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Heart rate variability biofeedback therapy and graded exercise training in management of chronic fatigue syndrome: An exploratory pilot study

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ABSTRACT

Objective: Chronic fatigue syndrome (CFS) is characterised by persistent fatigue, exhaustion, and several physical complaints. Research has shown cognitive behavioural therapy (CBT) and graded exercise training (GET) to be the most effective treatments. In a first step we aimed to assess the efficacy of heart rate variability biofeedback therapy (HRV-BF) as a treatment method comprising cognitive and behavioural strategies and GET in the pilot trial. In a second step we aimed to compare both interventions with regard to specific parameters.
Methods: The study was conducted in an outpatient treatment setting. A total of 28 women with CFS (50.3 ± 9.3 years) were randomly assigned to receive either eight sessions of HRV-BF or GET. The primary outcome was fatigue severity. Secondary outcomes were mental and physical quality of life and depression. Data were collected before and after the intervention as well as at a 5-month follow-up.
Results: General fatigue improved significantly after both HRV-BF and GET. Specific cognitive components of fatigue, mental quality of life, and depression improved significantly after HRV-BF only. Physical quality of life improved significantly after GET. There were significant differences between groups regarding mental quality of life and depression favouring HRV-BF.
Conclusion: Both interventions reduce fatigue. HRV-BF seems to have additional effects on components of mental health, including depression, whereas GET seems to emphasise components of physical health. These data offer implications for further research on combining HRV-BF and GET in patients with CFS.
Trial registration: The described trial has been registered at the International Clinical Trials Registry Platform following the number DRKS00005445.

1. Introduction

Chronic fatigue syndrome (CFS) is characterised by intense, disabling fatigue persisting more than six months that is not explained by on-going exertion or organic disease and that cannot be alleviated within a normal period by rest or distraction [1,2]. In addition, several physical or somatic symptoms, such as muscular pain, dizziness, headache, sleep disorder, inability to relax and/or irritability have to exist [3]. The prevalence of CFS varies widely depending on disease definition, but it is assumed that the syndrome could affect 1% of the adult population [1], and is more often seen in women and in adults [4,5,6]. Furthermore, there is an increased risk of completed suicide in patients with CFS [7]. Until now, no distinct agents either exclusively physiological or exclusively psychopathological have been identified [8]. Most promising theoretical concepts assume that the experience of fatigue and chronic physical symptoms combined with loss of functioning is influenced by multiple biological, affective, behavioural, cognitive, and social factors [6,8,9]. Wyller et al. [10] proposed a model of sustained arousal in patients with CFS based on the cognitive activation theory

Abbreviations: APT, adaptive pacing therapy; BF, biofeedback; BMI, body-mass index; CBT, cognitive behavioural therapy; CDC, Centers for Disease Control and Prevention; CFS, chronic fatigue syndrome; EEG, Electroencephalography; EMG, Electromyography; FSS, functional somatic syndromes; GET, graded exercise training; HRV, heart rate variability; MFI, Multidimensional Fatigue Inventory; RSA, respiratory sinus arrhythmia; SCID, structured clinical interview; SD, standard deviation; SDS, Somatoform Disorder Schedule; SF36, Short Form General Health Survey; SMC, specified medical care; QoL, quality of life.

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of stress (CATS) by Ursin and Eriksen [11]. This model takes into account predisposing (e.g. genetic traits such as polymorphisms in the autonomic and endocrine systems and personality traits such as inappropriate illness perceptions), precipitating (e.g. long-lasting infections, critical life events, and perceived chronic difficulties), perpetuating, and associated factors (e.g. hemodynamic, immune, endocrine, muscle, and cognitive alterations) [10]. The authors suggest that patients with CFS experience homeostatic instability as a result of precipitating factors, followed by vicious cycles of reinforced arousal response and dysfunctional cognitive beliefs that elicit a state of sustained arousal [10]. Similarly, Hyland [12] developed an extended network learning error theory of CFS to combine the psychological and immunological perspectives as well as that concerning the hypothalamic-pituitary-adrenal axis. He proposed that those three mechanisms interact and should be treated as complementary rather than as competing explanations within a network system. Knoop et al. [13] focused on the cognitive components. The authors described three different cognitive processes that may play a role in the maintenance of CFS: a general cognitive representation averse to fatigue, a process of focusing on fatigue, and specific dysfunctional beliefs about fatigue and activity.

Therapeutic approaches in patients with CFS are very limited. Three Cochrane reviews published thus far have summarised the evidence and suggested that cognitive behavioural therapy (CBT) and graded exercise training (GET) are effective therapies for patients with CFS [14,15, 16]. The meta-analysis of Castell et al. [17] shows positive effect sizes for both CBT and GET and replicates the findings of previous reviews [18, 19], but the research did not manage to find any significant difference between the two intervention types [17]. However, CBT seemed to emphasise the role of emotional aspects as perpetuating factors of fatigue and resulted in a greater reduction in depression and in anxiety [17]. In another randomised controlled trial that included 641 patients, White et al. [20] found CBT, GET, and adaptive pacing therapy (APT) in combination with specified medical care (SMC) to be more effective compared to SMC alone as a non-specific control condition. The long-term follow-up from this trial shows that the beneficial effects of CBT and GET were maintained for a median of 2.5 years after randomisation [21]. Moss-Morris et al. [22] analysed 49 CFS patients after a 12-week graded exercise programme in comparison to standard medical care. Patients showed less mental and physical fatigue and improved physical functioning. The authors stated that a decrease in symptom focusing, rather than an increase in fitness, mediated this treatment effect. Recently, Christensen et al. [23] highlighted the changes of illness perception as an important process in CBT for severe functional somatic syndromes (FSS). Concerning complementary medicine a recent systematic review provides limited evidence for the effectiveness of complementary and alternative-medicine therapy in relieving symptoms of CFS [24].

Biofeedback therapy (BF) is a treatment method that includes cognitive and behavioural strategies, and thus – based on the above mentioned – can be considered for application in the management of CFS patients. It comprises psychoeducational and interoceptive aspects, stress reduction and relaxation training, and improvement of self-efficacy in addition to the training of one or several specific parameters [25, 26,27]. Heart rate variability biofeedback (HRV-BF) is a subtype of biofeedback training that aims to control ones breathing frequency at the level of 6 to 7 cycles per minute. Slow pace breathing has shown to increase a vagal tone, stimulate baroreflex regulation and contribute to the "restoration" of sympathetic/parasympathetic shift [28]. The most comprehensive review of HRV-BF by Wheat and Larkin [29] points out that changes in baroreflex activity could be the underlying physiological mechanism that explains beneficial effects of HRV-BF on health. HRV-BF has shown to be efficient in management of stress-related psychiatric disorders [30,31], chronic pain [32,33] as well as for the stress modulation in postpartum period [34] and in healthy subjects [35].

Surprisingly, our literature research revealed very few data about elaborated treatment protocols using HRV-BF in adult patients with CFS. In one study, 50 adolescents (ages 10–14) with CFS were treated with Electromyography- (EMG-) and HRV-biofeedback and compared with wait-list controls ($n = 42$), showing a significant reduction in fatigue severity and higher school attendance after intervention [36]. James and Folen [37] and Hammond [38] each reported single-case studies with EEG- biofeedback in a woman with CFS. Both reported considerable improvement in fatigue and cognitive functioning.

This led us to the idea to develop a HRV-biofeedback treatment manual for patients with CFS and to test its effect on fatigue perception as well as on self-estimated mental and physical functioning. Based on the evidence that HRV and respiratory sinus arrhythmia (RSA) trainings improve the regulation of the autonomic nervous system [28,39] which is affected in FSS as CFS [40], we chose breathing and heart rate as specific training parameters [25]. In regard to the maintaining cognitive and affective processes of CFS [13,41], we hypothesize that HRV-BF might help to normalise individual physiological reactions, to reflect specific dysfunctional beliefs about fatigue and activity, and to shift the point of concentration from fatigue to other aspects [42,43]. Based on Hyland's extended network learning error theory of CFS, HRV-BF might promote self-organisational learning at the interface between physiological and psychological events [12]. Finally, we thought about HRV-BF having an effect on the positive belief of personal control over one's symptoms, which has been proven to be an important mediating factor in the treatment of FSS [23,44].

If our HRV-BF protocol shall proof its efficacy in this pilot-study it could be used in further randomised placebo-controlled or "head-to-head" trials. Having this scope in mind, we added a well-established treatment for CFS management – graded exercise training – in order to observe their influence on our variables of interest. We aim to explore the impact of both treatment methods on subjective fatigue, mental and physical functioning as well as on depression. As a secondary outcome we compare the two interventions with regard to above mentioned mental and physical parameters.

2. Material and methods

2.1. Study population

The study was conducted at the Department of Psychosomatic Medicine and Psychotherapy, in collaboration with the Department of Sports Medicine, University Hospital Tübingen (Germany). Patients were recruited through advertisements in local newspapers and by an Internet web page. The local ethics committee of the medical faculty approved the study protocol (project number 310/2009BO2) in accordance with the Helsinki Declaration. All participants provided written informed consent prior to study participation.

Participants were screened according to the criteria for CFS of the Centers for Disease Control and Prevention (CDC) [3]. These criteria include the requirement of feeling extraordinary exhaustion after slight physical or mental activity, with no possibility of recovery within a normal period of time. In addition, several physical or somatic symptoms, such as muscular pain, dizziness, headache, sleep disorder, inability to relax and/or irritability have to exist. Four or more of these symptoms must be concurrently present for at least six months.

Prior to the inclusion of participants in the study, two structured clinical interviews – the structured clinical interview for DSM-IV Axis Disorders (SCID-I) [45] and the Somatoform Disorder Schedule (SDS) [46] – were conducted by an experienced psychologist (PW) with the purpose of estimation of inclusion and exclusion criteria.

Exclusion criteria included somatic or medical conditions that explained fatigue (e.g. cancer), substance abuse, a primary psychiatric disorder (e.g. schizophrenia), major depression or anxiety disorder, an ongoing psychotherapy or activation programme, and a body-mass index (BMI) lower than 18.5 kg/m^2 or higher than 35 kg/m^2. Based on current knowledge that more women than men who experience CFS seek treatment, we decided to include only females in this pilot study [4].

Randomisation was conducted in blocks. Patients underwent a physical examination and, if necessary, additional laboratory testing.

In order to measure the impact of applied interventions for fatigue and other mental and physical parameters, a psychometric test battery (see below) was used before (T0) and after (T1) intervention as well as at a five-month follow-up (T2).

2.2. Multidimensional Fatigue Inventory (MFI)

To measure self-reported fatigue, we used the 20-item German version of the Multidimensional Fatigue Inventory (MFI) [47–49]. This instrument is widely used [1]. Lin et al. [50] recommended the MFI as an additional diagnostic tool in CFS. MFI measures subjective fatigue on five subscales (general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation). Each subscale includes four items on a five-point Likert scale from 1 ("agree") to 5 ("disagree"). A total score between 20 and 100 may be generated. The lower the score, the lower subjective fatigue is. German norm values including age- and gender-related norms are documented by Schwarz et al. [51].

2.3. Short Form General Health Survey (SF36)

The SF36 contains eight multi-item subscales (general health perceptions, physical functioning, physical role, bodily pain, general mental health, vitality, emotional role, and social functioning). There are two to six response choices per item. The range of each transformed subscale lies between 0 and 100 [52]. The highest score indicates the highest level of functioning. The SF36 is a well-validated instrument used to assess quality of life (QoL) [53,54]. There are two summary scores, physical functioning and mental functioning, which reflect the two-dimensional factor structure underlying the subscales [50].

2.4. Patient health questionnaire (PHQ-9)

To assess depression, we used the German version of the PHQ-9 [55]. This module consists of nine items (mood, sleep, fatigue, appetite, self-confidence, concentration, interest in doing things, psychomotorics, and suicidal tendency). Each item is scored from 0 to 3, providing a 0 to 27 severity score. Scores of 5 to 10 represent cut-off points for minor and major depressive syndromes, respectively [56].

2.5. Qualitative data

Qualitative data were assessed at follow-up (T2) by means of four open-ended questions: "What kind of positive changes did you experience during training?"; "What kind of negative changes did you experience during training?"; "Did any changes last longer than the training period? If so, what kind of changes?"; and "Do you have any suggestions for improving the training?"

2.6. Interventions

Both treatments consisted of eight individual training sessions of 50 min each at weekly intervals. HRV-BF was carried out by a trained clinical psychologist (PW). The GET therapist was a sports therapist and expert in sports medicine (KvH). Patients were instructed to keep a diary in order to assess the intensity of their fatigue, their daily activities, and their individual training at home and to connect these domains by exploring thoughts and feelings within the therapeutic contact. Keeping a diary took about 15 min per day. In both groups, the homework (see below for details) was prescribed during intervention. The diary and homework were discussed with patients at the beginning of each session.

2.6.1. Biofeedback therapy

We developed a structured treatment manual for HRV-BF [25] according to the literature on BF in somatoform disorders and FSS [39, 57,58], based on the evidence that HRV training improves the regulation of the autonomic nervous system [28,39]. Respiratory sinus arrhythmia is a type of heart rate variability in synchrony with respiration, by which the RR-interval on an electrocardiogram is shortened during inspiration (acceleration of the heart rate) and prolonged during expiration (deceleration of the heart rate) [59]. Pronounced, i.e. wavelike, RSA is an index of cardiac vagal function and reflects a state of relaxation [60]. We used the SOFT®med device (Insight Instruments, Hallein, Austria) for the HRV-BF treatment. In addition to these more physiological aspects, the therapist and the patient discussed the experience the patient had while training as well as at home during each BF session. Fear-avoiding behaviour as well as highly achievement-oriented activation and the following impact on physical symptoms were discussed through the use of the self-monitoring diary.

In short, HRV-BF sessions were structured as follows. The aim of the first treatment session was to become familiar with the setting, the equipment and the therapist. Each subsequent session started with 10-min review of the diary, followed by a 20–30 min HRV-BF practice. The HRV-BF training included practicing slow inspiration and expiration with 6–10 breaths per minute, visualised on a monitor as two separate lines (breathing curve, heart rate) and meant to alter the individual stress reaction and to induce individual alleviation of tension. Periods of exploring the body's reactions to the breathing and discussing these experiences alternated. After the practice interval, the therapist and patient reviewed the session records showing breathing, heart rate, skin conductance response, and skin temperature. Interactions of physiology and emotion/cognition were discussed. By gaining experience with HRV-BF, patients were successively instructed to improve their RSA under real-life conditions such as imagining actual situations of stress. In addition to self-monitoring (diary keeping), homework was given in the form of daily practice exercises without the biofeedback device two times per day 5–10 min each time.

2.6.2. Graded exercise training

For GET, the individual anaerobic threshold (IAS), collected by spirometry, was the individual training baseline. Patients were instructed in slow walking training on a treadmill adapted to their heart rate which equates about 70% of heart rate IAS. The duration and exercise intensity were set at a level previously identified as achievable under spirometry testing and unlikely to exacerbate the patients' symptoms. Similar to the BF, the aim of the first session was to familiarise the patient with the setting, the equipment, and the treadmill as well as the therapist. The subsequent sessions were subdivided into three parts, comparable to the HRV-BF training. The sessions began with a review and discussion of the diary entries and the experience created by doing the exercises at home, followed by 20–30 min of walking training adapted to a moderate heart rate. At the end of the session, the sports-therapist and patient reviewed the course of the session in regard to heart rate and physical reactions. Patients were encouraged to reduce resting and avoiding behaviour but simultaneously to watch carefully for symptoms and feelings of overload. In addition to continuing to keep a diary, homework consisted of two to three walking sessions per week at home (20–30 min), controlled by a pulse watch.

2.7. Statistical analyses

Statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL). The aim of this exploratory study was to describe differential effects of treatments; therefore, standardised effect sizes (SES) were calculated. SES were calculated related to T0. SES have been the appropriate procedure to show theoretical and practical significance [61,62]. Cohen's standardised mean difference (d) effect size is constructed as independent of the sample size but strongly dependent upon the

distribution of values [62–64]. SES have been calculated according to Cohen [64] and Kazis et al. [65] and are interpreted as small ($d \leq 0.20$), medium ($d \leq 0.50$), and large ($d \leq 0.80$). Due to the exploratory character of the pilot study and the small sample size, non-parametric testing was applied. The Friedman test was conducted to investigate effects over time within groups. To test potential differences between groups, the Mann-Whitney *U* test was used, analysing differences between follow-up and first measurement ($\Delta_{T2 - T0}$). The significance level was set at $\alpha = 0.05$. If participants completed four (i.e. only the half) or less sessions they were labelled as "non-completers" and their data were not included into final analysis. In cases of missing observations of completers a conservative "intension-to-treat" strategy with the last value carried forward was applied. Qualitative data are given in frequencies of topics.

3. Results

3.1. Description of participants

A total of 115 females and 3 males responded to the study announcement. According to exclusion criteria no male persons were included. Study information was provided to interested females via email or telephone. Subsequently, 57 individuals cancelled their participation because of the treatment frequency and training intensity, the long distance to the study centre, or the randomisation or ongoing psychotherapy or other regular exercise training. Finally, 58 persons were invited to an expert assessment of study eligibility with a trained psychologist (PW); 16 of the 58 women did not meet primary consent criteria or fulfilled exclusion criteria. The remaining 42 women were interviewed using the SCID-I and the SDS, whereby 6 did not meet inclusion criteria and 8 met exclusion criteria (primary psychiatric disorder). Finally, 28 persons were randomised to one of the treatments after their written informed consent had been obtained. Fig. 1 shows the trial profile.

The sample description is shown in Table 1. All patients were of German nationality. Formal education was predominantly a high school degree, and training qualifications were predominantly apprenticeships or polytechnic degrees. Most of the participants lived with a partner and children. There were no significant differences between groups with respect to education or social and living situation. Furthermore, at the time of inclusion, there were no differences in clinical measures of fatigue (MFI), quality of life (SF-36), or depression (PHQ-D) scores between groups.

In the GET group, four patients dropped out and terminated therapy prematurely (receiving four or fewer sessions). Two quit after one training session, and two others quit after four sessions; data from these participants were not included in the analysis. All four noted a lack of benefit as the major reason for quitting. A total of 24 patients regularly attended interventions. Two completers of HRV-BF did not answer the questionnaires at T2, so their last values were carried forward.

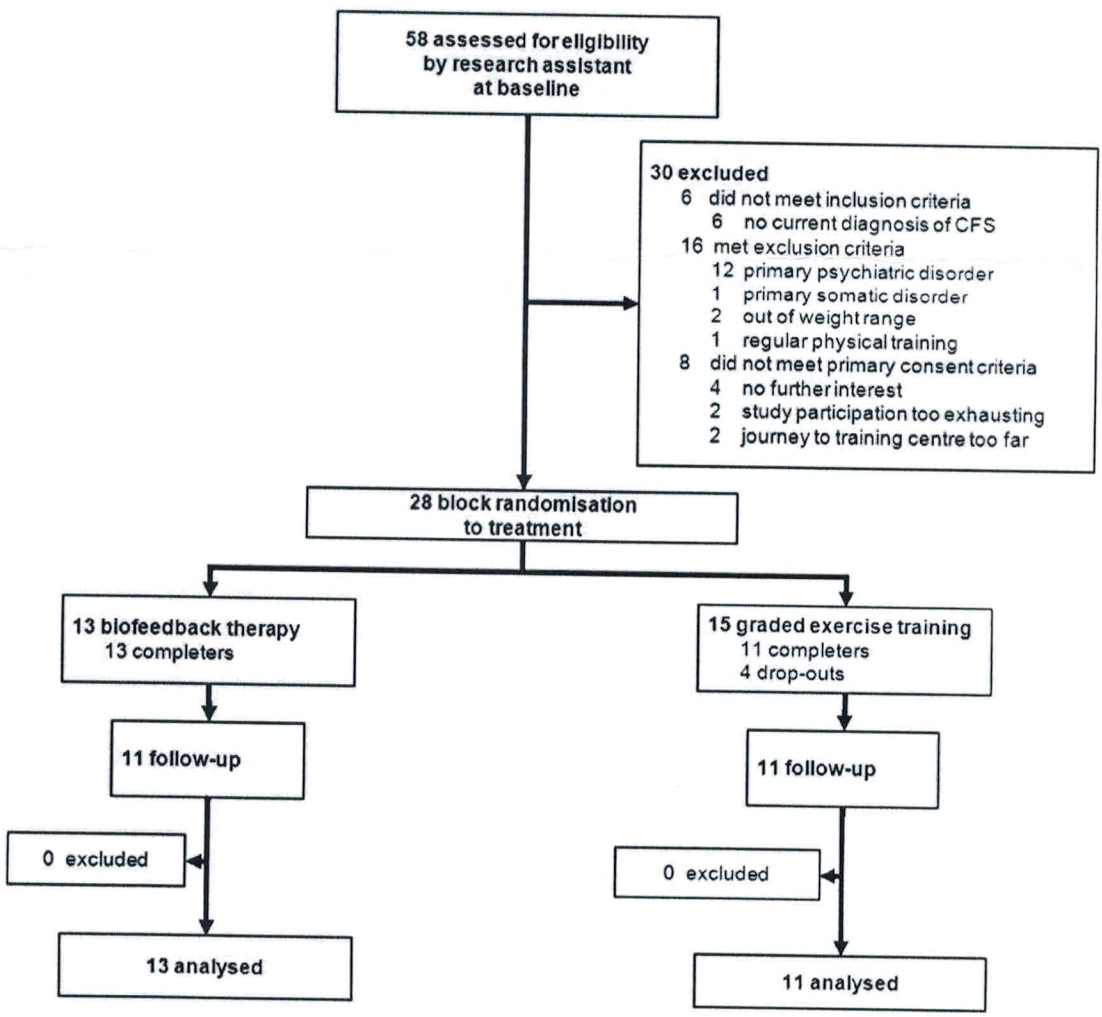

Fig. 1. Consort trial profile.

Table 1
Baseline demographics (T0); data are presented as mean (SD).

	Total study sample (n = 24)	Subsample receiving HRV-BF (n = 13)	Subsample receiving GET (n = 11)	Group difference
Age (years)	50.7 (9.3) (min 30, max 72)	51.4 (8.1) (min 42, max 72)	50.0 (10.9) (min 30, max 67)	n.s.
BMI (kg/m^2)	25.5 (4.7) (min 18.8, max 34.8)	25.6 (4.9) (min 18.8, max 34.8)	25.5 (4.8) (min 20.0, max 33.2)	n.s.
Duration of symptoms	91.7% (n = 22) ≥ 2 years 4.1% (n = 1) ≥ 1 year 4.1% (n = 1) = 6 months	84.5% (n = 11) ≥ 2 years 7.7% (n = 1) ≥ 1 year 7.7% (n = 1) = 6 months	100% (n = 11) ≥ 2 years	n.s.
Nationality	95.8% (n = 23) German 4.2% (n = 1) other	92.3% (n = 12) German 7.7% (n = 1) other	100% (n = 11) German	n.s.
Living situation	25.0% (n = 6) single 29.2% (n = 7) with partner 4.2% (n = 1) single with children 29.2% (n = 7) with partner and child(ren) 12.5% (n = 3) other	23.1% (n = 3) single 38.5% (n = 5) with partner 30.8% (n = 4) with partner and child(ren) 7.7% (n = 1) other	27.3% (n = 3) single 18.2% (n = 2) with partner 9.1% (n = 1) single with child(ren) 27.3% (n = 3) with partner and child(ren) 18.2% (n = 2) other	n.s.
Highest school leaving certificate	12.5% (n = 3) secondary modern school 41.7% (n = 10) junior high school 45.8% (n = 11) high school	7.7% (n = 1) secondary modern school 46.2% (n = 6) junior high school 46.2% (n = 6) high school	18.2% (n = 2) secondary modern school 36.4% (n = 4) junior high school 45.5% (n = 5) high school	n.s.
Highest training qualification	4.2% (n = 1) still in training 58.3% (n = 14) apprenticeship 33.3% (n = 8) college/university 4.2% (n = 1) without training qualification	61.5% (n = 8) apprenticeship 38.5% (n = 5) college/university	9.1% (n = 1) still in training 61.5% (n = 6) apprenticeship 27.3% (n = 3) college/university 9.1% (n = 1) without training qualification	n.s.
Mental QoL (SF36)	42.4 (9.8)	43.4 (10.5)	41.1 (9.4)	n.s.
Physical QoL (SF36)	40.4 (8.8)	42.6 (9.2)	37.7 (7.8)	n.s.
Depression (PHQ-9)	8.2 (4.2)	7.5 (3.1)	8.9 (5.4)	n.s.

HRV = heart rate variability; BF = biofeedback; GET = graded exercise training; QoL = quality of life.

3.2. Effects of treatment on fatigue

Fatigue scores improved significantly over time after HRV-BF in all subscales except 'reduced motivation' tested by the Friedman test. Fatigue scores showed a subsequent reduction for all fatigue subscales as well as for the total score from T1 to T2.

After GET, 'general fatigue' improved significantly over time tested by the Friedman test. At follow-up, subsequent reductions were found in 'general fatigue', 'reduced activation', and 'reduced motivation' in comparison to T1. Means and standard deviation (SD) of the five MFI subscales as well as the total score and significance values within groups analysed by the Friedman tests are shown in Table 2.

SES were large in all MFI subscales after HRV-BF, and in the subscales 'general fatigue', 'reduced activation' and 'total fatigue' after GET at follow-up (Table 2).

At T0, participants showed a 'general fatigue' score two SD above German normative values [51]. The values of the other MFI subscales of our population were one to two SD above the normative scores in both groups before treatment, with the exception of the subscale 'reduced motivation'. After treatment (T1), the mean scores of all MFI subscales were within one SD in comparison to the normative values with the exception of 'general fatigue' after GET. Mean scores remained stable or showed further reductions at five-month follow-ups (T2) in both groups.

There were no significant differences between groups in regard to $\Delta_{T2 - T0}$ tested by the Mann-Whitney U test.

3.3. Effects of treatment on QoL and depression

GET resulted in significant improvement of physical QoL over time as assessed by the SF36, whereas for HRV-BF, no significant improvement was found for this subscale tested by the Friedman test. Instead, we found significant improvement of mental QoL after HRV-BF over time, but not after GET.

HRV-BF also resulted in a significant reduction of depression as assessed by the PHQ-9, while GET had no effect on depression.

Changes in QoL are shown in Fig. 2 changes in QoL and depression are shown in Table 3.

SES showed large to medium effects on mental QoL and depression after HRV-BF and a large effect on physical QoL after GET at follow-up (Table 3).

There was no significant difference between groups in physical QoL. There were significant differences between groups in mental QoL

Table 2
Means and SD in fatigue (MFI) within groups across measurement points, standard effect sizes (SES) and χ^2 and significance level of the Friedman tests.

Group	T0	T1 (after treatment)		T2 (5 month follow up)		Within groups (Friedman test)	
	Mean (SD)	Mean (SD)	SES	Mean (SD)	SES	χ^2	p
MFI_{gen}							
HRV-BF	15.8 (2.9)	11.7 (3.6)	1.41	11.5 (4.2)	1.46	12.3	0.002
GET	17.5 (2.0)	14.4 (4.7)	1.53	13.8 (5.3)	1.80	8.9	0.012
MFI_{phy}							
HRV-BF	13.2 (4.0)	10.7 (4.2)	*0.62*	8.8 (3.6)	1.08	19.7	b0.001
GET	14.8 (4.4)	11.3 (5.2)	0.80	11.5 (5.4)	*0.74*	5.1	0.080
MFI_{ra}							
HRV-BF	11.9 (3.8)	9.1 (3.6)	*0.74*	7.9 (4.1)	1.04	11.3	0.004
GET	13.5 (3.9)	10.8 (4.1)	*0.67*	9.8 (4.6)	0.92	2.0	0.359
MFI_{rm}							
HRV-BF	9.6 (2.2)	8.3 (3.6)	*0.59*	7.5 (3.4)	0.94	5.3	0.070
GET	10.3 (3.3)	8.9 (3.9)	0.41	8.7 (4.2)	0.47	2.5	0.294
MFI_{me}							
HRV-BF	11.2 (3.8)	8.4 (3.8)	*0.72*	7.8 (3.8)	0.88	12.9	0.002
GET	12.8 (3.6)	11.2 (4.4)	0.45	11.6 (5.0)	0.33	0.6	0.735
MFI_{total}							
HRV-BF	61.5 (9.7)	48.2 (15.9)	1.37	43.6 (15.9)	1.84	16.3	b0.001
GET	68.8 (10.1)	56.6 (18.8)	1.21	55.6 (21.3)	1.31	2.3	0.319

HRV = heart rate variability; BF = biofeedback; GET = graded exercise training.
n = 13 for HRV-BF, n = 11 for GET.
MFI_{gen} = general fatigue; MFI_{phy} = physical fatigue; MFI_{ra} = reduced activation; MFI_{rm} = reduced motivation; MFI_{me} = mental fatigue; MFI_{total} = total score.
SES indicated as absolute values related to T0.
bold = large effect; italics = medium effect.

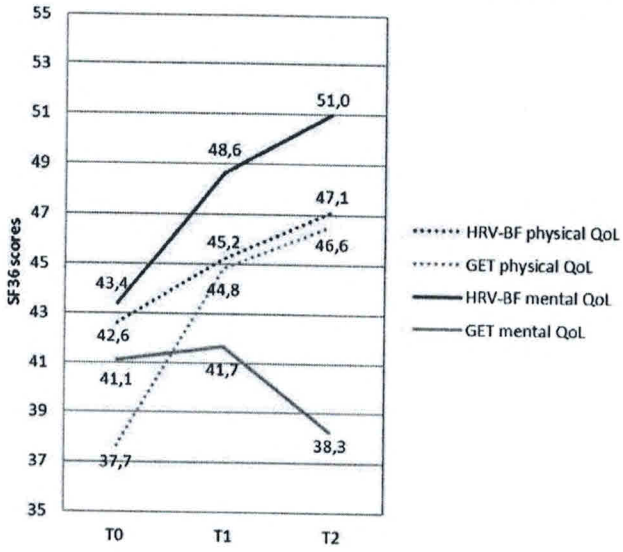

Fig. 2. SF36 scores of physical and mental QoL in HRV-BF and GET.

($Z\Delta_{T2 - T0} = -2.231$, $p = 0.026$) and in depression ($Z\Delta_{T2 - T0} = -2.039$, $p = 0.041$) tested by the Mann-Whitney *U* test.

3.4. Qualitative results

Of the completers, 20 of 24 answered the named four open-ended questions after intervention. Concerning positive influences of the interventions, completers of HRV-BF emphasised an improvement in interoception (6 persons), better regulation of states of stress and relaxation (6 persons), and greater perceived mental stability (4 persons). Completers of GET emphasised better fitness and capacity (8 persons), more pleasure in exercising (8 persons), and an improvement in well-being (4 persons). Concerning negative influences, one participant of HRV-BF named a change in daily routines and in role perception as a negative consequence. Another named an increase in migraines at the beginning of the treatment as a negative consequence. One participant of GET named a gain in appetite and in weight as negative consequences. Another reported the conversations about symptoms and individual issues as being stressful. One participant reported the development of a depressive episode due to external individual reasons while taking part in GET. Orally or written, several participants in GET expressed a wish to have group treatment and personal contact with other participants. Participants who dropped out stated that the GET did not fulfil their expectations and that they did not experience any benefit.

Table 3
Means and SD in QoL (SF36) and depression (PHQ-9) within groups across measurement points, standard effect sizes (SES) and χ^2 and significance level of Friedman tests.

Group	T0	T1 (after treatment)		T2 (5 month follow up)		within groups (Friedman test)	
	Mean (SD)	Mean (SD)	SES	Mean (SD)	SES	χ^2	p
Physical QoL							
HRV-BF	42.6 (9.2)	45.2 (9.9)	0.28	47.1 (12.2)	0.49	2.5	0.292
GET	37.7 (7.8)	44.8 (9.7)	0.92	46.6 (7.1)	1.14	9.0	0.011
Mental QoL							
HRV-BF	43.4 (10.5)	48.6 (9.0)	*0.50*	51.0 (8.9)	0.73	7.5	0.023
GET	41.1 (9.4)	41.7 (10.9)	0.06	38.3 (15.3)	0.30	1.8	0.404
Depression							
HRV-BF	7.5 (3.1)	4.3 (3.0)	1.05	4.2 (3.1)	1.10	10.3	0.006
GET	8.9 (5.4)	8.3 (4.6)	0.11	8.8 (6.0)	0.02	0.8	0.656

HRV = heart rate variability; BF = biofeedback; GET = graded exercise training; QoL = quality of life.
$n = 13$ for HRV-BF, $n = 11$ for GET.
SES indicated as absolute values related to T0.
bold = large effect; italics = medium effect.

4. Discussion

In this exploratory pilot trial patients with CFS received either HRV-BF training or GET. Results show an improvement in fatigue scores that last for at least 5 months in both intervention groups. Large to medium effect sizes suggest a clinical significance of the proven statistical changes. No significant differences between groups regarding general fatigue or any subtypes of fatigue in general and at any particular observation point were observed.

At the same time the treatments seem to differ with respect to mental and physical functioning. Our data show that HRV-BF with RSA as training parameter seems to have a specific beneficial influence on mental QoL and depression. These findings are consistent with research by Knoop et al. [13] on the cognitive components of CFS. The authors assume that biofeedback could improve QoL by a redefinition of the cognitive representations of fatigue, including general adversity to fatigue, focussing on fatigue, and dysfunctional beliefs about fatigue and activity. Biofeedback might facilitate this redefinition by supporting patients in developing models of how to influence fatigue positively and by directing attention to coping strategies [43]. Wheat and Larkin [29] critically discuss the efficacy of HRV-related biofeedback and its physiology in their review paper. Nevertheless, they appreciate the clinical and psychological outcomes offered by HRV-BF [29]. Similarly, our findings could be understood as consistent with Wheat and Larkin, who emphasise the mental and psychological factors of HRV training [29].

GET, by contrast, seems to have more beneficial effects on physical fatigue and physical functioning presumably by reducing avoidance behaviour and by gaining confidence in one's own physical capacity. GET was shown to counteract physical deconditioning [15,66]. Similarly to CBT, GET has a positive impact on dysfunctional perpetuating factors (e.g. cognitive and emotional) and helps to decrease symptom focussing [13,43]. Higher activity levels are associated with reduced fatigue [44].

In considering the possible effects of HRV-BF on mental functioning, the enhancement of self-efficacy and self-control might explain our results [41,43,67]. As described above, RSA training encourages an understanding of one's own physical processes and somatic complaints that are associated with stress exposure. By understanding these processes and developing the capacity to influence them positively, HRV-BF might enhance perception of self-efficacy and self-control. Furthermore, several patients reported an emerging interest in physical activity in their daily routine after HRV-BF when they were asked about changes during treatment. This might be best understood as a reduction in resting behaviour in correlation with new experiences and in correlation with the development of self-efficacy. Within a prospective cohort study with patients suffering from CFS, Hyland et al. [68] note that increased positivity with illness is associated with later recovery from CFS. They showed that this positivity arises within a therapeutic intervention. Therefore, a caring and invigorating therapeutic intervention might be an important contrast to the negative therapeutic attitudes that CFS patients often experience in general practice. However, our study is not able to substantially underpin these findings since we did not assess self-efficacy.

Research assumes that clinical improvement in patients with CFS and with FSS may be explained not only by physical changes, but also by cognitive variables and changes in attitudes [13,23,69]. The results of our pilot exploratory study allow speculating that HRV-BF and GET could improve different aspects of the complexity of CFS. But if the combination of both treatments would be superior to each of its components or to placebo remains unclear and should be addressed in further studies.

As a limitation, the small sample size must be mentioned. As one of the contributing factors for the reduction in the number of initially

contacted participants and those who were finally included in the study, strict inclusion criteria as well as meticulous diagnostic interviews should be mentioned. These allowed us to exclude disorders other than CFS that could partially or fully manifest with fatigue and to select a population that is most close to the modern understanding of CFS. Further research should involve larger and more homogenous samples according to age.

5. Conclusion

In conclusion, in this pilot study we evaluated a manualised programme for the HRV-biofeedback training for patients with CFS. We also investigated the impact of HRV-BF and GET on fatigue as well as on several other mental and physical parameters. Results show that both treatments improve fatigue as a core symptom of CFS with medium to large effect sizes. Moreover, HRV-BF training seems to have a specific positive influence on mental functioning and cognitive components, whereas GET seems to predominantly improve physical functioning.

Conflicting interests

The author(s) declare that they have no competing interests.

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