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Towards personalized assessment of fatigue perpetuating factors in patients with chronic fatigue syndrome using ecological momentary assessment: A pilot study

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ABSTRACT

Objective: This study aimed to explore the associations between cognitions, behaviours and affects and fatigue in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), and their relation to reduction of fatigue after cognitive behaviour therapy (CBT).
Methods: In CFS/ME patients, 22 behaviours, cognitions and affects, potentially perpetuating fatigue were registered 5 times a day using ecological momentary assessment (EMA) and an actigraphy. Simultaneous Components Analysis (SCA) was used to identify components of perpetuation, that were tested for their associations with fatigue in multilevel vector autoregressive (VAR) modelling. Fatigue severity was measured pre- and posttreatment with the Checklist Individual Strength. The relationship between perpetuation (the strength and direction of the possible associations between fatigue and the components) and therapy outcome was investigated.
Results: 58 patients met inclusion criteria (m age = 36.5; 65.5% female) and data of 50 patients were analysed in the multilevel analysis. Two perpetuating components were found: "psychological discomfort" and "activity". For the total group, both perpetuating components did not predict fatigue on a following time-point. For individual patients the strength and direction of the associations varied. None of the associations between perpetuating components and fatigue significantly predicted treatment outcome.
Conclusion: Results suggest that there is heterogeneity in perpetuation of fatigue in CFS/ME. Investigating fatigue and perpetuators on an individual rather than group level could lead to new insights.

1. Introduction

Patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) experience severe, ongoing and debilitating fatigue that cannot be explained by a known medical or psychiatric condition. The fatigue is accompanied by other symptoms such as pain, post-exertional malaise, concentration or memory problems and unrefreshing sleep [1]. The precise aetiology of CFS/ME is unknown and the diagnostic criteria are defined by consensus. To understand how fatigue can persist in CFS/ME, it can be helpful to distinguish between precipitating and perpetuating factors of CFS/ME [2]. Precipitating factors, such as a virus infection or psychological distress, are supposed to have triggered the symptoms, while perpetuating factors such as beliefs and behaviours are thought to perpetuate symptoms, even after the precipitating factors have disappeared [3]. CFS/ME can be treated with cognitive behaviour therapy (CBT) that aims at modifying perpetuating behaviour and beliefs to reduce fatigue and disability. CBT leads to a significant reduction in fatigue and disability in a substantial number of patients, although outcomes vary between studies and patients [4,5].

Several cognitive behavioural models of perpetuating factors in CFS/ME have been developed. One of the first models stated that CFS/ME patients avoid physical activity to prevent an increase in symptoms, resulting in a reduced level of physical activity and deconditioning [6]. Later, a distinction was made between patients with a constantly low

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activity pattern and those with a 'boom and bust' cycle. The latter group has peaks of activity to live up to their own standards, followed by inactivity. Both activity patterns are hypothesized to maintain fatigue [7]. Another model stated that, besides lowered activity, fatigue was maintained by a low self-efficacy towards the fatigue and symptom focussing [8]. Other studies investigated the role of the activity level and found that not the actual level of activity, but the perceived level of physical activity and perceived problems with activity (low self-efficacy regarding activity) perpetuated fatigue [9,10]. Moreover, additional factors were identified as potential perpetuators of fatigue, such as lack of social support [11], catastrophizing of symptoms [10] and depressive symptoms, although evidence of the latter is inconclusive [12]. Furthermore, there is growing evidence that both absence of positive and presence of negative affect might play a role in the perpetuation of somatic symptoms like fatigue [13]. Current CFS/ME models do not include affect, as its role has not yet been studied in this group.

All of the above-mentioned perpetuators, except for affect, are derived from empirical studies in groups of patients. An important limitation of studies in groups is that their findings are only generalizable to individuals if the processes are ergodic, i.e. if the processes are similar for all individuals in the group and stationary over time [14]. For perpetuation of fatigue this is probably not the case: differences in previous experiences and current environment might cause individual differences in the association between specific perpetuating factors and fatigue. Specific behaviours or beliefs may perpetuate fatigue only in some patients. In addition, group-level studies may have neglected potential perpetuating factors, if they were only relevant in a subset of the patients. One study demonstrated this by analysing data on a group-level as well as on an individual-level. The group-level analysis demonstrated that stress was only weakly associated with somatic symptoms, but the individual-level analyses showed that stress preceded somatic symptoms in some patients while the association was absent or reversed in others [15]. This illustrates a third problem of group-level studies: the direction of a relationship between possible perpetuators and fatigue can be heterogeneous.

CBT treatment manuals for CFS/ME are based on results of group-level analyses and therefore ignore possible individual variation in perpetuating factors and their associations with symptoms. All patients receive roughly the same treatment components with the exception of tailoring of the intervention to the level of pain symptoms, problems with concentrating or physical activity level [16]. Treatments could be more patient-tailored if more individualized perpetuating components could be identified. This tailoring to individual differences is what is aimed for in the field of personalized medicine. For treatment of CFS, one example is the distinction that is made between patients with low and with fluctuating activity patterns, which increased treatment efficacy in the former group [17]. Furthermore, if a patient shows no associations between beliefs or behaviour and fatigue, CBT may not be effective. This could apply to the subgroup of patients that does not profit from CBT. Such information could help identify these patients and would prevent them to be burdened by a non-effective intervention.

To be able to further personalize treatment for CFS/ME, we need to know to what extent perpetuation of fatigue is heterogeneous and what differences are relevant to treatment outcome. To this end, we collected time series of fatigue and its potential perpetuators in patients with CFS/ME, before starting manualized CBT for CFS/ME. We analysed heterogeneity in fatigue perpetuation using multilevel vector autoregressive (VAR) modelling, and studied its relevance for reduction of fatigue after manualized CBT.

2. Methods

2.1. Population

Participants were adult CFS/ME patients consecutively referred to a tertiary treatment centre for chronic fatigue at a university hospital (Radboud University Medical Centre, Nijmegen, the Netherlands) between October 2015 and March 2016. Inclusion criteria were: the patient gave written informed consent and CDC criteria for CFS (revised 2003 version [1]) were met. At referral, all patients were screened by a consultant of the outpatient clinic of the department of Internal Medicine of the hospital, to confirm if patients met CDC criteria for CFS/ME [18]. In accordance with existing literature [19,20], presence of severe fatigue was operationalized as having a fatigue severity score of $\geq$35 of the Checklist Individual Strength (CIS; [19]) and substantial disability by a score of $\geq$700 on the Sickness Impact Profile-8 (SIP8; [21]).

2.2. Design

During the diagnostic phase, patients with chronic fatigue syndrome (CFS/ME) completed a diary, five times a day for 15–16 days, measuring fatigue and potential perpetuating behaviours and beliefs. During the same period they wore the Actilog [22], a motion sensing device measuring activity of the leg, around their ankle. After completing the diary for 15–16 days, patients received CBT and the treatment outcome (i.e. fatigue severity) was measured at the end of the CBT. All patients gave written informed consent. The medical ethical committee of the Radboud university medical center ruled that the study did not fall under the scope of the Medical Research Involving Human Subjects Act, since diaries are routinely used during the diagnostic phase.

2.3. Procedures

The diaries were completed during the diagnostic phase of routine clinical care which consisted of two intake sessions and filling in of questionnaires, including the pre-treatment outcome assessment. During the first intake session, the therapist informed eligible patients about the study. If the patient wanted to participate and gave written informed consent, the psychological assistant demonstrated the use of the diary with a test entry. The patient was informed on the importance of not missing any entries. To obtain equidistant observations, we divided a day into eight time points, but only offered the diaries during five timepoints during daytime and not during the three night time points. When filling in the diary, the patient was asked to evaluate the past three hours. Therefore, the first time point was planned in the morning, three hours after waking up. Together, the patient and the psychological assistant chose the ideal time for the first diary prompt of the day, to minimize the chance of missing entries and to prevent the diary from affecting daily activities of the participant. Starting the next day at the agreed time points, the participant received a message with a link to the diary on his/her own smart phone. After receiving the diary prompt, patients had one hour to complete the diary. If they had not completed it after half an hour, they received a reminder. The diary was also accessible using a link in an e-mail. The assessment period was 16 days, of which the patient was asked to complete at least 15 days. If the patient had missed many entries on the first day, the extra day could compensate for this. During the same period, the participant also wore the actigraphy device measuring the activity level. At the second appointment with the therapist, patients were informed whether the diagnosis CFS/ME could be confirmed. If patients did not meet CFS/ME criteria, they were excluded. If they fulfilled CFS/ME criteria, they were offered CBT.

2.4. Intervention

CBT [16] aims at changing behaviour and cognitions assumed to perpetuate fatigue and functional impairment and is protocolised. CBT starts with goal setting. The first phase includes establishing a regulated sleep-wake cycle, learning to recognise and adapt dysfunctional cognitions, learning to redirect attention from fatigue to activities and the environment and learning how to communicate with others about CFS/ME. The second phase consists of an activity program in which physical

activity is gradually increased, time contingent. Relative active patients first divide their activities more evenly after which they start with a graded activity program. Low active patients immediately start with the graded activity program. In the third phase, personal goals, including work resumption, are realised applying the principles of the graded activity program. The CBT could be face-to-face (f2f), in that case 45 min sessions were held weekly or fortnightly. The CBT could also be given in the form of stepped care, with CBT via the internet as a first step and face to face CBT (when needed) as a second step. This was because some patients participated in an RCT as well, testing the non-inferiority of stepped care, compared to face to face CBT [23]. The web-based CBT was therapist guided, by e-mail.

2.5. Measures

2.5.1. Diary

The diary measured fatigue and twenty possible perpetuators of fatigue in CFS/ME resulting in a total of 21 items (Table 1). Participants were asked to think back to the three hours since the previous measurement and to indicate to what extent the items applied. All variables were measured using visual analogue scales, that were afterward transformed to a score ranging from 0 to 100, except for fatigue severity, which was measured on a 5-point Likert scale. The latter was done to make data comparable with data collected in other research projects.

The diary items were constructed to assess the possible perpetuators known from the literature and a range of affects. When possible, the items were derived from existing questionnaires measuring the construct. Specific items were selected, aided by item loadings according to principal components analysis in a group of 1407 CFS/ME patients referred to the treatment centre. This group was used for other validation purposes as well [24]. The suitability of the items were evaluated by the authors, considering face validity, the extent to which CFS/ME patients could relate to it, and usability in diary format.

2.5.2. Actigraphy

Objective physical activity was measured with the Actilog [22,29]. It registered movement on three axes: back-forth (X), up-down (Y) and side to side (Z). The activity level was represented by the tri-axial vector magnitude (VM3), which is used more often in research [30]. It is calculated for each time point with the formula $VM3 = \sqrt{(X^2 + Y^2 + Z^2)}$. Mean activity scores were calculated for the time intervals corresponding to the time periods between diary entries. The standard deviation of activity level was calculated to serve as a measure of fluctuation of activities. In accordance with previous studies, time periods of at least 90 min of no activity were registered as non-wear and recorded as missing data [31,32]. The Actilog was used in CFS/ME research previously, to assess activity in CFS/ME patients and other groups and to distinguish between low active and fluctuating active CFS/ME patients. During its development, the actigraphy was calibrated using an oscilloscope and its performance was tested on patients with CFS/ME, multiple sclerosis and healthy persons [22].

2.5.3. Treatment outcome: Fatigue severity

Fatigue was measured with the Checklist Individual Strength [19], pre and post treatment. The Fatigue Severity subscale was used to indicate fatigue severity, which consists of 8 items answered on a 7 point Likert scale with a sum score ranging from 8 to 56. A score higher than 35 indicates severe fatigue [33].

2.6. Analyses

2.6.1. Variable reduction using simultaneous components analysis (SCA)

Prior to the multilevel VAR analysis, the variables had to be reduced, because including all EMA variables in the vector autoregression, would make it difficult to interpret the results. More important, it could increase the chance of overfitting and multicollinearity, a problem common to VAR models [34,35]. We used Simultaneous Component Analysis (SCA) to reduce the dimensionality of the data by finding one common component structure which fits to all blocks, in this case, patients [36]. SCA was applied to the data of 22 possible perpetuating items (20 diary items, a physical activity score and a fluctuation in physical activity score) of 60 time points (5 times a day for 12 days) from 58 patients. The item 'fatigue' in the diary was not included to SCA since it is rather the outcome we are interested in, than a potential

Table 1
Diary.

Construct of interest	Diary item	Background
Fatigue	Have you been bothered by fatigue? 5-point Likert scale ranging from (not at all) to (to a very large extent). Transformed to 0–100	This item is adopted from the existing paper and pencil diary used in routine care in treatment center, to calculate the daily observed fatigue (DOF; [25]).
Physical activity level (subjectively measured)	In the past hours I was physically active. (VAS 0–100)	These items were constructed by the authors to measure activity.
Social activity level	In the past hours I was socially active. (VAS 0–100)	
Mental activity level	In the past hours I was mentally active. (VAS 0–100)	
Symptom focussing (cognitively)	I spent a lot of time thinking about my fatigue. (VAS 0–100)	Both were selected from the Illness Management Questionnaire Factor 3 (IMQ-III; [26]), assisted by the PCA. We chose a cognitive item and a sensory item as well, as some patients may not recognise thinking of the symptoms actively, although they are aware of them.
Symptom focussing (Sensory)	I was constantly aware of how I was feeling. (VAS 0–100)	
Catastrophizing	I couldn't help but concentrate on how terrible the fatigue actually feels. (VAS 0–100)	This item came from the JFCS (Jacobsen Fatigue Catastrophizing Scale; [27]). Based on face validity and the results of the PCA this item was considered the most suitable.
Self-efficacy regarding fatigue	I was able to influence my fatigue. (VAS 0–100)	This item was selected from the self efficacy scale (SES-28; [28]), with help of the PCA. The original item was 'Do you think you can influence your fatigue?'. It was modified as the diary asks about the past hours.
Self-efficacy regarding activity	I am confident that in the next few hours I can do what I want to do. (VAS 0–100)	This item was constructed by the authors to measure self-efficacy regarding activity.
Avoidance of activities to prevent symptoms	I avoided activities to prevent becoming exhausted. (VAS 0–100)	This item was constructed by the authors.
Lack of social support	I encountered Incomprehension for my complaints. (VAS 0–100)	This item was constructed by the authors.
Affects	I felt cheerful I felt enthusiastic I felt content I felt relaxed I experienced a depressed mood I felt sad I felt irritated I felt angry I felt tense I experienced anxiety (VAS 0–100)	These affects were chosen, to cover a wide range of positive and negative affects.

perpetuator. The analysis was performed by a standalone program, Multi Block Component Analysis (MBCA) software [36]. We analysed raw data by MBCA as the program can handle missing data. The MBCA software used autoscaling to eliminate the differences in variable means and variances. Since the perpetuating components are likely to be correlated, oblique rotation was chosen. The MBCA result file provided a component score for each patient on each time point, that was included in the multilevel VAR analysis.

2.6.2. *Multilevel multivariate vector autoregressive (VAR) modelling*

To investigate the associations between fatigue and the components obtained with SCA over time, while accommodating for the nested structure of the data (i.e., observations over time are nested within patients) we constructed multilevel multivariate vector autoregressive models within the Dynamic Structural Equation Model (DSEM; [37,38]) module in Mplus 8.4 [39]. DSEM decomposes total variability across individuals and time points into two components: a within-person component reflecting within-person fluctuations around the within-person mean and a between-person component reflecting the within-person means [38].

The within-person component was modelled using a time-series model; vector autoregressive (VAR) model of order 1 (VAR(1)). This model predicts each variable at one time-point (t) using all variables at the previous time-point (t-1), as such we could obtain the within-person associations between fatigue and the perpetuating components. These autoregressive (effect of variable on itself at the next time point) and cross-lagged (effect of variable on another variable at the next time point) parameters were allowed to be random (i.e., to vary across individuals). To reduce model complexity, random slopes and intercepts were specified to be independent.

In DSEM the random effects of the autoregressive and cross-lagged parameters from the within-person level become latent variables at the between-person level. As a result, the random effect parameters have means and variances at the between-level, which enables testing whether differences between individuals in these parameters are associated with variation in other variables measured at the between-person level. In our case, we were interested in whether treatment outcome (change in CIS fatigue between pre- and post-assessment) was associated with within-person dynamics between fatigue severity and perpetuating components. To investigate this, we specified in the between-level part of the model CIS fatigue severity change score (pre-post treatment) as the outcome variable and entered the random effects of the cross-lagged and autoregressive parameters as predictors. The CIS change score was grand-mean centered to allow interpretation relative to the overall sample mean. The cross-lagged and autoregressive parameters were within-person standardized using the method recommend by Schuurman et al. [40], which was implemented in Mplus [37].

To estimate DSEMs, Mplus utilizes Bayesian Markov Chain Monte Carlo (MCMC) with a Gibbs sampler. We used the DSEM default specifications of Mplus, that is, analyses were done using non-informative priors based on two independent MCMC chains. To ensure estimation was stable we used 40,000 iterations with a thinning of 4 iterations (meaning that one in 4 iterations is saved). Model convergence was assessed by inspecting the tracing plots for any irregularities (i.e., spikes and trends) and checking whether the potential scale reduction (PSR) criterion was below to 1.05 [41]. Point estimates are obtained by taking the median of the posterior distribution for each parameters. If the 95% credibility interval (CI) around a point estimate did not contain zero, we considered the effect to be non-null. To account for the fact that our timepoints were not equally spaced across time (there were no night entries), we used the TINTERVAL command in Mplus to specify a 180 min time interval interpretation for the effects [37]. This interval was chosen as it corresponds to the approximately 3-h intervals of the EMA diary. Prior to entering the data in Mplus, observations were linear detrended to ensure that the assumption of stationarity was met.

3. Results

As shown in Fig. 1, between October 2015 and March 2016, 179 patients were referred for treatment of CFS/ME. One hundred patients gave informed consent to participate. The diagnosis of CFS/ME was confirmed in 62 (62%) of these patients. Four patients were excluded from the analyses, because of too many missing data (>20%). Further analysis were performed on 58 patients with a mean age of 36.5 years (sd: 10.6); 38 (65.5%) were female.

Of the 58 patients included in the analysis, 51 started CBT and 7 did not (4 refused CBT, 2 started CBT elsewhere, and 1 would start later because of pregnancy). Of the 51 patients who started CBT, 32 received f2f CBT. The other 19 started with web-based CBT, as a first step of stepped care. Of them, 9 (9/19 = 47%) stepped up to f2f CBT after web-based CBT. Out of the 51 patients that started CBT, 50 patients completed a post treatment assessment. Therefore, only these 50 patients could be included in the multilevel VAR analysis. Time between pre and post assessment depended on the duration of treatment, which was 10 months on average (sd: 3 months). With respect to treatment outcome, the mean decrease in fatigue severity was 14.6 points (sd: 12.1).

After removal of the missing entries before the first and after the last entry of the diaries, the diaries contained 62 to 80 timepoints (mean: 74.2, sd: 5.7). Number of completed entries per patient ranged from 54 to 80 (mean: 68.8, sd: 6.2).

For actigraphy data it was found that patients had worn it for 12–20 days (mean: 14.3, sd:1.9). Since timeseries of equal size were needed for analyses, it was decided to use data of 12 days (60 timepoints), starting from the first full EMA day. When EMA and actigraphy did not start on the same day, the first day in which both were recorded was taken as the start date. In the total group, in the resulting 60 timepoints, 6.7% of the rows were missing.

3.1. *Variable reduction using simultaneous component analysis (SCA)*

The scree plot indicated a preference of a two component model (See Table 2). The first component had relatively high loadings on symptom focusing (both sensory and cognitively), catastrophizing, 5 out of 6 negative affects (all but 'anxious') and reversed loadings on the positive affects 'contented' and 'relaxed'. This component is named 'psychological discomfort'. The other component had high loadings on the activity measures (except for mental activity), the high arousal positive affects ('cheerful' and 'enthusiastic') and was named 'physical activity'. These two components were used in multilevel multivariate VAR modelling to derive component scores for each patient on each time point.

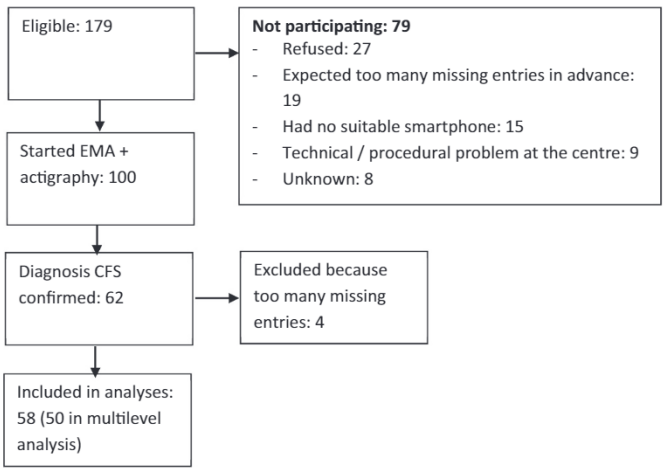

Fig. 1. Flowchart.

Table 2
Perpetuating components.

	Psychological discomfort	Physical activity
Physical activity level (self-reported)	0.12	**0.79**
Mental activity level (self-reported)	0.05	0.44
Social activity level (self-reported)	0.01	**0.66**
Symptom focusing (cognitively)	**0.65**	0.17
Symptom focusing (sensory)	**0.64**	0.17
Catastrophizing symptoms	**0.62**	0.14
Positive affect: Cheerful	−0.49	**0.57**
Positive affect: Enthousiastic	−0.47	**0.60**
Positive affect: Contented	**−0.62**	0.42
Positive affect: Relaxed	**−0.59**	0.13
Negative affect: Depressed mood	**0.69**	0.01
Negative affect: Sad	**0.62**	0.06
Negative affect: Irritated	**0.67**	0.10
Negative affect: Angry	**0.58**	0.13
Negative affect: Tense	**0.60**	0.16
Negative affect: Anxious	0.34	0.14
Self efficacy regarding fatigue	−0.18	0.20
Avoidance of activity to avoid symptoms	0.34	−0.29
Lack of social support	0.37	0.12
Self efficacy regarding activity	−0.44	0.11
Mean activity score (actography)	0.18	**0.77**
Standard deviation of the activity score (actography)	0.20	**0.71**

Component loadings >0.50 are shown in **bold**.

3.2. Multilevel multivariate vector autoregressive (VAR) modelling

The results of our DSEM analyses showed that when looking at the total group, scores on the components at the previous timepoint (at T-1) did not significantly predict fatigue at the next assessment (at T) at a p level of <0.001 (see Fig. 2). Likewise, on average, individuals' fatigue score at the previous timepoint did not predict their scores on any of the components at the next timepoint. We did observe significant autoregressive effects (i.e., variables predicting themselves at the next timepoint) for fatigue and the two components. Additionally, the psychological discomfort component significantly negatively predicted the activity component and the activity component significantly negatively predicted the psychological discomfort component.

To give an indication of the variation in the cross-lagged and autoregressive effects between individual patients, the variance in the within-person standardized effects (i.e., random effects) is provided in Table 3. The ranges in associations show that for most effects we identified patients with positive relationships (increase in variable at T-1 is followed by an increase in variable at T) as well as negative (increase in variable at T-1 is followed by a decrease in variable at T).

With the between-person part of the DSEM model we investigated whether between-person differences in the cross-lagged and autoregressive effects obtained the VAR(1) model were associated with treatment outcome in terms of improvement on the CIS Fatigue severity subscale. As shown in Table 4, none of the effects significantly predicted reduction in fatigue severity (at a one-tailed p-value of $P < .025$).

Table 3
Variation in within-person standardized effects.

Variable at T-1		Variable at T	within-person standardized effect variance	MIN-MAX of within-person effects
Fatigue	→	Fatigue	0.0091	0.019–0.376
Component 'Psychological discomfort'	→	Fatigue	0.0066	−0.183–0.241
Component 'Activity'	→	Fatigue	0.0006	−0.020–0.098
Fatigue	→	Component 'Psychological discomfort'	0.0018	−0.139–0.057
Component 'Psychological discomfort'	→	Component 'Psychological discomfort'	0.0044	0.243–0.522
Component 'Activity'	→	Component 'Psychological discomfort'	0.0013	−0.120–0.026
Fatigue	→	Component 'Activity'	0.0014	−0.130–0.101
Component 'Psychological discomfort'	→	Component 'Activity'	0.0015	−0.207 to −0.040
Component 'Activity'	→	Component 'Activity'	0.0028	0.046–0.358

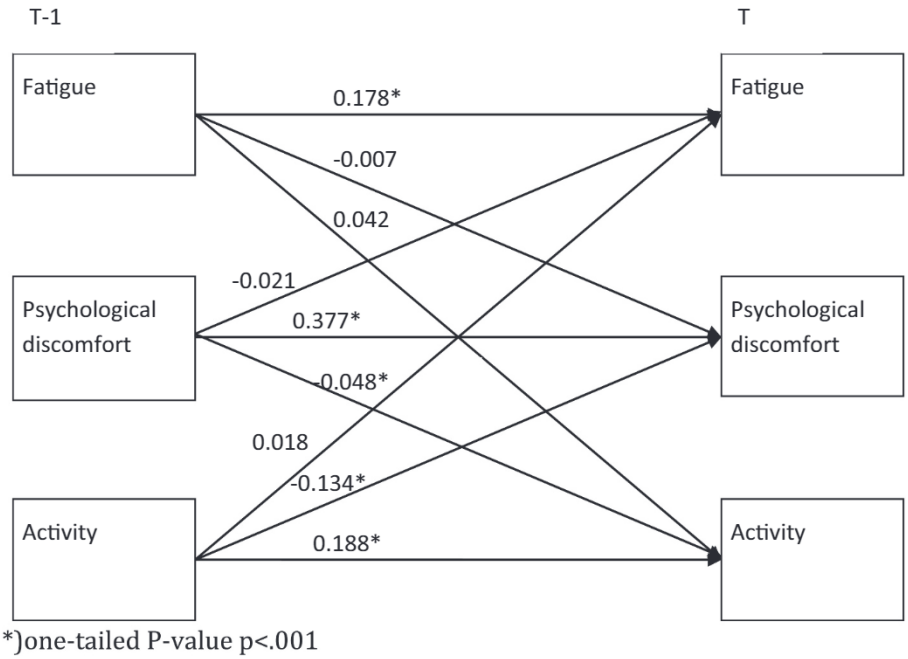

Fig. 2. Overall group result: average within-person standardized estimates for the autoregressive and cross-lagged effects. * One-tailed P-value $p < .001$.

Table 4
Association between average-within person (cross)lagged effects and CIS Fatigue severity change score.

(Cross)lagged parameter value			Association with improvement on fatigue severity on the CIS (95% credible interval)	Posterior standard deviation	One-tailed p-value
Variable at T-1		Variable at T			
Fatigue	→	Fatigue	0.073 [−0.266, 0.423]	0.177	0.342
Component 'Psychological discomfort'	→	Fatigue	−0.268 [−0.604, 0.131]	0.189	0.09
Component 'Activity'	→	Fatigue	0.083 [−0.399, 0.513]	0.237	0.369
Fatigue	→	Component 'Psychological discomfort'	−0.432 [−0.772, 0.048]	0.212	0.038
Component 'Psychological discomfort'	→	Component 'Psychological discomfort'	0.363 [−0.038, 0.672]	0.183	0.038
Component 'Activity'	→	Component 'Psychological discomfort'	0.045 [−0.379, 0.473]	0.219	0.419
Fatigue	→	Component 'Activity'	−0.044 [−0.475, 0.386]	0.223	0.425
Component 'Psychological discomfort'	→	Component 'Activity'	0.089 [−0.352, 0.492]	0.216	0.341
Component 'Activity'	→	Component 'Activity'	−0.015 [−0.417, 0.398]	0.211	0.474

4. Discussion

4.1. Principal findings

This study was a first attempt to identify perpetuators of fatigue in individual patients with CFS/ME, by means of time series analysis. Difficulties in time series analysis are to keep the results interpretable and to avoid overfitting and multicollinearity [35]. A challenge is to reduce variables measured with EMA to a small number of variables. We were able to summarize the perpetuators in two components, derived from SCA: 'Psychological discomfort' and 'Physical activity'. This data driven way of summarizing all measured variables could be a solution in this type of study.

When looking on the group level, no components were found that significantly perpetuated fatigue. When considering individual variation, we found that there was variation in strength and direction of the association between fatigue and both perpetuating components. For example, the score on component 'psychological discomfort' was associated with an inversed score of fatigue at the following timepoint (association = −0.183) in one patient. For another patient, 'psychological discomfort' was associated positively with fatigue in the next timepoint (0.241). The individual variations could not significantly predict reduction of fatigue severity after CBT.

The use of EMA in such an intensive time schedule was found to be feasible for CFS/ME patients. Patients were willing to participate (only 15% refused) and to complete the diary five times a day and wear an actigraphy device both night and day for 15 days. Of the 62 patients eligible for analysis, only 4 had too many (>20%) missing values. This is a promising result given the fact that CFS/ME is a heterogeneous condition and the expectation that progress can only be made if we understand more about the variation between patients in symptoms and disease related factors, for which EMA can be helpful.

4.2. Strengths and limitations

In this study, we were able to intensively measure fatigue and perpetuators in a naturalistic setting, accompanied by objective measurements of activity. This new method of assessing fatigue and possible perpetuators allowed us to identify perpetuators of fatigue within individual patients. A strength is that we were able to include affect in our study.

A difficulty in this type of study is that only a limited number of variables can be entered in a VAR model at once, while there were many potential perpetuators. To overcome this, two approaches can be taken: a data-driven approach or a theory-driven approach. The current study followed the former approach in which no a priori selection was needed for perpetuating factors. This is a strength of the study as it allowed us to cover a wide range of potentially relevant variables by using a small number of components. A limitation of this approach is that the perpetuating components are derived from analysis of scores on a group level and not on an individual level which could reduce variance between individuals in the contribution of different behaviours and beliefs that constitute the components. A further disadvantage is that the perpetuating components are more difficult to interpret than the individual perpetuating behaviours and beliefs assessed with the diary. This makes it difficult to relate these components to specific behaviours or beliefs addressed in CBT. Finally, we found that of the 22 perpetuators six items did not load on any of the components (27%). The finding that these did not load on any component does not necessarily mean their association with fatigue is less relevant than that of others. The theory-driven approach allows to interpret the results in a simpler way, but the perpetuators need to be selected before the analysis and therefore it has a risk of missing relevant perpetuating variables or giving variables too much weight.

There are some other limitations of the study. First, the validity of our diary items was not tested and it is possible that we did not measure all the constructs as intended. Especially the fact that we used a single item per construct could have reduced the reliability of our results. On the other hand, measuring five times a day is only feasible if the diaries contain a very limited number of items. It is also not known whether the length of the time lags (3 h) was ideal. It is possible that it would take less or more time for one factor to influence fatigue, and that the effect would no longer or not yet be visible after 3 h.

Furthermore, there are more ways of analysing this type of data and all have advantages and disadvantages. For example, it would have been interesting to know how fatigue is perpetuated in individual patients. This is possible with VAR(1) modelling, but when analysing multiple individual patients, it is difficult to compare results and there is the problem of multiple testing. The multilevel analysis enabled the analysis of a group of patients, while accounting for differences between individuals by modelling random effects. A disadvantage is that this multilevel approach gives limited insight in perpetuation in individual patients. For example, when looking at a group level, we found no components predicting fatigue in a later time-point. This might imply that this association does not exist or only in a minority of patients.

Another limitation is that we are not certain if our power was sufficient. The between level analyses show relatively wide credible interval, which could suggest there was insufficient power. Therefore we recommend to replicate the findings in a larger group of patients in order to draw conclusions.

Lastly, we excluded patients with too many missing data (>20%). This cut-off is somewhat arbitrary and it may have been too strict. It could have introduced bias into the results, which would limit generalizability of the results. In this study there were four cases with too many missing data. Additionally, 12 patients were not included in the multilevel analysis, as they had no post treatment assessment (in 7/8

cases this was because they had not received CBT). We tested if the baseline fatigue severity differed for the patients who were included ($n = 50$) and the patients who were excluded ($n = 12$) of the multilevel VAR and found both groups did not differ significantly ($p = .756$).

4.3. Interpretation

Several issues came forward that deserve further examination. First, fatigue and the perpetuating components did not seem to interact in the total group, while a variety of interactions appear to be present in individual persons. It shows that studying perpetuation of fatigue at the individual level may lead to different results than studying it on group level. Our findings give some directions to further investigate this, but did not yet lead to new insights that can be used in clinical practice.

4.4. Conclusions and implications for future studies

In conclusion, our study found no homogeneous model of perpetuation of fatigue in CFS/ME patients, but individual differences in the perpetuation of fatigue. When looking at the total group, most associations between perpetuators and fatigue were not associated with treatment result.

For further research it would be interesting to find a way in which we could use EMA and time series analysis to investigate the perpetuation of fatigue in individual patients. For example, individual VAR(1) models could identify perpetuators of fatigue in individual patients. If EMA and VAR(1) would be restricted to examining only a few variables, there is no need to reduce variables and perpetuation can be investigated more directly. For example, in individual patients it could be explored how negative affect and fatigue are associated, or how fatigue and activity are related. This would make results probably more relevant for clinical practice and could be a step towards personalized medicine. Second, it could be interesting to further investigate the predictive value of the association of the component 'psychological discomfort' and fatigue severity for treatment outcome.

The findings suggest that investigating on an individual level could lead to new insights, but that we have yet to discover how this can be incorporated optimally.

Declaration of Competing Interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare that H. Knoop receives royalties for the treatment protocol used in the study. R.N. Groen was supported by the Dutch Organisation for Scientific Research (NWO Talent Grant; grant number 406.16.507).

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