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Approach as a key for success: Reduced avoidance behaviour mediates the effect of exposure therapy for fibromyalgia

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ABSTRACT

Fibromyalgia (FM) is a prevalent chronic pain disorder associated with large suffering and substantial societal costs. Pain-related avoidance behaviour and hypervigilance to bodily symptoms are common in FM and contribute in maintaining and exacerbating the disorder. Exposure therapy targeting avoidance behaviours and hypervigilance has shown promise in the treatment of FM. The present study investigated mediators of treatment outcome in exposure therapy for FM. We used data from a randomised trial, where 140 participants were allocated to 10-week internet-delivered exposure therapy or to a waiting-list control condition. The main outcome variable (FM symptoms) and the hypothesized mediators (FM-related avoidance behaviour, mindful non-reactivity and FM-related worry) were measured weekly throughout treatment. Mediation analyses were conducted using linear mixed effects models with bootstrap replication and time-lagged analysis. Results indicated that all three process variables were significant mediators of FM severity. However, in the time-lagged analyses, only FM-related avoidance behaviour displayed a unidirectional relationship over time with FM symptoms, suggesting a causal effect. Thus, results illustrate that changes in avoidance behaviour mediate the outcome of exposure on FM symptoms, which implies that avoidance behaviour is an important treatment target in exposure therapy.

1. Introduction

Fibromyalgia (FM) is a common chronic pain condition that often leads to functional impairment and high levels of significant distress (Epstein et al., 1999; Fietta, Fietta, & Manganelli, 2007; Hudson, Goldenberg, Pope, Keck, & Schlesinger, 1992; Queiroz, 2013). Pharmacological treatments for FM are normally insufficient and, among psychological treatments, cognitive behaviour therapy (CBT) has shown promising results in some studies (Hsu et al., 2010; Montero-Marin et al., 2017; Nicassio et al., 1997; Thieme, Gromnica-Ihle, & Flor, 2003), but there is limited empirical support for its efficacy (Nüesch, Hauser, Bernardy, Barth, & Jüni, 2013).

Avoidance of pain and distress has been shown to be a central maintaining factor in cognitive-behavioural models of chronic pain, e.g., the fear-avoidance (FA) model (Vlaeyen & Linton, 2000). In an attempt to describe how some individuals with musculoskeletal pain develop and maintain a chronic pain disorder, the FA model stipulates that pain-related fear elicits avoidance of physical activity and hypervigilance toward pain symptoms, which results in functional disability and more pain. Given the importance of avoidance in exacerbating fibromyalgia, treatment that targets this behavioural pattern ought to be effective in reducing fibromyalgia symptoms.

Our research group has developed and evaluated an exposure treatment for FM (Hedman-Lagerlöf et al., 2018; Ljótsson et al., 2014). The treatment is based on learning theory and the FA model, and holds the assumption that pain and other distressful FM symptoms are partly maintained and exacerbated by generalized avoidance. During treatment, systematic and repeated exposure to both external (e.g., certain activities, movements or situations) and internal (e.g., pain and other aversive bodily sensations) stimuli is combined with systematic attention training in the form of mindfulness exercises to prevent covert avoidance (e.g., distraction). Results from our recently published randomised trial showed that internet-delivered exposure therapy (iExp) yielded significant decreases in FM symptoms compared to WLC, with

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large between-group effect sizes ($d = 0.90$ on the main outcome measure) (Hedman-Lagerlöf et al., 2018). The aim of the treatment is thus to reduce avoidance behaviour and symptom hypervigilance through exposure and mindfulness exercises, in order to decrease symptom severity and disability. However, the specific processes that actually contribute to the treatment effects are not known.

Investigating mediators of treatment outcome is a way of exploring treatment processes (Kazdin, 2009; MacKinnon, Fairchild, & Fritz, 2007), and may as such provide support for a new treatment concept. Two previous studies of psychological treatment targeting avoidance in FM have investigated avoidance as a potential treatment mediator (van Koulil et al., 2011; Wicksell et al., 2013). Both studies found that reduced avoidance mediated treatment outcome, but employed methods that are not well-suited to assess mediation. More specifically, the study by van Koulil et al. (2011) used pre- and post-treatment assessments only and was therefore unable to establish the temporal criterion (i.e., that a change in the mediator precedes a change in outcome), which is one prerequisite for mediation (Kazdin, 2007; 2009). The study by Wicksell et al. (2013) used a design where the mediator was measured using pre-to post change scores, and the outcome through pre-to follow-up change scores. This design cannot detect whether changes in the mediator and the outcome are correlated and occur gradually during the treatment. To explore mediation taking the temporality aspect as well as potential correlated and gradual changes into consideration, it has been recommended that the suggested mediator and the outcome are both assessed frequently with tight intervals and simultaneously during treatment (Hesser, 2015). This also enables the detection of a unidirectional relationship (i.e., that the mediator has a preceding effect on the outcome but not the other way around (Singer & Willett, 2003); and generates higher data resolution, which increases statistical power (Muthén & Curran, 2004; Raudenbush & Bryk, 2002). To summarize, we need to know not only what variables affects outcome, but also in what order changes occur and whether this impact is unidirectional or reciprocal.

In the present study, we aimed to investigate tentative mechanisms of change of this new exposure treatment for FM, based on our previously conducted outcome trial where data was collected continuously during treatment. We tested three theoretically potential mediators: FM-related avoidance behaviour, mindful non-reactivity and FM-related worry. Below, these three constructs are described in more detail and how they might relate to exposure treatment.

1.1. FM-related avoidance behaviour

Patients with chronic pain tend to avoid activities associated with pain and distress, which has been shown to contribute the maintenance of pain and disability (Crombez, Vervaet, Baeyens, Lysens, & Eelen, 1996; McCracken, 1997; Vlaeyen & Linton, 2012; Zetterqvist, Holmström, Maathz, & Wicksell, 2017). Similar avoidance patterns have been observed in patients with FM (Nijs et al., 2013). Avoidance may serve as short-term relief in patients suffering from chronic pain, but it is paradoxically linked to increased pain intensity, hypervigilance, and increased disability (Geisser, Haig, & Theisen, 2000; Goubert, Crombez, Eccleston, & Devulder, 2004; McCracken, 1997; McCracken & Eccleston, 2012; Prkachin, Schultz, & Hughes, 2007). FM-related avoidance behaviour may be overt (e.g., avoiding strenuous physical activity) or covert (e.g., mental distraction, worry and rumination) (Flink, Boersma, & Linton, 2013), and its function is to avoid not only pain, but also other aversive FM symptoms (e.g., fatigue). As mentioned above, decreasing FM-related avoidance behaviour is considered a key change process to reduce hypervigilance towards symptoms, which in turn may lead to symptom reduction.

1.2. Mindful non-reactivity

Mindful non-reactivity is a core aspect of mindfulness and reflects the observation of thoughts, emotions and bodily sensations without trying to alter them. This is a relevant therapeutic target against the backdrop that FM patients seem to display higher levels of hypervigilance to pain and other aversive bodily symptoms than other chronic pain patients (McDermid, Rollman, & McCain, 1996a; Rollman & Lautenbacher, 1993). Practicing mindful non-reactivity could theoretically counteract this process, and thereby lead to a decreased attention to, and perception of, aversive symptoms. Furthermore, to be mindfully present can be used as a means to prevent covert avoidance (e.g., worry, distraction), and is in itself an exposure to pain and other aversive symptoms (Treanor, 2011). Indeed, empirical studies have shown that mindfulness training reduces worry (Roemer, Orsillo, & Salters-Pedneault, 2008) and enhances willingness to undergo exposure (Arch & Craske, 2006; 2010).

1.3. FM-related worry

FM-related worry involves catastrophizing, worry and rumination about FM. Catastrophizing is a set of negative cognitive and emotional processes involving rumination and the interpretation of pain as having major negative consequences, and is associated with increased pain and dysfunction (Sullivan et al., 2001). In patients with FM, catastrophizing is strongly correlated with increased attention to pain (Roelofs, Peters, McCracken, & Vlaeyen, 2003) and greater hypervigilance to bodily sensations (McDermid, Rollman, & McCain, 1996b; Peters, Vlaeyen, & van Drunen, 2000). Moreover, patients with FM exhibit higher levels of anxiety, worry and anger rumination than other chronic pain patients (Ricci et al., 2016). Common psychological models conceptualize worry as a strategy to avoid cognitive and emotional distress (Behar, DiMarco, Hekler, Mohlman, & Staples, 2009), and within learning theory worry and rumination have been conceptualized as covert avoidance behaviours (Borkovec, 1994; Borkovec, Alcaine, & Behar, 2004; Martell, Addis, & Jacobson, 2001). Worry has also been successfully treated with exposure therapy (see for example Andersson et al., 2016). From our viewpoint, FM-related worry serves to avert attention from pain and other FM symptoms, hence serving as a potential target for exposure. In the present treatment, FM-related worry was targeted by using mindfulness exercises as a competing response, i.e., by labelling it as worry and describing it in an observing, matter-of-fact style.

In summary, changes in FM-related avoidance behaviour, mindful non-reactivity and FM-related worry are potential mediators of treatment outcome in exposure therapy with elements of mindfulness for FM. Knowledge about processes that underlie treatment outcome is important to develop more precise treatments targeting the specific problems in FM, and could also serve as a guide to promising areas for future investigation.

1.4. Objective

The aim of the present study was to evaluate the temporal relation between three potential mediators of change and the outcome variable in a previously reported RCT of exposure therapy for FM (Hedman-Lagerlöf et al., 2018), and further, to investigate whether there was a unidirectional causal relationship between the mediators and outcome. Our hypothesis was that improvements in FM symptoms would be mediated through FM-related avoidance behaviour, mindful non-reactivity and FM-related worry. Given the limited prior research in this area, no hypotheses were made regarding the relative significance and strength of each of the mediators.

2. Method

2.1. Design

This study used data from a randomised controlled trial comparing internet-delivered exposure therapy (iExp) to a waitlist control (WLC).

As reported previously (Hedman-Lagerlöf et al., 2018), the study included 140 adult participants diagnosed with FM. The outcome and putative mediators were assessed before treatment and weekly during treatment at a total of eleven assessment points. All participants provided informed consent. The trial was approved by the regional ethics review board in Stockholm, Sweden, and registered at ClinicalTrials.gov (registration ID: NCT02638636).

2.2. Sample and setting

Adults (≥18 years) within the general community in Sweden with a confirmed FM diagnosis were recruited through self-referral, and went through eligibility screening and a telephone interview to ensure eligibility. The typical participant was female (n = 137, 98%), with a mean age of 50.3 years (SD = 10.9), and a mean duration since obtaining the FM diagnosis of 10.1 years (SD = 7.5). A detailed description of inclusion procedure and eligibility criteria has been previously reported (Hedman-Lagerlöf et al., 2018).

2.3. Measures

2.3.1. Outcome

The Fibromyalgia Impact Questionnaire (FIQ; Burckhardt, Clark, & Bennett, 1991) is a ten-item self-rated questionnaire that assesses FM symptoms and their impact on the patient. Items include questions regarding FM symptoms, physical functioning and work loss. All items concern the last week, and the sum score ranges from 0 to 100 where a higher score indicates greater severity and impact of FM. The FIQ has demonstrated good construct validity, is regarded as a sensitive index of change in FM-related symptomatology, and discriminates well between FM and other chronic pain problems (Burckhardt et al., 1991). The internal consistency in the current sample at baseline was good (Chronbach's α = 0.75).

2.3.2. Mediators

2.3.2.1. FM-related avoidance behaviour. We used the avoidance subscale of The Psychological Inflexibility in Pain Scale (PIPS; Wicksell, Renöfält, Olsson, Bond, & Melin, 2008) as a measure of external and internal FM-related avoidance behaviour. PIPS is a self-rated questionnaire that was developed as a process measure in acceptance and commitment therapy for chronic pain patients. Out of a total of 12 items scored between 1 ("never true") to 7 ("always true), 8 items belong to the avoidance subscale measuring the self-rated tendency to engage in certain behaviours that lead to avoidance of pain and related distress. The measure has demonstrated good construct validity, test-retest reliability (Wicksell et al., 2008), and an ability to capture indirect effects (Wicksell, Lekander, Sorjonen, & Olsson, 2010a; Wicksell, Olsson, & Hayes, 2010b), which supports its use in mediation research. The internal consistency in the present study was good (Cronbach's α = 0.91).

2.3.2.2. Mindful non-reactivity. Mindful non-reactivity was assessed using the non-reactivity subscale of the Five Facet Mindfulness Questionnaire (FFMQ; Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006). The FFMQ non-reactivity scale (FFMQ-NR) measures the tendency to allow thoughts and emotions to come and go without getting caught up in them. Confirmatory factor analyses have demonstrated that mindful non-reactivity is a distinct facet of mindfulness and the FFMQ-NR subscale has been shown to be negatively correlated with experiential avoidance (r = −.39), difficulties with emotion regulation (r = −0.36), and psychological symptoms (r = −0.31) (Baer et al., 2006). The internal consistency in the present study was good (Chronbach's α = 0.89).

2.3.2.3. FM-related worry. FM-related worry was measured using the Pain Reactivity Scale (PRS; Klinga, Olsson, & Wicksell, 2010), a self-report instrument developed as a measure of pain reactivity (i.e., to react with worry or rumination) in chronic pain patients. The instrument contains 5 items, rated using a 5-point Likert scale ranging from 1 ("never") to 5 ("always"). Originally developed for pediatric populations, it has also been used in adolescent and adult populations (Kanstrup et al., 2016; Ljótsson et al., 2014). Analyses indicate that PRS has satisfactory psychometric properties, correlates with the Psychological Inflexibility in Pain Scale, and explains a substantial amount of variance in pain-related functioning (Klinga et al., 2010). The internal consistency in the present study was good (Cronbach's α = 0.88).

2.4. Treatment conditions

2.4.1. Internet-delivered exposure therapy

The treatment protocol has previously shown to be feasible, acceptable and preliminary efficacious for FM in an open pilot trial (Ljótsson et al., 2014), and in the randomised trial from which data for the present study were collected (Hedman-Lagerlöf et al., 2018). The treatment is text based and divided into 8 modules to which the participant gains gradual access by completing homework assignments. Throughout treatment the participant has continuous contact with an online therapist, whose main function is to guide the participant in how to plan and conduct exposure, provide positive reinforcement, and help problem solve when needed. Therapists responded to messages within 24 h on weekdays. On average, therapist spent 2.9 h per participant (SD = 2.1), and the average participant-therapist conversation amounted to 50 messages including homework reports (participants: 28 messages, therapists: 22 messages). The overarching treatment strategy is exposure to avoided situations and stimuli that elicit FM-related distress. Exposure exercises are based on an individual behaviour analysis and cover (a) refraining from avoidance behaviour (e.g., using analgesics, heat pads or other aids, excessive use of symptom-contingent resting), including covert behaviour (e.g., worry, distraction), and (b) approaching situations or behaviours normally avoided (e.g., wearing certain clothes or shoes, mindful observation of FM symptoms, planning social activities and pursuing these regardless of symptom level).

Throughout the treatment systematic attention training in the form of mindfulness exercises are used, both as a means to facilitate exposure (i.e., to refrain from distraction, worry and other covert avoidance behaviour) and as an interoceptive exposure in itself. Participants are also given instructions on how to use mindfulness during exposure to help counter distraction and impulses to abort the exposure. The treatment manual is further described in the main outcome study (Hedman-Lagerlöf et al., 2018).

2.4.2. Waitlist control

The participants who were randomised to WLC were asked not to engage in other concurrent psychological treatments during the waitlist period. After the post-treatment assessment, WLC participants were offered the same exposure treatment as in the experimental condition.

2.5. Data analyses

Analyses were based on the 11 weekly measures of the FIQ (outcome), the PIPS-Avoid, FFMQ-NR and the PRS (putative mediators) during treatment, with assessment points at pre-treatment, post-treatment and nine weekly assessments during treatment. All analyses were performed in R (R Foundation for Statistical Computing, 2015) using linear mixed modelling and restricted maximum likelihood estimation, which utilizes all available data and yields conservative estimates of standard errors (Galecki & Burzykowski, 2013). All models included random intercepts and random slopes were added if log-likelihood ratio tests indicated model improvement.

Table 1
Results of the single mediator models analyses. Estimates with bootstrapped confidence intervals (CI).

Mediator	*a*-path (95% CI)	*b*-path (95% CI)	*ab* product (95% CI)	*c′*	Proportion mediated effect
FM-related avoidance behaviour	−1.00 (−1.28; −0.74)	0.85 (0.64; 1.05)	−0.85 (−1.21; −0.53)	−1.07 (−1.64; −0.47)	.45 (.29; .67)
Mindful non-reactivity	0.37 (0.22; 0.52)	−0.92 (-1.27; −0.62)	−0.34 (−0.56; −0.18)	−1.61 (−2.23; −1.00)	.18 (0.09; 0.31)
FM-related worry	−0.66 (−0.86; −0.44)	1.20 (1.00; 1.41)	−0.79 (−1.09; −0.48)	−1.13 (−1.69; −0.58)	.42 (.28; .59)

Note: In all analyses, the outcome measure of fibromyalgia symptoms was the Fibromyalgia Impact Questionnaire (FIQ). *ab* product = mediated effect. *c′* = direct effect controlling for the mediated effect. The proportion of the mediated effect was defined as the ratio of the *ab* product to the total effect, i.e., the interaction effect of time by group on the outcome. FM-related avoidance behaviour measured by Psychological Inflexibility in Pain Scale-Avoidance subscale, mindful non-reactivity measured by Five Facets of Mindfulness Questionnaire-Non-Reactivity subscale, and FM-related worry measured by Pain Reactivity Scale, respectively.

2.5.1. Mediation analysis

Mediation analyses were performed according to the Preacher and Hayes (Preacher & Hayes, 2008) framework. First, we investigated possible mediators of treatment outcome, which was done by regression analyses estimating four paths: the *a*, *b*, *c,* and *c′* (*c* prime) paths connecting three variables; the independent (the *X* variable), the mediator (the *M* variable) and the outcome (the *Y* variable) (Baron & Kenny, 1986; MacKinnon et al., 2007). In the present study, the independent variable *X* was the group * time interaction effect (the differential development during treatment period between treatment and control group), the outcome variable *Y* was the weekly rating on the FIQ and the three putative mediators M_1, M_2 *and* M_3 were weekly ratings on the PIPS-avoid, PRS and the FFMQ-NR, respectively (absolute scores for all variables). The first step estimated the effect of the treatment on outcome (the *c*-path or *X→Y* relationship). The second step investigated the *a*-path or the *X→M* relationship, i.e., the effect of intervention on the mediators. The third step investigated the *b*-path or the *M→Y* relationship, i.e., effect of the mediators on the outcome FIQ while controlling for the effect of treatment. The effect of the treatment on outcome not explained by the mediator (the *X→Y* relationship) constitutes the *c′* path. Finally, we estimated the *ab* product, i.e., the indirect treatment effect, by multiplying the *a*- and *b*-coefficients (Preacher & Hayes, 2008). The criterion for mediation was that a bootstrapped 95% confidence interval (CI) of the *ab* product did not include the zero. The CIs of the *a*- and *b*-path and the *ab* product was obtained by 5000 bootstrap replications, clustered on participants, using the bias-corrected and accelerated CI calculation (Efron & Tibshirani, 1993).

All mediators were first analysed in single mediator models, and then evaluated simultaneously in a multiple mediator model, to account for possible covariance between the mediators (Preacher & Hayes, 2008). A multiple mediator model is identical to a single mediator model, with the difference that the *a*-paths are calculated for the mediators in separate analyses, while the *b*-paths (controlling for the independent variable *X*) are all calculated together in one model. The *ab* products are calculated both separately for each of the mediators, and as a total indirect effect, ab_{total}, i.e., the sum of the *ab* products for all three mediators. We also calculated the proportion of the total effect that was accounted for by the mediators, using the formula *ab/c* (Preacher & Kelley, 2011).

2.5.2. Time-lagged analyses

To investigate whether the relationship between mediators and outcome was consistent with a unidirectional causal relationship (i.e., if the mediator had a preceding effect on the outcome but not the reverse), time-lagged analyses were performed. A regression analysis where each week's standardized score (based on the standard deviation at the first week) on the mediators at time T was performed to predict the following week's (T + 1) score on the standardized outcome score, while controlling for the score on the outcome at week T. To control for any differential development over time between the treatment and the control group, we also included the time * group (iExp or WLC) interaction effect. The same time-lagged analyses were also performed in reversed order, i.e., where the outcome at week T was used to predict the mediator at T + 1 while controlling for the mediator at week T and the time * group interaction effect. The coefficients for the proposed mediator (in the first set of analyses) and the proposed outcome (in the second, reversed, set of analyses) were then compared. A larger coefficient for the mediator and non-overlapping 95% confidence intervals for the coefficients was interpreted as corroborating a unidirectional causal relationship.

3. Results

3.1. Data completion

The study had a total of 1540 possible observations (11 weeks * 140 participants). Data loss was low; participants completed on average 95% percent of the assessments on the outcome FIQ and the mediators PIPS-avoid, FFMQ-NR and PRS across all measurement points. Thus, the mediation analysis was based on an average of 1462 (range 1461–1464) assessments of each measure. The highest correlation between the three mediators at baseline was $r = 0.61$ (between PIPS-avoid and PRS), indicating that multicollinearity was not present between the mediators.

3.2. Mediation analyses

The change in the outcome (FM symptoms, measured by FIQ) over time as a function of treatment condition (internet-delivered exposure therapy or waitlist control), i.e., the *c*-path, was significant (estimate = −1.90 [CI -2.52; −1.2]). That is, participants in internet-delivered exposure therapy improved 1.90 points more per week on the FIQ than participants in the waitlist control group.

Results from the mediation analyses including the *a*, *b* and *ab* coefficients are presented in Table 1. Changes in the proposed mediators due to treatment (the *a*-path) was evident for all three mediators,

Table 2
Results of the multiple mediator model.

Mediator	*a*-path (95% CI)	*b*-path (95% CI)	*ab* product (95% CI)	Proportion mediated effect
FM-related avoidance behaviour	−1.00 (−1.28; 0.73)	0.41 (0.23; 0.59)	−0.41 (−0.67; −0.19)	.21 (.11; .36)
Mindful non-reactivity	0.37 (0.23; 0.51)	−0.44 (−0.75; −0.22)	−0.16 (−0.31; −0.08)	.09 (.04; .18)
FM-related worry	−0.66 (−0.88; −0.44)	0.87 (0.68; 1.07)	−0.57 (−0.81; −0.35)	.30 (.19; .45)
Total *ab* product			−1.14 (−1.52; −0.76)	.60 (.43; 86)

Note: In all analyses, the outcome measure of fibromyalgia symptoms was the Fibromyalgia Impact Questionnaire (FIQ). *ab* product = mediated effect. FM-related avoidance behaviour measured by Psychological Inflexibility in Pain Scale-Avoidance subscale, mindful non-reactivity measured by Five Facets of Mindfulness Questionnaire-Non-Reactivity subscale and FM-related worry measured by Pain Reactivity Scale, respectively.

Table 3
Results of the time-lagged analyses.

Primary analysis					Reversed analysis				
Variable	Estimate	S.E	CI (95%)	*p*-value	Variable	Estimate	S.E	CI (95%)	*p*-value
FM-related avoidance behaviour → FM symptoms	0.20	0.04	0.13; 0.28	< .0001	FM symptoms → FM-related avoidance behaviour	0.05	0.02	0.02; 0.09	.0031
Mindful non-reactivity → FM symptoms	−0.11	0.03	−0.17; −0.06	.0001	FM symptoms → Mindful non-reactivity	−0.09	0.02	−0.13; −0.04	.0005
FM-related worry → FM symptoms	0.09	0.04	0.02; 0.16	.0159	FM symptoms → FM-related worry	0.08	0.02	0.03; 0.12	.0016

Note: PIPS-avoid = Psychological Inflexibility in Pain Scale-Avoidance, FFMQ-NR = Five Facets of Mindfulness Questionnaire-Non-Reactivity, PRS = Pain Reactivity Scale, FIQ = Fibromyalgia Impact Questionnaire. PIPS-avoid measuring FM-related avoidance behaviour, FFMQ-NR measuring mindful non-reactivity and PRS measuring FM-related worry, respectively.

and in favour of the treatment group, as were the associations between mediators and outcome, controlling for the group * time interaction effect (the *b*-path). Thus, participation in iExp was associated with reduced FM-related avoidance behaviour, increased mindful non-reactivity and reduced FM-related worry, and these changes were all associated with a reduction in FM symptoms.

In the analyses of indirect effects we found that the *ab*-cross products were significant for all three mediators, i.e., none of the bootstrapped confidence intervals contained zero (see Table 1). Regarding the size of the individual mediation effects, analyses showed that changes in FM-related avoidance behaviour explained 48% of the outcome, mindful non-reactivity explained 17% and FM-related worry explained 42% of the outcome (i.e., difference in change on the FIQ between groups).

3.3. Multiple mediator analysis

Table 2 shows the results from the multiple mediator analysis. All indirect effects remained significant when the three mediators were entered into the full multiple mediation analysis. In the final model, the tree mediators together explained 60% of the outcome (i.e., difference in change on the FIQ between groups). The remaining effect of the treatment on outcome with all mediators controlled for, i.e., the *c′*-path, was significant (estimate = −0.79 [CI -1.33; −0.25]).

3.4. Time-lagged analysis

All three significant mediators were further tested in time-lagged analyses to investigate whether there was a unidirectional causal relationship between the mediators (FM-related avoidance behaviour, mindful non-reactivity and FM-related worry, respectively) and the outcome (FM symptoms). Avoidance behaviour at week T predicted FM symptoms score at week T + 1 (estimate = 0.20, [95% CI 0.13; 0.28], $p < 0.0001$) throughout the treatment period, controlling for FM symptoms at week T and the time * group interaction effect. In the reversed analysis, FM symptoms also predicted avoidance behaviour at T + 1 although to a smaller extent and with non-overlapping CIs (estimate = 0.05, [95% CI 0.02; 0.09], $p < 0.05$). For mindful non-reactivity and FM-related worry, the results were significant in both the primary and the reversed analyses and with overlapping CIs for the estimates, indicating similar strength of effects in both directions. See Table 3 for details on time-lagged analyses on all three mediators.

4. Discussion

This is, to the best of our knowledge, the first study to investigate mediators in exposure therapy for FM using weekly measurements during treatment. We found that all three process variables, i.e., FM-related avoidance behaviour, mindful non-reactivity and FM-related worry, were significant mediators of FM symptoms in internet-delivered exposure therapy and together explained 60% of the outcome. The time-lagged analysis showed that FM-related avoidance behaviour strongly predicted subsequent FM symptoms while the reversed direction was markedly weaker. This indicates a unidirectional relationship over time, which supports a model where avoidance behaviour have a causal effect on FM symptoms. Such a unidirectional relationship was not found for either mindful non-reactivity or FM-related worry, instead these constructs seem to be bidirectionally related to FM symptoms (i.e., the relationship is reciprocal), since the outcome also predicted subsequent scores on those mediators. Taken together, our results indicate that decrease in FM-related avoidance behaviour may be a key mechanism to decrease FM symptoms in exposure therapy for FM.

These findings are in line with the study by Wicksell et al. (2013), which showed that the PIPS (total scale, i.e., avoidance plus cognitive fusion subscales) mediated improvements in ACT treatment for FM, and also the study by van Koulil et al. (2011), where pain avoidance

behaviour was found to mediate improvements in physical functioning in patients scoring high on pain avoidance. The present study contributes to the field by providing analyses that allows for an adequate evaluation of the timeline criterion, i.e., the temporal relation between the putative mediator and the outcome variable.

Interestingly, the results from the current study show similarities with mediation studies within the field of irritable bowel syndrome (IBS), which is a highly prevalent comorbid disorder in FM marked by gastrointestinal pain symptoms (Hudson et al., 1992; Riedl et al., 2008). Hesser and colleagues (Hesser, Hedman-Lagerlöf, Andersson, Lindfors, & Ljótsson, 2018) demonstrated that avoidant behaviour mediated the effects of exposure therapy on gastrointestinal symptoms. A recent study (Bonnert et al., 2018) showed that reduction in avoidant behaviour, but not perceived stress, mediated changes in IBS symptoms during exposure-based CBT for adolescents. The findings of the present study are thus part of a growing body of research showing that exposure seems to achieve its effects through reduced avoidance across a range of chronic pain disorders. Notably, the present study further supports the theoretical underpinnings of exposure therapy, i.e., learning theory and the FA model. The results have clinical relevance, as they provide further evidence for the utility of exposure therapy in chronic pain, which may function as a motivator for patients.

The findings from the current study shed light on an important methodological issue that has impeded mediation studies at large, not only in the field of FM. We found that all three investigated mediators were significant in the mediation analyses, but a unidirectional relationship supporting a causal model could only be established for FM-related avoidance behaviour. This implies that not only should the mediators and outcome be assessed frequently throughout treatment, but a result indicating a significant mediator should preferably be followed up by a test of the direction of effects over time. With this being said, it should be acknowledged that it is possible that many mediator-outcome relationships may be reciprocal by nature and nevertheless be highly relevant to understand change processes. For example, exposure treatment may cause reductions in FM-related worry, which in turn leads to a reduced focus on and perception of FM symptoms, which leads to further reductions in FM worry and so forth. Although neither FM-related worry nor mindful non-reactivity were mediators of the treatment effect in this study, we cannot conclude that they are not still useful ingredients in the treatment as facilitators of exposure. Future studies are needed to reveal how these variables interact through treatment. Strengths of this study include the randomised design, a large sample yielding sufficient power and the use of weekly assessments of both putative mediators and outcome, which enabled the establishment of a correct timeline and detecting of a unidirectional effect. The present study also contributes methodologically to the field by providing analyses that allows for a better evaluation of the timeline criterion, i.e. the temporal relation between the putative mediator and the outcome variable.

Some limitations should be taken into account when interpreting the results. First, avoidance behaviour in this study was measured via self-report rather than by behavioural tasks. There may be aspects of avoidance that participants are unaware of that are not captured by the questionnaire. Thus, further studies involving more objective measures of avoidance are warranted. Second, the three investigated mediators were all theoretically coherent within the learning theory framework. One could argue that all the proposed measured mediators reflects different forms of avoidance and thus the relative specificity of them could be questioned. However, they were not highly correlated at baseline and the indirect effect of all mediators remained significant in the multiple mediator analyses, meaning that, although conceptually similar, they were not identical in a statistical sense. We view the mediators as different forms of avoidance that are targeted by different interventions (e.g., overt avoidance behaviour can be targeted by exposure while covert avoidance behaviour can be targeted by mindfulness training). The proposed mediators could also potentially interact with each other. For instance, since mindfulness practice was framed partly as a competing behaviour to covert avoidance behaviour, it is plausible that reductions in FM-related worry could be seen as an effect of an increased ability to mindfully observe and label impulses to worry and ruminate. From this perspective, mindful non-reactivity and FM-related worry are conceptually related. Future studies could benefit from comparing the active mediator found in this study with a putative mediator proposed from the theory behind another, theoretically divergent, treatment regimen. Another informative comparison would be to a variable that is *not* hypothesized to carry a mediating effect (e.g., self-efficacy). Including a competing mediator would increase the ability to test the specificity of each process variable as well as effects of general response patterns. Third, although the use of a waitlist control does have some merit in that any potential mediating effects are likely to be easier to detect than when comparing to active treatments (and thereby minimizing the risk of type II error), other treatments (e.g., physical exercise) could potentially also work through reduced avoidance. Therefore, we cannot conclude that the findings from the current study are specific to the exposure therapy protocol. Fourth, our design did not allow for precise manipulation of the mediators and investigation if that manipulation was associated with a subsequent change in FM symptoms. Caution is therefore warranted when it comes to drawing conclusions about the causal role of avoidance behaviour on FM symptoms. Future studies could evaluate different treatment protocols where each protocol specifically addresses one of the mediators and not the others.

5. Conclusions

Exposure therapy for FM reduces FM-related avoidance behaviour, which mediates a reduction in FM symptoms. Results support that successfully targeting the FM-specific pattern of avoidance behaviour may have beneficial effects on symptom severity in exposure therapy for FM.

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