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Study protocol

Official title: Are neuroticism, perceived stress, and adverse life events risk factors for functional somatic disorders?
DanFunD

Background

Functional somatic disorders (FSD) are common disorders with a multifactorial aetiology involving biological, social, and psychological factors (1, 2). An often used explanation of the illness mechanisms behind FSD which is provided to the patients is, that FSD may be understood as a multi systemic physical response to stress (3). This relationship can be modelled as proposed in the Cognitive Behavioural Therapy (CBT) model of emotional distress where several cognitive, behavioural and psychological factors are thought to contribute to the onset and perpetuation of FSD (4). in the Cognitive Behavioural Therapy (CBT) model of emotional distress where several cognitive, behavioural and psychological factors are thought to contribute to the onset and perpetuation of FSD. Personality traits e.g. neuroticism contribute to give rise to our cognitive, behavioural, and psychological reactions. Furthermore, neuroticism with its heightened reactivity to stressors, has shown to be an important predictor of a generic vulnerability to both physical and psychological conditions. Having been exposed to previous adverse life events/traumas and childhood adversities has also showed to impact the risk of having FSD. This relationship has been proposed to be induced by a heightened response to stimuli, i.e. sensitisation, caused by physical and emotional distress triggering a hormonal cascade in the hypothalamus pituitary adrenal (HPA) axis (4, 5).

So far, most studies into these aspects have been carried out in selected patient samples, and general population-based studies including a large randomly obtained are sparse. In three recent population-based studies, we have established strong associations between FSD and neuroticism, perceived stress, and the accumulated number of experienced adverse life events (ALE), respectively (6). However, these studies were cross-sectional, thereby not providing insight to whether these factors were risk factors of FSD. More studies are needed for further elucidation on these aspects.

Objective

The objective of this study is to explore the role of neuroticism, perceived stress, and the accumulated number of ALE, respectively, in the development and perpetuation of FSD.

Hypotheses

1) Higher neuroticism, higher perceived stress, and higher number of ALE at baseline are individual risk factors of having developed FSD in the 5-year period from baseline to follow-up:

FSD non-case at baseline → FSD case at follow-up

2) Neuroticism, perceived stress, and the accumulated number of ALE positively contribute to the perpetuation of FSD from baseline to follow-up:

FSD case at baseline → FSD case at follow-up

Methods

Study population

Data from the DanFunD (Danish Study of Functional Disorders) baseline and 5-year follow-up investigation cohorts will be included (7, 8). The baseline cohort (gathered in the years 2012-2015) is a random sample selected through the National Civil Registration system among people living in 10 municipalities in the western part of greater Copenhagen, Denmark, ages 18 to 76 years. The baseline cohort constitutes data from self-reported questionnaires (n=7,493) and diagnostic interviews data (n=1,590). The follow-up cohort (gathered in the years 2018-2020) consists of participants all born in Denmark, between 24 and 84 years of age. The follow-up cohort constitutes data from self-reported questionnaires (n=4,288) and diagnostic interviews data (n=1,094).

Primary outcome (dependent variables):

Preferably, if a sufficient number of incident and perpetuating cases are available at follow-up, participants with FSD will be defined as follows:

- Participants fulfilling the criteria of the unifying diagnostic concept Bodily Distress Syndrome single- and multi-organ type will be defined with both questionnaires (9) and diagnostic interviews (10, 11)

- Participants with irritable bowel, chronic widespread pain, and chronic fatigue will be defined with questionnaires (12-14)

Primary explanatory/independent variables:

All primary explanatory variables will be self-reported. Neuroticism will be measured with the Danish version of the short-form NEO Personality Inventory (NEO-PI-Rsf) (15). Perceived stress will be measured with the 10-item Cohen's Perceived Stress Scale (16). The accumulated number of ALE will be measured with the Danish version of the Cumulative Lifetime Adversity Measure (CLAM) (17).

Analytical plan

All analyses will be performed using STATA version 17.0 (18).

Descriptive statistics will be presented for all the three continuous explanatory variables across FSD diagnoses. Depending on data distribution, descriptive statistics will be presented as means and standard deviations or medians and interquartile ranges.

Depending on number of incident and perpetuating cases at follow-up, a range of analyses will be conducted with the purpose of investigating if higher neuroticism, higher perceived stress, and higher accumulated number of ALE at baseline

1) are individual risk factors for the development of FSD from baseline to follow-up

2) are positively contributing to the perpetuation of an FSD from baseline to follow-up

The first choice of analyses

For hypothesis one, multiple logistic regression models will be performed with incident FSD cases at follow-up as primary outcome and baseline neuroticism, perceived stress, and accumulated number of ALE as explanatory primary variables. The effect of neuroticism, perceived stress, and the accumulated number of ALE will be reported from the same analysis as the effect when controlled for the effect from the other primary explanatory variables. Odds ratio (OR) with 95% confidence intervals (CI) will be used as measure of association; an OR > 1 supports the hypothesis. The reference group will constitute participants without FSD at both baseline and follow-up. Reference value of neuroticism, perceived stress, and the accumulated number of ALE will be set as the median value of

the total sample. In each analysis there will be controlled for the confounding effect of sex (with male as reference) and age (the median value of the total sample).

For hypothesis two, multiple logistic regression models will be performed with FSD cases perpetuating from baseline to follow-up as primary outcome and baseline neuroticism, self-perceived stress, and accumulated number of ALE as primary explanatory variable. The effect of neuroticism, perceived stress, and the accumulated number of ALE will be reported from the same analysis as the effect when controlled for the effect from the other primary explanatory variables. Odds ratio (OR) with 95% confidence intervals (CI) will be used as measure of association; an OR > 1 supports the hypothesis. The reference group will constitute participants with FSD at baseline but without FSD at follow-up. Reference value of neuroticism, perceived stress, and the accumulated number of ALE will be set as the median value of the total sample. In each analysis there will be controlled for the confounding effect of sex (with male as reference) and (the median value of the total sample).

The second choice of analyses

If number of incident and perpetuated cases at follow-up are too low to perform the above multiple logistic regression models with incorporation of the three primary explanatory variables in one analyses per FSD definition, it will be investigated if the confounding primary explanatory variables can be reduced into one variable and incorporated in separate analyses instead. Hence, instead of performing one analysis per FSD definition, three logistic regression analyses will be performed for each FSD definition:

1. An analysis investigating the effect of baseline neuroticism (primary explanatory variable) as risk factor for incident FSD/contributor to perpetuating FSD (primary outcome) with adjustment for 1) perceived stress and the accumulated number of ALE reduced into one variable, 2) sex, and 3) age.

2. An analysis investigating the effect of baseline perceived stress (primary explanatory variable) as risk factor for incident FSD/contributor to perpetuating FSD (primary outcome) with adjustment for 1) neuroticism and the accumulated number of ALE reduced into one variable, 2) sex, and 3) age.

3. An analysis investigating the effect baseline accumulated number of ALE (primary explanatory variable) as risk factor for incident FSD/contributor to perpetuating FSD (primary outcome) with adjustment for 1) neuroticism and perceived stress reduced into one variable, 2) sex, and 3) age.

To find out if the confounding primary explanatory variables can be reduced into one variable, principal component analyses will be performed.

The third choice of analyses

If the second set of analyses cannot provide us with meaningful variables describing the primary explanatory variables, separate logistic regression analyses investigating the effect of neuroticism, perceived stress, and the accumulated number of ALE, respectively, will be performed with pre-defined prioritisation of confounders. The prioritisation will be as follows (depending on the primary explanatory variable): 1) neuroticism, 2) perceived stress, 3) accumulated number of ALE, 4) sex, and 5) age.

Dissemination of results

Results from this study will be presented as an original research article published in an international peer-reviewed journal.

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08.11.2022

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08.11.2022

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