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Cognitive dysfunction in adolescents with chronic fatigue: a cross-sectional study

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ABSTRACT

Objective To compare cognitive function in adolescents with chronic fatigue with cognitive function in healthy controls (HC).

Study design Cross-sectional study.

Setting Paediatric department at Oslo University Hospital, Norway.

Participants 120 adolescents with chronic fatigue (average age 15.4 years; range 12–18) and 39 HC (average age 15.2 years; range 12–18).

Methods The adolescents completed a neurocognitive test battery measuring processing speed, working memory, cognitive inhibition, cognitive flexibility, verbal learning and verbal memory, and questionnaires addressing demographic data, depression symptoms, anxiety traits, fatigue and sleep problems. Parents completed the Behaviour Rating Inventory of Executive Function (BRIEF), which measures the everyday executive functions of children.

Results Adolescents with chronic fatigue had impaired cognitive function compared to HC regarding processing speed (mean difference 3.3, 95% CI 1.1 to 5.5, p=0.003), working memory (−2.4, −3.7 to −1.1, p<0.001), cognitive inhibition response time (6.2, 0.8 to 11.7, p=0.025) and verbal learning (−1.7, −3.2 to −0.3, p=0.022). The BRIEF results indicated that everyday executive functions were significantly worse in the chronic fatigue group compared to the HC (11.2, 8.2 to 14.3, p<0.001). Group differences remained largely unaffected when adjusted for symptoms of depression, anxiety traits and sleep problems.

Conclusions Adolescents with chronic fatigue had impaired cognitive function of clinical relevance, measured by objective cognitive tests, in comparison to HC. Working memory and processing speed may represent core difficulties.

What is already known on this topic?

- Adolescents with chronic fatigue syndrome (CFS) have extensive school absence.
- Depression symptoms, anxiety and sleep problems are frequent in adolescents with CFS.
- Adolescents with CFS frequently report cognitive problems.

What this study adds?

- Adolescents with chronic fatigue perform worse than healthy peers in several cognitive functions.
- The cognitive impairments are of clinical importance.
- Anxiety traits and depression symptoms do not explain the cognitive impairments in adolescent chronic fatigue.

INTRODUCTION

Fatigue among adolescents is common,[1] and disabling fatigue at age 13 of more than 3 months' duration was recently reported with an estimated prevalence of 2.2%.[2] Adolescent chronic fatigue syndrome (CFS), with an estimated prevalence of 0.1–1.0%,[3 4] is an important cause of disability and has a negative impact on quality of life, school attendance and social and family functioning.[3 5] Among the many case definitions of CFS, that proposed by the Centers for Disease Control and Prevention (CDC) in 1994[6] is most often used in studies.[7] More than 80% of individuals with CFS report cognitive problems such as difficulty thinking, impairment of short-term memory, inability to concentrate, and difficulties with word-finding, information processing and planning/organising thoughts.[8 9]

Studies of cognitive dysfunction in CFS-affected children and adolescents report impaired interference control,[10] attention,[11 12] immediate recall, auditory learning,[11] motor skills and spatial working memory.[12] However, the studies included few patients (n=19–34), and the results should be confirmed by larger studies.

Executive functions (EF; higher-order cognitive functions, related to the control of thought, action and emotion) are essential to cope with the challenges of everyday life and school. Inhibition (interference control), working memory and cognitive flexibility (switching attention) have been proposed as essential subcomponents of EF.[13] The Behaviour Rating Inventory of Executive Function (BRIEF), which was designed to improve the ecological validity of EF assessment,[14] to our knowledge has not been used in studies of cognition in adolescent chronic fatigue.

Anxiety and depression symptoms are frequent in CFS[15 16] and may be associated with cognitive impairment.[17 18] Sleep problems are among the most prevalent symptoms in adolescent CFS.[3 9] A possible association between sleep problems and cognitive abilities in young people with CFS remains to be investigated. As anxiety, depression symptoms and sleep problems are associated with

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both CFS and cognition, they may be regarded as possible moderators of cognitive function in CFS.

The primary aim of this study was to characterise cognitive function (using both objective and inventory-based measures) in a large group of adolescents with chronic fatigue and in healthy controls (HC) and compare the results. The secondary aim was to explore the possible contributing impact of anxiety traits, depression symptoms and sleep problems on cognitive function.

METHODS

Design

This study is part of the NorCAPITAL project (The Norwegian Study of Chronic Fatigue Syndrome in Adolescents: Pathophysiology and Intervention Trial; ClinicalTrials ID: NCT01040429), which has a cross-sectional design and is a double-blind, randomised, placebo-controlled study. It was conducted at the Department of Paediatrics, Oslo University Hospital, Norway, which is a national referral centre for young CFS patients. The current study is based on cross-sectional data collected from March 2010 to May 2012 during a clinical in-hospital day. The following week, participants completed the questionnaires and returned them by mail. Parents completed the BRIEF. Cognitive testing was performed by the study physicians (DS and EF) and supervised by an experienced neuropsychologist (MGØ). All participants received a gift-card worth NOK 200. Informed, written consent was obtained from all participants and from parents/next-of-kin, if required. The study was conducted in accordance with the Helsinki Declaration of the World Medical Assembly and was approved by the Norwegian National Committee for Ethics in Medical Research.

Participants

All hospital paediatric departments (20), primary care paediatricians and general practitioners in Norway were invited to refer patients aged 12–18 years with long-lasting fatigue to our department. For inclusion in the present study, we required at least 3 months of unexplained, disabling chronic/relapsing fatigue of new onset. Eligibility was based upon the referral information, and inclusion was decided after a thorough evaluation by the study physicians (DS or EF). A group of HC matched by age and gender distribution to the chronic fatigue group was recruited from local schools. Table 1 displays inclusion and exclusion criteria.

Cognitive assessment

The cognitive tests and assessments (see table 2 for descriptions of the tests used) were conducted between 10 a.m. and 12 p.m., and lasted for approximately 40 min.

A cognitive inhibition contrast measure was calculated to control for potential difficulties with processing speed. From the time taken to complete Condition 3 (inhibition) of the Color Word Interference Test of the Delis–Kaplan Executive Function System, we subtracted the mean sum score of the preceding tasks of Condition 1 (colour naming) and Condition 2 (reading): (Condition 3−[Condition 1+Condition 2]/2).

The Norwegian version of the BRIEF[19] was completed by parents within a week of the adolescent tests. The BRIEF has shown high internal consistency.[20] It is composed of eight clinical scales, two broad indices and one overall score, the global executive composite (GEC).

Questionnaires

The Karolinska Sleep Questionnaire (KSQ) addresses sleep problems during the preceding month. Scores range from 1 to 6, with a lower score implying poorer sleep. The KSQ has been used in epidemiological studies of fatigue.[21]

The Mood and Feelings Questionnaire (MFQ) measures self-reported depression.[22] The Spielberger State-Trait Inventory (STAI-T) measures self-rated anxiety traits.[23] Higher scores indicate more problems on both scales.

Statistical analysis

Statistical software (IBM SPSS Statistics V.20; Armonk, New York, USA) was used for data analysis. χ^2, Student's t or Mann–Whitney tests were used to compare the chronic fatigue and HC groups.

Participants lacking all data in an inventory or a questionnaire component variable were excluded from analysis of that

Table 1 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Patients with chronic fatigue	Persisting or constantly relapsing fatigue lasting 3 months or more	Another current disease process or demanding life event that might explain the fatigue
	Functional disability resulting from fatigue that prevents normal school attendance	Another chronic disease
	Age ≥12 and <18 years	Permanent use of drugs (including hormones) possibly interfering with measurements Permanently bed-ridden Positive pregnancy test Pheocromocytoma Evidence of reduced cerebral and/or peripheral circulation due to vessel disease Polyneuropathy Renal insufficiency Known hypersensitivity towards clonidine or inert substances (lactose, sucrose) in capsula Abnormal ECG (apart from ectopic beats) Supine heart rate <50 bpm Supine systolic blood pressure <85 mm Hg Upright systolic blood pressure fall >30 mm Hg
Healthy control subjects	Age ≥12 and <18 years	Another chronic disease Permanent use of drugs (including hormones)

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Table 2 Cognitive tests and assessments

Cognitive function	Test name	Test description	Test score
Working memory	WISC-IV Digit span forward and backward	Repeat numbers verbatim or in reverse order as stated by the administrator	Sum score 0–32 Higher score implies better working memory
Processing speed	D-KEFS CWIT Conditions 1 and 2	Name the colours of different bars (Condition 1) and read written colour names aloud in that colour (Condition 2).	Response time (s) on each condition Mean of results from the two conditions Higher score implies slower processing speed
Cognitive inhibition	D-KEFS CWIT Condition 3	Read aloud the colour of the names of colours printed in a different colour	Response time (s) Higher score implies more difficulties with the task Number of errors Higher score implies more errors
Cognitive flexibility	D-KEFS CWIT Condition 4	Switch between reading colour words and naming dissonant ink colours	Response time (s) Higher score implies more difficulties with the task
Verbal learning	HVLT-R Total recall	The administrator reads 12 words aloud. The examinee repeats as many words as possible in three trials	Sum score of words remembered in all three trials together (0–36) Higher score implies better learning
Verbal delayed memory	HVLT-R Delayed recall	Examinee recalls words after a 20 min delay	Number of words remembered (0–12) Higher score implies better delayed memory
Everyday executive function	BRIEF Global executive composite	Parents score 86 statements regarding the daily executive functioning of their child	Score gives an overall measure of executive function Higher score implies higher degree of impairment

BRIEF, Behaviour Rating Inventory of Executive Function; D-KEFS CWIT, Delis–Kaplan Executive Function System Color Word Interference Test; HVLT-R, Hopkins Verbal Learning Test-Revised; WISC-IV, Wechsler Intelligence Scale for Children, 4th ed.

variable. If one or two of several items in a component variable were missing, this value was imputed, based upon the mean value of all other participants in that group.

Multiple linear regression analyses were applied to identify a possible contribution effect by depression symptoms, anxiety traits or sleep problems on the group differences in cognitive function. All tests were two-sided, and $p \leq 0.05$ was considered statistically significant. We applied no correction for multiple comparisons. Effect size was classified as small (0.2), medium (0.5) or large (0.8), according to Cohen.[24]

We regarded effect sizes of more than 0.5 to be of clinical interest. With 120 participants in the chronic fatigue group and 39 HC, the power to detect an effect size of more than 0.5 was about 80%.

RESULTS

A total of 120 adolescents with chronic fatigue (mean age 15.4 years) and 39 HC (mean age 15.2 years) were included. All but five in the chronic fatigue group were drug naive on inclusion and testing (three used melatonin, one used thyroxine on a regular basis, and one had taken paracetamol the day before participation). All members of the HC group were drug naive. Background characteristics and results from the questionnaires are given in table 3.

The chronic fatigue group performed worse than the HC group for processing speed ($p=0.003$), working memory ($p<0.001$), cognitive inhibition response time ($p=0.025$) and verbal learning ($p=0.022$), as well as on the BRIEF GEC score ($p<0.001$) (table 4). The groups did not differ with regard to errors or the contrast measure of cognitive inhibition. When adjusted for working memory in the analysis of verbal learning, the group difference disappeared.

In the HC group, the mean results of the cognitive tests and the BRIEF were both within 1 SD of standardised norms[25 26] and HC results in other studies in Norway.[27 28] In the chronic fatigue group, 28–65% performed more than 1 SD worse than the norms (see supplementary online eTable 1).

The group differences in processing speed, cognitive inhibition response time, verbal learning, and the BRIEF, remained largely unaffected when adjusted for symptoms of depression, anxiety traits or sleep problems in the multiple regression models. The group differences in working memory remained statistically significant when adjusted for depression symptoms or anxiety traits, but lost statistical significance when adjusted for sleep problems (KSQ). The regression coefficients and R^2 values are given in table 5.

The results from the analyses of the subgroup (defined by the CDC criteria) were not significantly different from those for the chronic fatigue group (tables 3–5 and supplementary online eTables 1 and 2).

DISCUSSION

This study demonstrates that adolescents with chronic fatigue, defined as persisting or relapsing fatigue of more than 3 months' duration, perform worse than HC on measures of processing speed, working memory, verbal learning and cognitive inhibition response time, but not on cognitive flexibility or delayed recall. According to parents' observations, their children with chronic fatigue have more problems with everyday EF. Adolescents with chronic fatigue also report more sleep problems, symptoms of depression and anxiety traits, but none of these fully explain the group differences in cognitive measures. An analysis of a subgroup that met the CDC criteria for CFS, shows results similar to those for the study's main chronic fatigue group.

Comparison with the literature

To our knowledge, our study of cognitive problems in adolescents with chronic fatigue has included more patients than any other study of similar groups. Reduced processing speed and

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Table 3 Demographic and clinical characteristics of the study participants

Characteristics	Mean values			Group comparisons (p value)	
	Chronic fatigue group N=120	CFS (CDC) subgroup N=88	Healthy controls N=39	Chronic fatigue group versus healthy controls	CFS (CDC) subgroup versus healthy controls
Gender					
Female (%)	86 (72)	64 (72)	28 (72)	0.98	0.91
Age					
Mean (SD)	15.4 (1.6)	15.3 (1.6)	15.2 (1.6)	0.57	0.79
Age range, years	12–18	12–18	12–18		
BMI					
Mean (SD, Z score)	21.5 (4.2, 0.4)	21.2 (4.2, 0.3)	20.3 (2.9)	0.04	0.14
CDC criteria fulfilled (%)	88 (73)		NA		
NICE criteria fulfilled (%)	107 (89)		NA		
MFQ					
Mean (SD)	17.2 (10.1)	18.7 (10.4)	6.6 (7.8)	<0.001	<0.001
Disease duration months (range)	21.4 (4–104)	21.1 (6–104)	NA	NA	NA
CFQ					
Mean (SD)	19.2 (6.2)	19.9 (6.0)	8.9 (4.5)	<0.001	<0.001
School absence					
Mean % (SD)	65 (30)	66 (30)	2 (7)	<0.001	<0.001
STAI-T					
Mean (SD)	42.8 (9.0)	44.0 (9.1)	32.1 (7.25)	<0.001	<0.001
KSQ					
Mean (SD)	3.4 (0.97)	3.3 (0.9)	4.9 (0.86)	<0.001	<0.001

CFS (CDC) subgroup: Participant subgroup that meets the CDC criteria for chronic fatigue syndrome; School absence: the percentage of days out of school during the last month (20 days/month is 100%).
BMI, body mass index; CDC, Centers for Disease Control and Prevention; CFS, chronic fatigue syndrome; CFQ, Chalder Fatigue Questionnaire; KSQ, Karolinska Sleep Questionnaire; MFQ, Mood and Feelings Questionnaire; NICE, National Institute for Health and Care Excellence; STAI-T, Spielberger State-Trait Inventory.

reduced working memory showed the most significant group differences. Kawatani *et al*[12] found reduced working memory and reduced processing speed in children with CFS. However, they used a spatial working memory task, while we used a verbal working memory task. They also used a different task for measuring processing speed. A direct comparison between these studies is therefore questionable.

In contrast to our results, Haig-Ferguson *et al*[11] did not demonstrate reduced processing speed or reduced working memory. A possible explanation for the contrasting results could be insufficient statistical power due to the small number of participants in the previous study. Furthermore, that study did not include a healthy comparison group and the patients were about 2 years younger than our participants.

Table 4 Results from cognitive tests (raw scores) and the BRIEF (T scores): comparison of chronic fatigue group and CFS (CDC) subgroup versus healthy controls

Cognitive measure	Mean values (SD)			Chronic fatigue group versus healthy controls			CFS (CDC) subgroup vs healthy controls		
	Chronic fatigue group N=120	CFS (CDC) subgroup N=88	Healthy controls N=39	Difference (95% CI)	p Value	d*	Difference (95% CI)	p Value	d
Processing speed									
CWIT condition 1+2 (s)	30.9 (6.3)	31.1 (6.5)	27.5 (5.1)	3.3 (1.1 to 5.5)	0.003	0.58	3.5 (1.2 to 5.9)	0.003	0.61
Executive function									
Working memory (sum score)	14.1 (3.4)	13.7 (3.2)	16.5 (3.8)	−2.4 (−3.7 to −1.1)	<0.001	0.67	−2.7 (−4.1 to −1.5)	<0.001	0.8
CWIT cognitive inhibition (s)	59.7 (15.2)	60.2 (15.9)	53.5 (14.0)	6.2 (0.8 to 11.7)	0.025	0.43	6.6 (0.8 to 12.5)	0.026	0.45
CWIT cognitive inhibition (errors)	2.0 (2.0)	2.0 (2.1)	1.6 (1.8)	0.4 (−0.4 to 1.1)	0.349	0.19	0.4 (−0.4 to 1.2)	0.367	0.20
CWIT cognitive flexibility (s)	67.2 (15.2)	66.1 (14.1)	62.4 (13.8)	4.8 (−0.8 to 10.4)	0.092	0.42	3.7 (−1.6 to 9.1)	0.167	0.27
Verbal learning									
HVLT-R total recall (sum score)	27.2 (4.1)	27.3 (3.8)	28.9 (3.7)	−1.7 (−3.2 to −0.3)	0.022	0.44	−1.6 (−3.1 to −0.2)	0.026	0.44
Verbal memory									
HVLT-R delayed recall (sum score)	9.4 (2.1)	9.5 (2.1)	10.1 (1.7)	−0.6 (−1.4 to 0.1)	0.119	0.33	−0.6 (−1.4 to 0.2)	0.119	0.31
BRIEF† GEC	55.1 (9.9)	55.9 (10.1)	43.8 (6.8)	11.2 (8.2 to 14.3)	<0.001	1.34	12.1 (8.3 to 15.9)	<0.001	1.46

*d: Cohen's d, expressing effect size.
†BRIEF: Due to logistic problems, some BRIEF results were missing, giving a total of 32 completed responses for that inventory in the healthy controls group.
BRIEF, Behaviour Rating Inventory of Executive Function; CFS, Chronic Fatigue Syndrome; CDC, Centers for Disease Control and Prevention; CWIT, Color Word Interference Test; HVLT-R, Hopkins Verbal Learning Test-Revised; GEC, global executive composite.

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Table 5 Multivariate analyses of the relationships between cognitive measures as dependent variables and group allocation (chronic fatigue group vs HC), depression symptoms (MFQ), anxiety traits (STAI-T) and sleep problems (KSQ) as independent variables

Dependent variable	Regression	Independent variables	B (95% CI)	β Coefficient	p Value	R^2
Processing speed	Multivariate 1	Group	2.9 (0.4 to 5.4)	0.201	0.022	0.06
		MFQ	−0.04 (−0.1 to 0.06)	−0.075	0.392	
	Multivariate 2	Group	2.9 (0.3 to 5.4)	0.200	0.027	0.06
		STAI-T	−0.04 (−0.2 to 0.07)	−0.069	0.443	
	Multivariate 3	Group	3.5 (0.8 to 6.2)	0.246	0.011	0.06
		KSQ	−0.1 (−1.2 to 0.9)	−0.023	0.807	
Working memory	Multivariate 1	Group	−1.9 (−3.3 to −0.4)	−0.220	0.011	0.10
		MFQ	0.05 (−0.01 to 0.1)	0.154	0.072	
	Multivariate 2	Group	−1.9 (−3.4 to −0.4)	−0.225	0.012	0.09
		STAI-T	0.05 (−0.02 to 0.1)	0.125	0.157	
	Multivariate 3	Group	−1.5 (−3.0 to 0.1)	−0.171	0.067	0.11
		KSQ	−0.7 (−1.3 to −0.06)	−0.202	0.031	
CWIT cognitive inhibition (time)	Multivariate 1	Group	5.7 (−0.4 to 11.8)	0.164	0.065	0.03
		MFQ	−0.05 (−0.3 to 0.2)	−0.034	0.701	
	Multivariate 2	Group	5.6 (−0.6 to 11.9)	0.161	0.079	0.03
		STAI-T	−0.06 (−0.3 to 0.2)	−0.036	0.696	
	Multivariate 3	Group	5.7 (−1.0 to 12.4)	0.164	0.092	0.03
		KSQ	0.3 (−2.2 to 2.9)	0.025	0.797	
HVLT-R verbal learning	Multivariate 1	Group	−1.6 (−3.2 to 0.05)	−0.169	0.057	0.03
		MFQ	0.01 (−0.05 to 0.08)	0.032	0.717	
	Multivariate 2	Group	−1.8 (−3.5 to −0.13)	−0.194	0.034	0.03
		STAI-T	−0.01 (−0.09 to 0.07)	−0.025	0.784	
	Multivariate 3	Group	−1.9 (−3.7 to −0.15)	−0.207	0.034	0.04
		KSQ	0.16 (−0.5 to 0.85)	0.044	0.649	
BRIEF global executive composite	Multivariate 1	Group	8.6 (4.9 to 12.5)	0.360	<0.001	0.23
		MFQ	−0.2 (−0.35 to −0.04)	−0.199	0.014	
	Multivariate 2	Group	7.6 (3.8 to 11.5)	0.318	<0.001	0.25
		STAI-T	−0.3 (−0.46 to −0.1)	−0.266	0.001	
	Multivariate 3	Group	7.6 (3.4 to 11.8)	0.315	<0.001	0.23
		KSQ	2.1 (0.5 to 3.7)	0.229	0.010	

BRIEF, Behaviour Rating Inventory of Executive Function; CWIT, Color Word Interference Test; HC, healthy controls; KSQ, Karolinska Sleep Questionnaire; MFQ, Mood and Feelings Questionnaire; STAI-T, Spielberger State-Trait Inventory.

Impaired cognitive inhibition has been reported,[10] but unlike that study we found no differences in errors for the cognitive inhibition task. When controlling for reduced processing speed for the cognitive inhibition task in our study, group differences disappeared, indicating that reduced processing speed may be the main problem and not cognitive inhibition per se. In line with results by Haig-Ferguson *et al*,[11] we found that the chronic fatigue group had impaired verbal learning, but there was no between-groups difference on delayed recall. In three Hopkins Verbal Learning Test-Revised learning trials, we observed impaired learning on the first and third trials, but not on the second trial, possibly demonstrating fluctuation in working memory. The term working memory refers to a brain system that provides temporary storage and manipulation of the information necessary for more complex cognitive tasks such as learning.[29] The group difference in verbal learning disappeared when we adjusted for working memory, which may indicate that the learning deficit may be explained by the working memory problems in our patient group.

Patients in the present study scored significantly higher than HC on anxiety traits and depression symptoms. When controlling for these two factors in the regression analyses, the group differences in all assessed cognitive measures remained unchanged. This is consistent with results from previous studies showing that impaired cognitive function in adolescents with CFS is not fully explained by depression symptoms or anxiety traits.[10 12] A similar result was reported in adult CFS patients.[30]

Participants with chronic fatigue reported significantly more sleep problems than the HC. When sleep problems were controlled for, the significant group differences for working memory disappeared, indicating that impaired sleep could contribute to reduced working memory. We did not observe the same effect when controlling for sleep problems in the analysis of processing speed, and this is in line with results from a study on adults with CFS.[31]

Strengths and limitations

The relatively high number of participants is a strength of the study. There were no missing data on the cognitive tests and few data missing in the questionnaire responses.

Test administrators were not blinded to the participant's chronic fatigue or HC status, and this could have introduced bias. Also, we did not assess the IQ of the participants; group differences in intelligence could have confounded the group differences in cognitive measures. On the other hand, there was no difference between the groups regarding the parents' highest educational level.[32] According to Lemos *et al*,[33] parents' education predicts adolescents' intelligence, so we assume that IQ is less likely to be a confounder.

Our test protocol and testing procedure may have underestimated the group differences. The quiet and structured test environment may have caused participants to perform above their normal capacity for everyday cognitive challenges. Use of repeated tests or testing sessions of longer duration could perhaps have detected effects of increasing fatigue or post-exertional malaise, as is frequently reported by patients with chronic fatigue.

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Lastly, as our inclusion criteria were too wide to meet published case criteria for CFS, we advise caution in extrapolating our findings to adolescents with CFS.

Clinical implications

We have shown group differences in processing speed, working memory and in everyday EF in line with results from a meta-analysis of adult CFS which concluded that performance around 0.5–1.0 SD below HC levels is likely to impact on day-to-day activities.[34]

Two thirds of the chronic fatigue group scored more than 1 SD worse than the HC or Norwegian normative data[28] on the BRIEF (see eTable 1), indicating that adolescents with chronic fatigue demonstrate clinically significant problems with everyday EF.

Further, these cognitive difficulties may negatively affect other cognitive functions such as verbal learning. Working memory is often the target of cognitive training programmes because of its assumed ability to influence a range of other cognitive processes.[35] These observations, together with impaired general EF in everyday life, demonstrate that the problems may be clinically relevant.

Caretakers, the health service and schools should recognise these problems and provide neuropsychological guidance. Such advice could include reducing the pace of teaching or work presentation and reducing the level of distraction in the learning environment, as suggested by Tucker *et al*.[36] In addition, repeated learning of new information and help structuring new information may be useful.

Future research

Neither our study nor studies on adolescents with CFS that have assessed cognitive function have employed repeated testing or cognitive effort (which could resemble a classroom setting). By using such an approach, future research could explore potential associations between cognitive impairment and post-exertional fatigue.

Sleep problems are frequently reported concurrently with chronic fatigue in adolescents, and the association between sleep and cognitive problems in chronic fatigue is still unclear. Further studies addressing cognitive problems and sleep in chronic fatigue, possibly applying a more objective assessment of sleep, could clarify the effect of therapeutic interventions to improve sleep.

To our knowledge, only one study with few participants[12] has evaluated how established treatment and healthcare advice affects cognitive performance in young people with chronic fatigue. Further studies are needed to improve support for these patients.

CONCLUSIONS

Adolescents aged 12–18 years with medically unexplained chronic fatigue have impaired cognitive function on objective cognitive tests and on measures of everyday EF compared to HC. It is important that the health service and school teachers address cognitive function when providing support to these patients. Future research should evaluate treatment interventions that can improve cognitive functioning in this patient group.

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REFERENCES

1 ter WolbeekM van DoornenLJP Kavelaars A, *et al*. Severe fatigue in adolescents: a common phenomenon? *Pediatrics* 2006;117:e1078–86.
2 Crawley E, Hughes R, Northstone K, *et al*. Chronic disabling fatigue at age 13 and association with family adversity. *Pediatrics* 2012;130:e71–9.
3 Nijhof SL, Maijer K, Bleijenberg G, *et al*. Adolescent chronic fatigue syndrome: prevalence, incidence, and morbidity. *Pediatrics* 2011;127:e1169–75.
4 Crawley EM, Emond AM, Sterne JAC. Unidentified Chronic Fatigue Syndrome/myalgic encephalomyelitis (CFS/ME) is a major cause of school absence: surveillance outcomes from school-based clinics. *BMJ Open* 2011;1:e000252.
5 Kennedy G, Underwood C, Belch JJ. Physical and functional impact of chronic fatigue syndrome/myalgic encephalomyelitis in childhood. *Pediatrics* 2010;125:e1324–30.
6 Fukuda K, Straus SE, Hickie I, *et al*. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994;121:953–9.
7 Brurberg KG, Fønhus MS, Larun L, *et al*. Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review. *BMJ Open* 2014;4:e003973.
8 Jordan KM, Landis DA, Downey MC, *et al*. Chronic fatigue syndrome in children and adolescents: a review. *J Adolescent Health* 1998;22:4–18.
9 NICE. *Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management of CFS/ME in adults and children*. CG53. London: National Institute for Health and Clinical Excellence (NICE), 2007.
10 Van de Putte EM, Boecker KB, Buitelaar J. Deficits of interference control in adolescents with chronic fatigue syndrome. *Arch Pediatr Adolesc Med* 2008;162:1196–7.
11 Haig-Ferguson A, Tucker P, Eaton N, *et al*. Memory and attention problems in children with chronic fatigue syndrome or myalgic encephalopathy. *Arch Dis Child* 2009;94:757–62.
12 Kawatani J, Mizuno K, Shiraishi S, *et al*. Cognitive dysfunction and mental fatigue in childhood chronic fatigue syndrome—a 6-month follow-up study. *Brain Dev* 2011;33:832–41.
13 Miyake A, Friedman NP, Emerson MJ, *et al*. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cogn Psychol* 2000;41:49–100.
14 Isquith PK, Roth RM, Gioia G. Contribution of rating scales to the assessment of executive functions. *Appl Neuropsychol Child* 2013;2:125–32.
15 Bould H, Collin SM, Lewis G, *et al*. Depression in paediatric chronic fatigue syndrome. *Arch Dis Child* 2013;98:425–8.
16 Bould H, Lewis G, Emond A, *et al*. Depression and anxiety in children with CFS/ME: cause or effect? *Arch Dis Child* 2011;96:211–14.
17 Airaksinen A. *Cognitive Functions in Depression and Anxiety Disorders. Findings from a population-based study*. Stockholm, Sweden: Doctoral Thesis from Department of Public Health, Division of Social Medicine, Karolinska Institutet, 2006.

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18 Castaneada AE, Tuulio-Henriksen A, Marttunen M, *et al*. A review of cognitive impairments in depressive and anxiety disorders with a focus on young adults. *J Affect Disord* 2008;106:1–27.
19 Gioia GA, Isquith PK, Guy SC, *et al*. Behavior rating inventory of executive function. *Child Neuropsychol* 2000;6:235–8.
20 Fallmyr O, Egeland J. Psychometric properties of the Norwegian version of BRIEF—for children from 5 to 18 years old. *J Norwegian Psychol Association* 2011;48:339–43.
21 Akerstedt T, Knutsson A, Westerholm P, *et al*. Work organization and unintentional sleep: results from the WOLF study. *Occup Environ Med* 2002;59:595–600.
22 Sund AM, Larsson B, Wichstrøm L. Depressive symptoms among young Norwegian adolescents as measured by the Mood and Feelings Questionnaire (MFQ). *Eur Child Adolesc Psychiatry* 2001;10:222–9.
23 Spielberger CD, Gorsuch RL, Lushene RE. *STAI Manual for the Stait-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press, 1973.
24 Cohen JW. *Statistical Power Analysis for the Behavioral Sciences*. 2nd edn. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988.
25 Wechsler D. *Wechsler Intelligence Scale for Children—fourth edition (Norwegian version)*. Stockholm, Sweden: The Psychological Corporation, 2004.
26 Delis D, Kaplan E, Kramer J. *Delis-Kaplan Executive Function System (D-KEFS) (Norwegian version)*. Stockholm, Sweden: Pearson System, 2001.
27 Holmèn A, Juuhl-Langseth M, Thormodsen R, *et al*. Neuropsychological profile in early-onset schizophrenia-spectrum disorders: measured with the MATRICS battery. *Schizophr Bull* 2010;36:852–9.
28 Hovik KT, Egeland J, Isquith PK, *et al*. Distinct patterns of everyday function problems distinguish children with Tourette syndrome from children with ADHD or autism spectrum disorders. *J Atten Disord* 2014. Published Online First: 24 Sep 2014. doi:10.1177/1087054714550336
29 Baddeley A. Working memory. *Curr Biol* 2010;20:136–40.
30 Vollmer-Conna U, Wakefield D, Lloyd A, *et al*. Cognitive deficits in patients suffering from chronic fatigue syndrome, acute infective illness or depression. *Br J Psychiatry* 1997;171:377–81.
31 Cockshell SJ, Mathias JL. Cognitive deficits in chronic fatigue syndrome and their relationship to psychological status, symptomatology, and everyday functioning. *Neuropsychology* 2013;27:230–42.
32 Sulheim D, Fagermoen E, Winger A, *et al*. Disease mechanisms and clonidine treatment in adolescent chronic fatigue syndrome: a combined cross-sectional and randomized clinical trial. *JAMA Pediatr* 2014;168:351–60.
33 Lemos GC, Almeida LS, Colom R. Intelligence of adolescents is related to their parents' educational level but not to family income. *Pers Individ Diff* 2011;50:1062–7.
34 Cockshell SJ, Mathias JL. Cognitive functioning in chronic fatigue syndrome: a meta-analysis. *Psychol Med* 2010;40:1253–67.
35 Jaeggi SM, Buschkuehl M, Jonides J, *et al*. Short- and long-term benefits of cognitive training. *Proc Natl Acad Sci USA* 2011;108:10081–6.
36 Tucker P, Haig-Ferguson A, Eaton N, *et al*. What to do about attention and memory problems in children with CFS/ME: a neuropsychological approach. *Clin Child Psychol Psychiatry* 2011;16:215–23.

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