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Cover Letter

Thank you for considering our paper for the Journal of Psychosomatic Research

We describe the piloting and outcome of a new attempt to improving the pre-assessment diagnosis of functional neurological disorder by questionnaire. Although we were only in part successful, we think there are useful lessons here both about the nature of diagnosis in FND for researchers in FND and somatic symptoms in neurological populations, as well as promising leads for future studies.

We state that:

- All authors of this article had access to complete study data, are responsible for all contents of the article, and had authority over manuscript preparation and the decision to submit the manuscript for publication.
- All authors have approved of the submission of the manuscript to the Journal of Psychosomatic Research.
- The submitted manuscript is original and the data and conclusions presented have not been published or submitted in any other format.

The Edinburgh Neurosymptoms Questionnaire: Is it possible to screen for a functional neurological disorder using a questionnaire?

Running head

The Edinburgh Neurosymptoms Questionnaire

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Abstract

Objective: Diagnostic screening for functional neurological disorders (FNDs) continues to pose a challenge. Simple symptom counts fail clearly to discriminate patients with FND but there is increasing recognition of 'positive' features which are useful diagnostically during face-to-face assessments. A self-completed screening questionnaire evaluating specific features of FNDs would be useful for screening purposes in clinical and research settings.

Methods: The Edinburgh Neurosymptoms Questionnaire (ENS) is a 30-item survey of presence and nature of: blackouts, weakness, hemisensory syndrome, memory problems, tremor, pain, fatigue, globus, multiple medical problems, and operations constructed via literature review and expert consensus. We conducted a pilot of the ENS on new general neurology clinic attendees at a large regional neuroscience centre. Patients were grouped according to consultant neurologist impression as having symptoms that were 'Not at all', 'Somewhat', 'Largely' or 'Completely' due to a functional disorder. ~~This classification was compared against~~ ????

Results: Blackouts, weakness and memory questions provided reasonable diagnostic utility (AUROC = 0.94, 0.71, 0.74 respectively) in single symptom analysis. All other symptoms lacked discriminating features. A multivariate linear model with all symptoms predicted functional classification with moderate diagnostic utility (AUROC = 0.83), specificity of 0.97, sensitivity of 0.47. Pain and blackout scores provided the most accurate predictor of functional classification.

Conclusion: The diagnosis of functional neurological disorders is difficult using unguided, self-reported questions. Our results suggest some promise however for differentiation of functional/dissociative blackouts from other causes, and further refinements could lead to a more useful clinical screening tool for other symptoms.

Key Words: Functional Neurological Disorders, Symptom Count, Screening Questionnaire.

Highlights:

- A novel screening questionnaire for functional neurological disorders (FNDs).
- Symptom counts provide no diagnostic utility in FNDs (AUC = 0.60).
- Questions regarding positive features of FND provide modest utility (AUC = 0.83).

Introduction

Functional Neurological Disorders (FNDs) have historically been considered a common but challenging diagnosis (Nicholson et al. 2011) with a considerable impact on patient quality of life(Gelauff et al. 2014). Patients with symptoms without a structural cause comprise 30% of general neurology outpatients (Stone, A. Carson, et al. 2009) and between 16-34% of primary care attendees (Steinbrecher et al. 2011; de Waal et al. 2004; Haller et al. 2015). They are commonly undiagnosed (Murray et al. 2016; Dimsdale et al. 2013; Hamilton et al. 2013; Leaver et al. 2016), over-investigated (Shaw & Creed 1991; Ring et al. 2005; Murray et al. 2016) and report poor clinical outcomes (Gelauff et al. 2014; Stone et al. 2003; Sharpe et al. 2010b).

Although challenging for a variety of reasons (Murray et al. 2016), there is a growing body of literature describing the reliable diagnosis of FNDs if undertaken by clinicians appropriately trained in neurological assessment (Carson et al. 2003). It is a diagnosis based upon positive signs of inconsistency such as distractibility, entrainment etc. in the context of particular precipitants and psychosocial factors. Recent work (Daum et al. 2014; Schwingenschuh et al. 2016; Avbersek & Sisodiya 2010) has described the diagnostic value of a broad range of these signs, which in a pilot sample provided specificities and sensitivities of 100% and 95% respectively for a variety of functional disorders (Daum et al. 2015). Consultation with a neurologist, although a reliable gold-standard, is financially prohibitive in large cohorts and scalable and accurate metrics of FND prevalence are lacking.

There have been several self-report questionnaire approaches to assessing somatic symptoms (Zijlema et al. 2013), the Patient Health Questionnaire-15 (PHQ-15) (Kroenke et al. 2002) being perhaps the most widely used, including in the validation of DSM-5 cross-cutting assessments (Regier et al. 2013; Narrow et al. 2013). These scores, although not initially intended for diagnostic use, have been applied (Van Ravesteijn et al. 2009; Körber et al. 2011) to the prediction of somatoform disorder with generally good sensitivities and specificities (78-80% and 59-71% respectively). In identifying FNDs specifically however, these tools fail to discriminate structural or “organic” from functional neurological disorders

and perform little better than chance when tested against clinical examination by a neurologist (Carson et al. 2014).

Questionnaires using specific items can be diagnostic however. Self-reported features of transient loss of consciousness using an 86-item tool could predict with accuracy a diagnosis of syncope, psychogenic non-epileptic seizures and epilepsy with sensitivities and specificities ranging from 80-95% and 74-93% between diagnoses (Reuber et al. 2016). There have so far been no attempts to construct a short, self-report questionnaire for the prediction of a functional neurological disorders in general. Such a questionnaire could be used to increase pre-test probabilities of a functional disorder diagnosis and assist in epidemiological research. We would not expect that a questionnaire would, or should, replace clinical diagnosis.

We therefore piloted a 30-item questionnaire that synthesised recognised diagnostic features of the neurological history in people with FND with the aim of exploring its diagnostic utility in screening for FND.

Methods

Patients

We recruited from consecutive newly referred general neurology patients who attended a clinic appointment at the Department of Clinical Neurosciences, Western General Hospital, Edinburgh in a 4-week period between September and October 2017. Prospective participants were sent an information letter in the post with their appointment describing the aims and nature of the study. All patients were approached and consented in the waiting room. Patients were excluded if: they were under 16, they did not attend their appointment, they had cognitive impairment or insufficient English language skills to provide informed consent or completion of the survey. Ethical approval for the study was granted by South East Scotland Research Ethics Committee.

Survey Design

A literature review was undertaken to identify differentiating features of history which may distinguish those reporting symptoms of a functional rather than an "organic" disorder. Expert consensus was used to construct a 30-item questionnaire (Appendix 1) from identified predictors which could be completed in under 10 minutes. We prioritised the most common symptoms presenting in outpatient neurology including: blackouts, pain, cognitive deficit, weakness, tremor, pain and fatigue. Features identified from the literature with evidence of diagnostic utility in these fields were:

- **Blackouts:** Lying still or shaking; Episodes in a medical setting (McGonigal et al. 2002); More than two seizures lasting more than 10 minutes (Alessi et al. 2013; Plug & Reuber 2009; Reuber et al. 2003); Ability to hear but not respond during a blackout (Avbersek & Sisodiya 2010); Pre-ictal dissociative symptoms (Stone 2006); Postictal crying/upset (Alessi et al. 2013).
- **Weakness:** Dropping things frequently; Variable severity; Worsening of weakness with attention (Pareés et al. 2013); Prodromal anxiety (Pareés et al. 2014; Stone, Alan Carson, et al. 2009); Associated depersonalisation (Stone et al. 2012);
- **Memory Problems:** Forgetting important details of everyday life(Schmidtke & Metternich 2009); Blank spells occurring during the day (Schmidtke & Metternich 2009); Oneself more bothered than others;
- **Tremor:** Sudden onset (Kenney et al. 2007); Precipitating traumatic event (Pareés et al. 2014); Variable severity (Kenney et al. 2007); Distractibility (Roper et al. 2013).
- **Pain:** Variable location and severity (Baker & Shaw 2007).
- **Fatigue:** Worsened by activity (Baker & Shaw 2007).

Patients only had to complete sub-questions regarding a symptom if they had reported experiencing the symptom as a "stem" question.

We also included questions about the presence of certain symptoms and features of clinical history that in themselves may be predictive of a functional disorder. These included hemisensory syndrome ('Do you have numbness or altered sensation that makes you feel like your body is cut in half?') (Toth 2003), globus (Finkenbine & Miele 2004), stutter (Baumgartner & Duffy 1997; Duffy 2016), multiple medical problems (McGorm et al. 2010),

and particular operations such as hysterectomy, appendicectomy, laparoscopy or tonsillectomy (Fink 1992; Longstreth & Yao 2004). These items did not have differentiating sub-questions. Demographic data including sex and age were also collected.

Diagnosis and Rating of explanation with respect to functional disorder

We asked neurologists to provide 1) their provisional diagnosis and 2) their assessment of the extent to which the patients' symptoms were related to a functional disorder. Functional neurological and somatic disorders remain a taxonomic challenge and often exist in a spectrum, concomitant with structural disease. For this reason, patients were scored according to a 4-point Likert scale: 'Not at All', 'Somewhat', 'Largely' and 'Completely' by clinicians in response to the question: "To what extent do you think the patient's clinical symptoms are explained by a functional disorder?". Definitions of functional disorders were supplied to clinicians as a guide to diagnostic category (Appendix 2). A graded classification like this allows for a broader evaluation of patients which may have symptoms without a structural cause but not a primary functional diagnosis. Note this question was an evolution of previous categorisations from our research group as 'not explained by disease' (Stone, A. Carson, et al. 2009). We were keen to move away from defining disorders by the absence of disease since they have their own positive diagnostic features, now recognised in DSM-5 criteria for Functional Neurological Symptom Disorder.

Questionnaire Analysis

For the purposes of analysis patients were grouped into having symptoms classed as 'Not at all/Somewhat' and 'Largely/Completely' due to a functional disorder. Univariate analysis was undertaken on individual questions by cross-tabulation and significance testing using Fisher's Exact test. Symptom and gross ENS score were assessed using two-tailed Student's T tests. Multivariate analysis was undertaken via logistic regression. We first analysed the diagnostic utility of sub-questions in predicting classification of 'Largely' or 'Completely' functional for reporters of a particular symptom. Linear models for each symptom were used to return a score for likelihood of functional classification. Scores from these symptoms were then combined in an aggregate model with symptoms and features that did not have sub-questions and demographic data to provide an overall score. This method

introduces a significant positive bias into the second round of modelling, as symptoms with sub-questions have already been weighted towards predicting a functional outcome. Alternative options such as hierarchical logistic regression and stratifying patients by reported symptoms were prohibited by sample size and the number of potential symptom combinations. We justify this method as exploratory and speculative in the context of a pilot that aims to obtain a broad picture of the potential utility of a general screening tool. Questions which provided perfect or quasi-separation were excluded from multivariate analysis and their contribution assessed during univariate analysis only. All analysis was conducted in MATLAB© Release 2015b using custom written scripts.

Results

Data were gathered on 165 patients, 56 (34%) participants had data missing and were excluded leaving 109 (Age = 44.6 ± 17.1 years; Female:Male Ratio = 1.53:1) responses available for analysis. 104/109 (95%) of those surveyed responded having at least one of the symptoms included in the questionnaire.

73/109 (67%) patients were classed as having symptoms 'Not at All/Somewhat (N/S)' and 36/109 (33%) as 'Largely/Completely (L/C)' due to a functional disorder. The most common diagnoses made in those classified as 'Not at All/Somewhat' were: Epilepsy 16/109 (15%), Migraine 11/109 (10%), peripheral neuropathy or radiculopathy 9/109 (8%), headache syndromes 6/109 (6%), first seizure 6/109 (6%) and demyelinating disease 5/109 (5%). In those classified as 'Largely/Completely': dissociative seizures 9/109 (8%), functional weakness 3/109 (3%), functional sensory changes 3/109 (3%), anxiety related symptoms 3/109 (3%), functional memory symptoms 1/19 (1%) and FND not otherwise specified 2/109 (2%) were the most common diagnoses. Female:Male ratio differed significantly between groups (N/S = 1.09:1; L/C = 3.5:1; Fisher's Exact p = 0.0098) whilst age did not (N/S = 46 ± 17.5; L/C = 41.6 ± 16.2; two-tailed Student's T p = 0.2).

The 56 participants excluded from analysis due to incomplete questionnaires or consultant diagnosis were marginally older than those included (47.15 ± 17.1 vs 44.6 ± 16.83 years; Student's t-Test p = 0.36) and had a greater F:M ratio (2.31:1 vs 1.53:1; Chi-square p =

0.72). 15/56 were excluded for lack of diagnosis outcome data, of those remaining 28/41 (68%) were classed as having symptoms 'Not at all/Somewhat' due to a functional disorder and 13/41 (32%), similar proportions to those included in analysis (Chi-Square p = 0.88).

Univariate Analysis: Few questions provide diagnostic utility and gross scores fail to discriminate patients.

Answers to all symptom questions and sub-questions are displayed in Table 1. Some symptoms were reported significantly more frequently by those classed as 'Largely/Completely' functional, including: hemisensory disturbance (N/S = 8/73 (11%); L/C = 11/36 (31%); p = 0.016), tremor (N/S = 19/73 (11%); L/C = 17/36 (31%); p = 0.016), pain (N/S = 24/73 (33%); L/C = 22/36 (61%); p = 0.007), fatigue (N/S = 40/73 (55%); L/C = 28/36 (78%); p = 0.022).

5/20 symptom features were reported significantly more often by patients classed as 'Largely/Completely' related to a functional disorder including: having had a blackout in a medical setting (N/S = 1/21 (5%); L/C = 5/9 (56%); p = 0.005); being able to hear others but not respond during a blackout (N/S = 5/21 (24%); L/C = 8/9 (89%); p = 0.002); crying or being upset after a blackout (N/S = 5/21 (24%); L/C = 6/9 (67%); p = 0.042); having blank spells occurring throughout the day if also experiencing memory problems (N/S = 12/39 (31%); L/C = 15/22 (68%); p = 0.007) and experiencing pain that is variable in severity and location (N/S = 10/24 (42%); L/C = 16/22 (73%); p = 0.042).

Gross symptom count was significantly different between 'N/S' and 'L/C' patients (N/S = 3.15 ± 2.07; L/C = 4.33 ± 2.27; 2-Tailed Student's T p = 0.008) (Figure 1A) but without diagnostic utility (Receiver-operator characteristic area under the curve (AUC) = 0.595). Raw Edinburgh Neurosymptom Score (ENS) scores, which include the addition of sub-questions designed to provide a positively discriminating score, yields greater gross scores for 'L/C' patients, again significantly so (N/S = 7.95 ± 5.48; L/C = 11.69 ± 7.27; 2-Tailed Student's T p = 0.003) (Figure 1B) but again without diagnostic utility (AUC = 0.602).

Multivariate sub-question analysis: Blackouts may be amenable to questionnaire diagnosis, but other symptom groups lack discriminating questions.

Logistic regression analysis of individual "common" symptoms is described in Figure 2. Only three sub questions obtained significance during multivariate analysis. Q1d: "Have you ever been able to hear people but not respond to them during your blackout?" ($p = 0.047$; OR = 20.72 (0.88-487.97)), Q4c: "Do you have blank spells which occur during the day?" ($p = 0.019$; OR = 4.066 (1.23-13.45)), and Q6a: "Is your pain worse in different parts of your body on different days?" ($p = 0.037$; OR = 3.73 (1.04-13.37)). Diagnostic utility (AUC) of sub-questions for each symptom were: blackouts = 0.94, weakness = 0.71, memory problems = 0.74, tremor = 0.63, pain = 0.66 and fatigue = 0.6.

Aggregate symptom score modestly predicts functional classification.

Scores from symptom sub-question modelling were input into an aggregate model with other symptoms, features of clinical history, sex and age. Variable coefficients for the resulting model are shown in Figure 3. Only adjusted pain score ($p = 0.047$) and adjusted blackout score ($p = 0.021$) achieved significance in the model, with odds ratios 26.80 (2.00-359.59) and 40.15 (1.73-930.21) respectively.

Resulting aggregate scores were capable of predicting functional disorder likelihood with modest utility (Figure 4) (AUC = 0.83) and "optimal" operating point, as determined by minimising false positive rate, resulting in specificity and sensitivity of 0.99 and 0.47 respectively. Positive and negative predictive values were 0.94 and 0.79. The model accounted for little of the variability in the outcome (Adjusted $R^2 = 0.23$) but performed better than the constant model (Chi-squared Test vs Constant model $p < 0.001$).

Symptom 'networks' may aid in differentiating functional patients.

We also investigated whether symptom combinations or interactions may provide insight into functional vs structural questionnaire responses. Inclusion of interaction terms in regression analysis was prohibited by sample size therefore conditional probabilities between symptom pairs were computed instead. Of the 110 possible bidirectional symptom

pairings, patients classed as 'Largely/Completely' functional were more likely to report one symptom after reporting another when compared to those classed as 'Not at All/Somewhat' in 76/110 pairings. Figure 5 exhibits how fatigue plays a central role in these interactions, being reported by more than 80% of those also reporting: stutter, memory problems, pain, weakness, blackouts, globus, altered sensation, tremor and multiple medical problems. Only one symptom pair (P(Memory problems | Multiple medical problems)) reaches this threshold in those with symptoms not explained by a functional disorder and none do so when paired with fatigue.

Discussion

This is the first reported pilot of a general screening questionnaire to improve the pre-test probability of a diagnosis functional neurological disorders. We find that gross number of symptoms, in the subset we investigate here, failed to distinguish cases from controls. Addition of items in our novel questionnaire about features reportedly specific to functional disorders also commonly failed to distinguish patient groups in our sample. We found some exceptions, where patients classified as having functional symptoms more commonly reported features of: Blackouts (having had a blackout in a medical setting, being able to hear people but not respond during a blackout, being upset following an episode); Memory problems (having associated blank spells during the day); Pain (reporting variability in bodily location and severity.

Symptoms scores weighted according to these features in an aggregate model show good specificity (0.99) but poor sensitivity (0.47) when compared to consultant neurologist impression as measured on a 4-point Likert scale. Resulting positive and negative predictive values (0.94 and 0.79 respectively) were however, promising, and had greater utility as a pre-screening diagnostic tool for FND than measures based on symptom counts such as PHQ-15 (Carson et al. 2014; Van Ravesteijn et al. 2009). Although effective for excluding those deemed to have symptoms of an "organic" cause, our linear score failed to reliably identify patients with FND from a general neurology outpatient population. Our speculative assessment of symptom interactions suggests that non-linear methods that take account of multivariate higher order interactions may prove a more valuable approach.

Eliciting self-reported positive features of functional disorders is challenging.

Although many discriminating features of history have been described in the literature and anecdotally, our data show that these are difficult to translate into specific and sensitive questions for patients to answer in an unguided way. The corollary being that although our understanding of the semiology and history of functional symptoms has improved, the ability to extract that from patients in a meaningful way is still the remit of an experienced diagnostic interview and physical examination.

Capturing the recognised linguistic features of FND descriptions is a core problem in constructing a viable self-reported screening questionnaire. There is now a significant body of work highlighting these discriminating features: Poor formulation effort (Schwabe et al. 2008), inconsistent metaphorical conceptualisation (Plug et al. 2009), and vague seizure experience descriptions in psychogenic non-epileptic seizures; preserved working memory, the ability to process compound questions and good recollection of personal information in functional memory disorders (Jones et al. 2016); post-exertional malaise in fatigue (Keech et al. 2015). However, those studies were all done on the basis of interactive conversation analysis. Self-report tools implicitly rely on a particular symptom being amenable to self-recognition. Transposing clinical observations into questions capable of eliciting introspection and 'accurate' response is a clear limitation to such an enquiry. It may be that questionnaire items need to be refined or that questionnaires are, themselves, too crude a tool.

Perhaps a surprising finding in this population is that questions regarding functional symptoms such as globus and stutter show poor diagnostic utility in both univariate and multivariate analysis. Although globus and adult onset stutter are generally considered to relate to a functional disorder they were reported with similar frequency in both functional and non-functional groups, albeit in small numbers. There were also interesting responses in those with symptoms unexplained by a functional disorder to questions that are commonly associated with functional disorders. For example, 8 out of 73 patients reported that they had numbness or altered sensation that made them feel 'like your body is cut in

half' (Toth 2003) and 5 out of 21 patients reported tearfulness after blackouts (Avbersek & Sisodiya 2010). Questions about movement disorders also indicated the difficulty of using questionnaires to elicit a history. All 19 patients who reported an abnormal movement such as tremor in the structural group said it came on suddenly. But what a neurologist understands as sudden, e.g. not there at 10.58am and present at 11.00am – may not be the same as how a patient understands that word – e.g. I didn't have it last year and suddenly this year I do. It was also surprising how many movement disorder patients said that their movements could go away for hours or days (16/19).

The importance of diagnostic tools and more effective diagnostic procedures in FNDs

A standardised and easily administrable tool for the screening of functional disorders has the potential to enhance clinicians' pre-test probability for making a diagnosis of functional disorder and, as a consequence of earlier intervention, reduce iatrogenic harm. A shorter duration of symptoms prior to diagnosis often predicts a favourable prognosis in FNDs (Gelauff et al. 2014; Sharpe et al. 2010a). Early identification of patients with likely functional symptoms could also assist in quantifying their prevalence and demographics at an epidemiological scale. So far this has been unattainable with the present non-specific tools and the expense of definitive clinical diagnosis.

Limitations

This was a pilot study of a new approach to FND diagnosis, with a relatively small sample size. Our reported predictive values are dependent on prevalence calculated on a relatively small population which, for certain symptoms, failed to meet the generally accepted rule of 5-10 participants per predictor variable (Kupper & Hafner 1989). The large variances observed during linear modelling may be a reflection of this, or a reflection of the variable nature of functional disorders. There is a risk that some patients were classified in to the wrong diagnostic group by the neurologists seeing them, although a similar study found a very low rate of misdiagnosis at 18 months follow up (Stone, A. Carson, et al. 2009). We also don't know whether, even if the neurologist rated the main diagnosis as "organic", the symptom the patient gave their responses about would have received the same rating. We are also cautious to highlight the limitations of the present two-stage modelling. Ideally,

sub-question coefficients should be computed on a separate population from the overall aggregate score to prevent a significant bias in favour of symptoms with sub-questions in the final model.

Our final model is biased to a degree by case deletion of those with incomplete questionnaires. 109 individuals were included in the final analysis, with 56 (34%) of the 165 participants excluded. Given this significant proportion we sought to establish whether their inclusion in analysis might mitigate some of the bias case deletion introduces. Given that we first model symptom sub-questions on a subset of those reporting that symptom, we sought to include every participant who had at least answered a single symptom's sub-questions completely in the first stage of modelling. Using symptom scores derived from this more inclusive criterion, we then reran the aggregate model with the 109 respondents who had complete questionnaires. Resulting sub-question coefficients were similar with Q1d: "Have you ever been able to hear people but not respond to them during your blackout?" and Q4c: "Do you have blank spells which occur during the day?" remaining significant with p values in the new model 0.039 and 0.006 respectively. And Q6a: "Is your pain worse in different parts of your body on different days?" becoming less significant ($p = 0.052$). In the final aggregate model, blackout scores become insignificant (OR = 7.97 (0.57-111.68)) but pain scores remain predictive (OR = 21.87 (1.34-358.05). Aggregate scores however retain similar discriminate utility (AUC = 0.80) and sensitivity of 0.64 and specificity of 0.84 at the 'optimal' operating point.

We also found that many of our questions, or question wordings, although constructed to elicit positive answers in those experiencing functional symptoms, failed to do so on many occasions. Only blackouts, memory problems and pain domains had sub-questions answered significantly more often by patients deemed 'Largely/Completely' functional. The heterogeneity of both FND and neurological pathology in general may be the limiting factor to such a broad goal. It is clear that if the present tool is to be developed, and sensitivities greater than 0.47 are to be achieved, question wording and inclusion needs to be adjusted considerably.

Readers may also wonder why we didn't study the performance of the relevant subsections of the questionnaire for diagnostic categories (e.g. functional gait disorder, non-epileptic seizures). This was firstly because the numbers involved would have been too small and secondly because patients with functional neurological disorders often have mixed symptoms which are not always picked up on diagnostically by neurologists.

Conclusions

Despite limitations, this pilot version of an ENS questionnaire was, in its complete form, surprisingly capable of reliably excluding patients diagnosed by neurologists as *not* having a functional disorder. It was capable of including a significant number of functional patients, particularly those that report blackouts, memory problems and pain. The use of specific positive features of functional disorder in an aggregate model rather than linear summation of symptom counts has shown promising utility. Future work could aim to investigate more systematically how those who experience functional symptoms, outside the domain of blackouts, report their disorder and therefore how to improve the questions or wording in later versions of this questionnaire.

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433 # Table 1

The Edinburgh Neurosymptoms Questionnaire	Symptoms explained by a functional disorder: Not at All/Somewhat	Largely/Completely	p-value
N	73/109 (67%)	36/109 (33%)	
Sex	F:M = 1.09:1	F:M = 3.5:1	0.01**
Age (Mean ± SD)	46 ± 17.5	41.6 ± 16.2	0.200
Symptom Count (Mean ± SD)	3.15 ± 2.07	4.33 ± 2.27	0.008**
Gross ENS Score (Mean ± SD)	7.95 ± 5.48	11.69 ± 7.27	0.003**
Q1: During the last 6 months have you been bothered by blackouts?	21/73 (29%)	9/36 (25%)	0.830
Q1a: During you blackouts do you get told you lie still or shake?	Lie Still: 5/21 (24%) Shake: 13/21 (62%) Unsure: 3/21 (14%)	Lie Still: 3/9 (33%) Shake: 4/9 (44%) Unsure: 2/9 (22%)	0.673
Q1b: Have you ever had a blackout in a medical setting e.g. visiting the hospital/GP/another doctor?	1/21 (5%)	5/9 (56%)	0.005**
Q1c: Have you had more than two seizures during which you shook without stopping for more than 10 minutes? (This does not include the time taken for you to come round after the seizure had finished)	2/21 (10%)	2/9 (22%)	0.563
Q1d: Have you ever been able to hear people but could not respond to them during your blackout?	5/21 (24%)	8/9 (89%)	0.002**
Q1e: Do you ever have moments before your blackouts of losing track of what is going on, of "blanking out" or "spacing out" or in some way feeling that you are not part of what is going on?	13/21 (62%)	9/9 (100%)	0.067
Q1f: Are you told that after an attack you cry or are upset?	5/21 (24%)	6/9 (67%)	0.042*
Q2: During the last six months have you been bothered by weakness in one or more limb e.g. arm(s) or leg(s)?	30/73 (41%)	20/36 (56%)	0.220
Q2a: Do you drop things frequently?	13/30 (43%)	13/20 (65%)	0.159
Q2b: Does your limb weakness get worse or better at different times of the day?	14/30 (47%)	10/20 (50%)	1.000
Q2c: Does concentrating on trying to move make the limb weakness worse?	6/30 (20%)	9/20 (45%)	0.114
Q2d: At the start of your limb weakness did you feel your heart pounding or did you feel frightened, anxious or very uneasy?	9/30 (30%)	10/20 (50%)	0.235
Q2e: Does your weak limb feel like it does not fully belong to you?	13/30 (43%)	11/20 (55%)	0.565
Q3: Do you have numbness or altered sensation that makes you feel like your body is cut in half?	8/73 (11%)	11/36 (31%)	0.016*
Q4: During the last six months have you been bothered by memory problems?	39/73 (53%)	22/36 (61%)	0.540
Q4a: Who is most bothered by your memory problems, you or your partner/family/friends?	Family: 3/39 (8%) Me: 32/39 (82%) Unsure: 4/39 (10%)	Family: 4/22 (18%) Me: 16/22 (73%) Unsure: 2/22 (9%)	0.467
Q4b: Are you bothered by forgetting important details such as the name of a family member or your PIN number?	17/39 (44%)	14/22 (64%)	0.184
Q4c: Do you have blank spells which occur during the day?	12/39 (31%)	15/22 (68%)	0.007**
Q5: During the last six months have you been bothered by tremor or an abnormal movement in one or more limb e.g. arm (s) or leg(s)?	19/73 (26%)	17/36 (47%)	0.032*
Q5a: Did your tremor or abnormal movement come on suddenly?	19/19 (100%)	15/17 (88%)	0.216
Q5b: Did your tremor or abnormal movement come on after an injury or accident?	2/19 (11%)	3/17 (18%)	0.650
Q5c: Can your tremor or abnormal movement go away completely for hours to days only to return again?	16/19 (84%)	16/17 (94%)	0.605
Q5d: Does your tremor or abnormal movement ever stop when you are distracted or concentrating on something else?	3/19 (16%)	5/17 (29%)	0.434
Q6: During the last three months have you had pain almost every day in more than one part of your body?	24/73 (33%)	22/36 (61%)	0.007**
Q6a: Is your pain worst in different parts of your body on different days?	10/24 (42%)	16/22 (73%)	0.042*
Q7: Have you been lacking energy every day or almost every day for the last six months?	40/73 (55%)	28/36 (78%)	0.022*
Q7a: Does activity make your fatigue worse?	25/40 (63%)	23/28 (82%)	0.107
Q8: In the last five years have you had to see doctors in the hospital for different problems more than four times? (E.g. problems with your heart, your joints, your brain and gut)	27/73 (37%)	16/36 (44%)	0.533
Q9: Do you get a feeling that there is a lump in your throat or something stuck when you are trying to eat or drink?	18/73 (25%)	8/36 (22%)	1.000
Q10: Do you have a stutter which started after you were more than 16 years old?	4/73 (5%)	3/36 (8%)	0.682
Q11: Have you needed any operations?	40/73 (55%)	16/36 (44%)	0.415

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Figure 1

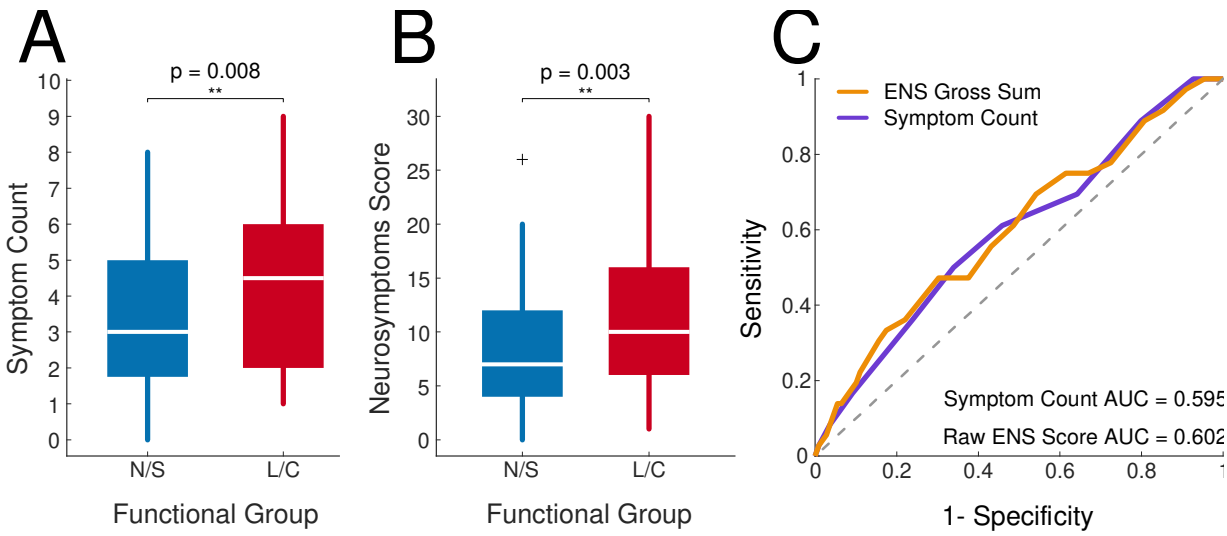

Figure 1: Comparison of gross scores. A - Boxplot of symptom counts separated by functional classification. Symptom counts are significantly greater in patients with functional disorder. **B -** Boxplot of gross scores for full 30-point ENS questionnaire. The addition of discriminating sub-questions yields greater scores for 'Largely/Completely' explained by functional disorder. **C -** ROC curve of symptom count and gross sum. Symptom count and raw ENS scores fail to provide diagnostic utility (N/S = Not at All/Somewhat; L/C = Largely/Completely explained by a functional disorder).

Figure 2

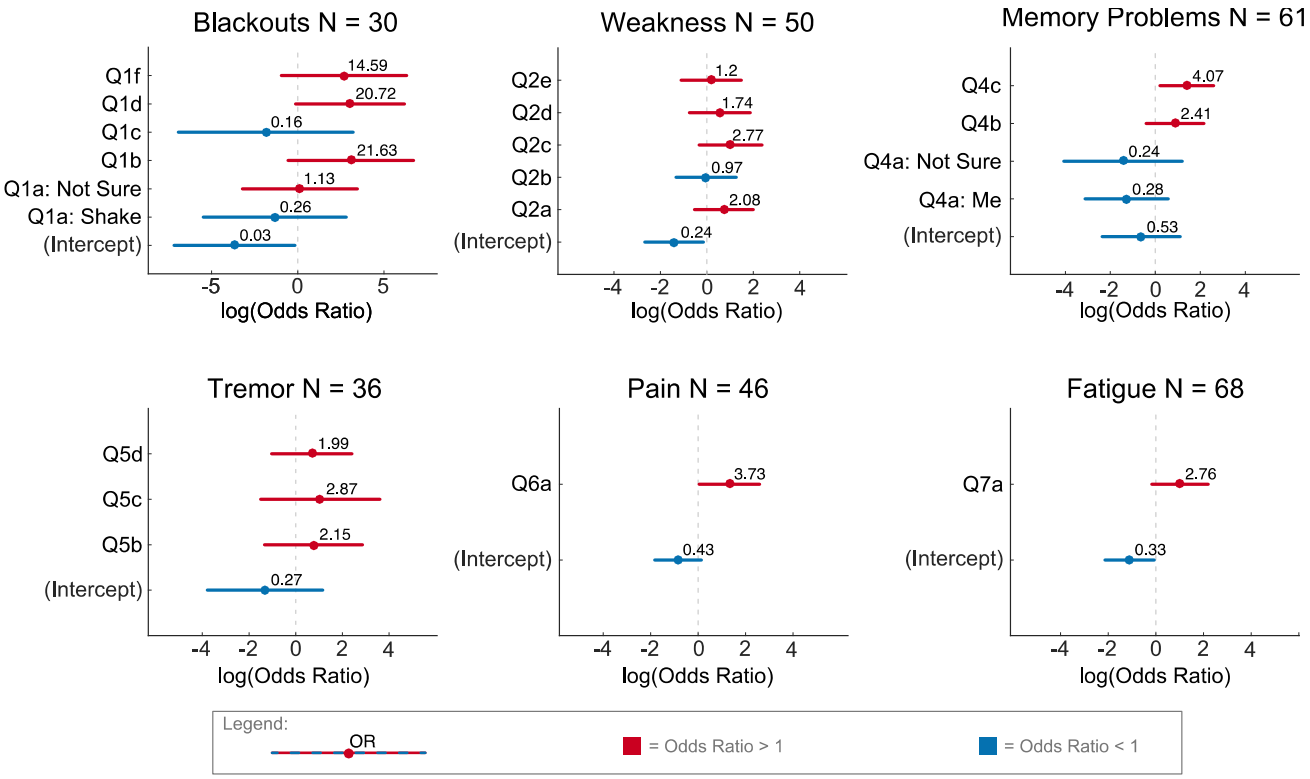

Figure 2: Results of multivariate sub-question analysis. Sub-questions were input as predictor variables and the resulting coefficients, confidence intervals and odds ratios are displayed above. Only Q1d, Q4c and Q6a achieve significance in their respective models. Most sub-questions provide, as expected, a positive predictive value for functional classification, but only 3 did so with odds ratios significantly greater than 1.

Figure 3

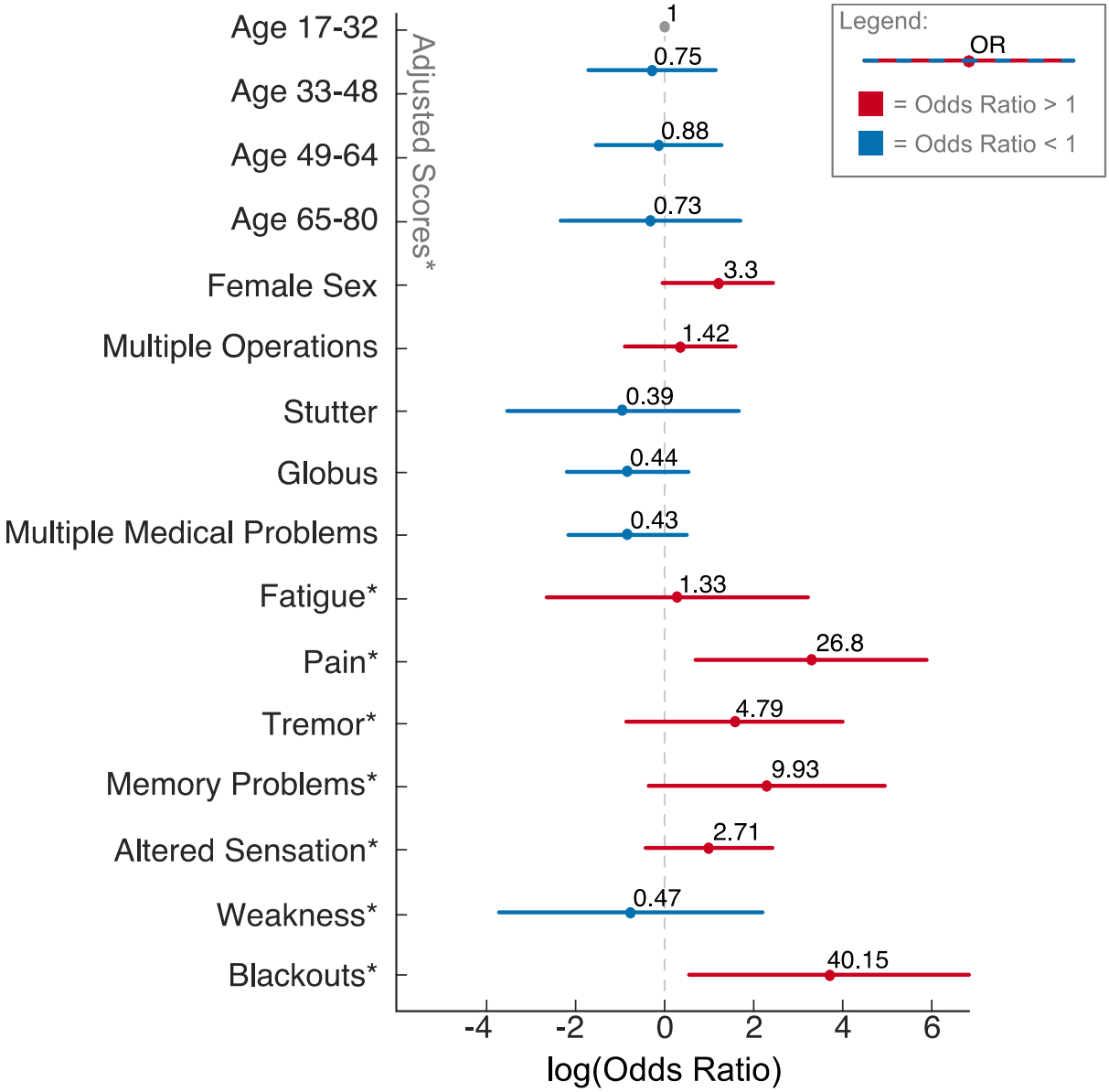

Figure 3: Aggregate score coefficients. Forest plot showing linear coefficients and confidence intervals for each variable in the aggregate model. “Common” symptoms have been replaced by the linear predictor scores from sub-question modelling. Odds ratios are displayed for each coefficient above the bar. Adjusted scores for pain and blackouts achieve significance and drastically increase the odds of correct classification.

Figure 4

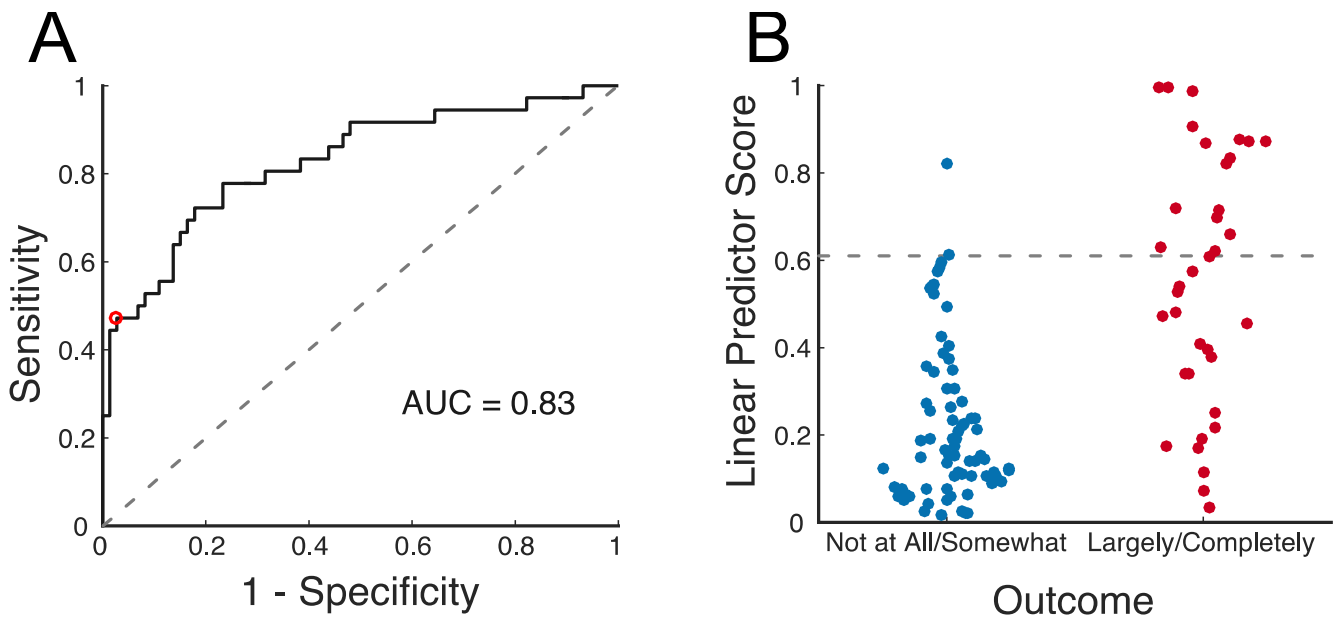

Figure 4: Diagnostic utility of the ENS questionnaire. A - ROC curve of aggregate linear model scores predicting consultant classification of patients with symptoms 'Not at All/Somewhat' or 'Largely/Completely' functional. The optimal operating point is displayed as a red circle on the curve. Predictor scores were capable of achieving an AUC of 0.83. **B -** Scatter plot of aggregate model scores separated by functional classification. The corresponding optimal score identified in ROC analysis is displayed as a grey dotted line. The model is capable of excluding non-functional patients effectively, but many functional patients are missed with the 'optimal' threshold.

Figure 5

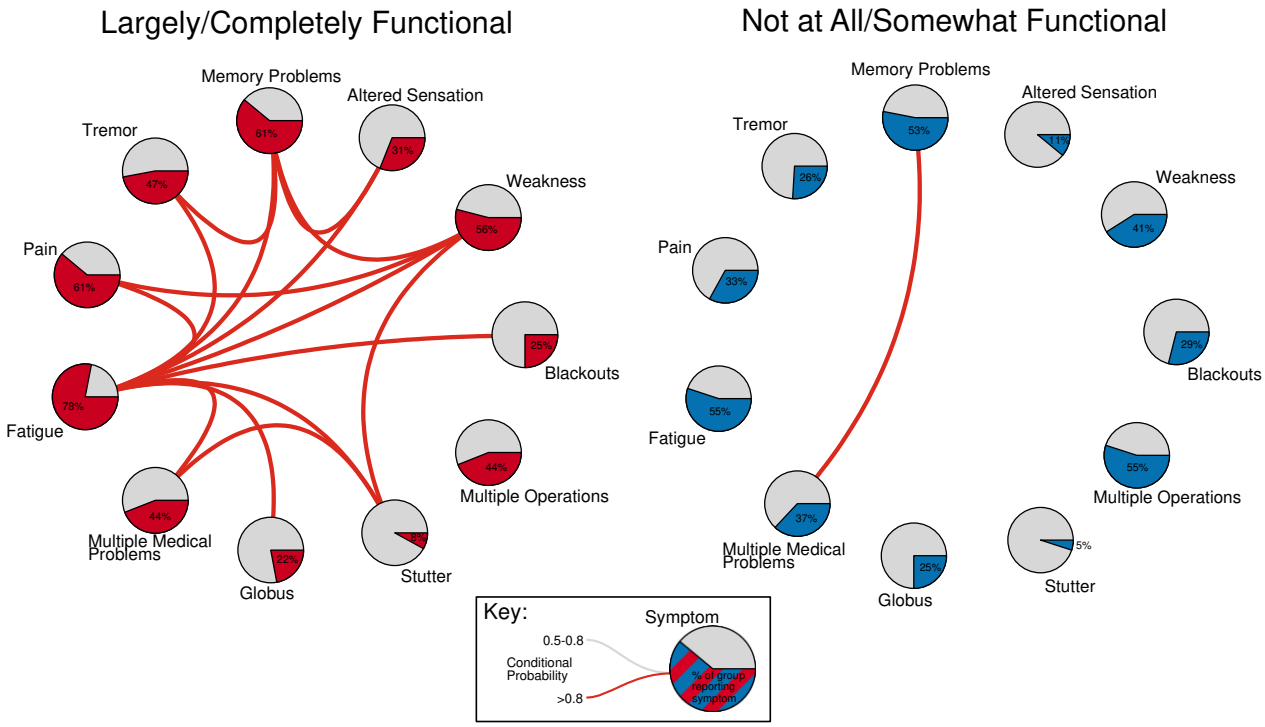

Figure 5: Symptom interactions. Paired conditional probabilities of symptoms occurring if another symptom is reported. Red lines indicate a symptom pair in which there is a more than 80% likelihood of a co-occurrence. Grey lines indicate co-occurrence > 0.5 and are weighted linearly between 0.5-0.8. Patients with functional disorders reported symptom networks that are far more connected than structural patients. Fatigue plays a central role in the visible differences. (Red: Functional class = 'Largely/Completely'; Blue: Functional class = 'Not at All/Somewhat').

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Appendix 1

Edinburgh Neurosymptoms Questionnaire (Attached by email)

Appendix 2

Consultant diagnostic/classification guidance (Attached by email)