# Atypical Behaviours in Developmental Disorders: The Association Between Fatigue and Autistic Symptoms in Children With Cri du Chat Syndrome

Anthony Claro

Department of Educational and Counseling Psychology

McGill University, Montreal

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**Abstract**

The goal of the current study is to examine whether fatigue level of children diagnosed with Cri du Chat syndrome or moderate to severe learning disabilities, is associated with their expression of autistic symptoms. Sixty-nine children with Cri du Chat syndrome and 47 children with moderate to severe learning disabilities were assessed using the ISQ-A for fatigue level and the CARS for autism level rating. In line with our hypothesis, results of hierarchical multiple regression analyses indicated that children who exhibited high levels of fatigue were more likely than children who exhibited low levels of fatigue to express high levels of autistic symptoms. Contrary to our hypothesis, children with moderate to severe learning disabilities who exhibited high levels of fatigue conferred the greatest vulnerability to the expression of autistic symptoms.

**Résumé**

L'objectif de la présente étude est de déterminer s'il y a un lien entre le niveau de fatigue et l'expression de symptômes associées à l'autisme chez les enfants ayant été diagnostiqués avec le syndrome du Cri du Chat ou des difficultés d'apprentissage modérées ou sévères. Soixante-et-neuf enfants ayant le syndrome Cri du Chat et quarante-sept enfants souffrant de difficultés d'apprentissage modérées ou sévères ont fait l'objet d'examen en utilisant le ISQ-A pour déterminer les niveaux de fatigue et le CARS pour l'évaluation du niveau d'autisme. En accord avec notre hypothèse, les résultats des analyses de régression multiple indiquent que les enfants exhibant des niveaux plus élevés de fatigue étaient plus sujets que les enfants exhibant des niveaux plus bas de fatigue à montrer des niveaux élevés de symptômes d'autisme. Contrairement à notre hypothèse, ce sont les enfants ayant des difficultés d'apprentissage modérées ou sévères et exhibant des niveaux élevés de fatigue qui étaient les plus sujets à l'expression de symptômes d'autisme.

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# Introduction

## Overview and Objectives

The current study describes a rare genetic disorder known as Cri du Chat syndrome and examines how atypical behaviours associated with this syndrome may be associated with fatigue. As fatigue has been shown to affect all individuals, atypically and typically developing, an interesting, yet unexplored concept is that individuals with developmental disorders and sleep difficulties may exhibit more autistic symptoms and at a greater severity level, than individuals with who lack the vulnerability factor fatigue.

The goal of the present study is to examine the association between fatigue and autistic symptoms. More specifically, in the present study we sought to examine whether fatigue level of children diagnosed with Cri du Chat syndrome is associated with their expression of autistic symptoms. The following sections will describe Cri du Chat syndrome and illustrate the relationships between intellectual disabilities, autistic symptoms and fatigue.

## Background

Certain genetic syndromes result in relatively specific patterns of behaviour; therefore the current trend in the field of genetic syndrome research involves uncovering these syndrome-specific signatures. The current study aims to further research surrounding behavioural phenotypes of rare genetic disorders by examining children with Cri du Chat syndrome (CDCS) in order to determine whether their expression of autistic symptoms is associated with their fatigue level. Such a study can adjoin itself to the growing body of literature that has identified behavioural signatures of many rare syndromes (Collacott, 1993; Turk,

1992). Findings from the current study can serve to advance the uncovering of the specific behavioural profile of children with CDCS and can be of significance for researchers, clinicians and families of children with CDCS.

Over the past decade, many advances have been made in the application of molecular genetics in determining the behavioural profiles of children with genetic disorders. These advances have made it possible to determine a diagnosis by identification of molecular markers, for a wide range of conditions, in more patients than was previously possible. Increasing accuracy, as well as earlier diagnoses can lead to better management of a wide range of genetic disorders, with increasing emphasis on early intervention to minimize the effects of the genomic anomalies. Furthermore, this approach can lead to an understanding of not only the specific physical strengths and weaknesses of the individual, but also the associated behavioural and cognitive changes unique to a particular genetic disorder.

Beginning in 1995, researchers at the Universities of Nottingham and Ulster had been investigating different behaviours sometimes shown by children and young people with Cri du Chat syndrome. With the goal of expanding this work, the current project entitled "*Cognitive, behavioural and nutritional characteristics of children and adolescents with cri-du-chat syndrome and the impact on the family"* began in October, 2000. This project aimed to investigate the pathways behind behaviour difficulties and developmental problems and was the first to assess children and young people with Cri du Chat syndrome across a wide range of abilities (e.g. sleep, problem behaviours including self-injury, nutrition, effect upon other family members). The overriding belief throughout

this project is that by establishing which characteristics are most commonly observed in persons with Cri du Chat syndrome, we can begin to determine the underlying causes of many problems. By doing this we can both improve the quality of life for families and help develop appropriate and early interventions (clinical and educational) that target specific strengths and difficulties in children with cri-du-chat syndrome.

**What is Cri du Chat Syndrome?**

Cri du Chat syndrome is a relatively rare genetic disorder that results from a terminal or interstitial deletion on the short arm of chromosome 5 at 5p15.1-15.3. Such a deletion can be genetically inherited or occur spontaneously by a genetic mutation. Although one of the most common deletion syndromes, there is as yet no clear consensus regarding incidence rates, with some reports estimating 1 in 37,000 live births (Higurashi et al., 1990) and others estimating a more conservative figure of 1 in 50,000 live births (Niebuhr, 1978). Most individuals with CDCS will present with the typical phenotypic features that consist of the cat-like cry due to underdevelopment of the larynx (from which the syndrome derives its name), severe intellectual delay, language impairment, dysmorphic facial features, delayed psychomotor development and significant behavioural concerns (e.g. self-injurious behaviour, stereotypy, aggression) (see Cornish & Bramble, 2002; Mainardi, 2006).

Small genomic changes (e.g. location and/or size of deletion) can have significant effects on the expressed phenotype of the individual (e.g. cognitive and behavioural profiles). Studies show the size and location of the chromosome 5p deletion dictates the severity of the disorder and that the chromosomal region

(5p15.2) is associated with the most severe and prototypical CDCS phenotype (Gersh et al., 1995; Overhauser et al., 1994). Furthermore, Cornish, Cross, Green, Willatt, and Bradshaw (1999) demonstrate a distinction between individuals with deletions in the critical CDCS range (5p15.1-15.3) who exemplify severe to profound learning disabilities and individuals with distal deletions of the critical region who present with a milder degree of cognitive impairment and a much-improved prognosis.

With regard to physical appearance, individuals with CDCS often present with round or "moon faces" with low set ears and an asymmetrical facial contour, microcephaly, hypertelorism, epicanthal folds, down-slanting palpebral fissures, strabismus, flat nasal bridge, micrognathia, down-turned mouth, short fingers, single palmar creases, and hypotonia (Niebuhr, 1978). Some of the aforementioned phenotypic characteristics become more pronounced with age, as demonstrated in a study that examined subjects with CDCS between the ages of 16 and 47 and found that as subjects age, some clinical characteristics become more evident (e.g. long face, macrostomia, and scoliosis) (Van Buggenhout et al., 2000).

Along with the aforementioned physical attributes, individuals with CDCS are susceptible to a particular set of medical problems. First and foremost, medical issues centre on respiratory, gastrointestinal and cardiac abnormalities which can occur in some, but not all children and adults with CDCS (Wilkins, Brown, Nance, & Wolf, 1983). Along with these major health concerns, there is a propensity for dental problems. However, at the moment there is a paucity of research with regards to the developmental trajectory of such medical issues in

individuals with CDCS and there is no information with regards to changing prevalence or severity rates with age.

In conjunction with the particular physical attributes and associated medical problems, individuals with CDCS typically exemplify a severe deficit in language ability. Cornish and Munir (1998) found a discrepancy between the chronological age of children with CDCS and their presumed language ages. Such findings support Carlin's (1990) findings that language and motor skills severely lag behind other developmental milestones for children with CDCS. Further studies identify the deficits in language ability as lying predominantly with expressive language (the ability to communicate), as opposed to receptive language (the ability to understand) (Cornish, Bramble, Munir, & Pigram, 1999; Cornish & Munir, 1998). An important implication of such findings involves intervention and remediation strategies that focus more on receptive skills, as opposed to traditionally verbal methods (Cornish & Munir, 1998).

Moreover, although early prognoses concerning language development were bleak, recent studies have begun to report encouraging findings. Specifically, Carlin (1990) found that although language ability lags behind other developmental milestones, that it had been acquired to some degree in more than 75% of individuals. Additionally, Cornish and Pigram (1996) examined the developmental profiles of children with CDCS and found that 95% of their sample was able to use basic sign or gestural language to communicate their needs. The prognosis of language ability has clearly changed over the years to an optimistic view that sees children with CDCS as able to communicate their needs, socially interact with others, and have some degree of mobility (Cornish &

Pigram, 1996). Another important implication for intervention and remediation strategies involves the early introduction of sign language and alternate communication techniques, which may prove useful for such children.

Such deficits in communicative ability may result in maladaptive behaviours that serve as an alternative for communicating needs and desires, or out of frustration from the inability of others to understand their expressive language. A maladaptive behaviour with high reported incidence rates among individuals with CDCS is self-injurious behaviours (Collins & Cornish, 2002; Cornish & Pigram, 1996; Dykens & Clarke, 1997). In particular, head banging, hitting the head against body parts, and self-biting are the most frequently occurring self-injurious behaviours in CDCS (Collins & Cornish, 2002). Individuals with CDCS not only express aggression towards themselves in the form of self-injurious behaviours, but also show signs of aggression to others. In fact, aggressive behaviour was reported in 88% of a sample of children with CDCS, with aggressive behaviour decreasing with age (Collins & Cornish, 2002).

The behavioural profile of children with CDCS not only consists of aggressive and self-injurious behaviours, but incorporates a reduced attention span, hyperactivity, impulsivity, sleeping difficulties, hypersensitivity to sound, clumsiness, obsessive attachments to objects, tantrums and autistic features (Chadwick, Piroth, Walker, Bernard, & Taylor, 2000; Clarke & Boer, 1998; Cornish & Pigram, 1996; Dykens & Clarke, 1997). Numerous studies have reported high levels of maladaptive behaviours in individuals with CDCS and it is likely that these maladaptive behaviours place serious restrictions on emotional and cognitive development (Cornish, Bramble, & Munir, 1998). Furthermore, the

best predictor of familial stress was the amount of maladaptive behaviours endorsed by their child with CDCS (Hodapp, Wijma & Masino, 1997).

Although all of the aforementioned maladaptive behaviours have been linked to the behavioural profile of CDCS, the behavioural phenotype of many rare disorders are not so well established. Perhaps one of a few exceptions is Cornelia de Lange syndrome. Over the past decade, significant advances have been made in identifying the specific behavioural profile of Cornelia de Lange syndrome. Specifically, self-injurious behaviour, compulsive behaviours, and autism spectrum disorder have all been found to be strongly associated with Cornelia de Lange syndrome (Hyman, Oliver & Hall, 2002; Moss et al., 2005; Oliver, Arron, Sloneem & Hall, 2008). Therefore, although uncovering aspects of the behavioural profiles of genetic disorders involving severe intellectual disability is difficult, it remains feasible. It is important to highlight the notion that severe intellectual disability does not mean global delay, and thus uncovering the specific profiles (i.e. strengths and weaknesses) of these populations is a critical area of research. With regard to CDCS, although the physical and intellectual phenotype is well documented, much less is understood about the unique behavioural phenotype associated with the syndrome. Numerous studies have shown tremendous variability amongst individuals with CDCS. For example, a case study by Cornish (1996) exemplified a child with CDCS who, contrary to the typical CDCS phenotype, only presented with a mild delay in motor and language development, had no evidence of a severe or profound learning disability, had good coping skills, and strong verbal and spatial abilities. Such a study warns of individual variation within syndromes and supports the

notion that there may be great variability in the developmental levels of individuals with CDCS.

Much of the variability found in CDCS may be due to genetics. As with all deletion syndromes, the location of the deletion matters. In particular, it is imperative to distinguish between 5p deletions that coincide with the typical CDCS phenotype that includes severe to profound learning disability and deletions that only delete the distal critical region that coincide with a milder degree of cognitive impairment and a much-improved prognosis (Cornish et al., 1999). Although the location of the deletion plays a critical role in the expressed phenotype of the individual, Marinescu, Johnson, Dykens, Hodapp, and Overhauser (1999) did not find a relationship between the size of the deletion and the level of developmental delay. Not only was their no effect of deletion size, but there was a wide range (20-75) in Vineland scores; once again suggesting great variability in the CDCS population. Although this type of genotype-phenotype approach has allowed for the clarification of a few behavioural phenotypes of some rare disorders such as Lesch-Nyhans (Hall, Oliver, & Murphy, 2001) and Fragile X syndrome (Turk, 1992), there is much to be done in order to unveil the unique behavioural phenotype associated with CDCS.

One study that implemented the genotype-phenotype approach by Dykens and Clarke (1997) found that the autistic-like features and social withdrawal seen in individuals with CDCS were more characteristic of individuals with genetic translocations, as opposed to deletions. These findings are particularly interesting as they illustrate a genetic vulnerability to the expression of autistic symptoms in individuals with CDCS and are very important due to the high incidence of

autistic-like behaviours in this population. Specifically, stereotypic behaviours were reported for 82% of a sample of children with CDCS, with more than half of the sample displaying these autistic-like behaviours on a daily basis (Collins & Cornish, 2002). Furthermore, Chadwick et al. (2000) found that autistic features, such as social withdrawal and stereotypies, were strongly associated with skills deficits, whereas other maladaptive behaviours such as aggression and temper tantrums were not. These findings suggest that autistic behaviours are not a permanent and stable symptom of CDCS, as they co-vary with other aspects of the individual's life. In addition, although there may be a genetic cause, such findings suggest the possibility of improving this pattern of behaviour and decreasing the expression of autistic symptoms by improving other areas of the child's life.

A study by de Bildt, Systema, Kraijer, Sparrow, and Minderaa (2005) found that for children with the highest level of a mild intellectual disability, adaptive functioning was the most important predictor of level of education attained. However, the authors also demonstrated that autistic behaviours seem to have such a restrictive effect on the level of adaptive functioning that children do not reach the level of education that would be expected based on IQ. The findings suggest that autistic symptoms can have deleterious effects for children with intellectual disabilities, and as children with CDCS have been shown to endorse autistic behaviours, this may be the case for CDCS as well, even though CDCS is classified as a severe intellectual disability. That is, when compared to Prader-Willi syndrome and Smith-Magenis syndrome, CDCS was rated as highest on hyperactivity, non-compliance and level of intellectual disability (Clarke & Boer,

1998). As aberrant behaviours such as autistic behaviours often emerge early and can be highly persistent during the preschool years, prevention initiatives should be undertaken as soon as possible in hope that such interventions can remedy and prevent many of the associated negative consequences related to the expression of autistic symptoms (Green, O'Reilly, Itchon, & Sigafoos, 2005).

**Autism**

The results of previous studies suggest that CDCS is associated with autism (Dykens & Clarke, 1997; Collins & Cornish, 2002; Chadwick et al., 2000), which is one of the most prevalent mental health problems among youth, with present prevalence rates indicating childhood autism at 1 case per 110 children (Rice, 2009). Autism is a brain development disorder with usual onset before the age of 3 years and generally follows a steady course without remission or relapse. Although autism is a brain development disorder that affects many parts of the brain and has a strong genetic basis, the exact mechanisms to which it occurs, remain unclear. The symptomatology of autism covers a wide spectrum, but is usually characterized by impaired social skills, qualitative language impairments, and restricted and repetitive behaviours, such as uncontrollable flapping and rocking. Furthermore, individuals with autism may also suffer from intellectual disabilities and muteness.

**Intellectual disabilities and the expression of autistic symptoms.**

Autism in youth has been found to be associated with impairment in multiple domains of functioning as well as co-occurring with other developmental disabilities. According to Dawson, Mottron and Gemsbacher (2008), there is a substantial subset of individuals with autism that present with an intellectual

disability, ranging from 25% to 70%. Despite such alarming statistics, researchers have only recently begun to examine theories of the co-occurrence of autism and various syndromes. As autism can be divided into syndromal (i.e. co-occurring with another disorder) and non-syndromal (i.e. occurring in the absence of another disorder) autism, it is important to note that there are significant differences between sub-groups. Most importantly, severe intellectual disability is primarily associated with syndromal autism (Cohen et al., 2005). Although autistic symptoms have been known to co-occur with various intellectual disabilities, it remains a poorly understood area of research and much remains to be done in terms of syndromal autism's relationship with syndromes such as fragile X syndrome, 22q11 deletion syndrome and cri du chat syndrome, amongst others.

Many genetic syndromes are associated with high levels of autistic symptoms e.g. Cornelia-de-Lange syndrome (62%; Moss et al., 2008), fragile x syndrome (47%; Demark, Feldman & Holden, 2003), and 22q11 deletion syndrome (44%; Niklasson, Rasmussen, Oskarsdóttir & Gillberg, 2009). These figures are all considerably higher than expected in the general population and therefore need detailed empirical investigation. Furthermore, it is likely that individuals with a comorbid genetic syndrome and autism will be at a greater risk for severe impairment in many areas of life. For example, a study by Capone, Grados, Kaufman, Bernard-Ripoll, and Jewell (2005) compared individuals with Down syndrome and autism, versus individuals with Down syndrome alone, and found that 87% of subjects with comorbid Down syndrome and autism scored in the severe-profound range (IQ 1-39) for cognitive function, whereas 32% of the

typical Down syndrome group scored in the severe range (IQ 25-54), with no participants scoring in the profound range (IQ <25).

**Cri du Chat syndrome and the expression of autistic symptoms.** In the case of CDCS, a recent study by Moss et al., (2008) identified approximately 40% of their sample of children and young adolescents as meeting criteria for autism using the Autism Diagnostic Observation Schedule (ADOS). Therefore, CDCS also shares similar high levels of autism as compared to other developmental and intellectual disabilities.

As there is great variability among individuals diagnosed with CDCS, it is possible that comorbid autism may affect individuals with CDCS differently. A study by Liss et al. (2001) highlights the differential effects of autism symptomology for high-functioning children, versus low-functioning children. Specifically, the authors found that low IQ was the most important limiting factor for low-functioning children with autism; however, autistic symptomology was the most important predictor of impairment for high-functioning children with autism. Therefore, perhaps the consequences of autism affect individuals with high-functioning CDCS and low-functioning CDCS differently. If autistic symptoms were shown to be a major debilitating factor in the lives of high-functioning children with CDCS, then uncovering the predictors of autistic symptomology in children with CDCS would prove to be a very important area of research. The discovery of predictors of autistic symptoms could lead to intervention and prevention programs and the eventual improved prognoses for children with high-functioning CDCS.

**Fatigue and Sleep Disturbances**

Fatigue and sleep disturbances have been shown to be associated with both CDCS (Maas et al., 2009) and autism (Meltzer & Mindell, 2008), and thus it is possible that fatigue may act as a vulnerability factor for the expression of autistic symptoms in children with CDCS. For the purposes of this paper, fatigue is defined as physical and/or mental exhaustion leading to the propensity to fall asleep. The ISQ-A asks caregivers specific questions concerning their child's propensity to fall asleep during the day; therefore the measure is consistent with the study's definition of fatigue.

Past studies have demonstrated that lack of sleep and fatigue are associated with numerous negative outcomes. For example, short sleep duration has been shown to have a strong link with obesity, especially in youth (Gangwisch, Malaspina, Boden-Albala, & Heymsfield, 2005; Patel & Hu, 2008; Spiegel, Tasali, Penev, & Van Cauter, 2004), as well as diminished academic achievement (Lazaratou, Dikeos, Anagnostopoulos, Sbokou, & Soldatos, 2005; Meijer, 2008; Meijer & van den Wittenboer, 2004) and attention (Corkum, Tannock, & Moldofsky, 1974; Owens, 2005; Sadeh, Pergamin, & Bar-Haim, 2006). Furthermore, lack of sleep and fatigue has been shown to be associated with increases in anxious and depressive symptoms, as well as increases in paranoia (Kahn-Greene, Killgore, Kamimori, Balkin, & Killgore, 2007) and decreases in emotion regulation (Johnson, Chilcoat, & Breslau, 2000; Smaldone, Honig, & Byrne, 2007). Although the body of literature examining sleep disturbances and fatigue in children and adolescents is lagging behind the literature on adults (Sadeh, 2007), the general findings appear to report substantial

difficulties in the behavioural, emotional and cognitive domains of the lives of individuals who lack sleep. As fatigue has been shown to have numerous negative consequences on an individual's daytime functioning, another area of research of particular interest for this study involves the potential consequences fatigue has on the expression of autistic symptoms.

**Fatigue and the expression of autistic symptoms.** Past research has shown a strong link between sleep disturbances and autism with prevalence rates of sleep difficulties in children with autism ranging between 44% and 83% (Meltzer & Mindell, 2008). Moreover, recent research supports the notion that children with autism have an increased vulnerability to such sleep problems as waking during the night, trouble settling, inability to self-soothe at bedtime, circadian rhythm disorders, bedtime resistance, sleep onset delay and sleep duration (Giannotti et al., 2008; Meltzer & Mindell, 2008). Furthermore, a study by Elia et al. (2000) found a strong negative correlation between autistic symptoms, as measured by the Childhood Autism Rating Scale, and sleep period time, wakefulness after sleep onset, and total sleep time. Also, the findings demonstrate that time in bed, sleep period time, and total sleep time were significantly lower in subjects with autism than in typically developing controls. Another recent study by Allik, Larsson and Smedje (2006) examined children with high-functioning autism or Asperger syndrome and found that 31% of participants met diagnostic criteria for pediatric insomnia, whereas none of the controls met criteria for such a diagnosis. The effects of the insomnia on children with autism and Asperger syndrome were examined and it was determined that participants who presented with insomnia had more autistic (i.e. social interaction,

communication, restricted and repetitive behaviours), emotional and hyperactive symptoms than participants without insomnia. The high prevalence of sleep problems in individuals with autism likely causes increases in fatigue for these individuals, which may in turn affect their behaviour. As the relationship between fatigue and autism is well documented, as well as the negative effects of fatigue for both typically developing children and children with autism, the next sections will examine the relationship between fatigue and intellectual disabilities as well as the potential consequences of fatigue for these individuals, including those with CDCS.

**Fatigue and intellectual disabilities.** If fatigue is known to have many negative consequences for typically developing children, then it is possible that the detrimental effects of fatigue will be more prominent in individuals with intellectual and developmental disorders due to deficits in communication, problem solving, self care and coping skills. Individuals with intellectual disabilities may not recognize the sources of their discomfort, be aware of the appropriate responses to fatigue, and/or may not be able to communicate their need for help. Furthermore, past research suggests that sleep problems are more common in individuals with an intellectual disability, as compared to the typically developing population, with 32% to 39% experiencing sleep problems, 27% to 29% experiencing settling problems, and 44% to 56% reporting waking at night (Brylewski & Wiggs, 1998; Stores et al., 1996). Although the aforementioned statistics incorporate the wide range of disability level, they do not highlight the phenomenon that individuals with a more severe or profound intellectual disability are more likely to present with greater sleep problems. For example, a

study by Hall, Arron, Sloneem, and Oliver (2008) examined individuals with Cornelia de Lange syndrome and a comparison group of individuals with intellectual disability of mixed aetiology, but of similar level of disability, and found that 55% of both groups experienced sleep problems. Although there is mounting evidence linking sleep disturbances with level of severity of intellectual disability, it is unclear whether there is a causal relationship, and if so in which direction, or whether there is an associative relationship between fatigue and level of intellectual disability. That is, it is possible that sleep disturbances naturally occur at a higher rate in individuals with an intellectual disability, and that these sleep difficulties negatively affect daytime functioning. However, it is equally plausible that such sleep disturbances are a consequence of the many associated behavioural and intellectual disturbances present in individuals with severe intellectual disability. Although the nature of the relationship between sleep and intellectual disability is yet to be determined, the strength of the relationship, as well as the consequences of fatigue are clear.

**Fatigue and Cri du Chat syndrome.** CDCS frequently results in severe intellectual disabilities and thus, individuals with a diagnosis of CDCS should be at a greater likelihood to express sleep disturbances and the resulting high levels of fatigue. However, there are currently only a limited number of studies that examine sleep disturbances in children with CDCS. One such study by Cornish, Oliver, Standen, Bramble, and Collins (2003) found a prevalence rate of 50% for night waking and 25% for settling problems. Another study by Maas et al. (2009) revealed that 30% of their sample had a severe or mild sleep problem and that the most significant disturbance was frequent night waking. Finally, Chadwick et al.

(2000) found that sleeping difficulties were a major component of the behavioural profiles of both ambulant and non-ambulant children with CDCS. Therefore, as with other intellectual disabilities, CDCS appears to have an elevated prevalence rate for sleep problems. Furthermore, such high prevalence rates could indicate high levels of fatigue amongst the CDCS population, as well as the associated negative consequences of fatigue.

**Cri du Chat Syndrome, Fatigue, and Autistic Symptoms**

One such negative consequence of fatigue could be an increase in frequency of expressed autistic symptoms by individuals with CDCS. Fatigue has been shown to have detrimental effects on daytime functioning; therefore it is possible that the behaviours of children with CDCS could be affected in a way that would increase their expression of autistic symptoms. Although a significant percentage of children with CDCS present with sleep disturbances, no study has examined the effects of these sleep disturbances (i.e. fatigue) on children with CDCS and their possible link to atypical behaviour. Therefore, this study addresses an empirical gap in the field of sleep research in children with intellectual disabilities. This is important because if the association between fatigue and autistic symptoms proves to be significant, then it would suggest that the frequency and/or intensity of autistic symptoms could be at least partially controlled by regulating an individual's fatigue level.

A study by Elia et al. (2000) examined sleep patterns and compared children with a diagnosis of autism, versus a diagnosis of an intellectual disability, versus a typically developing prognosis and found that children with autism had the highest occurrence of sleep problems, followed by children with an

intellectual disability, and finally followed by the typically developing children. This finding suggests that there are strong associations between sleep disturbances and autism, as well as sleep disturbances and intellectual disability.

## The Present Study: Aims and Hypotheses

### Goals of the Current Study

Past research has shown that there is a strong link between autism and sleep difficulties. While the vast majority of sleep research has concentrated on documenting the prevalence of sleep disturbances in children with developmental disorders, there is a paucity of research examining associated factors. Identifying factors that are associated with the negative impact of sleep on symptoms of children with developmental disorders could aid in the development of interventions aimed at improving daytime functioning of these children.

To date there is a growing body of literature describing the behavioural phenotype of CDCS, while linking the syndrome to a range of maladaptive behaviours. Only a few studies have examined the prevalence rates of sleep disturbances and autistic symptoms in children with CDCS, and no study has examined a possible link between sleep and autism in this population. Therefore, this study can act as a pioneer in the field of CDCS research, as it is the first to examine a potential correlate to autistic behaviour.

The goal of the present study is to examine the association between fatigue and autistic symptoms. More specifically, in the present study we sought to examine whether fatigue level of children diagnosed with CDCS or moderate to severe learning disabilities, is associated with their expression of autistic symptoms.

**Hypotheses of the Current Study**

1. It is hypothesized that individuals with elevated fatigue levels will demonstrate a greater amount of autistic symptoms, regardless of diagnosis.
2. The second hypothesis predicts that the children with a diagnosis of CDCS and high fatigue level will confer the greatest vulnerability to the expression of autistic symptoms.

Due to a lack of expressive language skills, individuals with CDCS may inappropriately and ineffectively express their feelings of fatigue to their caregivers. That is, in response to increased fatigue levels and frustration due to lack of understanding on the part of their caregivers, perhaps individuals with CDCS exhibit increases in ASD-like symptoms, as they are unaware of more efficient ways to communicate their fatigue. Cornish et al. (1999) showed that individuals with CDCS can communicate through non-verbal modalities such as sign language and symbol cards. However, non-verbal communication such as signing requires a certain amount of physical exertion and in times of high fatigue, especially for children with motor difficulties, as in children with CDCS, the physical effort required to communicate fatigue may be frustrating and cause the expression of maladaptive behaviours, including autistic behaviours. Therefore, if a child who has a higher level of expressive language ability becomes fatigued, they will express their feelings to their caregivers who will react appropriately to meet their needs, whereas children with diminished expressive language skills will be at a disadvantage. Although such individuals

can communicate, their fatigue may play a role in the effectiveness of their communication as fatigue plays a role in physical functioning.

## Method

### Participants

Sixty-nine children and adolescents with CDCS were recruited from the UK Cri du Chat Support Group. All participants had received a diagnosis of CDCS which was established by physical phenotype and chromosomal analysis which confirmed a deletion of the chromosome 5p15.2 region. Of the 69 children with CDCS, 30 (43.5%) were male and 39 (56.5%) were female. Age ranged between 3 and 18 years (mean age 9.30; SD 4.46). All participants were living with their families and educated in schools for children with moderate to severe learning disabilities.

Participants in the comparison group were selected from the same schools for children with moderate to severe learning disabilities. These children were matched to the CDCS group on the basis of chronological age, level of mobility, receptive language ability and education. The comparison group consisted of children of mixed etiology who were nominated by teachers to match members of the CDCS group. Participants were matched individually and nominated children were only excluded if they did not match their CDCS peer on any of the matching variables. Karyotypic information was only collected for the CDCS group and not the comparison group. In order to match groups of individuals with intellectual disabilities on level of intellectual disability, language ability is often used as a matching variable. In particular, the Receptive and Expressive subdomain scores from the Vineland Adaptive Behavior Scale are often used as

the measure of language ability (Collis, Moss, Jutley, Cornish, & Oliver, 2008). However, children with CDCS have been shown to have difficulty with expressive language (Cornish, Bramble, Munir, & Pigram, 1999; Cornish & Munir, 1998), but have the means to communicate through other nonverbal modalities (Carlin, 1990; Cornish & Pigram, 1996). Therefore, if the poor expressive language skills of children with CDCS do not impede their communication skills, matching children with CDCS on this ability is clearly inappropriate because expressive language ability is not a true reflection of intellectual disability in children with CDCS. In other words, the level of intellectual disability is likely to be lower for individuals with CDCS than their expressive language ability would suggest. Consequently, as the cognitive profile of children with CDCS includes a relative strength in receptive language ability, it is appropriate to match them on receptive language alone. Participants were matched on receptive language ability using raw scores because standard scores are restricted in range for young children and children with low ability (Carter et al., 1998). With regard to interpreting Vineland Adaptive Behavior Scale scores for low functioning individuals, there is little scatter in standard scores due to basal effects. Closer analysis is required when an individual scores the lowest possible standard score because such a score can reflect a wide range of raw scores (Mervis & Klein-Tasman, 2004). Our groups consist of children with high intellectual disability; therefore they can be "considered matched only if the raw scores are closely matched" (Mervis & Klein-Tasman, 2004, p. 7). Furthermore, with regard to the VABS, it is recommended that standard scores be used for clinical purposes and raw scores be used for research purposes (Carter et al.,

1998). Due to the severity of impairment in children with CDCS, a comparison to typically developing children would have been insignificant and inappropriate. None of the participants in the comparison group had ever received a diagnosis of CDCS. Of the 47 comparison children, 32 (68.1%) were male and 15 (31.9%) were female. Age ranged between 4 and 17 years (mean age 10.30; SD 3.86).

**Measures**

**Demographic questionnaire.** The demographic questionnaire provided information regarding chronological age, gender, diagnosis (the precise diagnosis made, when and by whom it was given) and mobility. Caregivers were asked to rate their child's mobility level on a 4-point scale: 1 = "wheelchair user, little use of arms"; 2 = "wheelchair user, can crawl"; 3 = "walks with assistance"; and 4 = "walks independently."

**Childhood Autism Rating Scale (CARS).** The CARS (Schopler, Reichler, DeVellis, & Daly, 1980) has been frequently used as a screening measure of autism spectrum disorder in clinical and research studies. The CARS comprises 15 items investigating the presence of behavioural characteristics associated with autism. Each item is rated on a scale from 1 (within normal limits for age) to 4 (severely abnormal for age), with half point scores also possible. The CARS has three cut-offs for establishing autism level rating: 15-30 (absence of autism); 30-36 (mild autism); 36-60 (severe autism). The CARS has shown strong validity through a correlation of 0.84 between scaled scores and clinicians' ratings and a good inter-rater reliability of 0.71.

One of the strengths of the CARS is that is based on behavioural observation as opposed to parent-report measures. However, the CARS has also

been criticized for a number of reasons. First, many clinicians and researchers argue that the CARS is no longer reflective of the modern day diagnostic criteria of the DSM-IV because it was published during the time of the DSM-III. Although the CARS does not include items pertaining to peer relationships, joint attention and symbolic play, it does include items tapping into social and emotional responses, verbal and nonverbal communication, and various repetitive behaviours, which are all DSM-IV criteria. Furthermore, the CARS includes items that are clinically relevant such as sensory abnormalities, anxiety and activity level, and imitation difficulties that are not necessarily universal or autism-specific, but are nonetheless clinically significant (Perry, Condillac, Freeman, Dunn-Geier, & Belair, 2005). Another common criticism is that the CARS cannot distinguish between diagnoses of autism and other developmental disabilities. However, past research has shown that scores on the CARS can distinguish between diagnoses of autism, pervasive developmental disorder and non-pervasive developmental disorders (i.e. oppositional disorder, adjustment disorder, attachment-related disorders, and intellectual disability) (DiLalla & Rogers, 1994; Garfin, McCallon, & Cox, 1988; Kurita, Miyake, & Katsuno, 1989; Teal & Wiebe, 1986). A study by Perry et al. (2005) demonstrated high concordance between the CARS and clinical diagnoses (DSM-IV) for children with an autistic disorder, PDD-NOS, or intellectual disability. In sum, although the reasons behind the expression of autistic symptoms for children with autism or another disorder such as CDCS may be different, the current study does not investigate the underlying etiology or attempt to distinguish between diagnoses,

but instead examines the overall quantity of autistic symptoms that are expressed by the participants.

**Adapted Infant Sleep Questionnaire (ISQ-A).** The ISQ (Morrell, 1999) is a 10-item, informant-based measure of sleep in infants. The original version was adapted by substituting the phrase "your baby" to "the person you care for." Informants respond to questions relating to the person's sleeping habits over the previous month. The ISQ taps issues surrounding common sleep disturbances such as insomnia, bedwetting, nightmares, daytime fatigue, sleep apnea, sleepwalking and sleep talking. Total scores on the ISQ range from 0-38 and a cut-off score of 6 or above has been found to designate a wide range of sleep problems, whereas a score of 12 or above indicates severe sleep problems. The ISQ-A includes five additional questions that are designed to address issues such as parasomnias and fatigue. Past comparisons of the ISQ to Richman's sleep diaries have demonstrated good concurrent validity as well as a strong test-retest reliability correlation coefficient of 0.92 (Morrell, 1999).

**Vineland Adaptive Behaviour Scale (VABS).** The VABS (Sparrow, Balla, & Cicchetti, 1984) is a semi-structured interview designed to assess adaptive behaviour for use with individuals up to the age of 18 years. The interview is conducted using open-ended questions regarding what the individual typically does in daily life. The scale is normally used to measure adaptive functioning in four domains: *Communication Skills*, *Socialisation*, *Daily Living Skills* and *Motor Skills*. For the purpose of this study, only the communication domain was used. Each of the 63 items of the VABS Communication Domain represents a single topography of communication (e.g. "Does the individual turn

their eyes or head towards sound?"). For each item a three point rating scale is used to asses the level of communication of the child: 0 = " behaviour is never performed"; 1 = "behaviour is sometimes or partly performed"; and 2 = "behaviour is usually or habitually performed." The Communication domain has three subscales; receptive language ability; expressive language ability; and written communication. For the purpose of this study, items relating to written and expressive communication were not relevant, so the respondent was not asked items belonging to this subscale. Raw scores for the receptive communication ability were calculated, and used to obtain age-equivalent scores from standardised tables provided. This provides an insight into whether the child is performing at a typical level of communication for their chronological age. Finally, de Bildt, Kraijer, Sytema, and Minderaa (2005) demonstrated that the VABS is a reliable and valid measure for children with and intellectual disability.

**Procedure**

Families were contacted via the UK Cri du Chat Support group. Families who were interested in the study responded by sending a reply slip with contact details for their family and for their child's school. Following participant confirmation, a more in depth information pack was sent that included a letter of explanation, a project booklet, all details of the tests and copies of the questionnaires (ISQ and VABS) that were to be completed by the primary caregiver and returned via post. Following the completion and receipt of the mailed questionnaires, the participants were visited at their school/day center. The CARS was completed at the child's school by a researcher who observed the child for the entire day and rated the child on 15 different behavioural scales.

**Statistical Analysis Overview**

Demographic, language, and mobility characteristics, along with autism level rating and fatigue were considered as dependent variables and were compared across diagnostic groups using one-way analysis of variance (ANOVA).

In order to reveal the internal structure of the data in a way that best explains the variance, a principal component analysis was used to reduce the number of variables and aggregate the 14 ISQ-A measures into reliable indices reflecting the different aspects of sleep. This type of analysis transformed the 14 ISQ-A measures, which are possibly correlated variables, into a smaller number of uncorrelated variables (i.e. the factors). Factors were included if they met both of the following criteria. First, the Kaiser criterion, which states that a factor is to be retained only if its eigenvalue is greater than 1, needed to be met (Kaiser, 1960). Essentially, unless a factor extracted at least as much as the equivalent of one original variable, it was excluded as a factor. Second, the scree test criterion proposed by Cattell (1966), which suggests identifying where the eigenvalues level off to the right of the scree plot, whereby anything to the right of this point is "factorial scree" was also used.

A hierarchical multiple regression was performed between autism level rating as the dependent variable and diagnostic group and fatigue level as the predictor variables. The matching variables mobility, age and receptive language were controlled for in the analysis, as only the effects of diagnostic group and fatigue level on autism level rating are of interest for this study. In hierarchical multiple regression, the independent variables are entered in two stages with the

variables to be controlled for entered in the first stage (i.e. mobility, age and receptive language), and the variables whose relationship will be examined entered in the second stage (diagnostic group and fatigue level). A statistical test of the change in $R^2$ from the first stage was used to evaluate the importance of the variables entered in the second stage. This method of multiple regression is the most conservative. All analyses were performed using SPSS 16.0 whereby $p < 0.05$ indicated statistical significance.

## Results

Table 1 presents the characteristics of all participants. Statistical comparison of the groups showed that individuals in the CDCS group were not significantly different from the comparison group on any of the matching variables (i.e. chronological age, level of mobility, and receptive language ability). However, there was a significant difference for average autism level rating between the two groups. Specifically, individuals with mild to moderate learning disabilities presented with a higher autism level rating than children diagnosed with CDCS.

The principal component analysis with varimax rotation produced a 5-factor solution for the ISQ measures. The five factors met both the Kaiser Criterion and the scree test criterion. Based on component loadings of 0.5, the five factors accounted for 68.31% of the variance (see Table 2). The following labels were provided for the five factors: (1) Severity of Sleep Disturbance (SEV), (2) Insomnia (INS), (3) Fatigue (FAT), (4) Bed Sharing (BED), and (5) Parasomnia (PAR). The labels of the factors were chosen as representations of the content of the loaded items (see Table 2). The third factor, fatigue, is of particular interest

for the present study given the expected consequences that fatigue has on an individual's daytime functioning and expression of autistic symptoms.

Table 1

*Means, Standard Deviations, Ranges, and Mean Comparisons of Demographic Characteristics by Diagnostic Group*

| Characteristic | Cri du Chat syndrome ($n$ = 69) | Comparison group ($n$ = 47) | $t$ | $df$ | $p$ |
|---|---|---|---|---|---|
| Age (in years) | | | | | |
| Mean | 9.30 | 10.30 | -1.24 | 114 | .22 |
| Standard Deviation | 4.46 | 3.86 | | | |
| Mobility | | | | | |
| Mean | 3.41 | 3.34 | .30 | 89 | .76 |
| Standard Deviation | 1.04 | 1.13 | | | |
| Receptive Language[a] | | | | | |
| Mean | 17.21 | 18.84 | -1.14 | 88 | .26 |
| Standard Deviation | 6.71 | 6.15 | | | |
| Autism Level Rating | | | | | |
| Mean | 1.20 | 1.87 | -4.25 | 83 | >.01 |
| Standard Deviation | .49 | .96 | | | |

[a]Total raw scores as measured by the Vineland Adaptive Behavior Scale.

Table 2

*Summary of Exploratory Factor Analysis Results for ISQ Measures Using Maximum Likelihood Estimation*

| | Factor Loadings | | | | |
|---|---|---|---|---|---|
| Item | SEV | INS | FAT | BED | PAR |
| Nights per week child wakes | **.82** | .09 | .04 | .25 | .07 |
| How long has waking problem existed | **.79** | -.07 | .14 | .14 | -.12 |
| How many times does child wake per night | **.78** | .17 | -.01 | .16 | .27 |
| Severity of sleeping problems | **.63** | **.50** | .18 | .28 | .18 |
| Does your child have sleeping difficulties | **.58** | **.53** | .09 | .30 | .14 |
| How long has settling problem existed | **.54** | .43 | .23 | .04 | -.18 |
| Any problem with overactivity | .29 | **.82** | .08 | .15 | -.05 |
| How long does it take to go to sleep | .24 | **.77** | -.06 | -.10 | -.19 |
| How many times per week, trouble settling | -.25 | **.59** | -.08 | .11 | .12 |
| Does child ever fall asleep during day | .09 | -.10 | **.89** | .03 | .07 |
| Trouble with sleepiness during day | .11 | .09 | **.89** | .02 | .06 |
| How often does child share bed | .28 | .10 | -.14 | **.82** | .06 |
| How long does child sleep in day | .05 | -.03 | -.01 | .15 | **.72** |
| Does child have a parasomnia | .32 | .11 | .34 | -.09 | **.65** |
| Eigenvalues | 3.48 | 2.48 | 1.88 | 1.76 | 1.34 |
| % of variance | 21.72 | 15.50 | 11.74 | 10.99 | 8.36 |

*Note.* Factor loadings over .50 appear in bold; SEV = Severity; INS = Insomnia; FAT = Fatigue; BED = Bed Sharing; PAR = Parasomnia.

**Diagnostic Group- and Fatigue-Associated Influences on Autism Level Rating**

Mobility, age and receptive language ability were included in the regression analysis as covariates, while diagnostic group and fatigue were included as the predictor variables. Table 3 displays the parameter estimate (*b*), the standard error, the *t*-value and the degrees of freedom for the three covariates and the two predictor variables. *R* for regression was significantly different from zero, $F(5, 110) = 10.78$, $p < .001$ with $R^2$ at .33, suggesting a statistically significant relationship between the set of five regression coefficients and the dependent variable. The adjusted $R^2$ value of .30 indicates that almost a third of the variability in autism level rating is predicted by diagnostic group, fatigue level, mobility, age and receptive language.

First, the matching variables were entered into the regression analysis. *R* for regression was significantly different from zero, $F_{inc}(3, 112) = 15.26$, $p < .001$ with $R^2$ at .13, suggesting a statistically significant relationship between the matching variables mobility, age and receptive language and the dependent variable autism level rating. The adjusted $R^2$ value of .11 indicates that a little more than a tenth of the variability in autism level rating is predicted by mobility, age and receptive language.

After accounting for the effects of the matching variables, diagnostic group was entered. Again, *R* for regression was significantly different from zero, $F_{inc}(4, 111) = 26.47$, $p < .001$ with $R^2$ at .30, suggesting a statistically significant relationship between the three matching variables and diagnostic group and the dependent variable autism level rating. The R Square Change statistic for the

increase in $R^2$ associated with the addition of diagnostic group is .17, indicating that the addition of diagnostic group to the model increased the predictability of the variability in autism level rating by 17%. The adjusted $R^2$ value of .27 indicates that mobility, age, receptive language and diagnostic group predict a little more than a quarter of the variability in autism level rating.

Table 3

*Predictors of Autism Level Rating*

| Predictor | Parameter Estimate (*b*) | Standard Error | *t*-Value | Degrees of Freedom |
|---|---|---|---|---|
| Mobility | 0.09 | 0.06 | 1.44 | 110 |
| Age | -0.01 | 0.01 | -0.57 | 110 |
| Receptive Language | -0.05 | 0.01 | -4.80** | 110 |
| Diagnostic Group | 0.46 | 0.11 | 4.14** | 110 |
| Fatigue | 0.08 | 0.04 | 2.24* | 110 |

*Note.* *$p<.05$, **$p<.001$

Last, the second predictor, fatigue, was entered into the model. *R* for regression was significantly different from zero, $F_{inc}$ (5, 110) = 4.99, $p < .05$ with $R^2$ at .33, suggesting a statistically significant relationship between the three matching variables, diagnostic group and fatigue and the dependent variable autism level rating. The R Square Change statistic for the increase in $R^2$ associated with the addition of diagnostic group is .03, indicating that the addition of fatigue to the model increased the predictability of the variability in autism level rating by 3%. This finding supports the research hypothesis that there is a statistically significant improvement in the relationship between the set of

independent variables and the dependent variable when fatigue is added to the model. That is, fatigue level of children diagnosed with CDCS or moderate to severe learning disabilities, is associated with their expression of autistic symptoms.

Altogether, 33% (30% adjusted) of the variability in autism level rating was predicted by knowing scores on these five regression coefficients. However, for the purpose of this study, the most significant finding is that fatigue level accounted for 3% of the total variance in autism level rating. The size and direction of the relationship suggest that a higher autism level rating is associated with the comparison group, low receptive language skills and high fatigue level. Between these three, however, fatigue was the weakest predictor, as indicated by the squared semi-partial correlations, but is nevertheless important.

A statistically significant relationship was found between diagnostic group and autism level rating, $t(5, 110) = 4.14$, $p < .001$. The *b* coefficient associated with diagnostic group is positive, indicating a direct relationship in which higher numeric values for diagnostic group (i.e. comparison group) are associated with higher numeric values for autism level rating.

A statistically significant relationship was found between fatigue level and autism level rating, $t(5, 110) = 2.24$, $p < .05$. The *b* coefficient associated with fatigue level is positive, indicating a direct relationship in which higher numeric values for fatigue level are associated with higher numeric values for autism level rating.

## Discussion

The present study is the first to examine the association between fatigue and autistic symptoms in children with CDCS. In line with our hypothesis, a significant association was found between fatigue level and the expression of autistic symptoms in children. The findings suggest that children with a high level of fatigue, regardless of diagnosis, are more likely to exhibit autistic symptoms, as compared to children with a low level of fatigue. However, contrary to our hypothesis, it was the children from the comparison group and who presented with a high fatigue level that conferred the greatest vulnerability to the expression of autistic symptoms. The findings are consistent with previous studies that highlight a strong link between sleep difficulties and autistic symptoms (Elia et al., 2000; Meltzer & Mindell, 2008).

Contrary to past research that demonstrates higher rates of autism in persons with intellectual disability (Demark, Feldman & Holden, 2003; Moss et al, 2008; Niklasson, Rasmussen, Oskarsdóttir & Gillberg, 2009), it was the group composed of children with learning disabilities who expressed more autistic symptoms. Perhaps fatigue is only one of few vulnerability factors for the comparison group, whereas children with CDCS may present with many vulnerability factors for the expression of autistic symptoms. Children with intellectual disability likely have a greater number of vulnerability factors due to complications related to their disability. Therefore, changes in fatigue level are more likely to affect an individual with fewer vulnerability factors, as it is likely to be more central to the emergence of autistic symptoms. Participants with CDCS who exhibit high levels of fatigue may not present with other vulnerability

factors and the absence of such possible vulnerability factors may be due to the presence of protective factors.

As no other study has examined fatigue in children with CDCS, especially with regards to the expression of autistic symptoms, the current study addresses an important empirical gap in the field of sleep research in children with intellectual disabilities. Such research has important theoretical and clinical implications, as the findings indicate fatigue has an important effect on behaviour. Furthermore, the exact mechanisms to which autism occurs remain unclear. Therefore, findings that link autism to sleep may aid in identifying the underlying mechanisms. If sleep and autism are strongly related, it is likely that both phenomena share structural and functional characteristics of the brain, as well as underlying biological mechanisms.

Although Maas et al. (2009) concluded that individuals with CDCS do not have an increased likelihood of sleep problems as compared to other individuals of similar demographic characteristics (i.e. Down's syndrome and non-specific intellectual disabilities), the effects of the sleep problems remain an important area of research. As the current findings illustrate, children with CDCS who exhibited a high level of fatigue, were more likely to present with a high autism level rating, as compared to children with CDCS and a low level of fatigue. As fatigue is known to have such negative consequences as behaviour difficulties and mood instability (O'Brien & Gozal, 2004; Smedje, Broman, & Hetta, 2001; Zuckerman, Stevenson, & Bailey, 1987), as well as impaired neurocognitive functioning, including memory, attention, verbal creativity, cognitive flexibility, and abstract reasoning (Dahl, 1996; Fallone, Acebo, Arnedt, Seifer, & Carskadon,

2001; O'Brien & Gozal, 2004) for typically developing children, the current study demonstrates that fatigue is also associated with the behaviour of atypically developing children diagnosed with CDCS. The etiology of sleep problems in children with autism and/or CDCS remains a largely unexplored area of research; therefore the current findings are important as they may lead to the discovery of shared underlying mechanisms between sleep, autism and CDCS. Genetic studies, as well as studies that include brain imaging could aid in examining structural or genetic anomalies that are shared by sleep, autism and CDCS. It is speculated that because the relationship between the phenotypes of sleep, autism and CDCS are well established, that there is likely common pathways with regards to their genotypes.

**Limitations of the Study and Directions for Future Research**

Several limitations of the present study should be noted. First, the current study used parent-report measures to assess fatigue and language ability. Given that parent-report measures may be prone to subjectivity, future research would benefit from using more sophisticated assessment techniques such as the Multiple Sleep Latency Test (MSLT). The MSLT is a diagnostic tool that assesses daytime fatigue by measuring the time it takes from the start of a daytime nap period to the first signs of sleep (i.e. sleep latency). The test is an objective measure of fatigue and is based on the idea that the more fatigued a person is, the quicker that person will fall asleep.

Second, the study lacked a direct measure of language ability. As an alternative to caregiver interviews (i.e. VABS), future research would benefit from direct measures of participant ability such as the Clinical Evaluation of

Language Fundamentals - Fourth Edition (CELF-4). The CELF-4 helps to determine the child's language strengths and weaknesses, as well as yielding a receptive language and expressive language score.

Third, as the research method is not prospective in design, it is impossible to determine whether there is a causal effect for fatigue on the expression of autistic symptoms, or whether the child's autism level is affecting his sleep patterns and subsequent fatigue level. Future research would benefit from longitudinal studies that would delineate the causal effects of fatigue.

Fourth, although the current sample of CDCS children represents one of the largest samples ever to be examined ($n$ = 69), it remains a considerably small number, which makes comparisons between the genetic subtypes of CDCS difficult. Future research should attempt international collaboration in order to increase sample size and examine the generalizability of the current findings.

Last, the percentage of variance for the relationship between fatigue and autistic symptoms is small. The CARS does not have strong inter-rater reliability, which may have depressed participant scores. With better measures of autistic behaviours, the percentage of variance for the relationship between fatigue and autistic symptoms will likely increase. Furthermore, there are many ways to use multiple regression and the method used in this study is the most conservative, resulting in a conservative percentage of variance. Although the percentage of variance for the relationship between fatigue and autistic symptoms is conservative, it remains a significant finding and is likely to be of great interest for families and clinicians. Hodapp, Wijma and Masino (1997) demonstrated that the best predictor of familial stress for families affected by CDCS was the amount

of maladaptive behaviours endorsed by the affected child. Such a finding highlights the need for intervention strategies that aim to decrease the occurrences of maladaptive behaviours, even if the decrease is only minimal.

**Clinical Implications**

Unfortunately, many parents today are unaware of the potentially harmful effects fatigue can have on their children. Other parents who may be conscious to the detrimental effects of fatigue, may be unaware of how to efficiently manage their child's sleep patterns. Sleep deprivation has been shown to impair learning and memory abilities (Stickgold & Walker, 2005), emotional regulation (Dahl & Lewin, 2002), neurobehavioural functioning and academic success (Sadeh, Gruber & Raviv, 2003; Wolfson & Carskadon, 1998). Our findings suggest that children who are fatigued during the day are more likely to exhibit autistic symptoms than children who are well rested. Although our findings are of particular interest for parents of children with intellectual disabilities, the behaviours of typically developing children are also affected by fatigue. Intervention programs would be well served to include strategies on how to cope with sleep disturbances and improve sleep habits in order to reduce fatigue and improve subsequent behaviour and daytime functioning.

**Implications for School Psychology**

Research examining the links between intellectual and developmental disabilities and behavioural phenotypes can serve as a valuable resource for school psychologists, teachers and school staff. This study informs us of the potentially harmful effects of fatigue on the behaviors of children with CDCS or learning disabilities. School psychologists should be made aware of factors that

may seem less obvious, but that have potentially detrimental effects for behaviour. That is, intervention plans for oppositional behaviours in schools may be well served to incorporate fatigue-reducing strategies as part of the overall plan.

Modern families often include both parents working full-time, which can cause delays in dinnertime, homework time, and bedtime. Hectic work schedules are often coupled with their children's extra curricular activities, resulting in later bedtimes and earlier mornings. Such schedules reduce sleep duration and cause increases in fatigue. Research findings centering on the detrimental effects of fatigue, combined with the present day hectic lifestyles of many families should suggest to school psychologists that sleep education is an overlooked, but essential contributing factor to the overall success of children.

Another important issue with regard to school psychology involves the nature of syndromal autism. For example, there is often debate as to whether syndromal autism is a qualitatively different disorder than non-syndromal autism. The debate centers on whether the autistic symptoms expressed in individuals with an intellectual disability are simply a manifestation of the disorder, or whether they are part of a legitimate comorbid diagnosis. Much of the debate is fueled by guidelines implemented by the school boards that determine the allocation of resources. Specifically, a large proportion of resources in schools are made available for children with autism diagnoses. Other children with intellectual disability and without an autism diagnosis receive far less support. Therefore, comorbid autism diagnoses for children with intellectual disability can be very beneficial, but can lead to ethical considerations. School psychologists aim to provide the best support available for every child, and the temptation to

increase syndromal autism diagnoses for the purpose of receiving supplementary resources may be an enticing proposition. Fortunately, genetic research could disentangle the controversy surrounding syndromal autism and pinpoint whether autism shares genetic markers with other disorders, or whether the behaviours associated with syndromal autism are not indicative of true autism, but instead a byproduct of the other disorder. It is a strong possibility that within the next decade or so that major genetic breakthroughs will occur; specifically with regards to identifying genetic causes for autism. Such findings could be a major benefit for school psychologists who could prepare for the emergence of symptoms and problem behaviours before they are observed.

Autism has been shown to co-occur with a wide range of disorders, and the following examples may exemplify the diversity of the genetic make-up of autism. That is, amongst others, autism can be comorbid with Cri du Chat syndrome, caused by a genetic deletion at 5p15.1-15.3, Smith-Magenis syndrome, caused by a genetic deletion at 17p11.2, as well as Phelan-McDermid syndrome, caused by a deletion at 22q13.3. Therefore, it is clear that more than one abnormality on more than one chromosome is likely responsible for the emergence of autism. In fact, along with chromosomes 5, 17 and 22, mutations on chromosomes 2, 3, 6, 15 and X have been linked to increased risk of autism (Glaser & Ouimet, 2010). In sum, autism has a strong genetic basis, yet much remains to be done with regard to clarification of its etiology. Within the next decade, it is likely that many advances will take place technologically that will allow for the elucidation of the genetic causes of autism.

Unfortunately, autism remains a behavioural diagnosis whereby it is only confirmed when the behavioural symptoms emerge in the child. This behavioural phenotype typically emerges around 3 years of age, however due to professional shortages and high prevalence rates, families of children with autism often wait years before an official diagnosis of an ASD is made. Special services in schools are only made available to children with an official diagnosis; therefore many children with autism only begin treatment years after the first signs of the disorder emerge. As autism in youth has been found to be associated with impairment in multiple domains of functioning, one can imagine the detrimental effects of prolonged delays in diagnoses and intervention implementation. It is often stressed that intervention strategies need to be put in place as early on as possible in the child's life, therefore through the identification of genetic markers of autism these intervention strategies can be put forth immediately.

In conclusion, the current study highlights a significant relationship between fatigue and autistic symptoms in children with CDCS and non-specific, moderate to severe learning disabilities. This study has provided several directions for future research and although there is currently no study examining the effectiveness of intervention and treatment programs for sleep problems in children with CDCS, developing a more thorough understanding of the potential detrimental effects of fatigue may result in the development and evaluation of treatment strategies by researchers and clinicians.

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**Appendix A**

# CONSENT FORM

## Cognitive, behavioural & nutritional characteristics of children & adolescents with Cri-du-Chat Syndrome and the impact on the family

**(Please circle)**

1. Have you read the information booklet? YES / NO
2. Have you had the opportunity to discuss the study and ask questions? YES / NO
3. Have you had satisfactory answers to all your questions? YES / NO
4. Have you received enough information about the study? YES / NO
5. Do you understand that your child is free to withdraw from the study:
   - at any time
   - without having to give a reason
   - without affecting your child's future medical care YES / NO
6. Do you agree for your child to participate in the study? YES / NO

PARENT

Signed.....

Date.....

Name (BLOCKCAPITALS).....

RESEARCHER

Signed.....

Date.....

Name (BLOCK CAPITALS).....

The attention of volunteers is drawn to the fact that in the case of injury to persons or damage to property no claim for damages can succeed against the University of Nottingham or against its employees unless legal liability resulting from negligence can be proved.

## Appendix B

## Sleep Questionnaire

*Here are a number of questions about your child / person you care for's sleeping habits. Please base your answers on what you have noticed over the last* ***MONTH****.*

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**Part 1**

**Going to bed/to sleep**

1. How long does it usually take for your child / the person you care for to settle off to sleep on average? (Tick one box only)

   ☐ Less than 10 minutes

   ☐ 10-20 minutes

   ☐ 20-30 minutes

   ☐ 30-40 minutes

   ☐ 40-50 minutes

   ☐ 50-60 minutes

   ☐ 1 hour or longer

2. How many times a week does your child / the person you care for have problems settling on average? (Tick one box only)

   ☐ Problems less than once a week

   ☐ Problems 1 night a week

- ☐ Problems 2 nights a week
- ☐ Problems 3 nights a week
- ☐ Problems 4 nights a week
- ☐ Problems 5 nights a week
- ☐ Problems 6 nights a week
- ☐ Problems every night of the week

3. How long has the settling problem been going on? _____months ☐ Not applicable

**Waking at night (between midnight and 6am)**

4. How many nights a week does your child / the person you care for wake on average? (Tick one box only)

- ☐ None or less than once a week
- ☐ 1 night a week
- ☐ 2 nights a week
- ☐ 3 nights a week
- ☐ 4 nights a week
- ☐ 5 nights a week
- ☐ 6 nights a week
- ☐ Every night of the week

5. How many times does your child / the person you care for wake each night and need resettling on average? (Tick one box only)

   ☐ Does not wake

   ☐ Once a night

   ☐ Twice a night

   ☐ 3 times a night

   ☐ 4 times a night

   ☐ 5 or more times a night

6. If your child / the person you care for wakes, how long does it take for them to go back to sleep on average? (Tick one box only)

   ☐ Less than 10 minutes

   ☐ 10-20 minutes

   ☐ 20-30 minutes

   ☐ 30-40 minutes

   ☐ 40-50 minutes

   ☐ 50-60 minutes

   ☐ 1 hour or longer

7. How long has the waking problem been going on? _____months

   Not applicable ☐

**Sleeping in Parent's / Carer's bed**

8. How often do you end up taking your child / person you care for into your bed because he/she is upset and won't sleep? (Tick one box only)

- ☐ Never, or less than once a week
- ☐ 1 night a week
- ☐ 2 nights a week
- ☐ 3 nights a week
- ☐ 4 nights a week
- ☐ 5 nights a week
- ☐ 6 nights a week
- ☐ Every night of the week
- ☐ Not applicable

9. How long has the problem been going on? _____months

Not applicable ☐

**PART 2**

**Your views**

10. Do you think that your child / the person you care for has sleeping difficulties?

- ☐ No
- ☐ Yes, mild

☐ Yes, moderate

☐ Yes, severe

11. Does your child have any of the following?

☐ Bedwetting

☐ Epilepsy

☐ Nightmares (wakes upset)

☐ Sleep walking

☐ Talks in sleep

☐ Rocking or head banging in sleep

(continued over)

☐ Snoring

☐ Gags or chokes in sleep

☐ Obstructive sleep apnoea (appears to stop breathing for a few seconds then takes a big breath)

12. Does your child have any problems with sleepiness during the day?

☐ No

☐ Yes, sometimes

☐ Yes, always

13. Does your child ever fall asleep during the day?

☐ No

☐ Yes, naps during the day sometimes

☐ Yes, naps during the day mostly

For how long generally? _____

14. Please mark on the line below how severe you think your child's sleeping problems are?

0 _____ 10

No problem Very severe problem

15. Does your child have any problem with over-activity?

☐ No

☐ Yes, occasionally

☐ Yes, mostly

☐ Yes, always very active