Eye Movement Desensitization and Reprocessing Therapy in Chronic Fatigue Syndrome: A Single-Case Experiment Testing the Effect on Persistent Negative Evaluation of Fatigue

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Background: While cognitive behavioral therapy (CBT) for chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME) can lead to the normalization of fatigue levels and resumption of activities, a subgroup of patients still evaluates fatigue negatively.
Objective: The objective was to investigate whether eye movement desensitization and reprocessing (EMDR) therapy leads to a less negative evaluation of fatigue.
Method: This was a randomized single-case experimental study. Five CFS/ME patients (all female, mean age of 35 years), who had completed CBT but still evaluated fatigue negatively, received EMDR therapy. The primary outcome, that is, negative evaluation of fatigue, was assessed daily (three items, e.g., "My fatigue is frustrating"). During EMDR therapy sessions, distress in response to a selected image was measured. Clinical assessments were performed before, directly after, and one month after EMDR therapy.
Results: During EMDR therapy sessions, all patients reported high distress related to memories of having CFS/ME. EMDR therapy led to a reduction in this distress. Daily measured negative evaluations of fatigue declined in three patients, albeit not significantly. Three of five patients showed clinically relevant improvement in evaluations of fatigue on clinical pre-/post measures.
Conclusion: EMDR therapy can reduce emotional distress associated with fatigue, but it is unclear whether it can change its negative evaluation.

Keywords: chronic fatigue syndrome; fatigue; EMDR therapy; evaluative conditioning; single-case experiments

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Chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME) is characterized by severe fatigue that lasts longer than six months and leads to substantial impairment (Prins et al., 2006). This fatigue fundamentally differs from everyday fatigue as it is not only persistent but also a physical and mental experience associated with a substantial disturbance of patients' functioning (Korenromp et al., 2012). According to the U.S. Centers for Disease Control (CDC) criteria for CFS/ME revised in 2003, there is no somatic explanation for fatigue and patients have to report at least four out of eight additional symptoms. These symptoms are unrefreshing sleep, postexertional malaise, headache, muscle pain, multi-joint pain, sore throat, tender lymph nodes, and concentration or memory impairment (Fukuda et al., 1994; Reeves et al., 2003). Estimates of the prevalence of CFS/ME vary with some suggesting a prevalence of around 1%, with women being at higher risk (Lim et al., 2020). Without treatment, the prognosis of CFS/ME is not favorable: the spontaneous recovery rate is only 5% (Cairns & Hotopf, 2005).

The etiology of CFS/ME is hotly debated, but there is no evidence for one single etiological mechanism. It is commonly assumed that this is a complex illness best explained by a multifactorial model with a biopsychosocial etiology (Cleare, 2004; Prins et al., 2006). According to the cognitive behavioral model of CFS/ME, severe fatigue can develop after stressors like a virus or life event in people who are vulnerable to developing chronic fatigue (Moss-Morris et al., 2013). Behavior and beliefs in response to these symptoms form a self-perpetuating cycle resulting in the persistence of symptoms and disability (Knoop et al., 2010). Cognitive behavioral therapy (CBT) for CFS/ME targets perpetuating factors of fatigue and disability such as all-or-nothing behavior, dysregulated sleep–wake pattern, a low level of physical activity, a tendency to focus on symptoms, and low self-efficacy with respect to fatigue (Knoop & Bleijenberg, 2010). These therapies lead to a significant reduction in fatigue and functional impairment (Castell et al., 2011). However, a subgroup of patients with healthy levels of fatigue after treatment still evaluates fatigue negatively. In a cohort study by Knoop et al. (2007), 44% of CFS/ME patients treated with CBT reverted to normal fatigue levels and physical functioning, but only 23% of patients did revert to an evaluation of fatigue comparable to population controls. Because fatigue is a normal daily experience, successfully treated CFS/ME patients who retain a negative evaluation of fatigue are likely to experience distress in response to fatigue. Janse and colleagues (2019) also showed that a negative evaluation of fatigue at the end of treatment increases the risk of relapse following CBT.

The Fatigue Quality List (FQL; Gielissen et al., 2007) was developed to assess patients' evaluation of fatigue. The FQL contains 18 adjectives of fatigue, and patients select those adjectives which best fit their experience of fatigue. Factor analysis showed four factors of which three referred to a negative evaluation of fatigue: frustrating, frightening, or exhausting. One factor reflected a positive or neutral evaluation of fatigue (labeled "pleasant," fatigue being, e.g., relaxing or normal). Before treatment, 97% of CFS/ME patients scored on one or more negative factors, after treatment, this was still 63%, whereas healthy people only scored 3.2%–7.7% on these factors and evaluated fatigue as temporary, relaxing, fulfilling, normal, and pleasant (Gielissen et al., 2007). This distinction between healthy people and successfully treated CFS/ME patients may be explained by a learning mechanism called evaluative conditioning, a form of classical conditioning. Evaluative conditioning "involves changes in liking for a neutral stimulus that result from its contingent presentation with (dis)liked stimuli" (De Houwer et al., 2001; Engelhard et al., 2014, p. 709). CFS/ME patients have had prolonged negative experience with fatigue: feeling fatigued is experienced contingent with symptoms of feeling ill and frustrated, or negative social reactions resulting from not being able to perform. We assumed that, in this way, the former neutral stimulus fatigue becomes disliked.

Existing CBT protocols for CFS/ME focus on predictive associations that have been learned by patients with respect to the outcome fatigue (Knoop & Bleijenberg, 2010). Exposure and cognitive restructuring target the expectancy of patients that activity will result in severe fatigue and that fatigue means they cannot be active. The crucial intervention for this is graded activity, which is a form of exposure *in vivo*. During the graded activity, patients gradually increase their level of activity in a consistent, time-contingent way, for example walking or cycling twice a day increasing from 5 up to 60 minutes (Knoop & Bleijenberg, 2010). Safety behaviors such as taking extra rest are stopped. Patients expose themselves to activity and learn that feared consequences, such as getting extremely fatigued and feeling sick, do not

take place. Mediation studies of CBT show that the reduction of fatigue cannot be explained by an increased level of objective activity but is explained by changes in beliefs about activity and self-efficacy regarding fatigue (Chalder et al., 2015; Heins et al., 2013; Wiborg et al., 2012). Expectancy learning of patients thus can be changed in CBT, but evaluative conditioning, the "dislike" of fatigue, may not always change consequently.

Hypothetically, counterconditioning could change evaluative conditioning: the conditioned stimulus is paired with an unconditioned stimulus (US) that is neutral or positive. Experimental studies show promising results in fear, disgust, and chronic pain, but clinical effects are not yet clear (Engelhard et al., 2014; Kerkhof et al., 2011; Meulders et al., 2015; Vansteenwegen et al., 2006). Another option is eye movement desensitization and reprocessing (EMDR) therapy, an evidence-based intervention for posttraumatic stress disorder (PTSD; Shapiro, 2002). EMDR therapy is based on the adaptive information processing model meaning, that current symptoms are assumed to be due to an activation of dysfunctionally stored memories (Shapiro, 2001; Solomon & Shapiro, 2008). EMDR therapy can directly revaluate US/unconditioned response (UR) memory representations, hypothetically resulting in a less negative evaluative conditioning (Engelhard et al., 2014). Performing eye movements taxes the working memory, and this probably influences the way in which US/UR representations are stored in the memory network (Van den Hout & Engelhard, 2012). Experimental and clinical studies in patients with PTSD and healthy individuals have shown that performing eye movements while recollecting emotionally charged memories results in decreased emotion and a more functional meaning of this memory (Lee & Cuijpers, 2013). There is also emerging evidence supporting the effect of EMDR on the treatment of individuals with medically unexplained symptoms (Staton et al., 2022; Van Rood & De Roos, 2009). In chronic pain, randomized controlled trials provide preliminary evidence for EMDR focused on memories of pain, currently experienced pain, and flashforwards about pain (Matthijssen et al., 2020; Tesarz et al., 2019). To the best of our knowledge, EMDR therapy for CFS/ME has been tested only in one case study so far. Royle (2008) treated one CFS/ME patient with EMDR therapy, who subsequently experienced more energy and better functioning. EMDR therapy was focused on past memories that appeared to have set the pathology in progress and on present distressing situations about CFS/ME. This study provides a first indication that EMDR therapy might hold promise for patients with CFS/ME.

The present study examined if EMDR therapy decreases the negative evaluation of fatigue in a subgroup of CFS/ME patients; these patients retained a negative evaluation of fatigue despite having increased their level of activity during the graded activity program of CBT.

Method

Participants

Patients were eligible if they (1) were ≥18 years; (2) were female (fostering homogeneity, as the majority of patients are female and evidence exists for sex differences in clinical phenotypes and triggers of the condition [Lim et al., 2020; Thomas et al., 2022]); (3) were diagnosed with CFS/ME according to the CDC criteria revised in 2003 (Fukuda et al., 1994; Reeves et al., 2003); (4) did not have a psychiatric disorder, assessed by a structured interview (Sheehan et al., 1998); (5) did not use psychotropic drugs or pain medication; (6) participated in CBT for CFS/ME targeting fatigue and successfully completed the graded activity program, that is, had walked at least twice a day for 30 minutes and indicated that they were able to be more active; and (7) reported a negative affective quality of fatigue, that is, scored >25% on one of the negative factors of the FQL (Gielissen et al., 2007).

Procedure and Design

CBT therapists from our center referred potential eligible patients and provided verbal and written study information. After informed consent was provided, patients received a phone call and questionnaires to confirm eligibility. After this, randomization was performed. During the experimental period, patients received no treatment for fatigue and had no contact with their CBT therapist. Ethical approval was obtained from the Medical Ethical Board of the Radboud University Medical Center (CMO Arnhem-Nijmegen, No. 20151709).

Given the novelty of the approach, conducting a pilot study seemed warranted. A replicated randomized single-case experiment (SCE) with daily assessments was chosen as a design. SCE designs form an alternative to between-group designs that provide a valid basis for testing causal effects, while

not requiring a large sample (Kratochwill et al., 2010; Michiels & Onghena, 2019; Poort et al., 2019). SCEs are experiments in which one subject is repeatedly observed during a fixed period, while the independent variable is actively manipulated, as explained below. In that way, each case serves as its own control (Onghena, 2005). A minimum of four replications or cases is advised in SCE standards (Kratochwill & Levin, 2010) to enable a demonstration of the effect.

In this SCE, Phase A existed for at least 9 days without intervention to enable a stable baseline. Phase B consisted of an intervention period (here: EMDR therapy) of a planned 14 days with 7 days follow-up. The treatment consisted of five 90-minute sessions dispersed over a planned duration of 2 weeks. An intervention effect can be shown if substantial changes in the dependent variable follow the introduction of the intervention and the dependent variable remains relatively stable within each phase (Michiels & Onghena, 2019). The intervention starting point was randomized by creating 20 different lengths of baseline. This is a way of getting statistical control over potential confounding variables, enabling randomization tests to determine if the intervention itself caused the observed improvement (Onghena & Edgington, 2005; Tanious & Onghena, 2019). These starting points were determined by computer-generated random numbers, created by an independent researcher, and put in sealed envelopes. These were opened in the presence of the patient, and the start of the intervention was planned on a predetermined day; only for practical reasons, such as weekends, was the actual start postponed.

Measures

Participants received an email every evening with a questionnaire that they completed on a provided tablet. The research assistant reminded them the next morning of incomplete measurements.

Primary Outcome: Daily Measures. The primary outcome measure was the negative evaluation of fatigue, assessed by an adaptation of the FQL to enable daily measurement. Three negative FQL items that best fit patients' experience of fatigue were rated on a visual analog scale (VAS, 0–10 cm, "totally disagree" to "totally agree"), for example: "My fatigue is frustrating." The mean daily VAS score of these three items was the primary outcome measure.

Secondary Outcome: Daily Measures. The secondary outcome measure was the daily experienced fatigue severity, measured by a VAS ranging from "no fatigue" to "the worst fatigue" (0–10 cm).

Clinical Outcomes: Validated Questionnaires. To describe the clinical status of patients before and after treatment, validated questionnaires were completed at baseline, directly after the experiment (post-treatment), and one month thereafter (follow-up). Following De Jong et al. (2005), a criterion for clinically relevant improvement was preset at a 30% decrease in symptoms, impairments, or negative evaluation. Evaluation of fatigue was assessed with the FQL, which has adequate psychometric properties (Gielissen et al., 2007). Fatigue severity was measured with the Checklist Individual Strength, subscale fatigue severity (CIS-F), a reliable and valid measure for chronic fatigue with a cut-off score of ≥35 for severe fatigue (Worm-Smeitink et al., 2017). The level of disability was measured with the Sickness Impact Profile 8 (SIP8), a reliable and valid measure of functional disability in eight domains: ambulation, home management, mobility, alertness behavior, sleep and rest, work, social interactions, and leisure activities (De Bruin et al., 1992, 1997).

Subjective Units of Disturbance. During EMDR therapy sessions, patients were asked to rate the distress they experienced in response to the image they were focusing on. This distress was then rated on a scale from 0 (no distress) to 10 (maximal distress; Shapiro, 2001). This assessment was used within the EMDR sessions to direct the therapy (see below) but not as an outcome measure. It differed conceptually from our primary outcome, the *negative evaluation* of the fatigue, as the subjective units of disturbance (SUD) assessed distress experienced when focusing on a disturbing image related to their fatigue but did not ask for a qualitative evaluation of the symptom (e.g., of fatigue being frustrating or exhausting).

Intervention

EMDR was conducted in three phases, focusing on past, present, and future. In the first phase, we treated the most distressing memories of being fatigued with the standard EMDR protocol. Secondly, following positive reports of EMDR in chronic pain (Aternali & Katz 2019; Gant 2010; Tesarz et al., 2014, 2019), patients were asked to estimate the intensity of the current fatigue from 0%–100% and this experienced fatigue was treated as an

EMDR target. Third, because patients still might have catastrophic expectations about getting severely fatigued in the future, a "flashforward" was used: a vivid and distressing image of a feared future event characterized by severe fatigue (Engelhard et al., 2010; Logie & De Jongh, 2014). A flashforward was used instead of a future template, because we assumed anticipatory anxiety was crucial in the negative evaluation of fatigue.

The past experiences with fatigue were addressed with the standard protocol, with the deletion of the future template. In the initial setup of each target, the patient was asked to narrow it down to the most distressing image of it. Patients were asked which negative cognition (NC) applies when they look at this image. Secondly, a positive cognition (PC) was formulated to counter the NC, and they were asked to rate the credibility of this PC on a scale of 1–7: the validity of cognition (VOC). Third, they were asked which emotion they were feeling and to estimate the actual experienced distress on a scale of 0–10 (SUD) in response to the image combined with the NC. Finally, patients were asked where in their body they felt this distress. Eye movements were then induced, and patients were asked to report associations that came to mind, while the therapist instructed them to focus on these associations. This is continued until the targeted image no longer elicited any distress (SUD = 0). Finally, the PC was installed with eye movements until VOC = 7, and this was checked with a body scan. In this study, determining the PC and VOC was omitted if the NC was in the powerlessness domain, as is taught in Dutch EMDR training (Hornsveld et al., 2018).

In the second phase, patients focused on the presently experienced fatigue, instead of focusing on an image. This experienced fatigue was then treated with the same steps as described for the first phase. In the third phase, patients were asked to focus on a still picture of their anticipated doom scenario regarding fatigue. This flashforward was treated with the same steps as in the first phase.

Five 90-minute EMDR sessions were planned within an anticipated duration of two weeks but stopped earlier if all targets were successfully treated (SUD = 0 and PC VOC = 7). The first author (SB), a trained and experienced EMDR psychotherapist, delivered all treatments.

Statistical Analyses

Assessments of daily FQL and daily fatigue were plotted and visually inspected, which is the main way of analyzing SCEs. Additionally, to test if a visible effect is caused by the intervention itself, randomization tests were carried out for the primary outcome measure (i.e., daily FQL) for every participant and for all participants together. Randomization tests are designed for SCE phase designs using the rationale of Edgington (Onghena & Edgington, 2005). The difference in means of the primary outcome measure between Phases B and A (d) was used as the test statistic, and it was hypothesized that EMDR therapy would reduce negative associations with fatigue for which a one-tailed p value $< .05$ was considered statistically significant. As effect size, we calculated the standardized mean differences (SMDs) using the pooled standard deviation (Busk & Serlin, 1992). Negative values indicate that the mean scores of Phase B are smaller than those of Phase A. Analyses were performed using an R package called Single-Case Randomization Tests (Bulté & Onghena, 2008).

Results

CBT therapists referred nine patients to the study. Three patients were excluded: one used psychotropic drugs, one was pregnant—which is a possible direct cause of fatigue—and one patient had not successfully completed the graded activity program. One eligible patient did not wish to participate because of the required effort.

Missing values were 6.1% of daily measurements, and eight measures were completed the following day. There was no drop-out, suggesting that EMDR therapy was feasible and acceptable for patients. There were no adverse events.

Patient 1

A single 37-year-old teacher was severely fatigued after a period of extreme working hours and bradycardia. Receiving a pacemaker dissipated her cardiac problems, but she developed a depressive disorder. Severe fatigue persisted after the remission of the depression, and she was diagnosed with CFS/ME. At the start of CBT, five years later, she reported severe levels of fatigue and disability (CIS-F = 56, SIP8 = 1,956, reporting 7 out of 9 CDC symptoms). She was inactive besides her full-time job, but after 23 CBT sessions, she resumed her activities partly. Though no longer severely fatigued, she still reported severe impairments (CIS-F = 32, SIP8 = 1,487) and negative evaluation of fatigue, which she experienced as frustrating, frightening, and upsetting.

It took five EMDR sessions to treat distressing memories of extreme fatigue. Consequently, other phases of the protocol were not attended to. The first target was a memory of being suicidal after the pacemaker did not relieve her fatigue. NC was "I am a failure," PC was "I am strong," VOC = 1, emotions: sadness and anger, SUD = 7, which reduced to SUD = 0 and increased to VOC = 7, in three sessions, in which sorrow and shame were prominent. The next target was related to the same period: NC: "I am weak," PC: "I am strong," VOC = 1; emotion: sadness, SUD = 10, which reduced quickly to SUD = 0 and increased to VOC = 7, after expressing intense sorrow. In the last session, two other memories about feeling severely fatigued, nauseous, and unable to function were treated. NC of both targets: "I am powerless"; emotions: anxiety and anger; SUD = 5, both reduced to SUD = 0 and PC "I can handle it" with VOC = 7; body scans showed no residual distress. There were no sessions left to attend to the second and third phases of the intervention.

Patient 1 experienced stress during the experiment due to her moving to another town and the threat of losing her job.

Outcomes. Visual inspection of Figure 1a indicates a fluctuating negative evaluation of fatigue and a downward trend is visible in the baseline phase. In the intervention phase, this decrease continues, but possibly due to bottom effects, no further decrease is measurable. The calculated difference in phase means is d = −3.96, which is statistically not significant (p = .30), SMD = −2.31. The measured daily fatigue is also not stable and shows a temporary increase followed by a decrease toward baseline values at the end of the experiment.

Validated questionnaires (Table 1) showed a clinically relevant (≥30%) decrease in the negative evaluation of fatigue, after EMDR and at follow-up. There was no relevant further decrease in fatigue, but impairments were decreased at follow-up.

Patient 2

A married 44-year-old occupational therapist with two children gradually developed fatigue, muscle weakness, and impaired vision in the past 4 years. After a thorough medical examination, she was diagnosed with CFS/ME. At the start of CBT, she worked part-time, was severely fatigued, and impaired (CIS-F = 55; SIP8 = 2,056; 9 of 9 CDC symptoms). After 24 sessions of CBT, she increased her working hours and was less fatigued and impaired (CIS-F = 34; SIP8 = 1,726) but still had a negative evaluation of fatigue, which she experienced as frustrating and upsetting.

The first EMDR target was a memory of a sexual encounter with her husband which was impeded by fatigue; NC: "I am guilty," PC: "I'm trying my best," VOC = 4, emotion: sadness, SUD = 9, reduced to SUD = 0 and VOC increased to seven, body scan being neutral. The next target memory was "being unable to join her children on the trampoline due to fatigue"; NC: "I am a bad mother," PC: "I am a good mother," VOC = 2–3; emotion: sadness; SUD = 9. Distressing childhood memories about not connecting to her family and being inadequate kept coming up despite being redirected to the target, which took two sessions with cognitive interweaves to desensitize to SUD = 0 and VOC = 7, body scan revealing no tension. The third target memory was yelling at her son, her being exhausted; NC: "I am a bad mother," PC: "I am a good mother," VOC = 2–3, emotion: sadness, SUD = 7. Childhood memories emerged again and SUD reduced to zero and VOC increased to six. Despite prolonged EMDR, basal core beliefs such as "I am worthless," originating from childhood, impeded the full credibility of the PC. Next, the currently experienced fatigue was treated: intensity was rated 55% and was felt in her legs; NC: "I am weak," PC: "I am strong," VOC = 1, emotion: sadness, SUD = 6. Fluctuating physical sensations in legs, head, and throat came up in the associations, SUD was quickly reduced to zero, and the PC: "I am strong" became fully credible: VOC = 7 and no tension on body scan. The last target was a "flashforward": an image of relapse in CFS/ME: sitting on the couch, feeling sick and being severely fatigued again, lonely, huddled, "like a zombie"; NC: "I am worthless," PC: "I am OK," VOC = 2, emotion: sadness, SUD = 5–6. Physical sensations as well as emotions came up, but these were quickly desensitized to SUD = 0, and PC: "I am OK" became fully credible, VOC = 7, no tension on body scan.

Outcomes. Figure 1b shows a stable daily negative evaluation of fatigue, with a slight downward trend in the baseline phase, which decreases faster after the start of the intervention and even faster toward the end of the experimental period. Daily fatigue was less stable but follows the same pattern of improvement. The

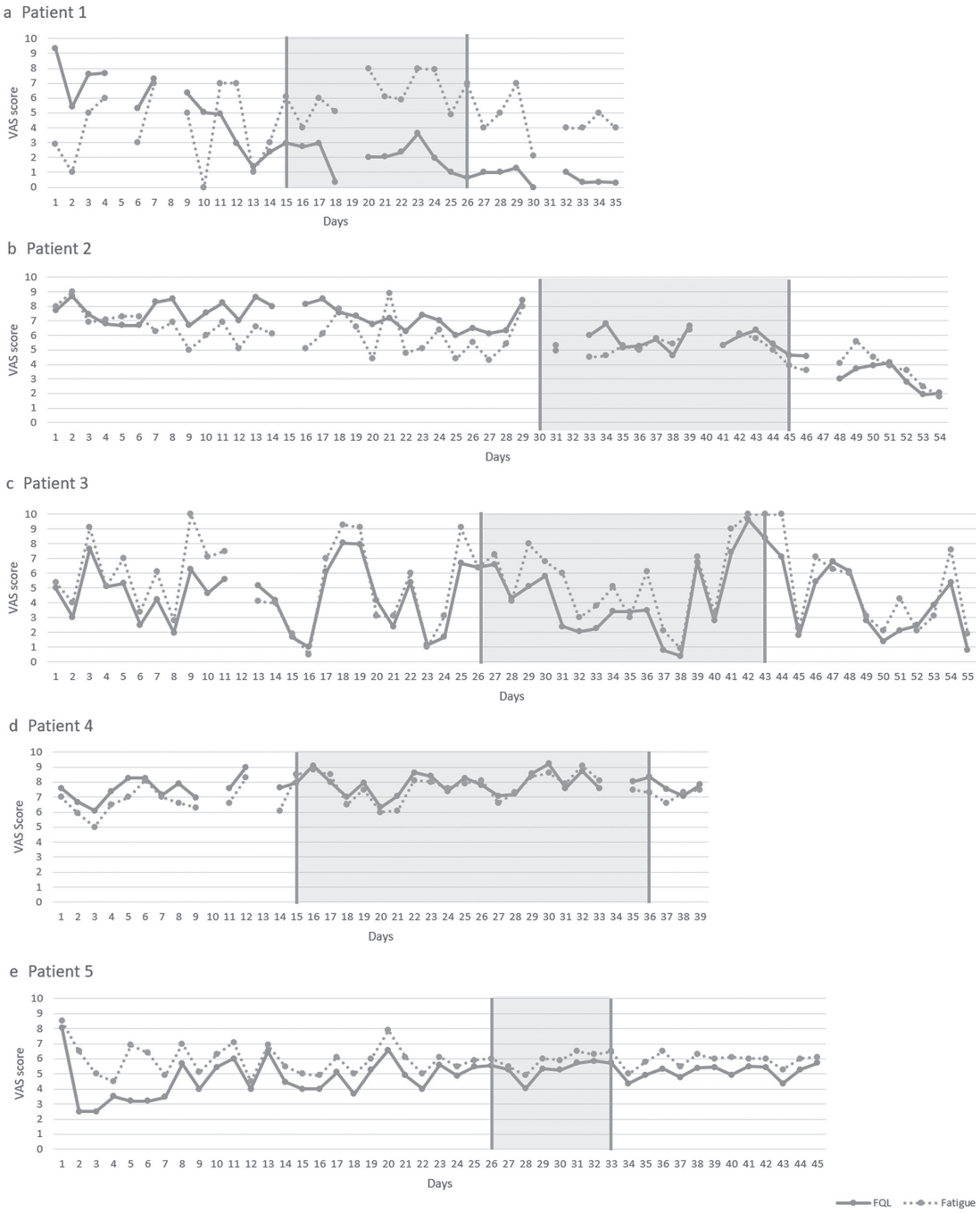

Figure 1. Daily measures (VAS 0–10) of negative evaluation of fatigue (FQL) and daily fatigue (Fatigue) across baseline, during EMDR (green/gray area), and after EMDR. (a) Patient 1, (b) Patient 2, (c) Patient 3, (d) Patient 4, and (e) Patient 5.
Note. FQL = Fatigue Quality List; VAS = visual analog scale.

calculated difference in phase means was $d = -2.59$. This was statistically not significant ($p = .09$). The SMD was −2.19.

Validated measures (Table 1) showed a clinically relevant decrease in the negative evaluation of fatigue directly after EMDR and at follow-up. Fatigue decreased at follow-up, but there was no change in impairments.

Patient 3

A 31-year-old account manager, about to get married, has been severely fatigued for 7 years after Pfeiffer's disease and a busy work period. At the start of CBT, she was severely fatigued and impaired (CIS-F = 50; SIP8 = 1,765; 8 of 9 CDC symptoms), working half of her contracted hours. After 19 CBT sessions, she improved but still experienced severe

TABLE 1. Clinical, Validated Measures

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
FQL-neg[a]					
Baseline	150	175	125	100	125
Posttreatment	90 (−40%)	60 (−66%)	80 (−36%)	100 (0%)	130 (+4%)
Follow-up	65 (−57%)	20 (−89%)	40 (−68%)	100 (0%)	125 (0%)
CIS-F[b]					
Baseline	37	48	38	44	43
Posttreatment	34 (−8%)	39 (−19%)	30 (−21%)	48 (+9%)	44 (+2%)
Follow-up	33 (−11%)	29 (−40%)	29 (−24%)	48 (+9%)	42 (−2%)
SIP8[c]					
Baseline	1,077	1294	963	551	1,065
Posttreatment	795 (−26%)	1,379 (+7%)	1,076 (+12%)	590 (+7%)	1,092 (+3%)
Follow-up	643 (−40%)	985 (−24%)	476 (−51%)	428 (−22%)	970 (−9%)

Note. Baseline (start of the experiment), posttreatment (end of the experiment), and follow-up (1 month after the experiment) (% difference with baseline).
[a]FQL-neg: Fatigue Quality List: scores of negative subscales
[b]CIS-F: Checklist Individual Strength subscale Fatigue severity
[c]SIP8: Sickness Impact Profile 8

fatigue and impairment (CIS-F = 41; SIP8 = 1,367) and still evaluated fatigue as frustrating, frightening, and upsetting. Life events like starting a new job and preparing for her wedding caused a delay in the start of the intervention.

The first target of EMDR therapy was a memory of not being able to help when her family worked in her new house, due to severe fatigue. NC: "I am powerless"; emotion: sadness; SUD = 8. This was reduced to SUD = 0 and "I can handle it" increased to VOC = 7 in two sessions, with a neutral body scan. The second target was receiving a text message from a friend, who criticized her for complaining about fatigue and stopped all contact. NC: "I am not important," PC: "I am important," VOC = 1, emotion: sadness, SUD = 6, this was reduced to SUD = 0 and VOC increased to seven in the next session, and the body scan revealed no tension. The third memory target was being criticized by a colleague, who saw her CFS/ME as a character flaw. NC: "I am powerless," emotion: sadness; SUD = 8, which quickly reduced to SUD = 0 and "I can handle it," increased to VOC = 7, body scan being neutral. The next step was treating the present fatigue: intensity 70%; NC: 'I am powerless'; emotion: anxiety; SUD = 7. During desensitization, both physical sensations and anxious thoughts about relapse in CFS/ME came up but SUD became zero and PC: "I can handle it" became fully credible, VOC = 7, and a body scan procedure was carried out. Finally, a flashforward about relapse in CFS/ME was treated: lying in bed, alone, unable to work, and no children. NC: "I am powerless"; emotion: anxiety; SUD = 10, and suicidal thoughts emerged which required the full remaining session to be desensitized to SUD = 1.

Outcomes. Visual inspection of Figure 1c indicated a high variability of negative evaluation of fatigue and daily fatigue, which seemed to fluctuate together. There is no stable baseline and no visible difference between phases on both outcome measures. The difference in phase means for the negative evaluation of fatigue is $d = -0.37$ ($p = .95$), SMD = −0.15.

Validated measures (Table 1) show a clinically relevant reduction in negative evaluation of fatigue, directly after EMDR therapy and at follow-up. Fatigue decreased to normal levels but not within our a priori criterion for clinical relevance. At follow-up, impairments decreased clinically relevant to normal levels.

Patient 4

A 32-year-old event planner, married, with no children, and CFS for 10 years without cause, is

severely fatigued and impaired (CIS-F = 56; SIP8 = 2,477; 7 of 9 CDC symptoms) at the start of CBT, working 10 of her 40 regular hours per week. After 28 CBT sessions, she was less fatigued and no longer severely impaired (CIS-F = 46; SIP8 = 548) but still experienced fatigue as frustrating, frightening, and upsetting. Starting a new job and getting ill during the experiment complicated planning and this resulted in a longer baseline phase and the decision to go on home visits and not to plan a fifth session.

The first EMDR therapy target was a memory of getting dizzy and sick while driving; NC: "I am powerless"; emotion: anxiety; SUD = 9. This was desensitized to SUD = 2, but a repeating intrusive fear of relapse hindered further desensitization, despite cognitive interweaves. Because of the limit of five sessions, the therapist decided to move on to another target. This was a memory of a family weekend where she could not fully participate, leading to a quarrel. NC: "I am powerless"; emotion: sadness; SUD = 8. Despite prolonged desensitization, SUD again did not get beneath 2 and fear of relapse intruded again. The therapist chose to continue to the second phase: the current fatigue. Intensity 65%, NC: "I am captivated, powerless"; emotion: sadness; SUD = 8, desensitized to SUD = 3, sadness and frustration kept coming up. Because of frequent intrusions about relapse, in the last session, the therapist chose to proceed to the third phase, a flashforward. This was an image of her hanging on the couch with noise-canceling headphones, relapse in CFS/ME, unable to work, worrying about a possible divorce; NC: "I am unsafe"; emotion: anxiety; SUD = 9, desensitized to SUD = 4.

Outcomes. Figure 1d shows stable measurements on both outcome measures without visible change after intervention started. The calculated mean difference for the negative evaluation of fatigue was -d = 0.30 (p = .70), SMD = 0.41.

Validated measures (Table 1) showed no relevant change.

Patient 5

A 33-year-old administrator, single, diagnosed with CFS/ME for 7 years without a clear trigger. She was severely fatigued and impaired when starting CBT (CIS-F = 48; SIP8 = 1,336, 8 of 9 CDC symptoms), working 16 of her regular 40 hours, receiving disability benefits, and stating that she accepted having CFS/ME. After 23 CBT sessions, she improved but still experienced severe fatigue and impairment (CIS-F = 35; SIP8 = 983) and evaluated fatigue as frustrating.

During EMDR therapy, feelings and thoughts seemed diffuse, and it was difficult for her to select specific memories, feelings, and thoughts. Few associations or emotions came up during desensitization. The therapist's impression was that the EMDR process was not fully activated. Four memories of fatigue were all quickly desensitized to SUD = 0 and increased to VOC = 7, with no tension coming up at the body scans. The first target was sitting on the couch, alone, in the dusk, unable to do anything. NC: "I am powerless"; emotion: sadness; SUD = 7. The second memory was visiting the zoo in a wheelchair. NC: "I am weak." She could not indicate SUD, PC, and emotion but started crying and eye movements were started. The third memory was not being able to participate during dance class: NC: "I am powerless"; emotion: sadness and anger; SUD = 3. The last memory was about feeling socially withdrawn in a group on a holiday: NC: "I am alone," and emotion and PC could not be made clear, SUD = 3–4. Next, the currently experienced fatigue was treated: intensity 70%, experienced as a heavy feeling and tendency to withdraw. NC: "I am doing it wrong"; PC: "I do my best"; emotion: sadness; SUD = 7–8. This target was quickly desensitized to SUD 6, with VOC 7, including a body scan. In the fourth session, a flashforward of relapse in CFS/ME was treated: lying on the couch, only being able to work, sleep, and eat, and lonely; NC "I am powerless," SUD = 7, which quickly desensitized to SUD = 0, with VOC = 7 and body scan being neutral.

Outcomes. Visual inspection of Figure 1e showed stable measurements on both measures without clear changes between phases. There is a slight increase in the negative evaluation of fatigue in the baseline period which seems to stabilize in Phase B. Calculated mean difference for the negative evaluation of fatigue was d = .56, with no significant effect of intervention in randomization test (p = .10). The SMD was 0.52.

Validated questionnaires (Table 1) did not show relevant changes.

Aggregated Outcomes

The combined p value for all five participants for the daily negative evaluation of fatigue (primary outcome) was p = .29 according to Edgington's additive method and p = .24 according to Fisher's

multiplicative method. None of the participants showed a difference in daily measured fatigue between phases and this was not further analyzed.

Discussion

To the best of our knowledge, this was the first experiment testing the efficacy of an intervention for the negative evaluation of fatigue in CFS/ME patients. Existing CBT protocols for CFS/ME pay no attention to the affective quality or memories of severe fatigue and not much is known about it. Four out of five eligible patients could easily select memories of being severely fatigued and experienced high associated distress: SUD scores were between 7 and 8. It is striking that the patients experienced such emotional distress in response to memories of being severely fatigued. These memories were desensitized with EMDR therapy in three to five sessions. Subsequently, the current fatigue and flashforwards of severe fatigue could be easily turned into EMDR targets and desensitized.

We expected that desensitizing these US/UR representations of severe fatigue would alter the evaluative conditioning of fatigue. Statistical analyses showed that daily measured negative evaluations of fatigue declined in three patients. These declines were not significant and visual inspection of the daily measures suggested such a trend in two out of five experiments; this trend already started in the baseline period and was not clearly induced by the intervention. Remarkably, three out of five patients showed more than 30% improvement on a standardized measure of the negative evaluation of fatigue, both directly after EMDR therapy and at follow-up.

Based on our results, we cannot conclude that EMDR therapy had an effect on the negative evaluation of fatigue. There are several possible explanations for this. Directly changing the US/UR representations of severe fatigue may not be sufficient to change the evaluative conditioning of fatigue. Negative memory representations may not be a main factor in perpetuating the negative evaluation of fatigue. One indication of this is the finding that in two patients, the successful reduction of the associated distress did not change the negative evaluation of fatigue. This can be due to the nature of the memory network in CFS/ME, where, different from trauma, memories are probably more diffuse and not closely related to one or more specific events. Another indication is that the selected memories in this study were generally not about fatigue itself but more about negative self-evaluation and problematic social interactions as a result of the experienced disabilities.

Other than we assumed, learned predictive associations may still be the main factor in perpetuating a negative evaluation of fatigue. We assumed that eligible patients had successfully changed their negative expectations regarding fatigue and activity, but in reality, extinction might be insufficient due to contextual learning and safety behavior (Bouton, 2004). More positive experiences associated with fatigue could support patients to adopt more helpful appraisals of fatigue: resuming work, making trips, or having children could convince patients that fatigue is normal and does not predict illness and being unable to function.

The results of this study should be interpreted in light of its limitations. First, the selected patients seem to form a relatively severe subgroup with long illness duration, many symptoms, and high fatigue scores. Though all patients had successfully increased their activity levels, four out of five patients were still severely fatigued at the start of the experiment, despite receiving an average of 23 CBT sessions, compared to 12–14 sessions according to the protocol (Knoop & Bleijenberg, 2010). It might be that our results had been more positive with less severely ill patients. Relatedly, we only included females in our study. It is difficult to predict whether our results would have differed in a male sample. Further, one patient experienced stress during the experiment, which could have caused increased symptom levels.

SCEs are often criticized for their low internal validity. This was (partly) addressed by randomizing the start point of the intervention and by applying replications ($n = 5$ cases). Yet, our study might have suffered from reduced power to detect a possible intervention effect: that is, while single-case AB experimental designs are appropriate to demonstrate efficacy when treatment effects are strong and immediate (Michiels & Onghena, 2019), diffuse or delayed effects are difficult to detect. The substantial variability in the negative evaluation of fatigue during baseline makes it difficult to detect a change after the introduction of the intervention. Future research could test the efficacy of more direct interventions for evaluative conditioning of fatigue, such as counterconditioning. Last, we only measured around 7 days after the EMDR treatment ended and it can be reasoned that the transfer from changing US/UR representations to changing negative evaluation of fatigue takes more time. A longer follow-up period may be needed to detect this change.

In sum, we performed an SCE in which EMDR therapy was used to target negative evaluations of fatigue in CFS/ME patients who previously had completed CBT. Our results suggest that EMDR therapy can successfully reduce emotional distress (SUD), as assessed during EMDR therapy sessions, in response to memories of being severely fatigued but this does not automatically change the negative evaluation of fatigue.

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Consent to Participate. All patients gave written informed consent.

Availability of Data and Material. The data that support the findings of this study are available from the corresponding author, HK, upon reasonable request, including a data analysis plan and research questions. Permission for data sharing will be asked from the medical ethical committee.

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