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Moderators of cognitive behavioural therapy treatment effects and predictors of outcome in the CODES randomised controlled trial for adults with dissociative seizures

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ABSTRACT

Objective: We explored moderators of cognitive behavioural therapy (CBT) treatment effects and predictors of outcome at 12-month follow-up in the CODES Trial (N = 368) comparing CBT plus standardised medical care (SMC) vs SMC-alone for dissociative seizures (DS).

Methods: We undertook moderator analyses of baseline characteristics to determine who had benefited from being offered CBT 12 months post-randomisation. Outcomes included: monthly DS frequency, psychosocial functioning (Work and Social Adjustment Scale - WSAS), and health-related quality of life (Mental Component Summary (MCS) and Physical Component Summary (PCS) SF-12v2 scores). When moderating effects were absent, we tested whether baseline variables predicted change irrespective of treatment allocation.

Results: Moderator analyses revealed greater benefits ($p < 0.05$) of CBT on DS frequency for participants with more ($\geq$22) symptoms (Modified PHQ-15) or $\geq$ 1 current (M.I.N.I.-confirmed) comorbid psychiatric diagnosis at baseline. The effect of CBT on PCS scores was moderated by gender; women did better than men in the CBT + SMC group.

Predictors of improved outcome included: not receiving disability benefits, lower anxiety and/or depression scores (PCS, MCS, WSAS); shorter duration, younger age at DS onset, employment, fewer symptoms and higher educational qualification (PCS, WSAS); stronger belief in the diagnosis and in CBT as a "logical" treatment (MCS).

Some variables that clinically might be expected to moderate/predict outcome (e.g., maladaptive personality traits, confidence in treatment) were not shown to be relevant.

Conclusion: Patient complexity interacted with treatment. CBT was more likely to reduce DS frequency in those with greater comorbidity. Other patient characteristics predicted outcome regardless of the received intervention.

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1. Introduction

Naturalistic studies of adults suggest that outcomes in adults with dissociative seizures (DS) are generally poor [1,2]. However, the time over which such outcome is evaluated, the nature of the study design and how outcome has been evaluated have all varied considerably. In terms of individual characteristics, male gender has been associated with improvement in DS [3]. The absence of learning disability has been associated with a future worsening in DS in one study [3] while elsewhere an IQ < 80 was found to be associated with poor outcome [4]. In terms of educational and occupational factors, higher educational attainment has predicted better outcome [1,5] while unemployment and receipt of state social security benefits have been associated with seizure persistence [3,6,7]. In terms of comorbidities, previous diagnoses of anxiety and depression, other psychiatric conditions, and more somatic symptoms [1,3,8–10] have been associated with worse outcome although McKenzie et al. [3] found that the absence of functional symptoms other than DS at baseline predicted increased seizure occurrence. In terms of personality dysfunction, greater evidence of "inhibitedness", "emotional dysregulation" and "compulsivity" has been associated with poorer global outcome [1]. Poorer social support has also been associated with poorer outcome [5,11]. In terms of characteristics associated with the seizures themselves, more recent diagnosis [8,10,12] and shorter duration of the disorder prior to diagnosis [13] were related to better outcome as were younger age at onset and diagnosis (but not time between onset and diagnosis) [1]. Studies of DS semiology have suggested that hypokinetic (or less dramatic) seizures are associated with better clinical outcomes than hyperkinetic seizures [1,5,12].

We carried out a fully powered pragmatic, parallel arm, multi-centre randomised controlled trial (RCT) in the United Kingdom (UK). This randomised 368 adults with DS and compared the effect of DS-specific cognitive behaviour therapy (CBT) plus standardised medical care (CBT + SMC) with SMC alone on DS frequency and a range of secondary outcomes [14]. While our study was negative for the primary outcome (i.e., despite a 22% advantage in the CBT + SMC group there was no significant between-group difference in monthly DS frequency at 12 months post-randomisation), nine of 16 secondary outcomes showed significant advantage in the CBT + SMC group at the unadjusted 5% level. No outcomes were better in the SMC-alone group, and where between groups differences were significant, standardised group differences were in the moderate range.

We therefore considered it helpful to identify moderators of treatment effects to inform which patient baseline characteristics might interact with the study intervention (in this case CBT + SMC) to influence outcome. Moderators are defined here as baseline variables associated with better outcome (greater improvement), when participants are in receipt of the study intervention (CBT + SMC); i.e., they indicate a differential beneficial effect of a variable on the outcome. In contrast, predictors are baseline variables associated with treatment outcome irrespective of treatment received.

The aim of this study was to evaluate potential moderators of treatment effects and predictors of outcome from the CODES trial [14] where the two treatment arms were CBT + SMC and SMC-alone. The outcomes considered here were change in monthly DS frequency and a range of mental, physical and social health variables. Since there are no previous studies investigating moderators and predictors of outcome in RCTs of DS-specific CBT, we undertook this as an exploratory investigation rather than a purely hypothesis-led study. Based on the studies outlined above and the data collected in our study [14], we investigated the ability of variables outlined below to either moderate treatment effects or predict outcome.

2. Method

2.1. The CODES trial

Details of the CODES trial and the planned and completed main outcome analyses are reported elsewhere [14–17]. In addition, full CONSORT reporting (providing details about study design, numbers of recruitment sites, eligibility criteria, study flowcharts, randomisation, blinding, sample size calculation, data collection, management and adverse events) has previously been undertaken [14,16]. In summary, after around a three-month screening period that followed receipt of DS diagnoses by neurologists / epilepsy specialists, recruited adults with DS underwent a clinical psychiatric assessment by a liaison / neuropsychiatrist and 368 eligible patients were then consented and randomised to receive SMC (n = 182) or DS-specific CBT + SMC (n = 186). At the 12-month follow-up, primary outcome data was obtained for 85% of the participants (CBT + SMC 84%; SMC 86%). The CBT intervention was designed to be delivered over 12 sessions across a four-to-five-month period with one booster session at nine months post-randomisation and was delivered by a range of therapists trained in CBT who underwent study-specific training and supervision. Therapy was manualised but sufficiently flexible to be tailored to the individual. The SMC intervention was delivered to both study arms by neurologists and, predominantly, liaison or neuropsychiatrists, according to guidelines provided by the study team [15], and patients were given information booklets (https://www.codestrial.org/INFORMATIONBOOKLETS) and directed to self-help websites. Both interventions, and inclusion / exclusion criteria, are described in more detail elsewhere [14–16].

The trial received ethics approval from the London - Camberwell St Giles Research Ethics Committee and was registered at Current Controlled Trials ISRCTN05681227 and ClinicalTrials.gov NCT02325544.

2.2. Measures

The CODES trial primary outcome was DS frequency at 12 months post-randomisation measured over the previous four-week period. It was derived from seizure diaries or, if not available, from a self-report questionnaire (see [14,16] for details). We considered it important to investigate potential moderators and predictors of the trial's primary outcome, as it was evident from the data that both groups had likely shown improvement in the study although there was no significant difference between groups at the 12-month follow-up point. Thus, understanding more about factors relating to that outcome could be informative for clinical practice. We also chose to select the following secondary outcomes for this moderator and predictor analysis. The WSAS [18], a five-item self-report scale that measured the ability of participants to engage in work, home management, leisure activities, and relationships and which had detected between groups differences at 12 months post-randomisation ($p < 0.001$) was chosen as an important index of psychosocial functioning and because it is widely used as an outcome measure by the Improving Access to Psychological Therapies (IAPT) services in the UK, so would have direct clinical relevance to a range of clinicians. We also chose to include the Mental Component Summary (MCS) score and the Physical Component Summary (PCS) score from the SF-12v2 as important measures of health-related quality of life (HRQoL) [19,20], which may be of relevance to those planning other intervention studies especially as quality of life has been documented to be low in people with DS [21] and affected by other factors such as mood. While there were 16 secondary outcomes in the CODES trial, we considered that some baseline characteristics such as mood or measures of other symptoms would be better used as potential moderators / predictors given the previous literature on outcome in people with DS.

We considered the moderating or predictive effects of a total of 16 baseline variables (i.e., all collected prior to randomisation). These

included self-reported years since onset of DS (duration of DS), age at DS onset, and gender. We also investigated: employment status (being in employment or education if ≤65); receipt of state disability benefits (for those aged ≤65 irrespective of work status); highest level of educational attainment and somatic symptom burden (Modified PHQ-15 [22]). For the latter, participants responded to being asked whether they were "bothered a lot over the previous month" by 30 different symptoms: 15 common symptoms seen in patients presenting in primary care, 10 'neurological' symptoms and five psychological symptoms. Higher total scores indicated greater numbers of symptoms. We chose to retain all 30 items since this combination had similar sensitivity and specificity when identifying patients with unexplained symptoms as had the more restrictive options of using the original PHQ-15 symptoms with or without the additional "neurological" symptoms [22]. Different versions of the PHQ-15 have shown sensitivity to change in the CODES and other treatment trials [14,23]. We have also shown that the total Modified PHQ-15 scores correlate with physical aspects of HRQoL as well as psychological aspects [24]. Given that DS is a heterogeneous disorder this approach maximised the opportunity for symptom detection. In addition, since the more "physical" symptoms may be driven by mood, it was considered unnecessarily dualistic to remove the mood items in this study. We have, in all our analyses of this scale, checked that men did not reply to the item on menstrual pain and, where the item on pain / problems during sexual intercourse was not answered, we then prorated for 13 or 14 complete symptoms from the original PHQ-15 as appropriate. The Mini - International Neuropsychiatric Interview (M.I.N.I. v6.0; [25]), a structured psychiatric diagnostic interview based on DSM-IV diagnostic categories, classified participants as to whether they had at least one current and / or past psychiatric diagnosis. We used the eight-item Standardised Assessment of Personality Abbreviated Scale, Self-Report (SAPAS-SR; [26]) as a measure of maladaptive personality traits. The nine-item Patient Health Questionnaire 9 (PHQ-9) [27] and the seven-item Generalised Anxiety Disorder Assessment (GAD-7) [28] were used to measure depression and anxiety symptoms respectively. We included doctors' ratings of participants' predominant DS semiology (hyperkinetic or hypokinetic), a measure of participants' belief that DS was the correct diagnosis (a single item 11-point scale, where 0 = Not at all and 10 = Extremely strongly [16]), and separate items asking "How logical does CBT as a treatment seem to you?" and "How confident are you that this treatment would help your illness?" [16], each scored from 0 = not at all to 4 = extremely.

2.3. Statistical analyses

Descriptive statistics were reported by trial arm and overall for all baseline variables and outcomes included in the analysis using appropriate summary measures. For the four outcomes, average change scores were calculated to aid interpretation of results.

For the exploratory analysis we repeated the same statistical modelling methods used in the primary analysis, i.e., multivariate imputation by chained equations (MICE) [14,16] with random effects for psychiatry site (randomisation stratification factor) and adjusting for baseline values of the outcome where possible; mixed effects negative binomial models were employed for monthly seizure frequency; and mixed effects multiple linear regression for WSAS, SF-12v2 MCS and PCS. Incidence rate ratios (IRRs) have been reported as the regression output for the negative binomial models, as per the primary analysis, whereas other coefficients can be interpreted on the scale of the outcome measure.

To examine whether each of the pre-specified baseline variables moderated the effectiveness of CBT for each of the four outcomes at 12 months, the following changes to the models were made: the baseline variable and an interaction term between the baseline variable and trial arm (a dummy variable of CBT*baseline measure) were included in the MICE procedure and analysis model. If the interaction term was significant at the $p = 0.05$ level we calculated the moderation effect estimates by subgroup for categorical variables, and derived subgroup level estimates using quartiles for continuous variables, as agreed *a priori* to aid interpretation. If an interaction with treatment was not demonstrated (i.e., was not significant at the $p = 0.05$ level), we repeated the process using only the baseline variable as a single additional term in the corresponding imputation step and analysis model to evaluate whether it predicted outcome.

P-values have been reported for all moderation and prediction tests; for statistically significant findings, regression coefficients (or IRRs for seizure frequency) with 95% confidence intervals have been given with estimated subgroup effects or interpretations, respectively.

The statistical models were computationally intensive and a minority of them failed to converge; therefore, to be able to include them in the results the psychiatry site random effects were omitted from the analysis models (but still included in the imputation step). Using complete cases, likelihood ratio tests were run to check that there was little or no psychiatry site variability for the corresponding models (with vs without random effects).

Stata V.16 (StataCorp, Texas) was used for all statistical analysis.

3. Results

Table 1 shows the baseline variables by trial arm and overall. Table 2 presents the four outcome variables at baseline and 12 months, with average change scores.

Table 3 presents results of the moderation and prediction analyses, described in the sections below. Estimated CBT effects within subgroups for the three significant moderators are displayed in Table 4 and are described in the text.

3.1. Moderators

3.1.1. Dissociative Seizure (DS) frequency

At 12 months follow-up, at $p < 0.05$, there was evidence that the effect of CBT on DS frequency was moderated by the number of baseline symptoms (Modified PHQ-15), $p = 0.037$, and the presence of at least one current M.I.N.I. diagnosis, $p = 0.007$ (Table 3). With respect to baseline Modified PHQ-15 scores, we estimated that the effect of CBT for participants in the upper quartile (≥22 symptoms) was a reduction in DS frequency of 41% ($p = 0.015$) compared to SMC alone; the CBT effect was not significant for those with low (12; $p = 0.932$) or median (17; $p = 0.109$) numbers of symptoms. Table 4 and Fig. 1a display the IRRs (and 95%CIs): 0.98, 0.76 and 0.59 respectively, where the latter is significant with a 95%CI less than 1.

The estimated CBT effect for those with ≥1 M.I.N.I. current diagnosis was a reduction in DS frequency of 44% compared to the SMC-alone group ($p = 0.007$). The estimated CBT effect for those without a current M.I.N.I. diagnosis was not significant ($p = 0.215$) (Table 4).

3.1.2. Work and Social Adjustment Scale (WSAS)

No baseline variables moderated treatment effects as measured by the WSAS.

3.1.3. SF-12v2 Mental Component Summary (MCS) and Physical Component Summary (PCS)

No baseline variables moderated treatment effects as measured by the SF-12v2 MCS.

There was evidence that the effect of CBT on PCS scores was moderated by gender ($p = 0.018$). Compared to the SMC-alone group, for women receiving CBT there was an estimated increase in physical HRQoL of 3.3 points on the SF-12v2 PCS scale (95%CI 0.92, 5.78, $p = 0.007$), i.e., an improvement in scores, while for men the estimate was not significant (Table 4; Fig. 1b).

Table 1
Baseline variables by trial arm and overall.

		SMC[a] N = 182	CBT + SMC[b] N = 186	Overall N = 368
Years since onset of DS[c]	median (IQR)[d] [range]	3 (1, 8) [0, 65] n = 181	3 (1, 7.5) [0, 44] n = 184	3 (1, 8) [0, 65] n = 365
Age at onset of DS (years)	median (IQR) [range]	29 (19, 42) [5, 76] n = 181	29 (19, 41.5) [1, 67] n = 184	29 (19, 42) [1, 76] n = 365
Gender n (%)	Female	126 (69.2)	140 (75.3)	266 (72.3)
	Male	56 (30.8)	46 (24.7)	102 (27.7)
Employed or in education (age ≤ 65) n (%)	Yes	58 (33.1)	65 (35.1)	123 (34.9)
	No	117 (66.9)	112 (63.3)	229 (65.1)
Receiving disability benefits (age ≤ 65) n (%)	Yes	99 (57.2)	84 (49.4)	183 (53.4)
	No	74 (42.8)	86 (50.6)	160 (46.6)
Highest level of qualification attained (within the UK educational system) n (%)	None	21 (11.6)	22 (11.8)	43 (11.7)
	Secondary	41 (22.7)	48 (25.8)	89 (24.3)
	Vocational	66 (36.5)	54 (29.0)	120 (32.7)
	Further (A-level or equivalent)	28 (15.5)	28 (15.1)	56 (15.3)
	Higher (BSc and higher/equivalent)	25 (13.8)	34 (18.3)	59 (16.1)
Modified PHQ-15[e] total (possible range 0–30; higher scores = more symptoms)	mean (SD)[f] [range]	16.7 (6.2) [2, 30] n = 181	16.7 (6.8) [2, 30] n = 183	16.7 (6.5) [2, 30] n = 364
PHQ-9[g] score (possible range 0–27; higher scores = greater symptoms of depression)	mean (SD) [range]	12.6 (6.5) [0, 26] n = 181	12.3 (6.7) [0, 27] n = 186	12.4 (6.6) [0, 27] n = 367
GAD-7[h] score (possible range 0–21: higher scores = greater symptoms of anxiety)	mean (SD) [range]	10.0 (6.2) [0,21]	9.6 (6.2) [0, 21]	9.8 (6.2) [0, 21]
SAPAS-SR[i] total (possible range 0–8; higher scores = more maladaptive personality traits)	mean (SD) [range]	4.0 (2.0) [0, 8] n = 181	3.9 (1.9) [0, 8] n = 182	3.9 (2.0) [0, 8] n = 363
At least 1 current M.I.N.I.[j] diagnosis n (%)	Yes	125 (68.7)	130 (69.9)	255 (69.3)
	No	57 (31.3)	56 (30.1)	113 (30.7)
At least 1 previous M.I.N.I. diagnosis n (%)	Yes	112 (61.5)	135 (72.6)	247 (67.1)
	No	70 (38.5)	51 (27.4)	121 (32.9)
Predominant seizure type n (%)	Hypokinetic	60 (33.1)	70 (37.8)	130 (35.5)
	Hyperkinetic	121 (66.9)	115 (62.2)	236 (64.5)
Strength of belief in a correct diagnosis.[k] (0 = Not at all, 10 = Extremely strongly)	median (IQR) [range]	9 (7, 10) [0,10] n = 180	9 (7, 10) [2, 10] n = 185	9 (7, 10) [0, 10] n = 365
How logical did CBT seem as treatment for DS[l] (0 = not at all, 4 = extremely)	median (IQR) [range]	3 (2, 4) [1, 4] n = 179	3 (3, 4) [0, 4] n = 180	3 (3, 4) [0, 4] n = 359
Confidence that CBT would help DS[m] (0 = not at all, 4 = extremely)	median (IQR) [range]	3 (2,3) [0, 4] n = 179	3 (2, 3) [0, 4] n = 180	3 (2, 3) [0, 4] n = 359

[a]SMC = Standardised Medical Care; [b]CBT + SMC = Cognitive Behavioural Therapy plus Standardised Medical Care; [c]DS = dissociative seizures; [d]IQR = inter-quartile range; [e] PHQ-15 = Patient Health Questionnaire-15 [f]SD = standard deviation [g]PHQ-9 = Patient Health Questionnaire-9; [h]GAD-7 = Generalised Anxiety Disorder Assessment-7;[i]SAPAS-SR = Standardised Assessment of Personality Abbreviated Scale, Self-Report; [j]M.I.N.I. = Mini - International Neuropsychiatric Interview; [k]"How strongly do you believe that you have been given the correct diagnosis of Dissociative Seizures?"; [l]"How logical does CBT as a treatment seem to you?"; [m]"How confident are you that this treatment would help your illness?"

Table 2
Outcome variables at baseline and 12 months, and average change scores.

		Baseline			12-months			Change from baseline to 12 months		
		SMC[b] N = 182	CBT + SMC[c] N = 186	Overall N = 368	SMC N = 182	CBT + SMC N = 186	Overall N = 368	SMC N = 182	CBT + SMC N = 186	Overall N = 368
Monthly seizure frequency (previous 4 weeks)[a]	median (IQR) [range]	19 (5, 49) [0, 649] n = 182	12.5 (4, 41) [0, 535] n = 186	15 (4, 47) [0, 649] n = 368	7 (1, 35) [0, 994] n = 157	4 (0,20) [0, 571] n = 156	5 (0, 27) [0, 994] n = 313	−25.5% (−95.3, 27.5) [−100,2233] n = 152	−50% (−100, 8) [−100, 587] n = 149	−38.7% (−97, 14.3) [−100, 2233] n = 301
WSAS[d] score (possible range 0–40; higher scores = more, i.e., worse, impact)	mean (SD) [range]	22.9 (10.5) [0, 40] n = 181	22.5 (10.5) [0, 40] n = 185	22.7 (10.5) [0, 40] n = 366	21.1 (12.7) [0, 40] n = 145	16.4 (13.1) [0, 40] n = 148	18.7 (13.1) [0, 40] n = 293	−1.7 (10.5) [−30, 37] n = 145	−5.8 (10.9) [−38.75, 19] n = 148	−3.8 (10.8) [−38.75, 37] n = 293
Physical Component Summary (PCS) score (possible range 0–100; 0 = worst health, 100 = best health)	mean (SD) [range]	38.8 (11.9) [13.9, 65.6] n = 181	40.5 (12.4) [13.4, 65.9] n = 185	39.7 (12.2) [13.4, 65.9] n = 366	38.0 (12.6) [10.4, 63.7] n = 145	41.5 (13.4) [12.2, 67.3] n = 148	39.8 (13.1) [10.4, 67.3] n = 293	−1.2 (9.4) [−40.6, 19] n = 144	0.9 (9.4) [−23.1, 39.5] n = 147	0.1 (9.5) [−40.6, 39.5] n = 291
Mental Component Summary (MCS) score (possible range 0–100; 0 = worst health, 100 = best health)	mean (SD) [range]	37.9 (11.4) [16.9, 68.1] n = 181	37.7 (12.2) [13.4, 67.6] n = 185	37.8 (11.8) [13.4, 68.1] n = 366	39.5 (11.8) [11.3, 62.9] n = 145	41.5 (12.8) [13.9, 65.7] n = 148	40.5 (12.4) [11.3, 65.7] n = 293	0.8 (11.2) [−28.3, 33] n = 144	3.0 (13.0) [−42.6, 36.1] n = 147	1.9 (12.1) [−42.5, 36.1] n = 291

[a]Change from baseline to 12 months is reported as a percentage for monthly seizure frequency to be consistent with the regression output (IRR); participants with zero seizures at baseline could not be included in the calculation. [b]SMC = Standardised Medical Care; [c]CBT + SMC = Cognitive Behavioural Therapy plus Standardised Medical Care; [d]WSAS = Work and Social Adjustment Scale.

3.2. Predictors

All significant predictors at the 0.05 level are illustrated in Fig. 2, in descending order of standardised effect size, by outcome.

3.2.1. Dissociative Seizure (DS) frequency

No baseline variables predicted DS frequency at 12 months post-randomisation.

3.2.2. Work and Social Adjustment Scale (WSAS)

Regardless of treatment allocation, there was a larger decrease in WSAS scores at 12 months post-randomisation (i.e., a greater improvement in functioning) in participants who at baseline: had shorter duration of DS [regression coefficient = −0.13 (95%CI -0.025, −0.01) p = 0.038]; were younger at the time of DS onset [regression coefficient = −0.10 (95%CI -0.18, −0.02) p = 0.013]; were employed or in education [regression coefficient = −4.38 (95%CI -7.12, −1.64) p = 0.002]; were of working age and not receiving state disability benefits [regression coefficient = −4.90 (95%CI -7.38, −2.42) p < 0.001]; had lower numbers of symptoms on the Modified PHQ-15 [regression coefficient = −0.30 (95%CI -0.51, −0.09) p = 0.005]; lower PHQ-9 depression scores [regression coefficient = −0.46 (95%CI -0.64, −0.27) p < 0.001]; and lower GAD-7 anxiety scores [regression coefficient = −0.30 (95%CI -0.49, −0.11) p = 0.002].

A greater improvement in functioning on the WSAS was predicted by the level of educational qualifications achieved (overall p = 0.024). Comparing Higher Level qualifications vs none indicated that those with Higher Level qualifications showed a better outcome [regression coefficient = −6.0 (95%CI -10.13, −1.81) p = 0.005].

3.2.3. SF-12v2 Mental Component Summary (MCS) and Physical Component Summary (PCS)

When considering mental HRQoL as measured by the SF-12v2 MCS, outcome at 12 months post-randomisation was better across both groups if, at baseline, participants: were of working age and were not in receipt of state disability benefits [regression coefficient = 3.31 (95%CI 0.68, 5.95) p = 0.014]; had lower PHQ-9 depression scores [regression coefficient = 0.45 (95%CI 0.19, 0.71) p = 0.001]; had lower GAD-7 anxiety scores [regression coefficient = 0.32 (95%CI 0.04, 0.60) p = 0.024]; had a stronger belief in the diagnosis [regression coefficient = 0.68 (95%CI 0.08, 1.28) p = 0.025]; and had a higher expectation of CBT as a logical treatment for DS [regression coefficient = 1.87 (95%CI 0.30, 3.45) p = 0.020].

When considering SF-12v2 PCS outcomes, the predictors were similar to those for the WSAS, i.e., there was greater improvement in physical HRQoL scores in participants with shorter duration of DS disorder [regression coefficient = 0.19 (95%CI 0.08, 0.30) p = 0.001]; who were younger at DS onset [regression coefficient = 0.08 (95%CI 0.003, 0.15) p = 0.042]; were employed / in education [regression coefficient = 5.23 (95%CI 2.72, 7.74) p < 0.001]; were of working age and not receiving state disability benefits [regression coefficient = 3.73 (95%CI 1.33, 6.12) p = 0.002]; who had lower numbers of symptoms on the Modified PHQ-15 [regression coefficient = 0.23 (95%CI 0.04, 0.41) p = 0.015]; and had lower PHQ-9 depression scores [regression coefficient = 0.17 (95%CI 0.01, 0.33) p = 0.034].

Greater improvement in PCS scores was predicted by educational qualification level (overall p = 0.049). Comparing Higher Level qualifications vs none indicated that those with Higher Level qualifications showed a better outcome [regression coefficient = 4.33 (95%CI 0.55, 8.11) p = 0.025].

4. Discussion

This is, to our knowledge, the first study to examine, in a large pragmatic, multi-centre, parallel arm RCT for adults with DS, whether there are baseline characteristics which either moderate differential responses to DS-specific CBT when added to SMC (vs SMC alone) or predict improvement in outcomes irrespective of treatment allocation.

Regarding our RCT's primary outcome measure, monthly DS frequency at 12 months post-randomisation, only two baseline variables

Table 3
Estimated *p*-values from moderation and prediction tests (interpretations given for significant [$p < 0.05$] predictor variables).

	Monthly seizure frequency		WSAS[c]		SF-12v2 MCS[d]		SF-12v2 PCS[e]	
Baseline variable	Moderator	Predictor	Moderator	Predictor Coef[f]. (95%CI[g])	Moderator	Predictor Coef. (95%CI)	Moderator	Predictor Coef. (95%CI)
Years since onset	$p = 0.128$	$p = 0.191$	$p = 0.707$	Shorter duration of DS predicts greater improvement in functioning: −0.13 (−0.25, −0.01) $p = 0.038$	$p = 0.537$	$p = 0.494$[b]	$p = 0.148$	Shorter duration of DS predicts greater improvement in physical QoL: 0.19 (0.08, 0.30) $p = 0.001$[b]
Age at onset	$p = 0.269$	$p = 0.138$	$p = 0.824$	Younger age at onset predicts greater improvement in functioning: −0.10 (−0.18, −0.02) $p = 0.013$	$p = 0.514$	$p = 0.096$	$p = 0.199$	Younger age at onset predicts greater improvement in physical QoL: 0.08 (0.003, 0.15) $p = 0.042$
Gender (ref = male)	$p = 0.510$	$p = 0.716$	$p = 0.916$	$p = 0.468$	$p = 0.057$[b]	$p = 0.315$[b]	$p = 0.018$[a]	n/a
Employed or in education (ref = employed) ($n = 349$)	$p = 0.366$	$p = 0.453$	$p = 0.996$	Employment predicts greater improvement in functioning: −4.38 (−7.12, −1.64) $p = 0.002$	$p = 0.471$[b]	$p = 0.473$	$p = 0.948$	Employment predicts greater improvement in physical QoL: 5.23 (2.72, 7.74) $p < 0.001$
Benefits (ref = not receiving benefits) ($n = 342$)	$p = 0.629$	$p = 0.131$	$p = 0.285$	Not receiving benefits predicts greater improvement in functioning: −4.90 (−7.38, −2.42) $p < 0.001$	$p = 0.579$[b]	Not receiving benefits predicts greater improvement in mental QoL: 3.31 (0.68, 5.95) $p = 0.014$[b]	$p = 0.701$	Not receiving benefits predicts greater improvement in physical QoL: 3.73 (1.33, 6.12) $p = 0.002$[b]
Modified PHQ-15[h]	$p = 0.037$[a]	n/a	$p = 0.332$	Lower number of symptoms predicts greater improvement in functioning: −0.30 (−0.51, −0.09) $p = 0.005$	$p = 0.270$	$p = 0.523$	$p = 0.833$[b]	Lower number of symptoms predicts greater improvement in physical QoL: 0.23 (0.04, 0.41) $p = 0.015$
At least 1 current M.I.N.I.[i] diagnosis (ref = no diagnoses)	$p = 0.007$[a]	n/a	$p = 0.110$	$p = 0.342$	$p = 0.964$	$p = 0.962$	$p = 0.671$	$p = 0.674$[b]
SAPAS-SR[j] score	$p = 0.251$	$p = 0.646$	$p = 0.570$	$p = 0.381$	$p = 0.806$	$p = 0.964$	$p = 0.474$	$p = 0.377$
PHQ-9[k] score (depression)	$p = 0.173$	$p = 0.338$	$p = 0.492$	Lower depression score predicts greater improvement in functioning: −0.46 (−0.64. -0.27) $p < 0.001$	$p = 0.537$	Lower depression score predicts greater improvement in mental QoL: 0.45 (0.19, 0.71) $p = 0.001$	$p = 0.220$	Lower depression score predicts greater improvement in physical QoL: 0.17 (0.01, 0.33) $p = 0.034$
GAD-7[l] score (anxiety)	$p = 0.108$	$p = 0.563$	$p = 0.472$	Lower anxiety score predicts greater improvement in functioning: −0.30 (−0.49, −0.11) $p = 0.002$	$p = 0.836$	Lower anxiety score predicts greater improvement in mental QoL: 0.32 (0.04, 0.60) $p = 0.024$	$p = 0.283$	$p = 0.112$
At least 1 previous M.I.N.I. diagnosis (ref = no diagnoses)	$p = 0.562$	$p = 0.400$	$p = 0.125$	$p = 0.371$	$p = 0.981$[b]	$p = 0.453$[b]	$p = 0.830$[b]	$p = 0.634$
Educational Qualifications	$p = 0.396$	$p = 0.200$	$p = 0.378$	Higher qualification predicts greater improvement in functioning compared to None: −6.0 (−10.13, −1.81) $p = 0.005$ ($p = 0.024$ overall)	$p = 0.145$	$p = 0.417$	$p = 0.999$	Higher qualification predicts greater improvement in physical QoL compared to None: 4.33 (0.55, 8.11) $p = 0.025$ ($p = 0.049$ overall)
Predominant seizure type (ref = hypokinetic)	$p = 0.117$	$p = 0.544$	$p = 0.457$	$p = 0.213$	$p = 0.846$	$p = 0.092$	$p = 0.729$[b]	$p = 0.821$
Belief in diagnosis[m]	$p = 0.781$	$p = 0.847$	$p = 0.165$	$p = 0.076$	$p = 0.339$	Greater belief in diagnosis predicts greater improvement in mental QoL: 0.68 (0.08, 1.28) $p = 0.025$[b]	$p = 0.405$	$p = 0.355$
How logical did CBT seem as	$p = 0.553$	$p = 0.894$	p = 0.277	$p = 0.368$	$p = 0.223$[b]	Higher expectation of CBT predicts greater	$p = 0.074$	$p = 0.798$

(*continued on next page*)

Table 3 (*continued*)

	Monthly seizure frequency		WSAS[c]		SF-12v2 MCS[d]		SF-12v2 PCS[e]	
Baseline variable	Moderator	Predictor	Moderator	Predictor Coef[f]. (95%CI[g])	Moderator	Predictor Coef. (95%CI)	Moderator	Predictor Coef. (95%CI)
treatment for DS[n]						improvement in mental QoL: 1.87 (0.30, 3.45) $p = 0.020$[b]		
Confidence that CBT would help DS[o]	$p = 0.675$	$p = 0.876$	$p = 0.992$	$p = 0.945$	$p = 0.863$	$p = 0.738$	$p = 0.092$	$p = 0.929$

[a]Statistically significant interactions at the p = 0.05 level are reported in more detail in Table 4; [b]the MI estimate model would not converge when including random effects for psychiatry site; therefore, psychiatry site dummy variables have been included in the imputation model but omitted from the analysis model. To check that there was little or no psychiatry site variability for this variable, a likelihood ratio test was run (using complete cases), with vs without the random effects; the p-value for the LR test was equal to 1.0, which implies there were no differences between the models. [c]WSAS = Work and Social Adjustment Scale; [d]SF-12v2 MCS Short Form 12-item (version 2) Health Survey Mental Component Summary; [e]SF-12v2 PCS = Short Form 12-item (version 2) Health Survey Physical Component Summary; [f]Coef = Coefficient; [g]95%CI = 95% confidence interval; [h]PHQ-15 = Patient Health Questionnaire-15; [i]M.I.N.I. = Mini - International Neuropsychiatric Interview; [j]SAPAS-SR = Standardised Assessment of Personality Abbreviated Scale, Self-Report; [k]PHQ-9 = Patient Health Questionnaire-9; [l]GAD-7 = Generalised Anxiety Disorder Assessment-7; [m]"How strongly do you believe that you have been given the correct diagnosis of Dissociative Seizures?"; [n]"How logical does CBT as a treatment seem to you?"; [o]"How confident are you that this treatment would help your illness?"
Please note: all analysis models were adjusted for baseline values of the outcome.

Table 4
Estimated CBT effects within subgroups for the three significant moderator variables, with interpretations.

		Treatment estimate (95% CI[a]) p-value	Interpretation of moderator variable on treatment effect
(1)	Gender modified the effect of CBT on physical QoL[b] (SF-12v2 PCS[c])	*p=0.018*	The offer of CBT increased physical QoL at 12 months for women compared to men
	Female	3.3 (0.9, 5.8) p=0.007	
	Male	-2.2 (-6.1, 1.7) p=0.277	
(2)	Modified PHQ-15[d] symptoms modified the effect of CBT on seizure frequency	*p=0.037*	The offer of CBT reduced monthly seizure frequency at 12 months for participants with a high (≥22) number of symptoms at baseline compared to those with few
	Lower quartile=12	0.98 (0.67, 1.44) p=0.932	
	Median=17	0.76 (0.55, 1.06) p=0.109	
	Upper quartile=22	0.59 (0.39, 0.90) p=0.015	
(3)	Current M.I.N.I.[e] diagnosis modified the effect of CBT on seizure frequency	*p=0.007*	The offer of CBT reduced monthly seizure frequency at 12 months for participants with at least 1 current M.I.N.I. diagnosis at baseline compared to those without
	None	1.43 (0.81, 2.53) p=0.215	
	At least one	0.56 (0.38, 0.84) p=0.005	

Please note: estimated treatment effects are reported on the SF-12v2 PCS scale for (1) and Incidence Rate Ratios for (2) and (3).
[a]95%CI = 95% confidence interval; [b]QoL = quality of life; [c]SF-12v2 PCS = Short Form 12-item (version 2) Health Survey Physical Component Summary; [d]PHQ-15 = Patient Health Questionnaire-15; [e]M.I.N.I. = Mini - International Neuropsychiatric Interview.

moderated the treatment effect: higher Modified PHQ-15 scores and having at least one current comorbid M.I.N.I. diagnosis. The DS-specific CBT intervention became more effective than SMC-alone in reducing DS frequency for participants who reported being "bothered a lot" by ≥22 symptoms on the Modified PHQ-15. This suggests that those patients with DS with comorbid psychiatric diagnoses and higher symptom load did better with DS-specific CBT in terms of DS occurrence. This raises the possibility that our SMC intervention (specialist and standardised medical care, rather than treatment as usual), may have been adequate for less complex cases when considering DS reduction. It is possible that this finding can be related to components of the DS-specific CBT intervention that addressed specific aspects of the person's disorder, namely physiological, behavioural, emotional, cognitive and social aspects [16]. We have described [16] how the key intervention change techniques included deriving an individual formulation that would take into account stress and trauma relevant to the person and their possible role in seizure development and gaining a detailed understanding of the person's seizures including the person's cognitive and behavioural responses to them. The CBT intervention also set out to teach distraction and refocusing techniques to interrupt seizures. In addition, it involved addressing avoidance behaviours using graded exposure, addressing unhelpful beliefs using cognitive techniques, trauma processing and, furthermore, stress management. We have reported elsewhere [16,29] that the most common M.I.N.I.-identified current comorbid diagnoses at baseline in the overall sample were agoraphobia (45%), major depressive disorder (31%), generalised anxiety disorder (29%), posttraumatic stress disorder (23%) and social anxiety disorder (20%), and it is likely therefore that aspects of these comorbid disorders would have been addressed during therapy; some components of our therapy might have been of less relevance / required less specific therapeutic input in patients without any of these or other M.I.N.I.-confirmed diagnoses. Since our therapeutic approach was based predominantly on a fear-avoidance model [15,16,30–32] the prevalence of agoraphobia and other anxiety-related diagnoses in our sample may also have made the therapeutic

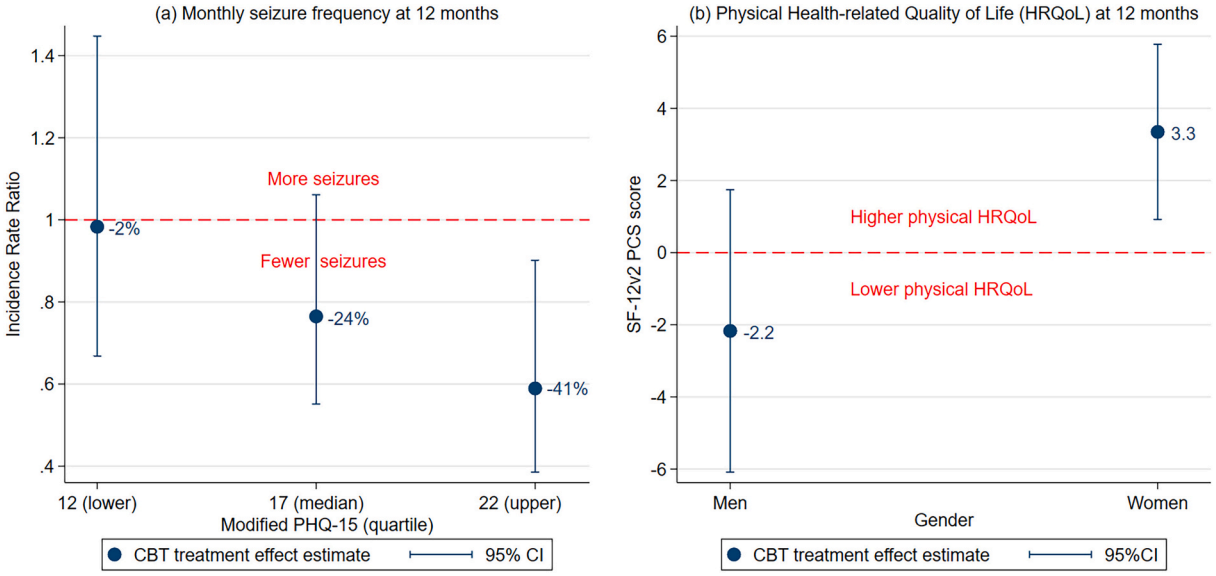

Fig. 1. A plot to illustrate that the estimated treatment effect of CBT was moderated by (a) number of other somatic symptoms in terms of monthly seizure frequency, and (b) gender in terms of physical HRQoL.

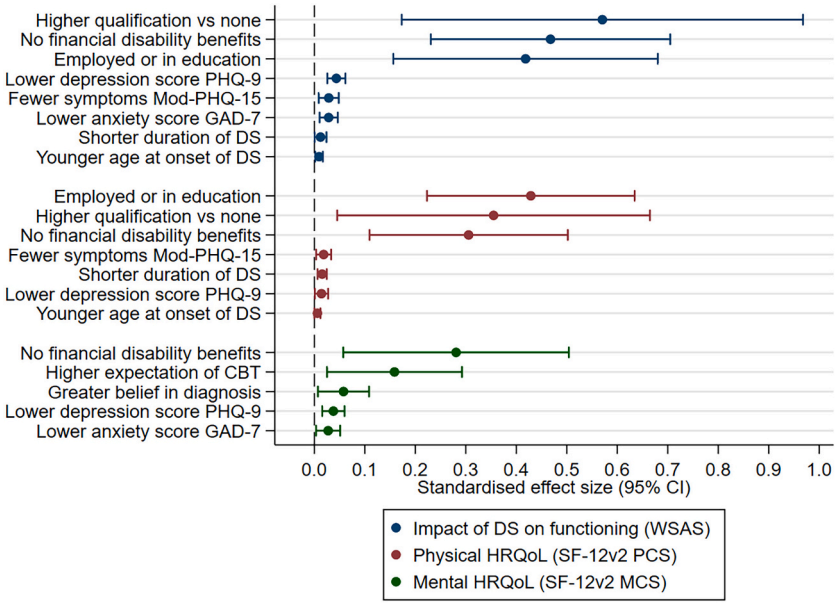

Fig. 2. A forest plot to illustrate the strength of relationships where baseline variables have been estimated to predict improvement in outcome at 12 months regardless of treatment allocation. To calculate these standardised coefficients, the regression coefficient was divided by the standard deviation of the outcome at baseline.

approach particularly relevant for reducing DS occurrence in people with these comorbid diagnoses or larger numbers of comorbid symptoms as assessed using the Modified PHQ-15; the latter may have reflected the generally greater level of symptomatology in patients with more M.I.N.I.-confirmed diagnoses. In contrast, for patients with no comorbid M.I.N.I.-confirmed diagnoses, the generally supportive nature of SMC along with practising distraction techniques may have been sufficient to bring about similar results to those from CBT.

Interestingly, age at onset of DS, duration of DS and predominant DS semiology did not modify the effect of CBT on DS frequency or interact with treatment allocation. Age at onset and DS duration have previously been shown to be important for DS-related outcomes [1,13]. It is often assumed that if patients have been ill for longer, they will be harder to treat. However, we did not find that the duration of the DS disorder predicted outcome in terms of DS frequency. We were not able to compare the effects of very rapid treatment provision (e.g., within weeks of manifestation of DS) with those who came to treatment later (e.g., more than six months after manifestation). In other studies that were not related to the systematic implementation of specific interventions [5,12] patients with hypokinetic-type seizures were reported to show better seizure outcome. However, our findings suggest that despite the inclusion of DS control techniques in our intervention, predominant seizure semiology did not affect CBT response. It is possible that discussion around distraction techniques during SMC [15], perhaps supported by the use of online resources such as www.neurosymptoms.org enabled patients from both groups to learn seizure control techniques. Our qualitative work [33] supports this perspective, although a recent randomised controlled trial of online self-help material for functional

motor disorder, another subtype of functional neurological disorder, showed no improvement in any outcome measure at 6-months follow up [34].

In the CODES trial [14,16], scores on the WSAS differed between groups in favour of the CBT + SMC group at 12 months post-randomisation. We found no moderators of the CBT effect on WSAS scores, suggesting that our model of DS-specific CBT was suitable as an intervention for a broad range of people when considering the reduction in the psychosocial impact of DS. Regardless of treatment allocation, scores indicated that greater improvement in WSAS scores at 12 months was predicted by a shorter duration of DS, DS presentation at an earlier age, baseline employment / being in education, being of working age and not receiving state disability benefits and reporting fewer somatic and anxiety / depression symptoms. Greater improvement in functioning was seen in participants who had attained higher level educational qualifications. This suggests that poor functioning in terms of these characteristics at baseline pose challenges for treatment provision, and that there is a need for specialist multidisciplinary services for DS.

Our main intention-to-treat analysis [14,16] did not elicit any between group differences on the SF-12v2 MCS and PCS scores 12 months post randomisation. Here, we did not find any moderators of treatment effects with respect to MCS scores. In both groups there was greater improvement in MCS scores in participants who, at baseline, were of working age and not in receipt of state disability benefits, and for those with lower anxiety and / or depression scores. In addition, SF-12v2 MCS scores improved more markedly for those who at baseline had a stronger belief in their diagnosis and who viewed CBT as a more logical treatment. These variables were predictive for both groups and may have served as proxy measures for being psychologically-minded or accepting of psychological models.

For the SF-12v2 PCS, gender moderated the treatment effect with women who had been allocated to receive CBT + SMC doing better than men. While 72% of our sample overall were women, the broad lack of predictive relationships between gender and outcomes suggests that our interventions were equally applicable to men and women in terms of the other outcomes measured here.

Baseline measures of DS duration, age at onset, being employed / in education, being of working age and not receiving state disability benefits, reporting fewer symptoms (Modified PHQ-15), and lower depression scores were predictors of higher PCS scores at 12 months. Participants with higher qualifications compared to none also showed greater improvement in PCS scores. These findings again attest to the importance of depression and symptom load in predicting HRQoL in people with DS [21] although they were not the strongest predictors in the current evaluation (Fig. 2).

Personality factors have previously been found to be associated with outcome [1,35]. We did not find that our chosen measure of maladaptive personality traits (the SAPAS-SR) moderated treatment effects or predicted change in any outcomes examined here. It is possible that this measure was non-specific in the current sample; we previously noted that 58.9% met the threshold of what we interpreted as maladaptive personality traits [29]. However, the failure to find any relationships between the SAPAS-SR and the outcomes reported here refutes the suggestion [36] that high levels of personality vulnerability might explain the findings of the CODES trial.

The finding that shorter DS duration predicts better change in outcomes (WSAS and PCS scores) may reflect the fact that irrespective of the treatment received, disability and quality of life worsen over time with longer DS duration, although the strength of the associations was low. Nonetheless, there may be value in clinical services reducing waiting times for treatment thereby minimising the potential negative effects of being ill for longer. It is less clear why earlier onset of DS may predict better outcome. We have demonstrated significant variability in the gender distribution and major fluctuations in the incidence of DS across the age spectrum [37]. Our data suggests that patients with DS have a different clinical profile according to age. We cannot say with certainty why an earlier age at onset was associated with better outcome but perhaps with increasing age there is greater opportunity for the development of comorbid difficulties, or the development of social situations that are more difficult to change. Being in receipt of state benefits has been identified previously as a predictor of poor outcome [3,38] and it is difficult to disentangle the specific mechanisms by which not receiving benefits and being employed combine to result in better outcomes. While these characteristics may all be linked to severity of illness, our analyses have adjusted for baseline characteristics.

There are several limitations to our study. The current study was exploratory, with many regression-model analyses (multiple tests) and findings evaluated at the unadjusted 5% level. This may explain why we have found some statistically significant associations that are less clinically meaningful. The study was not powered to allow for multivariable regression analyses. Although the sample was large, participants had been recruited according to specific eligibility criteria which may somewhat limit the generalisability of findings. In addition, our exploratory analysis is constrained by the variables measured at baseline and our decision to limit the outcome variables under current consideration. These findings are evaluated in the context of a pragmatic RCT but, as has been noted elsewhere [14,16] therapists did not pre-assess patients for their suitability for CBT as might normally occur in many clinical services. Thus, wider application of our DS-specific CBT, combined with specialist medical care (including information provision), may need further evaluation. In the current study we did not examine mediators of change so cannot speculate on the mechanisms underpinning change; we plan to report this in a future publication. Our use of the Modified PHQ-15 incorporated a range of previously classified somatic, neurological and psychological symptoms. Our approach here is in common with our other analyses of the CODES trial data and reflects the heterogeneity of presentations of our participants. While we have identified the extent of symptomatology that moderates treatment effects or predicts outcome, we have not attempted to identify whether a particular constellation of symptoms on the Modified PHQ-15 is particularly salient in this respect. Finally, while we asked patients in our main study "How logical does CBT as a treatment seem to you?" we appreciate that the term logical may have been ambiguously interpreted and potentially confused with "effective".

Nonetheless, the current findings suggest that patients with more complex symptom presentations and comorbid psychiatric disorder(s) may particularly benefit from our DS-specific CBT compared to receiving SMC alone. In terms of more physical aspects of HRQoL and psychosocial functioning, patients with earlier onset and shorter duration of their DS disorder may show greater benefit from both of our interventions, although greater benefit appears to be related to being in employment / education and not receiving state disability benefits. Being unemployed and in receipt of state disability benefits are not barriers to treatment but pose additional challenges for healthcare providers to consider.

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Declaration of Competing Interest

All authors have completed the Unified Competing Interest form at http://www.icjme.org/coi_disclosure.pdf. AC reports being a paid editor of the Journal of Neurology, Neurosurgery and Psychiatry, and is the director of a research programme on functional neurological disorders; he gives independent testimony in Court on a range of neuropsychiatric topics (50% pursuer, 50% defender). SL is a paid editor of the Journal of Child Psychology and Psychiatry. MR is the paid Editor-in-Chief of Seizure - European Journal of Epilepsy and receives authorship fees from Oxford University Press in relation to a number of books about dissociative seizures. JS reports independent expert testimony work for personal injury and medical negligence claims, royalties from UpToDate for articles on the functional neurological disorder and runs a free non-profit self-help website, www.neurosymptoms.org. The remaining authors have no conflicts of interest to declare.

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