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The process of cognitive behaviour therapy for chronic fatigue syndrome: Which changes in perpetuating cognitions and behaviour are related to a reduction in fatigue?

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ABSTRACT

Objective: Cognitive behaviour therapy (CBT) can significantly reduce fatigue in chronic fatigue syndrome (CFS), but little is known about the process of change taking place during CBT. Based on a recent treatment model (Wiborg et al. J Psych Res 2012), we examined how (changes in) cognitions and behaviour are related to the decrease in fatigue.

Methods: We included 183 patients meeting the US Centers for Disease Control criteria for CFS, aged 18 to 65 years, starting CBT. We measured fatigue and possible process variables before treatment; after 6, 12 and 18 weeks; and after treatment. Possible process variables were sense of control over fatigue, focusing on symptoms, self-reported physical functioning, perceived physical activity and objective (actigraphic) physical activity. We built multiple regression models, explaining levels of fatigue during therapy by (changes in) proposed process variables.

Results: We observed large individual variation in the patterns of change in fatigue and process variables during CBT for CFS. Increases in the sense of control over fatigue, perceived activity and self-reported physical functioning, and decreases in focusing on symptoms explained 20 to 46% of the variance in fatigue. An increase in objective activity was not a process variable.

Conclusion: A change in cognitive factors seems to be related to the decrease in fatigue during CBT for CFS. The pattern of change varies considerably between patients, but changes in process variables and fatigue occur mostly in the same period.

INTRODUCTION

Chronic fatigue syndrome (CFS) is diagnosed when someone experiences medically unexplained, severe fatigue that has been present for at least six months and results in severe impairment in daily functioning. The fatigue is accompanied by at least four out of eight of the following symptoms: post-exertion malaise, unrefreshing sleep, short-term memory/concentration problems, muscle pain, joint pain without swelling or redness, tender lymph nodes in the neck or armpit, sore throat or

headaches [1] and [2]. Several cognitive behavioural models of CFS exist, which try to explain the perpetuation of symptoms in CFS patients [3], [4],[5] and [6]. All start with a period of severe fatigue that many patients, rightfully or not, attribute to a physical illness. In order to recover, patients often rest and become less active. Most models assume that because of this inactivity, patients' physical condition will decline and they will become increasingly sensitive to fatigue. In one of these models, that of Vercoulen et al. [7], a low level of physical activity, a low sense of control over fatigue, and a high level of focusing on symptoms explain the perpetuation of fatigue and impairment. The low level of physical activity is related to somatic attributions, as patients may avoid physical activity when they attribute their symptoms to a somatic illness. Although there are more recent models that also include physiological and social factors [8], this is still the only model that simultaneously tested the influence of several perpetuating factors. Based on these models, several protocols for CBT were developed [9], [10],[11] and [12] that lead to a significant reduction of fatigue and impairment [13] and [14]. Although protocols differ, they all encompass a stepwise increase in physical activity and challenging of dysfunctional fatigue-related beliefs.

Recently, Wiborg et al. developed a comprehensive treatment model of CBT for CFS [15], based on the model of Vercoulen et al. [7]. For their analyses they used data from previous randomised controlled trials (RCTs) testing the efficacy of CBT for CFS. Wiborg et al. first tested for each variable in the model of Vercoulen whether it was a mediator of CBT for CFS, i.e. whether it changed more in patients receiving CBT than in the control group and whether it indirectly explained (part of) the effect of treatment on symptom change. Two adaptations were made to the original variables: somatic attributions were not analysed, as previous research had shown that somatic attributions do not change during treatment [10], so they could never be a mediator of CBT; and perceived problems with activity were analysed, rather than objective activity assessed with actigraphy, as previous research had shown that objective activity or physical fitness do not mediate the effect of CBT for CFS [16] and other behavioural interventions for chronic fatigue[17] and [18]. In the final model, the decrease in fatigue is explained by an increased sense of control over fatigue, an increase in perceived activity, and improved physical functioning.

There are three limitations to the model of Wiborg et al. First, the model relied only on measurements before and after therapy and did not study the process of change during therapy. We therefore do not know whether changes in mediating variables indeed precede changes in fatigue. This makes it impossible to draw causal conclusions. Furthermore, temporary changes, which may catalyse other change processes, will go unnoticed. For example, a permanent change in objective activity does not mediate the treatment effect, but a temporary increase in activity might lead to changes in cognitions, which then lead to a decrease in fatigue. Second, focusing

on symptoms was measured with the subscale 'somatic complaints' of the Symptom Checklist 90. As the authors argued themselves, this questionnaire may have been unsuitable. Third, the model was tested in an RCT of a minimal intervention based on CBT for CFS [19]. Patients received a self-help booklet explaining the different components of CBT. In addition, they had regular email contact with a therapist. Tummers et al. showed that fatigue and impairment decrease significantly when patients follow additional CBT after such a minimal intervention [20]. So individual

CBT may have a more complex mechanism of change, i.e. it may target more processes, than the minimal intervention Wiborg et al. tested.
We built on the treatment model of Wiborg et al. by studying the change in different process variables during individual CBT. In Fig. 1 all proposed process variables are depicted. First of all, we selected the variables of the model of Wiborg et al., i.e. sense of control over fatigue, perceived activity and self-reported physical functioning. We added focusing on symptoms because this variable mediated the effect of CBT for CFS in an earlier RCT [21] and may have been measured inadequately in the study of Wiborg et al. These four variables had thus been proven to mediate the effect of CBT for CFS in formal mediation analyses of RCTs. Although objective activity was previously discarded as a mediator of CBT for CFS [16], we included this variable because a temporary change in objective activity might elicit other changes.

[FIGURE 1]

METHODS

Patients

Consecutively referred patients who started CBT at our tertiary CFS specialist care centre between April 2008 and September 2010 were eligible to participate if they:

- Met the criteria for CFS as stated by the US Centers for Disease Control and Prevention [1] and [2], i.e. severe fatigue, severe functional impairment and experiencing at least 4 out of the eight accompanying symptoms of the Fukuda criteria. Severe fatigue was defined as a score of ≥ 35 on the Checklist Individual Strength (CIS) subscale fatigue severity [22], and severe functional impairment was defined as a total score ≥ 700 on the Sickness Impact Profile (SIP) [23], [24], [25] and [26]. If a consultant or primary care physician had not ruled out any somatic disorder that excludes the diagnosis of CFS following the Fukuda criteria [1], patients first received a standard medical examination at the outpatient clinic of our department of internal medicine.
- Were between 18 and 65 years old
- Were able to read and write Dutch.

Patients were excluded if:
- They were currently applying for a disability claim until their application was completed, as this has previously been found to negatively influence treatment outcome [27].

The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humanshttp://www.wma.net/en/30publications/10policies/b3/index.html; uniform requirements for manuscripts submitted to biomedical journals http://www.icmje.org. It was approved by the ethical committee of the Radboud University Nijmegen Medical Centre. All participants gave written informed consent before participation.

CBT protocol

According to the protocol of CBT for CFS used in this study [9] and [28] the therapy needs approximately 12 one-hour sessions during 6 months. Actually the duration of therapy is jointly determined by the patient and therapist. At the start of therapy patients define concrete personal goals, usually including resumption of work, hobbies and other activities that imply recovery for the patient. Recovery, i.e. no longer being severely fatigued and impaired, is according to this protocol the highest goal to strive for in therapy. Patients are asked to regulate bedtimes and stop sleeping during the day, to stop possible disruption of the circadian rhythm. During the sessions, the therapist challenges non-accepting and catastrophising thoughts that inhibit adequate coping, and patients learn to distract their attention from their fatigue. Two groups of patients are discerned: Relatively active patients characterised by bursts of activity followed by prolonged periods of rest, and low active patients, who score below the mean of CFS patients on at least 90% of the days during actigraphic measurement [29]. Low active patients start with a graded activity programme immediately after the initial cognitive interventions. Relatively active patients first spread their activities more evenly across the day, after which they start the graded activity programme. This activity programme consists of daily walking or cycling, which is gradually increased. The increase in activity is not determined by the level of symptoms, but is time contingent. When patients succeed in increasing their physical activity, they start to increase social and mental activities. In the last phase of therapy, patients work systematically towards reaching their goals and experiment with fluctuating their bedtimes and activity level again. They are encouraged to perceive feelings of fatigue as a normal part of an active and healthy life and stop labelling themselves as a CFS patient. In total 12 therapists participated in our study, who had been thoroughly trained in the protocol of CBT for CFS and received frequent intervision and supervision. We did not use therapy aids, such as books or handouts and phone support between sessions was only provided when needed urgently. Costs of treatment were covered by standard medical insurance.

Measurements

Besides the regular pre- and post-therapy measurements we planned three interim measurements at 6, 12 and 18 weeks after the start of therapy. Patients received the questionnaires from the researcher and were told that their answers would not be communicated with their therapist. This was also mentioned in the written study information and the written instructions accompanying the questionnaires.

Fatigue

Fatigue was assessed with the subscale fatigue severity of the Checklist Individual Strength (CIS) [22], indicating the level of fatigue in the previous two weeks, measured with eight items on a seven-point scale (range 8–56). A score of 35 or higher (i.e. 2 standard deviations above the mean of a healthy control group) indicates severe fatigue. Cronbach's alpha ranges from .83 to .92 [7] and [30].

Process variables

Sense of control over fatigue

Sense of control over fatigue was assessed with the Self-Efficacy Scale (SES) [31] and [32]. This scale consists of five items (examples: Do you think you can influence your fatigue?; No matter what I do, I can't change my fatigue (reverse scoring); I think I could positively influence my fatigue). Items are scored on a 5-point Likert scale ranging from 'No, I am convinced that is not true' to 'Yes, I am convinced that is true'. The total score ranges from 5 to 25, with higher scores indicating a higher sense of control over fatigue. The internal consistency of this scale ranges between .68 and .77 [31] and [32].

Focusing on symptoms

Focusing on symptoms was measured with the subscale 'focusing on symptoms' of the Illness Management Questionnaire [33]. This questionnaire measures the patient's approach to fatigue in the last 6 months, but for this study we changed this to the last few weeks. The subscale consists of 9 items measured on a 6-point Likert-scale (ranging from 'never' to 'always'). Cronbach's alpha is 0.88 [33].

Objective activity

Objective activity was measured using an actometer, a motion sensing device developed at the Radboud University, worn around the ankle [29]. The mean number of accelerations was calculated automatically every 5 min, based on which a mean daily activity score was calculated. Activity was registered during 12 days both before and after treatment. During treatment, objective activity was registered during 4 complete days to limit the burden for participants. At the end of the measurement period data were visually checked by a research assistant to ensure that the device had worked properly and to check compliance. Days on which the device was worn for less than 22 h were excluded. Patients did not receive feedback on their activity level during the measurements, but they were told their activity level after the baseline measurement.

Perceived physical activity

Perceived physical activity was measured with an adapted version of the subscale physical activity of the Checklist Individual Strength [22]. This subscale indicates the perceived level of physical activity in the previous two weeks, measured with three items (I am physically very active (reverse scoring); I am physically not very active; My level of physical activity is low). These items are measured on a seven-point scale ranging from 'Yes, that is true' to 'No, that is not true'. Scores range from 3 to 21, with higher scores indicating a lower level of physical activity. The mean (SD) of the subscale in 915 untreated CFS patients was 18.0 (4.24) and Cronbach's alpha was .81.

Physical functioning

Limitations in self-reported physical functioning were measured with the corresponding subscale of the Medical Outcomes Survey SF36 [34]. Scores range from 0 (maximum limitations) to 100 (no limitations). The Cronbach's alpha of the subscale of the Dutch version is .92 [35].

Therapy components

At the end of therapy we asked patients 'which therapy components have been most helpful?'. They could select any number of 13 different components (setting goals, helping thoughts, focusing attention away from fatigue, changing your sleep–wake pattern, spreading activities more evenly, increasing physical activity, getting back to work, communicating differently with significant others with respect to fatigue, increasing mental activity, increasing social activity, reaching your goals, no longer seeing yourself as a patient, solving future problems with fatigue).

Statistics

First, we determined the size of change in fatigue during CBT (uncontrolled Cohen's d) in our participants. We then assessed whether it was within the confines of a prior statistical benchmark of RCTs testing the efficacy of CBT for CFS [36].
Our goal was to determine how the pattern of change in fatigue during CBT was related to the pattern of change in process variables. To get a first visual impression of the relation between the change in fatigue and process variables, patients were divided into response groups. These were based on their levels of fatigue at the different measurements: fast responders (no severe fatigue at the first interim measurement and post-therapy); mid-term responders (severe fatigue at the first interim measurement, but no longer at the second interim measurement and post-therapy); slow responders (severe fatigue at the first and second interim measurements, but no longer post-therapy); very slow responders (severe fatigue at the first, second and third interim measurements, but no longer post-therapy); and non-responders (severe fatigue post-therapy). Severe fatigue was defined as a score ≥ 35 on the subscale fatigue of the CIS. Mean values of the potential process variables at the different measurements were calculated and depicted for each of these response groups.
We then calculated Pearson's correlations between fatigue and process variables at the different measurements. To see whether levels of fatigue were predicted by process variables we built multiple regression models with fatigue at the different measurements as dependent variable and values of process variables at the previous measurement as independent variables. We then built regression models with the changes in process variables between the previous and current measurements to see whether these changes were related to levels of fatigue. Missing values were imputed in SPSS using multiple imputation with 20 replications and pooled results are reported.
Data analysis was performed using SPSS 21 for Windows®. Variables were checked for normal distribution and mean/standard deviation or median/interquartile range was calculated for normally distributed and skewed data respectively. Regression

models were tested for multicollinearity (tolerance < .10). A p-value < .05 was considered statistically significant.

RESULTS

Patients

In Fig. 2 a flow chart depicting the selection process is presented. Between April 2008 and December 2010, 297 CFS patients meeting all inclusion criteria started CBT. Fifty-five refused to participate; the most frequent reason given was the perceived effort of having to do extra assessments during treatment. Ten patients decided not to start with therapy in the first session, before informed consent was given. Of the 232 patients who gave written informed consent, 192 completed at least two interim measurements during the study: Fourteen decided to stop therapy before 12 weeks, 14 no longer experienced severe fatigue (fatigue < 35) and therapist and patient agreed to stop, and 12 patients no longer want to participate in the study. At the end of treatment, 9 patients did not fill in the questionnaires. So data of 183 patients could be included in the analyses. They had on average 12.9 sessions (SD 3.6). In 49 of them one or more variables were missing, which were imputed using multiple imputation with 20 replications. Baseline characteristics are given in Table 1.

[FIGURE 2]

Treatment outcome

We compared the change in fatigue during our intervention to a statistical benchmark of CBT for CFS. The uncontrolled Cohen's d [37] for the change in fatigue severity during CBT was 2.11. This is higher than the statistical benchmark of CBT for CFS (1.44, 95% CI 0.97–1.89) [36]. Post-hoc analyses suggested that patients participating in the study had a better treatment outcome than those who refused to participate and had data on post-treatment available (n = 41, post-treatment CIS subscale fatigue 27.5 (13.9) in participants vs. 36.0 (15.0) in non-participants: df = 257; t = 3.56; p < .001).

Response groups and trajectories of process variables

Based on their level of fatigue at the different measurements, 42 patients were classified as fast-responders (fatigue < 35 at first interim measurement), 44 as mid-term responders (fatigue < 35 at second interim measurement), 17 as slow-responders (fatigue < 35 at third interim measurement), 24 as very slow responders (fatigue < 35 at post-measurement) and 52 as non-responders (fatigue >= 35 at post-measurement). Four patients could not be assigned to a subgroup because of missing data. We combined the slow and very-slow responders into one group of slow responders to obtain four groups of sufficient sample size. Because we combined the slow and very slow responders, we also combined the change scores between interim measurement 2 and the post-measurement. Mean values of the potential process variables in the different response groups during therapy are depicted in Fig. 3. Patterns of change in all process variables resembled that of fatigue, except for actual

objective activity. At post-treatment, non-responders differed significantly from the other groups on all process variables.

[FIGURE 3]

Correlations between process variables and fatigue

Pearson's correlations of fatigue with process variables (Table 2) showed that at all four measurements a higher level of fatigue was related to lower sense of control over fatigue, poorer physical functioning, lower perceived activity and higher focusing on symptoms in the same period. All correlations increased during treatment. Only post-treatment was objective activity related to fatigue, i.e. lower activity was related to higher fatigue.

[TABLE 1]

Multiple regression models of process variables and changes in fatigue

The first set of regression analyses, in which fatigue at different measurements was predicted by process variables at the previous measurement (Table 3), showed that only pre-treatment objective activity predicted fatigue at the first interim measurement, i.e. lower activity pre-treatment predicted lower fatigue at the first interim measurement.

[TABLE 3]
Regression analyses in which changes in process variables between the previous and current measurements were added showed different results (Table 4). Lower levels of fatigue were related to increases in perceived activity, physical functioning and sense of control over fatigue together with decreases in focusing on symptoms. Changes in objective activity did not predict levels of fatigue. Changes in process variables added 46%, 20% and 33% of explained variance in fatigue.

[TABLE 4]

What do patients themselves see as most helpful?

The most frequently given answers to the question "what therapy component was most helpful to you?" were: changing your sleep–wake rhythm (72%), increasing physical activity (65%), spreading activities more evenly (60%), and helping thoughts (57%). Setting goals (36%), focusing attention away from fatigue (31%), increasing mental activities (22%), increasing social activities (20%), no longer seeing yourself as a patient (19%), communicating differently with significant others with respect to fatigue (18%), reaching goals (14%) and solving future problems with fatigue (11%) were mentioned less.

DISCUSSION

This is the first time the process of change during CBT for CFS has been studied. We found a large variation in the time it takes to normalise fatigue. In around a quarter of the patients fatigue is already within normal limits 6 weeks after the start of CBT. Others are still severely fatigued after 18 weeks of therapy, but fatigue normalises thereafter. Anderson and Lambert found a similar variation in outpatient psychotherapy [38], but they studied a variety of diagnoses and therapeutic orientations. Despite this individual variation, we were able to discern four groups of patients (fast, mid-term, slow and non-responders) who show discernible patterns of change in fatigue and process variables.

During the entire therapy, an increase in perceived activity, physical functioning and sense of control over fatigue together with a decrease in focusing on symptoms is related to lower levels of fatigue. This supports the importance of changes in cognitive factors in CBT for CFS. Although process variables were related to fatigue and changed simultaneously, they did not predict subsequent changes in fatigue. As our study did not include a control group, we could not perform mediation analyses to determine whether changes in process variables cause the decrease in fatigue, or whether they are simply correlated. A decrease in fatigue may have permitted patients to be more active, may have given them a feeling of control over their fatigue and may have decreased their focus on fatigue. For most of the process variables we tested, previous mediation analysis of RCTs had shown that they mediated the effect of CBT for CFS [15] and [21]. Probably, the relationship

between process variables and fatigue is not a simple cause–effect relationship, but a complex feedback process in which changes in cognitions lead to a decrease in fatigue, which leads to further changes in cognitions and so on. Such a reciprocal relationship has previously been described for other forms of CBT [39] and [40]. Lower pre-treatment objective activity predicted lower fatigue at the first interim measurement. This finding is difficult to explain. Levels of objective activity during treatment were not related to subsequent levels of fatigue at other measurements. In the early phases of treatment, even patients who remain severely fatigued after treatment increase their level of physical activity (see Fig. 3). So an increase in physical activity per se does not seem sufficient to reduce fatigue. An increase in perceived activity, however, does seem important. Besides, the increase in physical activity was frequently mentioned by patients as being helpful. An increase in physical activity may merely catalyse other change processes because patients experience that they can be more active despite being fatigued, which possibly facilitates a greater sense of control over fatigue and perhaps also leads to a decrease in focusing on symptoms. If such a change in cognitive processes does not occur, we could hypothesise that patients do not experience a decrease in fatigue and fall back in their old patterns and levels of physical activity, even though their level of physical activity increased temporarily. Indeed, patients who remained severely fatigued did not retain their initial increases in activity; at the end of the treatment they were significantly less physically active, as measured by actigraphy, than the patients who had responded to treatment. This was also reflected in the significant negative correlation between post-treatment levels of fatigue and levels of actual activity.

The process variables we examined seem to play an important role in CBT for CFS, as changes in these variables explained up to half of the changes in fatigue. Previous studies have found other process variables besides those included in the model of Vercoulen. Godfrey et al. found that emotional processing, defined as the expression, acknowledgement and acceptance of emotional distress, was a possible process variable of CBT for CFS [41]. Deale et al. found changes in fear-related avoidance of exercise to be a mediator of the treatment effect [10], although Wiborg et al. could not replicate this finding [21]. It could be that this factor only plays a role in a subgroup of patients, probably those with a passive activity pattern.

Future studies should try to identify other process variables. One of them may be regulation of the sleep wake rhythm. In fact, this was the therapy component patients most often mentioned as being helpful. Another candidate may be high standards that patients set for themselves, i.e. perfectionism [3],[4] and [42]. These may lead to the bursts of activity that are characteristic of relatively active patients. Expectations of future performance may also be a process variable. When patients already expect symptoms before starting a physical activity, they may also focus on possible feelings of fatigue, which will make them more sensitive to fatigue [5]. Another candidate is the qualitative experience of fatigue. When asked to describe their fatigue, CFS patients use more negative adjectives than healthy persons[10] and [43]. A change in the negative representations of fatigue also mediates the effect of CBT for chronic fatigue in multiple sclerosis [39].

Our study focused on fatigue, but most CFS patients also experience other symptoms. The processes related to a decrease in fatigue may not be the same as those leading to e.g. a decrease in pain. Future studies should therefore study the mechanisms leading to a decrease in other symptoms.

Another question to be answered by future studies is the role of physical activity in subgroups of patients. A gradual increase in objective activity does not mediate the treatment effect of CBT for CFS [16], but some extremely high active patients may experience less fatigue by reducing activity and an increase in physical activity may be necessary in some extremely low active patients. Future studies could experiment with various levels of activities and simultaneously monitor patients' change in fatigue. With initial increases in activity, patients may realise that they can be active in certain ways without increasing fatigue. The relatively small number of patients in our study limited our analytic possibilities. We could not perform subgroup analyses and could only perform simple correlations and regression analyses, whereas it would certainly have been interesting to use more sophisticated models, such as latent difference score models [44], or include factors that may possibly affect the process of change. We therefore consider this an exploratory study.

A relatively large percentage of the patients starting CBT refused to participate in the study (19%), mainly because of the perceived effort of extra assessments during treatment. The patients who participated in our study may be those who were most motivated for the treatment, which may have led to a selection bias. The post-hoc analyses reported in the Results section indeed suggest that treatment outcome in study participants was better than in patients who refused to participate. However, it is unlikely that the process of change was entirely different in those who refused to participate.

We did not control for possible confounders, such as psychiatric comorbidity or social functioning, that could both be related to process variables and fatigue.

However, given previous mediation analyses of controlled trials on CBT for CFS and the fact that changes in process variables occur in the same period as changes in fatigue, it is unlikely that the relation between process variables and fatigue would be entirely explained by these possible confounders.

This study has also implications for current models of CFS. First, most models include a reduced level of physical activity, and consequent physical deconditioning, as a fatigue-perpetuating factor. However, in our study, average levels of activity pre-treatment were not very low and the lack of a relationship between objective activity and fatigue makes it unlikely that physical deconditioning is a fatigue-perpetuating factor. Our results indicate that rather than objective activity, it might be low perceived activity that perpetuates fatigue. This should be taken with caution, as a distinction has to be made between models trying to explain the persistence of symptoms in CFS and those trying to explain the treatment processes. Besides, we did not measure physical fitness directly and physical deconditioning may still play a role in low active patients. A second implication of our results is that they emphasise the importance of cognitive changes during CBT for CFS. Both findings have also implications for the training of CBT therapists. Instead of objective activity, it could be more productive to focus on changes in cognitions and behaviour related to physical activity. Careful monitoring of these cognitions could be used as a means to assess patients' progress. This enables therapists to intervene when patients are not making progress.

In conclusion, levels of fatigue during CBT for CFS do not seem to be related to objective physical activity, whereas they do seem related to a change in cognitive factors such as the sense of control over fatigue, focusing on symptoms, perceived activity and physical functioning. The pattern of change in these latter variables varies considerably between patients, but changes in process variables and fatigue occur mostly in the same period, which suggests a complex feedback process in which fatigue and process variables influence each other.

CONFLICT OF INTERESTS

The authors have no competing interests to report.

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FIGURES AND TABLES

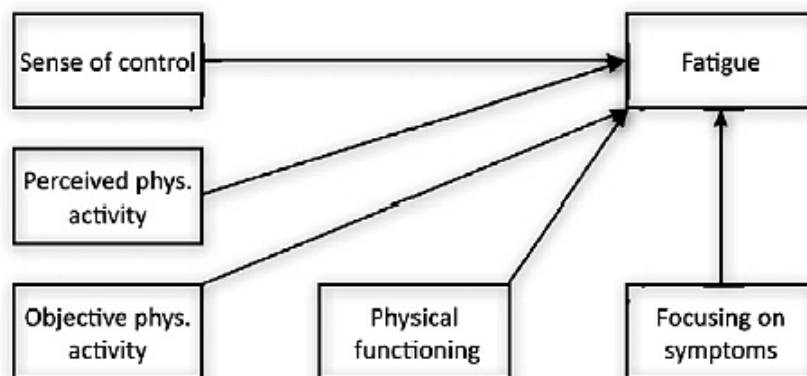Fig. 1. Potential process variables that we tested, based on the models of Wiborg [15] and Vercoulen [30].

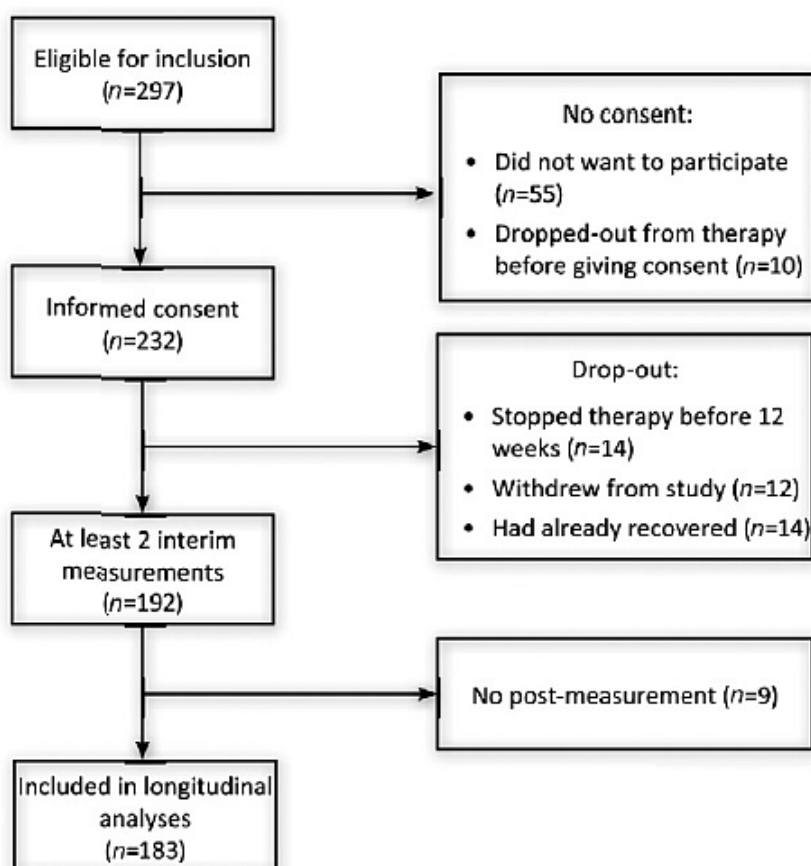Fig. 2. Flow chart of the selection of the study participants.

Table 1
Patient characteristics (n = 183)

Variable	Mean (SD)
Age (years)	38.2 (11.5)
Female	137 (75%)
Fatigue	
Pre	49.8 (5.2)
Interim 1	39.7 (10.0)
Interim 2	34.3 (12.5)
Interim 3	32.7 (12.4)
Post	27.0 (13.8)
No. CDC symptoms	7.1 (1.7)
BDI-PC >4	40 (22%)
SCL-90	163 (33.8)
SIP total score	1543 (553)
SF36 social functioning	45.2 (21.8)
SF36 physical functioning	57.5 (20.1)
Low activity pattern	38 (21%)

Fatigue = Checklist Individual Strength subscale fatigue severity; BDI-PC = Beck depression inventory primary care; SCL-90 = Symptom Checklist 90; SIP = Sickness Impact Profile; SF-36 = MOS SF-36; low activity pattern: actometer score below the mean of CFS patients more than 11 of 12 days.

Fig. 3. Mean fatigue and process variables during therapy in the different fatigue response groups. Pre = pre-measurement; 1 = 1st interim measurement; 2 = second interim measurement; post = post-treatment measurement; Fast = fast responders (fatigue within normal limits at first interim measurement and post-treatment); mid = mid-term responders (fatigue within normal limits at second interim measurement and post-treatment); slow = slow responders (fatigue within normal limits post-treatment); non = non-responders; Fatigue = Checklist Individual Strength subscale fatigue severity; Perceived activity = Checklist Individual Strength subscale physical activity; objective activity = mean daily score asmeasured with actometer; sense of control = SES28 total score; focusing on symptoms = subscale focusing on symptoms of the IllnessManagement Questionnaire.
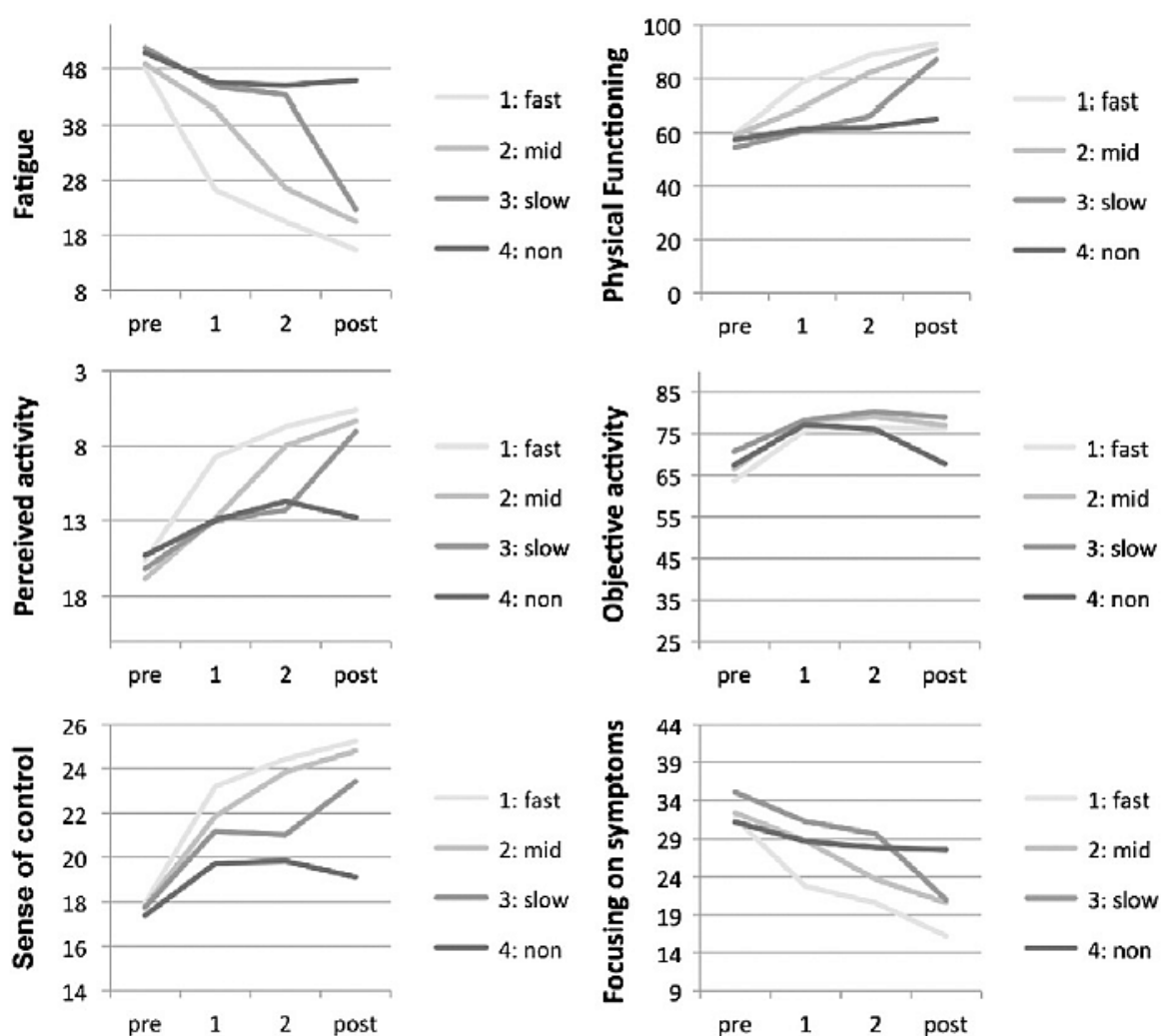
Table 2
Correlations of process variables with fatigue at different measurements (n = 183)

Process variables at same measurement	Fatigue pre		Fatigue interim 1		Fatigue interim 2		Fatigue post	
	r	p	r	p	r	p	r	p
Perceived act	.404	<.001	.568	<.001	.635		.728	
Focus	.256	<.001	.469	<.001	.544	<.001	.576	<.001
Sense of control	−.276	<.001	−.550	<	−.661	<.001	−.723	<.001
Objective act	−.083	.267	−.051	.513	−.076	.335	−.262	<.001
Physical funct.	−.288	<.001	−.492	<.001	−.620	<.001	−.686	<.001

Fatigue = Checklist Individual Strength subscale fatigue severity; perceived act = subscale perceived activity of the Checklist Individual Strength; focus = subscale focusing Illness Management Questionnaire; sense of control = Self-Efficacy Scale; objective activity = mean daily activity score as measured with the actometer; physical funct. = subscale physical functioning of the SF36.

Table 3
Multiple regression models of levels of fatigue predicted by process variables at the previous measurement (n = 183)

	Fatigue interim 1				Fatigue interim 2				Fatigue post			
	b	SE	t	p	b	SE	t	p	b	SE	t	p
Fatigue prev	.601	.161	3.725	<.001	.880	.097	9.028	<.001	.717	.106	6.783	<.001
Perceived activity prev	−.063	.190	−.332	.740	−.270	.181	−1.494	.135	−.339	.218	−1.559	.119
Focus prev	−.008	.086	−.096	.924	−.007	.096	−.074	.941	−.169	.120	−1.411	.158
Sense of control prev	−.094	.241	−.390	.697	−.352	.273	−1.290	.197	−.569	.292	−1.948	.051
Objective activity prev	.098	.041	2.393	.017	−.022	.031	−.710	.478	−.018	.034	−.537	.591
Physical funct. prev	−.027	.039	−.685	.493	−.051	.039	−1.309	.191	−.036	.051	−.712	.476

R^2 is 0.10, 0.59 and 0.46 respectively. Estimates are unstandardised and reflect predicted fatigue when the predictor (process variable at previous measurement) increases 1 point; fatigue = Checklist Individual Strength subscale fatigue severity; perceived act = subscale perceived activity of the Checklist Individual Strength; focus = subscale focusing Illness Management Questionnaire; sense of control = Self-Efficacy Scale; objective activity = mean daily activity score as measured with the actometer; physical funct. = subscale physical functioning of the SF36.

Table 4
Multiple regression models of levels of fatigue predicted by changes in process variables during the same period (n = 183)

	Fatigue interim 1				Fatigue interim 2				Fatigue post			
	b	SE	t	p	b	SE	t	p	b	SE	t	p
Fatigue prev	.934	.106	8.847	<.001	.922	.048	19.136	<.001	.850	.038	22.102	<.001
Δ perceived activity	.637	.121	5.269	<.001	.753	.119	6.341	<.001	.807	.110	7.311	<.001
Δ focus	.243	.071	3.404	.001	.217	.078	2.798	.005	.252	.072	3.481	.001
Δ sense of control	−.641	.185	−3.472	.001	−.726	.211	−3.449	.001	−.841	.181	−4.658	<.001
Δ objective activity	−.028	.024	−1.146	.252	−.005	.020	−.250	.803	−.001	.024	−.034	.973
Δ physical funct.	−.109	.032	−3.364	.001	−.112	.040	−2.759	.006	−.248	.039	−6.402	<.001

Adjusted R^2 is 0.54, 0.76 and 0.77 and r2 change 0.46, 0.20 and 0.33 respectively. Estimates are unstandardised and reflect change in fatigue when the predictor (process variable at the start of period or change in process variable during the period) increases 1 point; prev = value at previous measurement; Δ = change since previous measurement; fatigue = Checklist Individual Strength subscale fatigue severity; perceived act = subscale perceived activity of the Checklist Individual Strength; focus = subscale focusing Illness Management Questionnaire; sense of control = Self-Efficacy Scale; objective activity = mean daily activity score as measured with the actometer; Physical funct. = subscale physical functioning of the SF36.