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Individual variation in temporal relationships between stress and functional somatic symptoms $\overset{\bigstar}{\approx}$

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ABSTRACT

Objective: Medically unexplained or functional somatic symptoms (FSSs) constitute a major health problem because of their high prevalence and the suffering and disability they cause. Psychosocial stress is widely believed to be a precipitating or perpetuating factor, yet there is little empirical evidence to support this notion. Prior studies mainly focused on comparing groups, which has resulted in the obscuring of temporal complexity and individual differences. The aim of this study is to elucidate the relationship between stress and FSSs over time within individual patients.

Methods: Twenty patients (17 females, ages 29–59) with multiple, persistent FSSs were included in the study. They used electronic diaries to report stress and FSSs twice daily over the course of 12 weeks. For each individual data set, Vector autoregressive (VAR) modelling was used to investigate possible associations between daily average stress and FSSs scores.

Results: In six subjects (30%), an increase in stress was followed by an increase in one or more FSSs. In three subjects (15%), an increase in FSSs was followed by an increase in stress. Additionally, negative and mixed associations were found. Only two subjects (10%) showed no cross-lagged association between stress and FSSs in either direction. We did not find specific types of symptoms to be more stress-related than others.

Conclusion: Although stress does not seem to be a universal predictor of FSSs, an increase in stress precedes an increase in symptoms in some individuals. Identifying these individuals using time-series analysis might contribute to a more patient-tailored treatment.

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Introduction

Approximately 20% of newly presented physical complaints in primary care are not caused by medical disease [1–3]. In hospital settings this proportion is even higher: around 30–50% of physical symptoms cannot be (fully) explained by organic pathology [4–6]. These symptoms are referred to as medically unexplained or functional somatic symptoms (FSSs). If FSSs are persistent, they can cause considerable suffering and disability. FSSs are associated with repeated referrals and medical investigations, which are often unhelpful but produce extensive costs [7,8]. Even though FSSs clearly represent a major health problem, their aetiology is largely unknown. Among clinicians, psychosocial

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http://dx.doi.org/10.1016/j.jpsychores.2014.04.006 0022-3999/© 2014 Elsevier Inc. All rights reserved. stress is widely believed to be a precipitating or perpetuating factor in FSSs, but is this notion supported by evidence?

Epidemiological research shows that people who suffer from FSSs report more stressful life events [9–12] and daily hassles [13–15] than controls. However, these findings are almost exclusively based on cross-sectional studies. Inherent to the design of these studies is the use of retrospective questionnaires, which are often subject to recall bias. Moreover, these studies were not able to adequately assess temporal precedence, which is one of the criteria to establish a causal relationship: the cause must precede the effect in time [16]. Furthermore, these studies all analysed the association between stress and FSSs at a group level. A small association at the group level is often interpreted as clinically irrelevant. But it might also mean that stress is highly relevant for a subset of patients and not related to symptoms in the other patients, which would be reflected in a small average effect for the group as a whole. Especially in the heterogeneous group of patients with FSSs, such individual differences should not be obscured. Diary studies using repeated measurements to evaluate associations between stress and FSSs within individual subjects over time can address these problems. A few of these studies have been performed, indicating that

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an increase in stress predicts an increase in FSSs within subjects [17,18]. These studies however are limited by their short duration and specific study population. Overall, no conclusive evidence has been provided to support the notion that FSSs arise as a consequence of psychosocial stress. In addition, one of the diary studies showed that certain patients experienced an increase in stress following an increase in FSSs [17]. The possibility of reverse or bidirectional causality is rarely considered, but seems to be in accordance with the finding that persistent unexplained symptoms are associated with worries and health anxiety [19,20].

The aim of this study was to investigate relationships between stress and FSSs within individual patients over time by re-analysing data from a diary study that was performed in patients with multiple, persistent FSSs [21]. In that study, multilevel analyses were used to investigate concurrent associations between psychological states and FSSs. Stress was weakly associated with FSSs in the group as a whole. However, the researchers found evidence for large differences between individual patients, as reflected by the random effects. This suggests that stress might be a significant predictor of FSSs in some subjects, but not in others. Yet, these individual differences could not be disentangled with the multilevel analyses applied. Therefore, we took a completely different approach: instead of comparing subjects to each other, we investigated the relationship between stress and FSSs purely within individuals using time-series analyses. This also enabled us to examine temporal precedence and consider the possibility of bidirectional associations. Vector autoregressive (VAR) modelling was used to analyse the associations between stress and FSSs within each individual patient. These analyses were performed on data collected by 20 patients with twice daily reports of 3 different FSSs over the course of 12 weeks. For each individual we evaluated 1) whether there was a significant association between stress and FSSs and 2) the direction of this association. We hypothesized that stress precedes FSSs in some individuals. At the same time it seems likely that some individuals will experience stress because of their FSSs. Since different types of FSSs were reported, we also investigated whether some FSSs are more likely to be stressrelated than others.

Method

Study design

The current study consists of secondary analyses of data from a sample of patients with multiple, persistent FSSs. Electronic diaries were used to collect data on stress and FSSs twice daily. The target duration of data collection was 12 weeks. Data were collected between January 2004 and February 2006. Since a detailed description of the original study protocol can be found elsewhere [21], a summary of the methodology is provided below.

Participants

Participants were recruited through medical practitioners (general practitioners as well as medical specialists) and local media in southwest Scotland. Inclusion criteria were 1) age between 21 and 65 years and 2) regular experience of at least three symptoms that affected at least two bodily systems, which were inadequately explained by organic pathology. In order to assess the latter, information on medical history was acquired. Exclusion criteria were 1) history of severe physical illness such as cancer, coronary heart disease and active inflammatory disease, 2) continuing investigations to rule out organic pathology, 3) new or severe depression (including thoughts of self harm and recent start of an antidepressant) and 4) incapacity to comprehend or complete the diary and attend two clinic appointments. Patients with past or stable depression (unchanged antidepressant treatment for >3 months) and those taking antidepressants for physical symptoms were not excluded. Approval for the study was given by Dumfries and Galloway Local Research Ethics Committee. Written consent was obtained from all participants after explanation of the study. Patients were not paid for their participation.

Participants were selected from 54 referrals. Sixteen patients were referred by their doctors, 38 were self-referred. Twenty-seven patients (50%) withdrew or were excluded during the screening phase. Twenty-seven patients were enrolled in the study. One of these patients withdrew after 4 weeks without a specific reason. Data from 5 participants were discarded due to excess (>25%) missing data. One participant was excluded because of poor compliance with the times of data entry, leaving 20 participants whose data were suitable for analysis.

Electronic diary measures

The study diaries were designed to run on standard handheld personal digital assistant (PDA) computers running the Palm^M operating system. Data input was by stylus on a touch-sensitive screen using a Visual Analogue Scale (VAS) with a range between 1 and 150. Participants were given a brief demonstration on how to use the diary. Subsequently, a test entry was completed under supervision. Participants received written instructions, but the diary was designed to be used after minimal training [22]. Twice daily data entry was prompted by an audible alarm at agreed times, with the first entry in the late morning or early afternoon and the second entry in the evening. At the end of each entry session, data were date- and time-stamped and automatically stored.

FSSs

During the recruitment interview, participants were asked to indicate their symptoms from a list of 14 symptoms (muscle pain, joint pain, back pain, headache, abdominal pain, pelvic pain, bowel symptoms, dyspepsia, nausea, tight throat, chest pain, weakness, numbness and palpitations). When more than three complaints were reported, the three most severe or frequent symptoms were selected. Consequently, these three symptoms were assessed using the electronic diary. Diary questions with regard to FSSs were phrased as follows: "How much have you been bothered by symptom X? Please mark a point on the line between severe symptom X and no symptom X at all." (1-150). Instead of creating an FSSs sum score for each individual, the three FSSs of each subject were analysed separately, because preliminary analyses revealed that the time series of different FSSs in the same subject often showed a different course. To answer the question whether certain FSSs are more stress-related than others, FSSs were divided into four clusters, based on factor analyses of previous studies: musculoskeletal (muscle pain, joint pain, back pain, weakness, and numbness), gastrointestinal (abdominal pain, nausea, bowel symptoms, dyspepsia, and pelvic pain), cardiopulmonary (chest pain, tight throat, and palpitations), and general FSSs (headache) [23,24].

Stress

The perceived level of stress relating to the subject's environment was assessed with the following question: "How stressful are people and things around you? Please mark a point on the line between very stressful and not stressful at all." (1–150).

Other measures

Besides the main variables of this study, the diary also contained questions on depression, anxiety, and illness concern. Similar to stress and FSSs, these variables were assessed with a single question, using the same VAS scale. In the current study, these variables were used exclusively for the imputation of missing values.

Statistical method

For each individual data set, all missing values were imputed using the Expectation Maximization method in SPSS 20. The following variables were used in the imputation model: time (date), day of the

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