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Shared and distinct effect mediators in exposure-based and traditional cognitive behavior therapy for fibromyalgia: Secondary analysis of a randomized controlled trial

Maria Hedman-Lagerlöf [a,*], Monica Buhrman [b], Erik Hedman-Lagerlöf [c,d], Brjánn Ljótsson [c], Erland Axelsson [e,f]

[a] Center for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet & Stockholm Health Care Services, Stockholm, Region Stockholm, Sweden
[b] Division of Clinical Psychology, Department of Psychology, Uppsala University, Uppsala, Sweden
[c] Division of Psychology, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[d] Gustavsberg University Primary Health Care Center, Academic Primary Health Care Center, Stockholm, Region Stockholm, Sweden
[e] Division of Family Medicine and Primary Care, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden
[f] Liljeholmen University Primary Health Care Center, Academic Primary Health Care Center, Stockholm, Region Stockholm, Sweden

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ABSTRACT

Fibromyalgia is a chronic pain condition associated with substantial suffering and societal costs. Traditional cognitive behavior therapy (T-CBT) is the most evaluated psychological treatment, but exposure therapy (Exp-CBT) has shown promise with a pronounced focus on the reduction of pain-related avoidance behaviors. In a recent randomized controlled trial ($N = 274$), we found that Exp-CBT was not superior to T-CBT ($d = -0.10$) in reducing overall fibromyalgia severity. This study investigated pain-related avoidance behaviors, pain catastrophizing, hypervigilance, pacing, overdoing and physical activity as potential mediators of the treatment effect. Mediation analyses were based on parallel process growth models fitted on 11 weekly measurement points, and week-by-week time-lagged effects were tested using random intercepts cross-lagged panel models. Results indicated that a reduction in avoidance behaviors, pain catastrophizing, and hypervigilance were significant mediators of change in both treatments. An increase in pacing and a reduction in overdoing were significant mediators in T-CBT only. Physical activity was not a mediator. In the time-lagged analyses, an unequivocal effect on subsequent fibromyalgia severity was seen of avoidance and catastrophizing in Exp-CBT, and of overdoing in T-CBT. Exposure-based and traditional CBT for fibromyalgia appear to share common treatment mediators, namely pain-related avoidance behavior, catastrophizing and hypervigilance.

1. Introduction

Fibromyalgia is a prevalent and disabling chronic pain condition that commonly involves symptoms of fatigue, cognitive weariness, sleep disturbance, and depressed mood (Häuser et al., 2015). Given the clear contribution of psychological, behavioral and cognitive factors to the experience of pain (Eccleston, 2001; Linton & Shaw, 2011), psychotherapeutic interventions are an integral part of the clinical repertoire (Macfarlane et al., 2017). While medications may offer relief of pain, they are unlikely to address problematic behaviors that maintain awareness of pain and lead to disability. Thus, for patients who have developed a behavioral repertoire of avoidance and control, behavioral treatments may be necessary to break this behavioral pattern. Traditional cognitive behavior therapy (T-CBT) is the most studied psychological treatment; evaluated in more than 40 randomized controlled trials (Bernardy, Klose, Welsch, & Hauser, 2018). T-CBT for fibromyalgia typically focuses on challenging negative thoughts about pain and conveying key coping strategies with the goals of reducing functional impairment and improving the patient's quality of life (Bernardy, Klose, Busch, Choy, & Hauser, 2013). Exposure-based cognitive behavior therapy (Exp-CBT) is a newer treatment based on learning theory and stipulates that pain-related avoidance behavior and hypervigilance to bodily symptoms maintain and exacerbate fibromyalgia symptoms and functional impairment. In a recent randomized controlled trial (N =

* Corresponding author. Center for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Norra Stationsgatan 69, SE-113 64, Stockholm, Sweden.
E-mail address: maria.hedman-lagerlof@ki.se (M. Hedman-Lagerlöf).

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274), we found that there was no significant difference between Exp-CBT and T-CBT in mean effect on overall fibromyalgia severity ($d = -0.10$, $p = 0.544$) (Hedman-Lagerlöf, Gasslander, et al., 2023). These results raise the question of how and why the respective treatment works, and to what degree the mechanisms of change overlap and differ between Exp-CBT and T-CBT.

Understanding how and why psychological treatments work is a central task within clinical science. Knowledge on how a treatment achieves its outcome can increase efficiencies by streamlining the treatment content to the active ingredients. To address these questions, it is necessary to identify treatment *mediators*: the specific variables that drive change within specific treatments. The overarching aim of the present study was to evaluate theoretically informed potential mediators of change in Exp-CBT and T-CBT for fibromyalgia, as based on the aforementioned randomized controlled trial ($N = 274$) (Hedman-Lagerlöf, Gasslander, et al., 2023). We also intended to conduct secondary tests of temporal precedence, ie, if week-by-week deviations in each of the potential mediators were systematically predictive of subsequent deviations in overall fibromyalgia severity. All potential mediators and corresponding a priori hypotheses are listed in Table 1.

1.1. Pain catastrophizing: exposure-based and traditional CBT

Pain catastrophizing is the tendency to interpret pain and pain-related cues as highly threatening. Common themes of catastrophic thoughts include a fear that the pain may increase in intensity or become unmanageable, and that the pain may be a sign of serious disease or tissue damage (Sullivan et al., 1995, 2001). According to the influential fear-avoidance model of pain (Vlaeyen & Linton, 2000), pain catastrophising is the main driver of avoidance. In this framework, catastrophizing maintains pain-related avoidance behavior over time, further exacerbating functional impairment, disuse and depression. Though strategies to address catastrophizing differ somewhat between Exp-CBT and T-CBT (at least in terms of emphasis), it is clearly the case that, from a theoretical standpoint, the reduction in catastrophizing would be expected to mediate the outcome of both treatments. A broad systematic review of 28 mediation analyses pertaining to various psychological treatments for chronic musculoskeletal pain found support for the reduction in pain catastrophizing as a typical mediator of effects on disability, but not on pain intensity (Murillo et al., 2022). The relevance of pain catastrophzsing for both T-CBT and newer cognitive-behavioral therapies in the treatment of chronic pain is also supported by a systematic review which identified these therapies as especially likely to affect pain catastrophizing (Schütze et al., 2018).

1.2. Pain-related avoidance behavior: exposure-based and traditional CBT

Pain-related avoidance behavior, i.e., the avoidance of situations and activities that give rise to pain or pain-related distress, is widely believed to increase the risk of pain chronicity (McCracken & Morley, 2014; Vlaeyen & Linton, 2000). Pain-related avoidance behavior has been found to predict pain intensity, hypervigilance towards bodily symptoms, disability and psychological distress, as well as pain catastrophizing (Geisser, Haig, & Theisen, 2000; Goubert, Crombez, Eccleston, & Devulder, 2004; Prkachin, Schultz, & Hughes, 2007). There are several potential reasons for this. According to learning theory, the avoidance of unwanted sensations or stimuli (or situations associated with these sensations or stimuli) increases the individual's attention to and awareness of these sensations or stimuli (as a consequence of keeping a lookout of the stimuli to be avoided), thereby increasing the subjective perception of them (Gatzounis, Schrooten, Crombez, & Vlaeyen, 2012; Hayes, Wilson, Gifford, Follette, & Strosahl, 1996; McCracken, 1997; Olatunji, Etzel, Tomarken, Ciesielski, & Deacon, 2011). In the context of chronic pain, the effort of avoiding pain paradoxically increases subjective pain experience (Berntzen & Götestam, 1987). As mentioned above, according to the fear-avoidance model of pain (Vlaeyen & Linton, 2000), pain catastrophizing is the hypothesised main driver of avoidance, as the tendency to avoid and escape the perceived threat are among the main features of fear and anxiety. However, potentially, there could also be other drivers of avoidance. Firstly, avoidance may be elicited without the conscious feeling of fear, for instance as a habitual response (Cain, 2019; LeDoux, Moscarello, Sears, & Campese, 2017). Secondly, chronic pain can elicit a multitude of negative emotions besides fear; all of which can become conditioned and trigger avoidant behavior. There is a pronounced focus on avoidance behaviors in Exp-CBT, and a mediation analysis based on the aforementioned waitlist-controlled trial found fibromyalgia-related avoidance behavior to be a significant mediator of the reduction of fibromyalgia severity (Hedman-Lagerlöf et al., 2-a019). There is also good reason, however, to expect the reduction in pain-related avoidance to be a mediator in T-CBT where activity planning – i.e., to plan and schedule activities – is a central component.

1.3. Hypervigilance to pain: primarily exposure-based CBT

Hypervigilance refers to an excess of attending to and evaluating the

Table 1
A priori hypotheses about mediators of change in exposure-based cognitive behavior therapy (Exp-CBT) and traditional cognitive behavior therapy (T-CBT) for fibromyalgia.

Potential mediator	Definition	Hypothesis in Exp-CBT	Hypothesis in T-CBT
Pain catastrophizing	The tendency to interpret pain and pain-related cues as highly threatening (Sullivan et al., 1995, 2001)	Yes, reduction positively associated with reduction in overall fibromyalgia severity	Yes, reduction positively associated with reduction in overall fibromyalgia severity
Pain-related avoidance behavior	The avoidance of situations and activities that give rise to pain or pain-related distress (McCracken & Morley, 2014; Vlaeyen & Linton, 2000)	Yes, reduction positively associated with reduction in overall fibromyalgia severity	Yes, reduction positively associated with reduction in overall fibromyalgia severity
Hypervigilance to pain	The excessive attention to pain and related bodily sensations (McCracken, 1997)	Yes, reduction positively associated with reduction in overall fibromyalgia severity	Exploratory only
Pacing	The breaking of activities into smaller parts and alternating between activity and rest on a time-contingent basis (Nielson, Jensen, Karsdorp, & Vlaeyen, 2013)	Exploratory only	Yes, *increase* positively associated with reduction in overall fibromyalgia severity
Overdoing	The overly active phase of the "all-or-nothing"-pattern commonly observed in patients with chronic pain, where the individual perseveres in excessive task persistence despite increased pain and other negative health outcomes (Cane, Nielson, McCarthy, & Mazmanian, 2013)	Exploratory only	Yes, reduction positively associated with reduction in overall fibromyalgia severity
Physical activity	Bodily movement produced by skeletal muscles that results in increased energy expenditure (Health & Services, 1996)	Yes, *increase* positively associated with reduction in overall fibromyalgia severity	Yes, *increase* positively associated with reduction in overall fibromyalgia severity

body for painful sensations, and has been found to be a significant predictor of disability, distress and healthcare utilization regardless of pain intensity (McCracken, 1997). Individuals with fibromyalgia have been found to exhibit a higher vigilance to pain (Crombez, Eccleston, Van den Broeck, Goubert, & Van Houdenhove, 2004; McDermid, Rollman, & McCain, 1996) and other noxious stimuli (McDermid et al., 1996) in relation to other chronic pain patients. In Exp-CBT, based on a learning theory perspective, hypervigilance may be conceived of as a subtle subtype of avoidance behavior. Within this theoretical framework, increased vigilance to pain may serve to reduce short-term discomfort or uncertainty, or may enable overt behavioral patterns that reduce pain or pain-related distress. Over time, this subtle pattern of hypervigilance may become habitual, and generalize. We regarded the reduction in hypervigilance to be a probable mediator of the treatment effect primarily in Exp-CBT, where an important component in addition to exposure was systematic training in observing and labelling of bodily sensations, with the aim to increase tolerance for discomfort and hence enhance the effects of exposure. In T-CBT however, this is not commonly a targeted area for behavioral change.

1.4. Overdoing and pacing: primarily traditional CBT

In the field of chronic pain, a common clinical observation has been that many patients exhibit "all-or-nothing behavior": a highly fluctuating pattern of functioning, where periods of intense and prolonged activity are followed by periods of diminished activity and fatigue (Cane et al., 2013). "Overdoing" refers to the overly active phase of this pattern, where the individual perseveres with activities despite increased pain and other negative health outcomes. This excessive intermittent task persistence has been found to be associated with poor health outcomes. Cane et al. (2013) found that chronic pain patients who reported a higher level of overdoing also reported higher levels of depression and disability, even when the general level of avoidance was taken into consideration. Kindermans et al. (2011) found that excessive persistence was associated with greater disability and depressive symptomatology, while controlling for pain intensity. A coping strategy commonly promoted within T-CBT for chronic pain is that of *pacing,* which refers to breaking activities into smaller parts and alternating between activity and rest on a time-contingent basis (Nielson et al., 2013). The aim of pacing is typically to reduce overdoing in patients who tend to engage in task persistence (see above), as well as to support behavioral activation (ie to systematically engage in positive and enjoyable activities to enhance one's mood). Even if all-or-nothing behavior is addressed to some extent within the context of exposure and response prevention in Exp-CBT, the explicit promotion of recuperating behaviors (resting, relaxation) and pacing as a coping strategy is arguably more central to T-CBT.

1.5. Physical activity: exposure-based and traditional CBT

Physical exercise is an evidence-based treatment for fibromyalgia, where aerobic exercise is associated with reductions in pain, fatigue, depressed mood, improved health-related quality of life and physical fitness (Häuser et al., 2010). Although not comparable to physical exercise treatment, it might be that an increase in physical activity occurs over the course of both Exp-CBT and T-CBT, and that this will produce improvements regardless of change in general avoidance behavior. In Exp-CBT, exposure commonly – though not always – entail an increase in the patient's activity level. In T-CBT, behavioral activation and strategies to challenge negative thoughts about pain can entail an increase in physical activity. We included physical activity as a potential mediator in this study primarily to establish whether a potential effect of reduced avoidance behaviour could be partly or fully accounted for by a parallel increase in physical activity.

2. Method

2.1. Design

This was a secondary study of mediators of the treatment effect in a single-blind randomized controlled trial of exposure-based cognitive behavior therapy (Exp-CBT) vs. traditional cognitive behavior therapy (T-CBT) for fibromyalgia (Hedman-Lagerlöf et al., 2023). This trial was a collaboration between Karolinska Institutet, Stockholm, Sweden, and Uppsala University, Uppsala, Sweden. Potential mediators and the outcome were all measured on a weekly basis during the treatment phase (see Figure A.1), measured by self-report questionnaires and collected via the online study platform. The procedures, including a detailed statistical analysis plan with a priori hypotheses, were preregistered on September 16th' 2021 at ClinicalTrials.gov (NCT05058911) and the study was approved by the Swedish Ethical Review Authority (2021–03302). On May 11th' 2023, prior to the analysis of mediation outcomes, a more detailed statistical analysis plan with a priori hypotheses pertaining to mediation was amended to the protocol. Outcomes are reported in accordance with the Consolidated Standards for Reporting Trials (CONSORT) statement (Moher et al., 2010). The study design, including power analysis and randomization procedure, as well as comprehensive data on study participants are detailed in the primary outcome article (Hedman-Lagerlöf, Gasslander, et al., 2023).

2.2. Sample and setting

Participants diagnosed with fibromyalgia by a physician were self-referred to the trial which was advertised via social media, newspapers, and patient organizations, under the caption "Are you bothered by fibromyalgia?". Applicants provided informed consent online, before completing a screening battery that comprised routine clinical questions followed by a series of validated questionnaires. Those who completed the screening battery were scheduled for an eligibility interview with a psychologist or master-level psychologist student, working under the supervision of the trial steering committee. In order to be included in the trial, participants were required to: A) be at least 18 years old, B) living in Sweden, C) acknowledge having been diagnosed with fibromyalgia by a physician, and D have access to a laptop, smartphone or other web-enabled device. Exclusion criteria were: A) severe depression as indicated by a score of at least 30 on the Montgomery-Åsberg Depression Rating Scale – Self Rated (MADRS-S) (Svanborg & Asberg, 1994), B) suicidal ideation as indicated by a score of at least 4 on the MADRS-S suicidality item, C) psychosis, D) an alcohol or substance use disorder likely to severely interfere with treatment, E) another ongoing psychological treatment, F) pregnancy beyond week 29, G) a medical condition other than fibromyalgia that was primary or that required immediate attention, and H) insufficient technical prowess or knowledge of the language to participate in a text-based online treatment. Participants who were on continuous psychotropic medication were instructed to maintain the same regimen throughout the trial.

2.3. Measures

Primary outcome: overall fibromyalgia severity. The primary outcome measure in this trial was the Fibromyalgia Impact Questionnaire (FIQ), which is a composite measure of the overall severity of fibromyalgia in terms of pain, fatigue, sleepiness, mood disturbance, and impact on daily life (disability) (Burckhardt, Clark, & Bennett, 1991). As such, the FIQ combines measures of pain, physical functioning, and emotional functioning, in accordance with guidelines for chronic pain clinical trials (Turk et al., 2003). The FIQ is scored from 0 to 100. For sensitivity analyses (see below), we also rescored the FIQ without the 11 disability items. Because these items contribute with a maximum of 10 points on the conventional FIQ, the rescored variant had a theoretical range of 0–90. In calculating Chronbach's α, it is necessary for all items

to be assigned a value per respondent. In contrast, for the FIQ disability items, the respondent is given the option of "not applicable", which disqualifies that particular item from contributing to the FIQ sum score. In order to approach the question of internal consistency, we therefore calculated the α in two ways: First, over all items, with all disability items simply assigned a value of 0 for "*not applicable*" and this was acceptable (α = 0.70). Second, without the disability items, and the outcome was again acceptable (α = 0.75).

2.4. Potential mediating variables

Pain-related avoidance behavior. External and internal avoidance behaviors were measured using the avoidance subscale of The Psychological Inflexibility in Pain Scale (PIPS-A) (Wicksell et al., 2008, 2010). This instrument was developed as a process measure focusing on acceptance and commitment therapy for chronic pain patients. The PIPS-A contains 8 items, scored from 1 ("*never true*") to 7 ("*always true*") that measure the tendency to engage in behaviors relating to the avoidance of pain and related distress. This results in a sum score of 1–56. A typical item is: *"I cancel planned activities when I am in pain"*. Internal consistency in this study was good (α = 0.88).

Pain catastrophizing. We used the Pain Catastrophizing Scale (PCS), a self-report instrument containing 13 items scored between 0 ("*not at all*") to 4 ("*all the time*"), intended to capture pain-related catastrophic cognitions and emotions. A typical item is: *"I become afraid that the pain will get worse"*, and the sum score ranges from 0 to 52. The PCS has demonstrated good test-retest reliability (Wheeler, Williams, & Morley, 2019) and construct validity (Osman et al., 2000). Internal consistency in this study was excellent (α = 0.92).

Hypervigilance to pain. Excessive attention to pain was measured using the 8-item version of the Pain Vigilance and Awareness Questionnaire (PVAQ-8) (Ahnlund Hoffmann, Frostell, Hedman-Lagerlöf, McCracken, & Axelsson, 2023; McCracken, 1997). This is a self-report questionnaire with items rated 0 ("*never*") to 5 ("*always*"), which results in a sum score of 0–40. A typical item is: *"I focus on sensations of pain"*. The 8-item version has demonstrated good internal consistency and constructive validity, and a better factor solution than the original 16-item version (Ahnlund Hoffmann et al., 2023). Internal consistency in this study was good (α = 0.89).

Pacing. Self-reported tendency to cope with pain by pacing, ie, by balancing activity and rest, was measured using the Pacing subscale of the Patterns of Activity Measure – Pain short form (POAM-P-pacing) (Cane & Mazmanian, 2020). The POAM-P-pacing is a 5-item scale, which each item rated from 0 ("*not at all*") to 4 ("*all the time*"), resulting in a sum score of 0–20. A typical item is: *"When I do an activity I break it into small parts and do one part at a time"*. The POAM-P-pacing has shown good internal constancy and construct validity (Cane & Mazmanian, 2020). Internal consistency in this study was excellent (α = 0.92).

Overdoing. Overdoing was measured using the 5-item Overdoing subscale of POAM-P (POAM-P-overdoing; see "Pacing" above)(Cane & Mazmanian, 2020). Each item is scored 0–4, which results in a sum score of 0–20. A typical item is: *"When I do an activity I do the whole thing all at once"*. Internal consistency in this study was good (α = 0.84).

Physical activity. Physical activity was measured using the first three items of Godin-Shepard Leisure-Time Exercise Questionnaire (GSLTPAQ)(Godin & Shephard, 1985). The GSLTPAQ is a 4-item self-report questionnaire where the first three items ask the respondent to quantify the number of times one engages in mild, moderate and strenuous leisure-time physical activity bouts exceeding 15 min in duration over a typical week. In the current trial, the instruction was slightly revised to concern the last week, to be able to capture change over time. Examples of activities are provided for each intensity category. The number of bouts at each intensity multiplied by 3, 5 and 9 metabolic equivalents and summed to a total weekly Leisure Score Index. The 3-item version has previously shown ability to adequately discriminate between physically active and inactive respondents (Amireault & Godin, 2015). Internal consistency in the current trial was poor, if the measure was to be considered continuous (α = 0.56; partly due to the fact that this was a three-item scale).

2.5. Pain intensity as a moderator of indirect effects

Pain intensity was measured using the severity subscale of the Brief Pain Inventory - short form (BPI-SF) (Cleeland & Ryan, 1991). An initial portal question is used to discriminate chronic pain from temporary pain states (eg, a light headache), and asks whether the respondent has experienced more noteworthy pain during the past week. Items three to six yield the composite measure of pain intensity in the past 24 h, in general, and at the time of completing the questionnaire. Each item is scored on a 10-point rating scale from 0 ("*no pain*") to 10 ("*worst imaginable pain*"). The total sum score is then averaged, resulting in a pain intensity score from 0 to 10, where 0 corresponds to no pain, 1–4 to mild pain, 5–6 to moderate pain, and 7–10 severe pain. Internal consistency was good (α = 0.88).

2.6. Count variables pertaining to treatment engagement

Three measures of treatment engagement were developed as count variables for this trial. In Exp-CBT, the number of conducted exposure exercises and mindfulness exercises were reported by the participants. In T-CBT, participants reported the number of conducted relaxation exercises. All were reported on a weekly basis. The item used for capturing work with exposure read "*How many exposure exercises have you conducted during the last 7 days? If unsure, please try to estimate to the best of your ability*". Engagement with mindfulness exercises was quantified by summarizing the responses on the following items: "*How many times have you conducted the exercise 'mindfulness through focussing on breathing, the body and the surrounding environment', during the last 7 days? If unsure, please try to estimate to the best of your ability*", "*How many times have you conducted the exercise 'everyday mindfulness', during the last 7 days? If unsure, please try to estimate to the best of your ability*" and "*How many times have you conducted the exercise 'mindfulness when experiencing symptoms', during the last 7 days? If unsure, please try to estimate to the best of your ability*". The item for capturing work with relaxation exercises read "*How many times have you practiced relaxation during the last 7 days? If unsure, please try to estimate to the best of your ability*". The sum score of each variable was divided by the number of available data points (1–10; first assessment after treatment week 1); yielding a value of the average treatment engagement for each participant. For example, if the respondent had completed eight weekly assessments and reported 40 exposures in total, this resulted in a weekly average score of 40/8 = 5. In Exp-CBT, the exposure variable was coded as zero when there was no information about exposure exercises and the participant had never reached module 4 where exposure was first introduced. In T-CBT, the week-by-week specific number of reported relaxation exercises was also analyzed separately (see below).

2.7. Treatment conditions

Common treatment features. Both treatments were manualized and followed the respective protocol further described below; were 10 weeks in length and delivered online via a secure platform with therapist support. Both protocols were about equally long, about equally easy to read, and included a roughly similar number of illustrations. The treatment content consisted of eight interactive modules containing self-help texts, worksheets, instructions for exercises, and self-reflective questions, all of which could be downloaded as audio files. Participants were encouraged to log in and work with treatment regularly, to raise any questions or problems with their therapist, and to report on progress about once a week. Therapists were a combination of students in their last year of the master-level psychology program and licensed psychologists. Therapist training prior to study start consisted of a joint

go-through of internet-delivered treatment, the study platform and study procedures, as well as specific go-through of the treatment protocol with each therapist group (Exp-CBT and T-CBT, respectively) with the authors of the respective protocol (MHL and MB, respectively). All therapists were also given a written guide, including Q&As for the respective treatments as well as examples of written communication to facilitate learning and model expected therapist behavior. The therapists participated in weekly supervision sessions with the primary author of the respective treatment protocol (MHL and MB, respectively). The primary focus during these sessions was to foster allegiance and encourage adherence to the designated treatment components. In both treatment approaches, the therapist's primary responsibility involved providing support for progress through positive reinforcement, addressing any arising questions, and assisting participants in customizing the treatment content, including individualized daily homework assignments. For an overview of the treatment content of Exp-CBT and T-CBT respectively, see Table A.1.

Internet-delivered exposure-based cognitive behavior therapy. Exposure-based CBT was administered in accordance with the previously evaluated protocol (Hedman-Lagerlöf et al., 2018). The fundamental tenet of this treatment is that behavioral avoidance and safety behaviors contribute to chronicity and even deterioration in the long term. Treatment was therefore heavily focused on exposure, meaning that participants were encouraged to repeatedly and systematically engage in activities that gave rise to pain, other fibromyalgia symptoms and associated distress (exposure), while refraining from behaviors intended to reduce pain and pain-related distress in the short term (response prevention). The initial phase of treatment focused on treatment rationale and stimulus discrimination. Here, participants were encouraged to identify and track their avoidance behaviors (enabled by promoting simple registering in a behavioral log) before proceeding to exposure exercises tailored to the individual's clinical presentation and pattern of behavioral avoidance. Avoidance characterized by diminished activity level was targeted by encouraging the participant to conduct exposure exercises involving more activity, whereas subtle avoidance characterized by distraction from pain or pain-related distress or persistence behaviors, was targeted by encouraging participants to abstain from this strategy and instead practice deliberate observation of unwanted physical sensations. Systematic mindfulness training was an integrated component throughout treatment, meaning that participants practiced intentionally observing and labeling symptoms and other experiences in the present moment. This was intended as a means of increasing the participant's willingness to engage in exposure by becoming aware of mental strategies to avoid contact with pain (eg distraction), and also as a form of interoceptive exposure in itself, by practicing approach behavior instead of avoidance, in the presence of negative inner events. It was stressed that the function of pain-related avoidance can encompass all from the immediate reduction of pain or other distressing fibromyalgia symptoms, negative emotions like uncertainty, or other discomfort, and that avoidance also could be a habitual response that easily increases in frequency and generalizes over contexts.

Internet-delivered traditional cognitive behavior therapy. The traditional CBT protocol was delivered in accordance with a protocol previously evaluated for chronic pain (Buhrman, Faltenhag, Strom, & Andersson, 2004). Small changes were made to this protocol primarily to ensure that the first module of both treatments began with identical psychoeducational texts about fibromyalgia, as well as making the treatments equal with regard to treatment length and readability. The rationale for T-CBT stemmed from the biopsychosocial perspective (Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Turk & Monarch, 1996), where fibromyalgia was described as involving, and bidirectionally interacting with, a large number of problems besides pain and fatigue such as depressed mood, anxiety, sleep disturbances, stress and muscle tension, impaired social capacity, and reduced physical activity. It was emphasized that the individual could address any or all of these areas based on individual needs and wants, in order to achieve improved quality of life and functional capacity. Each module presented the participant to 1–2 new components, resulting in a wide spectrum of components including activity planning, pacing, relaxation, cognitive restructuring techniques, sleep-promotion techniques, mindfulness and acceptance strategies, stress management strategies, assertiveness training and physical activity. The emphasis of T-CBT was that the participant should work continuously with activity planning and making use of coping strategies such as pacing, stress management strategies or relaxation before, during, and after activities in order to manage pain and pain-related distress.

2.8. Data analyses

This analysis of potential mediators of treatment effects followed a preregistered plan (ClinicalTrials.gov NCT05058911) and was conducted in Stata 16.1 and R 4.3.0 (R Core Team, 2021) with lavaan 0.6–15 (Rosseel, 2012). Because we were more interested in the potential mechanisms of each treatment (Exp-CBT and T-CBT) than in quantifying the difference in mechanisms (Exp-CBT versus T-CBT), and also to ensure acceptable statistical power, we analyzed each treatment separately rather than to focus on between-group effects. This study of mediators was concerned with the pre-to post-treatment main phase only.

We used the analytic framework of Baron and Kenny (1986) where the direct effect of the treatment on the potential mediator is denoted "*a*" ("the *a*-path"), the effect of the mediator on the outcome is denoted "*b*" ("the *b*-path"), and the indirect effect on the outcome via the mediator is denoted $a \times b$ (ie, the mediated effect). In order to determine the suitability of various modelling strategies, we first inspected baseline distributions, correlations, and individual change trajectories pertaining to the variables of interest. Four types of analyses were conducted. All were conducted fully intention-to-treat, ie, with all participants in the analysis.

1 Main tests of mediation. The analysis of primary interest was the main test of mediation, ie, of the indirect effect (a × b) of time in the treatment (*x*), via the potential mediator (*m*), on the outcome (*y*). We conducted these analyses in a structural equation modelling framework, based on parallel process growth curve models. As part of model building, univariate models were first fitted to ensure that change in each variable could be adequately captured using a random linear slope and a random intercept which was centered at the pre-treatment assessment. Conceptually, the effect of time in treatment (*x*) on the potential mediator (*m*) constituted the *a*-path. In our modelling framework, this *a*-path corresponded to the slope of the mediator. In the same model, the slope of the outcome was regressed on the slope of the mediator to represent the *b*-path (Fig. 1). The indirect (ie, mediated) effect ($a \times b$) was tested using bias-corrected confidence intervals derived from bootstrapping (2000 samples). One potential mediator, namely physical activity (GSLTPAQ), was highly skewed, and appeared to follow a zero-inflated negative binomial distribution. We therefore analyzed this using hierarchical quantile regression, focusing on the effect on the median rather than the effect on the mean.
2 Conditional indirect effects. A conditional indirect effect refers to a situation where the strength of an indirect effect (such as those tested in analysis 1 above) varies as a function of a moderator (for example a baseline variable) (Preacher, Rucker, & Hayes, 2007). A conditional indirect effect can exist either due to moderation of the *a*-path, due to moderation of the *b*-path, or both (Muller, Judd, & Yzerbyt, 2005). For each potential mediator, we evaluated if the general level on the potential mediator (eg, the general level of avoidance) was a moderator of mediation via the same variable (eg, mediation via avoidance). To evaluate conditional indirect effects due to moderation of the *a*-path, we tested the indirect path from the random

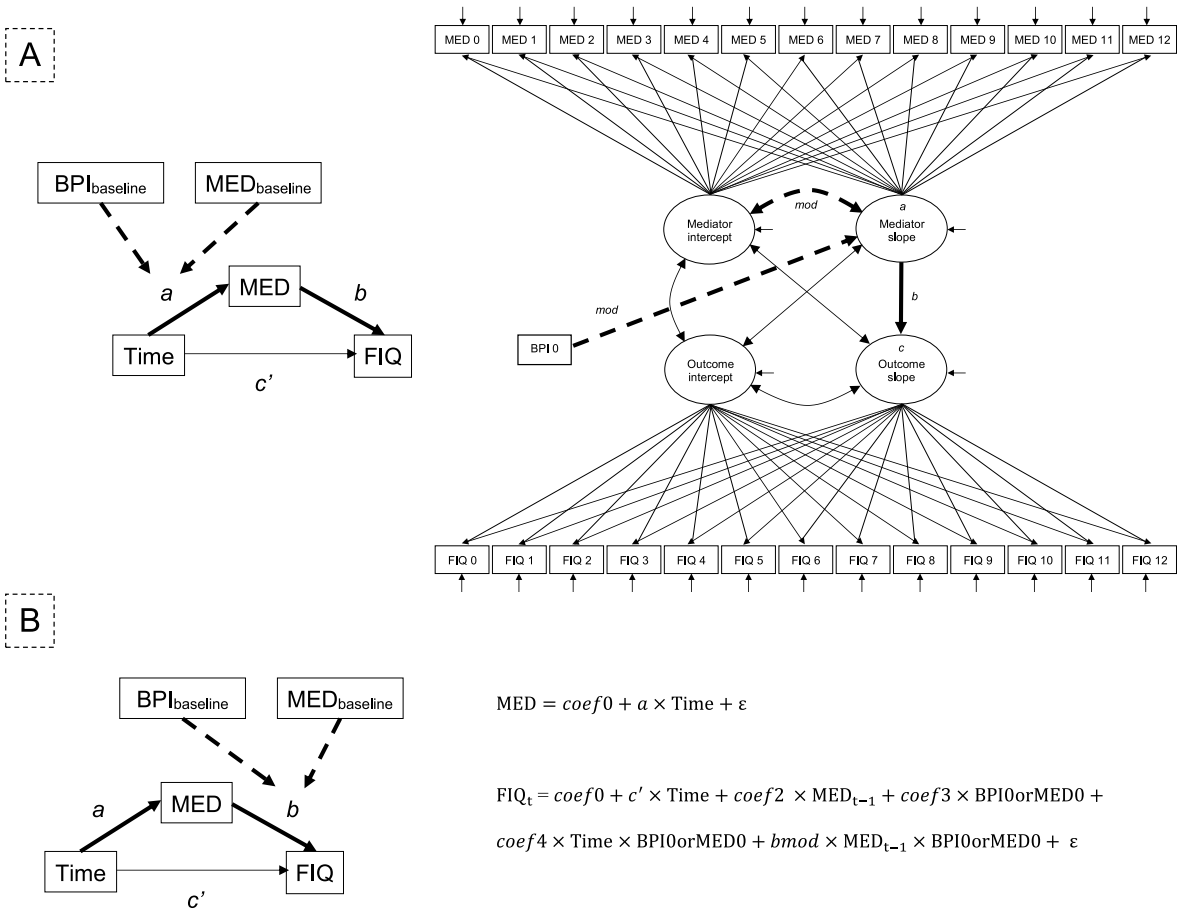

Fig. 1. Overview of main statistical analyses. Panel A: Conceptual framework (left) and specification of primary mediation models (right). The a × b coefficients were tested on the basis of bias-corrected bootstrapped confidence intervals. For each week, time-specific covariance was specified over the outcome and the potential mediator (i.e., the manifest variables), which was omitted from this figure for clarity of presentation. Conditional indirect effects due to moderation of the a-path were also tested within this framework, as: mod × a × b. Panel B: Conceptual framework and specification of linear mixed effects regression models (random intercept only), for the purpose of evaluating conditional indirect effects due to moderation of the b-path. For these models, the putative moderator (BPI0 and MOD0) was grand mean centered and conditional indirect effects were tested as a × bmod, using bias-corrected bootstrapped confidence intervals. Abbreviations: BPI, Brief Pain Inventory; FIQ, Fibromyalgia Impact Questionnaire (i.e., the outcome); MED, putative mediator; mod, path illustrative of potential moderation.

intercept of the potential mediator (here considered the potential moderator) to the slope of the potential mediator (*a*-path), to the slope in the outcome (*b*-path). We also evaluated conditional indirect effects due to moderation of the *b*-path. Conceptually, this is a situation where the moderator alters the impact of the mediator on the outcome. This could not be captured in our main parallel process growth curve framework, and we therefore employed conventional linear mixed modelling instead. Here, we fitted one model of the *a*-path, and another model to derive a coefficient indicative of moderation of the *b*-path (Fig. 1) (see Muller et al., 2005). As in analysis 1, all tests of indirect effects were based on bootstrapping.

3 Mediator as moderator of the overall treatment effect. Conditional indirect effects (2 above) can be difficult to interpret. Even if a variable (moderator) is predictive of the strength of the mediated effect, this does not necessarily mean that the same variable determines the overall strength of the treatment effect (that is, on the main outcome, eg, FIQ). To facilitate the interpretation of possible conditional indirect effects, we also tested the path directly from the intercept of the potential mediator to the slope of the outcome. Similar to the main test of mediation, this analysis was done within a structural equation modelling framework based on parallel process growth curve models.

4 Week-by-week temporal precedence. Even if there is an indirect effect such that time in the treatment is associated with change in the mediator, which in turn is associated with change in outcome (analysis 1 above), this does not necessarily mean that change in the mediator systematically precedes (ie, occurs before) change in the outcome. We evaluated such week-by-week ordering effects using random-intercepts cross-lagged panel models (Hamaker, Kuiper, & Grasman, 2015). In order to improve power (with few exceptions, see below), and as both treatments involved recurrent themes with which the participant worked during the main phase of the treatment, we imposed constraints so that all autoregressive and cross-lagged paths were assumed to remain similar regardless of treatment week. Thus, for each model, we estimated only one coefficient for each of the autoregressive week-by-week components (α and β), one for the effect of the mediator on the subsequent outcome (γ), and one for the effect of the outcome on the subsequent mediator (δ). We regarded a significant γ as being indicative of temporal precedence.

2.9. Secondary analyses

Homework count variables as predictors of the outcome. We did not expect the three homework count variables (exposure and mindfulness exercises in Exp-CBT, relaxation exercises in T-CBT) to change gradually over the course of treatment. Rather, for example, we encouraged participants in Exp-CBT to work consistently with exposure

each week. The three variables were all highly skewed, and in order to assess their importance we therefore calculated Spearman correlations with the reduction in the FIQ over the course of treatment, as based on fitted regression lines from linear mixed effects regression models with a random intercept and slope. We were also able to model week-by-week change (similar to analysis 4) with regard to relaxation in T-CBT but not for the other two count variables (for exposure exercises the model did not converge, for mindfulness exercises due to poor model fit).

Pain intensity as a potential moderator of processes of change. In a previous trial, we found that the Brief Pain Inventory – Short form, severity subscale (BPI-SF) was a moderator of the effect of Exp-CBT versus a waitlist control (Hedman-Lagerlöf, Andersson, et al., 2023). Though, in this trial, the BPI-SF was not a moderator of the between-group effect of Exp-CBT versus T-CBT (Hedman-Lagerlöf, Gasslander, et al., 2023), we intended to explore if BPI-SF was a moderator of the processes of change in Exp-CBT and T-CBT respectively. Therefore, the baseline BPI-SF value was evaluated in a manner analogous to the intercept of the mediator in steps two and three above, ie, we evaluated conditional indirect effects with pain intensity (the BPI-SF) as the potential moderator of the *a* and *b*-path, and in the *a*-path was specified directly from baseline pain intensity to the slope of the outcome without any indirect paths via any potential mediator.

Avoidance as a potential mediator of catastrophizing and hypervigilance. In Exp-CBT, avoidance behavior was also tested as a potential mediator of the effect on catastrophizing and hypervigilance. The rationale for this analysis was to more directly evaluate the validity

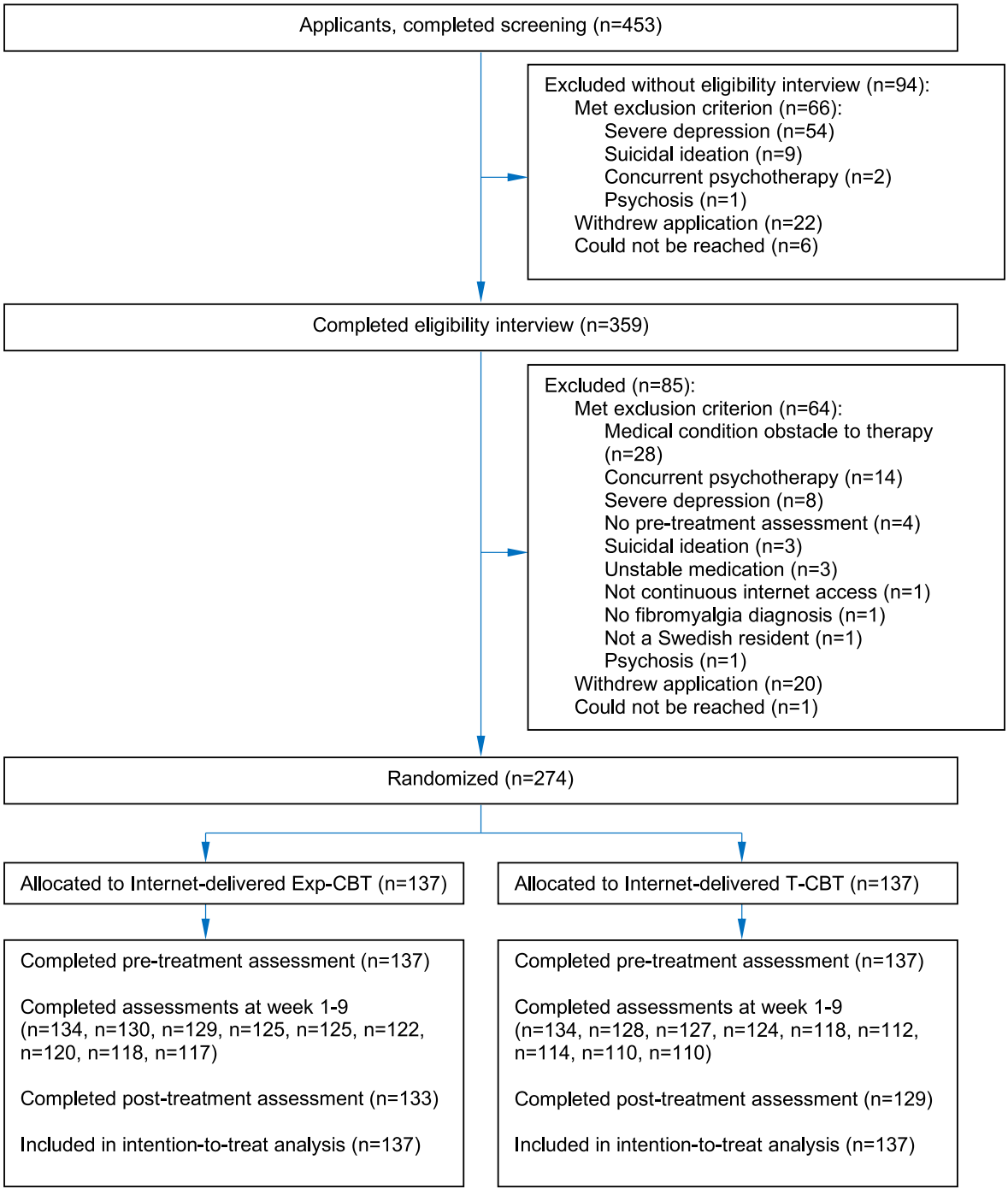

Fig. 2. Recruitment flow and data completion.

of the fear-avoidance model of pain which emphasizes that catastrophizing is the driver of avoidance and the main mediator of long-term disability (Vlaeyen & Linton, 2000).

For all structural equation models, we report indices of model fit. Common rule of thumb are that the Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI) should be at least ca 0.90 or ideally ca 0.95, that the Root Mean Squared Error of Approximation (RMSEA) should be below ca 0.08 and ideally below ca 0.06, and that the Standardized Root Mean Square Residual (SRMR) should be below ca 0.08 (Hu & Bentler, 1999; Wu, West, & Taylor, 2009).

3. Results

3.1. Data completion

In Exp-CBT, the 11 assessment points of the main phase were completed by 137, 134, 130, 129, 125, 125, 122, 120, 118, 117, and 133 participants. In T-CBT, the corresponding figures were 137, 134, 128, 127, 124, 118, 112, 114, 110, 110, and 129. Thus, all participants completed the pre-treatment assessment, and 2734 out of 3014 (91%) weekly FIQ scores were collected. Recruitment flow, including reasons for exclusion, and data completion are depicted in Fig. 2.

3.2. Inspection of distributions, baseline correlations, and change trajectories

Most variables of interest were approximately normally distributed, and with a relatively wide range of observed values. As mentioned above, we found the physical activity variable to be highly skewed and therefore proceeded to analyze mediation via this variable using hierarchical quantile regression instead of parallel process growth curve or linear regression models. Baseline correlations between the variables of interest are reported in Table A.2. We deemed all other non-homework potential mediators to be suitable for the planned analysis, and there were no clear indications of curvilinear change. Estimates of univariate change are presented in Table 2.

3.3. Main tests of mediation

Outcomes from the main tests of mediation are reported in Table 3 and Table A.3. In Exp-CBT, $a \times b$, ie, the test of mediation, was significant for avoidance behavior, pain catastrophizing, and hypervigilance, such that a mean reduction was seen in these variables, and this reduction was associated with the mean reduction in overall fibromyalgia severity. There was no such mediated effect via pacing, overdoing or physical activity.

In T-CBT, $a \times b$ was significant for all potential mediators except physical activity. For avoidance behavior, pain catastrophizing, hypervigilance, and overdoing, a mean reduction was seen, and this reduction was associated with the mean reduction in overall fibromyalgia severity. For pacing, a mean increase was seen, and this increase was associated with the mean reduction in overall fibromyalgia severity. For all main models of mediation, it was necessary to add covariance over manifest variables from the same week to achieve acceptable model fit (see Table 3 and Table A.4).

3.4. Moderation of the overall treatment effect, and conditional indirect effects

None of the potential mediator variables had intercepts (centered at the baseline) that moderated the overall treatment effect, neither in Exp-CBT nor in T-CBT (Table A.7). Conditional indirect effects – ie, variability in the strength of the mediated effects (ie, contribution of pathways to the overall treatment effect) – were seen when intercepts were allowed to have a moderating effect on the *a*-path (Table 3): In both Exp-CBT and T-CBT, larger mediated effects were seen with higher baseline

Table 2
Univariate models with covariance over the intercept and slope, and also over.

	Exposure-based cognitive behavior therapy (n = 137)						
	Latent variables			Fit indices			
	Std cov	Intercept	Slope	CFI	TLI	RMSEA (90% CI)	SRMR
Fibromyalgia severity (FIQ)	0.0	54.7	−1.0 [d]	0.94	0.93	0.11 (0.09, 0.14)	0.09
Symptoms only[a]	0.0	50.4	−0.9 [d]	0.94	0.93	0.11 (0.09, 0.14)	0.09
Avoidance behavior (PIPS-A)	−0.4 [c]	29.5	−0.8 [d]	0.90	0.90	0.16 (0.14, 0.19)	0.14
Pain Catastrophizing (PCS)	−0.3 [b]	18.1	−0.6 [d]	0.96	0.95	0.11 (0.08, 0.13)	0.10
Hypervigilance (PVAQ-8)	−0.2	19.6	−0.6 [d]	0.96	0.96	0.11 (0.09, 0.14)	0.08
Pacing (POAM-P-pacing)	−0.3 [c]	9.0	0.0	0.97	0.96	0.11 (0.08, 0.13)	0.08
Overdoing (POAM-P-overdoing)	−0.2 [b]	12.3	−0.1 [d]	0.97	0.97	0.09 (0.07, 0.12)	0.05
	Traditional cognitive behavior therapy (n = 137)						
	Latent variables			Fit indices			
	Std cov	Intercept	Slope	CFI	TLI	RMSEA (90% CI)	SRMR
Fibromyalgia severity (FIQ)	0.1	58.5	−1.2 [d]	0.96	0.95	0.09 (0.06, 0.12)	0.10
Symptoms only[a]	0.2	53.8	−1.0 [d]	0.96	0.96	0.08 (0.05, 0.11)	0.10
Avoidance behavior (PIPS-A)	−0.3 [c]	30.8	−0.5 [d]	0.95	0.95	0.13 (0.10, 0.15)	0.11
Pain Catastrophizing (PCS)	−0.2	18.8	−0.6 [d]	0.96	0.96	0.11 (0.08, 0.13)	0.09
Hypervigilance (PVAQ-8)	−0.4 [c]	19.7	−0.4 [d]	0.95	0.94	0.14 (0.11, 0.16)	0.11
Pacing (POAM-P-pacing)	−0.3 [b]	8.9	0.3 [d]	0.95	0.95	0.11 (0.09, 0.14)	0.10
Overdoing (POAM-P-overdoing)	−0.3 [b]	12.2	−0.4 [d]	0.95	0.94	0.12 (0.10, 0.15)	0.12

Adjacent measurement points.
Note. All intercepts were statistically significant. Paths are coded so that a change of 1 stands for the weekly change over the 10-week main phase. Covariances was specified over adjacent measurement points. Exp-CBT, Internet-delivered exposure-based cognitive behavior therapy; FIQ, Fibromyalgia Impact Questionnaire; PCS, Pain Catastrophizing Scale; PIPS-A, Psychological Inflexibility in Pain Scale – Avoidance subscale; POAM-P- overdoing, Patterns of Activity Measure – pain, short form – Overdoing subscale; POAM-P-pacing, Patterns of Activity Measure – pain, short form – Pacing subscale; PVAQ-8, 8-item Pain Vigilance and Awareness Questionnaire; T-CBT, Internet-delivered traditional cognitive behavior therapy.
[a] This was the FIQ, but without item 1, ie, without the functional impairment items.
[b] $p < .05$.
[c] $p < .01$.
[d] $p < .001$.

Table 3
Mediated effect on fibromyalgia severity.

	Exposure-based cognitive behavior therapy (n = 137)									
	a	*b*	Mediated effect (a × b)		Conditional indirect effect		Fit indices			
	est	*est*	*est* (95% CI), sig	Stdtd	*est* (95% CI), sig	Std	CFI	TLI	RMSEA (90% CI)	SRMR
Avoidance behavior (PIPS-A)	−1.0	1.2	−1.2 (−1.7, −0.8), [b]	−0.7	4.0 (2.0, 7.1), [b]	0.3	0.90	0.90	0.10 (0.09, 0.11)	0.10
Effect on symptoms only[a]	−1.0	1.1	−1.1 (−1.5, −0.7), [b]	−0.6	3.6 (1.8, 6.4), [b]	0.2	0.90	0.90	0.10 (0.09, 0.11)	0.10
Pain Catastrophizing (PCS)	−0.7	1.5	−1.1 (−1.5, −0.8), [b]	−0.6	2.7 (0.9, 5.5), [b]	0.2	0.88	0.88	0.11 (0.10, 0.12)	0.10
Hypervigilance (PVAQ-8)	−0.6	1.5	−0.9 (−1.3, −0.6), [b]	−0.5	0.9 (0.0, 2.1), [b]	0.1	0.91	0.91	0.10 (0.09, 0.11)	0.08
Pacing (POAM-P-pacing)	0.0	0.3	0.0 (−0.1, 0.0), N·S.	0.0	0.0 (0.0, 0.1), N·S.	0.0	0.92	0.92	0.09 (0.08, 0.11)	0.07
Overdoing (POAM-P-overdoing)	−0.1	1.2	−0.2 (−0.4, 0.0), N·S.	−0.1	0.1 (0.0, 0.3), N·S.	0.0	0.92	0.92	0.10 (0.09, 0.11)	0.07
	Traditional cognitive behavior therapy (n = 137)									
	a	*b*	Mediated effect (a × b)		Conditional indirect effect		Fit indices			
	est	*est*	*est* (95% CI), sig	Std	*est* (95% CI), sig	Std	CFI	TLI	RMSEA (90% CI)	SRMR
Avoidance behavior (PIPS-A)	−0.5	1.6	−0.9 (−1.2, −0.6), [b]	−0.6	1.7 (0.4, 5.0), [b]	0.2	0.93	0.93	0.09 (0.08, 0.10)	0.10
Effect on symptoms only[a]	−0.5	1.4	−0.8 (−1.1, −0.6), [b]	−0.5	1.5 (0.3, 4.6), [b]	0.2	0.93	0.93	0.09 (0.08, 0.10)	0.10
Pain Catastrophizing (PCS)	−0.6	1.6	−1.0 (−1.4, −0.7), [b]	−0.6	1.3 (0.2, 3.5), [b]	0.2	0.93	0.93	0.08 (0.07, 0.10)	0.09
Hypervigilance (PVAQ-8)	−0.4	1.6	−0.6 (−1.0, −0.3), [b]	−0.4	1.0 (0.3, 2.7), [b]	0.2	0.89	0.89	0.11 (0.10, 0.12)	0.09
Pacing (POAM-P-pacing)	0.3	−2.1	−0.7 (−1.2, −0.4), [b]	−0.5	0.3 (0.1, 0.6), [b]	0.2	0.89	0.89	0.10 (0.09, 0.11)	0.09
Overdoing (POAM-P-overdoing)	−0.4	1.7	−0.7 (−1.1, −0.2), [b]	−0.4	0.2 (0.0, 0.5), [b]	0.1	0.90	0.89	0.10 (0.09, 0.11)	0.10

Note. Paths are coded so that a change of 1 stands for the weekly change over the 10-week main phase. "Conditional indirect effect" refers to the effect of the intercept of the putative mediator, on the outcome, via the mediation path (see Fig. 1); Exp-CBT, Internet-delivered exposure-based cognitive behavior therapy; FIQ, Fibromyalgia Impact Questionnaire; PCS, Pain Catastrophizing Scale; PIPS-A, Psychological Inflexibility in Pain Scale – Avoidance subscale; POAM-P- overdoing, Patterns of Activity Measure – pain, short form – Overdoing subscale; POAM-P-pacing, Patterns of Activity Measure – pain, short form – Pacing subscale; PVAQ-8, 8-item Pain Vigilance and Awareness Questionnaire; T-CBT, Internet-delivered traditional cognitive behavior therapy.

[a] In this sensitivity analysis, the outcome variable was identical to the FIQ but without item 1, ie, without the functional impairment items.

[b] $p < .05$.

avoidance, catastrophizing, and hypervigilance. In T-CBT but not Exp-CBT, larger mediated effects were also seen with lower baseline pacing and higher baseline overdoing. Conditional indirect effects were also seen due to moderation of the *b*-path (Table A.5): In Exp-CBT, larger mediated effects were seen with higher baseline overdoing. In T-CBT, larger mediated effects were seen with higher baseline avoidance and hypervigilance.

3.5. Week-by-week temporal precedence

In Exp-CBT, the random intercepts cross-lagged panel model γ-path – indicative of temporal precedence – was significant for avoidance behavior, for pain catastrophizing, and in 1 out of 10 weeks for pacing (where the model could only be fitted without constraints). In other words, a lower score in avoidance or catastrophizing (ie, a larger deviation from the random intercept) was predictive of a lower score in overall fibromyalgia severity in the following week. The γ-path was not significant for hypervigilance, overdoing, or 9 out of 10 weeks for pacing (Table 4).

In T-CBT the γ-path was significant for overdoing and in 2 out of 10 weeks for pacing. A lower score in overdoing (ie, a larger deviation from the random intercept) was predictive of a lower score in overall fibromyalgia severity the following week. The γ-path was not significant for avoidance behavior, pain catastrophizing, hypervigilance, or 8 out of 10 weeks for pacing (Table 4).

3.6. Secondary analyses

Baseline pain intensity as a moderator of the overall effect, and driver of conditional indirect effects. Baseline pain intensity did not moderate the overall treatment effect in Exp-CBT or T-CBT (Table A.7). Conditional indirect effects – ie, variability in the strength of the mediated effects – were seen when baseline pain intensity was allowed to have a moderating effect on the *a*-path (Table A.6): In Exp-CBT only, larger mediated effects via pain catastrophizing and hypervigilance were seen with higher baseline pain intensity. There was no such conditional indirect effect in any other test, neither when pain intensity was allowed to have an effect on the *a*-path (Table A.6), nor when it was allowed to have an effect on the *b*-path (Table A.5).

Homework count variables in relation to outcome. In Exp-CBT, a larger reduction in overall fibromyalgia severity correlated with a higher participant-level average weekly number of reported exposure exercises ($\rho = 0.27$, $p = 0.002$, $n = 134$) and mindfulness exercises ($\rho = 0.27$, $p = 0.002$, $n = 136$). In T-CBT, a larger reduction in overall fibromyalgia severity correlated with a higher participant-level average weekly number of relaxation exercises ($\rho = 0.27$, $p < 0.002$; $n = 135$). In T-CBT, the random intercepts cross-lagged panel model γ-path was not significant for the number of relaxation exercises (Table 4).

Avoidance as a potential mediator of the effect on catastrophizing and hypervigilance. In Exp-CBT, avoidance behavior was a significant mediator of the effect on both catastrophizing and hypervigilance (Table A.8).

4. Discussion

This was a study of treatment processes based on a single-blinded randomized controlled trial investigating the effect of Internet-delivered exposure-based cognitive behavior therapy (Exp-CBT) as compared to Internet-delivered traditional cognitive behavior therapy (T-CBT) for fibromyalgia. An overview of key results is presented in Table 5.

In Exp-CBT, the effect on overall fibromyalgia severity was mediated by a reduction in avoidance behavior, pain catastrophizing and hypervigilance. There was no such significant mediating effect of pacing, overdoing, or physical activity. In T-CBT, the effect on overall fibromyalgia severity was mediated by a reduction in avoidance behavior, pain catastrophizing, hypervigilance, and overdoing. The outcome was also mediated by an increase in pacing. There was no such significant mediating effect of physical activity. Regarding ordering effects, in Exp-CBT, changes in avoidance, pain catastrophizing, and possibly pacing (week 3–4 only), were systematically predictive of subsequent reduction in overall fibromyalgia severity. In T-CBT, such ordering effects were seen for overdoing, and possibly pacing (week 5–6, 7-8). In a secondary analysis, we found that behavioral avoidance could also be regarded a

Table 4
Effects derived from random-intercepts cross-lagged panel model, with overall fibromyalgia severity as measured using the Fibromyalgia Impact Questionnaire as outcome.

	Exposure-based cognitive behavior therapy (n = 137)										
	Trait correlation	Effect of the putative mediator on the FIQ (γ)			Effect of the FIQ on the putative mediator (β)			Fit indices			
	r (p)	*est* (95% CI)	Median Std	*p*	*est* (95% CI)	Median Std	*p*	CFI	TLI	RMSEA (90% CI)	SRMR
Avoidance behavior (PIPS-A)	0.59 (<0.001)	0.4 (0.1, 0.6)	0.14	0.002	0.1 (0.0, 0.1)	0.17	<0.001	0.95	0.94	0.08 (0.07, 0.10)	0.08
Pain Catastrophizing (PCS)	0.55 (<0.001)	0.3 (0.2, 0.5)	0.14	<0.001	0.0 (0.0, 0.1)	0.10	0.002	0.93	0.93	0.09 (0.08, 0.10)	0.11
Hypervigilance (PVAQ-8) [a]	0.48 (<0.001)	−1.2 - 0.4	−0.08	0.064–0.842	0.0–0.1	0.10	0.012–0.892 [a]	0.94	0.92	0.09 (0.08, 0.11)	0.14
Pacing (POAM-P-pacing) [a]	0.03 (0.730)	−0.7 - 1.9	0.03	0.009–0.922 [c]	0.0	0.06	0.021–0.985 [b]	0.94	0.92	0.10 (0.08, 0.11)	0.10
Overdoing (POAM-P-overdoing)	−0.03 (0.753)	0.3 (0.0, 0.7)	0.06	0.059	0.0 (0.0, 0.0)	0.03	0.287	0.94	0.93	0.08 (0.07, 0.10)	0.11
	Traditional cognitive behavior therapy (n = 137)										
	Trait correlation	Effect of the putative mediator on the FIQ			Effect of FIQ on the putative mediator (β)			Fit indices			
	r (p)	*est* (95% CI)	Median Std	*p*	*est* (95% CI)	Median Std	*p*	CFI	TLI	RMSEA (90% CI)	SRMR
Avoidance behavior (PIPS-A)	0.53 (<0.001)	0.2 (0.0, 0.4)	0.08	0.070	0.1 (0.0, 0.1)	0.23	<0.001	0.94	0.94	0.08 (0.07, 0.09)	0.12
Pain Catastrophizing (PCS)	0.41 (<0.001)	0.1 (0.0, 0.3)	0.05	0.087	0.1 (0.1, 0.1)	0.24	<0.001	0.95	0.95	0.07 (0.06, 0.08)	0.12
Hypervigilance (PVAQ-8)	0.21 (0.064)	0.2 (0.0, 0.5)	0.06	0.079	0.0 (0.0, 0.1)	0.14	0.001	0.94	0.93	0.09 (0.07, 0.10)	0.12
Pacing (POAM-P-pacing) [a]	0.15 (0.227)	−3.3 - 0.3	−0.14	<0.001 - 0.981 [e]	−0.1 - 0.0	−0.21	<0.001 - 0.961 [d]	0.96	0.94	0.07 (0.06, 0.09)	0.10
Overdoing (POAM-P-overdoing)	−0.34 (0.029)	0.7 (0.2, 1.1)	0.14	0.002	0.0 (0.0, 0.1)	0.20	<0.001	0.90	0.89	0.10 (0.09, 0.11)	0.12
Number of relaxation exercises [f]	−7.34 (0.155)	−0.1 (−0.3, 0.1)	−0.06	0.276	0.0 (0.0, 0.0)	−0.01	0.815	0.92 [f]	0.91 [f]	0.09 (0.07, 0.11) [f]	0.15

Note. Change on a weekly basis. Paths were constrained so that the average effect per week was modelled. CIE, conditional indirect effect of the intercept of the putative mediator, via the path of mediation; Exp-CBT, Internet-delivered exposure-based cognitive behavior therapy; FIQ, Fibromyalgia Impact Questionnaire; PCS, Pain Catastrophizing Scale; PIPS-A, Psychological Inflexibility in Pain Scale – Avoidance subscale; POAM-P- overdoing, Patterns of Activity Measure – pain, short form – Overdoing subscale; POAM-P-pacing, Patterns of Activity Measure – pain, short form – Pacing subscale; PVAQ-8, 8-item Pain Vigilance and Awareness Questionnaire; T-CBT, Internet-delivered traditional cognitive behavior therapy.
For these models, the cross-lagged regression paths and the autoregressive paths were not constrained to be equal over time.
[a] Significant at alpha = 5% for week 1 on week 2, but not the other tests.
[b] Significant at alpha = 5% for week 6 on week 7, but not the other tests.
[c] Significant at alpha = 5% for week 3 on week 4, but not the other tests.
[d] Significant at alpha = 5% for week 3 on week 4, 5 on 6, 8 on 9, and 9 on 10.
[e] Significant at alpha = 5% for week 5 on week 6, and 7 on 8.
[f] Robust maximum likelihood due to skewed potential mediator.

mediator of the effect of Exp-CBT on catastrophizing and hypervigilance. This is an interesting finding that opens up for alternative interpretations and highlights the fact that many of the variables studied here could be part of the same complex change processes. In summary, whereas avoidance, pain catastrophizing, and hypervigilance showed promise as mediators in both Exp-CBT and T-CBT, pacing and overdoing appeared to play an important role in T-CBT only.

We also investigated conditional indirect effects, ie, whether the importance of the different mediational paths differed as a function of patient characteristics. In both Exp-CBT and T-CBT, larger mediated effects were seen with higher baseline avoidance, catastrophizing, and hypervigilance. In T-CBT but not Exp-CBT, larger mediated effects were also seen with lower baseline pacing and higher baseline overdoing. In Exp-CBT but not T-CBT, a higher level of pain intensity was associated with a larger mediated effect via reduced catastrophizing and hypervigilance. These findings indicate that depending on the symptom profile of the individual patient, change processes are likely to differ, and improvement in overall fibromyalgia severity can come about in many ways.

An intriguing finding of this study was that even though the distribution in behavioral avoidance, pain catastrophizing, and hypervigilance – key target variables derived from cognitive-behavioral theory – spanned all the way from very low to very high levels, all variables were approximately normally distributed, and this study confirmed the importance of these variables as mediators of the treatment effect; all overall moderator analyses resulted in null findings. This could indicate that it may not be important to select patients with particularly high levels of avoidance, pain catastrophizing, or hypervigilance for these to benefit from treatment. A widely cited clinical guideline (Macfarlane et al., 2017) emphasizes that psychological treatments should be targeted to patients with "mood disorders and unhelpful coping strategies" (p. 324), and several previous studies evaluating exposure-based CBT for chronic pain have underscored the importance of selecting patients on their level of catastrophizing and pain-related fear (den Hollander et al., 2016; Leeuw et al., 2008; Linton et al., 2008; Vlaeyen, de Jong, Geilen, Heuts, & van Breukelen, 2001; Woods & Asmundson, 2008). We wish to emphasize, however, that when we tested for moderation, the overall level of fibromyalgia severity (random intercept) was also included as a

Table 5
Overview of key results.

Exposure-based cognitive behavior therapy						
	A priori mediation hypothesis	Main test of mediation	Mediated effect was moderated by baseline?		Intercept was overall moderator of the outcome?	Week-by-week temporal precedence
			Moderation of *a*-path	Moderation of *b*-path		
Avoidance behavior	Yes	Yes	Yes	No	No	Yes
Catastrophizing	Yes	Yes	Yes	No	No	Yes
Hypervigilance	Yes	Yes	Yes	No	No	No
Pacing	–	No	No	No	No	No (1 out of 10 weeks)
Overdoing	–	No	No	Yes	No	No
Physical activity	Yes	No	–	–	No	–
Traditional cognitive behavior therapy						
	A priori mediation hypothesis	Main test of mediation	Mediated effect moderated by the intercept?		Intercept was overall moderator of the outcome?	Week-by-week temporal precedence
			Moderation of *a*-path	Moderation of *b*-path		
Avoidance behavior	Yes	Yes	Yes	Yes	No	No
Catastrophizing	Yes	Yes	Yes	No	No	No
Hypervigilance	–	Yes	Yes	Yes	No	No
Pacing	Yes	Yes	Yes	No	No	No (2 out of 10 weeks)
Overdoing	Yes	Yes	Yes	No	No	Yes
Physical activity	Yes	No	–	–	No	–

covariate in the model. To some extent, this opens up for alternative interpretations, such that certain sub facets of pain catastrophizing that do not overlap with overall fibromyalgia severity are predictive of a smaller treatment effect whereas other sub facets of pain catastrophizing could have other roles.

Despite the many evaluations of CBT for fibromyalgia, the number of previous trials investigating mediators of the treatment effect are scarce. The findings of this study expand on a previous randomized controlled trial of the waitlist-controlled effect of Exp-CBT on fibromyalgia severity (Hedman-Lagerlöf et al., 2018). In both that and the present study, behavioral avoidance was found to be a significant mediator of the effect of Exp-CBT, and also showed evidence of temporal precedence relative to changes in fibromyalgia severity. Similarly, other previous studies have found avoidance to be a mediator of the effect of disability in fibromyalgia and other chronic musculoskeletal pain (Murillo et al., 2022; van Koulil et al., 2011).

Our finding that pain catastrophizing mediated the effect of Exp-CBT and T-CBT on overall fibromyalgia severity is in line with previous studies that have identified catastrophizing as a mediator of the effect on functional impairment, and sometimes pain itself, in other chronic pain conditions (Trompetter, Bohlmeijer, Fox, & Schreurs, 2015; Turner, Holtzman, & Mancl, 2007), and that it appears to be a common mediator throughout various CBT protocols (Murillo et al., 2022) and non-CBT-based treatments for chronic pain conditions (Burns, Day, & Thorn, 2012; Lackner & Jaccard, 2021). Moreover, the finding that exposure-based CBT and traditional CBT have several shared mediators in the treatment of chronic pain are in accordance with research from Schemer, Schroeder, Ørnbøl, and Glombiewski (2019), who showed that effects from both exposure and CBT for chronic pain was mediated through the same treatment processes. However, Schemer et al. found no support for unique treatment processes whereas in our study, pacing and overdoing were unique mediators for T-CBT.

The finding that catastrophizing was a mediator in Exp-CBT might seem a bit contradictory as mindfulness, being an important part of the treatment, downplays the importance of formal cognitive restructuring strategies. From our point of view, it is not only possible but perhaps also plausible, that change in pain catastrophizing comes about by different mechanisms in Exp-CBT and T-CBT, respectively. In T-CBT, cognitive restructuring is used specifically to target catastrophic thoughts, whereas in Exp-CBT cognitive restructuring is not part of the treatment. In Exp-CBT, one way that change in catastrophizing may come about is by the same mechanism as in response prevention. As stated above, the specific focus of mindfulness practice in the current study is to become aware of mental strategies to avoid contact with pain, discomfort and other negative inner events, and to practice approach behavior instead of avoidance in the presence of these events. That is, practicing mindfulness may make you less inclined to act on catastrophic thoughts, which can lead to the thoughts becoming less frequent over time and also less frightening.

The finding that there was a positive correlation between homework completion and outcome was expected. However, when interpreting these results, one should bear in mind that these are within-group correlations. That is, it may be that there could be an underlying variable (eg being less depressed or having good social support) that explains both variables (both better adherence and better effect).

Of note, both protocols were CBT-based and we cannot rule out the possibility that the processes that were identified as mediators in both treatment conditions (avoidance, catastrophizing, and hypervigilance) are common to all or most behavioral interventions for chronic pain conditions. As mentioned above, there is evidence that change in catastrophizing as a process of improvement is not specific to CBT (Burns et al., 2012; Lackner & Jaccard, 2021). Avoidance, catastrophizing, and hypervigilance are proposed as central maintaining mechanisms of disability in chronic pain conditions (Crombez, Van Damme, & Eccleston, 2005; Edwards, Dworkin, Sullivan, Turk, & Wasan, 2016). One could therefore argue that any behavioral treatment that positively affects disability is likely to work through changing these processes, and thus the processes are not specific to the treatments per se, but rather a function of the maintaining mechanism of chronic pain. On the other hand, treatment protocols may differ in how effective they are in targeting these specific processes. In the present study, we did not identify any differences in overall effectiveness between T-CBT and Exp-CBT, which makes it impossible to judge if the mediated effects through avoidance, catastrophizing, and hypervigilance were specific to these protocols or rather general, non-specific, processes of change in any behavioral intervention for chronic pain.

4.1. Clinical implications

Results from the current study underline the importance of addressing avoidance behavior, catastrophizing and hypervigilance in CBT for fibromyalgia, regardless of whether the treatment is exposure-based or traditional CBT. In traditional CBT, other key processes appear to be the increase of pacing and the reduction of overdoing. Tentatively, it does not appear to be important to select patients with high levels of avoidance (at least measured using the PIPS-A), high levels of catastrophizing (at least measured using the PCS), or high levels of hypervigilance (at least measured using the PVAQ-8) for any of the treatments when overall fibromyalgia severity (FIQ) is the outcome of interest. For Exp-CBT, this study supports the implementation of exposure and mindfulness exercises, and for T-CBT, this study supports the implementation of relaxation exercises. Several findings of the present study, primarily the complete lack of variables acting as overall moderators of change in the FIQ, were unexpected and contradict the previous literature, which underlines the importance of replication.

4.2. Strengths and limitations

Strengths of this study include the relatively large sample from one of the largest clinical trials of psychological treatment ever conducted for fibromyalgia, and the use of eligibility criteria that allowed for comorbidities and medications commonly seen in the fibromyalgia population. Moreover, the online treatment format, including regular supervision of the main author of the treatment protocol (MHL and MB, respectively), allowed for high control over treatment quality and therapist adherence to the protocol. Importantly, all steps in the analysis, including a priori hypotheses and definitions of primary and secondary outcomes, were pre-registered in a public repository (ClinicalTrials.gov) and sophisticated modelling techniques were used that allowed data from all participants to be used for the analysis.

This study also had limitations. Because we found it more meaningful to formulate hypotheses on the level of the individual treatments (*What mediates the effect of Exp-CBT and T-CBT, respectively?*) than for the difference between the treatments (*What mediates the difference in effect between Exp-CBT and T-CBT?*), all mediation analyses were concerned with within-group effects only. This opens up for the threat of confounding, not only over the *b*-, but also over the *a*-path; from time in the treatment, to the potential mediator. In other words, the change observed in the mediator may not necessarily reflect a causal effect of the treatment but could also reflect regression towards the mean and spontaneous remission. On the other hand, at least a substantial proportion of the change seen is likely to have been caused by the therapies. Exp-CBT has been found to produce large waitlist-controlled reductions in fibromyalgia severity, fatigue and disability in a previous fibromyalgia trial (Hedman-Lagerlöf et al., 2018); which should be interpreted in light of the fact that fibromyalgia has a relatively low rate of notable clinical improvement over a three-month timeline. Similarly, T-CBT has been found to produce waitlist-controlled improvements in catastrophizing, control over pain and ability to decrease pain (Buhrman et al., 2004). Another limitation relates to the great difficulty of, even using best-practice statistical methods, testing for temporal precedence of change in the mediator relative to change in the outcome. As in all studies, we collected data at a certain time interval (in our case once each week), which means that our analyses of temporal precedence pertain to week-by-week time-lagged effects only. Conceivably, even when change in a potential mediator does not systematically precede change in the outcome on a week-by-week basis, an analogous relationship may very well be present if studied another time interval (such as days, hours, or minutes). It should also be noted that there is an ongoing debate over which statistical modeling techniques are to be preferred for the study of time-lagged effects, and how such effects should be interpreted (eg, [36]). A third limitation is that this study was entirely reliant on self-report questionnaires as opposed to objective measures. Future studies could for example attempt to measure behavioral avoidance using electronic devices, such as the extent to which participants, in real time, report engaging in activities in milieus previously avoided. Another possibility is to make use of experimental paradigms to measure objective hypervigilance or reactivity to pain. Fourth, pertaining to the choice of outcome variable, it is possible that we would have seen different effects of the mediating variables if we had looked at its effect on the different subscales (fatigue, pain, function, etc.) rather than the composite measure. However, FIQ is a well-known measure of fibromyalgia severity capturing several symptom domains that patients with fibromyalgia find relevant. Fifth, we lacked a formal measurement of treatment integrity and cannot therefore rule out the possibility of therapist drift and/or contamination between the two treatment protocols. Nevertheless, all therapists were under close supervision of experts in T-CBT (MB) and Exp-CBT (MHL), which may have mitigated these issues. Lastly, although all participants reported having received a fibromyalgia diagnosis from a physician, there was no formal validation of diagnosis in the study, hence we cannot be absolutely certain that all participants met diagnostic criteria for fibromyalgia at the time of the study. However, it should be noted that the study sample scored relatively high on the FIQ at baseline (58.5 for the whole group), which could be compared to the average fibromyalgia patient who scores about 50 (Bennett, 2005).

4.3. Conclusions

Pain-related avoidance behavior, catastrophizing, and hypervigilance are all mediators of treatment effect in exposure-based and traditional CBT for fibromyalgia. Pacing and overdoing appear to be mediators specific to traditional CBT. We encourage further investigations into the processes of psychological treatments for fibromyalgia.

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CRediT authorship contribution statement

Maria Hedman-Lagerlöf: Writing – review & editing, Writing – original draft, Software, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Monica Buhrman:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Erik Hedman-Lagerlöf:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Brjánn Ljótsson:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Erland Axelsson:** Writing – review & editing, Writing – original draft, Software, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Erik Hedman-Lagerlof reports a relationship with Hedman-Lagerlöf och Ljótsson Psykologi AB that includes: board membership and equity or stocks. Brjann Ljotsson reports a relationship with Hedman-Lagerlöf och Ljótsson Psykologi AB that includes: board membership and equity or stocks. EHL, BL, and EA have co-authored a self-help book for pathological health anxiety that is based on exposure-based cognitive behavior therapy, and for which they receive royalties. BL and EHL are members of the editorial board of the Journal. If there are other authors,

they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data used in this study are not publicly available. Reasonable requests may be directed to the corresponding author, and will be considered on a case-by-case basis, in accordance with GDPR.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brat.2024.104546.

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