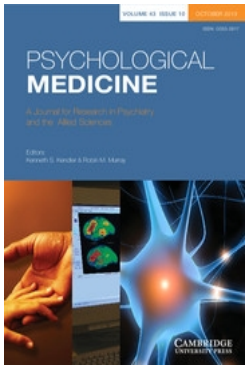

Mechanisms of change underlying the efficacy of cognitive behaviour therapy for chronic fatigue syndrome in a specialist clinic: a mediation analysis

D. Stahl, K. A. Rimes and T. Chalder

Psychological Medicine / *FirstView* Article / August 2013, pp 1 - 14
DOI: 10.1017/S0033291713002006, Published online: 12 August 2013

Psychological Medicine, Page 1 of 14. © Cambridge University Press 2013
doi:10.1017/S0033291713002006

ORIGINAL ARTICLE

Mechanisms of change underlying the efficacy of cognitive behaviour therapy for chronic fatigue syndrome in a specialist clinic: a mediation analysis

D. Stahl[1]*, K. A. Rimes[2] and T. Chalder[3]

[1] *Department of Biostatistics, Institute of Psychiatry, King's College London, UK*
[2] *Department of Psychology, University of Bath, UK*
[3] *Department of Psychological Medicine, Institute of Psychiatry, King's College London, UK*

Background. Several randomized controlled trials (RCTs) have shown that cognitive behavioural psychotherapy (CBT) is an efficacious treatment for chronic fatigue syndrome (CFS). However, little is known about the mechanisms by which the treatment has its effect. The aim of this study was to investigate potential mechanisms of change underlying the efficacy of CBT for CFS. We applied path analysis and introduce novel model comparison approaches to assess a theoretical CBT model that suggests that fearful cognitions will mediate the relationship between avoidance behaviour and illness outcomes (fatigue and social adjustment).

Method. Data from 389 patients with CFS who received CBT in a specialist service in the UK were collected at baseline, at discharge from treatment, and at 3-, 6- and 12-month follow-ups. Path analyses were used to assess possible mediating effects. Model selection using information criteria was used to compare support for competing mediational models.

Results. Path analyses were consistent with the hypothesized model in which fear avoidance beliefs at the 3-month follow-up partially mediate the relationship between avoidance behaviour at discharge and fatigue and social adjustment respectively at 6 months.

Conclusions. The results strengthen the validity of a theoretical model of CBT by confirming the role of cognitive and behavioural factors in CFS.

Received 26 September 2012; Revised 30 April 2013; Accepted 16 July 2013

Key words: Chronic fatigue syndrome, cognitive behavioural therapy, mediation, model selection, path analysis.

Introduction

Chronic fatigue syndrome (CFS) is a condition characterized by chronic disabling fatigue and other symptoms that are associated with profound disability and are not better explained by an alternative diagnosis (Sharpe & Chalder, 1994). There is now a growing body of evidence suggesting that specific treatments can improve these poor outcomes. A systematic review found that both cognitive behavioural psychotherapy (CBT) and graded exercise therapy (GET) are the most promising treatments for CFS/myalgic encephalomyelitis (ME) in secondary care (Chambers *et al.* 2006). A Cochrane review confirmed that around 40% of patients with CFS report improvements in fatigue and social adjustment if they receive CBT (Price *et al.* 2008) and this finding was confirmed more recently in a large multi-centred randomized controlled trial (RCT) (White *et al.* 2011). In a non-randomized study CBT was effective in routine clinical practice although slightly less so than in the RCT (Quarmby *et al.* 2007).

Although CBT seems to be an effective treatment for CFS, a substantial proportion of patients do not improve. Identifying mechanisms of change may elucidate ways in which treatment can be developed, tailored or optimized to suit the needs of different individuals (Laurenceau *et al.* 2007). It may also provide us with information about the clinical utility of the model on which treatment is based.

The cognitive behavioural approach involves enabling individuals to develop a consistent approach to activity, gradually increase activity, develop healthy sleep patterns and identify and challenge unhelpful cognitions (Wessely *et al.* 1989; Sharpe & Chalder, 1994), with the primary aim of improving fatigue and social adjustment. In CFS, treatment is usually initially directed at behaviour change, with cognitive strategies being introduced once a consistent approach to activity has been established.

* Address for correspondence: D. Stahl, Ph.D., Department of Biostatistics, Institute of Psychiatry, King's College London, UK
(Email: daniel.r.stahl@kcl.ac.uk)

CBT for CFS is based on a fear avoidance beliefs model about physical activity. This model supposes that unhelpful catastrophic interpretations of symptoms and excessive focus on symptoms are central in driving disability and symptom severity (Wessely *et al.* 1989; Burgess *et al.* 2011). These cognitive responses are also associated with behavioural patterns that contribute to outcome, including avoidance of activity together with excessive rest, and all-or-nothing behaviour; a pattern of pushing too hard or being overactive when feeling well and then needing to rest up or do very little for prolonged periods.

Evidence for this model is growing. Catastrophic beliefs about the consequences of increasing activity have been shown to be associated with worse disability and fatigue in a cross-sectional study of CFS (Petrie *et al.* 1995). Similarly, avoiding exercise or activity and accommodating to the illness are all associated with greater disability in patients with CFS (Antoni *et al.* 1994; Ray *et al.* 1995; Chalder *et al.* 1996). In a laboratory-based experiment, patients' beliefs about the negative effects of activity predicted lack of persistence on an exercise bike over and above physiological correlates of exertion, symptom severity and distress (Silver *et al.* 2002). This finding was confirmed in a questionnaire study that showed that kinesiophobia was associated with activity limitations/participation restrictions in patients with CFS (Nijs *et al.* 2004).

In two of the earlier CBT trials (Sharpe *et al.* 1996; Deale *et al.* 1998), patients were significantly less likely to believe that avoidance of exercise was helpful after CBT. More recently, Wiborg *et al.* (2010) looked at whether actual physical activity changed with CBT in the context of three different trials: one compared CBT with 'guided support' and 'no intervention' control conditions (Prins *et al.* 2001), one trial in adolescents compared CBT with a waiting list control (Stulemeijer *et al.* 2005), and the other compared minimal CBT (self-help materials and email contact) with a waiting list control (Knoop *et al.* 2008). Physical activity, as measured by an actometer, was not associated with CBT or fatigue in any of the trials (Wiborg *et al.* 2010). The same authors set out to examine whether avoidance of activity, avoidance of aversive stimuli and focusing on fatigue mediated the effect of CBT on fatigue and impairment (Wiborg *et al.* 2010). The results suggested that symptom focusing but not behavioural avoidance may have mediated the effect of CBT on the outcomes.

In summary, studies to date suggest that change in cognitive responses but not behavioural avoidance may mediate the effect of CBT. However, none of the studies used mediators measured before the outcomes.

We hypothesized that, as CBT in this context focuses initially on changing avoidance behaviour, fearful cognitions will at least partially mediate the relationship between change in avoidance behaviour and illness outcomes (fatigue and disability). The current study allowed preliminary investigation of this possibility. We aimed to assess the hypotheses using data collected from routine cognitive behavioural psychotherapy patients. We first wanted to investigate whether reported improvements in disability and fatigue after CBT, within the context of a large RCT (White *et al.* 2011), can be replicated in routine treatment and will remain stable for up to 1 year after treatment has finished. A similar pattern of changes to that seen for CBT in the trial are expected for putative cognitive and behavioural responses. We then assessed the proposed model using mediational analysis based on path and structural equation models (MacKinnon, 2008) and compared our proposed model with the alternative that the relationship between fearful cognition and fatigue symptoms and disability respectively is mediated by avoidance behaviour. We introduced an information theoretic approach that allowed us to compare the strength of evidence for each of the competing models (Akaike, 1973; Burnham & Anderson, 2002). Subjects were measured at several time points after finishing CBT, which enabled us to assess variables in the order that reflected the putative temporal order of the model. Although the majority of changes in CBT usually occur by the end of the treatment, longitudinal modelling can potentially also take account of small changes between post-treatment and follow-up. Longitudinal mediation models with at least three waves of measurements are preferred over cross-sectional models because they allow us to examine whether a change in one variable is more likely to produce changes in another variable than vice versa, even if the changes are small (MacKinnon, 2008). This approach allows the comparison of different partial mediation models using information criteria, which would not be possible if we used measurements taken at the same time point only. This is because such models would be structurally equivalent models and would produce the same model-data fit. Finally, in an exploratory study we aimed to generalize the results of the mediation analysis using putative latent traits of behavioural and cognitive responses.

Method

Participants

Participants were recruited from consecutive general practitioner (GP) and consultant referrals to the CFS Research and Treatment Unit at King's College

London and the South London and Maudsley National Health Service (NHS) Trust between 2002 and 2006. All participants who were treated at this Unit between 2002 and 2006 were included in the analysis. The intervention was evidence based and stable this time period.

The diagnosis of CFS was made by either an experienced consultant psychiatrist or an experienced cognitive behavioural psychotherapist according to Oxford (Sharpe *et al.* 1991) or US Centre for Disease Control case definitions. (Fukuda *et al.* 1994). The diagnosis was then confirmed by patients completing self-report questions that assessed all aspects of the case definitions. Treatment was offered to patients who fulfilled either definition according to the assessing health professional. Routine physical investigations were performed by either the patient's GP or the CFS Unit to exclude medical causes for fatigue. Eleven therapists trained specifically in cognitive behavioural psychotherapy and experienced in the treatment of CFS treated the patients. All received regular clinical supervision.

The study was approved by the Audit Committee of the Psychological Medicine Clinical Academic Group of King's Health Partners.

Outcome measures and potential mediators

All measures were completed by patients before their treatment started, at discharge from treatment (about 8 months after the start of treatment) and at 3, 6 and 12 months after discharge.

Chalder Fatigue Questionnaire (CFQ; Chalder et al. 1993)

This 11-item scale measures physical and mental fatigue. Item responses range from 'less than usual' to 'much more than usual'. Either a Likert (0, 1, 2, 3) or a bimodal (0, 1) scoring system can be used. The Likert method was used in this study. It has been shown to be both reliable and valid (Chalder *et al.* 1993; Cella & Chalder, 2010; Knudsen *et al.* 2011) and has been used in previous treatment trials of CFS (Deale *et al.* 1997; Quarmby *et al.* 2007).

Work and Social Adjustment Scale (WASA; Mundt et al. 2002)

This disability scale measures the extent to which the person's main problem of fatigue interferes with work, home management, social and private leisure activities and relationships. A Likert scoring system, ranging from 0 to 8, is used. Responses range from 'not at all impaired' (0) to 'very severely impaired' (8). Scores on the five items are added and divided by the number of items to get a total score. The scale is reliable and valid and has also been used in a previous trial of CFS (Quarmby *et al.* 2007; Cella *et al.* 2011*a*).

Cognitive Behavioural Responses to Symptoms Questionnaire (CBRSQ; Skerrett & Moss-Morris, 2006; Knudsen et al. 2011)

This scale has seven subscales. Five of the subscales measure cognitive responses to symptoms: catastrophizing (e.g. 'I think that if my symptoms get too severe they may never decrease'), damage beliefs (e.g. 'Symptoms are a signal that I am damaging myself'), symptom focusing (e.g. 'When I experience symptoms, I think about them constantly'), fear avoidance beliefs (e.g. 'I am afraid that I will make my symptoms worse if I exercise') and embarrassment avoidance (e.g. 'I am embarrassed about my symptoms'). The other two subscales measure behavioural responses: avoidance behaviour (e.g. 'I tend to avoid activities that make my symptoms worse') and all-or-nothing behaviour (e.g. 'I tend to do a lot on a good day and rest on a bad day'). The subscales are reliable and valid and were associated with fatigue and social adjustment in previous studies of CFS and multiple sclerosis (Skerrett & Moss-Morris, 2006; Knudsen *et al.* 2011.

Statistical analysis

Descriptive statistics for the 389 people who participated in the study are presented. Completers and drop-outs at discharge and at the 6-month follow-up were compared on baseline data using the t test and χ^2 test for homogeneity.

The analysis was conducted in two stages. In the first stage we investigated whether patients' scores changed during the study. We used general linear mixed models (see Brown & Prescott, 2006) to compare the outcome scores between the five measures at pre-treatment (baseline), discharge, and 3-, 6- and 12-month follow-ups. For each variable we used a mixed model with time as a fixed factor and an unstructured covariance matrix that allows unequal variances and covariances (correlations) between repeated measures. To account for the possible dependency due to therapy effects (in other words that patients treated by a particular therapist may respond in a similar manner and may no longer be assumed to act independently), we included therapist as a random factor in the model. If the time effect was significant, pairwise comparisons were performed. As an estimate of effect size we calculated the estimated mean difference between baseline and the 6-month follow-up divided by the baseline standard deviation.

To assess the sensitivity of our results to missing data we used multiple imputation (Little & Rubin, 2002). By using a large number of variables to impute missing measurements, the missing at random (MAR) assumption becomes more tenable than the mixed effect model approach (Little & Rubin, 2002). Variables used to impute missing values included gender, age, therapist and behavioural and cognitive variables at all five time points. Twenty data sets were imputed using the ICE procedure in Stata (Royston, 2005) and we reran the mixed effects model analyses.

Therapist effect

To quantify the effect of therapist on treatment outcome, we estimated the intraclass correlation coefficient (ICC) at the 6-month follow-up (Cella *et al.* 2011*b*). The ICC is the estimated proportion of therapists' explained variance, defined as the ratio of the variance attributable to the therapists to the total variance. To estimate the variances we used a conditional multi-level model with measurement at 6 months as the dependent variable, therapist as a random effect and baseline levels as a covariate to control for baseline differences. Bias-corrected and accelerated bootstrap confidence intervals (CIs) are presented around estimates.

Mediation analysis

In the second stage, we performed a path analysis to assess possible mediating effects (Judd & Kenny, 1981; Baron & Kenny, 1986; MacKinnon & Luecken, 2008). Mediation is a hypothesized causal chain in which one independent variable *X* affects a mediating variable *Y*, which in turn affects the outcome variable *Z*. If the intervening mediator *Y* explains the correlation between *X* and *Z*, we have a full mediational model. If *X* still has an effect on *Z* after including the mediator *Y* in the model, the model is consistent with partial mediation.

For each of the two outcome variables (fatigue and social adjustment), we compared full and partial mediation processes for two proposed pathways: behaviour → cognition → outcome and cognition → behaviour → outcome. We used 'avoidance behaviour' as the behavioural response and 'fear avoidance beliefs' as the cognitive variable. We used the scores of the independent variable at discharge, of the mediator at the 3-month follow-up and scores of the dependent outcome variable at the 6-month follow-up. The temporal order was chosen because the mediation model assumes that the independent variable precedes and causes the mediator, which precedes and causes the dependent variable outcome (Kraemer *et al.* 2002). We expect that changes in the outcome variables are established during CBT and only small changes are expected after discharge from CBT. However, longitudinal mediation models with at least three waves of measurements are still preferred over cross-sectional models because they allow us to explore different temporal ordering of variables in the process, even if the changes are small (MacKinnon, 2008). Such multiwave models are important for model comparisons because it is not possible to compare quantitatively the strength of support for different models using a cross-sectional approach if the models are structurally equivalent. For example, the two models 'cognition is dependent on behaviour' and 'behaviour is dependent on cognition' are very different substantively; however, the fit of the models will be identical in a cross-sectional study. In this situation, path analysis cannot resolve the issue of which model should be preferred. However, the temporal order with which the data are collected can often exclude the problem of assessing equivalent models because causal effects cannot travel backwards (Shipley, 2003). Even small changes after discharge should result in the same mediation process, which allows us to compare models with differences in the proposed temporal order using information criteria. If no changes occur after discharge, our mediation model would be identical to a cross-sectional model using measurements at discharge only and we would expect to see no differences in model fit of equivalent models. It should be noted that the longitudinal approach assumes that the mediational processes are the same during and after treatment.

Finally, for all variables we included a path from their baseline measure to control for baseline differences in the measures (ANCOVA approach; MacKinnon, 2008).

Model selection

To assess the different models we used Akaike's Information Criterion (AIC), which attempts to select a parsimonious model that best explains the data with a minimum number of estimated parameters (Burnham & Anderson, 2002; Claeskens & Lid, 2008). AIC is a measure of the goodness of fit that includes a penalty for the number of variables estimated. AIC selects the best of several competing models as the one that predicts best in a new data set. The best model is the one with the lowest AIC. Unlike model selection based on null hypothesis testing, AIC model selection enables an evaluation of the quality of other models by assessing AIC-related measures (ΔAIC_i, Akaike weights and evidence ratio). ΔAIC_i is the difference in AIC between model i and the best model. As a rule of thumb, a ΔAIC_i value of<2 times the AIC_i value of the best model has substantial support and

should be considered with the best model. A ΔAIC_i value>4 times the AIC_i of the best model has substantially less support and models with a ΔAIC_i>10 times the AIC_i of the best model can be omitted from further consideration (Burnham & Anderson, 2002). An Akaike weight is an estimate of the probability that model *i* is the best model among the candidate set of models. The evidence ratio for a given model *i* is the ratio of Akaike weights of the best model and of model *i*. Unlike Akaike weights, the evidence ratio of two models is independent of other candidate models.

Structural equation and path model assessments compare the fit of the predicted covariances matrix relative to the observed covariance matrix. This means that AIC model selection can only be used to compare non-nested models with the same set of observed variables. We therefore used the full set of observed variables in the analyses and fixed the paths that were not of interest to zero. For example, if we want to determine the AIC for the path model behaviour at discharge → cognition at 3 months → outcome at 6 months, we need to include the variables cognition at discharge, behaviour at 3 months and outcome at 6 months (and their baseline measures) in the model but constrain their paths to zero.

Model fit assessment

The goodness of fit of the models was further assessed by performing a test for lack of fit using the χ^2 goodness-of-fit statistic and assessing the Comparative Fit Index (CFI) and the root mean square error of approximation (RMSEA), which are recommended for smaller sample sizes (Fan *et al.* 1999; Kline, 2004). Support for good fit of a target model is obtained if the χ^2 goodness-of-fit test is not significant, the RMSEA value is<0.05 (adequate fit:<0.08) and the CFI is>0.95 (adequate fit:>0.90).

The final best models for fatigue and social adjustment are presented as path diagrams with standardized regression coefficients. We used Huber–White sandwich standard errors, which are robust against some failure to meet assumptions about normality and heteroscedasticity to establish CIs and statistical significance tests of direct, indirect and total (=direct +indirect) effect for each variable in the model.

Latent variable path model

The behavioural and cognitive variables can be assumed to measure more general underlying latent variables 'behavioural responses' and 'cognitive responses'. In the final exploratory analysis, we assessed whether the best model held for behavioural and cognitive variables in general by creating a composite score of the two behavioural variables (avoidance and all-or-nothing behaviour) and a latent variable for cognition using the five cognition variables (fear avoidance beliefs, catastrophizing, damage control, embarrassment avoidance and symptom focusing) as indicator variables. A latent variable for behaviour was not possible because of the small number of items. We obtained a composite score by standardizing the two variables by calculating the difference of a score and the mean of the baseline divided by the standard deviation of the baseline, and then adding up the two *z* scores for each individual (Cutter *et al.* 1999). The composite score is used as a proxy for the latent trait 'behaviour' and assumes equal contributions from each item to the latent trait. We reran the analyses of the best models using the composite score and the latent variable as the independent and mediating variables and fatigue and social adjustment respectively as the dependent outcome variable. Again, to control for baseline differences we included a path from their baseline measure for all manifest and latent variables. These paths are not shown in the figures to maintain clarity.

Multi-level modelling analyses were performed with Stata version 11.1 (StataCorp, 2007) and Amos 20 (Arbuckle, 2006) was used for path analysis. The user-written R package lavaan (Rosseel, 2012) was used for calculating robust standard errors for the best path and the latent variable models.

Results

Recruitment, demographics and follow-up attendance

Demographic data and information on the recruitment of subjects and participation in the study are summarized in Table 1. A total of 389 people (mean age 40.5 years, 82.1% white British, 72.5% women) participated in the study. Adherence to treatment, measured by the number of therapy sessions attended, ranged from 0 to 31 with a mean of 13.1. Of the 209 subjects attending therapy sessions, 95% attended more than five of these sessions. The pre-treatment session was attended by 340 (87.4%) people. Baseline data for the seven behavioural and cognitive variables were available for between 314 (avoidance behaviour) and 340 (embarrassment avoidance) people. The attendance rate decreased to 266 (68.4%) at post-treatment, 223 (57.3%) at 3 months, 195 (50.1%) at 6 months and 183 (47%) at 12 months after treatment. Thirty-six individuals (9.3%) did not attend any post-treatment or follow-up sessions.

Comparison of completers and drop-outs at 6 months

A comparison of available baseline data (behavioural and cognitive measures, age, sex, ethnicity and

Table 1. *Demographic characteristics and attendance*

Age (years) (n=346)	40.5±11.4
Gender (n=382)	
Male	105 (27.5)
Female	277 (72.5)
Marital status (n=347)	
Single	149 (42.9)
Married/living together	156 (45)
Divorced/separated	41 (11.8)
Widowed	1 (0.3)
Ethnicity (n=340)	
White	279 (82.1)
Mixed	7 (2.1)
Asian or Asian British	9 (2.6)
Black or Black British	18 (5.3)
Chinese	4 (1.2)
Other ethnic group	2 (0.6)
None given	21 (6.2)
Number of therapy sessions attended (n=209)	13.1±5.1
Attendance at:	
Pre-treatment	
Yes	340 (87.4)
No	49 (12.6)
Post-treatment	
Yes	266 (68.4)
No	123 (31.6)
3-month follow-up	
Yes	223 (57.5)
No	165 (42.5)
6-month follow-up	
Yes	195 (50.1)
No	194 (49.9)
12-month follow-up	
Yes	183 (47)
No	206 (53)
Number of assessments completed (out of 5)	3.1±1.36

Values given as mean±standard deviation or n (%).

education status) between 'refusers' and those who attended at least one follow-up session after treatment revealed a significant lower mean score in embarrassment avoidance behaviour (refusers: 14.3 *versus* others: 11.6 points, t_{338}=2.71, p=0.007, Cohen's d=0.48) A similar comparison between attendees and drop-outs at 6 months revealed small differences in mean avoidance behaviour (non-attendees: 13.7 *versus* attendees: 12.5 points, t_{312}=1.89, p=0.06, Cohen's d=0.21).

Scale reliability

Cronbach's α ranged between 0.76 and 0.94 for all scales and subscales at baseline, confirming their internal consistency (for details see online Supplementary Table S1).

Longitudinal mixed model analysis

Descriptive mean scores and standard deviations for fatigue and social adjustment and for each subscale on the CBRSQ are presented in Supplementary Table S1.

Fatigue and social adjustment (WASA)

The results of the mixed model analyses revealed significant decreases in mean fatigue and WASA scores from baseline to discharge (Fig. 1 and online Supplementary Table S2). The significant difference remained at all follow-up measures at 3, 6 and 12 months for fatigue. However, for social adjustment (WASA), a small increase from discharge to the 3-month follow-up was observed (p<0.05) and the mean score remained at a similar level afterwards. There were no significant changes in fatigue score after discharge. At 6 months the effect sizes were similar (fatigue: d=−0.57, WASA: d=−0.58).

CBRSQ subscales

The results of the mixed model analyses revealed significant decreases in the mean scores from baseline to discharge on all five subscales of cognition (fear avoidance beliefs, catastrophizing, damage control, embarrassment avoidance and symptom focusing and on both subscales of behaviour (all-or-nothing and avoidance behaviour). There was a small significant further decrease from discharge to the 12-month follow-up in catastrophizing, embarrassment, symptom focusing and all-or-nothing behaviour (all p's<0.05). For most scales effect sizes were similar at the 6-month follow-up to those reported for fatigue and social adjustment (catastrophizing: d=−0.55, symptom focusing: d=−0.49, all-or-nothing behaviour: d=−0.61, avoidance behaviour: d=−0.69, fear avoidance beliefs d=−0.68, damage control: −0.6, but the embarrassment avoidance effect was somewhat smaller at d=−0.37).

Multiple imputation sensitivity analysis

The longitudinal multi-level modelling analyses were similar after multiple imputations for missing values, which suggests that the mixed model approach with missing data is robust.

Therapist effect

To quantify the effect of therapist on treatment outcome we estimated the ICC at the 6-month follow-up. The therapist effect was estimated as zero for most measures. Only for fear avoidance beliefs and damage control was a small (~1%) but not significant effect observed (see Supplementary Table S2).

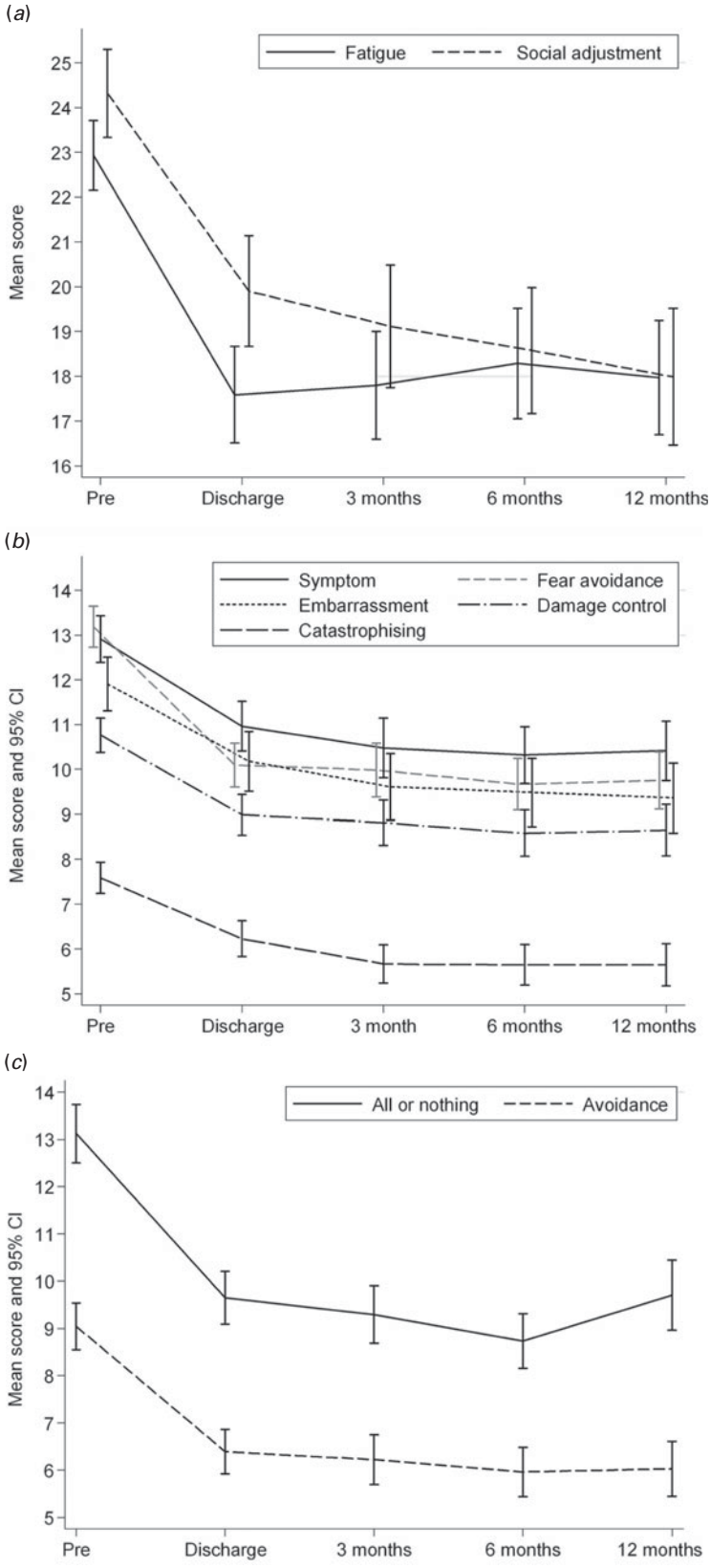

Fig. 1. Changes over time in (*a*) fatigue and social adjustment, (*b*) cognitive variables (symptom focusing, fear avoidance beliefs, embarrassment avoidance, damage control and catastrophizing) and (*c*) behavioural variables (all-or-nothing and avoidance behaviour).

Table 2. *Mediation analysis of fatigue and social adjustment with avoidance behaviour and fear avoidance beliefs (and baseline variables). AIC and AIC-related measures (ΔAIC_i, Akaike weights and evidence ratio) are presented for the four different path models for fatigue and social adjustment*

	Path model Post→ 3 months→ 6 months	Mediation model	AIC	ΔAIC_i	Likelihood	Akaike weights	Evidence ratio
Fatigue (F)	A→FA→F	Partial	493.6	0	1	0.957	1
	A→FA→F	Full	499.9	12.6	0.002	0.002	552.5
	FA→A→F	Partial	506.2	6.3	0.043	0.041	23.3
	FA→A→F	Full	517.8	24.3	<0.0001	<0.0001	185 535
Social adjustment (SA)	A→FA→SA	Partial	514.7	0	1	0.851	1
	A→FA→SA	Full	521.8	7.1	0.029	0.025	34.7
	FA→A→SA	Partial	518.6	3.9	0.143	0.121	7.02
	FA→A→SA	Full	525.6	10.9	0.004	0.004	232.2

AIC, Akaike's Information Criterion; ΔAIC_i, the difference in AIC between model *i* and the best model; A, avoidance behaviour; FA, fear avoidance beliefs.

Mediation analysis

Because there were no, or only negligible, therapist effects, these effects were not incorporated in the following analyses. The mediation analysis revealed that the path 'behaviour→cognition→outcome', with cognition as a mediator between behaviour and outcome, explained the data better than behaviour as a mediator between cognition and both outcome variables, fatigue and social adjustment (Table 2). For both fatigue and social adjustment, a partial mediation model was selected as the best model.

For fatigue, the partial model with fear avoidance beliefs as mediator between avoidance behaviour and fatigue as outcome had large AIC differences (6.3) compared to the path model where avoidance behaviour mediated fear avoidance beliefs. In addition, the evidence ratio suggests that the model with fear avoidance beliefs as a mediator is 23 times more likely to be the best model than the partial model with avoidance behaviour as a mediator (Table 2).

Similar results were obtained for the social adjustment models: the partial model with fear avoidance beliefs as mediator between avoidance behaviour and fatigue as outcome had an AIC 3.9 points lower and is seven times more likely to be the best model than the partial model with behaviour as a mediator.

Fig. 2*a* shows the best model for fatigue and social adjustment with standardized regression coefficients. The arrows reflect the hypothesized relationships between variables. Standardized regression coefficients are shown next to each path. This figure shows that avoidance behaviour at discharge was positively associated with fear avoidance beliefs at 3 months and fatigue and social adjustment at 12 months. Changes in the mediator 'fear avoidance beliefs' were also positively associated with the outcome variables fatigue and social adjustment respectively. All direct, indirect and total effects were significant. Table 3 shows details of the results of the statistical analyses. Fit indices for the two path models were good for fatigue [χ^2_6=10.1, p=0.12, RMSEA=0.042 (95% CI 0–0.085), CFI=0.985] and adequate for social adjustment [χ^2_6=18.4, p=0.002, RMSEA=0.079 (95% CI 0.04–0.12), CFI=0.964].

Composite score and latent variable mediation model

The partial mediation models for fatigue and social adjustment were replicated using a composite score for behaviour and modelling cognition as a latent variable with the five cognitive response variables as indicator variables (Fig. 2*b*). The standardized direct and indirect effects were similar or slightly larger than those in the previous models and again significant (standardized indirect effect for fatigue: b=0.16, p=0.012, for social adjustment: b=0.17, p=0.003, p values for all direct effects<0.01). Fit indices for two models were adequate [fatigue (χ^2_{55}=72.1, p=0.06, RMSEA=0.076 (95% CI 0.05–0.10), CFI=0.90] and nearly adequate for social adjustment [χ^2_{55}=88.7, p=0.003, RMSEA=0.085 (95% CI 0.06–0.12), CFI=0.89].

Discussion

In this study we assessed the theoretical foundations of a CBT model for CFS, namely that fearful cognitions would at least partially mediate the relationship between change in avoidance behaviour and illness outcomes (fatigue and disability). As expected from previous RCTs (White *et al.* 2011), which established

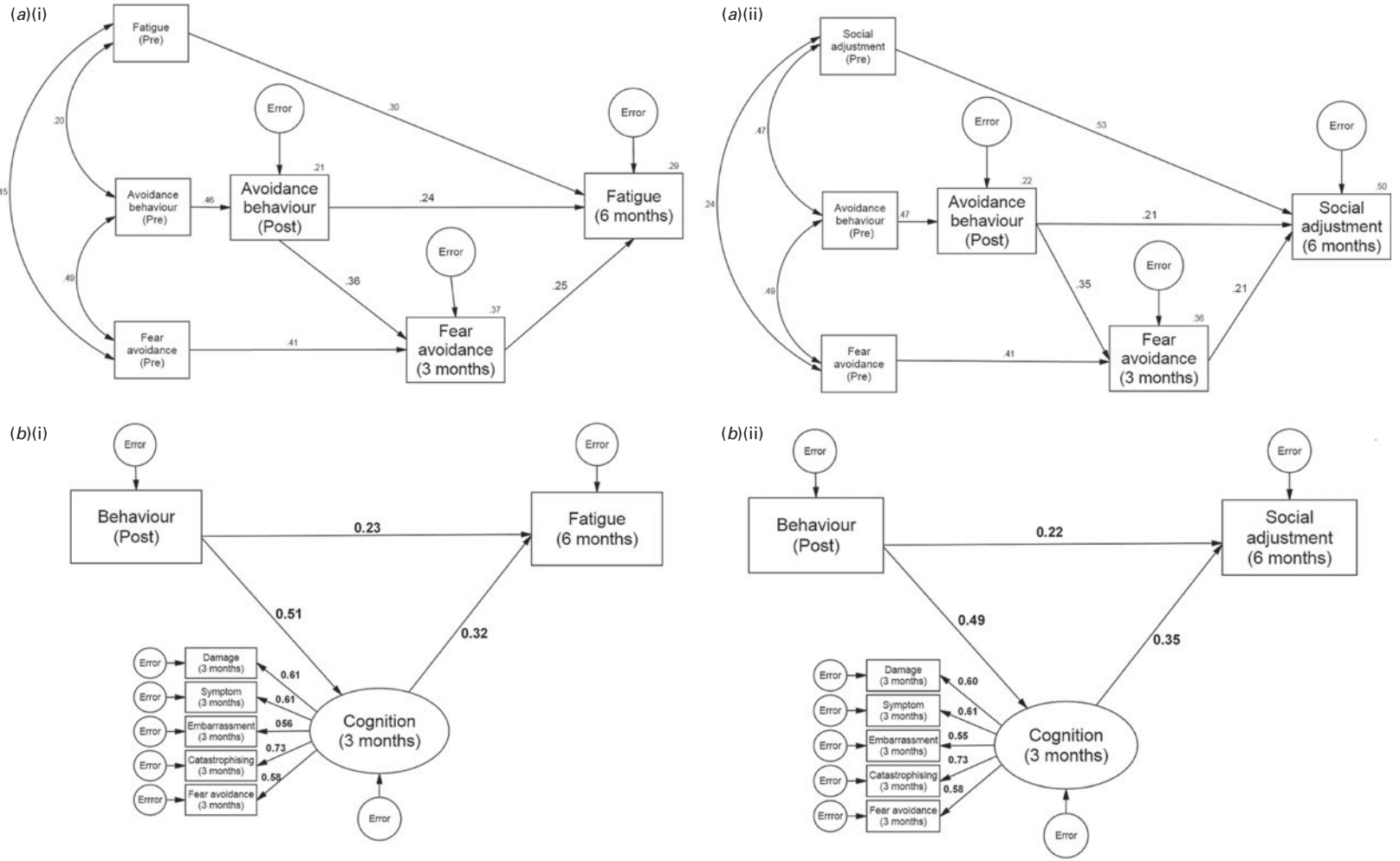

Fig. 2. Best models of mediation analysis. (*a*) Best model for (i) fatigue and (ii) social adjustment. Full mediation model with behaviour (avoidance behaviour) at discharge (post-treatment) as the independent variable and cognition (fear avoidance beliefs) at 3 months as the mediator. Single-headed arrows reflect hypothesized relationships between variables. Standardized regression coefficients are shown next to each path. Double-headed arrows represent covariation between two variables. The correlation coefficient is shown next to the path. The explained variance of endogenous variables is on the top right on the rectangle. Circles represent error terms. Pre-treatment measurements of all three variables were included to control for baseline differences. (*b*) Best latent variable model for (i) fatigue and (ii) social adjustment. Full mediation model with behaviour (composite score of avoidance and all-or-nothing behaviour) at discharge (post-treatment) as the independent variable and the latent variable 'cognition' (circle with the five indicator variables: symptom focusing, fear avoidance beliefs, embarrassment avoidance, damage control and cathastrophizing) at 3 months as the mediator. Single-headed arrows reflect hypothesized relationships between variables. Standardized regression coefficients are shown next to each path. Circles represent error terms. Pre-treatment measurements of all three observed and latent variables were included to control for baseline differences but are not shown for reasons of clarity.

Table 3. *Best mediation models: standardized regression coefficients (95% robust CIs) and z value and robust p values for significance tests for direct, indirect and total effects for the mediation models for fatigue and social adjustment (WASA)*

	Fatigue				Social adjustment			
	B (95% CI)	Standardized effect	*z*	*p*	*B* (95% CI)	Standardized effect	*z*	*p*
Direct effects								
Avoidance at 3 months→FA beliefs at 6 months	0.36 (0.202–0.519)	0.36	4.45	<0.001	0.347 (0.186–0.509)	0.35	4.22	<0.001
Avoidance at 3 months→Fatigue/Social adjustment at 9 months	0.471 (0.086–0.857)	0.24	2.4	0.016	0.483 (0.11–0.855)	0.21	2.54	0.011
FA beliefs at 6 months→Fatigue/Social adjustment at 9 months	0.484 (0.153–0.815)	0.25	2.87	0.004	0.502 (0.164–0.84)	0.21	2.92	0.004
Indirect effects								
Avoidance at 3 months→Fatigue/Social adjustment at 9 months	0.174 (0.034–0.314)	0.09	2.44	0.015	0.174 (0.035–0.314)	0.075	2.45	0.014
Total effects								
Avoidance at 3 months→Fatigue/Social adjustment at 3 months	0.646 (0.31–0.982)	0.33	3.77	<0.001	0.657 (0.32–0.995)	0.28	3.82	<0.001
Baseline effects								
Avoidance at baseline→Avoidance at 3 months	0.381 (0.271–0.491)	0.46	6.78	<0.001	0.391 (0.285–0.496)	0.47	7.28	<0.001
FA beliefs at baseline→FA beliefs at 6 months	0.443 (0.332–0.553)	0.41	7.83	<0.001	0.435 (0.324–0.546)	0.41	7.65	<0.001
Fatigue/Social adjustment at baseline→Fatigue/Social adjustment at 9 months	0.376 (0.199–0.553)	0.30	4.16	<0.001	0.62 (0.485–0.755)	0.53	8.99	<0.001

WASA, Work and Social Adjustment Scale; FA, fear avoidance; CI, confidence interval.

that CBT is an effective treatment for CFS, our study demonstrates persistent improvements in fatigue and social adjustment after routine CBT training. Changes in improvement were accompanied by similar changes in illness-related cognitive and behavioural responses. All changes remained on lower levels for 12 months. The results of the mediational analyses were consistent with our hypothesized model in which fear avoidance beliefs partially mediate the relationship between avoidance behaviour and fatigue and social adjustment respectively. There was little support for the alternative models with avoidance behaviour as a mediator between fear avoidance belief and fatigue and social adjustment respectively. However, the partial mediation effect suggests that other potential mediators should be considered in further studies. An exploratory latent trait model suggests that the observed partial mediation model generalizes to illness-related behavioural and cognitive traits.

Our results are consistent with previous findings that also suggest that cognitive processes are a mediator between behaviour and outcome. Wiborg *et al.* (2011) found that a decrease in symptom focusing on fatigue mediated the effect of CBT for CFS on fatigue and impairment. The measure of symptom focusing they used included items that could be construed as catastrophizing (e.g. 'When I feel fatigued I think that the fatigue will get worse'). In contrast to our findings, unexpectedly they did not find an effect of CBT on avoidance of activity and so did not examine whether change in avoidance mediated the effect of CBT on fatigue or impairment. The authors suggested that the needs of the pervasively passive patients were being more adequately addressed in recent trials so this modification in the treatment protocol may explain their findings. One of the key components of CBT in our study is behavioural activation, which consists of encouraging patients to adopt a more consistent approach to activity with a view to gradually increasing activity thereafter.

Given these findings, even greater emphasis should be placed on behavioural change in the early stages of treatment, which may result in greater subsequent cognitive change and superior treatment outcomes. There is some supporting evidence from other studies (e.g. the PACE trial; White *et al.* 2011), which suggests that GET is as effective as CBT. In GET, cognitions are not a specific focus of treatment but are likely to be changed indirectly. We will be reporting our investigations of mediational processes in the PACE trial in future papers. Other studies that measure mediational factors at mid-treatment, prior to the main outcomes, will help to clarify these issues.

There are considerable strengths to this study. We considered a large routine clinic sample and the measures are used routinely as they inform the therapist and ultimately the patient about progress. The specific cognitive and behavioural responses are targeted in therapy. The statistical methods used are robust and also have major advantages over simpler methods such as the Baron & Kenny (1986) approach or standard bootstrap extensions (Preacher & Hayes, 2004). In the case of missing data, path analysis models using full maximum likelihood estimation allow analysis of all available data with less restrictions on the missingness assumptions and more power than standard complete case analyses. Robust standard errors correct CIs and p values for some violations of the distribution assumptions, such as normality and heteroskedasticity. Finally, the empirical support for the different models was assessed using an information-theoretic approach. Unlike model selection based on null hypothesis testing, AIC model selection enables an evaluation of the relative support in the observed data for each model by assessing AIC-related measures (Burnham & Anderson, 2002). It is therefore not restricted to evaluating a single model, where significance is measured against some arbitrary probability threshold and quantitative comparisons between models are not possible.

The strengths have to be set against the weaknesses. First, our study was not an RCT and as such did not allow us to formally assess whether the observed changes are due specifically to CBT. However, a previous RCT has shown that CBT induces changes in our described mediators (Wiborg *et al.* 2011). Second, mediation requires temporal precedence of the outcome by the mediator and of the mediator by the mediated variable. Our cohort allowed us to model the temporal order of the proposed and alternative mediation models, which strengthens the conclusions about the causal pathway. However, the time points of measurements were not frequent enough to detect changes in behavioural responses at different time points. The main changes in all measures occurred between baseline and discharge, with few changes occurring afterwards, so that true causality could not be proven. However, the small changes allowed us to select the path 'behaviour→cognition→outcome' as the better mediation model. Our model selection approach of longitudinal mediation models provides more evidence for causality than using traditional modelling approaches. Third, the standard mediation model makes the verifiable assumption that there is no unmeasured confounder between mediator and outcome (Emsley *et al.* 2010). The good fit indicates that the model is consistent with the data, although other models might account for the data equally. As with any other mediation analysis, the results should be interpreted with caution.

Future research should include measurement of the potential mediators at more regular intervals during and after therapy; this would allow assessment of causal pathways during the establishment of changes in addition to comparison of the pathways that mediate the sustainment of the treatment outcome. Multivariate latent growth curve models (MLGMs) could then be applied for testing mediation longitudinally, that is they model longitudinal change simultaneously across multiple variables while allowing one change process to predict another (Cheong *et al.* 2003; Duncan *et al.* 2006; Carey *et al.* 2010). As CBT was not compared to any other treatment, we cannot conclude that these mediators are specific to CBT. Ideally, a gold standard RCT would be used and controls for therapist time and attention would be included in the model. An RCT would also allow an estimation of the indirect effect in the presence of unmeasured confounders using instrumental variables (Emsley *et al.* 2010). Clearly there are mechanisms of change in the context of CBT that are not yet fully understood. Focusing on changing fear avoidance cognitions along with change in behaviour in the early phases of treatment may bring about more rapid change in the desired outcomes of fatigue and social adjustment. In this setting a detailed formulation of the patient's problems is usually offered to the patient and precedes a rationale for treatment. Invariably, the rationale for treatment includes the role of cognitive and behavioural responses in perpetuating symptoms and disability. As a consequence it can be difficult to disentangle the respective contribution of cognitive and behavioural mechanisms during treatment. However, the results of this study go some way in suggesting that it is change in fearful cognitions that mediates the relationship between change in avoidance behaviour and illness outcomes.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291713002006.

Acknowledgements

The National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and King's College London provided T. Chalder salary support and D. Stahl other support.

Declaration of Interest

T.C. has published self-help books related to chronic fatigue.

References

Akaike H (1973). Information theory and an extension of the maximum likelihood principle. In *Second International Symposium on Information Theory* (ed. B. N. Petrov and F. Csaki), pp. 267–281. Akademiai Kiado: Budapest.

Antoni MH, Brickman A, Lutgendorf S, Klimas N, Imia-Fins A, Ironson G, Quillian R, Miguez MJ, van Riel F, Morgan R, Patarca R, Fletcher MA (1994). Psychosocial correlates of illness burden in chronic fatigue syndrome. *Clinical Infectious Diseases* **18** (Suppl. 1), S73–S78.

Arbuckle JL (2006). *Amos (Version 7.0)*. SPSS: Chicago, IL.

Baron RM, Kenny DA (1986). The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology* **51**, 1173–1182.

Brown H, Prescott R (2006). *Applied Mixed Models in Medicine*. John Wiley & Sons Ltd: New York.

Burgess M, Manoharan A, Chalder T (2011). Cognitive behaviour therapy for chronic fatigue syndrome in adults: Face to face versus telephone treatment; a randomised controlled trial. *Behavioural and Cognitive Psychotherapy* **20**, 1–17.

Burnham KP, Anderson DR (2002). *Model Selection and Multimodel Inference: A Practical Information-Theoretical Approach*. Springer: New York.

Carey KB, Henson JM, Carey MP, Maisto SA (2010). Perceived norms mediate effects of a brief motivational intervention for sanctioned college drinkers. *Clinical Psychology: Science and Practice* **17**, 58–71.

Cella M, Chalder T (2010). Measuring fatigue in clinical and community settings. *Journal of Psychosomatic Research* **69**, 17–22.

Cella M, Sharpe M, Chalder T (2011*a*). Measuring disability in patients with chronic fatigue syndrome: reliability and validity of the Work and Social Adjustment Scale. *Journal of Psychosomatic Research* **71**, 124–128.

Cella M, Stahl D, Reme SE, Chalder T (2011*b*). Therapist effects in routine psychotherapy practice: an account from chronic fatigue syndrome. *Psychotherapy Research* **21**, 168–178.

Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, Wallace EP (1993). Development of a fatigue scale. *Journal of Psychosomatic Research* **37**, 147–153.

Chalder T, Power MJ, Wessely S (1996). Chronic fatigue in the community: 'a question of attribution'. *Psychological Medicine* **26**, 791–800.

Chambers D, Bagnall AM, Hempel S, Forbes C (2006). Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/myalgic encephalomyelitis: an updated systematic review. *Journal of the Royal Society of Medicine* **99**, 506–520.

Cheong J, MacKinnon DP, Khoo ST (2003). Investigation of mediational processes using parallel process latent growth curve modeling. *Structural Equation Modeling* **10**, 238–262.

Claeskens G, Lid N (2008). *Model Selection and Model Averaging*. Cambridge University Press: Cambridge, UK.

Cutter GR, Baier ML, Rudick RA, Cookfair DL, Fischer JS, Petkau J, Syndulko K, Weinshenker BG, Antel JP, Confavreux C, Ellison GW, Lublin F, Miller AE, Rao SM, Reingold S, Thompson A, Willoughby E (1999). Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain* **122**, 871–882.

Deale A, Chalder T, Marks I, Wessely S (1997). Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. *American Journal of Psychiatry* **154**, 408–414.

Deale A, Chalder T, Wessely S (1998). Illness beliefs and treatment outcome in chronic fatigue syndrome. *Journal of Psychosomatic Research* **45**, 77–83.

Duncan TE, Duncan SC, Strycker LA (2006). *An Introduction to Latent Variable Growth Curve modeling: Concepts, Issues, and Applications*. Lawrence Erlbaum Associates: Mahwah, NJ.

Emsley R, Dunn G, White IR (2010). Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. *Statistical Methods in Medical Research* **19**, 237–270.

Fan X, Thompson B, Wang L (1999). Effects of sample size, estimation methods, and model specification on structural equation modeling fit indexes. *Structural Equation Modeling* **6**, 56–83.

Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A (1994). The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Annals of Internal Medicine* **121**, 953–959.

Judd CM, Kenny DA (1981). Process analysis: estimating mediation in treatment evaluations. *Evaluation Review* **5**, 602–619.

Kline RB (2004). *Principles and Practice of Structural Equation Modeling*. Guilford Press: New York.

Knoop H, van der Meer JW, Bleijenberg G (2008). Guided self-instructions for people with chronic fatigue syndrome: randomised controlled trial. *British Journal of Psychiatry* **193**, 340–341.

Knudsen AK, Henderson M, Harvey SB, Chalder T (2011). Long-term sickness absence among patients with chronic fatigue syndrome. *British Journal of Psychiatry* **199**, 430–431.

Kraemer HC, Wilson GT, Fairburn CG, Agras WS (2002). Mediators and moderators of treatment effects in randomized clinical trials. *Archives of General Psychiatry* **59**, 877–883.

Laurenceau J-P, Hayes AM, Feldman GC (2007). Some methodological and statistical issues in the study of change processes in psychotherapy. *Clinical Psychology Review* **27**, 682–695.

Little RJA, Rubin DB (2002). *Statistical Analysis with Missing Data*. Wiley: New York.

MacKinnon DP (2008). *Introduction to Statistical Mediation Analysis*. Erlbaum: Mahwah, NJ.

MacKinnon DP, Luecken LJ (2008). How and for whom? Mediation and moderation in health psychology. *Health Psychology* **27**, S99–S100.

Mundt JC, Marks IM, Shear MK, Greist JH (2002). The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *British Journal of Psychiatry* **180**, 461–464.

Nijs J, De Meirleir K, Duquet W (2004). Kinesiophobia in chronic fatigue syndrome: assessment and associations with disability. *Archives of Physical Medicine and Rehabilitation* **85**, 1586–1592.

Petrie K, Moss-Morris R, Weinman J (1995). The impact of catastrophic beliefs on functioning in chronic fatigue syndrome. *Journal of Psychosomatic Research* **39**, 31–37.

Preacher KJ, Hayes AF (2004). SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behavior Research Methods, Instruments, and Computers* **36**, 717–731.

Price JR, Mitchell E, Tidy E, Hunot V (2008). Cognitive behaviour therapy for chronic fatigue syndrome in adults. *Cochrane Database Systematic Review* **3**, CD001027.

Prins JB, Bleijenberg G, Bazelmans E, Elving LD, de Boo TM, Severens JL, van der Wilt GJ, Spinhoven P, van der Meer JW (2001). Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *Lancet* **357**, 841–847.

Quarmby L, Rimes KA, Deale A, Wessely S, Chalder T (2007). Cognitive-behaviour therapy for chronic fatigue syndrome: comparison of outcomes within and outside the confines of a randomised controlled trial. *Behaviour Research and Therapy* **45**, 1085–1094.

Ray C, Jefferies S, Weir WR (1995). Coping with chronic fatigue syndrome: illness responses and their relationship with fatigue, functional impairment and emotional status. *Psychological Medicine* **25**, 937–945.

Rosseel Y (2012). lavaan: an R-package for structural equation modeling. *Journal of Statistical Software* **48**, 1–36.

Royston P (2005). Multiple imputation of missing values: update of ice. *Stata Journal* **5**, 527–536.

Sharpe M, Chalder T (1994). Management of the chronic fatigue syndrome. In *Neurological Rehabilitation* (ed. L. S. Ellis), pp. 282–294. Blackwell Scientific Publications: Oxford.

Sharpe M, Hawton K, Simkin S, Surawy C, Hackmann A, Klimes I, Peto T, Warrell D, Seagroatt V (1996). Cognitive behaviour therapy for the chronic fatigue syndrome: a randomized controlled trial. *British Medical Journal* **312**, 22–26.

Sharpe MC, Archard LC, Banatvala JE, Borysiewicz LK, Clare AW, David A, Edwards RH, Hawton KE, Lambert HP, Lane RJ (1991). A report – chronic fatigue syndrome: guidelines for research. *Journal of the Royal Society of Medicine* **84**, 118–121.

Shipley B (2003). From biological hypotheses to structural equation models: the imperfection of causal translation. In *Structural Equation Modeling: Applications in Ecological and Evolutionary Biology* (ed. B. H. Pugesek, A. Tomer and A. von Eye), pp. 194–211. Cambridge University Press: Cambridge, UK.

Silver A, Haeney M, Vijayadurai P, Wilks D, Pattrick M, Main CJ (2002). The role of fear of physical movement and activity in chronic fatigue syndrome. *Journal of Psychosomatic Research* **52**, 485–493.

Skerrett TN, Moss-Morris R (2006). Fatigue and social impairment in multiple sclerosis: the role of patients' cognitive and behavioral responses to their symptoms. *Journal of Psychosomatic Research* **61**, 587–593.

StataCorp (2007). *Stata Statistical Software: Release 10*. StataCorp LP: College Station, TX.

Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G (2005). Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. *British Medical Journal* **330**, 14.

Wessely S, David A, Butler S, Chalder T (1989). Management of chronic (post-viral) fatigue syndrome. *Journal of the Royal College of General Practitioners* **39**, 26–29.

White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M (2011). Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* **377**, 823–836.

Wiborg JF, Knoop H, Prins JB, Bleijenberg G (2011). Does a decrease in avoidance behavior and focusing on fatigue mediate the effect of cognitive behavior therapy for chronic fatigue syndrome? *Journal of Psychosomatic Research* **70**, 306–310.

Wiborg JF, Knoop H, Stulemeijer M, Prins JB, Bleijenberg G (2010). How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. *Psychological Medicine* **40**, 1281–1287.