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Subjective versus objective measures of distress, arousal and symptom burden in patients with functional seizures and other functional neurological symptom disorder presentations: A systematic review

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ABSTRACT

Symptoms and functioning can be measured subjectively using self-report measures or objectively, based on physiological changes. This raises the question whether subjective and objective measures are closely correlated and – if not – whether one is more accurate or meaningful than the other, especially in patients with Functional Seizures (FS) or other Functional Neurological Symptom Disorders (FND), where subjective and objective observations may be thought particularly likely to deviate. This systematic review explores these questions focussing on measures of distress, arousal and symptom burden. Eighteen studies (12 FS, 6 other FND) capturing 396 FND patients were included. Eleven reported no correlation between subjective and objective measures. Only four studies reported significant correlations (r's = −0.74–0.59, p's < 0.05). The small number of studies and diverse methodologies do not provide conclusive answers to the questions posed. Given that subjective and objective measures capture different aspects of current state or function, a combination of measurement approaches is likely to provide optimal information about patients' health state. In view of the attentional and perceptual alterations implicated in FND, the difference between objective and subjective measures may represent an interesting observation in its own right.

Contents

Abbreviations: FS, Functional Seizures; FND, Functional Neurological Symptom Disorder; FMD, Functional Movement Disorder; DSM-5, Diagnostic and Statistical Manual, 5th edition; FCD, Functional Cognitive Disorder; ILAE, International League Against Epilepsy.

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Introduction

Functional Neurological Symptom Disorder (FND) is defined by the presence of distressing neurological symptoms not explained by readily identifiable structural or physiological pathological changes capable of explaining the clinical presentation [1]. The process of diagnosing FND is not limited to the exclusion of neurological disease but involves the identification of typical manifestations of FND suggesting that FND is a condition caused by abnormalities of functioning in brain networks underpinning attention, perception and association [2–5]. Different forms of FND are distinguished on the basis of the predominant neurological symptom, including but not limited to: Functional Seizures (FS), Functional Movement Disorder (FMD) and Functional Cognitive Disorder (FCD).

FND is the second most common diagnosis made in neurology outpatient clinics. It accounts for 11% of neurological outpatient attendances or 9% of neurological hospital admissions and causes levels of disability similar to those found in neurological diseases causing similar symptoms (such as epilepsy or multiple sclerosis) [3]. FND most commonly presents to neurologists as FS. Many patients presenting with FS develop chronically disabling disorders with considerable impact on social/occupational functioning, mental health and physical health. Chronic FS disorders are associated with significant healthcare and societal costs [6–7].

Subjective and objective measures in FND

A number of treatment approaches have been proposed for FS disorders, but the choice of outcome measures poses particular challenges in patients with FND [21–22]. As research in this disorder has moved beyond the emphasis on psychosocial stressors and psychological theories to potentially relevant neuro-biological mechanisms, researchers have increasingly adopted objective measurement approaches including physiological, performance-based testing or neuroimaging. While symptoms (such as FS frequency or core symptom severity in other types of FND) may seem like the most intuitive aspect of disorders to measure [23]; core symptom, physical and psychological heterogeneity, as well as variability in life impact, disability, social functioning and illness perception in FND confound the selection and utilisation of outcome measures. No single standardized way of recording these outcomes has been established. A focus on one particular FND symptom (e.g., seizures) is only conceivable in particular subgroups of patients with this disorder. Additionally, discrepancies exist between subjective and objective findings in patietns with FND. Objective "positive" indicators of an FND referred to in the DSM-5 include examples such as the subjective inability to move a limb but an ability to execute motor movements within the context of a Hoover's test and thus there is ongoing discussion about the validity of subjective reporting in FND [24–25].

The understanding of "objectivity" of outcome measures varies in the literature depending on methods, researcher perspectives or aims. Objective measures can be considered as any measure distinct from the influence of patients' subjective experience: this can include routine neurological examination (clinician grading of power), impression of symptoms or function by an observer (clinical or caregiver-rated). However, some clinician-rated measurements are not truly objective due to the degree of subjectivity involved in the grading based on observation. Objective measures based on biological/physiological changes, for example, seizure frequency during continuous EEG telemetry, changes measured using wearable monitoring devices, or differences in biological indicators of arousal may be more reliable.

Measures of stress, distress or arousal are of particular interest in the clinical context of FND because most current aetiological models consider these factors relevant in the pathogenesis of this disorder and not simply a consequence of experiencing FS/FND [8,9]. Evidence for this association comes from subjective self-reporting and suggest that patients with FND experience their lives as more stressful, are more aroused or anxious and often use maladaptive emotion processing strategies [10–14]. In those with FS, there is also objective evidence that ictal events are associated with physiological arousal [15], and in FND more generally there is accumulating objective evidence of heightened stress sensitivity [16]. Increased activation of multiple components of the stress system including the hypothalamic–pituitary–adrenal axis (HPA) and the autonomic nervous system [17,18] have been reported, while brain imaging studies suggest networks involved in arousal and emotion-processing are hyper-active in patients with FND [19–20].

Based on these observations, FND has been theorized as a behavioral or dissociative response to distressing emotional, physiological or social stimuli [8,19]. As such, evidence of how effectively patients cope with stress and regulate their emotions is particularly relevant to function and symptom control in FND.

The wide range of available and suggested subjective and objective/behavioral current state and outcome measures for patients with FND raises the questions: to what extent findings of subjective/objective approaches correlate with each other, and whether one approach provides a more accurate and/or clinically meaningful picture than the other. To address these questions this systematic review provides an up-to-date synthesis of studies that have combined both subjective 'self-report' measures and objective 'physiological or experimental task-based' or 'behavioral' measures of stress, distress and arousal in individuals with FND.

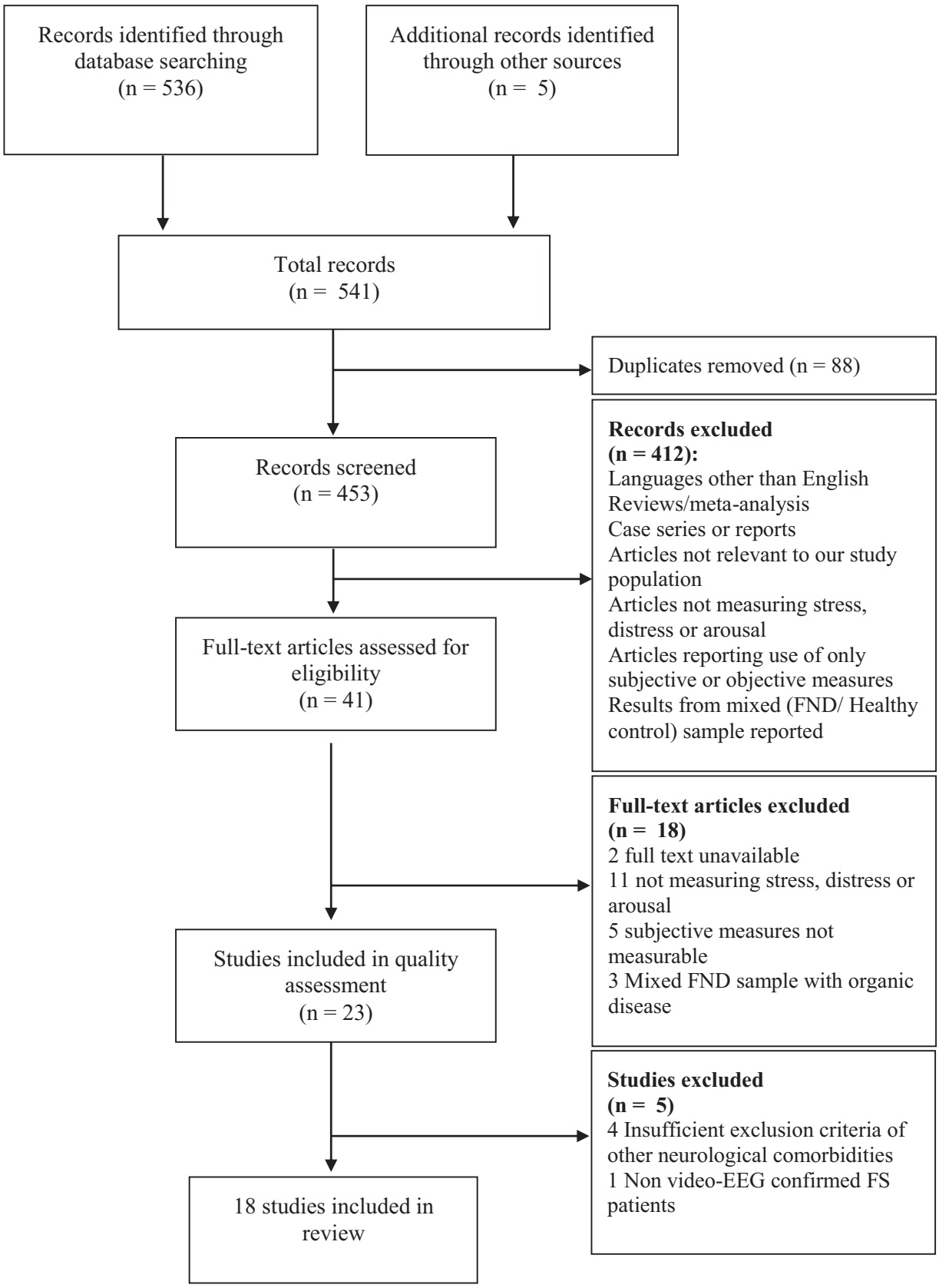

Fig. 1. PRISMA flow diagram detailing the database searches, and study selection.

Methods

Literature search

A systematic literature search of the PubMed and Science Direct and Embase databases was conducted on 17/08/2021 to capture relevant studies. The search terms to identify relevant publications were *"conversion disorder" OR "functional neurological disorder" OR "psychogenic" OR "non-epileptic" OR "dissociative seizures") AND ("heart rate", "heart rate variability", "interoception" "interoceptive sensitivity" "interoceptive ability" "cortisol", "respiration" "skin conductance" "stress" "distress" "arousal" "anxiety" "blood pressure") AND ("subjective" OR "self-report" OR "questionnaire"*.

Following removal of duplicates and citations from non-English journals, paper titles and abstracts were scrutinised by JA in a first screening to identify potentially eligible studies; those evidently outside the scope of the review were rejected. Full-text articles of the remaining studies were screened using the defined inclusion criteria. The reference lists of eligible studies and reviews were searched for additional articles. Several synonyms for FS and FND were used to capture the relevant subject population. These were used in combination with terms describing commonly used objective and subjective measures of (di-)stress, arousal and symptom burden.

Study selection

Studies were included if the following criteria were met: 1) they report on patients with functional neurological disorders, described as functional, non-organic, psychogenic, hysterical or conversion disorder; 2) they report data measuring stress, distress, arousal or symptom burden with at least 1 objective (physiological) outcome and at least 1 subjective (self-reported) outcome; 3) the size of each patient group was at least 10. Studies in paediatric as well as adult populations and studies with or without healthy controls were included.

For studies to be included, diagnostic criteria for patients had to meet DSM-5 criteria for FND by individual study authors or by the authors of this current review if predating the DSM-5.

The descriptive terminology for objectivity and subjectivity was ill defined in the reviewed studies. In order to address the research question accurately, there was a need to impose a taxonomy to allow quantitative study and analysis. "Objective" outcome measures were defined as those having a physiological or biological basis; and/or explicitly measuring physiological or cognitive functioning with minimal interference/bias/ influence of patients' own perception. "Subjective" measures were defined as measures completed by patients/study participants with quantifiable ordinal scoring. This excluded qualitative assessment or data acquired from unstructured interviews.

Studies were excluded: 1) when only subjective or objective measures were utilized in isolation and not used in combination; 2) where the FND population included patient with comorbid organic disease – particularly in the case of non-epileptic seizures and epilepsy; 3) when the full text was not available; 4) when studies were not available in English. Other exclusion criteria included review articles, meta-analyses and case reports or series, conference abstracts, book reviews, journal notes, and journal letters. Fig. 1 shows a PRISMA flow diagram of the systematic review methodology utilized for this article.

Data extraction and analysis

All articles were reviewed independently by JA. The following data were systematically extracted: (a) investigative aim; (b) symptoms of the FND population; (c) objectives and outcome measures; (d) study design; (e) type of study; (f) year of the study; (g) main findings and (h) conclusions.

For the sake of uniformity, we chose to use the term 'functional' in line with its use in the DSM-5 when describing different studies, even when the authors themselves used another terminology (i.e., "hysterical", "psychogenic", "conversion", "medically unexplained"). Objective outcomes and ordinal subjective scores were scrutinised. Correlations from studies directly comparing scores within group are reported in Table 1.

Quality assessment

The methodology used in assess study quality in those deemed eligible for inclusion was formally appraised using an adaptation of the Critical Appraisal Skills Programme (CASP). The scale was adapted for relevance to this research field following recommendations from Brown and Reuber [26] and the authors knowledge of the area with respect to the review question. The final appraisal tool combined quality items from the CASP checklist (using the relevant checklist for the respective study design), and the reliable rating system designed specifically for quantitative research in this field [8]. This incorporated assessment of the attempt of researchers to identify appropriate and representative participants, appraising whether: i) the FND diagnoses for inclusion were reliable and referenced (e.g. all FS diagnoses had been video-EEG confirmed); ii) if additional neurological diseases had been explicitly ruled out or controlled for within analysis; iii) recruitment was consecutive; and iv) dependent variables had been standardized. Given the aims of this review, we included further specific quality items pertaining to data analysis; i.e. whether study authors carried out appropriate assessment of the measures utilised in the study, multivariate analysis and corrections for multiple comparison (when required). Individual quality indicators can be found in supplementary Table 2.

Results

Included studies

In total, 18 studies met the inclusion criteria, providing data on subjective and objective measures of stress, distress (including symptom burden) or arousal for 396 FND patients. All of the studies had a control group which included either healthy participants (n = 303) and/or participants with a neurological or psychiatric diagnosis (n = 134). All of the studies were observational and did not include any treatment intervention. The identified studies and key findings are summarised in Supplementary Table 1.

Quality of studies

All of the eligible studies were included in the quality assessment (Supplementary Table 2). None presented formal sample size calculations. Patients were recruited consecutively in 39% of studies (n = 7). An explicit reference to other neurological disorders being ruled out was made in 88% of reports (n = 16).

DSM-5 criteria were still in development at the time of publication for some of the included studies. However, all FS diagnoses were confirmed by the recording of a typical non-epileptic event with video-EEG, the current gold standard for diagnosis, and other authors reported inclusion of FND patients based on the new DSM-5 criteria (Fig. 1). In total 261 patients with FS and 135 with other or mixed manifestations of FND were recruited. The methods of confirming diagnoses varied widely in studies with other functional disorders. Some studies with FMD patients reported

exclusive participation of patients with "clinically established" FMD [27], or with "clinically definite" FMD [28]. Two studies relied only on a "clinically probable" diagnosis based on Fahn et al [28] and ILAE criteria [29]. The clinical evaluation of included patients, based on either the above criteria or DSM-5, comprised neurological examinations, interviews and reviews of clinical histories by neurologists and/or psychiatrists. In one study, participants were reviewed by consensus of a board of neurologists and another study required consensus between two neurologists to confirm positive symptoms.

Categorization of studies

Based on the research question and constructs of focus, the studies were categorized into three research areas: (1) stress response, (2) emotion processing, and (3) illness burden. Some studies overlapped categories but were placed based on the primary outcome of the study. Their most relevant methodologies and findings are summarized in the following sections.

Stress response

Eight studies [11–12,17,30–34] explored the neurobiological stress response utilizing a range of known physiological stress markers as objective measures. These included measures of salivary cortisol and salivary alpha-amylase to identify response in the hypothalamic pituitary adrenal axis (HPA-axis, known as the 'stress system'), while skin conductance responses was used in one study [34] as a marker of the peripheral sympathetic autonomic nervous system to assess arousal and non-conscious responses. These studies adopted a range of self-report measures including direct reports of acute stress and anxiety levels on a visual analogue scale, a self-assessment manikin, or validated stress scale as well as questionnaires exploring other key outcomes such as quality of life, psychiatric comorbidity, physical disability and seizure severity. Overall aims included profiling stress response in FND in variable conditions, where some studies focused on basal levels of arousal. Six studies aimed to compare subjective and physiological, or autonomic and objective experiences, that were particularly relevant to this review.

Three of the studies were observational [31–33] and solely investigated basal stress measurements with no intervention. The other five incorporated an experimental paradigm or included a repeat measurement in a different condition e.g. after stress induction such as the Trier Social Stress test, Cold-pressor test or viewing of affective images [12,17,30,32,34]. One study compared findings with an epilepsy control group, rather than healthy seizure free controls in the remaining stress response studies, adding an interesting level of analysis; notably, the authors reported no significant differences in self-reported or physiological stress between the two patient groups. All eight studies were very consistent in their findings reporting increased basal stress levels, autonomic hyperactivity and elevated levels of arousal in FND patients, as well as subjective reports of elevated stress compared to controls.

Emotion processing

Eight studies [10,35–41] aimed to investigate emotion processing in FND utilising a variety of approaches. Objective measures utilised in these studies included the heartbeat detection task as a measure of interoceptive ability [10,35,37,41]. Skin conductance responses/levels (SCR/SCL) indicative of peripheral sympathetic autonomic nervous system response [36,40] were evaluated. The cardiac inter-beat interval (IBI) or respiratory sinus arrhythmia (RSA) were indicative of sympathetic nervous system response. These were measured in response to affective images that included films and facial expressions [38,39]. Subjective measures included a range of validated self-report questionnaires assessing symptom burden, anxiety, depression, history of trauma, and health-related quality of life, as well as measures related to emotion dysregulation, such as dissociation, depersonalisation and alexithymia scales. Two studies utilized a Self-Assessment Manikin emotion rating scale to record participant self-ratings for emotional valence and arousal in response to affective images of the International Affective Picture System (IAPS) [38,40]. Pertinent to the current review, one study primarily aimed to assess physiological, cognitive, and behavioural responses to emotional stimuli, while three others included comparisons as exploratory or secondary investigations. All of these studies recruited healthy controls for comparison [40].

Illness burden

Two studies [25,42] directly compared physiological measures of symptoms with patients' self-perceived experience of symptoms. The studies explored reports of tremor duration and severity in organic and functional tremor patients. Objective tremor duration was recorded using a wrist worn actigraph and were compared to patient's perception of duration or severity recorded in a self-completed diary.

Associations between subjective versus objective measures in FND

Studies providing correlational analysis

Twelve studies provided quantitatively calculated or descriptively referenced correlational analyses conducted between findings from objective and subjective measures (see Table 1 for details). Three studies did not report nor reference any attempt to assess the relationship between objective and subjective measures, rather subjective measures were included in order to control for potential confounders in the analysis of findings from the primary objective measures [10,11,39].

Studies reporting no significant associations

Eleven studies (92%) report no significant correlations in any comparisons between a self-reported outcome and an objective measurement of related constructs within the studied FND group [17,25,30,36–37,32–34,40–42].

Eight studies analysed directly corresponding objective measures of the same symptom, or construct, such as visual analogue scales of stress or validated perceived stress scales versus physiological stress markers (e.g., heart rate, skin conductance, salivary amylase or cortisol), actigraphy measured tremor vs self-reported tremor severity, and alexithymia or dissociative experience scales versus interoceptive sensitivity scores. None of these analyses identified significant correlations between closely corresponding constructs.

Studies reporting significant associations

Four studies did find a significant correlation in at least one subjective vs objective comparison [12,17,30,40]. Consistently significant correlations were found in the analysis conducted by Herrero *et al.* [40] where five comparisons between self-reported dissociative and alexithymic tendencies and physiological responses to emotional images were carried out. The moderate correlations ranged between 0.44–0.59 (p's < 0.05). Notably, only this study had the primary aim of assessing different (physiological, cognitive and behavioural) responses to emotional stimuli, which neatly fit the definitions of 'objective' and subjective' measurement which we adopted for this review. Allendorfer *et al.* [30] reported a strong negative correlation between perceived stress and change in HR in response to induced physiological stress ($r = -0.74$, $p = 0.0063$). This result matched the authors' expectations (i.e it was inversely proportional) and suggests that the specific subjective stress measure

Table 1
Correlations between self-report scores and objective measures reported in the included studies.

Category (n. comparative studies/ n. number of studies in category)[b]	Study	Subjective self-report measure[a]	Objective correlate measure[a]	Within group correlation analysis	
				Descriptive	Quantitative (r values, range)
Stress Response (6/8)	Novakova, Harris and Reuber [33]	Smith Stress Symptoms Inventory (SSSI)	HRV, cortisol	No significant correlations between self-reported stress and any of the physiological measures*	r = -0.174–0.244, p's > 0.05
	Pick, Mellers and Goldstein [34]	Subjective valence and arousal rating (SAM)	SCR, SCL	Correlations between autonomic response and subjective experience were not consistent within PNES population.*	-
	Apazoglou et al [17]	Evaluation of stress on visual analogue scale, Beck Depression Inventory, State-Trait Anxiety Inventory, Ameil-Lebigre Questionnaire (Life Events) Childhood Trauma Questionnaire Clinical Global Impression (CGI) Mobility subscale of Neuro-Qol	Salivary cortisol and amylase	The number (1) and subjective impact (2) of adverse life events positively correlated with cortisol AUCg. The number (3) and subjective impact (4) of adverse life events did not correlate with amylase values (AUCg). No correlation between self-reported stress (VAS) and objective values at rest, nor after stress induction in VAS vs amylase (5) and VAS vs cortisol values (6) No correlations between self-reported duration and severity of symptoms and salivary cortisol and amylase (7)*	(1) r = 0.67, p < 0.01 (2) r =- 0.6, p < 0.05 (3) r = 0.24, p > 0.05 (4) r = 0.33, p > 0.05 (5) r = 0.13, p = 0.65 (6) r = -0.17, p > 0.05 (7) r = -0.45–0.45, p's > 0.05
	Maurer et al [32]	Beck Depression Inventory, State-Trait Anxiety Inventory, Childhood Trauma Questionnaire, Traumatic Life Events Questionnaire	Salivary cortisol	No correlation between cortisol levels and self-report scores on any of the psychometric questionnaire measuring anxiety, depression, history of traumas and disorder duration and severity*	r = -0.212 – 0.173, p's > 0.05
	Allendorfer et al [30]	Perceived Stress Scale (PSS)	Heart rate, Salivary cortisol and alpha-amylase and fMRI	Perceived stress negatively correlated with change in HR to physiological stress (1).Perceived stress was not associated with change in cortisol (2) or in alpha-amylase (3). No significant associations were found between fMRI stress response and perceived stress (4) *	(1) r_s = -0.74, p = 0.0063 (2) r_s = -0.47, p = 0.12 (3) r_s = -0.45, p = 0.14 (4) r = nr, p > 0.0125
	Bakvis et al [12]	Traumatic Experiences Checklist (TEC), subjective anxiety on a VAS	Masked emotional Stroop test Salivary cortisol Systolic and diastolic BP, HR, HRV	Positive attentional bias for angry faces at baseline positively correlated to the presence of sexual trauma reports	r = -0.46, p < 0.05
Emotion Processing (4/8)	Kotwas et al [36]	Beck Depression Inventory State Trait Anxiety Index	Skin conductance response	No correlation between depression & anxiety scores and skin conductance responses *	-
	Ricciardi et al [37]	Toronto Alexithymia Scale-20, Self-Objectification Questionnaire, Montgomery Asberg Depression Rating scale	Interoceptive sensitivity score	No significant correlations between IS and depression (1), alexithymia (2), self-objectification (3) scores. *	(1) r = -0.51, p = 0.13 (2) r = -0.38, p = 0.44 (3) r = -0.40, p = 0.37
	Herrero et al [40]	Hamilton Anxiety Rating Scale, Dissociative Experiences Scale, Childhood Trauma Questionnaire, Toronto Alexithymia Scale, m measures of valence and arousal on SAM	Skin Conductance Response, Heart rate deceleration	Self-reported dissociation tendency was negatively correlated to physiological response SCR (1) and heart rate deceleration (2). Alexithymia 'Difficulty in describing feelings" subscore was negatively correlated with SCR rate (3), SCR latency (4), and heart rate deceleration (5) for all images. For cognitive response, no correlation was found.*	(1) r = -0.48, p = 0.0083 (2) r = -0.49, p = 0.021 (3) r = -0.44, p = 0.012 (4) r = -0.50, p = 0.013 (5) r = -0.59, p = 0.0037
	Wiliams et al (2021)	The Emotional Processing Scale (EPS), Patient Health Questionnaire (PHQ-9), Generalised Anxiety Questionnaire (GAD-7)	Interoceptive sensitivity (IS), Heart rate, Cold Pressor Test	No significant associations between IS scores and EPS-25 main or subscale scores when examined within-groups.	-
Illness burden (n = 2/ 2)	Parees et al [25]	Self-rated assessment of tremor duration in self-completed diary	Actigraph measurement of tremor	Psychogenic tremor patients showed a significantly greater bias towards over-estimation of tremor (65%), rated themselves as significantly more disabled and as having poorer QOL - but this did not correlate with actigraphy data*	-
	Kramer et al [42]	Self-rated assessment of tremor burden in self-completed diary	Actigraph measurement of tremor	No significant difference found in the subjective and objective associations within the OrgT group and the FT group*	r = nr, p = 0.168

Table includes only information pertinent to relevant correlation analysis.
Comparative studies = those providing results from a correlational analysis between subjective and objective outcome measures.
A dash ("-") represents inapplicable information, or not included in the study.
In significant correlations * signifies p-value of <0.05; ** siginifies p-value of <0.001.
orrelations * signifies p-value of <0.05; ** signifies p-value of <0.001.

used in this study could be used as a proxy of HR response or vice versa in similar studies.

In two studies, closely related variables yielded significant correlations; positive attentional bias for angry faces at baseline positively correlated with self-reported sexual trauma [12], and the number and subjective impact of adverse life events positively correlated with salivary cortisol [17]. These correlations were consistent with the authors' hypotheses or the expectations of outcomes in the patient group based on current evidence.

Notably, three of these studies explored stress response and all of these studies utilised a relatively wide range of objective and subjective measures. Otherwise there was no consistent pattern, for example, similarities in specific measures used, distinctive study samples or other methodological factors, that could be used to deduce why correlations were found in these but not the other studies discussed above (see Table 1 for subjective vs objective comparisons within FND groups reported in the included studies).

Associations within the research categories

These associations will be further described as they relate to each research area:

Stress response. Three of the six studies in the stress response category reported a significant correlation between objectively and subjectively measured outcomes. This category accounted for three of the four studies reporting significant correlations across all the studies included in this review. Allendorfer et al [30], Apazoglou et al. [17], and Bakvis et al. [12] reported significant correlations between several different measures. Some measures were more directly pertinent to the stress response than others. In other studies in this category, correlations between both baseline and post-stress biological/physiological markers (e.g., HRV, salivary cortisol and amylase) and perceived stress or subjective arousal (measured by the Stress Symptoms Inventory and stress on visual analogue scales) widely ranged in strength (r = -0.74 – 0.33) but did not reach statistical significance [17,30,32–33]. Correlations between skin conductance and subjective experience described on a valence and arousal rating scale were not consistent within a FS population described by Pick, Mellers and Goldstein [34]. No significant correlations were found between a visual analogue score for self-assessed stress levels and biological markers of stress using salivary cortisol and amylase both before and after stress induction in an FMD study (r = 0.13, p = 0.65; [17]. The self-reported duration and severity of symptoms also failed to correlate with these biological measures after stress, however, at baseline, these same subjectively assessed measures correlated with baseline cortisol (r = 0.67, p=<0.01; r = -0.6, p < 0.05, respectively). Likewise, there were no correlations between circulating cortisol levels and self-report scores on psychometric questionnaire measuring anxiety, depression, history of trauma and disorder duration and severity in another FMD patient group (r = -0.212 – 0.173, p's > 0.05) [32].

Emotion processing. In emotion processing studies, four studies included analyses between objective and subjective measures and three of these studies reported no or insignificant correlations. Ricciardi et al. [37] reported decreased cardiac interoceptive accuracy in patients with motor FND, thought to reflect awareness of interoceptive signals. This study showed that performance on the interoceptive sensitivity task was not associated with self-reported alexithymia, self-objectification or depression scores. Similarly, Williams et al. [41] reported no significant associations between pre- and post- stress induction interoceptive sensitivity scores and self-reported emotion processing scores when examined within their FND patient group and also interestingly within their healthy control group.

In response to emotional stimuli, there were mixed results. Kotwas et al. [36] did not find any correlations between self-reported depression and anxiety scores with SCR measures in response to emotions induced by short film. However, there was no report on subjective emotional intensity and SCR. Meanwhile, Herrero et al. [40] specifically compared physiological, cognitive, and behavioural emotional responses of female FS patients. The authors reported negative correlations between self-reported dissociation tendency and physiological responses (SCR and heart rate deceleration), while an alexithymia subscore ('Difficulty in describing feelings") was negatively correlated with SCR rate, SCR latency, and heart rate deceleration for all images. The authors also reported no significant correlations between 'cognitive responses' (measured by self-reported valence and arousal elicited by the images) and any of the other measures. The significant results indicated lower physiological emotional response associated with a greater subjectively perceived response.

Illness symptom burden. In the two studies categorised as assessing illness symptom burden, Parees *et al* [25] and Kramer *et al* [42] compared objectively measured tremor using an actigraphy watch with patient self-report of tremor burden and reported inconsistent results. Parees *et al* [25] found that functional patients reported tremor 84% of the day while the actigraphy watch recorded tremor for only 4% of the day. The overreporting of symptoms was nearly twenty-fold in these patients and substantially mismatched between the subjective, objective measures. This also contrasted significantly with the findings from neurological patient controls in the same study, who self-reported tremor for 58% of the day while the actigraphy watch recorded tremor for 25%, just over a two-fold overreporting of symptoms. However Kramer *et al* [42] reported no significant difference between the objective tremor duration (21.6% of the time) and subjective symptom burden (38.72, as measured on a 0–100 VAS) in functional patients. Unlike Parees *et al* [25], they did not find a difference between the functional and organic patient groups regarding the associations between subjective and objective symptoms.

Discussion

Our review revealed no close or consistent relationship between subjective and objective approaches to measure stress, distress and arousal or symptom burden in patients with FND. The few significant correlations identified between measures lacked a distinct or conclusive pattern when evaluated across primary study outcome categories (stress response, emotion processing and illness symptom burden). While demonstrating a general lack of correlation of objective and subjective state or outcome measures in patients with FND, our review gives some indication of specific research scenarios in which findings from subjective/objective approaches correlate more closely with each other. Our review cannot answer whether one approach provides a more accurate and/or clinically meaningful picture than the other. Indeed, given that subjective and objective measures assess different, but equally valid constructs, this question would be impossible to answer. The most appropriate kind of measure will depend on the particular question asked or hypothesis to be tested. In scenarios in which a comprehensive understanding of a patient's health and functional state is required, the lack of consistent correlation means that both types of measures should be used because they yield complementary information.

In view of the conceptualized links between stress, distress, arousal and emotion dysregulation and FS or FND [9,16,43], the lack of a closer correlation between subjective and objective measures of these features may be surprising, especially as previous

large prospective cohort and case-control studies in other populations have demonstrated clear associations between self-reported stress and objective long-term outcomes such as mortality or rates of medical disease [9].

Recent thinking about the cognitive processes associated with FND proposes two important mechanistic factors: self-focused attention and brain-expectations which infer that top-down influences, and prior beliefs are likely to modify any bottom-up sensory information [44]. Several of the reviewed studies provided evidence for an impaired interoceptive awareness in FND [10,35,37]. Similarly, abnormal symptom perception, body-centred attention and the subsequent tendency to interpret bodily sensations in a negative manner have been reported in other FNDs [25,45] as well as several related functional conditions including chronic pain, somatoform disorders, fatigue, health anxiety and hypochondriasis [46–49]. Taking account of the high levels of alexithymia reported in some patient groups with FND and the hypothesised perceptual abnormalities underpinning FND [44,50], it would be tempting to interpret the discrepancy between physiological response and subjective stress perceptions in this patient group as demonstrating that self-reports simply cannot be used as a proxy of physiological arousal in FND. However, rather than simply invalidating self-reported symptoms, the size of the discrepancy between subjective and objective measures of stress, distress or arousal could be of particular scientific interest in patients with FND. If the perceptual theories about the pathogenesis of FND symptom generation are correct, the difference between subjective and objective measures may reflect an important aspect of the cognitive pathology underpinning this disorder.

Despite the absence of objective evidence of structural, biochemical or physiological abnormality, the discrepancy between objective and subjective measures of stress or arousal in FND patients does not mean that the manifestations of this disorder must be consciously produced (as in malingering or factitious disorders) or exaggerated. The lack of association between subjective and objective measures of stress and arousal in the reviewed studies include scenarios in which objective measures captured elevated arousal, but patients' self-perception of this did not match [17,30,33–34]. It is a matter of continuing debate whether the inability of FND patients to recall or perceive symptoms of distress or potentially relevant distressing experiences means that they never occurred, that they are unwilling or unable to recall them, or that the methods used to capture this information are inadequate. Increased dissociative tendencies such as avoidant coping strategies [51], are commonly found in patients with FND, in particular in FS [52] and could explain some of these discrepancies. The lack of close correlation between subjective and objective measures in the reported FND populations is certainly not the result of a systematic over-reporting of arousal symptoms.

Other explanations for the discrepancy of subjective and objective findings could be the impact of current state, or the difference in time window between self-report measures (typically exploring time periods extending from minutes to months) and objective measures (often capturing milliseconds to minutes). These considerations could explain why the discrepancy of subjective and objective measures discussed above is not exclusive to patients with FND. While large longitudinal observational studies mentioned above have documented that subjective reports of stressful experiences are associated with adverse "hard" objective health outcomes years later, a lack of correlation of subjective and apparently related objective measures has also been demonstrated in many other psychiatric and neurological disorders. For instance, the dementia literature shows inconsistent correlations between pathological changes and self-reported levels of functioning; as well as discrepancies of self-report and behavioural findings [53–56]. Similarly poor correlations between have been found in multiple sclerosis [57–58] and Parkinson's Disease [59–60]. Similar to the situation in FNDs, some researchers have concluded that these discrepancies may be due to a lack of insight needed to accurately complete self-ratings; particularly when such insights could be affected by the disease itself, or to adaptive/maladaptive coping mechanisms, rather than being due to inaccurate measurement, factitious disorder or malingering.

In light of this, it is important not only to seek explanations for the subjective/objective discrepancy by focusing on processing abnormalities in the FND patient group but also by considering the nature of the self-report measures employed and their specific applicability. The primary research reviewed largely used generic measures of health status. Scales to assess quality of life (e.g. SF-36), and psychiatric comorbidity (e.g. PHQ-19, GAD-7, HADS) to evaluate symptoms of clinical depression, state and trait anxiety were employed. Emotion dysregulation, processing and response scales, including stress or emotion response analogue scales have also been used, alongside measures pertaining to specific symptoms or disorders (e.g. Symptom Revised Checklist, Porges' Body perception questionnaire). Very few specific measures have been developed for FND symptoms and the generic or even disease-specific measures found to be valid, reliable and sensitive to change in other relevant populations may not be equally sensitive or appropriate across the heterogeneous population of patients with FND. As such, they may become suboptimal instruments that capture indirect or broader features of the disorder, rather than changes more directly related to the underpinning pathology in this patient group.

Our observations suggest that a greater degree of specificity to the targeted disorders may be required when assessing patients with FND. The most important and informative outcomes may be those that are most meaningful to the patient [61]. Broader symptoms of anxiety and depression may overshadow other relevant psychological processes in patients with FND. An overriding focus on markers of distress may increase the risk of overlooking other relevant health indicators and may lead to patients to developing detrimental and illness-promoting perceptions of their health (Hagger and Orbell, 2003). Some of the self-report measures used in the reviewed studies may have suffered from these generic weaknesses of self-reported data, including a lack of clarity of the measured construct [62]. Ultimately, patients and research participants are likely to have better insight into cognitive content (e.g. knowledge, facts, opinions), than the cognitive processes that have generated this knowledge [63]. Therefore, these findings also highlight the need for self-report measures that have been specifically validated in patients with FND, a more refined understanding and development of measures that capture the required information from this heterogeneous clinical population and to take account of the inherent complexities of the disorder. This is particularly important when researchers aim to study the variable relationship between subjective symptoms as felt and expressed by patients, and objectively measured physiological dysfunction or structural change.

Last but not least, the lack of consistently correlating findings of objective and subjective measures of stress, distress, arousal and symptom burden may be due to the fact that these parameters are actually less relevant to the etiology of FND than emphasized by current theories. Or alternatively, perhaps they may only be relevant to subgroups of patients with FS and FND.

Limitations

The conclusions of this review must be interpreted within constraints reflected by the limitations of the studies that were included. One principal limitation that is relatively typical of FND research studies was the small number of patients included. This

was consistently recognized as a limitation within the included articles and a-priori analysis to calculate an adequately powered sample size was lacking in all studies. In a disorder like FND, population heterogeneity means that small sample sizes and the use of mean scores might conceivably lead to false-positive results. In addition, analyses involving multiple comparisons introduce a risk of type 1 errors. Several of the studies did not reference any procedures to correct for this, meaning their results must be interpreted with caution.

In addition to the small samples, our quality appraisal revealed the tendency for studies to omit important methodological criteria, such as the measures taken for diagnostic certainty of the included patients or whether FS had been formally differentiated from other neurological comorbidities. Unclear or unreported study design was the only reason why some studies were excluded from this review after quality appraisal. To improve study design quality and reporting in this area, researchers may benefit from specific recommendations relevant to the field [26] and established guidelines for publication (e.g., www.strobe-statement.org).

Despite the inclusion criteria for this review, there was still significant variability in diagnostic certainty found in the included studies. The current review included only studies that included patients that fit the DSM-5 criteria for FND, or referenced established diagnostic criteria for the study sample. However, the studies varied in their inclusion criteria and the extent to which they scrutinised the diagnosis of the patients. Given the variable sensitivity and specificity of signs of FND, and the lack of a gold standard to differentiate between different FNDs, incorrect diagnoses may have been given to participants. Diagnostic certainty is paramount to ensure accurate representation of the patient group and to avoid potential reasoning bias among patients [64]. Furthermore, recruitment and inclusion bias were potentially present in most samples due to recruitment within specialist healthcare clinics and non-consecutive sampling.

A further limitation of the reviewed studies is the reliability of the included measures. While some studies supplied at least one appropriate measure of reliability [33,37,38], such as Cronbach's alpha, there were several omissions across studies and data were generally incomplete.

Finally, the studies in this review were limited to those that included directly comparable data by way of correlation between self-report and objective measures or included a reference to any relationship explored or identified. Access to primary data from each study was not feasible; therefore, we relied solely on reported comparison. This reduced the number of studies with relevant analyses and limited our ability to accurately assess the degree of agreement between the two measures. The review did not assess in detail the agreement between individual correlations for corresponding measures but rather made use of categorising the studies to investigate any emerging patterns. Finally, this review did not discern between differences in study protocols related to or collection of the measurements and other population specific characteristics.

Future directions

The limited literature regarding the discrepancy between subjective and objective measures as well as the limitations of the available literature necessitate further research before firm conclusions about this relationship in patients with FS and other manifestations of FND can be reached.

Future research involving sufficiently powered studies should explore the factors that affect or moderate patients' self-perceptions of their physiological state and the clinical relevance of discrepancies between subjective and objective measures. An interesting factor to explore would be whether psychological intervention and other treatment modalities affect the relationship between subjective and objective findings in this patient group. This is particularly important as making aspects of the 'unconscious conscious' is an primary aspect of psychotherapies for FND. The development of specific measures for FND should involve researchers talking to patients with FND to identify the most important determinants of disability and distress in this disorder, while generic self-report measures that are commonly used in FND-related research require validation in specific FND samples.

Conclusions

FND has features that make outcome measurement particularly complex. Some of these features, such as the heterogeneity and variability of FND manifestations including FS limit the use and interpretability of subjective and objective current-state measures. The very limited correlations between objective and subjective measures in this patient group do not mean that symptoms are willfully produced or that outcomes simply cannot be measured. In many cases the combination of subjective and objective measures is likely to produce the most comprehensive understanding of patients' current state or treatment outcome, and the size of the discrepancy between subjective and objective measures may provide additional useful insights into the underlying pathology. The findings of this review underscore the importance of a better validation of outcome measures in patients with FND and for a careful selection of the most appropriate measures for the particular research objectives.

Ethics statement

Our review "Subjective versus objective measures of distress, arousal and symptom burden in patients with Psychogenic nonepileptic seizures and other Functional Neurological Symptom Disorder presentations: a systematic review" does not contain any original patient data and does not raise any ethical issues. All authors have contributed to the writing of this manuscript and have approved the version of the manuscript submitted for review. This manuscript represents original work by the authors and has not been submitted for consideration of publication elsewhere.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Markus Reuber: Payments from Elsevier as Editor-in-Chief of Seizure, educational grant from UCB Pharma, income from book authorships (including books about PNES). None of these interests should have any bearing on the content of this article. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2021.100502.

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