OPEN ACCESS

University of BRISTOL

Loades, M., Stallard, P., Morris, R. W., Kessler, D. S., & Crawley, E. M. (2020). Do adolescents with Chronic Fatigue Syndrome (CFS/ME) and co-morbid anxiety and/or depressive symptoms think differently to those who do not have co-morbid psychopathology? *Journal of Affective Disorders*, *274*, 752-758. https://doi.org/10.1016/j.jad.2020.05.113

Publisher's PDF, also known as Version of record

License (if available):
CC BY-NC-ND

Link to published version (if available):
10.1016/j.jad.2020.05.113

Link to publication record in Explore Bristol Research
PDF-document

This is the final published version of the article (version of record). It first appeared online via Elsevier at https://doi.org/10.1016/j.jad.2020.05.113 . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research
General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/

Journal of Affective Disorders 274 (2020) 752–758

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Do adolescents with chronic fatigue syndrome (CFS/ME) and co-morbid anxiety and/or depressive symptoms think differently to those who do not have co-morbid psychopathology?

Maria E Loades[a,b,*], Paul Stallard[c], Richard Morris[b], David Kessler[b], Esther Crawley[b]

[a] Department of Psychology, University of Bath, BA2 7AY England, United Kingdom
[b] Bristol Medical School, University of Bristol, United Kingdom
[c] Department of Health, University of Bath, United Kingdom

ARTICLE INFO

Keywords:
Paediatric
CFS/ME
Mood
Depression
Anxiety
Cognitions
Psychopathology

ABSTRACT

Background: Co-morbid anxiety and/or depression is common in adolescents with Chronic Fatigue Syndrome (CFS/ME). Adolescents with psychopathology typically endorse more negative cognitive errors. We do not know whether they make negative cognitive errors in response to fatigue. We examined the thinking patterns of adolescents with CFS/ME and co-morbid psychopathology compared to those without this co-morbidity.

Methods: This cross-sectional study recruited 205 adolescents (age 11–18) with CFS/ME, who completed measures of anxiety and depression, information processing biases and responses to fatigue. We grouped participants as having co-morbid psychopathology (or not) by applying a threshold score. We compared groups' thinking pattern subscale scores using independent samples T tests. We examined the association between psychopathology and general negative thinking and specific responses to fatigue symptoms.

Results: Adolescents with CFS/ME with co-morbid psychopathology more strongly endorsed general negative cognitive errors (d = 0.61–1.31). They also more strongly endorsed damage beliefs (d = 0.49), embarrassment avoidance (d = 1.05), catastrophising (d = 0.97) and symptom focusing (d = 0.75) in response to fatigue but did not differ significantly on fear avoidance from those without co-morbid psychopathology. Both negative cognitive errors and unhelpful responses to symptoms explained 43% of the variance in psychopathology.

Conclusions: Adolescents with CFS/ME with co-morbid psychopathology tend to be negatively biased in their thinking, both generally and about their symptoms of fatigue specifically. This may have implications for the sequencing of cognitive and behavioural strategies to address both fatigue and psychopathology.

1. Introduction

Between 0.1 and 2% of adolescents are affected by Chronic Fatigue Syndrome (Brigden et al., 2017). Chronic Fatigue Syndrome, also known as myalgic encephalomyelitis (CFS/ME) is a diagnosis of exclusion; the cardinal symptom is medically unexplained disabling, severe and persistent fatigue, which has lasted for ≥3 months (NICE, 2007). Concomitant symptoms may also include sleep disturbance, headaches, nausea, dizziness, muscle and joint pain, and problems with attention and concentration (NICE, 2007). Providing depression or anxiety are not the primary cause of the fatigue, it is possible for an individual to meet the criteria for both CFS/ME and a psychiatric disorder co-morbidly (NICE, 2007). Psychiatric co-morbidity is particularly common in adolescents with CFS/ME; at least one in five adolescents with CFS/ME also have depression (Loades et al., submitted; Bould et al., 2013; Loades et al., 2017) and one quarter of adolescents with CFS/ME also meet the criteria for at least one anxiety disorder (Loades et al., 2017) (Loades et al., submitted). As is the case in the general population (Ormel et al., 2015; Weller et al., 2018), there is a high degree of co-morbidity between anxiety and depression, with around two thirds of adolescents with CFS/ME not meeting the criteria for either depression or anxiety. Thus, the remaining one third present with significant psychopathology (Loades et al., submitted).

There is no clear guidance or evidence on the best approach to treating adolescents with CFS/ME and co-morbid anxiety or depression (Loades et al., 2016; Stoll et al., 2016). Cognitive Behaviour Therapy (CBT) is an evidence-based treatment for anxiety, depression and CFS/ME (Creswell et al., 2014; NICE, 2007, 2015). However, the

* Corresponding author at: Department of Psychology, University of Bath, Bath, BA2 7AY England, United Kingdom.
E-mail addresses: m.e.loades@bath.ac.uk (M.E. Loades), p.stallard@bath.ac.uk (P. Stallard), Richard.morris@bristol.ac.uk (R. Morris), david.kessler@bristol.ac.uk (D. Kessler), esther.crawley@bristol.ac.uk (E. Crawley).

https://doi.org/10.1016/j.jad.2020.05.113
Received 15 January 2020; Received in revised form 25 March 2020; Accepted 17 May 2020
Available online 22 May 2020
0165-0327/ © 2020 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Table 1
Descriptive statistics for overall sample, including Cronbach's alphas for questionnaire measures.

		N (%)		
Gender	Male	76 (37.1)		
	Female	129 (62.9)		
Ethnic Origin	White British	193 (94.15)		
	Other white	1 (0.50)		
	Mixed race	8 (3.90)		
	Asian	3 (1.46)		
School Attendance	≤ 40%	106 (51.71)		
Measure	**Subscale**	**Mean (S.D.)**	**Range**	**Cronbach's α**
Age (years)		**14.16 (1.69)**	11–18	
Duration of fatigue (months)		23.18 (19.88)	3–156	
CFQ	Total Score	24.68 (4.93)	9–33	.857
SF36PFS	Physical Functioning Subscale	50.17 (22.94)	0–95	.889
RCADS	Total psychopathology (anxiety + depression score)	47.57 (21.66)	9–121	.945
CNCEQ-R	Underestimating ability to cope	8.77 (3.29)	3–15	.670
	Personalisation without mindreading	7.08 (3.16)	3–15	.804
	Selective abstraction	6.68 (2.91)	3–15	.638
	Mindreading	8.83 (3.97)	4–20	.773
	Overgeneralising	7.52 (3.53)	3–15	.785
CBRQ	Fear Avoidance	16.03 (4.43)	3–24	.799
	Damage Beliefs	10.35 (3.61)	1–19	.746
	Embarrassment Avoidance	9.31 (6.07)	0–24	.893
	All-or-nothing Behaviour	12.70 (4.19)	0–20	.820
	Symptom Focusing	12.55 (5.30)	0–24	.870
	Catastrophising	7.74 (3.78)	0–16	.793
	Avoidance/Resting Behaviour	18.98 (5.43)	4–32	.741

CBRQ = Cognitive and Behavioural Responses to Symptoms Questionnaire, CFQ = Chalder Fatigue Questionnaire, CNCEQ-*R* = Children's Negative Cognitive Errors Questionnaire – Revised, RCADS = Revised Children's Anxiety and Depression Scale, SF36PFS = Short Form 36 Physical Functioning Subscale.

maintenance models of psychopathology and fatigue are different, which has implications for what techniques are used and in what order in CBT (Loades and Chalder, 2017). Therefore, we need to understand the cognitive and behavioural processes contributing to the maintenance of both fatigue and psychopathology to know which techniques might be most helpful.

The cognitive (Beckian) model informs both CBT for depression (CBT-D) and CBT for anxiety (CBT-A). This purports that internal, global and stable negative cognitions about the self, others/world, and the future, interact with behavioural patterns of withdrawal and avoidance, to maintain low mood (Beck, 1979) and anxiety (Beck et al., 2005). Behavioural activation, combined with cognitive reappraisal, has been shown to be at least moderately effective in adolescents who are depressed (Goodyer et al., 2017) and exposure based therapies, combined with cognitive reappraisal has well established evidence of effectiveness for adolescents with anxiety disorders (Creswell et al., 2014).

Consistent with the Beckian model, thinking patterns are important in the aetiology and treatment of psychopathology. Cognitive tendencies, such as negative cognitive style and rumination, for instance, prospectively predict depression and depressive symptoms in adolescence (Hankin, 2015; Sfarlea et al., 2019). Adolescents with both anxiety and depression symptoms tend to particularly endorse the cognitive biases of threat perception, probability estimation, catastrophising and personalisation (Weeks et al., 2017). Overgeneralisation and selective abstraction uniquely predict depression in adolescents and higher cost estimates, mindreading and underestimating the ability to cope uniquely predicting anxiety (Schwartz and Maric, 2015; Weeks et al., 2017). Understanding the thinking patterns in adolescents with CFS/ME with co-morbid psychopathology compared to those without would help us understand problem development and maintenance and improve treatment.

CBT for fatigue (CBT-F) aims to stabilise activity levels before gradually increasing them, and to use behavioural experiments to test out the specific thoughts about fatigue. CBT-F assumes that fatigue, once triggered, can be made worse or maintained by unhelpful cognitions about the physical illness and its sequelae, such as 'My fatigue will get worse if I do more' (Browne and Chalder, 2006). There are several types of unhelpful cognitions about fatigue, including fear avoidance beliefs, damage beliefs, embarrassment avoidance, catastrophising and symptom focusing (Moss-Morris and Chalder, 2003). Adolescents with CFS/ME have been found to endorse these cognitions in response to fatigue more strongly than adolescents with asthma do (Loades et al., 2019). Furthermore, in that study, in adolescents with CFS/ME, damage beliefs at initial assessment (i.e. believing that symptoms are indicative of a significant disease) predicted subsequent fatigue and physical functioning, and catastrophising predicted physical functioning, approximately 3 months later (Loades et al., 2019). Fatigue is also maintained by consequent behavioural responses, either of excessive rest, or of adopting a 'boom-and-bust', all-or-nothing approach to activity, doing lots on one day and then very little the next (Loades et al., 2019).

To enable the development of a conceptual model of problem maintenance in adolescents with CFS/ME with co-morbid psychopathology, we need to examine how their biases in general information processing and specific cognitive responses to fatigue differ from those who do not have significant co-morbid mental health symptoms. Therefore, the current study aimed to investigate how the cognitions adolescents with CFS/ME with and without co-morbid psychopathology differ. Specifically, we examined whether there are differences in (1) negative cognitive errors, as would be predicted by the Beckian cognitive model, and (2) cognitive responses to fatigue in adolescents with and without co-morbid psychopathology. We expected that those with co-morbid psychopathology would endorse more global negative cognitive errors, and more unhelpful cognitive responses to fatigue symptoms. We also expected that both general and fatigue specific cognitive errors would predict psychopathology.

2. Method

This was cross-sectional study using data collected at baseline in the FITNET-NHS trial.

2.1. Participants

Participants were recruited via primary care and paediatric settings. Adolescents in the UK who were aged 11–18 with a diagnosis of CFS/ME made by a local paediatrician, with no access to a local specialist CFS/ME service were eligible to participate. Adolescents not disabled by fatigue, those whose fatigue is due to another cause, and those unable to complete FITNET-NHS modules were excluded. Those who were pregnant at assessment were also excluded (Baos et al., 2018).

2.2. Measures

Adolescents completed several questionnaires as follows (see Table 1 for Cronbach's alphas in the current study):

The *Children's Negative Cognitive Error Questionnaire Revised* (CNCEQ-R) (Maric et al., 2011) is composed of 16 items. Each item presents a hypothetical scenario and then a distorted thought. Respondents are asked to imagine that the scenario happens to them. They are required to indicate how similar to their thinking the given thought would be on a 5-point scale ranging from 'not at all like I would think' (scored as 1) and 'almost exactly like I would think' (scored as 5). Factor analysis has established that the CNCEQ-R contains five subscales, measuring the following cognitive errors: underestimation of coping ability, personalising without mindreading, mindreading, selective abstraction and overgeneralising in 9–17 year olds (Maric et al., 2011). Total scores range from 16 to 80, and higher scores indicate more negative cognitive errors. The CNCEQ has good test-retest reliability and moderate to good internal consistency (Maric et al., 2012; Maric et al., 2011).

The *Cognitive Behavioural Responses to Symptoms Questionnaire* (CBRQ, also known as the CBRSQ) provides a measure of beliefs about symptoms and behavioural responses to symptoms (Ali et al., 2017). It is a 40-item measure which contains five cognitive responses subscales: symptom focusing, catastrophising, damaging beliefs, fear avoidance and embarrassment avoidance, and two behavioural subscales: all-or-nothing and avoidance/rest. For the purposes of the current study, only the 27 cognitive items were of interest. Each item is scored on a 0 to 4 scale. Total scores on the cognitive items range from 0 to 108 and higher scores indicate more unhelpful responses. The CBRQ has been used previously with adolescents with CFS/ME (Loades et al., 2019). The CBRQ subscales have an acceptable internal reliability and validity in adolescents with CFS/ME (Loades et al., 2020).

The *Revised Children's Anxiety and Depression Scale* (RCADS) assesses anxiety and depression symptoms (Chorpita et al., 2000) and is made up of 47 items. Respondents are given 4 response options, which are scored on a 0 (not at all) to 3 (always) scale. Scores on each item are summed, and total scores range from 0 to 141. Higher scores indicate greater endorsement of symptoms of psychopathology (anxiety and/or depression).

Additionally, participants completed the 11-item *Chalder Fatigue Questionnaire*, CFQ (Chalder et al., 1993) as a measure of fatigue severity and the 10-item *Short Form 36 Physical Functioning Subscale*, SF36PFS (Ware and Sherbourne, 1992) as a measure of functional impairment. On the CFQ, higher scores indicate greater fatigue. On the SF36PFS, higher scores indicate better functioning.

2.3. Procedure

On receiving a referral from the GP or a paediatrician, a research nurse made an initial telephone call to the adolescent and their parents to discuss the possibility of taking part in the research. Those who expressed an interest were sent a Participant Information Sheet by email and asked to complete the RCADS and a consent to contact form online. The research nurse then conducted a more detailed eligibility screening assessment via telephone or video call, including questions about fatigue, symptoms, disability and mood, and by checking the screening blood test results. Eligible participants were given further information about the trial and the treatment arms. Those who consented to participate were asked to complete baseline measures, including the CBRQ and the CNCEQ-R. Measures were completed electronically using Research Electronic Data Capture (REDCAP), a web-based system (Harris et al., 2012). Further information about the intervention arms and treatment trial itself is available from the trial protocol (Baos et al., 2018) and findings will be reported elsewhere.

2.4. Ethical permissions

The FITNET-NHS study had full ethical permission IRAS ref 211,202, NHS REC ref 16/SW/0268, HTA reference 14/192/109, trial registration number ISRCTN18020851. Recruitment commenced on the 1st of November 2016, and the number of participants required for this sub-study ($N \geq 204$) was reached in July 2019, following which the CBRQ and CNCEQ-R were removed from the trial baseline measures to minimise unnecessary participant burden.

2.5. Data analysis plan

Data was analysed using SPSS version 23.0. Based on mean differences found in previous literature using comparable measures (Hughes et al., 2017; Schwartz and Maric, 2015), we assumed an effect size of 0.5 standard deviations. Assuming a 90% power and 5% significance level, the sample size required to detect a difference of 0.5 standard deviations on the CBRQ and CNCEQ-R was at least 84 participants per group.

Participants were grouped as having co-morbid psychopathology (anxiety and/or depression) using the optimum screening threshold on the RCADS-total raw score of ≥ 49 (Loades et al., submitted). This score has a sensitivity of 0.897 and a specificity of 0.720. The assumptions for the use of parametric analysis were met as no significant outliers were identified and the dependant variable was approximately normally distributed. Therefore, the two groups' (i.e. those with co-morbid psychopathology vs those without co-morbid psychopathology) mean values were compared on the CNCEQ-R subscales and the cognitive subscales of the CBRQ using a series of independent samples T tests. Cohen's d was calculated to establish by how many standard deviations the groups differed, with $d = 0.2$ considered to be a small effect size, $d = 0.5$ a medium effect size, and $d = 0.8$ a large effect size (Cohen, 1988).

Bivariate Pearson's correlations were conducted to establish which subscales of the CNCEQ-R and cognitive subscales of the CBRQ were significantly associated with RCADS total score. A hierarchical multiple linear regression was conducted to examine the extent to which negative cognitive errors and unhelpful cognitive responses to symptoms were associated with psychopathology (RCADS-total), whilst controlling for age, fatigue severity and fatigue duration as co-variates.

3. Results

We recruited 205 participants, 76 (37.1%) of whom were male (see Table 1). The mean participant age was 14.16 (S.D. 1.69), see Fig. 1. More than half the participants were attending school 40% of the time or less, and the mean score on the SF36PFS as a measure of disability was 50.17 (Table 1). Of the 205 participants, 117 (57.1%) scored < 49 on the RCADS-total. The remaining 88 (42.9%) scored ≥ 49, indicative of elevated anxiety and/or depression symptoms. Thus, we had more than 90% power to detect differences of 0.5 standard deviations at the 5% level.

Participants who were depressed/anxious were more likely to underestimate their ability to cope (mean difference −3.64, 95% CI −4.40- −2.87) and to mindread, i.e. to assume they know what other people are thinking (mean difference −3.82, 95% CI −4.84- - 2.81) compared to those who were not. Smaller differences (but in the same direction) were seen for the other subscales on the CNCEQ-R

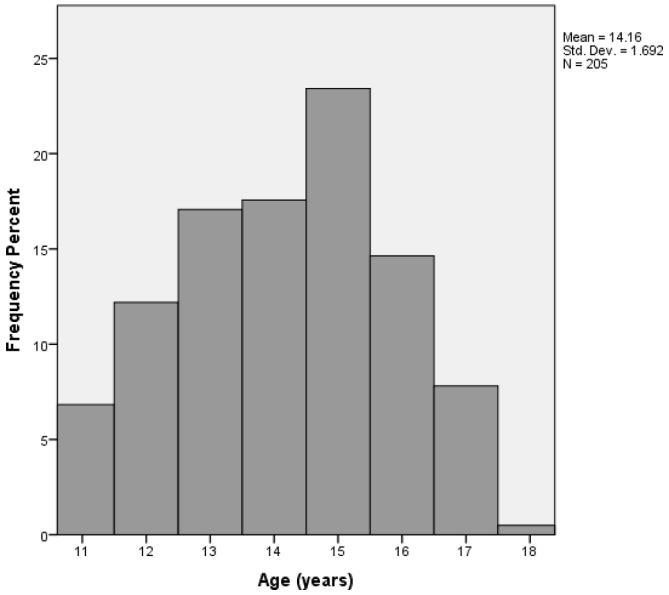

Fig. 1. Age distribution of sample.

(personalisation without mindreading, selective abstraction, overgeneralising, see Table 2). The differences between groups were large in effect size for underestimation of the ability to cope, mindreading and overgeneralisation (Cohen's d ranging from 0.95–1.31), and medium in effect size for personalisation without mindreading and selective abstraction (Cohen's d of 0.79 and 0.61 respectively). Thus, participants with elevated anxiety and/or depression endorsed more negative cognitive errors.

Furthermore, participants who were depressed/anxious were more likely to endorse unhelpful damage beliefs (mean difference −1.69, 95% CI −2.67- −0.71), embarrassment avoidance (mean difference −5.69, 95% CI −7.18- - 4.19), symptom focusing (mean difference −3.72, 95% CI −5.11- −2.33) and catastrophising (mean difference −3.29, 95% CI −4.24- −2.34) on the CBRQ. The differences between groups were medium in effect size for the damage beliefs ($d = 0.49$) and symptom focusing ($d = 0.75$) subscales, and large in effect size for catastrophising ($d = 0.97$) and embarrassment avoidance ($d = 1.05$). Participants with elevated anxiety and/or depression endorsed more unhelpful cognitive responses to symptoms (see Table 2).

All negative cognitive errors (CNCEQ-R subscales) and all unhelpful cognitive responses to symptoms (CBRQ subscales) apart from fear avoidance were associated with symptoms of anxiety and/or depression (RCADS-total), see Table 3. The CNCEQ-R and CBRQ were not highly correlated with one another (see Supplementary materials Table S1.). Therefore, these 9 variables were included in the regression analysis. Age (years), fatigue severity (CFQ) and fatigue duration predicted 8.6% of the variance in psychopathology symptom score (RCADS-total; $R^2 = 0.086$, $p < .001$, see Table 4). The addition of the negative cognitive errors and unhelpful cognitive responses subscales each separately added significantly to the proportion of the variance explained (CNCEQ-R subscales: $R^2 = 0.437$, $p < .001$, R^2 change = 0.351; cognitive subscales of the CBRQ apart from fear avoidance: $R^2 = 0.386$, $p < .001$, R^2 change = 0.300). The final model including both the negative cognitive errors and the unhelpful cognitive responses subscales together accounted for 52% of the variance in psychopathology symptom score ($R^2 = 0.519$, $p < .001$, R^2 change = 0.429). The only subscales which were independent significant predictors of psychopathology symptom scores were the CNCEQ-R underestimation of the ability to cope subscale and the CBRQ embarrassment avoidance subscale (see Table 4). Higher underestimation of the ability to cope and greater embarrassment avoidance predicted greater psychopathology symptoms.

Table 3
Bivariate correlations between RCADS total score and CNCEQ-R and CBRQ subscales.

Scale	Subscale	R	p
CNCEQ-R	Underestimation of the Ability to Cope	.55	<0.001
	Personalisation without Mindreading	.37	<0.001
	Selective Abstraction	.92	<0.001
	Mindreading	.48	<0.001
	Overgeneralising	.43	<0.001
CBRQ	Fear Avoidance	.10	.153
	Damage Beliefs	.23	.001
	Embarrassment Avoidance	.47	<0.001
	Symptom Focusing	.35	<0.001
	Catastrophising	.43	<0.001

4. Discussion

This is the first study to show adolescents who have CFS/ME have different cognitive biases if they have co-morbid psychopathology compared to those who just have CFS/ME. This is clinically important because it suggests that different cognitive strategies may need to be utilised in treatment when an adolescent is also depressed and/or anxious. We found that adolescents with co-morbid anxiety and/or depression more strongly endorsed all the general cognitive errors. They also more strongly endorsed most types of unhelpful cognitive responses to fatigue, specifically damage beliefs, embarrassment avoidance, catastrophising and symptom focusing. We were surprised to see

Table 2
Results from independent samples t-tests.

		No depression &/ anxiety ($N = 117$) Mean (S.D.)	Elevated depression &/anxiety ($N = 88$) Mean (S.D.)	Mean difference	95% CI for mean difference	T	d.f.	p	Effect Size (Cohen's d)
CNCEQ	Underestimation of the ability to cope	7.21 (2.74)	10.84 (2.80)	−3.64	−4.40 - −2.87	−9.33	203	<0.001	1.31
	Personalisation without mindreading[a]	6.05 (2.59)	8.43 (3.34)	−2.37	−3.22 - −1.52	−5.53	159.32	<0.001	0.79
	Selective abstraction	5.94 (2.75)	7.66 (2.85)	−1.71	−2.49 - - 0.93	−4.34	203	<0.001	0.61
	Mindreading[a]	7.19 (2.97)	11.01 (4.09)	−3.82	−4.84 - −2.81	−7.42	151.91	<0.001	1.07
	Overgeneralising[a]	6.20 (2.93)	9.27 (3.49)	−3.08	−3.99 - - 2.17	−6.68	168.29	<0.001	0.95
CBRQ	Fear Avoidance	15.65 (4.51)	16.55 (4.30)	−0.90	−2.13 - 0.33	−1.44	203	.153	0.20
	Damage Beliefs	9.62 (3.69)	11.31 (3.29)	−1.69	−2.67 - −0.71	−3.41	203	.001	0.49
	Embarrassment Avoidance	6.87 (5.30)	12.56 (5.51)	−5.69	−7.18 - −4.19	−7.48	203	<0.001	1.05
	Symptom focusing	10.95 (5.06)	14.67 (4.88)	−3.72	−5.11 - −2.33	−5.29	203	<0.001	0.75
	Catastrophising	6.32 (3.54)	9.61 (3.25)	−3.29	−4.24 - −2.34	−6.82	203	<0.001	0.97

[a] unequal variances assumed
CBRQ = Cognitive and Behavioural Responses to Symptoms Questionnaire, CNCEQ-*R* = Children's Negative Cognitive Errors Questionnaire – Revised.

Table 4
Hierarchical multivariable linear model of predictors of psychopathology symptoms score (RCADS-total).

Model		Unstandardised Coefficients		Standardised Coefficients	t	p
		B	Std. Error	Beta		
1	(Constant)	11.35	13.23		0.86	.392
	Fatigue duration (months)	0.16	0.08	0.15	2.12	.035
	Age (years)	0.09	0.91	0.01	0.10	.922
	Fatigue (CFQ)	1.27	0.32	0.29	3.98	<0.001
$R^2 = 0.086$, adjusted $R^2 = 0.072$, $p < .001$						
2	(Constant)	−7.40	10.83		−0.68	.495
	Fatigue duration (months)	0.06	0.06	0.06	0.96	.337
	Age (years)	−0.14	0.74	−0.01	−0.18	.854
	Fatigue (CFQ)	0.79	0.26	0.18	3.07	.002
	CNCEQ Underestimation of the ability to cope	2.03	0.51	0.31	4.03	<0.001
	CNCEQ Personalisation without mindreading	0.52	0.55	0.08	0.96	.338
	CNCEQ Selective abstraction	−0.30	0.55	−0.04	−0.55	.584
	CNCEQ Mindreading	1.14	0.48	0.21	2.37	.019
	CNCEQ Overgeneralising	0.86	0.47	0.14	1.85	.065
$R^2 = 0.437$, adjusted $R^2 = 0.414$, $p < .001$						
3	(Constant)	16.08	11.52		1.40	.164
	Fatigue duration (months)	0.10	0.07	0.09	1.47	.145
	Age (years)	−1.06	0.76	−0.08	−1.40	.164
	Fatigue (CFQ)	0.87	0.28	0.20	3.16	.002
	CBRQ Damage Beliefs	−0.29	0.40	−0.05	−0.71	.479
	CBRQ Embarrassment Avoidance	1.39	0.26	0.39	5.35	<0.001
	CBRQ Symptom Focusing	0.31	0.31	0.08	0.99	.321
	CBRQ Catastrophising	1.16	0.47	0.20	2.49	.014
$R^2 = 0.386$, adjusted $R^2 = 0.364$, $p < .001$						
4	(Constant)	3.02	10.63		0.28	0.777
	Fatigue duration (months)	0.03	0.06	0.03	0.51	0.612
	Age (years)	−0.79	0.70	−0.06	−1.14	0.255
	Fatigue (CFQ)	0.67	0.25	0.15	2.68	0.008
	CNCEQ Underestimation of the ability to cope	1.69	0.49	0.26	3.47	0.001
	CNCEQ Personalisation without mindreading	0.64	0.52	0.09	1.22	0.223
	CNCEQ Selective abstraction	0.12	0.52	0.02	0.22	0.823
	CNCEQ Mindreading	0.49	0.47	0.09	1.05	0.296
	CNCEQ Overgeneralising	0.34	0.45	0.06	0.76	0.448
	CBRQ Damage Beliefs	−0.52	0.37	−0.09	−1.41	0.161
	CBRQ Embarrassment Avoidance	0.86	0.25	0.24	3.42	0.001
	CBRQ Symptom Focusing	0.18	0.28	0.04	0.62	0.533
	CBRQ Catastrophising	0.89	0.43	0.15	2.04	0.042
$R = 0.720$, $R^2 = 0.519$, $p < .001$, R^2 change = 0.429						

that fear avoidance beliefs did not differ between the groups. Both general negative cognitive errors and specific unhelpful cognitive responses to symptoms contributed to the variance in psychopathology symptom scores.

There is a high prevalence of depression and anxiety in adolescents with CFS/ME (Bould et al., 2013; Loades et al., 2017), although no studies had previously examined how thinking processes in those individuals with CFS/ME who are also depressed and/or anxious compared to those with CFS/ME who are not also depressed and/or anxious. Our findings confirmed our hypothesis that those with co-morbid psychopathology would endorse general information processing biases typical of depression and anxiety (Schwartz and Maric, 2015; Weeks et al., 2017). Thus, those who are also depressed and/or anxious tend to think more negatively, both about themselves, others and the world generally, consistent with the Beckian model (Beck, 1979).

The pervasive negative thinking patterns in those who are depressed and/or anxious also extends to fatigue specific cognitions. Those who are also depressed and/or anxious more strongly endorsed damage beliefs, embarrassment avoidance, catastrophising and symptom focusing in response to their symptoms of fatigue. As these thinking patterns could contribute to the maintenance of fatigue (Browne and Chalder, 2006), it may be that their pervasive negative thinking, about their lives generally and their illness specifically, has a detrimental impact on prognosis and outcome in CFS/ME, although this is yet to be empirically investigated. Catastrophising has previously been specifically found to predict subsequent physical functioning (Loades et al., 2019).

All participants, irrespective of psychopathology, strongly endorsed fear avoidance beliefs, consistent with the cognitive behavioural model of fatigue (Browne and Chalder, 2006). The mean score for fear avoidance beliefs in our sample was comparable to mean scores in a previous sample of adolescents with CFS/ME (Loades et al., 2019), who scored significantly higher on fear avoidance than adolescents with asthma as an illness control group. Thus, it seems that fear avoidance beliefs as a core feature of CFS/ME and should be targeted in CBT for fatigue.

Currently, no particular specific psychological treatment for adolescents with depression outperforms the other specific psychological treatments (Goodyer et al., 2017; NICE, 2015). CBT is the treatment with the strongest evidence base for both anxiety (Creswell et al., 2014) and CFS/ME(Lloyd et al., 2012; Nijhof et al., 2012; Stulemeijer et al., 2005) in adolescents. Given the findings of the current study, the prominence of both general information processing biases and more strongly endorsed fatigue-specific cognitions indicates that cognitive behaviour therapy (CBT) might be preferable to other approaches as it has the capacity to tackle negative thoughts generally as well as more specifically about fatigue symptoms.

4.1. Strengths and limitations

We recruited a large clinical cohort with clinician confirmed CFS/ME. Both groups exceeded the required sample size of 84 participants per group, thus giving us the power to undertake the analysis performed. The participants we recruited were predominantly female, which is consistent with the expected epidemiology of CFS/ME in adolescents (Crawley, 2014). Although this sample was recruited from

geographical areas without access to specialist CFS/ME services, they were similar to those recruited to other cohort and experimental studies conducted in specialist services by the same research group (Bould et al., 2013; Collin et al., 2015; Crawley et al., 2017) (see Supplementary materials Table S2.). Whilst our findings may be generalisable to other clinical cohorts of adolescents with a confirmed diagnosis of CFS/ME, generalisability may be limited when considering a more ethnically diverse population, those with severe CFS/ME, which may have precluded participation, and those not accessing healthcare services.

Although we used the optimum threshold for diagnosis of psychopathology on the RCADS questionnaire, the sensitivity and specificity of this measure means that we probably misclassified some participants in both groups, in the absence of a gold standard psychiatric interview. It may be that this accounts for the elevated rates of psychopathology in this population compared to other samples which have used more robust approaches to examining psychiatric co-morbidity (Loades et al., 2017) (Loades et al., submitted).

Furthermore, we only evaluated biases in information processing, and not biases in attention or memory, which also merit attention in depression. The internal consistency of the CNCEQ-R underestimation of the ability to cope and selective abstraction subscales was also questionable, and further work analysing the reliability and validity of measures of biased information processing in this population are required.

As this is a cross-sectional study, we are unable to draw any conclusions about the extent to which negative thinking patterns predict outcomes over time.

4.2. Clinical and research implications

Cognitive behaviour therapy (CBT) seeks to address negative and unhelpful thinking patterns by developing skills in catching and evaluating automatic thoughts, with the aim of identifying more realistic and helpful thoughts through cognitive restructuring (Stallard, 2005). Given that those adolescents who have CFS/ME and co-morbid psychopathology tend to think negatively about both general situations and about their symptoms of fatigue specifically, cognitive restructuring could be useful to address both. By introducing these strategies to combat negative thinking broadly, including attending to fatigue-specific examples, clinicians could help adolescents to break the negative cycles maintaining both psychopathology and fatigue.

Not only did adolescents with CFS/ME with co-morbid psychopathology endorse the same unhelpful cognitive and behavioural responses to fatigue symptoms as those who did not have co-morbid psychopathology, they endorsed these responses more strongly, and it may be that these patterns will take more time and effort to overcome as a result. CBT for fatigue (CBT-F) most commonly starts by tackling unhelpful behavioural patterns, addressing unhelpful fatigue-specific cognitions as and where necessary. With patients who also have anxiety and/or depression, tackling broader negative thinking patterns and fatigue-specific unhelpful cognitions more directly at an early stage in treatment may be more of a priority to enable the changes in behavioural patterns, which may otherwise be thwarted by negative thinking. It may be that addressing embarrassment avoidance about symptoms of fatigue, as well as a general tendency to underestimate one's ability to cope are particularly important when a patient is also anxious and/or depressed.

Further investigations of biases in cognition in those with co-morbid psychopathology, including of biases in attention and memory as well as cognition, and using laboratory based experimental paradigms for examining this in action (e.g. Button et al., 2015), rather than relying on self-report would be useful. Longitudinal studies would improve our understanding of the malleability of thinking patterns over time and including measures of both general negative thinking and fatigue-specific negative thinking in treatment trials would enable further investigation of mechanisms of change over the course of treatment.

4.3. Conclusion

A substantial minority of adolescents with CFS/ME are also depressed and/or anxious. Those who have co-morbid psychopathology can be distinguished by both their general negative information processing bias, and by more strongly endorsing catastrophic thoughts about their fatigue symptoms, focusing more strongly on their fatigue symptoms, and more strongly endorsing embarrassment avoidance and damage beliefs in response to fatigue. This may have implications for the sequencing of cognitive and behavioural interventions for this subgroup and further longitudinal research is needed to determine the extent to which this predicts outcomes and to investigate both the effectiveness of treatments and the mechanisms of change in this group.

CRediT authorship contribution statement

Maria E Loades: Conceptualization, Data curation, Formal analysis, Writing - review & editing. **Paul Stallard:** Writing - review & editing. **Richard Morris:** Data curation, Writing - review & editing. **David Kessler:** Writing - review & editing. **Esther Crawley:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

EC acts as a non-paid medical advisor for the Sussex and Kent ME society. The other authors declare that there is no conflict of interest.

Funding

This study did not receive any specific funding. The FITNET trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (14/192/109). The sponsor is the University of Bristol.

Acknowledgements

Prof Crawley was partially funded by the NIHR (Senior Research Fellowship, SRF-2013–06–013). Dr Loades is funded by the National Institute for Health Research (NIHR, Doctoral Research Fellowship, DRF-2016–09–021). This report is independent research. The views expressed in this publication are those of the authors(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

The authors would like to thank all the young people and families who took part in this study, and the FITNET study team who facilitated recruitment to the study and questionnaire completion. The authors would also like to thank Ms Manmita Rai for her help with the data curation.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.05.113.

References

Ali, S., Matcham, F., Irving, K., Chalder, T., 2017. Fatigue and psychosocial variables in autoimmune rheumatic disease and chronic fatigue syndrome: a cross-sectional comparison. J. Psychosom. Res. 92, 1–8. https://doi.org/10.1016/j.jpsychores.2016.11.002.

Baos, S., Brigden, A., Anderson, E., Hollingworth, W., Price, S., Mills, N., . . ., Crawley, E., 2018. Investigating the effectiveness and cost-effectiveness of FITNET-NHS (Fatigue In Teenagers on the interNET in the NHS) compared to activity management to treat paediatric chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME): protocol for a randomised controlled trial. Trials 19 (1), 136. https://doi.org/10.1186/s13063-018-2500-3.

Beck, A.T., 1979. Cognitive Therapy of Depression. Guilford Press.

Beck, A.T., Emery, G., Greenberg, R.L., 2005. Anxiety Disorders and Phobias: A Cognitive

Perspective. Basic Books.
Bould, H., Collin, S.M., Lewis, G., Rimes, K.A., Crawley, E., 2013. Depression in paediatric chronic fatigue syndrome. Arch. Dis. Child 98 (6), 425–428. https://doi.org/10.1136/archdischild-2012-303396.
Brigden, A., Loades, M., Abbott, A., Bond-Kendall, J., Crawley, E., 2017. Practical management of chronic fatigue syndrome or myalgic encephalomyelitis in childhood. Arch. Dis. Child 102, 981–986. https://doi.org/10.1136/archdischild-2016-310622.
Browne, T., Chalder, T., 2006. Chronic fatigue syndrome. Psychiatry 5 (2), 48–51. https://doi.org/10.1383/psyt.2006.5.2.48. doi:http://dx.doi.org/.
Button, K.S., Kounali, D., Stapinski, L., Rapee, R.M., Lewis, G., Munafò, M.R., 2015. Fear of negative evaluation biases social evaluation inference: evidence from a probabilistic learning task. PLoS One 10 (4), e0119456.
Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., Wallace, E., 1993. Development of a fatigue scale. J. Psychosom. Res. 37 (2), 147–153.
Chorpita, B.F., Yim, L., Moffitt, C., Umemoto, L.A., Francis, S.E., 2000. Assessment of symptoms of DSM-IV anxiety and depression in children: a revised child anxiety and depression scale. Behav. Res. Ther. 38 (8), 835–855.
Cohen, J., 1988. The effect size index: d. Stat. Power anal. Behav. Sci. 2, 284–288.
Collin, S., Nuevo, R., van de Putte, E.M., Nijhof, S.L., Crawley, E., 2015. Chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) is different in children compared to in adults: a study of UK and Dutch clinical cohorts. BMJ Open 5 (10), e008830. https://doi.org/10.1136/bmjopen-2015-008830.
Crawley, E., 2014. The epidemiology of chronic fatigue syndrome/myalgic encephalitis in children. Arch. Dis. Child 99 (2), 171–174. https://doi.org/10.1136/archdischild-2012-302156. doi:http://dx.doi.org/.
Crawley, E., Gaunt, D.M., Garfield, K., Hollingworth, W., Sterne, J.A.C., Beasant, L., . . ., Montgomery, A.A., 2017. Clinical and cost-effectiveness of the Lightning Process in addition to specialist medical care for paediatric chronic fatigue syndrome: randomised controlled trial. Arch. Dis. Child. https://doi.org/10.1136/archdischild-2017-313375.
Creswell, C., Waite, P., Cooper, P.J., 2014. Assessment and management of anxiety disorders in children and adolescents. Arch. Dis. Child 99 (7), 674–678.
Goodyer, I.M., Reynolds, S., Barrett, B., Byford, S., Dubicka, B., Hill, J., . . ., Roberts, C., 2017. Cognitive-behavioural therapy and short-term psychoanalytic psychotherapy versus brief psychosocial intervention in adolescents with unipolar major depression (IMPACT): a multicentre, pragmatic, observer-blind, randomised controlled trial. Health Technol. Assess. 21 (12), 1.
Hankin, B.L., 2015. Depression from childhood through adolescence: risk mechanisms across multiple systems and levels of analysis. Curr. Opin. Psychol. 4, 13–20. https://doi.org/10.1016/j.copsyc.2015.01.003.
Harris, P., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. (2012). Citing REDCap. *available at: www. project-redcap. org/cite. ph*p.
Hughes, A.M., Hirsch, C.R., Nikolaus, S., Chalder, T., Knoop, H., Moss-Morris, R., 2017. Cross-cultural study of information processing biases in chronic fatigue syndrome: comparison of Dutch and UK chronic fatigue patients. Int. J. Behav. Med. https://doi.org/10.1007/s12529-017-9682-z.
Lloyd, S., Chalder, T., Rimes, K.A., 2012. Family-focused cognitive behaviour therapy versus psycho-education for adolescents with chronic fatigue syndrome: long-term follow-up of an RCT. Behav. Res. Ther. 50 (11), 719–725. https://doi.org/10.1016/j.brat.2012.08.005.
Loades, M.E., Chalder, T., 2017. Same, same but different? Cognitive behavioural treatment approaches for paediatric CFS/ME and depression. Behav. Cogn. Psychother. 45, 366–381. https://doi.org/10.1017/S1352465817000108.
Loades, M.E., Rimes, K., Lievesley, K., Ali, S., Chalder, T., 2019. Cognitive and behavioural responses to symptoms in adolescents with chronic fatigue syndrome (CFS): a case control study nested within a cohort. Clin. Child Psychol. Psychiatry. https://doi.org/10.1177/1359104519835583.
Loades, M.E., Rimes, K.A., Ali, S., Lievesley, K., Chalder, T., 2017. The presence of co-morbid mental health problems in a cohort of adolescents with chronic fatigue syndrome. Clin. Child Psychol. Psychiatry 1359104517736357.
Loades, M.E., Sheils, E.A., Crawley, E., 2016. Treatment for paediatric chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME) and comorbid depression: a systematic review. BMJ Open 6 (10), e012271.
Loades, M.E., Vitoratou, S., Rimes, K., Ali, S., Chalder, T., 2020. Psychometric properties of the Cognitive and Behavioural Responses Questionnaire (CBRQ) in adolescents with chronic fatigue syndrome. Behav. Cogn. Psychother. 48 (2), 160–171. https://doi.org/10.1017/S1352465819000390.
Loades, M.E., Read, R., Smith, L., Higson-Sweeney, N., Laffan, A., Stallard, P., Kessler, D., & Crawley, E. (submitted). Depression and anxiety in adolescent Chronic Fatigue Syndrome (CFS): A clinical cohort study. Eur. Child Adolesc. Psychiatry.
Maric, M., Heyne, D.A., de Heus, P., van Widenfelt, B.M., Westenberg, P.M., 2012. The role of cognition in school refusal: an investigation of automatic thoughts and cognitive errors. Behav. Cogn. Psychother. 40 (3), 255–269.
Maric, M., Heyne, D.A., van Widenfelt, B.M., Westenberg, P.M., 2011. Distorted cognitive processing in youth: the structure of negative cognitive errors and their associations with anxiety. Cogn. Ther. Res. 35 (1), 11–20.
Moss-Morris, R., Chalder, T., 2003. *Illness representations: where to from here?*. In: Paper presented at the 16th Conference of the European Health Psychology Society Kos. Greece.
NICE. (2007). *Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (or Encephalopathy): Diagnosis and Management of CFS/ME in Adults and Children.*
NICE. (2015). *Depression in children and Young People: Psychological interventions FOR Mild Depression and Pharmacological Interventions for Moderate to Severe Depression (update)*.
Nijhof, S.L., Bleijenberg, G., Uiterwaal, C.S., Kimpen, J.L., van de Putte, E.M., 2012. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. The Lancet 379 (9824), 1412–1418.
Ormel, J., Raven, D., Van Oort, F., Hartman, C., Reijneveld, S., Veenstra, R., . . ., Oldehinkel, A., 2015. Mental health in Dutch adolescents: a TRAILS report on prevalence, severity, age of onset, continuity and co-morbidity of DSM disorders. Psychol. Med. 45 (2), 345–360.
Schwartz, J.S., Maric, M., 2015. Negative cognitive errors in youth: specificity to anxious and depressive symptoms and age differences. Behav. Cogn. Psychother. 43 (5), 526–537. https://doi.org/10.1017/S1352465814000228.
Sfarlea, A., Lochner, J., Neumuller, J., Asperud Thomsen, L., Starman, K., Salemink, E., . ., Platt, B., 2019. Passing on the half-empty glass: a transgenerational study of interpretation biases in children at risk for depression and their parents with depression. J. Abnorm. Psychol. 128 (2), 151–161. https://doi.org/10.1037/abn0000401.
Stallard, P., 2005. A Clinician's Guide to Think Good Feel Good: the Use of CBT with Children and Young People. John Wiley, Chichester.
Stoll, S., Loades, M., Crawley, E., 2016. Anxiety in Paediatric Chronic Fatigue Syndrome (CFS/ME): A Systematic Review. Paper presented at the British Association for CFS/ME.
Stulemeijer, M., de Jong, L.W., Fiselier, T.J., Hoogveld, S.W., Bleijenberg, G., 2005. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. BMJ 330 (7481), 14. https://doi.org/10.1136/bmj.38301.587106.63.
Ware, J.E., Sherbourne, C.D., 1992. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Med. Care 30 (6), 473–483. https://doi.org/10.1097/00005650-199206000-00002.
Weeks, M., Coplan, R.J., Ooi, L.L., 2017. Cognitive biases among early adolescents with elevated symptoms of anxiety, depression, and co-occurring symptoms of anxiety-depression. Infant Child. Dev. 26 (5). https://doi.org/10.1002/icd.2011.
Weller, B.E., Blanford, K.L., Butler, A.M., 2018. Estimated prevalence of psychiatric comorbidities in U.S. adolescents with depression by race/ethnicity, 2011-2012. J. Adolesc. Health 62 (6), 716–721. https://doi.org/10.1016/j.jadohealth.2017.12.020.