A dive into the deep, mysterious waters of chronic fatigue and cognition in adolescents:

Investigating subjective experiences of cognitive difficulties and objective measures of cognitive functioning

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Submitted as cand.psychol. thesis
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May 2020

Abstract

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Title: "A dive into the deep, mysterious waters of chronic fatigue and cognition in adolescents"

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Objective: The focus of the current study was to examine cognitive functioning by objective and subjective measures in adolescents with chronic fatigue (CF) and chronic fatigue syndrome (CFS). The results were compared between adolescents who developed CF/CFS and those who did not develop CF/CFS following acute EBV infection and healthy controls. To the extent of our knowledge, no studies to date on adolescents with CF/CFS have examined both subjective and objective cognitive functioning six months post EBV infection. **Methods:** Cognitive functioning of 195 adolescents was assessed six months after identification of acute EBV infection against 70 healthy controls. The EBV patients were divided into two main groups at six months; EBV (CF+), those who developed CF/CFS, and EBV (CF-), those who did not develop CF/CFS. Those who met the symptom requirements for CFS were further distinguished from the total group of adolescents with CF/CFS. Objective measures were assessed with neuropsychological tests. For subjective and clinical measures, various self-report questionnaires were applied. The data used in this thesis is cross-sectional and based on data already collected as part of the CEBA project[1]. The groups were compared applying one-way ANOVA and Student's t-test. **Results:** The total EBV (CF+) was not adversely affected on objective cognitive measures compared to EBV (CF-) and healthy controls. When measuring cognitive flexibility, verbal learning and verbal memory, the CFS subgroups performed worse compared to the total EBV (CF+) group. EBV (CF+) reported significantly more cognitive problems compared to EBV (CF-) and healthy controls. The CFS subgroups reported more subjective cognitive difficulties compared to the total EBV (CF+) group. **Conclusion:** The total group of adolescents with CF/CFS was not adversely affected on objective measures compared to the non-fatigued and healthy controls. Our findings suggest that adolescents who were diagnosed with CFS were more severely affected on both subjective and objective measures of cognitive functioning, which may indicate that symptom severity in patients with CF/CFS contributes to reduced cognitive functioning and should be addressed in future research.

[1]The Chronic Fatigue Following Acute EBV Infection in Adolescents (CEBA) project is a doctoral thesis and a prospective cohort study investigating fatigue development, conducted at the Department of Paediatrics, Akershus University hospital.

Acknowledgements

A special and huge thank you to our main supervisor, Merete Glenne Øie at the Department of Psychology, University of Oslo. Thank you, Merete, for being patient with us, and for always being available for small and big questions. It has been a long journey from the start of the project to the finish line, and we greatly appreciate your constructive feedback and detail-orientated approach along the way. This project would not have been possible without you. A big thank you to our co-supervisor, Vegard Bruun Bratholm Wyller at the Dept. of Paediatrics, Akershus University hospital, for being available for inquiries regarding chronic fatigue and statistics. We appreciate all the knowledge you have been willing to share with us, and the great inputs. We also want to thank Maria Pedersen at the Dept. of Paediatrics, Akershus University hospital, for letting us be part of the CEBA project and for providing the data used in the current study.

We both want to thank Gyssestadkollen and Rosings gate for providing alternative offices during the corona pandemic. Thank you, Albert, for letting us have the living room daily for months. A big thank you to our great families and friends for cheering us on!

I, Maria, want to thank my partner Aksel for all your patience during this time, for believing in me and for always looking after my well-being. Thank you for all your support, I love you! Further, I want to thank my parents, Beate and Toralf, and my sisters Anna and Selma, for their ongoing care, love and support.

I, Sofie, want to give a special thank you to my parents, Elisabeth and Hans-Jacob, for always believing in me and supporting me in all the projects I have going on in life, “Turgruppa” for being the best study group through six years, and H.P.L for always reminding me that life is short and inspiring me to always chase my goals in life.

Finally, we want to thank each other. We could not have done this without one another, and we thank each other for all the laughter, cheese-and-cracker-breaks, optimism, support and hard work. What better way to celebrate fifteen years of friendship than to turn in our master thesis together!

Oslo, May 2020

Maria Bølgen and Sofie Buer

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1 Introduction

1.1 Introduction

The current study is based on data collected for the prospective cohort research project labelled Chronic Fatigue Following Acute EBV Infection in Adolescents (CEBA). The overarching aim of CEBA is to investigate fatigue development in adolescents after acute Epstein-Barr Virus (EBV) infection. The focus of the current study is to explore subjective experiences of cognitive difficulties and objective cognitive functioning in the CEBA participants who developed chronic fatigue and Chronic Fatigue Syndrome (CFS) six months after the acute infection compared with those who did not develop fatigue and healthy controls. Firstly, a historical perspective on chronic fatigue as a phenomenon as well as different case definitions of CFS will be presented, before introducing the case definitions typically applied today. Secondly, pathophysiological models for CFS, prevalence, gender differences and prognosis will be presented, before introducing previous research findings that shed light on the focus for our master thesis.

1.1.1 Background

Today, fatigue is considered to be a common symptom in the general population (Engberg, Segerstedt, Waller, Wennberg, & Eliasson, 2017). Fatigue is often observed accompanying physical and mental disorders, and it is therefore natural to classify fatigue as a nonspecific symptom. Today, it is common to distinguish chronic fatigue from CFS. CFS is a formal diagnosis based on a set of criteria (see below). CF represents a more unspecific experience of fatigue, commonly reported by patients after different viral infections. However, many researchers believe there to be only quantitative differences between the CF phenomenon and CFS. Recent findings also suggests that there are similar underlying disease mechanisms for CF and CFS (Pedersen et al., 2019). The main difference appears to be that individuals with CFS experience more symptoms and a greater decline in daily function compared to those with CF. As for objectively measured cognitive functioning, more severe fatigue has been associated with worse performance on cognitive tests (Teodoro, Edwards, & Isaacs, 2018). Pedersen et al. (2019)

found higher fatigue associated with lower cognitive functioning in the same sample of adolescents with CF/CFS as the current study. However, the effect of fatigue on cognitive performance in CFS patients remains unclear (Constant et al., 2011).

Historical evidence suggests that CF was rarely reported as a symptom of complaint, in the absence of any evident organic illness, until the mid-19th century (Shorter, 1993). One of the first known outbreaks of the condition was the so-called "bed-cases" or "sofa-cases" among middle class females in the period from 1860 to about 1910 (Shorter, 1993). In the 1860s, George Beard introduced the diagnosis neurasthenia in the US, which quickly spread to Europe with fatigue being the main symptom (Lillestøl & Bondevik, 2013). Today, many researchers believe neurasthenia to be identical to CFS. Furthermore, the background for the development of a "syndrome" based on fatigue as the dominant symptom appears to have been a result of several, but separate chains of events particularly in the 20th century, for instance, the epidemic that spread among the employees at the Royal Free Hospital in London in 1955 (The Medical Staff Of The Royal Free, 1957). Altogether, these events, mainly characterized by isolated instances of muscle weakness and fatigue, spread in an almost epidemic-like manner without any identified etiology (Gilliam, 1938; Henderson & Shelokov, 1959).

In 1964, the Epstein-Barr virus (EBV) was discovered (Epstein, Achong, & Barr, 1964), and its connection to infectious mononucleosis was evident in 1968 (Henle, Henle, & Diehl, 1968). In the aftermath, EBV was linked to several other clinical conditions such as CFS. For instance, in the mid-1980s, there were two immense outbreaks of an illness in Nevada and New York which resembled mononucleosis. The distinction between mononucleosis and CFS seemed to have been made depending on the duration of the illness. The immense outbreaks were characterized by "chronic or recurrent debilitating fatigue and various combinations of other symptoms, including sore throat, lymph node pain and tenderness, headache, myalgia, and arthralgias" (Holmes et al., 1988). The illness was essentially linked to the EBV and given the name "chronic Epstein-Barr virus syndrome," implying a causal relationship with EBV (Holmes et al., 1988).

The existence of such a causal relationship was not evident, and in 1987 the US Centers for Disease Control and Prevention (CDC) organized a working group to reach consensus on the clinical features of the illness (IOM, 2015). However, the illness did not represent a completely new phenomenon, and it had been given numerous different names throughout the history

(Straus, 1991). The different names applied for the illness all reflect different understandings of the etiology and epidemiology of the phenomenon. It appeared to be dependent on whether its features were attributed to environmental, metabolic, infectious, immunologic or psychiatric disturbances (Straus, 1991). As new research emerged, various causes of the illness, including EBV, could be ruled out as the sole cause. Therefore, the CDC working group found it necessary to give the illness a new name, "chronic fatigue syndrome," as it was less misleading and more inclusive. This name was more in line with the fact that the cause was indeed unknown (IOM, 2015). Today, however, there is no doubt that EBV represents a trigger for CFS in many cases.

After the very first definition of CFS was published in 1988 (Holmes et al., 1988), there have been several attempts to update this definition. The most frequently used diagnosis definitions applied today are the Fukuda-criteria (Fukuda et al., 1994) and/or the Canadian criteria (Carruthers et al., 2003; Carruthers et al., 2011). These definitions are often used simultaneously in research.

The Fukuda criteria were developed in 1994 by the US Centers for Disease Control and Prevention, and the main criteria require that the fatigue is unexplained and persistent or relapsing for six months or more. Moreover, it must affect daily activities, have a clear and defined onset, and the fatigue is not eased by rest. In addition to these main criteria, the patients must also meet at least four out of eight described accompanying symptoms (Fukuda et al., 1994).

Carruthers and colleagues developed the Canadian Consensus Criteria in 2003 (Carruthers, 2003) and the International Consensus Criteria in 2011 (Carruthers et al., 2011). These definitions were developed in order to try to acquire narrower selection of CFS patients, and consequently achieve a higher specificity for patients with a certain pathophysiology. The Canadian Consensus Criteria for chronic fatigue syndrome (CFS) are more detailed in symptom requirements, but have not been formally validated (Asprusten et al., 2015). Asprusten and colleagues explored the content validity of the Canadian Consensus Criteria in a sample of adolescents with CFS selected based on a wide case definition (Asprusten et al., 2015). They found that there were hardly any differences in disease markers between adolescent patients with CFS that adhered to this case definition versus those who did not. Implications of such findings indicate that stricter criteria are not necessarily beneficial. Taken together, the Canadian criteria are more detailed and stricter.

When this definition is applied in research or clinical settings, it may consequently lead to lower prevalence estimates as opposed to the Fukuda-criteria.

CFS is today recognized as a severely devastating condition, and there are no known biomarkers that can, with any certainty, be directly linked to CFS to this date (Rasouli et al., 2019). CFS is characterized by persistent, pronounced and disabling fatigue with a definite onset and exhaustion even after the slightest physical or mental exertion (Rasouli et al., 2019). In addition, it involves a combination of other symptoms such as post-exertional malaise, headaches, sleep disturbances, sore throat, tender lymph nodes, cognitive dysfunction, and musculoskeletal pain (IOM, 2015). Case-definitions applied today are based solely on self-perceived fatigue and accompanied symptoms as mentioned above, since no biomarker has yet been identified (Pedersen et al., 2019). Validated self-report questionnaires are typically applied (Holtzer et al., 2016).

According to the most frequently used case definitions, the fatigue is considered chronic if the subject has experienced the fatigue to have lasted for 6 months or more (Carruthers et al., 2003; Carruthers et al., 2011; Fukuda et al., 1994). However, for children and adolescents a requirement that the symptoms have lasted 3 months is recommended (NICE, 2007). The severity is determined based on the extent the fatigue interferes with daily function (Son, 2019), and may be evaluated differently depending on the case definition applied by the general practitioner (Jordan et al., 2006).

Today, there is still much more to learn about the potential existence of common underlying mechanisms of CF and CFS (Pedersen et al., 2019). Despite a considerable degree of diversity in the patient group (Huber, Sunnquist, & Jason, 2018), it is possible that there might be certain common underlying mechanisms. However, the heterogeneity within the patient group may have hindered researchers from finding a common understanding of its etiology.

1.1.2 Pathophysiological features and models for CFS

Adolescent CFS has been found associated with several pathophysiological features such as hormonal-, autonomic- and immunological alterations, impairment in executive function, sleeping problems, specific personality traits, emotional instabilities and negative life events (Pedersen et al., 2019). Over the years several models have been developed to explain etiology

and maintaining factors in CFS. The models offer frameworks that conceptualize fatigue from different perspectives.

The cognitive behavioral model, introduced by Sharpe (1997) posits that the development of CFS occurs due to an initial trigger such as a virus or a stressor, but is sustained by behavioral factors such as activity avoidance and illness perceptions (Deary, Chalder, & Sharpe, 2007). These behavioral factors affect biological factors negatively and contribute to the maintenance of CFS. A model developed by Harvey and Wessely (2009) emphasizes the role of predisposed individuals. In this model, the development of fatigue occurs in predisposed individuals with specific characteristics in the presence of a triggering event such as a viral infection or stressor. The development of fatigue is also influenced by maintaining factors such as reduced activity and biological changes. Lenaert, Boddez, Vlaeyen, and van Heugten (2018) introduced a model that conceptualizes fatigue from an associative learning perspective based on principles from classical and operant conditioning. The model suggests that interceptive and exteroceptive stimuli may evoke behavioral change, including fear, avoidance and fatigue.

More recently, Kube, Rozenkrantz, Rief, and Barsky (2020) provided an integrative model that focuses on the maintenance of persistent physical symptoms, including chronic fatigue. This integrative model connects relevant psychological models and neuroscientific knowledge as an attempt to better understand the maintaining mechanisms behind persistent physical symptoms. The model suggests that persistent physical symptoms may be related to abnormal processing of benign bodily sensations; more specifically, it is hypothesized that aberrant brain predictions of internal body states leads to erroneous percepts that are not properly corrected by sensory information (Kube et al., 2020). Furthermore, the model suggests that negative reappraisal of disconfirmatory evidence such as subjective reports of physical symptoms accompanied by lack of objective findings may have an impact on persistence and illness perception.

The models based on viral theories, on the other hand, posit that CFS may be caused directly or indirectly by a virus (Bansal, Bradley, Bishop, Kiani-Alikhan, & Ford, 2012). Even though EBV, for instance, was ruled out as a potential causal agent in the development of CFS, it still plays a significant role in the understanding of CFS to this date. Today, acute EBV infection is a well-known trigger for acute fatigue, chronic fatigue and CFS (Blomberg, Gottfries, Elfaitouri, Rizwan, & Rosen, 2018). Other infections have also been linked to the development of CF/CFS.

Hickie et al. (2006), for instance, propose a post-infective model as one possible pathway to CF/CFS based on their findings of a relatively uniform post-infective fatigue in patients suffering from glandular fever, Q fever and Ross River virus. One of the challenges with viral theories is that there is yet no single virus that can account for all incidents of CFS development. Even though several virus antibodies are commonly found in patients, these can also be found in healthy controls such as with the EBV. It has also been proposed that CFS is an autoimmune disease with a gradual elimination of autoantibodies, but consistent findings to support this hypothesis are lacking (Fluge et al., 2011). Generally, in biological models, CFS development is explained with a greater emphasis on biological processes such as the role of hormonal-, autonomic- and/or immunological alterations in the development of CFS, and infections or other diseases as triggers for these alterations (Maes & Twisk, 2010).

In 2009, Wyller and colleagues introduced the sustained arousal model to explain the pathophysiological features in CFS. The model suggests that predisposing factors such as genetics and personality traits accompanied by triggering factors such as long-lasting infections and negative life events, consequently lead to an extended bodily stress response, called "sustained arousal" (Wyller, Eriksen, & Malterud, 2009). The sustained arousal explains cognitive impairment as well as hormonal-, autonomic- and immunological alterations, and in return these alterations function as active agents to the continuation of sustained arousal and fatigue (Wyller et al., 2009). The conceptualization of fatigue from an understanding of sustained arousal has provided the framework applied in the overall CEBA project.

1.1.3 Prevalence and gender differences in adolescents

Few studies have investigated the prevalence of CFS in children and adolescents specifically. Results from relevant population-based studies provide varying estimates (Chalder, Goodman, Wessely, Hotopf, & Meltzer, 2003; Elgen, Hikmat, Aspevik, & Hagen, 2013; Jordan et al., 2006; Rimes et al., 2007). Prevalence appears to vary from about 0.2% to 2.0% for children and adolescents (Chalder, 2003; Collin, 2016; Crawley, 2012; Farmer, 2004; Rimes, 2007). Findings from studies on adolescents also support existing gender differences, with a higher prevalence of CFS for females (Nijhof et al., 2011). A population-based registry study from Norway in the period of 2008 to 2012 found the female to male incidence rate ratio of CFS to be 3:2 (Bakken et

al., 2014). Bakken et al. (2014) also found two age peaks in the incidence of CFS; the first peak was found to be in the age group 10 to 19 years, with a second peak in the age group 30 to 39 years (Bakken et al., 2014). These age peaks, as well as the findings on gender differences may indicate that gender and age modulate the risk of development of CFS.

1.1.4 Prognosis for adolescents

It appears that prognosis is significantly better in children and adolescents compared to adults (Crawley, 2018). A more recent population study from Great Britain provides estimates of recovery time of 2-3 years for approximately 75% of all adolescents with CFS (Norris et al., 2017). However, it is uncertain whether recovery can be solely attributed to treatment received, and may be better explained by the individual differences in recovery speed (Nijhof et al., 2013). Another long-term follow-up study found that children and adolescents with CFS had symptoms with a mean duration of 5 years (1-15), with up to 68% reporting recovery by 10 years (Rowe, 2019). Furthermore, findings also suggested there to be no certain baseline predictors for recovery (Rowe, 2019). However, follow-up data provided an indication that depression, anxiety, orthostatic intolerance and to a lesser extent pain appeared to affect recovery time and/or function (Rowe, 2019).

1.2 Cognitive functioning in adolescents with CFS

1.2.1 Previous research on objective measures of cognitive functioning

Haig-Ferguson, Tucker, Eaton, Hunt, and Crawley (2009) investigated cognitive functioning in 20 children and adolescents with CFS with a mean age of 13.5 years (SD 2.6, range 8-16 years) compared to standardized age norms. They found reduced verbal learning (immediate recall), assessed with Word Pairs from Children's Memory Scale (CMS). Haig-Ferguson et al. (2009) did not demonstrate reduced processing speed, assessed with Symbol Search from Wechsler Intelligence Scale for Children, 4th edition (WISC-IV). They did not find impaired working memory assessed with Letter Number Sequencing and Digit Span from WISC-IV, nor did they find reduced verbal memory (delayed recall) assessed with Word Pairs from CMS. The children and adolescents in the study by Haig-Ferguson et al. (2009) had been ill with CFS in the range of

10-67 months, however, they do not specify illness duration further for the CFS sample included in the study.

Sulheim et al. (2015) investigated cognitive functioning in 120 adolescents with CF/CFS with a mean age of 15.4 years (SD 1.6, range 12-18 years) compared to healthy controls. They found reduced processing speed and reduced cognitive inhibition, assessed with the Color-Word Interference Test (CWIT) from the Delis-Kaplan Executive Function System. Further, they reported impaired working memory, assessed with Digit Span from WISC-IV, and reduced verbal learning (immediate recall), assessed with the Hopkins Verbal Learning Test - Revised (HVLT-R). Sulheim et al. (2015) did not demonstrate reduced verbal memory (delayed recall), assessed with HVLT-R. Group differences between adolescents with CF/CFS and healthy controls disappeared when working memory was adjusted for sleep problems, cognitive inhibition was adjusted for reduced processing speed and verbal learning (immediate recall) was adjusted for reduced working memory. Group differences in processing speed remained unaffected when adjusted for sleep problems. The study sample consisted of a subgroup diagnosed with CFS (n=88) according to the Fukuda criteria. The results from the analysis of the CFS subgroup were not significantly different from those in the CF group. The adolescents in the study by Sulheim et al. (2015) had been ill with CF/CFS for 21 months on average (range 4-104 months).

Josev et al. (2019) investigated cognitive functioning in 25 adolescents with CFS with a mean age of 16.0 years (SD 1.5, range 13-18 years) compared to healthy controls. They found reduced processing speed, assessed with the CogState Computerized Battery (www.cogstate.com). Josev et al. (2019) did not demonstrate reduced working memory assessed with CogState, but the results were close to significance. The adolescents in the study by Josev et al. (2019) reported illness duration range; approximately 50% had been ill for 3 to 12 months and the rest 13 to >24 months.

Kawatani et al. (2011) investigated cognitive functioning in 19 adolescents with CFS with mean age 13.6 years (SD 0.7, range 13-15 years) compared to healthy controls. They found reduced cognitive inhibition and reduced cognitive flexibility, assessed with the computerized modified Advanced Trail Making Test (mATMT). The adolescents in the study by Kawatani et al. (2011) had been ill with CFS for 7.6 months on average (SD 5.8).

Van de Putte et al. (2008) investigated cognitive functioning in 34 adolescents with CFS (age range 12-18 years) compared to healthy controls. They found reduced cognitive inhibition, assessed with a modified Eriksen Flanker Task (EFT). Illness duration was not reported in the study by Van de Putte et al. (2008).

In sum, some of the previous studies on children and adolescents with CFS have reported deficits in processing speed, working memory, cognitive inhibition, cognitive flexibility, and verbal learning (immediate recall). Results from the mentioned studies are inconsistent, which may be due to differences in sample size, selection of tasks, age differences or variations in illness duration. None of the previous studies have had an additional control group consisting of adolescents with an acute onset viral infection that have not developed CF/CFS, to control for the possible contribution of a virus on cognitive difficulties.

1.2.2 Subjective experience of cognitive functioning

Haig-Ferguson et al. (2009) examined subjective cognitive functioning in children and adolescents with CFS. Haig-Ferguson et al. (2009) investigated qualitative properties of memory and attention problems in 20 children (age range 8 to 16 years) diagnosed with CFS from a specialized service. The children and adolescents, their teachers and parents were all given a four-item semi-structured questionnaire that was used to map out the children's subjective experience of cognitive difficulties. The study did not include a healthy control group but used standardized norms. Children and adolescents with CFS, along with their parents and teachers, described problems with focused attention (problems attending to external cues, such as conversations or instructions), sustained attention (ability to maintain mental stamina and successfully complete tasks over time) and recall (difficulty retrieving specific information from memory).

Sulheim et al. (2015) also investigated subjective cognitive functioning in adolescents. However, they based the adolescent's subjective experience of cognitive function on information given solely by their parents, using the parent form of the Behavior Rating Inventory of Executive Function (BRIEF). The BRIEF was developed to provide information about everyday behaviors associated with specific domains of the executive functions in children and adolescents aged 5 to

18 years. The informants in Sulheim et al. (2015) reported significantly more subjective cognitive difficulties in the CFS group compared to the healthy controls.

Other studies have investigated subjective experience of cognitive functioning in adults with CFS. Rasouli et al. (2019) investigated the relation between subjective and objective findings within several cognitive domains in a total of 236 adults with CFS (age ranging from 18 to 62 years). For subjective cognitive difficulties, the Everyday Memory Questionnaire (EMQ) was applied, primarily assessing memory and attention problems. The participants in Rasouli et al. (2019) reported a high level of cognitive difficulties. The EMQ score was also found to be positively associated with fatigue, pain and depression levels (Rasouli et al., 2019).

Cockshell and Mathias (2014) investigated the subjective experience of cognitive functioning in 50 adults diagnosed with CFS and 50 healthy controls (age range 18 to 60 years). The cognitive domains investigated in Cockshell and Mathias (2014) were also memory and attention. The Centers for Disease Control (CDC) CFS Symptom Inventory, Cognitive Failures Questionnaire and a scale to rate symptom severity were applied to assess memory. As for attention, the Everyday Attention Questionnaire, CDC CFS Symptom Inventory and a scale to rate symptom severity were applied. Cockshell and Mathias (2014) also found that the CFS group reported more cognitive problems than the healthy controls.

However, subjective complaints of cognitive difficulties are a common symptom in CFS patients and part of the CFS diagnostic criteria (Carruthers et al., 2003; Carruthers et al., 2011; Fukuda et al., 1994). Therefore, it is perhaps not very surprising that previous studies illustrate that those with CFS tend to subjectively experience more cognitive difficulties compared to healthy controls. Yet, it is important to investigate because everyday life is complex and might not be compatible with tests that measure specific cognitive functions in a controlled and structured test environment (Snyder, Miyake, & Hankin, 2015). Self-report measures typically ask about general cognitive functioning experienced by patients with CFS during everyday tasks, which has the advantage of capturing a broad range of subjective experiences in a realistic setting (Cockshell & Mathias, 2014). There is a possibility that objective cognitive tests fail to capture the struggles experienced by adolescents with CFS in school and social situations of everyday life. Some objective cognitive tests may not be sensitive enough to capture more subtle cognitive difficulties experienced by CFS patients as many tests were developed to detect more severe deficits, e.g. in

patients who have suffered traumatic brain injury (Snyder et al., 2015); some tests might be affected by ceiling effects. Hence, it is likely that if impairments are detectable from objective measures, this might indicate that cognitive difficulties are experienced in real-life situations as well.

A quiet, structured and controlled test environment may also enhance performance in adolescents with CFS compared to complex real-world situations such as at school where there might be many more distractions. Taken together, subjective and objective forms of measurement might not reflect the same construct (Snyder et al., 2015). Cockshell and Mathias (2014) concluded in their study that there is little evidence of a relationship between subjective and objective measures of cognitive functioning for both the adults with CFS and healthy control. Cockshell and Mathias (2014) further suggest that subjective and objective measures capture different constructs. Self-report measures may have higher ecological validity than neuropsychological tests, but may be influenced by contextual factors to a greater extent than objective tests (Snyder et al., 2015). Both measures have advantages and disadvantages, and both provide important insight into cognitive functioning, highlighting the need to explore subjective experience as well as objective tests of cognitive functioning.

1.2.3 Comorbidity in CFS

Anxiety and depression is common in patients with CFS, but is also known to affect cognition in general (Constant et al., 2011). Most studies on adolescents with CFS find increased symptoms of depression and anxiety, but the symptoms do not appear to fully explain cognitive impairments (Kawatani et al., 2011; Sulheim et al., 2015; Van de Putte et al., 2008). Sulheim et al. (2015) reported that the group differences between adolescents with CF/CFS and healthy controls remained unaffected when they adjusted for symptoms of depression and anxiety.

Some studies on adults with CFS support the notion that symptoms of depression contribute to, but do not necessarily account for, the severity of self-reported cognitive difficulties in patients with CFS (Cockshell & Mathias, 2010; Teodoro et al., 2018). There are findings suggesting that adults with CFS are more anxious than healthy controls (Constant et al., 2011). Some studies have found that higher levels of depression correlate positively with greater subjective cognitive problems in patients with CFS (Cockshell & Mathias, 2014; Rasouli et al., 2019). It is possible

that depression symptoms may affect subjective measures to a greater extent than objective test measures, based on the assumption that a structured and controlled test environment might enhance performance on objective cognitive tests, as mentioned above.

1.3 The current study

In summary, given the devastating impact on quality of life, school attendance and general development for adolescents affected by CF/CFS, it is important to continue to dig deeper into this somewhat enigmatic condition. Scientific research on CF/CFS, however, faces numerous challenges due to its complex nature, as mentioned above. On that note, the patient group in the current study is narrowed down to adolescent patients only 6 months after acute EBV infection. In addition to controlling for illness duration, the patient group has a viral infection as a trigger for eliciting illness, which allows us to investigate a less heterogeneous group with CF/CFS, compared to samples in other studies which consist of CFS patients with different illness triggers. Another of our study's strengths is the larger sample size used compared to previous studies. We compare cognitive functioning across three groups: Those who developed chronic fatigue, denoted as EBV (CF+), those who did not, denoted as EBV (CF-), and a healthy control group without any current EBV infection. Thus, the study design allows us to control for effects of the EBV infection not associated with CF/CFS. We have chosen not to discriminate between CF and CFS in the main analysis of the current study, based on findings by Sulheim et al. (2015), where the CFS subgroup did not display significant differences in cognitive functioning compared to the adolescents with CF. To the extent of our knowledge, no studies to date on adolescents with CF/CFS have examined both the subjective complaints of cognitive difficulties and objective tests of cognitive functioning in a sample of adolescents 6 months post EBV infection. The main purpose of our master thesis is to explore cognitive functioning in all three groups, measured using both subjective reports and objective tests. Hopefully, it will add new, useful insight into the role of cognitive functioning in adolescents with CF/CFS after acute EBV infection.

1.4 Aims and hypotheses in the current study

The first aim of the current study is to investigate results on objective measures of cognitive functioning between the EBV (CF+) group, the EBV (CF-) group, and healthy controls. We will not present a clear hypothesis of which cognitive functions will be reduced, based on inconclusive findings from previous research.

The second aim of the current study is to investigate subjective experiences of cognitive functioning between the EBV (CF+) group, the EBV (CF-) group, and healthy controls. We hypothesize that adolescents with CF/CFS in the EBV (CF+) group will report significantly more cognitive difficulties compared to non-fatigued adolescents in the EBV (CF-) group and healthy controls. Our hypothesis is based on frequent reports of subjective cognitive difficulties in CFS patients and cognitive difficulties as part of the required symptoms leading to a CFS diagnosis.

2 Methods

2.1 Study design and participants

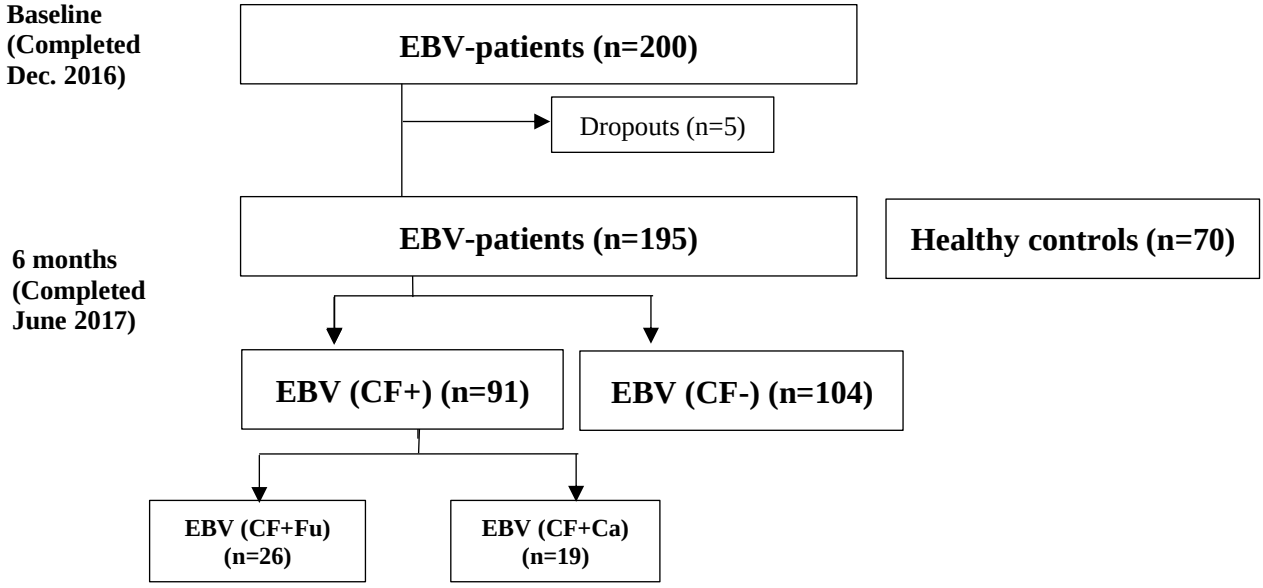
In the CEBA project, a total of 200 adolescents with acute EBV infection were included from counties in the South-East part of Norway (Oslo, Akershus, Buskerud, Vestfold and Østfold) and followed prospectively for 6 months. The recruitment period lasted for 20 months (March 2015 to November 2016).

Participants in the age range of 12 ≤ to < 20 years old were recruited after identification of acute EBV infection based on their antibody response characteristics through microbiological analyses requested by their general practitioner. Individuals with a serological confirmation of acute EBV infection were eligible for participation in the CEBA project. The exclusion criteria comprised of a time limit of six weeks since debut of symptoms, pregnancy, medical treatment for another disease or medication due to chronic illness. A pregnancy test for the girls was conducted before any further examination. Healthy controls (n=70) were recruited among the patients' peers with the equivalent age and demographic conditions as the patients. The EBV patients were asked to bring a healthy friend of the same age and sex to the 6-month follow-up, and 60 out of 70 healthy controls were recruited through this method. The last ten were recruited from local schools, with the same distribution of age and sex as the EBV patients. The healthy controls were also excluded from participation in the study if treated medically for another disease or due to pregnancy. Exceptions from exclusion were contraceptive pills (including hormonal contraception) and antibiotics against tonsillitis/pharyngitis for all participants including healthy controls. Participants on any other medication were excluded.

During the 6 months from baseline, 91 (47 %) of the 195 adolescents developed chronic fatigue. Five participants dropped out. At 6 months, the EBV patients were divided into two main groups: EBV chronic fatigue plus (CF+); those who developed chronic fatigue, and EBV chronic fatigue minus (CF-); and those who did not develop chronic fatigue. Within the EBV (CF+) group, a CFS diagnosis was made according to self-reported symptoms and specified criteria depending on the applied definition. In the current study, the Fukuda-criteria and the Canadian criteria were applied. In the current study, 26 participants – within the group of 91 participants who fulfilled

the requirements for chronic fatigue at 6 months after acute Epstein-Barr virus infection – also fulfilled the symptom requirements for chronic fatigue syndrome according to the Fukuda-criteria. Nineteen participants fulfilled the symptom requirements for chronic fatigue syndrome according to the Canadian criteria. It is possible that CF and CFS exist on a dimension with graded differences related to illness severity. Therefore, the subgroup in the current study diagnosed with CFS will be included in the analysis for comparison. All data was collected at 6 months after acute infection unless otherwise specified. See the overview of the participants in the described groups below in the flowchart.

2.1.1 Participants flowchart



Note. EBV= Ebstein- Barr Viurs. CF= Chronic fatigue. CF+= those who developed chronic fatigue or CFS. CF-= those who did not develop chronic fatigue or CFS. HC= healthy controls. Fu= Fukuda criteria met. Ca= Canada criteria met.

2.1.2 Baseline investigational program

An investigational program was conducted at baseline (0 months) and 6 months. Upon clinical investigation all the participants were instructed to fast overnight and abstain from tobacco products and caffeine for at least 48 hours. The total length of the clinical investigation was stipulated to three and a half hours. Participants were tested and interviewed on a large battery of measures (see Pedersen et al. (2019) for details) and only selected data are included and presented in the current study. Data from the following measures are included: objective cognitive tests, self-report questionnaires of clinical symptoms and self-report questionnaires of subjective cognitive symptoms.

2.1.3 Sample Characteristics

Sample characteristics are shown in Table 3.1. The variables of estimated IQ, sex and the Hospital Anxiety and Depression Scale (HADS) score are significantly different between the EBV (CF+) group and the EBV (CF-) group. These variables need to be adjusted for in the statistical analyses of cognitive measures if we find significant group differences.

Table 1.3
Sample characteristics

	EBV (CF+) (n=91)	*EBV (CF-) (n=104)*	*p-value EBV (CF+) vs. EBV (CF-)*	*Healthy controls (n=70)*
Constitutional				
Sex - no. (%)				
Male	24 (26)	44 (42)	**0.020**	26 (37)
Female	67 (74)	60 (58)		44 (63)
Age, years - mean (SD)	17.4 (1.5)	17.4 (1.7)	0.780	17.0 (1.8)
IQ, estimated - mean (SD)	108.4 (11.7)	112.6 (11.8)	**0.014**	113.4 (8.8)
Biomarkers				
Epstein-Barr Virus (EBV) load, copies in blood - no. (%)				
Negative (<160)	44 (51)	38 (37)	0.123	60 (86)
Low (1600 to 2000)	26 (30)	35 (34)		8 (11)
Moderate/high (>2000)	16 (19)	29 (28)		2 (3)
Clinical symptoms				
Chalder Fatigue Questionnaire (CFQ) total score – median (IQR)	19.0 (5.0)	11.0 (2.0)	**<0.001**	11.0 (5.0)
Post-exertional malaise score - mean (SD)	2.9 (1.1)	1.6 (0.6)	**<0.001**	1.7 (0.7)
Hospital anxiety and depression symptoms (HADS), total score - mean (SD)	13.4 (6.3)	8.0 (5.3)	**<0.001**	10.6 (4.6)

Note. Differences in mean and median values for EBV (CF+) vs. EBV (CF-): Student's t-test or Mann-Whitney U-test (CFQ) were applied for continuous data, dependent on variable distribution. Pearson's Chi-Square was applied for categorical data. In order to estimate the participants IQ, two subtests (Matrix Reasoning and Vocabulary) from the Wechsler Abbreviated Scale of Intelligence (WASI) were applied (Wechsler, 2007).

2.2 Measures

2.2.1 Measures of clinical symptoms

Symptoms of physical and mental fatigue

The Chalder Fatigue Questionnaire (CFQ) is a validated (Chalder et al., 1993), and widely used self-report questionnaire in CFS research to map out subjective experience of physical and mental fatigue (Fong et al., 2015). Examples of questions asked are as following: "Do you have

problems with tiredness?", "Do you have difficulties concentrating?", "Do you lack energy?" and "Do you have less strength in your muscles?" The CFQ has been translated and validated for the Norwegian population (Loge, Ekeberg, & Kaasa, 1998). The questionnaire consists of 11 items, and in this study the CFQ total linear score is based on the sum across all 11 items. Each item is scored on a zero to three Likert scale. The total range is from zero to 33. Higher scores reflect greater fatigue. For binary scoring, a global score of four or more will qualify for fatigue caseness when each item is scored 0-0-1-1 (Chalder et al., 1993). The discriminative abilities of the questionnaire seem satisfactory, and the questionnaire has proven to discriminate reliably between clinical and nonclinical conditions (Cella & Chalder, 2010). In terms of normative data, mean ± SD Likert scores in a community population (n=1,615) have been documented to be significantly lower compared to patients with CFS. The community population scored 14.2 ± 4.6 of 33 versus 24.4 ± 5.8 in patients with CFS (n=361) (Cella & Chalder, 2010).

Symptoms of depression and anxiety

The Hospital Anxiety and Depression Scale (HADS) is a brief self-report questionnaire used to determine the presence of anxiety and depression symptoms (Zigmond & Snaith, 1983). The HADS has demonstrated adequate test-retest reliability and factor structure, and has been proven to perform satisfactorily when discriminating between adolescents diagnosed with depressive or anxiety disorders and those without these diagnoses (White, Leach, Sims, Atkinson, & Cottrell, 1999). It has also been proven useful in clinical settings as a screening instrument for detecting the need of psychiatric assessment for depressive or anxiety disorders in the adolescent population (White et al., 1999). It is a validated questionnaire consisting of fourteen items, where seven of these items relate to anxiety and the last seven items relate to depression (Bjelland, Dahl, Haug, & Neckelmann, 2002). The participants rate to what degree certain statements correspond to their own subjective experiences of symptoms of depression and anxiety such as: "I feel tense or "wound up" and "I look forward with enjoyment to things." The items are rated zero to three on a Likert scale. Higher scores indicate more severe symptoms. The sum raw score based on all 14 items was used.

Post-exertional malaise

In order to investigate post-exertional malaise, the following question was set as a single item proxy in the Centers for Disease Control and Prevention (CDC) Chronic Fatigue Syndrome

(CFS) Symptom Inventory: “How often do you feel more fatigued the day after an exertion?” This formulation is in line with previously used definitions of post-exertional malaise (Jason, Sunnquist, Kot, & Brown, 2015). A higher score implies more severe post-exertional malaise. The Norwegian version of the CDC CFS Symptom Inventory and its psychometric properties is further described below under subjective cognitive symptoms as the main purpose of the self-report questionnaire in the current study is to map subjective experiences of cognitive symptoms.

Subjective cognitive symptoms

A revised version of the original CDC Symptom Inventory for CFS was applied to assess subjective experiences of cognitive functioning such as concentration, decision making, memory and confusion/disorientation. The original CDC Symptom Inventory for CFS is a self-report questionnaire used to collect information about the presence, frequency and intensity of 19 fatigue and illness-related symptoms (Wagner et al., 2005). The inventory was translated to Norwegian by Vegard Bruun Wyller (Wyller, 2007), and adjustments to the original inventory have been made to include measures on post-exertional malaise as described above, as well as subjective experience of cognitive functioning. The Norwegian version of the CDC Symptom Inventory for CFS used in the current study has never been formally validated. It has, however, been found useful in several studies, it is well incorporated, and it appears to have an acceptable face validity (Asprusten et al., 2015; Asprusten et al., 2018; Kristiansen et al., 2019; Pedersen et al., 2019; Sulheim et al., 2014; Wyller & Helland, 2013). The fundamental structure of the inventory remains the same, and the scores correlate greatly to the scores on other instruments with an established validity, such as the Chalder Fatigue Scale (Wyller, V.B.B, personal communication, 04-02-2020). In general, it appears to have an accepting validity, even though its validity ideally should be tested formally.

The self-report questionnaire consists of 24 common symptoms of CFS, where four of these questions explore subjective cognitive symptoms. Perceived frequency of each symptom was graded on a five-point Likert scale from “never/rarely present” to “present all of the time” (Sulheim et al., 2014; Wagner et al., 2005; Wyller, Saul, Walloe, & Thaulow, 2008). Higher scores imply more severe experience of cognitive difficulties. The participants were asked to think about the time after they became ill, and then asked how often they had experienced the

following: 1) difficulties with concentration, 2) difficulties with decision-making, 3) difficulties remembering things, 4) felt confused or disorientated.

2.2.2 Objective cognitive assessment

All participants underwent cognitive testing in the following order: The Digit Span test from the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) (Wechsler, 2008); the Color-Word Interference test from the Delis-Kaplan Executive Function System (D-KEFS) (Stroop, 1935); the Hopkins Verbal Learning Test - Revised (HVLT-R) (Benedict, 1998); and the Matrix Reasoning and Vocabulary tests from the Wechsler Abbreviated Scale of Intelligence, Fourth Edition (WASI) (Wechsler, 2007). T-scores were applied, except for the HVLT-R and the Digit Span test. The HVLT-R raw scores were applied due to lack of normative data for the adolescent age group. Raw scores were also applied for the Digit Span test because scores on the different conditions, Digit Span forward condition and Digit Span backward condition, were considered separately as well as the total sum of both conditions. Normative data for the adolescent age-group in the forward and backward conditions are lacking.

Estimate of general cognitive functioning (IQ)

Two subtests (Matrix Reasoning and Vocabulary) from the Wechsler Abbreviated Scale of Intelligence (WASI) were used to estimate the patients' IQ (Wechsler, 2007). The Matrix and Vocabulary tests are two of four subtests of the complete WASI, and are validated for estimation of Full Scale Intelligence Quotient (FSIQ) (Canivez, Konold, Collins, & Wilson, 2009; Saklofske, Caravan, & Schwartz, 2000). The Matrix Reasoning test assesses the participants' nonverbal-fluid ability, and the Vocabulary test assesses the participants' verbal-crystallized ability (Wechsler, 2007). The Vocabulary subtest consists of 31 items (including three picture items). The participants are asked to define and/or describe a word or concept presented orally by the examiner (McCrimmon & Smith, 2012). All the participants begin with the fourth item, but if necessary, the examiner will revert back to the picture items. The subtest is discontinued after three repeated failures. The Matrix Reasoning test consists of 30 items in total. The participants are given a visual presentation of an incomplete matrix or series. Thereafter, they will have to choose the response option that completes the matrix or series. The subtest is designed to test the participants' fluid intelligence, broad visual intelligence, classification and spatial ability,

knowledge of part-whole relationships, simultaneous processing, and perceptual organization (Moccow, 2011). T-scores were applied, and FSIQ was estimated from sum T-scores.

Processing speed

The Color-Word Interference test (CWIT) from the Delis-Kaplan Executive Function System (D-KEFS) is a variant of the Stroop test, and includes four different conditions (Stroop, 1935). It is a widely used test, and its psychometric properties of reliability and validity have been reported as satisfactory (Delis, Kramer, Kaplan & Holdnack, 2004). The two baseline conditions assess verbal processing speed (Delis, 2001). The participants are asked to name different color bars on a paper (condition 1) and read aloud the words printed in that color (condition 2). Mean completion time (seconds) on the two conditions is recorded; higher completion time implies slower processing speed. T-scores were applied, hence lower scores will thereby imply slower processing speed. Processing speed was estimated from mean T-scores from the sum of condition 1 and 2.

Executive functions: Working memory, cognitive inhibition and cognitive flexibility

Working memory

For assessment of verbal or auditory working memory the Digit Span test is widely used (Wechsler, 2008). The examiner reads aloud sequences of random numbers (approximately one per second). The test starts with two random numbers, and for every new sequence one random number is added, gradually increasing the degree of difficulty. The Digit Span forward condition is referred to as working memory maintenance in the current study. This condition requires the subject to repeat the numbers in the exact same order as they were read aloud by the examiner, which possibly captures more of the participants' attention efficiency and capacity rather than their working memory alone.

The Digit Span backward condition is referred to as working memory manipulation in the current study. This condition appears to be more dependent on working memory since it requires the subject to repeat the sequence of numbers in reverse order. For instance, the correct answer to the sequence "1,2,3" read aloud by the examiner is "3,2,1". The condition requires not only a great deal of attentional capacity in order to retain the sequences of numbers read aloud. It also requires the participants to retain them for a longer period of time in order to allow the working memory

to produce the reverse order of the number sequence. Each given answer is scored either 1 (correct) or 0 (incorrect). The test is discontinued if two sequences of equal length are answered incorrectly. Raw scores were applied in order to analyze the scores on the Digit Span forward condition and Digit Span backward condition separately as well as the total sum of both conditions. Total scores are the sum of correct answers for both the forward and the backward condition.

Cognitive inhibition

The third condition of the CWIT from D-KEFS assesses cognitive inhibition (Delis et al.,2001) by requiring the participant to inhibit an overlearned verbal response. The participants must name the color of the ink, not the dissonant color-words printed. Higher completion time implies less cognitive inhibition. All time measurements were transformed into T-scores. The number of errors was recorded as well, raw scores were used and compared to age-appropriate norms.

Cognitive flexibility

The fourth condition in the CWIT from D-KEFS was used as a measure of cognitive flexibility (Delis et al., 2001). The participants were instructed to switch back and forth between naming the dissonant ink colors and reading the words. Higher completion time suggests less cognitive flexibility. All time measurements were transformed into T-scores. The number of errors was recorded as well, raw scores were used and compared to age-appropriate norms.

Verbal learning (immediate recall) and verbal memory (delayed recall)

The Hopkins Verbal Learning Test - Revised (HVLT-R) is a test of verbal learning (immediate recall) and verbal memory (delayed recall) (Benedict, B., Schretlen, David Groninger, & Lowell Brandt, 1998). The HVLT-R has six comparable and equivalent forms, which makes the HVLT-R particularly useful in research where patients are assessed at frequent intervals as they are in the current study. The examiner reads out a list of 12 words, and the participant is asked to repeat as many of these words as possible, in three consecutive trials; the combined score of remembered words (0-36) in the three trials is a measure of verbal learning. After 20 minutes, the participant is asked to recall the same 12 words; the number of remembered words (0-12) is a measure of delayed verbal memory. Raw scores were applied, because normative data for

adolescents is lacking. Discriminant validity and test-retest reliability for the HVLT-R has been reported as satisfactory in research (R. H. B. Benedict, & Brandt, J. , 2007).

2.3 Procedures

All participants were subjected to the same one-day assessment program at the hospital study center (Dept. of Paediatrics and Adolescent Health, Akershus University Hospital). Cognitive assessments and questionnaires were performed at 10 am, after breakfast was served (a light meal). All examinations and assessments were performed by the project's two main researchers (Medical Doctors and PhD research fellows Maria Pedersen and Tarjei Tørre Asprusten), and the whole examination program lasted for about three and a half hours including breakfast. The main researchers were also given guidance on interpreting the results of the cognitive assessments by specialist in clinical neuropsychology, Merete Glenne Øie.

2.4 Ethical considerations

2.4.1 General considerations regarding confidentiality during recruitment

The CEBA project has been approved by the Norwegian Committee for Ethics in Medical research (Ref nr. 2014/2069 in REK). Participants were recruited as patients undergoing examination with their general practitioners. The recruitment implies a violation of confidentiality for the lab as they provided microbiological information indicating EBV infection. To minimize the violation, the only information given was limited to the name of the eligible patient and their personal identification number. It was possible to accept this procedure ethically because the information provided was limited. Furthermore, the potential societal benefits of carrying out a research project on this group of patients was also considered to be higher than the potential cost for the individuals involved.

2.4.2 Informed consent

The common factor for all the participants in the current study is that they all went to their general practitioner for various reasons and completed an examination including blood sampling. If the microbiological information from patients in the relevant age group indicated acute EBV

infection, the general practitioner provided this information as well as the patient's name and their personal identification number to the PhD research fellows Maria Pedersen and Tarjei Tørre Asprusten. Thereafter, the participants (and their parents depending on the patients' age, < 16 years) were contacted and given information about the study, provided by phone according to a standardized procedure. In addition, all participants received written information prior to the first examination and official inclusion. Before inclusion, all participants (and parents to participants under 16 years of age) had to sign a written consent. The participants were given at least 24 hours from when they received the information about the study to consider whether they wanted to participate or not. They were also informed that they could withdraw from the study at any time, without justifying this decision.

2.4.3 Risk factors upon participation

The most serious ethical concern in the CEBA project was whether the focus on fatigue itself could potentially increase the risk of fatigue development within this group, generating a self-fulfilling prophecy. In order to handle this concern, the participants were given realistic information about the risk of developing fatigue, and behavior thought to reduce fatigue development (such as maintaining normal school and leisure activities) was generally encouraged. Furthermore, an important goal in the CEBA project was to apply investigational methods that would be as painless and as comfortable for the participants as possible. In general, there are no harmful effects associated with any of the methods applied, and these were also considered no more unpleasant than a regular visit to the general practitioner.

2.4.4 Financial compensation

The participants were given financial compensation for travel expenses to and from each consultation at the hospital. In addition, they received a gift voucher worth 200 NOK when participating. The participants were informed that they would be given necessary support at the Dept. of Paediatrics and Adolescent Health, Akershus University Hospital, if an injury or any other form of complication were to occur as a direct result of participation. All participants were covered by general patients' insurance arrangements at the hospital.

2.5 Statistical analyses

All cases (n=195) were included in the analyses, and there was no missing data. Statistical analyses were carried out using IMB Statistical Package for Social Sciences (SPSS), version 24. Cross-sectional comparisons were carried out for objective (aim 1) and subjective (aim 2) measures across all three groups; EBV (CF+), EBV (CF-) and healthy controls applying one-way ANOVA. Thereafter, differences across the EBV (CF+) and EBV (CF-) groups were performed using Student t-tests; such comparisons were only carried out if the p-values across all groups were ≤ 0.1. The p-values for the EBV (CF+) vs. EBV (CF-) comparisons were adjusted for group differences in sex, symptoms of depression and anxiety (HADS) and estimated IQ score (WASI) at baseline, applying multiple linear regression modeling.

3 Results

3.1 Aim 1 – Objective measures of cognitive functioning

As shown in Table 3.1, our results showed that the EBV (CF-) group performed significantly better than the EBV (CF+) group on working memory manipulation. However, the result was no longer significant when adjusted for sex, symptoms of anxiety and depression, and estimated IQ. There was no significant group difference on working memory maintenance and working memory sum score. Notably, there was no significant group difference between the EBV (CF+) group and healthy controls on any of the working memory measures. However, a group difference was evident between the EBV (CF-) group and healthy controls on working memory manipulation and working memory sum score (see 95% CI), where the EBV (CF-) group performs better than healthy controls. The EBV (CF+) group and healthy controls present with near equal mean scores on all measures of working memory.

The EBV (CF-) group had significantly less errors on the cognitive inhibition measure compared to the EBV (CF+) group, even when adjusted for sex, symptoms of anxiety and depression, and estimated IQ. Notably, healthy controls had significantly more errors compared to the EBV (CF+) group. There was no significant difference between groups on the cognitive inhibition time measure (sec.). Our results showed that the healthy control group had significantly more errors, but significantly better performance regarding the time measure on the cognitive flexibility measure as opposed to the two EBV groups. However, the healthy control group performed within ± 1 SD of the standardized age norm on the error measure.

Our results showed no significant group differences on processing speed, verbal learning (immediate recall) and verbal memory (delayed recall), as shown in Table 3.1.

Table 3.1
Objective measures

	EBV (CF+) (n=91)	*EBV (CF-) (n=104)*	*Healthy controls (n=70)*	*p-value (across all groups)*	*p-value EBV (CF+) vs. EBV (CF-)*	*Adjusted p-value* EBV (CF+) vs. EBV (CF-)*
Processing speed[1] sec. – mean (SD)	26.5 (5.0)	25.9 (3.8)	26.4 (5.0)	0.671	NA	NA
95% CI	[25.4, 27.5]	[25.2, 26.7]	[25.2, 27.6]			
Working memory maintenance[2] score – mean (SD)	9.3 (1.7)	9.5 (1.8)	9.2 (1.8)	0.580	NA	NA
95% CI	[9.0, 9.7]	[9.1, 9.8]	[8.8, 9.6]			
Working memory manipulation[2] score – mean (SD)	6.1 (1.7)	6.7 (2.2)	6.1 (2.0)	0.076	**0.037**	0.445
95% CI	[5.7, 6.4]	[6.2, 7.1]	[5.7, 6.6]			
Working memory sum score[2] – mean (SD)	15.4 (3.0)	16.1 (3.6)	15.3 (3.2)	0.174	NA	NA
95 % CI	[14.8, 16.0]	[15.4, 16.8]	[14.5, 16.1]			
Cognitive inhibition[3] sec. – mean (SD)	48.2 (8.9)	48.3 (9.7)	49.8 (11.6)	0.526	NA	NA
95% CI	[46.3, 50.0]	[46.4, 50.1]	[47.0, 52.5]			
Cognitive inhibition[3] no. of errors – mean (SD)	1.6 (1.5)	1.2 (1.3)	2.4 (2.1)	**<0.001**	**0.040**	**0.050**
95% CI	[1.3, 2.0]	[1.0, 1.5]	[1.9, 2.9]			
Cognitive flexibility[4] sec. – mean (SD)	52.7 (10.0)	53.4 (11.1)	59.7 (12.6)	**<0.001**	0.650	NA
95% CI	[50.6, 54.8]	[51.2, 55.5]	[56.7, 62.7]			
Cognitive flexibility[4] no. of errors – mean (SD)	1.7 (1.6)	1.7 (1.8)	3.1 (2.2)	**<0.001**	0.494	NA
95% CI	[1.4, 2.1]	[1.3, 2.0]	[2.6, 3.6]			
Verbal learning[5] sum score – mean (SD)	27.4 (3.7)	27.8 (4.2)	27.5 (3.8)	0.739	NA	NA
95% CI	[26.6, 28.1]	[27.0, 28.6]	[26.5, 28.4]			
Verbal memory[6] score – mean (SD)	9.7 (1.9)	9.8 (1.8)	9.6 (2.0)	0.831	NA	NA
95% CI	[9.3, 10.1]	[9.4, 10.1]	[9.1, 10.0]			

Note. The level of significance was set at p = 0.05. However, a total of 40 statistical tests were performed for the main outcome variables, and according to a Bonferroni correction, the level of significance should be set at p = 0.05/40 = 0.001.

P-values ≤ 0.05 are shown in bold for clarity. CI = confidence interval. SD = standard deviation.

*Adjusted for group differences in sex, HADS-score at 6 months, and estimated IQ at baseline applying multiple linear regression modeling.

[1]Processing speed (CWIT, condition 1 and 2). Mean score = sum of mean scores from condition 1 and 2. T-score presented.

[2]Working memory (WISC-IV): Maintenance=Digit Span forwards, Manipulation=Digit Span backwards. Raw scores presented.

[3]Cognitive inhibition (CWIT, condition 3). Scores in sec. presented as T-scores. No. of errors presented as raw scores.

[4]Cognitive flexibility (CWIT, condition 4). Scores in sec. presented as T-scores. No. of errors presented as raw scores.

[5]Verbal learning (HVLT-R, immediate recall). Sum of immediate recall trials 1, 2, 3. Raw scores presented.

[6]Verbal memory (HVLT-R, delayed recall). Raw scores presented.

In the CFS subgroup analyses, as shown in Table 3.2, the mean for both the EBV (CF+Fu) group and the EBV (CF+Ca) group were outside of the 95% CI for the EBV (CF+) group on the cognitive flexibility error measure, verbal learning and verbal memory. The mean on the cognitive flexibility time measure for the EBV (CF+Fu) group, but not EBV (CF+Ca) group, was outside of the 95% CI for the EBV (CF+) group. There were no differences between the CFS subgroups and the EBV (CF+) group on processing speed, working memory and cognitive inhibition.

Table 3.2

Objective measures – CFS subgroups

	EBV (CF+) *(n=91)*	*EBV (CF+Fu)* *(n=26)*	*EBV (CF+Ca)* *(n=19)*
Processing speed[1] sec. – mean (SD)	26.5 (5.0)	26.0 (4.3)	27.0 (4.3)
95% CI	[25.4, 27.5]	[24.3, 27.7]	[24.9, 29.0]
Working memory maintenance[2] score – mean (SD)	9.3 (1.7)	9.2 (1.9)	9.3 (1.9)
95% CI	[9.0, 9.7]	[8.5, 10.0]	[8.4, 10.2]
Working memory manipulation[2] score – mean (SD)	6.1 (1.7)	6.2 (1.9)	6.4 (1.9)
95% CI	[5.7, 6.4]	[5.4, 7.0]	[5.5, 7.3]
Working memory sum score[2] – mean (SD)	15.4 (3.0)	15.4 (3.5)	15.7 (3.5)
95 % CI	[14.8, 16.0]	[14.0, 16.8]	[14.0, 17.4]
Cognitive inhibition[3] sec. – mean (SD)	48.2 (8.9)	48.5 (8.3)	49.6 (7.9)
95% CI	[46.3, 50.0]	[45.1, 50.8]	[45.8, 53.4]

Cognitive inhibition[3] no. of errors – mean (SD)	1.6 (1.5)	1.8 (1.4)	1.5 (1.2)
95% CI	[1.3, 2.0]	[1.3, 2.4]	[0.9, 2.0]
Cognitive flexibility[4] sec. – mean (SD)	52.7 (10.0)	50.2 (8.0)	50.8 (8.5)
95% CI	[50.6, 54.8]	[46.9, 53.4]	[46.7, 54.9]
Cognitive flexibility[4] no. of errors – mean (SD)	1.7 (1.6)	2.3 (2.0)	2.3 (2.5)
95% CI	[1.4, 2.1]	[1.4, 3.1]	[1.1, 3.5]
Verbal learning[5] sum score – mean (SD)	27.4 (3.7)	25.9 (3.3)	26.3 (4.1)
95% CI	[26.6, 28.1]	[24.6, 27.3]	[24.3, 28.3]
Verbal memory[6] score – mean (SD)	9.7 (1.9)	9.2 (1.9)	9.0 (1.8)
95% CI	[9.3, 10.1]	[8.4, 9.9]	[8.1, 9.9]

CI = confidence interval. SD = standard deviation.

[1]Processing speed (CWIT, condition 1 and 2). Mean score = sum of mean scores from condition 1 and 2. T-score presented.

[2]Working memory (WISC-IV): Maintenance=Digit Span forwards, Manipulation=Digit Span backwards. Raw scores presented.

[3]Cognitive inhibition (CWIT, condition 3). Scores in sec. presented as T-scores. No. of errors presented as raw scores.

[4]Cognitive flexibility (CWIT, condition 4). Scores in sec. presented as T-scores. No. of errors presented as raw scores.

[5]Verbal learning (HVLT-R, immediate recall). Sum of immediate recall trials 1, 2, 3. Raw scores presented.

[6]Verbal memory (HVLT-R, delayed recall). Raw scores presented.

3.2 Aim 2 - Subjective experience of cognitive functioning

As shown in Table 3.3, the EBV (CF+) group reported significantly more subjective cognitive difficulties as opposed to the EBV (CF-) group and healthy controls. When adjusted for sex, symptoms of anxiety and depression, and estimated IQ, the measure “feeling confused or disoriented” was no longer significantly different between the EBV (CF+) group and the EBV (CF-) group. Notably, the healthy controls reported significantly more subjective cognitive difficulties compared to the EBV (CF-) group based on 95% CI.

Table 3.3
Subjective measures

	EBV (CF+) (n=91)	*EBV (CF-) (n=104)*	*Healthy controls (n=70)*	*p-value (across all groups)*	*p-value EBV (CF+) vs. EBV (CF-)*	*Adjusted p-value* EBV (CF+) vs. EBV (CF-)*
Concentration problems score – mean (SD)	3.5 (1.1)	1.8 (0.9)	2.2 (1.0)	**<0.001**	**<0.001**	**<0.001**
95% CI	[3.2, 3.7]	[1.6, 1.9]	[1.9, 2.4]			
Problems making decisions score – mean (SD)	2.6 (1.3)	1.4 (0.9)	1.9 (0.8)	**<0.001**	**<0.001**	**<0.001**
95% CI	[2.2, 2.9]	[1.2, 1.6]	[1.7, 2.1]			
Memory problems score – mean (SD)	2.5 (1.4)	1.4 (0.8)	1.7 (0.8)	**<0.001**	**<0.001**	**0.001**
95% CI	[2.2, 2.9]	[1.3, 1.6]	[1.5, 1.9]			
Feeling confused or disoriented score – mean (SD)	1.9 (1.1)	1.3 (0.7)	1.3 (0.6)	**<0.001**	**<0.001**	0.154
95% CI	[1.6, 2.1]	[1.1, 1.4]	[1.1, 1.4]			
Cognitive symptoms sum score – mean (SD)	10.4 (4.0)	5.9 (2.5)	7.1 (2.5)	**<0.001**	**<0.001**	**<0.001**
95% CI	[9.5, 11.4]	[5.3, 6.4]	[6.4, 7.7]			

Note. Subjective experience of cognitive difficulties measured by the revised CDC symptom inventory questionnaire (see section 2.2.1).
The level of significance was set at p = 0.05. However, a total of 40 statistical tests were performed for the main outcome variables, and according to a Bonferroni correction, the level of significance should be set at p = 0.05/40 = 0.001.
P-values ≤ 0.05 in the right column are shown in bold for clarity. CI = confidence interval. SD = standard deviation.
*Adjusted for group differences in sex, HADS-score at 6 months, and estimated IQ at baseline applying multiple linear regression modeling.

In the CFS subgroup analyses, as shown in Table 3.4, the mean of both the EBV (CF+Fu) group and the EBV (CF+Ca) group were outside of the 95% CI for the EBV (CF+) group on all measures of subjective cognitive difficulties.

Table 3.4
Subjective measures – CFS Subgroups

	EBV (CF+) *(n=91)*	*EBV (CF+Fu)* *(n=26)*	*EBV (CF+Ca)* *(n=19)*
Concentration problems score – mean (SD)	3.5 (1.1)	4.2 (0.9)	4.3 (1.0)
95% CI	[3.2, 3.7]	[3.8, 4.5]	[3.8, 4.8]
Problems making decisions score – mean (SD)	2.6 (1.3)	3.3 (1.3)	3.0 (1.5)
95% CI	[2.2, 2.9]	[2.8, 3.8]	[2.3, 3.7]
Memory problems score – mean (SD)	2.5 (1.4)	3.5 (1.3)	3.3 (1.5)
95% CI	[2.2, 2.9]	[3.0, 4.0]	[2.6, 4.1]
Feeling confused or disoriented score – mean (SD)	1.9 (1.1)	2.4 (1.3)	2.4 (1.4)
95% CI	[1.6, 2.1]	[1.9, 3.0]	[1.8, 3.1]
Cognitive symptoms sum score – mean (SD)	10.4 (4.0)	13.4 (3.7)	13.1 (4.2)
95% CI	[9.5, 11.4]	[11.8, 14.9]	[10.9, 15.2]

Note. CI = confidence interval. SD = standard deviation.

4 Discussion

4.1 Aim 1 – Objective measures of cognitive functioning

4.1.1 Processing speed

Our results did not show any significant group differences on processing speed and the CFS subgroups were no different to the EBV (CF+) group. Our findings are in accordance with the results of the study by Haig-Ferguson et al. (2009), who assessed processing speed using Symbol Search from WISC-IV. They did not find reduced processing speed in their sample of children and adolescents with CFS compared to normative data.

In contrast to our results and the study of Haig-Ferguson et al. (2009), other previous studies on adolescents with CFS have reported reduced processing speed (Josev et al., 2019; Kawatani et al., 2011; Sulheim et al., 2015) compared to healthy controls. These studies have applied different tests compared to our study and the study by Haig-Ferguson et al. (2009) in order to assess processing speed. Josev et al. (2019) used The CogState Computerized Battery (www.cogstate.com), and Kawatani et al. (2011) used the mATMT. Both the CogState and the mATMT are computerized cognitive tests and require hand motor function with the use of a computer mouse, possibly making these tests more difficult for the participants, which may have affected the results in these studies.

Sulheim et al. (2015) reported that processing speed was significantly reduced in adolescents with CF/CFS compared to healthy controls. Sulheim et al. (2015) suggested that processing speed may represent a core deficit in adolescents with CFS, in line with arguments made in studies on adults with CFS (Cockshell & Mathias, 2010, 2013; Shanks, Jason, Evans, & Brown, 2013). In our sample we used the same test to measure processing speed (CWIT condition 1 and 2) as Sulheim et al. (2015). Symptom severity and sample size in our study seem to match that of Sulheim et al. (2015), with equivalent mean scores on the CFQ and approximately the same number of participants. However, their sample of adolescents were fatigued for a longer period of time with a mean of 21.4 months, compared to the adolescents in our sample who were fatigued for 3-6 months. Illness duration may be a possible explanation as to why our results are different to those in Sulheim et al. (2015). Other studies on children and adolescents with CFS have

included participants with longer CFS duration as opposed to our sample, with the majority of participants being fatigued for more than 7 months (Josev et al., 2019; Kawatani et al., 2011). It has been proposed that particular cognitive domains, such as processing speed, might be more susceptible to the effects of fatigue than other domains (Josev et al., 2019). The results from our sample of adolescents may suggest that reduced processing speed might be a consequence of mental and physical passivity from long-term fatigue. Although our study design is cross-sectional, our results suggest that reduced processing speed may not be caused by chronic fatigue *per se* but may rather by an unspecific consequence of disease chronicity.

4.1.2 Executive functions: Working memory, cognitive inhibition and cognitive flexibility

The non-fatigued adolescents in the EBV (CF-) group performed significantly better than the other groups on working memory manipulation (Digit Span backwards), and slightly better than the other groups on working memory maintenance, which was close to significance. No group differences were displayed between the fatigued adolescents in the EBV (CF+) group and healthy controls, and the CFS subgroups were no different to the EBV (CF+) group. The findings suggest that group differences between the EBV groups cannot be attributed to fatigue directly, considering there were no differences between the adolescents with CF/CFS and healthy controls. It is very likely that the results reflect the differences in estimated IQ score, symptoms of anxiety and depression, or sex, as the group difference lost significance when adjusted for these variables.

Previous CFS studies have revealed mixed findings on working memory. Haig-Ferguson et al. (2009) applied the Letter-Number Sequencing test and the Digit Span test from WISC-IV and did not find reduced working memory in children and adolescents with CFS compared to normative data. Although they did not include a healthy control group, the result in the study by Haig-Ferguson et al. (2009) was in line with our findings; working memory maintenance and manipulation was not reduced in adolescents with CF/CFS compared to healthy controls in our study. Josev et al. (2019) applied the CogState, a computerized cognitive test, and working memory was measured using an n-back paradigm. They did not find impaired working memory, in line with our results, but their result was close to significance compared to healthy controls.

Sulheim et al. (2015) applied the same test used in our study, the Digit Span test from WISC-IV. The adolescents with CF/CFS in the study by Sulheim et al. (2015) performed significantly worse than healthy controls, in contrast to our results. However, the group differences for working memory in the study by Sulheim et al. (2015) disappeared when they adjusted for sleep problems. The finding highlights sleep as a core symptom in CFS (Carruthers et al., 2003; Fukuda et al., 1994). We did not assess sleep quality in the current study, however it is possible that our participants may not have such severe sleep difficulties, or that sleep quality may be associated with illness duration, and poor sleep over an extended period of time might conceivably affect working memory performance in adolescents with CF/CFS. Poor working memory performance has been linked to insufficient sleep in healthy adolescents (Gradisar, Terrill, Johnston, & Douglas, 2008). Furthermore, a study on adults with CFS (Constant et al., 2011) found a negative correlation between correct responses on a computerized working memory task from the TEA1-5 battery and length of illness. This finding supports the notion that illness duration may be positively related to reduced cognitive function.

There were no group differences on the cognitive inhibition time measure in the current study and the CFS subgroups were no different to the EBV (CF+) group. In contrast to our results, Sulheim et al. (2015) found reduced cognitive inhibition (CWIT condition 3) on the time measure in adolescents with CF/CFS compared to healthy controls. However, when adjusted for reduced processing speed using an inhibition contrast measure, the group differences disappeared on the cognitive inhibition time measure (Sulheim et al., 2015). This indicated that reduced processing speed may be the main problem for the adolescents with CF/CFS in the study by Sulheim et al. (2015), and not cognitive inhibition *per se*.

Furthermore, in contrast to our findings, a study on children with CFS demonstrated reduced cognitive inhibition compared to healthy controls (Kawatani et al., 2011). However, Kawatani et al. (2011) used the mATMT task and inferred reduced cognitive inhibition based on poor performance on alternative attention. Response inhibition is considered to be involved in alternative attention (Davidson, Amso, Anderson, & Diamond, 2006). The mATMT is a computerized cognitive test which requires hand motor function (Mizuno, Tanaka, Fukuda, Imai-Matsumura, & Watanabe, 2011). The results may thus be difficult to compare with the test results in the current study. Another study on adolescents with CFS has reported reduced cognitive

inhibition compared to healthy controls using the Eriksen Flanker Task (EFT) with poor performance on incongruent trials (Van de Putte et al., 2008). The EFT measures the ability to inhibit irrelevant stimuli, similar to CWIT condition 3 used in the current study (Wöstmann et al., 2013). The results from the study by Van de Putte et al. (2008) are in contrast to our results, however, the study uses a small sample size (n=34). Taken together, several studies on children and adolescents with CFS have revealed reduced cognitive inhibition. A possible explanation for the difference between those results and the ones in our sample may be that reduced cognitive inhibition is affected by illness duration and chronicity as discussed previously.

The fatigued adolescents within the EBV (CF+) group had significantly more errors on the cognitive inhibition measure compared to the non-fatigued adolescents within the EBV (CF-) group. Furthermore, healthy controls had significantly more errors compared to the EBV groups. In contrast to our findings, Sulheim et al. (2015) did not find group differences on the cognitive inhibition error measure. The non-fatigued adolescents in the EBV (CF-) group had the least amount of errors in our sample. Possible explanations for these findings may be other confounding variables not considered in our study, such as personality factors or sleep quality. The EBV groups displayed a significant group difference that cannot be attributed to sex, symptoms of anxiety and depression, or estimated IQ, suggesting the error measure might be affected by other variables not measured.

The healthy controls performed significantly better than the EBV groups on the cognitive flexibility time measure (CWIT condition 4). Furthermore, the subgroup in our sample diagnosed with CFS according to the Fukuda criteria had worse performance on the cognitive flexibility time measure compared to the EBV (CF+) group. The healthy controls had significantly more errors compared to the EBV groups, however, the CFS subgroups had more errors than the EBV (CF+) group. Kawatani et al. (2011) demonstrated reduced cognitive flexibility in adolescents with CFS compared to healthy controls on the mATMT task, in line with our results. Similarly, to their finding on cognitive inhibition, they inferred reduced cognitive flexibility from poor performance on alternating attention. Cognitive flexibility is also considered to be involved in alternative attention (Davidson et al., 2006). The mATMT is a computerized cognitive test, and as mentioned above, requires hand motor function (Mizuno et al., 2011). Sulheim et al. (2015) did not find reduced cognitive flexibility in CF/CFS compared to healthy controls, in contrast to

our results. The time measure was reported in Sulheim et al. (2015), but not the error measure, so this measure cannot be compared. Although the adolescents with CF/CFS in the current study perform worse than healthy controls in terms of time used on the task, their performance is not significantly different to the EBV (CF-) group. However, since the CFS subgroups performed worse than the EBV (CF+) group, it is possible that illness severity may have negatively affected cognitive flexibility in our sample. Another explanation may be that reduced cognitive flexibility is due to other variables not measured.

4.1.3 Verbal learning and verbal memory

Our results did not show any significant group differences in the main analyses on verbal learning (immediate recall) and verbal memory (delayed recall), measured by the HVLT-R. However, the CFS subgroups had worse performance on both verbal learning and verbal memory compared to the EBV (CF+) group.

In line with our findings of the CFS subgroups, both Haig-Ferguson et al. (2009) and Sulheim et al. (2015) reported reduced verbal learning (immediate recall) in adolescents with CFS. Haig-Ferguson et al. (2009) found reduced verbal learning in children and adolescents with CFS compared to normative data, using Word Pairs from Children's Memory Scale. Sulheim et al. (2015) found reduced verbal learning in adolescents with CF/CFS compared to healthy controls, using the HVLT-R. However, Sulheim et al. (2015) attributed reduced verbal learning to poor working memory performance in their sample, and we did not find reduced working memory in our sample of adolescents with CF/CFS. In contrast to Sulheim et al. (2015), our results did not show reduced verbal learning in adolescents with CF/CFS in the total EBV (CF+) group compared to healthy controls.

Verbal learning (immediate recall) may be affected by other cognitive domains such as processing speed and working memory. Shanks et al. (2013) suggest that CFS patients do not necessarily have problems with recall, but rather with the processing of new and complex information, particularly when information is presented quickly. However, the CFS subgroups in our study had reduced verbal learning compared to the EBV (CF+) group, but not reduced processing speed or working memory. It is possible that verbal learning is affected by illness severity based on our findings, whereas the cognitive domains of processing speed and working

memory is conceivably more affected by illness duration and chronicity. Both Haig-Ferguson et al. (2009) and Sulheim et al. (2015) used samples with considerably longer duration of illness compared to the current study, and as mentioned earlier, Sulheim et al. (2015) found reduced processing speed and working memory.

Our results on verbal memory (delayed recall) of the CFS subgroups are in contrast with the results of the study by Sulheim et al. (2015), who did not find significant deficits in verbal memory in adolescents with CF/CFS compared to healthy controls. Further, Haig-Ferguson et al. (2009) as well did not find reduced verbal memory in children with CFS compared to normative data, using Word Pairs from Children's Memory Scale. Haig-Ferguson et al. (2009) have suggested that information successfully stored in memory is also sufficiently recalled by children and adolescents with CFS, but this is not supported by our results. Further investigation is needed to conclude that verbal memory is not impaired in adolescents with CFS.

4.1.4 General discussion of results on objective cognitive functioning

Thus, our results indicate that the adolescents with CF/CFS in the total EBV (CF+) group is not adversely affected on objective cognitive measures compared to non-fatigued adolescents in the EBV (CF-) group and healthy controls. However, the CFS subgroups showed worse performance on measures of cognitive flexibility, verbal learning and verbal memory, compared to the total EBV (CF+) group. What could possibly explain why the adolescents with CF/CFS in the current study do not display significantly more difficulties on most objective measures as opposed to the EBV (CF-) group and healthy controls? As mentioned previously, illness duration and chronicity may to some degree explain the lack of group differences in our study. Other studies on adolescents with CFS have included participants with longer duration of illness compared to our study, and it is possible that reduced cognitive functioning is a consequence of illness duration and chronicity. Adolescents who have had CFS for years, compared to months in our study, have also been absent from school for long periods of time, which is also likely to affect cognitive functioning. Illness severity may also play a role, indicated by our results from the CFS subgroups. Other studies have mostly included participants with a CFS diagnosis, and their cognitive functioning may be more severely affected compared to adolescents with chronic fatigue who do not fulfill the diagnosis criteria.

It has been proposed that CFS patients perform comparably to healthy controls on objective measures by expending additional cognitive effort (Capuron et al., 2006). Cognitive effort is regarded as a cost of controlled cognitive processes (Shenhav et al., 2017), and the cost for CFS patients may also possibly entail post-exertional malaise that is a defining characteristic of CFS (Carruthers et al., 2003; Fukuda et al., 1994). The fatigued adolescents in the EBV (CF+) group in our study reported significantly higher post-exertional malaise with mean score 2.9 (SD 1.1), compared to the non-fatigued adolescents in the EBV (CF-) group with mean score 1.6 (SD 0.6) and healthy controls with mean score 1.7 (SD 0.7). Post-exertional malaise may not be reflected in scores on objective cognitive tests but may adversely impact recovery time after cognitive exertion. Studies on both adults (Cockshell & Mathias, 2014) and adolescents (Josev et al., 2019) with CFS have found that mental fatigue after cognitive exertion was significantly higher compared to healthy controls. Further, the studies found that the CFS patients needed significantly longer time to recover compared to healthy controls. Cockshell and Mathias (2014) concluded that adults with CFS may not expend more effort than healthy controls, but they are adversely affected by cognitive exertion as is evident by significantly longer recovery times. We did not consider potential differences in recovery time between the fatigued and non-fatigued adolescents in our sample. However, it is possible that the adolescents with CF/CFS in the current study took longer to recover after testing compared to the non-fatigued adolescents. This hypothesis is consistent with the group differences evident on post-exertional malaise in our study. The effects of cognitive exertion are not detected during objective cognitive tests, as it is likely that the adolescents expend the same amount of effort, but differential recovery times may be detected with repeated assessment and should be addressed further in future research.

4.2 Aim 2 - Subjective experiences of cognitive functioning

The results from our analyses showed, in line with our hypothesis, that adolescents in the EBV (CF+) group reported significantly more subjective cognitive difficulties regarding concentration, decision making, memory, and feeling confused/disorientated, compared to non-fatigued adolescents in the EBV (CF-) group, and healthy controls. Furthermore, those who developed CFS in the EBV (CF+) group reported significantly more cognitive difficulties compared to the total EBV (CF+) group. In sum, it is possible that the findings in the current study support the notion that CF and CFS exist on a continuum with few, if any qualitative differences related to

subjective cognitive functioning. Our results are in line with findings in other studies that have investigated subjective complaints in the cognitive domains of concentration and memory (Cockshell & Mathias, 2014; Haig-Ferguson et al., 2009; Rasouli et al., 2019; Sulheim et al., 2015).

Haig-Ferguson et al. (2009) investigated children and adolescents with CFS and found them to be significantly bothered by subjective cognitive difficulties in line with our results. These complaints were also supported by their teachers and parents. Sulheim et al. (2015) included adolescents who developed CF and CFS in their statistical analysis, but in contrast to the current study, they based subjective cognitive functioning (executive functions) solely on information given by the parents. They found that parents of adolescents with CF/CFS reported significantly more difficulties in executive functioning compared to the healthy controls. However, in contrast to the findings in the current study, Sulheim et al. (2015) did not find significant differences in parent-reported executive difficulties between those who developed CF to those who developed CFS.

Haig-Ferguson et al. (2009) and Sulheim et al. (2015) as well as the current study all used different questionnaires, which could make a direct comparison challenging. Yet – although questionnaires may differ in the number of items and the questions might be phrased differently – it could also be argued that a comparison is possible. Self-report questionnaires are often designed to capture a broad range of subjective experiences, and typically tap on similar cognitive domains.

However, in order to map out potential quantitative differences in subjective cognitive functioning between patients with CF and CFS, it may be necessary to not base these subjective experiences solely on the self-reports of parents. Yet, it is interesting that the informants in both Haig-Ferguson et al. (2009) and Sulheim et al. (2015) confirm the children and adolescents' subjective experiences of cognitive difficulties. Based on these findings, subjective experience of cognitive difficulties seems to interfere with daily function to a degree that consequently lead teachers and parents to notice the problems as well.

Studies on adults with CFS have also provided similar findings to the current study. The participants with CFS in Rasouli et al. (2019) reported a high level of cognitive difficulties.

Cockshell and Mathias (2014) also found that the CFS group reported more cognitive problems compared to healthy controls. It is, however, difficult to say whether the consistencies in findings to the current study can be attributed to qualitative or quantitative similarities of CF/CFS across age groups. Potential qualitative differences in subjective cognitive functioning in adolescents with CF/CFS compared to adults may not hit the surface by simply comparing self-reported cognitive complaints. It is possible that adolescents interpret their subjective cognitive functioning differently compared to adults; adults and adolescents will have different ideas about their premorbid functioning and the extent to which their cognitive function is subjectively reduced. Moreover, adolescents may face different challenges when they experience changes in cognitive functioning, with a possibly greater negative impact on different developmental aspects, as opposed to adults. Adolescents' phase of development may consequently lead adolescents to understand their cognitive difficulties as relevant to other aspects of daily function compared to adults.

Taken together, the findings in the current study indicate a tendency of more subjective cognitive difficulties for those with CF/CFS compared to healthy controls, in line with previous studies. In the current study, the adolescents with CFS reported significantly more subjective cognitive difficulties compared to the total EBV (CF+), thereby providing reasons to believe that illness severity is related to subjective experience of cognitive function.

4.2.1 General discussion of results on subjective cognitive functioning

In general, patients with CFS often report impaired memory and concentration (Fukuda et al., 1994). Therefore, it is not surprising that the sample of adolescents with CF/CFS in the current study also reported more difficulties compared to the EBV (CF-) group and healthy controls. However, it is interesting that only minor differences on objective cognitive performance between the EBV (CF+), EBV (CF-) and healthy controls were evident in the current study. Thus, the subjective cognitive difficulties reported by the patients with CF/CFS were not reflected in their objective cognitive performance. What could possibly explain the discrepancy between their subjective reports of cognitive functioning and objective cognitive performance?

Studies on adults with CFS have failed to find a strong relationship between subjective and objective measures of cognitive function (Cockshell & Mathias, 2014; Rasouli et al., 2019). Self-

report measures typically ask about general cognitive functioning experienced by patients with CFS during everyday tasks, which has the advantage of capturing a broad range of subjective experiences in a realistic setting (Cockshell & Mathias, 2014). However, everyday life is complex and might not be compatible with tests that measure specific cognitive functions in a controlled and structured test environment (Snyder et al., 2015). There is a possibility that objective cognitive tests fail to capture the struggles experienced by adolescents with CFS in school and social situations of everyday life. A quiet, structured and controlled test environment may enhance performance in adolescents with CFS compared to complex real-world situations such as in school where there might be many more distractions. Hence, subjective and objective forms of measurement might not reflect the same construct, thereby creating a discrepancy in subjective and cognitive findings on cognitive functioning (Snyder et al., 2015). Self-report measures may have higher ecological validity than neuropsychological tests, but may be influenced by contextual factors to a greater extent than objective tests (Snyder et al., 2015). Both measures have advantages and disadvantages, highlighting the need to explore the subjective experience as well as the objective tests of cognitive functioning.

Alternatively, it has been suggested that CFS patients might overestimate the extent of their cognitive difficulties (Short, McCabe, & Tooley, 2002). A study investigating clinical factors associated with the discrepancy between subjective and objective cognitive impairment in patients with depression, found that patients with greater depression severity, illness chronicity and younger age overreported cognitive impairments (Petersen, Porter, & Miskowiak, 2019). Similarly, it is possible that CFS patients are more susceptible to the tendency of overestimating their subjective cognitive problems (Cockshell & Mathias, 2013). This might be explained by heightened self-monitoring of cognitive processes and an increase in bodily focus that lead to an overinterpretation of subjective cognitive difficulties (Teodoro et al., 2018). This may, in return, lead to higher perceptions of cognitive effort after completing demanding tasks. If those with CF/CFS believe they have put an extreme amount of effort into solving a given task, it is possible that this belief facilitates an interpretive bias which ultimately leads to a greater need to control and monitor cognitive processes. As a result, it is possible that patients with CFS overestimate the degree of exertion (Metzger & Denney, 2002). If adolescents with CF/CFS tend to overestimate the extent of their cognitive difficulties, it may explain the discrepancy between their subjective

reports of cognitive functioning and objective cognitive performance evident in the current study's findings.

The sustained arousal model mentioned in the introduction, suggests that a threat to homeostasis provokes an arousal response, characterized by both nervous and endocrine adjustments aiming at recovering homeostatic stability (Wyller et al., 2009). It has been suggested that this mechanism is connected to cognitive processes, as well as influenced by personality, genetic traits and sensitization (Wyller et al., 2009). If homeostasis is restored, the arousal response is switched off. If the brain continues to misinterpret signals, however, there is a possibility that one may become hypersensitive to signals of fatigue; and consequently feel more distress, experience an increase in cognitive reactivity, and develop more negative expectations (Wyller et al., 2009). The belief of cognitive processes guiding interpretations of CFS symptoms and the emphasis on negative expectations as contributing factors in the continuation of subjective cognitive symptoms is also recognized by Kube et al. (2020). Subjectively perceived cognitive difficulties may be strengthened through mechanisms of conditioning and develop negative response outcome expectancies that facilitate self-fulfilling prophecies (Kube et al., 2020; Wyller et al., 2009). In sum, it is possible that the adolescents with CF/CFS in the current study are guided by cognitive processes that lead them to become more susceptible to overestimate their cognitive difficulties, have higher perceptions of cognitive effort, and develop more negative response outcome expectancies. Taken together, it is possible that these processes may lead adolescents with CF/CFS to more negative evaluations of their cognitive functioning.

Additionally, personality traits may partly explain and/or contribute to the subjective experience of cognitive difficulties reported by the adolescents with CF/CFS in the current study. Personality traits may be related to specific cognitive and behavioral factors that possibly contribute to maintaining, but also intensifying subjective experience of cognitive difficulties in adolescents with CF/CFS. Seidenberg, Taylor, and Haltiner (1994) investigated the relationship of personality traits on self-reports of cognitive functioning in 96 healthy participants. Seidenberg et al. (1994) found that traits of anxiousness and neurotic predisposition contribute to a tendency towards more critical self-evaluations of cognitive performance. Deary and Chalder (2010) found the participants with CFS to score significantly higher on neuroticism and unhealthy perfectionism compared to healthy controls. If those with CFS generally tend to have higher scores on

neuroticism and unhealthy perfectionism as found by Deary and Chalder (2010), it is possible that the adolescents with CF/CFS in the current study would also display higher scores on these traits. If some of the adolescents in the current study show traits of anxiousness, a higher level of neuroticism, and/or more unhealthy perfectionism, it is possible that these traits may contribute in their evaluation of cognitive performance as well. Subjective reports of cognitive symptoms accompanied by a lack of objective findings may potentially have a negative impact on maintenance of cognitive symptoms and illness perception as suggested by Kube et al. (2020).

The current study did not investigate personality traits. Therefore, it is not certain if the personality traits mentioned above contribute to a tendency toward more critical self-evaluations of cognitive performance in the sample of adolescents with CF/CFS in our study. However, if the adolescents with CF/CFS in the current study were found to show more traits of neuroticism and unhealthy perfectionism, it is possible that these traits would contribute to and/or partly explain why those with CF/CFS in the current study have more subjective cognitive difficulties compared to the EBV (CF-) group and healthy controls. In sum, one possibility is that personality traits may play a role in the interpretation of CFS symptoms, as well as the adolescents' evaluation of their cognitive functioning. Thus, the role of personality traits in the development and continuation of symptoms in CFS should be explored further in future research.

4.3 Strengths and limitations in the current study

4.3.1 Strengths

General strengths of the current study include a large group of EBV-infected adolescents recruited soon after the debut of infectious mononucleosis (IM). The problem with heterogeneity in the CFS population might be partly overcome in our sample by studying post-infectious adolescents exclusively; our sample consisted of adolescents with EBV infection as the only known illness trigger. We followed up the patients with acute EBV at 6 months which enabled us to compare those who developed chronic fatigue, denoted as EBV (CF+), to those who did not, denoted as EBV (CF-), against a healthy control group. This also allowed us to control for illness duration. To the extent of our knowledge, no other study on CFS has included three groups consisting of adolescents in their study design. Furthermore, we were able to control for the

infection as a possible contributor to subjective and/or objective measures on cognition and adjust for long-term effects of the EBV infection not associated with chronic fatigue. Additionally, we adjusted for sex, symptoms of depression and anxiety, and estimated IQ in the comparisons of EBV (CF+) vs. EBV (CF-).

4.3.2 Limitations

The findings in the current study should be interpreted carefully and may not be representative across all ages of patients with CFS. Besides, not all adolescents who develop CFS are exposed for a viral trigger such as an EBV infection and thereby possibly reducing the generalizability of our results to all adolescents with CF/CFS. Furthermore, at the follow-up at six months, the adolescents with acute EBV infection were divided into subgroups before carrying out statistical analysis. However, these subgroups may not have overcome the challenges of heterogeneity, because the EBV (CF+) group consists not only of adolescents that developed CF, but also those who developed CFS. We attempted to control for some of the variance by comparing the adolescents who developed CFS to the total group of adolescents with CF/CFS. Another limitation of the current study is that p-values may show an inaccurate picture; the scores and confidence intervals should be considered. For instance, difference between EBV groups does not necessarily mean the EBV (CF+) group is different from healthy controls. Moreover, we did not control for socioeconomic status, personality traits, sleep quality, and motivation in the statistical analysis. It is possible that these variables also affect the results on subjective and objective measures of cognition.

4.4 Clinical implications

Based on our findings on objective cognitive measures, it is likely that adolescents who have not been fatigued for longer than six months are not as severely affected by chronic illness as opposed to adolescents who have been fatigued for a longer time period. Our results indicate that it may be of clinical importance to have emphasis on cognitive functioning in early interventions, as an attempt to prevent reduced cognitive functioning as a result of long-term illness.

Subjective cognitive difficulties experienced by adolescents with CF/CFS are also of clinical relevance, and these experiences should be considered during treatment. Subjective cognitive

difficulties might contribute to a heightened sense of distress, hopelessness, reduced motivation, lower self-esteem, increased cognitive reactivity and more negative expectations to mention some potential negative contributors at play. Insight into subjective cognitive functioning may boost knowledge of CFS for patients and clinicians, hopefully improving the patients ability to cope with such deficits and consequently improve quality of life (Shanks et al., 2013). However, we might have to learn more about the mechanisms at play behind subjective cognitive difficulties before considering adjustments in school and homework situations. Helpful adjustments may depend on how these subjective experiences of cognitive difficulties are understood by clinicians. For instance, if these experiences are partly caused by, or maintained by the adolescents' negative expectations of their cognitive functioning, it may be helpful for the adolescents to receive guidance on how to prove for themselves that these expectations may not necessarily reflect reduced cognitive abilities.

When the mechanisms behind subjective cognitive difficulties are better understood, it is possible this will allow these adolescents to experience more self-efficacy and a greater sense of achievement. In return, it may provide a greater sense of hope that they might recover from CFS. Perhaps, it will also help the adolescents suffering from CFS to change their focus, which in return may contribute positively to their quality of life. Thus, it is important to recognize subjective experiences of cognitive difficulties as equally important as the impairments displayed by objective measures.

4.5 Recommendations for further research

Based on our results, we recommend future studies to consider illness duration of participants with CFS, preferably as longitudinal studies. Longitudinal study design will allow for a more in-depth exploration of the relationship between illness duration and cognitive functioning throughout the course of illness. Variables that should be considered in more detail in future research include personality factors and sleep quality. Further exploration of cognitive deficits in patients with CFS using objective tests should consider repeated assessment, in order to assess recovery time after mental exertion.

4.6 Conclusion

The focus of the current study was to explore cognitive functioning in adolescents who developed CF/CFS six months after acute EBV infection compared with those who did not develop fatigue and healthy controls. The adolescents with CF/CFS reported significantly more subjective cognitive difficulties. However, the adolescents with CF/CFS was not adversely affected on objective measures compared to non-fatigued adolescents and healthy controls. Furthermore, the subgroups with CFS reported more subjective cognitive difficulties and had reduced cognitive flexibility, verbal learning and verbal memory compared to the total group of adolescents with CF/CFS. Our findings suggest that adolescents who were diagnosed with CFS were more severely affected on both subjective and objective measures of cognitive functioning, which may indicate that symptom severity in patients with CF/CFS contributes to reduced cognitive functioning and should be addressed in future research.

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