drop attacks during pregnancy. However they found no clear links between hormonal changes and drop attacks, although 45% of their sample did experience onset either during pregnancy or within three years either side of the start of the menopause.

2.2.4 Impact

Injuries were frequently reported as an outcome of drop attacks. In Stevens and Matthews [3], 93% sustained injuries to their knees, and often also to their hands, chest or face, and 18% reported fractured or broken bones as a result of a drop attack. Hoeritzauer and colleagues [4] noted that 29% of their sample had documented soft tissue injuries following drop attacks, which is likely to be underreported. Of these, 71% had recurrent facial injuries, 50% injured their knees and 9% also reported fractured bones. The authors of both studies reported that many women would become afraid to go out due to both the risk of injury and embarrassment, impacting on their everyday functioning.

2.2.5 Mechanism

The underlying mechanism for drop attacks is unclear, due to the lack of research in this area. Other than the two papers mentioned above, the only additional research investigating this group in isolation is a small number of case reports. Butsch and Schneemann [5] reported the cases of two women aged 56 and 79, with recurrent drop attacks while walking, occurring over several years. Another case study identified a 47 year old woman's drop

attacks as occurring following recollection of traumatic experiences, suggesting a psychological mechanism [6].

It has been suggested that some patients with idiopathic drop attacks can be reclassified within the category of functional neurological disorder [FND; 4], a term which describes neurological symptoms where clinical signs provide positive evidence of a disorder of abnormal nervous system functioning rather than of neurological disease [7]. Functional neurological symptoms are reported to be experienced by 9-30% of those accessing neurology services [8, 9]. Motor ability, speech and vision can all be affected. Some clusters of symptoms, because they are more common, have been grouped together and researched more than others, such as non-epileptic seizures [NES; 10] and functional motor disorders [FMD; 11].

Although there are similarities between drop attacks and NES, drop attacks are not widely included in studies of NES, which tend to focus on events with generalised shaking that superficially resemble epilepsy or events where patients fall down and lie still and unresponsive, superficially resembling syncope. Hubsch et al. [12] analysed clinical signs in 145 NES and identified different subtypes of seizure, none of which covered drop attacks. However, Galimberti et al. [13] and Devinsky et al. [14] included patients with drop attacks within an NES sample, accounting for around 10% of each sample. This suggests that, at least in some cases, drop attacks have significant similarities to NES.

Hoeritzauer and colleagues [4] developed a hypothesis that drop attacks represent a conditioned behavioural response to negative external (environmental or situational) or internal (anxiety symptoms or dissociation) stimuli. It is proposed that this association is maintained through fear of collapse and/or through the fall providing relief from negative stimuli. This mechanism overlaps with models of NES previously reported in the literature [15, 16].

2.2.6 Therapeutic intervention

Due to the limited literature, there are no recommended evidence-based interventions for drop attacks. However, Hoeritzauer and colleagues [4] report that for 12% of patients, drop attacks abated following an explanation of the episodes as conditioned responses, and the use of distraction techniques. However, they noted that 51% of their sample had reduced or no drop attacks when followed-up at an average of 38 months and therefore it is unclear how many would have experienced spontaneous resolution.

A better understanding of drop attacks is required to guide both formulation and treatment approaches. Given the potential overlap between drop attacks and other functional symptoms, especially NES, a deeper understanding of drop attacks could help to identify whether psychological interventions which show some efficacy in NES, such as cognitive behavioural therapy [CBT; 17], may also be helpful at reducing falls in this population. A

CBT intervention could also focus on helping individuals to manage their condition and improve the ways they cope with the anxiety surrounding future falls.

2.2.7 Aims

The aim of our study was to explore whether a cognitive-behavioural understanding of drop attacks could help to guide formulation and treatment. This was investigated through the collection of qualitative data from interviews and diaries from individuals experiencing drop attacks. The data were analysed using a grounded theory approach [18] in order to better understand the onset of drop attacks, the impact of life stressors as well as thoughts, feelings and behaviour both directly before and after a drop attack.

The primary research question was as follows:

- What are the predisposing and precipitating factors related to drop attacks?

Secondary research questions were:

- What are individuals' thoughts, emotions and behaviour immediately prior to a drop attack?
- What are individuals' thoughts, emotions and behaviour immediately following a drop attack?

2.3 Methods

2.3.1 Participants

Participants were individuals who were experiencing ongoing drop attacks who were recruited from a neurology outpatient clinic at a regional neuroscience unit in Edinburgh, UK (the Department of Clinical Neurosciences, serving a population of approximately 800,000). Inclusion criteria were 1) Diagnosis of idiopathic drop attacks, following assessment and relevant investigations, 2) Aged 18+, 3) Drop attacks occurring 6+ times per year, 4) Able to provide informed consent. Ethical approval (Appendix D) was granted by the South Yorkshire Research Ethics Committee (Reference: 17/YH/0438) and the NHS Lothian Research and Development Office (Reference: 2017/0335). The study protocol (Appendix E) was registered with Clinicaltrials.gov (Reference: NCT03694769).

Due to the relatively small numbers of people diagnosed with drop attacks under the care of the Department of Clinical Neurosciences, approximately eight new diagnoses per year [4], we aimed to recruit a homogenous sample of ten participants. Due to the low numbers of men presenting with drop attacks, an entirely female sample was therefore recruited. In order to maximise data, and the likelihood of approaching saturation, two methods of data

collection were used: interviews and written diaries. All those who had been seen at a single neurology clinic between 2016 and 2018 were screened for eligibility, and contacted if they met inclusion criteria and fit with the sampling method (Figure 2.1).

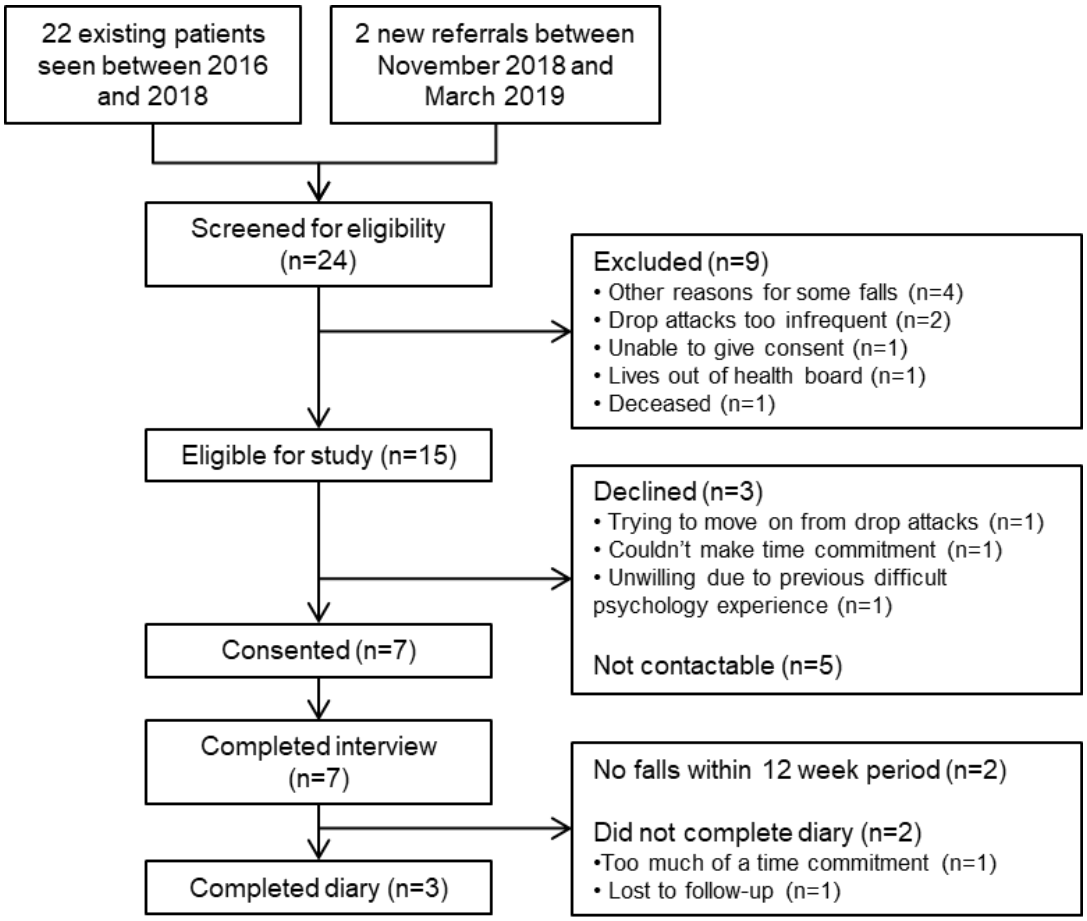

Figure 2.1: Participant flowchart

2.3.2 Design

In this exploratory qualitative study, neurology outpatients with ongoing drop attacks underwent a semi-structured interview and completed written diaries for eight weeks. Throughout the study, participants received treatment as usual from their neurologist.

2.3.3 Procedure

Participants were approached by their neurologist who gave them a participant information sheet. If they were interested in taking part, a meeting was arranged to discuss the study further and obtain written informed consent. Participants met with the researcher to give consent and complete an hour-long interview. Following this initial interview, participants

were asked to record written accounts of any drop attack that occurred over the subsequent eight weeks during which the researcher contacted them fortnightly by telephone to discuss any difficulties or concerns. If participants did not experience any drop attacks during this period, they were asked if they would be willing to continue keeping a diary for an additional two to four weeks. Participants then met again with the researcher to return the diaries and discuss any reflections that they had about any aspect of the process.

2.3.4 Data collection

2.3.4.1 Semi-structured assessment interview

The audio-recorded interview was semi-structured, with suggested questions designed to facilitate discussion related to the research questions. The interview schedule (see Appendix F) was based on a cognitively-informed clinical interview schedule, and was refined based on factors found previously to be relevant in this population [4], and factors commonly reported in discussions with a neurologist working with patients with drop attacks. The schedule included questions about recent drop attacks, the onset of these and relevant personal and social history. Participants' experiences of drop attacks were also discussed, focussing on thoughts, feelings and behaviour before and after the episodes. Participants were also asked about the impact that drop attacks had on their everyday functioning.

2.3.4.2 Drop attack diary

Participants were given diaries along with an accompanying prompt sheet (Appendix G) which asked them to record what had happened, along with their thoughts, physical symptoms, feelings and behaviour, as close to the event as possible. They were encouraged to write detailed accounts, outlining the period before, during and after the episode, in order to identify any potential triggers.

2.3.5 Analysis

The content of the interviews and diaries was analysed using a grounded theory approach [18]. Following Charmaz, a constructivist stance was taken, with research questions, based on knowledge of the existing literature, used as a starting point to guide data collection. The constructivist approach also acknowledges the influence of the researcher in the collection and interpretation of research data. As such, critical reflexivity throughout the research design, data collection and interpretation process was important. A reflective journal and memo-writing was used throughout this process, documenting any decision making, and the reasons behind these, including assessing the influence of any preconceptions or prior knowledge. The journal was also used to record personal 'gut feelings' about the data, in order to assess this for bias, and address the influence of this on the refinement of interview questions and interpretation of data.

Using both interviews and diaries allowed information to be obtained from different viewpoints, enriching the data. Data from both interviews and diaries was coded in three stages. Initial line-by-line open coding of transcripts was completed, followed by focused coding which involved sorting and grouping both frequently occurring codes, and those which were more relevant to the research questions. The third coding stage was theoretical coding. This comprised looking at relationships between codes in order to identify hypotheses which could be integrated into a theory. An excerpt of transcript and codes is included in Appendix H.

Coding was completed as data were collected, allowing refinement and changes to be made over the course of the data collection period. The codes that emerged from the first four interviews, along with memos written alongside these, were used to refine questions used in subsequent interviews. Focused codes and theoretical codes were refined and altered over time, based on information from subsequent interviews and memos.

Several steps were taken to reduce potential bias. Memo-writing was used throughout data collection and analysis, in order to record reflections on the meaning in data and codes, explore connections between data, and outline methodological decision making. Particular focus was given to identifying data which was contrary to emerging themes, and which would not fit with a cognitive-behavioural model, or an understanding consistent with FND. Participants were also invited to review the codes that were identified within their interviews. Any discrepancies were discussed within the research team until consensus was reached.

2.4 Results

Seven participants, all women between the ages of 40 and 71, completed interviews which ranged from 57 to 73 minutes. Three participants also completed diaries of their drop attacks, writing between 250 and 1000 words. Within the eight-week diary period, one participant experienced one drop attack, and another had two drop attacks. The third participant had no drop attacks within the eight-week period and agreed to continue keeping a diary for a further four weeks. She subsequently experienced a cluster of five drop attacks over the four weeks, the first of which was a very painful fall resulting in a hospital visit. Four participants did not complete diaries; two did not have any drop attacks within the prolonged diary period, one was lost to follow-up, and another declined to take part in the diary portion of the research due to the perceived burden of doing so, as she was experiencing multiple drop attacks each day. Most participants preferred to call their drop attacks simply ‘falls’ with one individual also referring to them as ‘drops’. This is reflected in the content below, where these terms are used interchangeably.

2.4.1 Main themes

The three key categories (predisposing, precipitating and maintaining factors) and nine main themes from the interviews and diaries are displayed in Figure 2.2. No new key themes were identified from the final two interviews, suggesting that theoretical saturation was approached [18]. Themes are described in further detail below, grouped by the categories given, and with relevant example quotes.

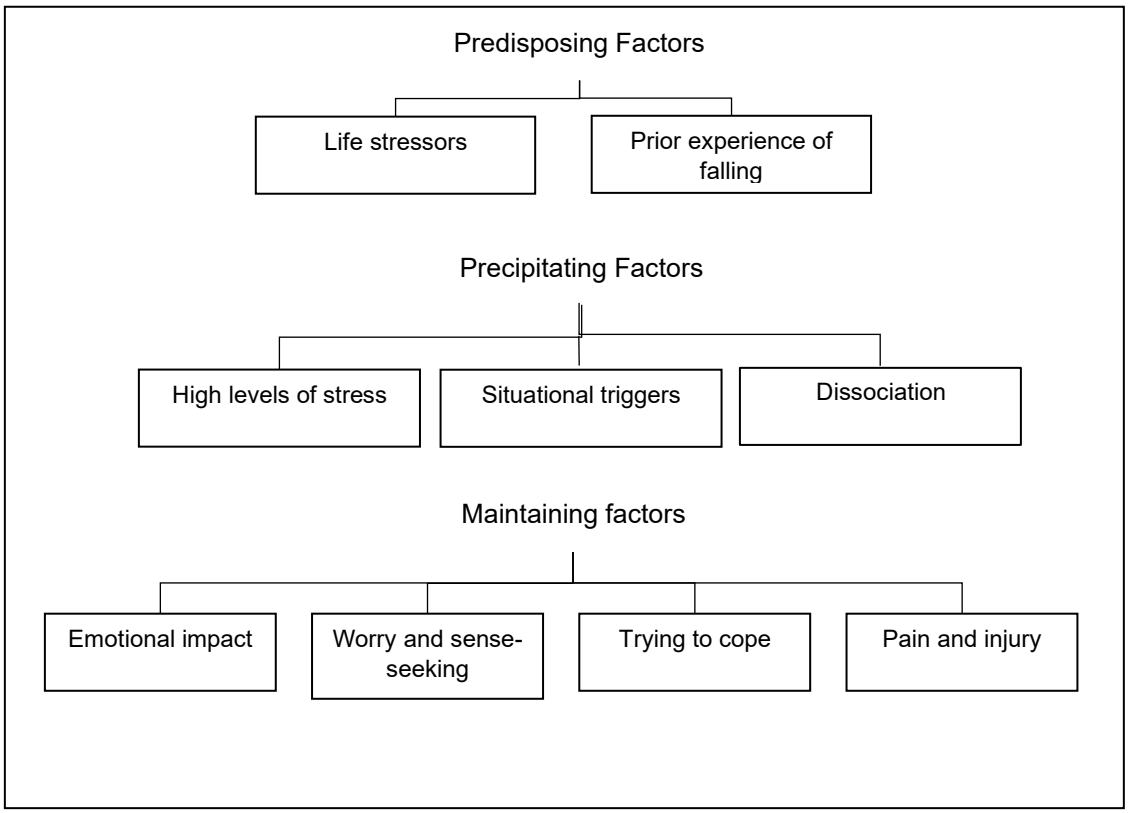

Figure 2.2: Main categories and themes

2.4.1.1 Predisposing factors

Table 2.1 shows example quotes illustrating the two main themes which emerged as predisposing factors: prior experience of falling, and life stressors. For all participants, the initial experience of falling was notable in one of two ways. In some, the first falls occurred during a particularly stressful time, and were related to medical reasons, such as low blood pressure, pain, Meniere's disease or migrainous stroke. In other cases, the first falls themselves were the stressful event, with falls leading to significant injuries or risk to children. In all cases, the falls then continued, with varying courses, despite there no longer being a clear cause or trigger.

Past life stressors were mentioned by all participants who experienced traumatic or stressful experiences in their lives prior to developing drop attacks. Most participants also reported current life stressors including relationship and family difficulties, chronic health difficulties,

caring for family members, and work stress. Only one participant reported no current life stressors, and she did not experience any drop attacks during the course of the study.

Table 2.1: Themes and supporting quotes within the predisposing factors category

Themes	Quotes
Prior experience of falling	P07: "I fell down the stairs, my neighbour was with me, she stayed with me in (place). She stayed along the landing from me and she was with me and she shouted '(Name)!' I slipped and tumbled right down to the bottom and blood was everywhere." P03: "I went down between the kerb and the road and I broke my ankle and then I had a blood clot. And I don't know if it was the blood clot that I had, because I was out of action for such a long time, and I don't know if it's... and then I had to try to learn to walk again because I was frightened to walk because of the pain." P06: "(The first drop was) not long after my migrainous stroke and it was scary. It just, just like the right side of my body wouldn't do anything. And I couldn't get up from that one. I was kind of like frozen."
Life stressors	P02: "The stress of having my little boys on my own. I worried about having a vertigo attack when they were just going about the house. That was very stressful as well." P05: "When you go through difficult situations, can that make it worse? So I've got (daughter) through leukaemia twice. My youngest…who was very unhappy, has gone through severe depression and self-harming." P07: "I had three jobs at one point just to survive…Just to survive, to pay the bills and survive. It's hard on your own." P06: "My mum's not been well, so I've been having a lot of episodes of things."

2.4.1.2 Precipitating factors

Table 2.2 shows the main themes in the precipitating factors category: situational triggers, high levels of stress, and dissociation. Participants reported falling in different locations and situations, both outside and in the home. Falling in the home was mentioned less frequently, which may have been due to a lower incidence, or due to under-reporting as these falls tended to be accompanied by less embarrassment. For some, falls were more likely to happen in specific situations, particularly in places where falls had happened before. Stairs and steps were a particularly common place for falls to happen, with five participants describing falls that had happened in these circumstances. It appeared that situational triggers were linked to increased levels of stress, as described in the quote from participant two in Table 2.2.

Five participants identified high levels of stress as a trigger for their drop attacks. ‘Stress’ was the preferred word for participants to describe this feeling, although ‘anxiety’ was also used. For some, it was stress immediately prior to a fall which they noticed was a trigger. For others, they noticed falls were more likely during periods when they had a higher general level of stress. However, stress was not always a factor, with some falls not being linked to stress, as noted in the ‘Fall even when calm’ theme in Table 2.2. Two people who identified stress as a trigger for their falls reported that they also had falls when they were feeling calm. Another participant stated that they did not fall at all during particularly stressful periods but were more likely to have falls in the period following this. For another participant, they had never considered the possibility of a link between stress and their falls and were unsure whether this could be a factor.

‘Detachment-type’ dissociation [19] was identified as another precipitating factor. Four participants reported episodes of dissociation. In some cases, these were linked to falling (as described in quotes in Table 2.2), with participants describing a sense of dissociation either prior to the fall or after they had fallen to the floor. Three participants also described periods of dissociation in everyday life, for example, *“I would be sitting and talking to a friend and I would just go. And I remember talking to a friend of mine and she was going further and further back. She wasn’t but she was going further and further back and I had like tunnel vision.” (P05).*

Table 2.2: Themes and supporting quotes within the precipitating factors category

Themes	Quotes
Situational triggers	P02: “If I’m in a situation like boarding an aeroplane where I’ve had a drop attack before then I can feel myself tensing up and thinking what if I do this again, which in turn probably makes it more likely that it will happen” P04: “the majority of times (the fall is) either out the back or coming down the stairs.”
High levels of stress	P01: “It makes me feel anxious, because I know I’ve got all this happening and all this that needs to be done… but as I said I don’t know if that’s maybe part of why I could be falling” P02: “I know definitely that if I get anxious or stressed, that will mean I’m more likely to get an attack.” P03: “I do know that if I get stressed, and I get worried about something, I’ll have more falls.” P05: “I don’t want to be in a situation where I have to worry about (falling), because that would probably just make it worse. You know, people who have stomach problems, the more you worry about it the worse it gets.” P06: “I’ve had a few (falls) but I think that’s because I’ve been stressing myself…”

Themes	Quotes
Fall even when calm	P02: “Although, ones that happen when I’m perfectly calm, I can’t explain these at all.” P06: “you could say reduce your stress and then it won’t happen, well it still can. You can be totally stress free and standing washing your dishes and (fall).” P04: “What seems to happen is that, if I have a really stressful period, it can be not too bad, but then when the stressful period finishes, that’s me.”
Dissociation	P02: “It’s like I’m there but I’m not there. It’s somebody talking not to me but to somebody else. And although I can see them and I can hear them, it’s as if I’m away somewhere else if you see what I mean. It’s like a sort of dreamlike situation I’m in.” P05: “It’s hard to separate (the falls) from the dissociation, because the dissociation comes first.” P01: “You know, there’s nothing going on in my head, nothing happening, when I actually fall. Even although I’m thinking this that and the other, when I actually fall, there’s nothing there. When I get up again, I start thinking again.”

2.4.1.3 Maintaining factors

Table 2.3 contains the themes and subthemes which fall under the maintaining factors category, along with supporting quotes.

Emotional impact

The emotional burden of drop attacks could be conceptualised in two subthemes: embarrassment and depression. All but one participant reported feeling embarrassed after a fall outside the house. Embarrassment was less, or absent, when falls happened within the home, and was mainly linked to falls being witnessed by other people. This theme linked to the ‘trying to cope’ subtheme of ‘avoidance’, where, due to embarrassment, participants reported going out less frequently, or trying to get out of a situation quickly after they had fallen. However, one participant reported no embarrassment when she fell, stating *“I’ve really never been embarrassed or anything like that about it.”* (P02). She instead preferred to be in places where there were more people around, which provided reassurance.

Five participants described current low mood, often linked to their reduced levels of functioning due to their drop attacks, for example, *“If I try to live a more normal life, and I do at times try, I start dropping again and it’s difficult.”* (P05). Drop attacks impacted on areas of independence, occupation and caring for children and grandchildren: *“After I had been in the (hospital) and stuff, my work wouldn’t take me back because they weren’t insured to have me in the building.”* (P04). Some had experienced times where they felt that their quality of life was so poor that they did not feel life was worth living.

Worry and sense-seeking

The first of the subthemes captured by this theme was 'Why is this happening?' Participants reported having lots of questions about why this was happening to them, compared to other people. They also talked about spending a lot of time trying to work out if there were any patterns or triggers to their falls, with the aim of trying to prevent the falls from happening. Four participants reported feelings of self-blame about the falls, thinking that it was their fault that they were happening, describing themselves as 'stupid' and 'silly'.

Four participants described worry as being a factor, both generally in daily life, and specifically around falling. Participants also described worrying about falls becoming worse, about the potential for bad injuries, and about the impact of previous injuries on their health in the future. This worry included 'catastrophic' thinking about their falls, contemplating worst case outcomes including death. Two participants reported that thinking about falling made it more likely that they would fall. In some instances, participants linked not thinking about falling to having fewer falls, as described in the quotes from participant one and participant three in Table 2.3. However, this took the form of having something else to attend to, rather than suppressing thoughts which participants did not find to be effective.

Trying to cope

Two subthemes were identified within this theme: 'just get on' and 'avoidance'. Six participants reported that the approach they took towards their drop attacks was to 'just get on'. For some this was a feeling of being resigned to having to cope with drop attacks being a part of their lives, and for others this was more a defiance that they were going to carry on regardless. However, despite trying to manage the impact of drop attacks on their lives, all participants still made adjustments to their lives to help them to live with the falls, either by avoiding certain situations or taking actions to prevent themselves from falling. Five participants reported avoiding certain situations, either due to fear of the response of others, or due to the fear of injury. This included social situations, particular locations such as supermarkets, and places within the home where risk was deemed to be higher, such as the shower. Two participants also stated that they would avoid standing or walking when they felt unsteady, despite this not often being a sensation that they would feel prior to a fall.

Pain and injury

All participants discussed sustaining injuries as a result of falls, with injuries to the face and knees most common. Although some participants did report significant injuries, such as broken bones, this was not a frequent result of a fall. One participant who could experience several falls a day, mentioned that she was unsure how she had not been more severely injured, considering she had fallen down the stairs multiple times, stating *"I've never broke a bone…I don't understand how I've never broke a bone"* (P04).

Participants reported that they were not usually injured after every fall, but that existing injuries could make falls more painful. When they were not injured, participants recovered

quickly, and were able to get up off the floor immediately after a fall. However, for two of the participants who experienced dissociation around a fall, they stated that they needed longer to recover, for example, *"if I'm on the ground, nobody could have hauled me up because I think that would have made me worse. So what I say to people is if I do drop, just leave me and I'll come round in my own time."* (P02).

Table 2.3: Themes and supporting quotes within the maintaining factors category

Themes	Subthemes	Quotes
Emotional impact	Embarrassment	P01 (diary): "I felt so embarrassed and it was as quick as I could get up and into my car and drove away. I then felt so stupid and glad that there was no-one around." P03: "The thing that I worry about is the embarrassment of falling. It's got to the stage now I don't care how bad it is after I've fallen, it's just the fact that I've fallen and people see me." P05: "Yeah when someone is helping me and then I'm just mortified and I'm embarrassed because I've fallen over." P07: "You do feel embarrassed. I don't think anybody saw me, that time. But you do feel embarrassed, even though your just by yourself."
	Depression	P04: "there was one stage when, not for a wee while, but one stage when I was like 'what's the point? What's the point in going on anymore?'" P07: "I just can't be bothered. Just feeling on a wee bit of a downer." P06: "(I) don't want to see anyone, don't want to do anything."
Worry and sense-seeking	'Why is this happening?'	P03: "Sometimes I keep thinking why does it happen to me? Why can't somebody else have this? Why is it me that's got it?" P06: "It's also a lot of 'why me'. Why did I get this? Was I a really cruel person in a previous life?" P01: "I can't put my finger on anything that would say why I'm falling." P02: "I'm trying to fathom out what I've been doing or what I've eaten or if I've overdone things, but I can't find a common denominator anywhere." P04: "But it's just like, it's mad. How can your body just fall down without any warning?" P05: "It had been years of me trying to deal with a situation that was a debilitating situation where I thought 'what is this? Is it my fault? Am I depressed? Am I doing this to

Themes	Subthemes	Quotes
		myself? You know, just beating myself up as to why this kept happening" P07: "I still call myself stupid for doing it because I don't know why I do it."
Worry and sense-seeking (cont.)	Worrying about falling	P04: "Standing at the top of a flight of stairs scares the living daylights out of me. I'll grab my husband and be like 'take my hand' and he says 'you'll be fine' but I says 'you dinnae know that'" P03: "There was a space but I kept looking at it and thinking, I'm going to fall and because I thought, I did fall." P06: "Sometimes when I do have them…I've been thinking about them, and I don't know if that can bring them on" P01: "If I've got something in my head to concentrate on, I might not have a fall, if that's possible." P03: "When I've got (grandson), and he's not in his pushchair and we're talking and I'm holding his hand, I'm fine because I think I'm concentrating so much on him that I'm not thinking (about falling)" P07: "I try to just say 'oh it doesn't worry me, it doesn't worry me' but I think it really does worry me. Because I've had a few bad ones and I don't want to go through all that again but I just don't know when it's going to happen."
Trying to cope	'Just get on'	P02: "I'm not going to stop going on holidays or doing anything because of it because I feel it would be taking control of me then. So you've just got to accept it and just carry on." P03: "I go on holiday, I travel a lot and I travel myself as well. I travel all over the world. But I still fall. But I don't want it to stop me going because, It's a case of if I don't go I'm actually giving in to this and I don't want this to happen."
	Avoidance	P03: "Even when I go on holiday, when I'm on the flight, because it's long flights, I won't even get up to go to the toilet, because I'm terrified I'm going to fall." P04: "Unless I'm going with somebody, I don't feel secure going somewhere different. And if it's somewhere I've never been before, I'm not going, definitely not." P07: "If I've nothing to do, well what's the point (in going out). And that's a wee bit piece of mind. Because I've only fallen twice in the house, it's always been outside." P06: "I think that is why I tend not to go out and do things. Just in case. Even though now I know what (the falls) are, I don't really want to have them in public."

Themes	Subthemes	Quotes
Pain and injury		P01: “It felt as though my back was broken. I got a really excruciating pain.” P02: “The worst I’ve had is cracked ribs when I fell on my wooden floor in the house. Apart from that, a bump on the head or something.” P03 (diary): “(I) fell against the toilet bowl hit my ribs, hip, shoulder and neck. Also broke my front teeth and couldn’t breathe for a bit. Had to go to hospital.” P04: “the amount of times I’ve been in A&E with concussion it’s just unbelievable.” P05: “I fell on the wrist that I had broken and my knees and I was in so much pain I could barely walk.” P07: “I’ve got black eyes and nose and forehead swollen and fractured my thumb and hurt my ribs and coccyx. I was in agony.” P06: “Once I did crack a rib or something, and I did the muscle in between because I fell forward onto… I think it was the table. And that’s the only injury I’ve actually had, other than bruising.”

2.4.2 Emergent theory

The proposed grounded theory model of the links between themes and categories is displayed in Figure 2.3 below. The links reported are based on those made by participants in interviews and diaries, however, experiences varied between participants, so not all factors will be relevant for all individuals or for all falls. The experiences that the participants reported were shaped by the research questions which were designed to elucidate potential predisposing and precipitating factors, along with thoughts, feelings and behaviour around drop attacks. The model therefore uses these as a framework to group themes, although it is acknowledged that this may introduce bias into the interpretation.

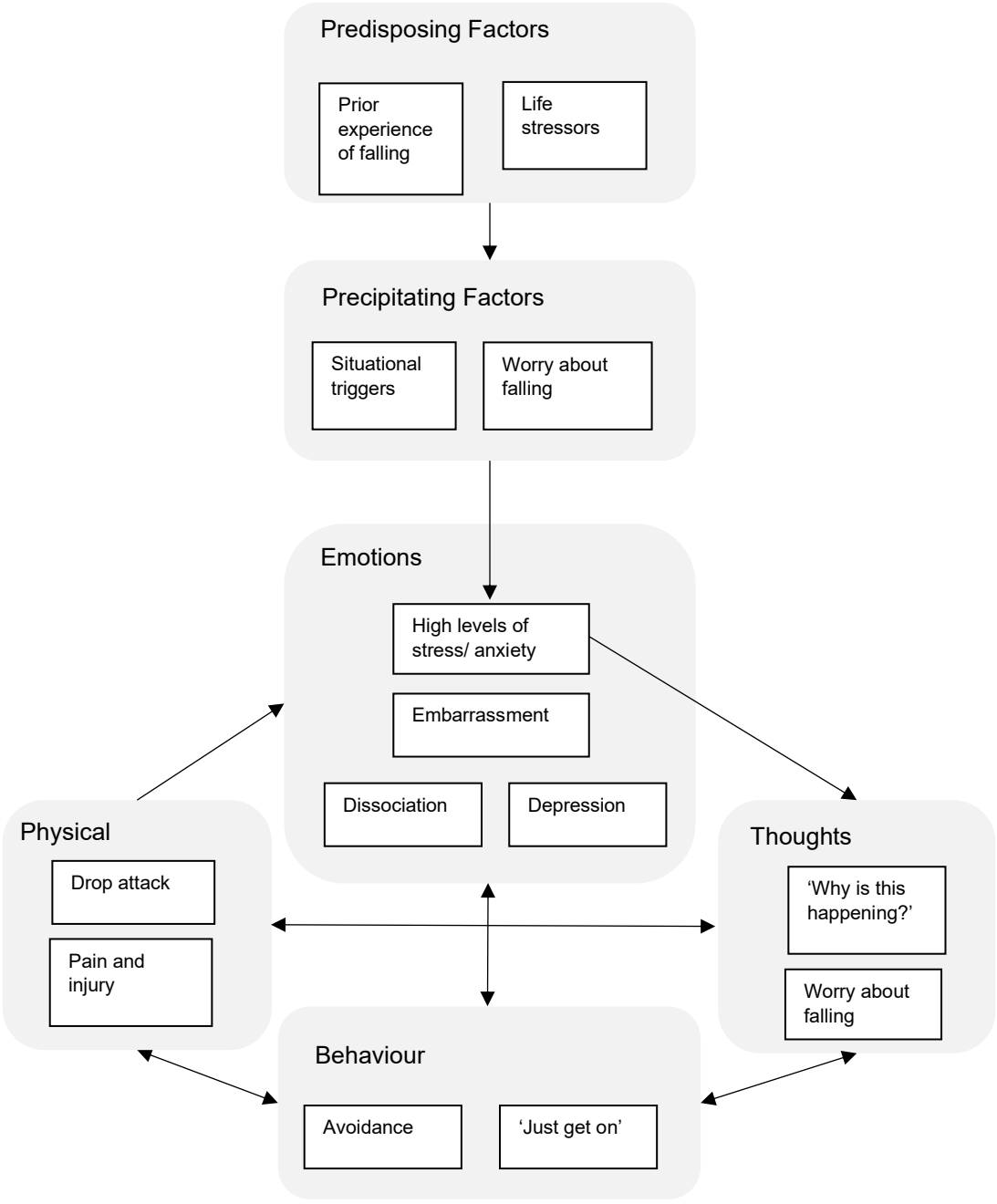

Figure 2.3: Grounded theory model of idiopathic drop attacks

The proposed theory is that individuals initially had an experience of a traumatic fall, which in most cases was due to factors such as illness or a mechanical fall. The increased stress around this, either due to the stress of the fall, or the stressful life situation that this happened within, led to the belief that falls are dangerous or to be feared. The impact of previous life stressors, particularly those around the period of onset, may have also influenced the development of drop attacks, by raising stress levels more generally, leading to an increase in physiological anxiety symptoms and dissociation.

We propose that there is a maintenance cycle for ongoing drop attacks, whereby external triggers for drop attacks, such as being in a place where a fall has happened before, and/or internal triggers such increased worry about falling, or general heightened anxiety, lead to higher levels of stress. Individuals have thoughts of 'why is this happening?' and increasingly worry about falling. Stress levels and physical arousal become elevated, increasing the risk of a drop attack occurring. Falls frequently result in injury, pain, embarrassment and/or dissociation. This in turn serves to reinforce worries about falling, and leads to rumination about factors that may be causing the falls.

Individuals with drop attacks try to cope with their falls by avoiding places where they feel they are likely to fall, or where the risk of injury from falling is higher. Some also avoid social situations due to the potential for embarrassment. However, the impact this has on their daily functioning contributes to low mood. Avoidance reinforces the belief that falls are dangerous and to be feared, and individuals experience increased stress when they cannot avoid 'risky' situations, further increasing the likelihood that they will have subsequent falls. In contrast, another approach to the falls is to 'just get on'. However, it appeared from our sample that this approach was only taken in certain aspects of life, such as continuing to travel abroad, with all participants making some adjustments to their lives due to drop attacks. For some, 'just get on' manifested as resignation to the changes they felt they had to make to reduce their falls.

2.5 Discussion

2.5.1 Integration of findings to existing literature

Overall, our model has significant overlap with a previously hypothesised understanding of drop attacks as a conditioned behavioural response [4]. In this previous model, a mechanical fall or syncope was highlighted as a precipitating factor, and internal and external triggers were outlined, such as high anxiety and specific situations. Maintaining factors were also described, such as avoidance. These factors are all present in the model presented here.

There is considerable overlap between the model outlined in this study, and the functional symptoms literature, and in particular as it relates to non-epileptic seizures (NES). The fear-avoidance model of NES, as reported in a recent paper outlining different theoretical understandings of NES [20] provides a CBT framework used to inform CBT interventions for NES [e.g. 21], and overlaps significantly with our proposed theory. This model outlines catastrophic thinking, fear of seizures, avoidance, and reduced functioning as important maintaining factors, all of which feature in our model. A more recent cognitive model of NES also highlights the role of internal and external cues as precipitating factors, as in our model [22].

Our model also fits with the cognitive behavioural model of health anxiety, which highlights the maintaining factors of safety behaviours, such as avoidance, and excessive worry [23]. A cognitive behavioural model of somatoform disorder [24] describes a theory where an innate tendency towards somatic distress symptoms, along with early adverse experiences predispose an individual to experience increased somatic symptoms. This is further increased through stressful life events, and attention to symptoms. A lack of understanding or explanation for the symptoms increases physical anxiety and attention to symptoms, which become paired through classical conditioning. Avoidance of triggers for symptoms feeds into an operant conditioning cycle of further sensitisation. This in turn becomes a vicious stress maintenance cycle of increased stress and physical symptoms, avoidance and selective attention.

This model of health anxiety has significant overlaps with our proposed model. However, in our model it is a traumatic first fall which predisposes the individual to falling rather than having other symptoms. Hoeritzauer et al. [4] proposed that, in individuals who are vulnerable to developing drop attacks through biological or biopsychosocial factors, an event such as a mechanical trip or fall, or an experience of syncope, can act as a triggering event. Worry about this then leads to a cognitive representation of drop attacks. This is in agreement with a recent perspective on functional symptoms was outlined by Van den Bergh and colleagues [25], based on a review of the functional symptom literature. The authors suggest that functional symptoms are a set of perceptions, based on the brain's interpretation of information from the body, which is guided by past experience. A cognitive representation of a symptom, which is preconscious in nature, is activated when certain triggers are present, such as physiological stress. This fits with our model, where an experience of one or more falls may have led to the expectation of falling within certain conditions. The idea of a functional symptom developing as a result of a similar physical experience has been highlighted previously [26], for example, with limb weakness often being preceded by an injury [27] or persistent postural-perceptual dizziness (PPPD) being preceded by vestibular disorders [28].

Overall, although there are factors within our model that would be present in those with recurrent mechanical falls, such as avoidance and embarrassment, there are also elements which highlight this as a potential form of FND. Namely, that stress and worry can be precursors to a fall, along with dissociation. Dissociation was a significant theme in our study and is also central to NES. Goldstein and Mellers [29] proposed a model of NES where seizures are described as a dissociative response to arousal, despite a lack of reported general anxiety, with avoidance as a key maintaining factor. This fits within our model and may also help to explain drop attacks which occur without a subjective feeling of stress.

Therefore, our theory appears to fit best with a cognitive behavioural model of functional symptoms, with particular overlap with models of NES. This model may be best understood as a 'meta-model', as are other cognitive behavioural models of functional symptoms [24],

whereby individuals' experiences differ but the model serves as a framework to make sense of their experiences, rather than showing prescriptive pathways.

2.5.2 Methodological limitations

A limitation was that participants were recruited from the clinic of a single neurologist with a special interest in functional neurological disorders, and who often explained drop attacks to patients within a conditioned behavioural framework. To assess possible bias from this, participants were asked what their neurologist's understanding of their drop attacks was. It transpired that participants had not taken on this understanding, and instead the predominant view was that nobody knows why the falls are happening. However, this potential bias was also held in mind throughout analysis, and particular care was taken to look for codes and themes which were contrary to this.

Due to the fact that data about drop attacks were collected from individuals who had been experiencing falls for a long time, more information was available to inform the maintenance of drop attacks rather than their onset. Future research with individuals who have had a more recent onset would help to develop this part of the model further. However, this is limited by the delay individuals usually experience between first onset and diagnosis, due to referral pathways and the need for diagnostic tests.

Our study included a small sample, although it was homogenous, and theoretical saturation was approached, with no new key themes identified in the final two interviews. Recruitment was carried out in a systematic way but it is possible that those who were willing to engage with a psychologist may not be representative of most of those who have drop attacks, given that those with functional neurological symptoms are often reluctant to engage in psychological treatment [30]. However, only one participant who was approached stated that she was not willing to take part due to previous negative experience of psychology services.

The demographics of our sample fit with those in previous studies of drop attacks [3, 4], but there are others who experience falls who were not captured in this sample, such as men and younger women. Although onset was at a younger age for many participants, their beliefs, contributing factors and life circumstances may have changed significantly and will not be captured in this data. A larger sample would be required to explore this further.

2.5.3 Clinical implications and future research

The themes and links highlighted in this research may help to aid formulation and treatment planning in clinical settings. If a cognitive-behavioural model fits with an individual's symptoms, it may be that a CBT approach could be beneficial for them. Given the significant overlap between NES and drop attacks, understanding and formulating drop attacks as a form of NES may be beneficial in terms of understanding and treating them. As the unpredictability of drop attacks appeared to increase worry about falling, giving patients a

clear formulation of their falls could help to begin to reduce their worry and anxiety about them, and encourage them to make behavioural changes to reduce their avoidance and improve their daily functioning. Participants also reported feeling very alone with their falls, and some mentioned that they would appreciate contact with others who had similar experiences.

Randomised controlled trials of CBT for NES have shown positive results, reducing seizure frequency and improving daily functioning [17, 31], and a large multicentre randomised controlled trial is currently ongoing [32]. These interventions provide psychoeducation about NES and use CBT techniques to help patients to identify triggers, address thoughts and illness beliefs, develop coping strategies for life stressors, engage in avoided activities, learn seizure control techniques and address low self-esteem, low mood, or anxiety. These techniques would all be relevant within our proposed theory of drop attacks.

It would be beneficial for future research to further explore the spontaneous resolution that some individuals experience and identify factors which potentially contribute to this. This could help to determine optimum treatment approaches. Future research should also focus on identifying individuals who were not included demographically in this sample, such as men and younger women, to see whether their experiences also fit with our model.

2.5.4 Conclusion

Idiopathic drop attacks may be best understood in the category of functional neurological symptoms. Our theory shows significant overlap with cognitive behavioural models of NES and other functional symptoms, and suggests that formulation and treatment within this model may be appropriate for those experiencing drop attacks.

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Appendices

Appendix A: Author guidelines for *Neuropsychology Review*

Neuropsychology Review

Editors-in-Chief: S.C. **Bowden**; D.W. **Loring**

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Review, Editorial, Commentary

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- Online document

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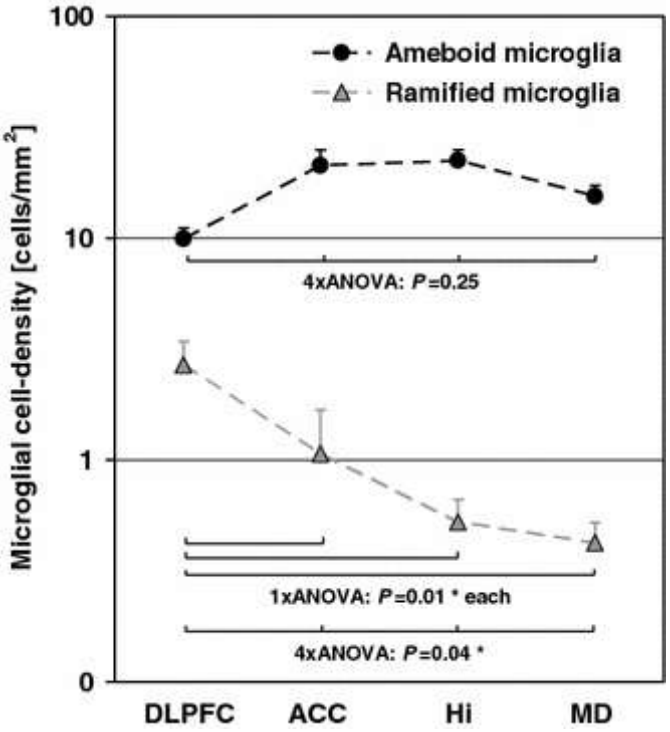

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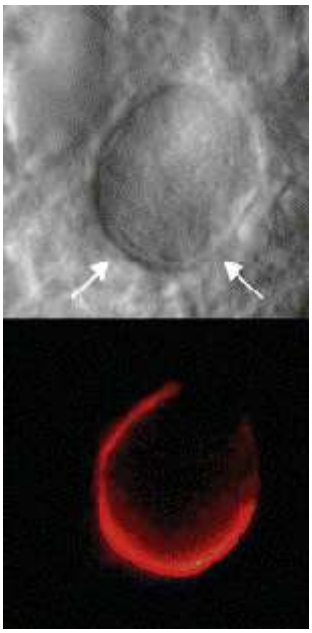

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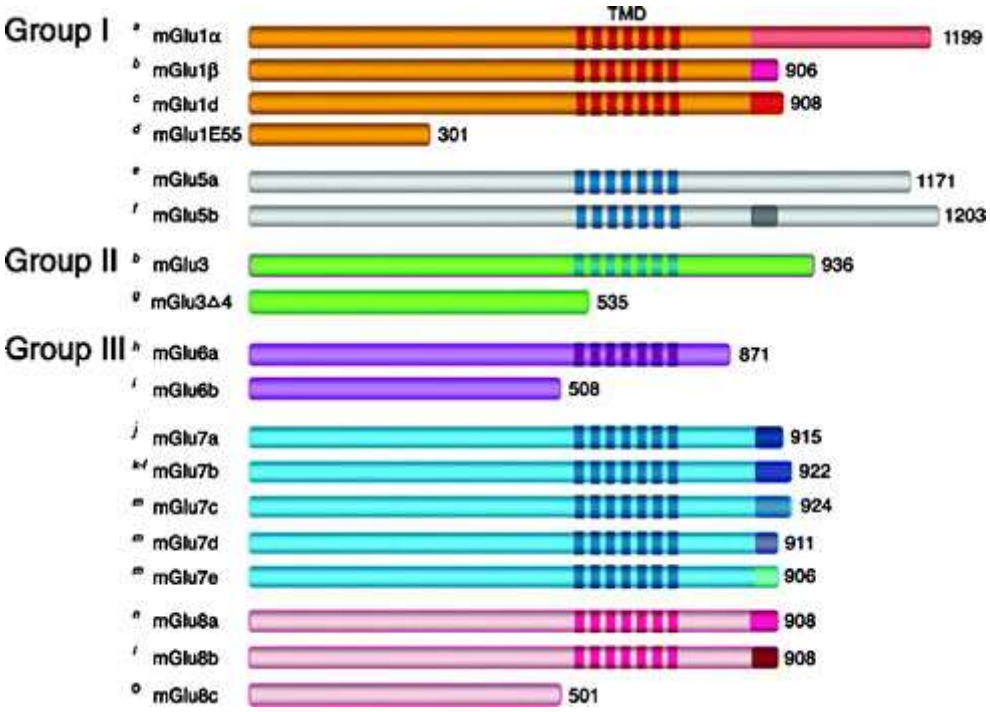

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Appendix B: PRISMA checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	8
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	9
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	10-12
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	12
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	12
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	13-14
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	13
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	13

Section/topic	#	Checklist item	Reported on page #
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	13-14
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	15-16
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	15-16
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	16
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	16
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	16
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	16
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	16
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	15
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	17-25
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	26-27
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	28-33
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	28-33
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	28

Section/topic	#	Checklist item	Reported on page #
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	28-33
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	33-34
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	34
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	35
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix C: Author guidelines for *Epilepsy & Behavior*

EPILEPSY & BEHAVIOR

AUTHOR INFORMATION PACK

TABLE OF CONTENTS

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DESCRIPTION

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Yorkshire & The Humber - South Yorkshire Research Ethics Committee

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Tel: 0207 104 8082

14 December 2017

Dr Emily Revell
Clinical Psychology, School of Health in Social Science
University of Edinburgh, Medical School (Doorway 6)
Teviot Place, Edinburgh
EH8 9AG

Dear Dr Revell

Study title:	**Developing a psychological understanding of idiopathic drop attacks**
REC reference:	**17/YH/0438**
Protocol number:	**CAHSS1710/03**
IRAS project ID:	**233998**

The Proportionate Review Sub-committee of the Yorkshire & The Humber - South Yorkshire Research Ethics Committee reviewed the above application on 14 December 2017.

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 hra.studyregistration@nhs.net outlining the reasons for your request. 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.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

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

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

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Summary of discussion at the meeting

Social or scientific value; scientific design and conduct of the study

Members requested further information on the process for participants to be involved in analysing the results as mentioned in the Participant Information Sheet and A62 of the IRAS form. This "option" was not detailed in A18 of the IRAS form and was not mentioned in the protocol, members requested that these were to be amended.

You replied that participants would be invited to review the themes that were identified within their interviews. This would take the form of the researcher presenting the themes and recording whether participants agreed with them or not. This would help the researcher to ensure that their analysis was valid. The text had been added to both A18 of the IRAS form and the protocol accordingly.

Members requested justification on why no PPI was completed for this study as stated in A14-1 of the IRAS form.

You replied as the experiences that this research was hoping to explore were very specific to a relatively small group of people, it was not appropriate to consult members of the public. As those who have experienced drop attacks were potential participants, consultation with those people may have introduced bias and made them unsuitable as participants. Therefore, in order to maintain as large a participant pool as possible, only consultation with experienced professionals in the field was undertaken in order to shape the study. The text has been added to A14-1.

The Sub Committee was satisfied with the responses given to the issues raised.

Recruitment arrangements and access to health information, and fair participant selection

Members requested clarification on whether all potential participants should "Opt in" as was the planned recruitment via letter. The Participant Covering Letter should be given by the introducing Neurologist along with the Participant Information Sheet in the OPD clinic so the potential participant could take all the information away to consider and then decide.

You replied that the covering letter would be given to all participants along with the Participant Information Sheet when meeting with the neurologist in the outpatient clinic.

The Sub Committee was satisfied with the response given to the issue raised.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

Members requested confirmation of the process to ensure ALL audio recording were permanently deleted and not recoverable from the audio recording device and for which this process should meet NHS data protection requirements as stated at A37 of the IRAS form.

You replied that all audio recordings would be permanently erased from the audio recording devices, using software designed for this purpose and NHS Lothian policy on audio recordings would be followed at all times. This had been added at A37 of the IRAS form.

Members stated that having made the case that research in this area was lacking and potentially of great significance, the research needed to be registered by placing information in the public domain that it was being undertaken from the beginning. An acceptable means of registering the research was by placing the accepted Research Summary (A6.1) with appropriate contact details for the research team on an appropriate publicly accessible website i.e. Trust, University, Charity website which was searchable by any of the common internet search engines. Therefore A50 of the IRAS form needed to be amended.

You replied that the research study would be uploaded to clinicaltrials.gov and would therefore be publicly accessible and amended A50 accordingly.

The Sub Committee was satisfied with the responses given to the issues raised.

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Employers liability]		01 August 2017
GP/consultant information sheets or letters [GP Letter V1]	1	13 November 2017
Interview schedules or topic guides for participants [Interview guide (for interviewer) V1]	1	13 November 2017
Interview schedules or topic guides for participants [Audio Diary Guide V1]	1	13 November 2017
IRAS Application Form [IRAS_Form_13122017]		13 December 2017
Letters of invitation to participant [Participant covering letter]	1	13 November 2017
Other [Clinical Trial Liability Confirmation]		27 July 2017
Other [Public Liability Confirmation]		26 July 2017
Other [Professional Indemnity Insurance]		04 August 2017
Participant consent form [Consent Form V1]	1	13 November 2017
Participant information sheet (PIS) [Participant Information Sheet V1]	1	13 November 2017
Referee's report or other scientific critique report [Supervisors' project appraisal]		03 August 2017
Research protocol or project proposal	Version 2	12 December 2017
Summary CV for Chief Investigator (CI) [Emily Revell CV]		13 November 2017
Summary CV for supervisor (student research) [Paul Morris CV]		23 November 2017

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

17/YH/0438	**Please quote this number on all correspondence**

Yours sincerely

pp

Dr Ian Woollands
Chair

Email: nrescommittee.yorkandhumber-southyorks@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

"After ethical review – guidance for researchers"

Copy to: *Ms Charlotte Smith, University of Edinburgh*
Miss Melissa Taylor, NHS Lothian

Yorkshire & The Humber - South Yorkshire Research Ethics Committee

Attendance at PRS Sub-Committee of the REC meeting on 14 December 2017 via correspondence.

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Ahmed H Abdelhafiz	Consultant Physician, Elderly Medicine	Yes	
Mr Martin Edmunds	Editor	Yes	
Dr Ian Woollands (Chair)	Retired Clinical Director, Occupational Health	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Kerry Dunbar	REC Manager

University Hospitals Division

NHS Lothian

Queen's Medical Research Institute
47 Little France Crescent, Edinburgh, EH16 4TJ

DY/LM/approval

22 December 2017

Dr David Gillespie
NHS Lothian
Department of Clinical Psychology
Astley Ainslie Hospital
Edinburgh
EH9 2HL

Research & Development
Room E1.16
Tel: 0131 242 3330

Email:
accord@nhslothian.scot.nhs.uk

Director: Professor Tim Walsh

Dear Dr Gillespie

Lothian R&D Project No: 2017/0335 **REC No:** 17/YH/0438

Title of Research: Developing a psychological understanding of idiopathic drop attacks

Participant Information Sheet:
Version 1 dated 13 November 2017

Consent Form (Main Cohort):
Version 1 dated 13 November 2017

Protocol: Version 2.0 dated 12 December 2017

I am pleased to inform you this letter provides Site Specific approval for NHS Lothian for the above study and you may proceed with your research, subject to the conditions below.

Please note that the NHS Lothian R&D Office must be informed of any changes to the study such as amendments to the protocol, funding, recruitment, personnel or resource input required of NHS Lothian.

Substantial amendments to the protocol will require approval from the ethics committee which approved your study and the MHRA where applicable.

Please keep this office informed of the following study information, **which is a condition of NHS Lothian R&D Management Approval**:

1. Date you are ready to begin recruitment, date of the recruitment of the first participant and the monthly recruitment figures thereafter.
2. Date the final participant is recruited and the final recruitment figures.
3. Date your study / trial is completed within NHS Lothian.

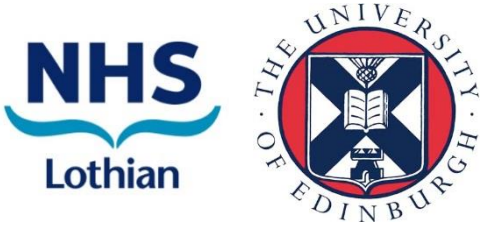
I wish you every success with your study.

Yours sincerely

Dr Douglas Young
Principal R&D Manager

CC: Mr Michael Pearson, General Manager, Surgical Services Directorate, RIE
Dr Emily Revell, Chief Investigator, NHS Lothian

Appendix E: Study protocol



Developing a psychological understanding of idiopathic drop attacks

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Study Protocol

Version 3

Emily Revell

15th January 2018

1 Introduction

Idiopathic drop attacks (IDAs) have been defined as falls to the floor without warning, where there is no identified organic cause, despite diagnostic testing. They are not caused by malfunction of the lower limbs, changes in body or head posture, or vertigo. There is also no loss of consciousness and recovery is rapid. Despite this fast recovery, people can experience significant injuries and fear about further falls, impacting on their everyday functioning.

This phenomenon was highlighted by Stevens and Matthews (1973) who recruited 33 patients from a neurology clinic and seven from a gynaecological clinic. They also approached 100 men who were admitted for routine surgery but found that none of these had experienced drop attacks. Therefore their sample was entirely female, with onset occurring on average at age 44. Although the age-range of onset spanned from 19 to 69, in two thirds of the sample onset was between the ages of 40 and 59.

The authors ruled out obesity, vascular disease, epilepsy, vestibular disease, limb weakness and hypothyroidism as contributing to IDAs. They investigated hormonal changes, given that the age of onset coincided with when menopause could be likely to start and due to the fact that 60% of the younger patients had onset of IDAs during pregnancy. Despite this, the authors found no clear links between hormonal changes and IDAs, although 45% did experience onset either during pregnancy or within 3 years either side of the start of the menopause.

The frequency of IDAs varied greatly between individuals but ranged from two to more than 12 falls per year, usually while walking. This was more likely to happen when out of the house but over half of the sample also reported falling at home. These falls would lead to injury to the knees and often also to the hands, chest and face. 18% reported having fractured or broken bones as a result of an IDA. Given the age of onset, the increased likelihood of osteoporosis would also increase the risk of more severe injury as a result of IDAs. The authors also reported that many women would become afraid to go out due to both the risk of injury and embarrassment.

Although it is undocumented, the prevalence of IDAs could be relatively high. As part of their recruitment process, the Stevens and Matthews (1973) asked 200 consecutive patients at a gynaecology clinic whether they had experienced falls and

found that 3.5% met the criteria for IDA. This suggests that this phenomenon could account for a significant number of falls in women in the general population.

There are similarities between IDAs and psychogenic non-epileptic seizures (PNES). However, IDAs are not included widely included in studies of PNES, which tend to focus on 'convulsive' seizures. Hubsch et al. (2011) analysed clinical signs in 145 PNES and identified different subtypes of seizure, none of which covered IDAs. However, Galimberti et al (2003) and Devinsky et al (1996) included patients with IDA within a PNES sample, accounting for around 10% of each sample. There has been no published research investigating this group in isolation since Stevens and Matthew's (1973) study other than a small number of case reports (Butsch & Schneemann, 2014), one of which identified a woman's IDAs as occurring following recollection of traumatic experiences, suggesting a psychological mechanism (Wilner at el., 2010).

A paper which is currently being prepared for submission by Dr Hoeritzauer, Dr Carson & Dr Stone at the Department of Clinical Neurosciences, Edinburgh, identified 83 patients who had attended a neurology clinic over nine years who described experiencing these attacks. This led the authors to develop a hypothesis that IDAs are a conditioned behavioural response to negative external (environmental or situational) or internal (anxiety symptoms or dissociation) stimuli. This association is maintained through fear of collapse and/or through the fall providing relief from the negative stimuli. This type of mechanism has been highlighted previously in functional neurological disorders, where limbic regions were found to have a greater influence on motor preparatory regions when in a state of arousal (Voonet al., 2011).

As the underlying mechanism of IDAs is unknown, there is currently no treatment available. However, Hoeritzauer and colleagues report that a small number of patients saw their IDAs resolve following an explanation of the episodes as conditioned responses and the use of distraction techniques. A psychological understanding of the problem could help to identify a potential psychological intervention. Such interventions have been found to be effective for PNES, particularly cognitive behavioural therapy (Goldstein et al., 2010). This type of intervention could focus on helping individuals to manage their condition and improve the ways they cope with the anxiety surrounding future falls, rather than necessarily seek to resolve the IDAs.

This research aims to explore a psychological understanding of drop attacks. This will be investigated through the collection of qualitative data from interviews and recorded diaries from individuals experiencing IDAs. The data will be analysed using a grounded theory approach in order to better understand the onset of drop attacks, the impact of life stressors as well as thoughts, feelings and behaviour both directly before and after a IDA.

2 Aims

The main aim of this research is to develop a psychological understanding of idiopathic drop attacks. The primary research question is as follows:

- What are the predisposing and precipitating factors related to the onset of IDAs?

Secondary research questions are:

- What are individuals' thoughts, emotions and behaviour immediately prior to an IDA?
- What are individuals' thoughts, emotions and behaviour immediately following an IDA?

3 Methods

3.1 Participants

Participants will be ten individuals who are experiencing ongoing IDAs. Inclusion criteria are 1) Aged 18+, 2) IDAs occurring 6+ times per year, 3) Able to provide informed consent. Exclusion criteria are 1) Diagnosis which would provide an alternative explanation for drop attacks.

3.2 Design

In this exploratory qualitative study, neurology outpatients with ongoing IDAs will undergo psychological assessment and complete written diaries for eight weeks. Throughout the study, participants will receive treatment as usual from a neurologist.

3.3 Procedure

Participants will be recruited from a neurology outpatient clinic at the Department of Clinical Neurosciences in Edinburgh where they will be approached by their

consultant who will give them a participant information sheet. If they are interested in taking part, a meeting will be set up with the researcher to discuss the study further and obtain written informed consent.

Participants will then meet with the researcher to complete an initial psychological interview which will be audio recorded. This interview will follow a standard initial psychological interview structure and will aim to gain information about the person's experiences of IDAs, along with relevant personal and social history. The interview schedule is included in appendix 1.

Following this initial interview, participants will be asked to record written accounts of any IDA, detailing their thoughts, physical arousal, feelings and behaviour, as close to the event as possible. They will be encouraged to record detailed accounts, outlining the period before, during and after the episode, in order to identify any potential triggers. They will be shown an example of a completed diary in order to help them to understand what they need to do. Participants will be asked to record such events over a period of eight weeks during which the researcher will contact them fortnightly to discuss any difficulties or concerns. If participants do not experience any drop attacks during this period, they will be asked if they want to continue recording diaries for an additional two to four weeks.

Following completion of this period, participants will meet again with the researcher to return the diaries and discuss any patterns noticed in the interview and diaries. The researcher will also answer any further questions that the participant has about the study.

3.4 Measures

3.4.1 Semi-structured assessment interview

This audio-recorded 60-minute interview will follow the format of an initial psychological assessment and will allow discussion of presenting problems and relevant personal and social history. This will allow potential predisposing and precipitating factors to be identified. Participants' experiences of IDAs will also be discussed, focussing on thoughts, feelings and behaviour before and after the episodes. The participants will also be asked about the impact that these have had on their everyday functioning.

3.4.2 IDA record

Participants will be asked to write an account of any IDAs. They will be shown an example diary and will also be given a prompt sheet, asking them to recall any triggers, feelings, physical arousal, thoughts and behaviour both directly before and after the episode. This diary will be completed by participants as close to the episode as possible.

4 Sample size

In order to address all three of the research questions, a qualitative approach will be used. An overall sample size of ten should be sufficient to allow themes to be identified. A purposive sampling method will be used to recruit younger participants as well as those who are in the average age range for onset. This will allow any differences between these two groups to be explored further. As the inclusion criteria specifies 6+ IDAs per year, this will ensure a fairly homogenous sample in terms of frequency of IDAs.

There is a sample of approximately 40 patients who had ongoing drop attacks in July 2016 which can be recruited from. One to two new referrals per month are currently being made to Dr Jon Stone, and these patients can also be approached. This is a relatively small pool and there can be some unwillingness to engage with a psychological approach within the functional neurological population. However, as this study is aiming to help better understand participants' experiences, rather than investigating psychological treatment, this may enhance engagement. Attrition is also a factor but, as the primary research question relies on information from the initial interview, the risk of this is reduced. Therefore, recruiting a purposive sample of ten participants should be achievable.

5 Analysis

The content of the psychological interviews and diaries will be analysed using a grounded theory approach in order to meet all of the study objectives. Using both initial interviews and recorded accounts will allow information to be obtained from different viewpoints, enriching the data. This data will be coded by initially naming each segment of data and then synthesising the most common codes to identify themes. From these, theories can be developed regarding predisposing and precipitating factors. Themes regarding thoughts, emotions and behaviour can also be explored.

Participants will be invited to review the themes that were identified within their interviews. This will take the form of the researcher presenting the themes and recording whether participants agree with them or not. This will help the researcher to ensure that the analysis is valid.

6 Timetable

- Recruitment start – January 2018
- Data collection start – January 2018
- Data collection finish – December 2018
- Analysis – January 2019
- Article ready for submission – April 2019

7 References

Butsch, R., & Schneemann, M. (2014). Two women with recurrent falls: La maladie des genoux bleus alias cryptogenic drop attacks. *BMJ Case Reports*, *2014*, DOI: 10.1136/bcr2013200855.

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Appendix F: Interview schedule

Version 1 (28/09/2017)

INTERVIEW GUIDE

Developing a psychological understanding of unexplained drop attacks

Name of Researcher: Emily Revell (Trainee Clinical Psychologist)

This guide follows a standard initial psychological assessment structure. It includes general areas of discussion as well as examples of questions that will be asked in each area. The interview will cover these general areas but additional and alternative areas may be explored and different questions asked in order to gain rich data.

Throughout the guide, suggested statements by the interviewer are in italics.

Introduction

Thank you for agreeing to be interviewed as part of this research project. As you are aware, this interview is being recorded.

Anything you tell me will be kept confidential. The only time I may need to break this confidentiality is if I believe there is a risk of harm to either yourself or others. If this comes up, we can discuss it and make a plan together.

I am going to ask you some questions about your drop attacks and other aspects of your life to try to help me understand what it is like for you. If at any point you feel that you do not want to continue, or if you don't want to answer any questions, please let me know.

Do you have any questions?

Drop attacks

- Description of attacks
    - *Can you tell me a bit about your drop attacks?*

- Why was help sought?
    - *Why and when did you start seeing Dr Stone?*

- Recent examples of drop attacks (with as much detail as possible)
    - *Can you tell me about the last drop attack you had?*

- Frequency, duration, severity, distress
    - *How often do you have them?*
    - *How long do they last?*
    - *What do they feel like?* (0-100 rating for intensity of emotion)
    - *How do you feel before/after?* (0-100 rating for intensity of emotion)
    - *Do you have injuries as a result?*

- How the problem impacts on functioning/interferes with daily life
    - *Do the drop attacks make it hard to do other things?*
    - *If you didn't have drop attacks, what would your life look like?*
    - *On a scale of 1-100, how much does it interfere with your life?*

- Situational triggers
    - *Do the attacks happen in particular places/times/with certain people?*

- Modulators
    - *Is there anything that makes them not as bad/frequent?*
    - *Is there anything that makes them worse?*
    -
- Avoidance
    - *Is there anything that you don't do anymore because of the drop attacks?*
    - *Have they changed the way you do things?*

- Coping strategies – adaptive or maladaptive
    - *What helps you to cope?*
    - *On a scale of 1-100, how well do you feel you are coping with them?*

- Beliefs about the problem
    - *Why do you think the drop attacks happen?*
    - *What do your close family members/friends think about the drop attacks?*
    - *What is Dr Stone's explanation? Does this sound right to you?*
    - *How much control do you think you have over the drop attacks? (0-100 rating)*
    - *How much control do you think Dr Stone / your medical team has over the drop attacks?* (0-100 rating)

History and Onset of Problems

- *When did you first start having drop attacks?*
- *Can you tell me about the first time it happened?*

- Precipitants
    - *What was going on when they first started?*
    - *Had there been any changes in your life?*
    - *Was anything stressful happening in your life at the time?*
    - *Why do you think they started? Why then?*

- Time course
    - *Have the drop attacks changed over time?*
    - *Have they got better/worse?*

- Previous episodes
    - *Have you had drop attacks or something similar another time in your life?*
    - *Was there anything that helped then?*
    - *Did you see anyone about them then?*

- Family history
    - *Is there a family history of drop attacks/related disorders/medical issues/mental health issues?*

Mood/mental state

- General enquiries about distress, concerns and well-being– stability/changes

- Co-morbidity
    - *How do you generally feel in yourself?*
    - *Do you ever feel down/low mood?*
    - *Do you ever feel anxious/worried/stressed?*
    - *Has this changed recently or has it been stable?*
    - *Have you felt down or anxious at some point in the past?*

- Other difficulties
    - *How is your sleep?*
    - *How is your appetite?*
    - *Do you find it hard to concentrate?*

- Self-harm/suicidality – risk assessment

- Current functioning
    - *What does your day look like at the moment?*
    - *Has this changed recently?*

Optional/Additional questions

Developmental/Personal History

- Early memories – including experience of trauma/abuse/neglect/losses
    - *What was it like for you growing up?*

- Relationships with parents, siblings, significant others
    - *Who was around when you were growing up?*
    - *How did you get on with….?*

- Primary and Secondary School
    - *Can you tell me a bit about school?*
    - *How did you find the academic work?*
    - *Did you have friends?*

- Educational/occupational history - timeline
    - *When did you leave school?*
    - *What did you do afterwards?*

- Experiences of social exclusion, discrimination, stigma etc
    - *Have you ever not been able to do something you wanted to do?*
    - *Do you feel you've been discriminated against?*

- Medical history
    - *Have you ever had any major illnesses or health problems?*
    - *Have you ever spent any time in hospital?*

- *Is there anything else I should know about?*

Psychosocial Factors

- Interpersonal relationships
    - *Who is in your life at the moment?*
    - *Do you have a partner/children?*
    - *Tell me about your friends*
    - *Who do you talk to if you have a problem/need support?*

- Occupation
    - *Do you work? What do you do?*
    - *Do you enjoy it?*
    - *What did you do in the past?*

- Accommodation/financial worries
    - *Do you worry about money?*
    - *Are you happy with where you live and who you live with?*

- Hobbies/interests
    - *What hobbies/interests do you have?*
    - *Is there anything you used to do that you don't do anymore?*
    - *Is there anything you'd like to do?*

- Alcohol/Cigarettes/Drugs

- Other concerns
    - *Is there anything else in your life at the moment that worries you or that you'd like to be different?*

Thank you very much for talking to me today. Is there anything else that we haven't talked about that you feel is relevant? Do you have any questions you'd like to ask me?

Appendix G: Diary prompt sheet

Version 2 (15/01/2018)

DIARY GUIDE

Investigating drop attacks

Please use these guidelines when making your written diaries. However, there is no right or wrong information to record and this is a guide only.

Try to record your diary as soon after the drop attack as you can. Try to write after every drop attack you have.

Try to give as detailed an account of what happened before the attack, during the attack and afterwards. You can use the following questions to help you to remember different aspects of the experience:

Before

- What had you been doing in the hours before the drop attack?
- What had you been doing immediately beforehand?
- Who were you with? Where were you? What was the environment like?
- How were you feeling beforehand? Happy, sad, stressed, worried, excited etc.
- How did your body feel? Any aches/pains? Shaking or unsteadiness?
- What was going through your head? What was on your mind?

During

- Try to describe the drop attack.
- What do you remember about it?
- How did your body feel?
- How did it feel? Were you frightened/embarrassed/calm?
- Was there anything going through your head?
- Were other people around? How did they react?

After

- What happened afterwards?
- Did other people help you? What was that like?
- How did you feel (e.g. happy, sad, calm, upset, scared, relieved, worried etc.)
- What were you thinking about what had just happened?
- What did you do next? Did you change your plans?
- Did you need to take time to recover?

If you have any questions about writing your diary, please contact me on Tel: xxxxxxxxxxx

Appendix H: Excerpt of transcript and initial codes

P02 interview transcript

Do you want to start by telling me a little bit about your drop attacks?

Em, they first started, no I'm (age) this month so they must have started about 30 years ago. It was shortly after I was diagnosed with Meniere's disease which was very bad then. I was always taking really bad vertigo attacks, sickness and diarrhoea, all that. Back then the drop attacks weren't regular at all, I would maybe have one or two a year. Hardly any more and I could go longer than that without any. So I just assumed it was part of Meniere's disease. So it's really in the last, I would say, I've noticed in the last roughly 10 years, when the vertigo attacks have really not been such a bother to me, the drop attacks became far more common. Again I was just putting it down to being related to Meniere's disease, but when I started seeing Dr Stone, it must have been the end of last year, it's hard to remember. He reckoned that, because my Meniere's was easing, the drop attacks had somehow taken over from that. So with the drop attacks, they can happen anytime. I suffer from dizziness and giddiness, light-headedness quite a lot. Certainly when I was working, up until I retired in March, the drop attacks were much worse. But they didn't necessarily happen after, or when I was feeling giddy or dizzy. I could be feeling absolutely normal and literally just fall. I've been trying to work out is it anything I've eaten, anything I've drunk. I can't see any pattern there at all.

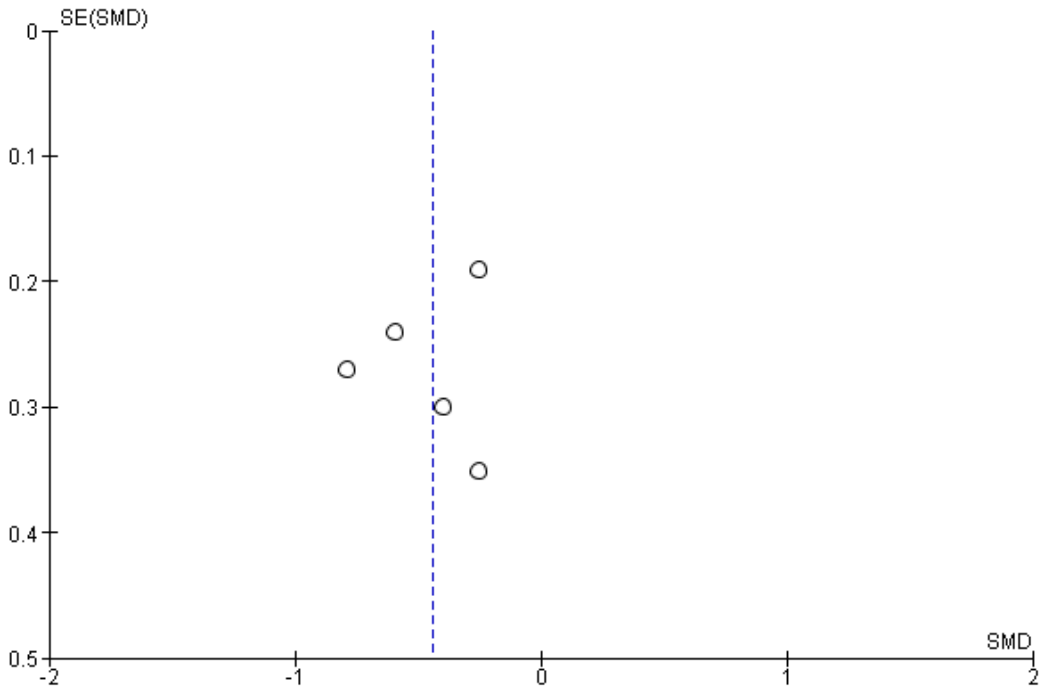
One pattern I have noticed is because I suffer with anxiety with my Meniere's disease, and I'm on paroxetine for that, if I get very anxious or stressed, that's very much when they can come more frequency. I've actually brought some notes with me for you. I started taking notes months ago but since March they've gone down a lot and I've been very absent minded about taking the notes recently. Very often if I'm travelling, I'll have a drop attack. I very often go on holiday on my own, because I'm determined not to let the condition really control my lifestyle. And I love going on holiday. And there's always somebody around when you collapse in a heap. But I noticed... There was one time, I think about a couple of years ago, my plane to (destination 1) was delayed by three days for bad ongoing weather and I had a collapse in the airport then. I could feel myself getting a little bit anxious and uptight. Because with my deafness as well I wasn't quite sure what was going on. And as I was going to collect my case back from the airport, I had a collapse in the general luggage place. Another time a few years previously, I boarded a plane to (destination 2) and I hadn't booked any seat so everybody was dashing on and it was hot and everybody, tempers were getting frayed and whatever. And with the heat and with all that was going on around me, again I had a drop attack then.

Last year, when I was in (destination 3) with an ex of mine I had a drop attack on the morning of the day I was going to get a plane home in the evening and I was just walking along a path near the beach on my own. He was a very Jekyll and Hyde character and for 7 days out of the 14 he was shouting at me on the holiday for no reason at all and that morning he had started that so I just left the apartment to go away on my own but I was still stressed. All of a sudden I just collapsed. I don't normally black out for long. It's hard to tell if I'm actually totally blacking out. But what I do find when I'm on the ground is that I'm very often aware of people being around me but I can't respond. I can't answer then. Very often I get a lot of spit and I've got to spit quite a bit while I'm still on the ground. I'm lucky in that... Well that particular time last year I was taken by ambulance to the hospital in (destination 3) and they wanted to keep me in but I knew myself there was no need to keep me in. Because even by the time I arrived at the hospital I was absolutely ok.

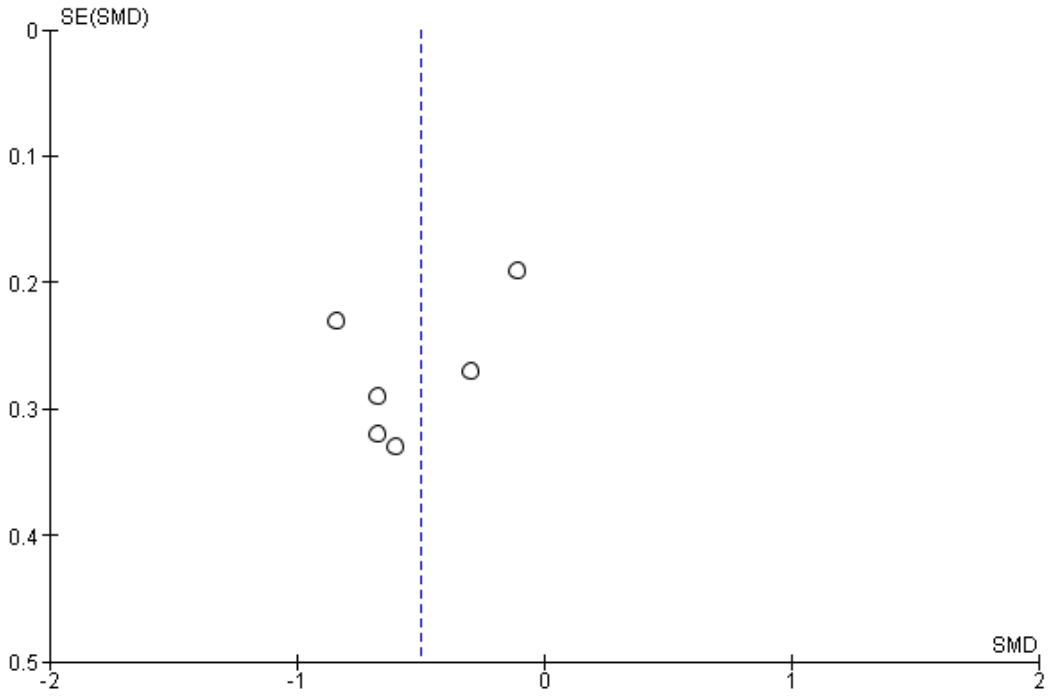

Not sure if lose consciousness
No fall if feel that going to collapse
No dizziness or lightheadedness (before fall)
Sudden drop
No warning before fall
No warning
Other life stressors
Trying to understand contributing factors
Keeping fall diary
No major injuries as a result of fall
Injury from fall
Trying to retain independence
Health condition
Drop attacks taken over from health condition
Falls happen any time
Fall on bottom
Fall forwards
Excess spit during fall
Embarrassment
Dizziness and lightheadedness
Fall but aware of people and can'
Started a long time ago
Irregular drop attacks
Drop attacks becoming more frequent
Break between falls
Health condition causing fall (belief)
Have anxiety
Recover quickly
Didn't take time to recover, leading to another fall
Ambulance after drop
Coding Density


Important to have people around if you fall
Stress reduced recently
Falls when sitting (dissociative)
Falling while walking
Falling while travelling
Falling while standing or walking
Falling outside
Onset after stressful life event
Onset
Stress makes falls more frequent
Stress and anxiety contributing factors
Falls linked to stressful situations
Fall prior to situation in which previously dropped
Environmental triggers
Drop attacks worse when working (stressor)
(Trigger) Being shouted at as trigger

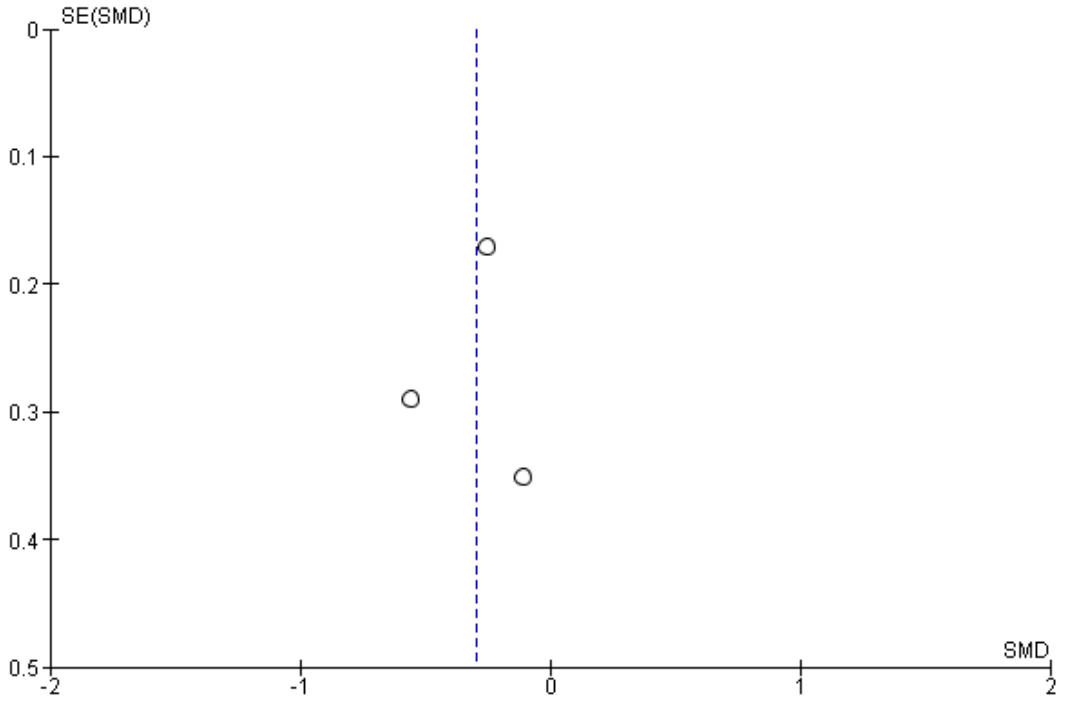
Appendix I: Funnel plots



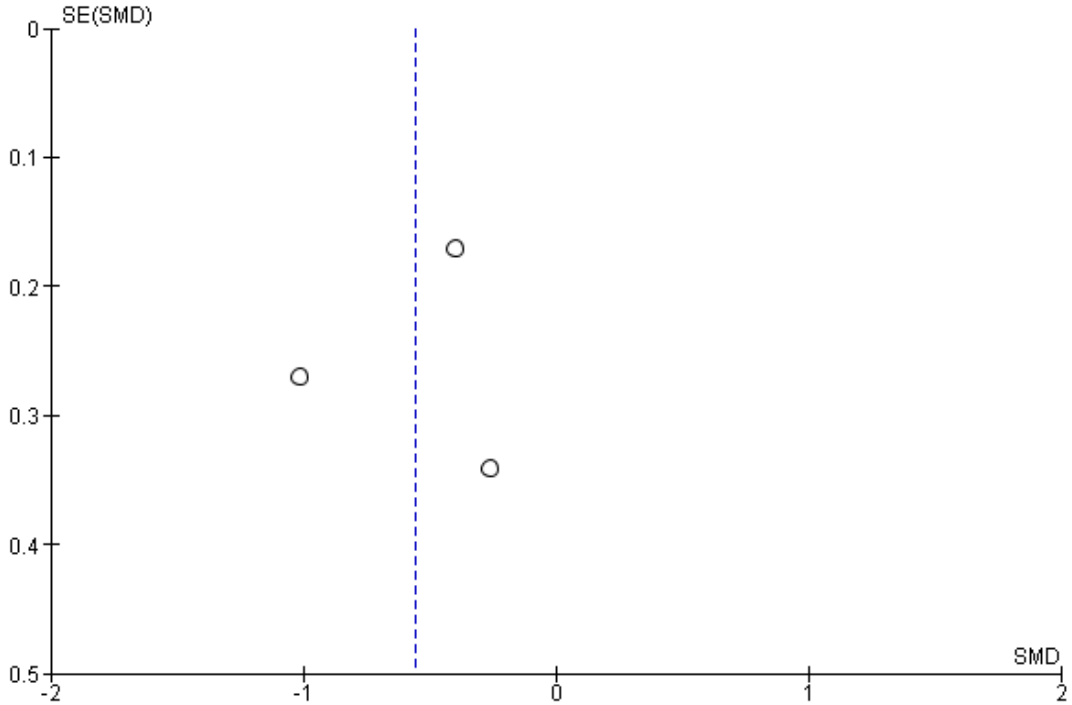
Funnel plot of studies in the between-groups daily functioning comparison



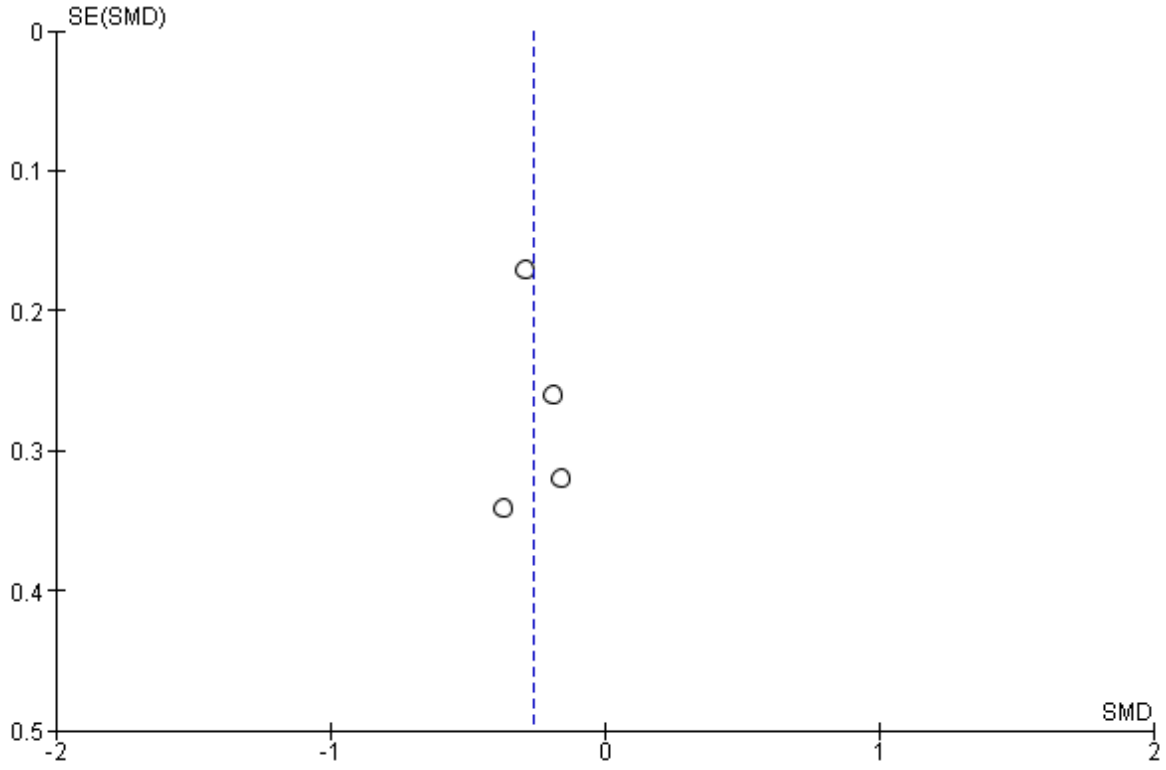
Funnel plot of studies in the repeated measures daily functioning comparison



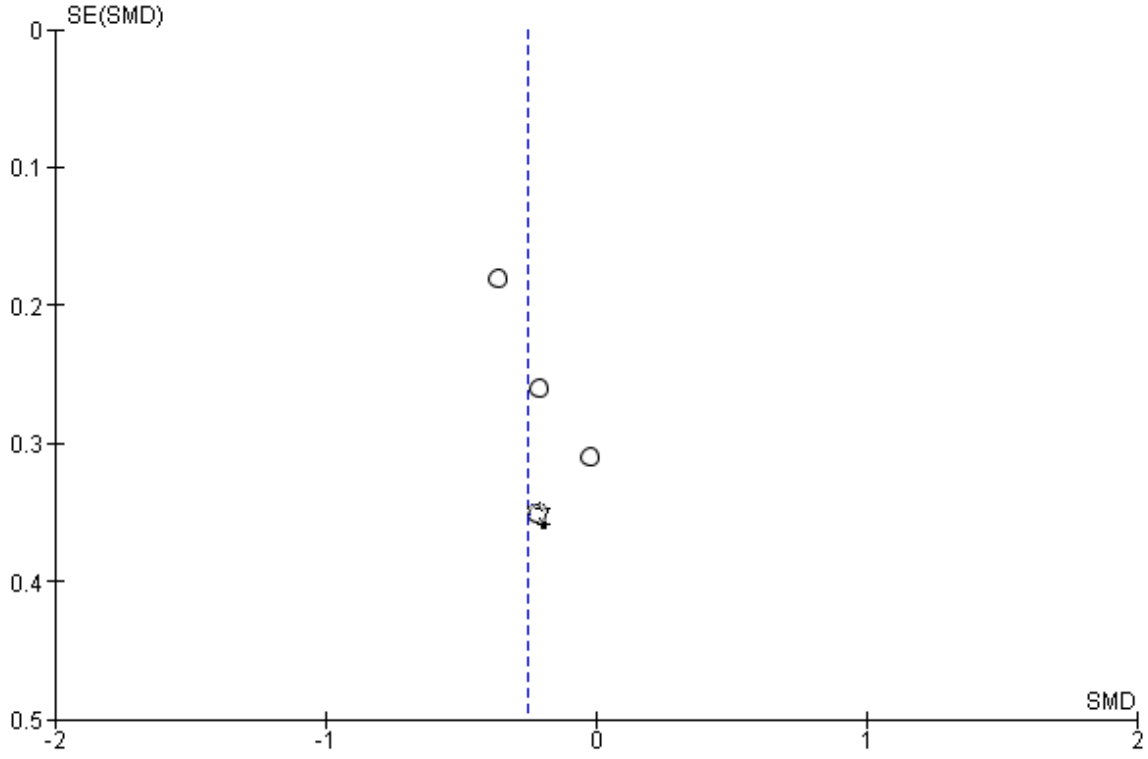
Funnel plot of studies in the between-groups functional symptoms comparison



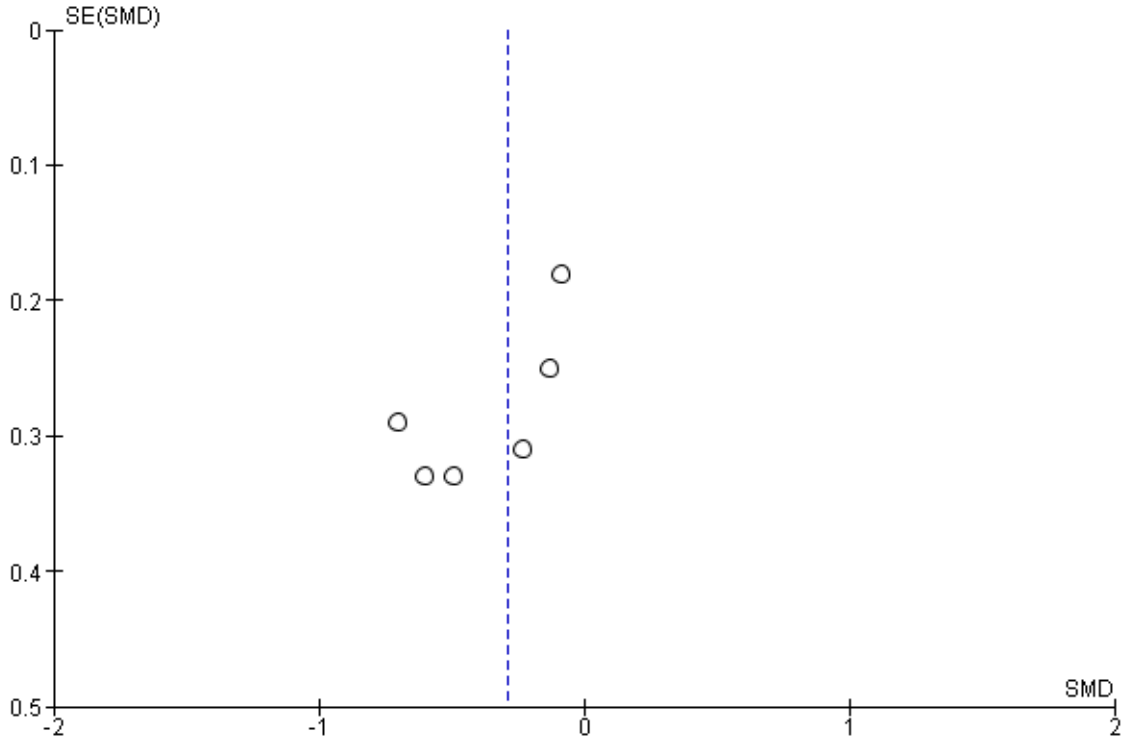
Funnel plot of studies in the repeated measures functional symptoms comparison



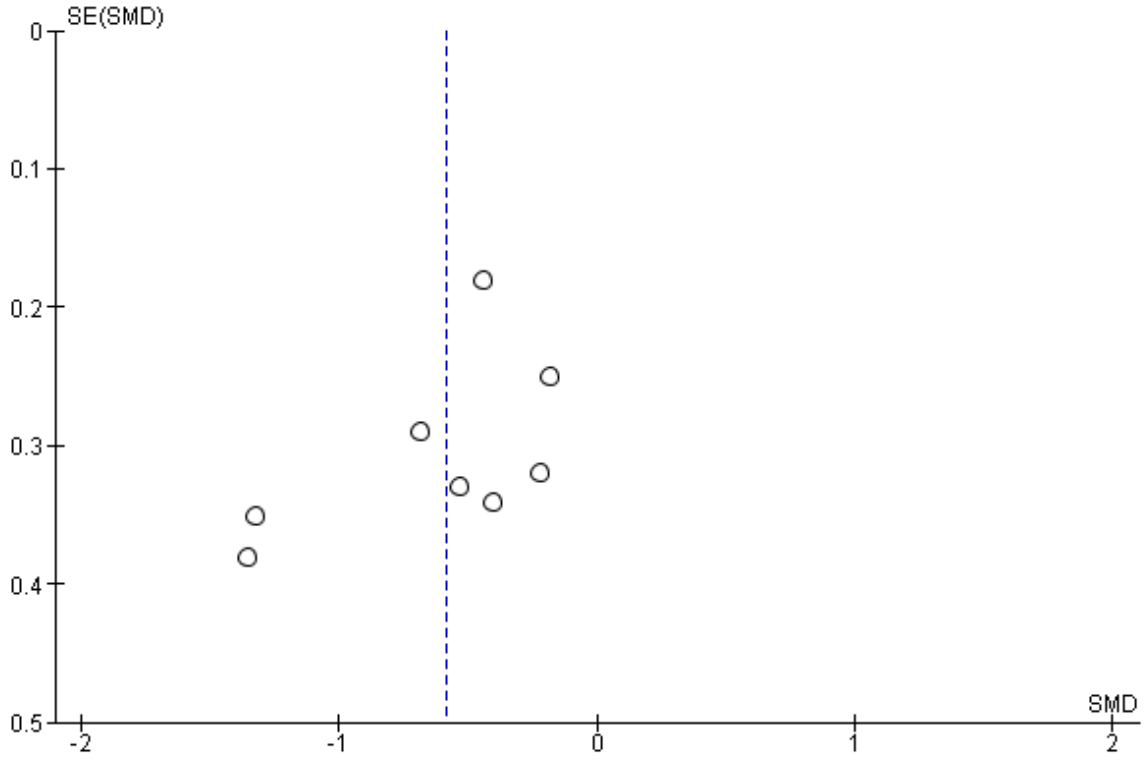
Funnel plot of studies in the between-groups depression symptoms comparison



Funnel plot of studies in the between-groups anxiety symptoms comparison



Funnel plot of studies in the repeated measures depression symptoms comparison



Funnel plot of studies in the repeated measures anxiety symptoms comparison