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Aetiological factors and symptom triggers in functional motor symptoms and functional seizures: a pilot investigation

Short running title: Aetiological factors in FND

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Abstract

Objective: In this pilot investigation, we aimed to examine aetiological factors and symptom triggers in a sample with functional motor symptoms (FMS) and/or functional seizures (FS). We also sought to assess potential relationships with relevant clinical features (i.e., functional symptoms, quality-of-life, general functioning). **Methods:** Seventeen participants with FMS/FS and 17 healthy controls (HCs) underwent an in-depth clinical interview and completed questionnaires assessing adverse life events, psychological and physical symptoms, alexithymia, autistic traits, illness perceptions, health-related quality-of-life (HRQoL), and work/social functioning. **Results:** Participants with FMS/FS perceived varied causes of the disorder including physical (65%), emotional (53%), environmental (47%) and work-related factors (29%). FMS/FS triggers included physical activity/exertion (59%), stress/emotion (59%), sensory experiences (47%) and fatigue (41%). The FMS/FS group reported more adverse events during adolescence (p=.003), alexithymia (p=.001), somatoform dissociation (p<.001), aspects of psychological dissociation (disengagement [p=.003], depersonalisation [p<.001], derealisation [p=.005]), anxiety (p<.001), depression (p<.001), and physical symptoms (p<.001). Participants with FMS/FS had worse HRQoL than HCs (all p-values=.01-<.001) and impaired work/social functioning (p<.001). There were negative associations between HRQoL scores and somatoform dissociation, anxiety and adverse life events (p-values=.034-.005). **Conclusion:** This sample with FMS/FS reported diverse biopsychosocial aetiological factors and symptom triggers. Current psychological symptoms and lifetime adverse experiences were associated with worse HRQoL. Our future work will examine these factors in larger samples with FMS or FS to better understand their shared and distinct aetiological underpinnings.

1 Introduction

Functional neurological disorder (FND) is a neuropsychiatric condition encompassing neurological symptoms that are not explained by identifiable neuropathology [1] and that are incongruent with symptoms caused by neurological disease [2]. A wide range of factors might contribute to the aetiology of FND [3, 4], with possible predisposing roles for biological vulnerability [5], social/environmental adversity [6, 7], and psychological factors [8-10]. Later adverse/stressful experiences, physical or mental health disorders [11], and physical injury/accidents have been proposed to precipitate the onset of FND [12]. Factors which might perpetuate FND include iatrogenic harm, social/environmental factors, ongoing psychological distress, coping behaviours, and illness-related cognitions [9].

Further research is needed to identify common and distinct aetiological factors in specific FND subgroups, such as functional seizures (FS), functional motor symptoms (FMS), functional cognitive disorder, and functional sensory symptoms. Importantly, factors that might trigger or exacerbate FND symptoms on an ongoing basis require further investigation [2, 3, 13], as these can provide insights into underlying pathophysiological mechanisms.

This study was part of a broader project investigating biopsychosocial causes and mechanisms in FMS and FS. Here, we aimed to conduct a pilot investigation of aetiological factors and symptom triggers in people with primary diagnoses of FMS and/or FS. We also aimed to assess possible relationships between these factors and clinical features including FND symptom severity and impact, health-related quality of life (HRQoL) and general functioning. We sought to obtain preliminary data to inform the design of a subsequent larger-scale investigation.

We predicted that participants with FMS/FS would report a greater number and impact of adverse life events compared to healthy controls [14], as well as elevated

alexithymia [8], psychological distress (anxiety, depression) [9], physical symptoms [15], somatoform dissociation [14], psychological dissociation [11, 14], and autistic traits [16]. Preliminary evidence suggested that patients may perceive that both physical and psychosocial factors contribute to the development of the disorder or act as symptom triggers [8, 13]. We also predicted that the FMS/FS group would report impaired work and social functioning and worse HRQoL than HC [17], with exploratory analyses used to assess relationships between these clinical variables and specific aetiological factors.

2 Materials and Methods

2.1 Participants

Patients with FMS/FS were recruited through FND charities (FND Action, FND Hope UK). HCs were recruited through community websites (Gumtree, Facebook). The study conformed to the World Medical Association Declaration of Helsinki and was approved by the King's College London Health Faculties High-Risk Research Ethics Sub-Committee (ref: HR/DP-21/22-28714). All data were collected between July and October 2022.

All participants were aged 18-65 years, with fluency in English and normal or corrected eyesight. Participants in the FND group were required to have a primary diagnosis of FND [1], with FMS and/or FS as their primary complaint, confirmed with medical documentation clearly stating the diagnosis. This documentation was checked by SP, a research psychologist with expertise in FND, with ambiguous cases checked by a Consultant Neurologist (BS).

Exclusion criteria were: diagnosis of a major comorbid cardiovascular (e.g., heart disease) or neurological (e.g., epilepsy, multiple sclerosis) disorder, active severe psychiatric disturbance (e.g., psychosis, alcohol or substance dependence), physical symptoms, disability or medication impairing one's ability to complete the questionnaires. It was important to ensure that diagnoses which could have confounded the findings and/or impaired a

participant's ability to complete the tasks were considered and excluded. Some of these exclusion criteria were important considerations for other aspects of the larger pilot study, including measures of autonomic function and cardiac interoception (i.e., [18]). HCs were excluded if they disclosed an active major mental or physical health disorder or lifetime FND diagnosis.

2.2 Procedure

Participants provided written consent prior to completing an in-depth clinical interview covering sociodemographics and medical history. Participants with FMS/FS were also asked about their perceptions of current symptom triggers. An abbreviated structured clinical interview [19] was administered to assess the presence of psychiatric disorders relevant to the eligibility criteria. Eligible participants completed self-report questionnaires (Table 1) online via Qualtrics (www.qualtrics.com). After completing the self-report questionnaires and a laboratory session (consisting of neurocognitive and experimental tasks reported separately; [18, 20]), participants were reimbursed with a £50 shopping voucher.

2.3 Measures (Table 1)

<insert Table 1 here>

2.4 Analysis

Data were analysed independently by two investigators using *R* [21]. For participants missing 20% or less of a given scale/subscale, the missing item/s were imputed with the mean of that individual's scores for the scale/subscale. If more than 20% of the data for one scale/subscale was missing, the participant was excluded from that analysis. Outliers (*M*+/-2.5*SD*s) were identified and winsorised (1%; replaced with the less extreme neighbouring value). Normality was evaluated with QQ-plots and the Shapiro-Wilk test. Categorical variables were analysed with Pearson's chi-square or Fisher's exact tests. Continuous variables were analysed with independent samples Welch's t-tests (normally distributed data,

M/SD) or Wilcoxon rank sum tests (non-normal distributions, Median/IQR). Hedges' g and r-values were computed as measures of effect size. Exploratory Pearson's (normal distributions) or Spearman's correlations (non-normal distributions) assessed associations between clinical features and relevant aetiological factors in the FND group. Holm-Bonferroni corrections were used in the case of multiple tests on related variables.

3 Results

Seventeen patients with FND and 17 healthy controls were included. Twelve participants in the FND group reported FMS as their primary symptom, and five reported FS as their primary symptom. There were no significant group differences in age (p=.51), gender (p=.66), ethnicity (p=.69), or relationship status (p=.73). The FND group was more likely to be currently unemployed (p<.001), taking medication (p<.001), and experiencing a comorbid physical (p=.007) or mental health disorder (p=.001), as self-reported by participants (Supplementary Table 1). Seventy-six percent of the total sample was White, 9% Black, 9% Asian, 6% mixed race, 0% Hispanic and 0% Native American.

The most commonly reported FMS/FS triggers were physical activity/exertion (59%), stress/emotion (59%), sensory (47%) and fatigue (41%). Other triggers included crowds (18%), cognitive exertion (12%), pain (12%), work (12%), eating (6%), sleep (6%), and menstruation (6%). The number of reported triggers per participant ranged from zero (6%) to five (24%), with three and four triggers also reported by 24% and 35% of the sample, respectively.

Perceived causes of FND (B-IPQ) were physical (65%), stress/emotions (53%), adverse life events (47%) and work-related factors (29%). Mean B-IPQ scores (min=0, max=10) suggested that the FMS/FS group held the following illness-related beliefs: FND greatly affects their lives (M=7.29, SD=2.08) and emotions (M=7.00, SD=2.72), FND will continue for a long time (M=7.24, SD=2.97), FND has many severe symptoms that patients

feel little control over (M=6.19, SD=2.48), and treatment is unlikely to help (M=5.94, SD=2.24).

In the FMS/FS group, there was a trend towards a higher number and greater impact of adverse life events (TEC; Table 2), as well as significantly more adverse events between the ages of 13-18 (W=68, p=.003, r=.51), and more instances of sexual abuse than HCs (W=93.5, p=.018, r=.41), although the latter did not withstand Holm-Bonferroni correction (adjusted alpha=.007). No other significant differences regarding type or age of adverse events were present (all p-values>.11, r=.20-.28).

Participants with FMS/FS exhibited elevated total scores on the SDQ-20, GAD-7, PHQ-9, PHQ-15, and TAS-20, as well as MDI-Depersonalisation, Derealisation, and Disengagement, and TAS-20 Difficulty Identifying Feelings subscales (Table 2). Elevated MDI-Memory Disturbance and AQ-Attention Switching scores did not survive Holm-Bonferroni correction. There were no significant group differences in the proportion of participants exceeding cut-off scores on the AQ (≥32 clinical threshold for autism; p=.48)[22] and TAS-20 (≥61 indicating alexithymia; p=.10)[23]. The FMS/FS group reported significantly worse HRQoL across all SF-36 domains, and lower WSAS scores, compared to HC (Table 2).

<insert Table 2 around here>

Exploratory correlations (Supplementary Table 2)

The findings described below were significant (p<.05) but did not withstand Holm-Bonferroni corrections and should be interpreted as trends.

In the FMS/FS group, poorer functioning (WSAS) was associated with elevated depression (PHQ-9) and FND symptom severity. FND symptom count was positively associated with MDI-Disengagement, Depersonalisation, and Derealisation subscale scores.

FND symptom severity was positively associated with total TAS-20, MDI-Disengagement, and B-IPQ Consequences and Coherence scores. FMS/FS symptom impact ratings were similarly positively associated with total TAS-20, B-IPQ Consequences, Coherence and Personal Control scores.

Lower SF-36 General Health scores were significantly associated with elevated TEC total adverse event scores and TEC impact scores. Worse HRQoL across several domains was associated with higher dissociation (somatoform, disengagement), anxiety and/or depression scores. Specifically, SF-36 Role Limitations-Emotional Problems, Emotional Wellbeing, Social Functioning, and Pain subscale scores were all negatively associated with the GAD-7. SF-36 General Health and Role Limitations-Emotional Problems subscale scores were negatively related to the SDQ-20. SF-36 Emotional Wellbeing was negatively related to total PHQ-9, MDI-Disengagement and Derealisation scores.

4 Discussion

This pilot investigation aimed to capture preliminary data on a range of aetiological factors and symptom triggers in individuals with FMS/FS. The results support the relevance of diverse aetiological factors in this population, including physical, psychological, social, and environmental variables, also highlighting several factors that were associated with impaired quality-of-life and general functioning. Supplementary Figure 1 illustrates our key findings in relation to existing evidence.

Self-reported causes of FND included physical factors, stress/emotions, adverse life events, and work-related issues, consistent with previous studies [7]. A trend towards a higher number and impact of adverse life events, and sexual abuse, in the FMS/FS group aligns with previous evidence for adversity as an important risk factor in FND [6, 7]. The significant elevation in adversity during adolescence in the FMS/FS group suggests the possible value of preventative interventions targeting adolescents with this risk factor [24].

Elevated depression, anxiety, physical symptoms, somatoform dissociation, aspects of psychological dissociation, and alexithymia were also present in this FMS/FS sample, strengthening further the evidence for their aetiological relevance in FND [9-11, 14]. Although autistic traits have been shown to be elevated in FND [16], we observed no significant group differences on the AQ.

This FMS/FS sample reported a range of symptom triggers including physical activity/exertion, stress/emotion, sensory stimuli and fatigue, consistent with Geroin et al. [13]. A diverse range of factors may contribute to the immediate initiation or worsening of FND symptoms, and these may vary by symptom subtype. Future studies should examine triggering factors in specific FND subgroups.

A possible role for illness beliefs in perpetuating FND was supported here. Individuals with FMS/FS reported FND-related beliefs about chronicity, lack of personal control and poor treatment efficacy, suggesting more threatening illness-related representations [9]. A possible perpetuating role for other psychological factors was also supported, including anxiety, depression, dissociation and alexithymia.

Potential associations between greater FND severity/impact and elevated dissociation and alexithymia were present in this FMS/FS sample. Worse HRQoL and work/social functioning were tied to elevated psychological symptoms in this FMS/FS group, and lower general health scores were significantly associated with elevated adverse events and impact scores. These findings suggest the possible need for targeted, customised interventions, already a consideration by many FND clinicians, for individuals with FND reporting greater lifetime adversity, psychological symptoms and emotional processing difficulties [25]. Therapies including eye-movement desensitisation and reprocessing, cognitive-behavioural therapy, prolonged exposure therapy, and dynamic psychotherapies, may prove particularly beneficial.

5 Conclusion

Although interpretation is limited by the small sample size and cross-sectional design, this pilot study provides additional evidence for the complex, multifactorial aetiology of FMS and FS, encompassing physical, psychological and social/environmental factors that vary considerably between individuals. FMS/FS symptom triggers ranged from physical activity/exertion to stress/emotion, sensory stimuli and fatigue. Individuals with FMS/FS also reported more adverse life events in adolescence and elevated dissociation, anxiety, depression, alexithymia, and physical symptoms. FND severity and poorer HRQoL were associated with dissociation, anxiety, alexithymia and lifetime adversity. Our future work will examine aetiological factors and symptom triggers in larger FMS and FS samples in comparison to both clinical and healthy control groups.

Author contributions: LSMM conducted the data processing/analysis and led the writing (original manuscript and revisions). ES programmed the online questionnaires (Qualtrics). ES, EW, ABW, and YS contributed to data preparation/processing. BS contributed to screening/recruitment. BS, JSW, TRN, MAM, AATSR, MJE, LHG, ASD, MH, and TC formed a steering group for the larger project and contributed to refinements of study design, oversight of implementation, and manuscript revisions. MH and TC contributed to funding acquisition and conceptualisation. SP (principal investigator) led funding acquisition, study conceptualisation/design, and data collection, supervised data processing/analysis and contributed significantly to writing (original manuscript and revisions). All authors reviewed and approved the final manuscript.

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Table 1. Self-report measures.[a]

Questionnaire	Content of scale	Scoring
Functional neurological symptoms questionnaire (FNSQ, Supplementary File 1)	13-item measure designed for this study to assess the presence, frequency, severity and impact of FND	Participants report the presence (yes/no), frequency (less than weekly-constant), severity (1, "symptom not present" to 7, "very severe") and impact (1, "no impact at all" to 7, "very severe impact") of FND symptoms, including seizures, motor, and sensory symptoms, within the past week. Participants are also asked to identify the symptom which currently had the most impact on them and those with functional seizures were asked to identify the earliest or most consistent premonitory symptom they experience prior to seizure onset.
Generalized Anxiety Disorder Assessment - 7 (GAD-7) (Spitzer et al., 2006)	7-item brief self-report scale of generalized anxiety	Asks about symptoms over the last two weeks rated from 0 ("not at all") to 3 ("nearly every day") with total scores ranging from 0-21 (α=.91). Higher scores indicate higher anxiety levels.
Patient Health Questionnaire – 9 (PHQ-9) (Kroenke et al., 2001)	9-item measure of the frequency and severity of symptoms of depression (Kroenke & Spitzer, 2002)	Indexes symptoms over the last two weeks with items rated from 0 ("not at all") to 3 ("nearly every day") and total scores ranging from 0-27 with a separate tenth question concerning the person's level of functional impairment (α=.89). Higher scores indicate greater depressive symptomatology.
Patient Health Questionnaire – 15 (PHQ-15) (Kroenke et al., 2002)	15-item questionnaire examining common physical symptoms	For each symptom, respondents rate how much they have been bothered by it during the past four weeks as follows: "not bothered at all" (0), "bothered a little" (1), "bothered a lot" (2), with total scores ranging from 0-30 (α=.88).
Multiscale Dissociation Inventory (MDI) (Briere et al., 2005)	30-item self-report measure to assess psychological dissociative symptoms	Items are scored from 1 ("never") to 5 ("very often"), with scores on each subscale ranging from 5-21. Raw scores are converted to T-scores. Higher scores indicate increased dissociative symptomatology. Scored across six subscales: Disengagement (5 items; α=.92), Depersonalisation (5 items; α=.96), Derealisation (5 items; α=.93), Memory Disturbance (5 items; α=.89), Emotional Constriction (5 items; α=.98), Identity Dissociation (5 items; α=.71).
Traumatic Experiences Checklist (TEC) (Nijenhuis et al., 2002)	29-item measure assessing a range of adverse life events and their subjective impact	For each event, respondents indicate if it happened to them (yes/no). If yes, they are asked to indicate at what age, as well as rating the level of impact from 1 ("none") to 5 ("an extreme amount"). Total (number of adverse events ranging from 0-29) and impact scores (total impact of adverse events, rated from 1-5 for each event) are calculated, alongside six severity sub-scores (3 items each: emotional neglect, emotional abuse, physical abuse, bodily threat, sexual harassment, sexual abuse) and developmental composite scores indicating adverse events experienced according to four age ranges (0-6, 7-12, 13-18, >19).
Somatoform Dissociation Questionnaire – 20 (SDQ-20) (Nijenhuis et al., 1996)	20-item self-report measure of bodily dissociative symptoms	Items are scored from 1 ("this applies to me not at all") to 5 ("this applies to me extremely), with total scores ranging from 20-100 (α=.79). For each statement, if an individual endorses a symptom or experience, they are asked to indicate if the physical cause is known.
Autism Spectrum Quotient (AQ) (Baron-Cohen et al., 2001)	50-item self-report questionnaire examining autism spectrum traits	Respondents are asked to indicate how strongly they agree or disagree with each statement ("definitely agree," "slightly agree," "slightly disagree," "definitely disagree"). Agree statements are given 1 point whereas disagree statements are 0. Total scores lie between 0-50 (α=.80). Scores are also calculated for five subscales: Attention Switching (10 items; α=.69), Attention to Detail (10 items; α=.72), Social Skills (10 items; α=.72), Communication (10 items; α=.70), Imagination (10 items; α=.52).
Toronto Alexithymia Scale –	20-item scale measuring difficulties with	Questions are scored from 1 ("strongly disagree") to 5 ("strongly agree"), with total scores ranging from 20-100 (α=.84). Total scores greater than or equal to 61 indicate high alexithymia (Bagby et al., 1994). This scale also

20 (TAS-20) (Bagby et al., 1994)	identifying, describing and experiencing emotions	includes three subscales: Difficulty Describing Feelings (5 items; α=.74), Difficulty Identifying Feelings (7 items; α=.88), Externally Oriented Thinking (8 items; α=.57).
Brief Illness Perception Questionnaire (B-IPQ) (Broadbent et al., 2006)	9-item self-report assessment of illness representations	Each question addresses one dimension of illness perceptions including: consequences, timeline, personal control, treatment control, identity, coherence, emotional representation, concern, and causes. Eight items are individually scored from 0 (e.g., no symptoms/no effect/no concern, etc.) to 10 (e.g., many severe symptoms/severe effect/extremely concerned, etc.), with item nine asking respondents to rank order the three most important factors that they believe caused their illness.
36-item Short Form survey (SF-36) (Hays et al., 1993)	36-item measure designed to quantify HRQoL in chronic health conditions	Participants are asked questions regarding their current physical health including how they would rate it (from Poor to Excellent), if their current health limits their ability to complete certain daily activities, and if they have experienced any problems as a result of their physical and/or emotional health, levels of pain, and interference with social activities within the past four weeks. Higher scores (ranging from 0-100) indicate better HRQoL measured across eight subscales: Physical Functioning (10 items; α=.96), Role Limitations due to Physical Health (4 items; α=.96), Role Limitations due to Emotional Problems (3 items; α=.91), Energy/Fatigue (4 items; α=.88), Emotional Wellbeing (5 items; α=.87), Social Functioning (2 items; α=.91), Pain (2 items; α=.93), General health (5 items; α=.87).
Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002)	5-item measure of impairments in social and occupational functioning	Questions rated from 0 (“not at all”) to 8 (“severely”), with total scores ranging from 0-40, and higher scores indicating more severe impairment (α=.96).

[a]See Supplementary File 2 for references included in this Table.

Table 2. Self-report questionnaires.[a]

Variable	FND[b]		Control[c]					
	M	**SD**	**M**	**SD**	***t***	***df***	***p***	***g***
AQ Total Autistic Traits	20.4	7.19	17.3	6.91	-1.26	31.95	.11	.44
AQ Attention to Detail	4.35	2.55	4.53	2.67	.20	31.93	.42	.07
AQ Attention Switching	6.24	2.61	4.41	1.70	-2.41	27.48	.01	.81
MDI Disengagement	75.6	26.95	53.7	8.37	-3.20	19.06	.003	1.04
PHQ-15 Physical Symptoms	13.5	4.02	3.24	2.44	-8.98	26.37	<.001	3.01
TAS-20 Alexithymia	53.47	10.2	42.00	9.97	-3.32	31.99	.001	1.11
TAS-20 Difficulty Describing Feelings	12.5	3.68	12.3	4.70	-.16	30.24	.44	.05
TAS-20 Difficulty Identifying Feelings	21.5	5.66	11.5	3.69	-6.10	27.54	<.001	2.04
TAS-20 Externally Oriented Thinking	19.5	3.12	18.3	3.69	-1.00	31.16	.16	.34
SF-36 Energy/Fatigue	25.9	17.4	65.3	13.3	7.41	29.90	<.001	2.48
SF-36 General Health	34.7	19.2	74.1	14.5	6.76	29.80	<.001	2.26
	Median	**IQR**	**Median**	**IQR**	***W***		***p***	***r***
TEC Average impact of events	13	10	8	11	87.5		.051	.34
TEC Total adverse events	4	5	2	3	90		.061	.32
AQ Communication	2	2	2	4	146		.97	.01
AQ Imagination	2	2	2	1	140.5		.90	.02
AQ Social Skills	3	4	2	2	95.5		.09	.29
GAD-7 Anxiety	8	8	2	4	46		<.001	.58
MDI Depersonalisation	56	79	47	0	68		<.001	.58
MDI Derealisation	57	44	46	0	76		.005	.49
MDI Memory Disturbance	58	31	52	7	80		.023	.39
MDI Emotional Constriction	46	4	46	4	134.5		.70	.07
MDI Identity Dissociation	47	0	47	0	119		.08	.31
PHQ-9 Depression	12	8	1	3	16.5		<.001	.76
SDQ-20 Somatoform Dissociation	29	9	20	0	14.5		<.001	.79
SF-36 Emotional Wellbeing	60	24	84	16	236.5		.002	.55
SF-36 Pain	35	25	100	22.5	274.5		<.001	.78
SF-36 Physical Functioning	40	25	95	5	289		<.001	.86
SF-36 Role Limitations-Emotional	0	100	100	33.3	213		.011	.44
SF-36 Role Limitations-Physical	0	0	100	0	276		<.001	.84
SF-36 Social Functioning	37.5	37.5	100	25	261.5		<.001	.70
WSAS Work and social functioning	25	8	1	4.5	1		<.001	.84

[a]Higher scores on SF-36 Energy/Fatigue indicate elevated energy/less fatigue. AQ = Autism Spectrum Quotient Total; GAD-7 = Generalized Anxiety Disorder – 7; IQR = interquartile range; M = mean; MDI = Multiscale Dissociation Inventory; PHQ-9 = Patient Health Questionnaire – 9; PHQ-15 = Patient Health Questionnaire – 15; SD = standard deviation; SDQ-20 = Somatoform Dissociation Questionnaire – 20; SF-36 = 36-item Short Form survey; TAS-20= Toronto Alexithymia Scale – 20; TEC = Traumatic Experiences Checklist; WSAS = Work & Social Adjustment Scale.
[b]FND n=17
[c]Control n=17