

A Longitudinal Follow-Up Study of Affect in Children and Adults With Cornelia de Lange Syndrome

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Abstract

Studies of individuals with Cornelia de Lange syndrome (CdLS) have described changes in mood and behavior with age, although no empirical or longitudinal studies have been conducted. Caregivers of individuals with CdLS ($N = 67$), cri du chat syndrome (CdCS; $N = 42$), and Fragile X syndrome (FXS; $N = 142$) completed the Mood, Interest and Pleasure Questionnaire (MIPQ) at Time 1 and 2 years later (Time 2). Scores on the MIPQ were significantly lower in the CdLS group compared with the CdCS and FXS groups at Time 1 and Time 2. Lower MIPQ scores were characteristic of older adolescents (> 15 years) and adults with CdLS. However, there were no significant differences in MIPQ scores between Time 1 and Time 2. Age and insistence on sameness predicted MIPQ scores in CdLS.

Key Words: *Cornelia de Lange syndrome; behavioral phenotypes; affect; longitudinal; follow-up*

Introduction

The behavioral phenotypes literature has expanded significantly in the past two decades and has progressed from single-syndrome group description toward more fine-grained, comparative approaches and evaluation of developmental trajectories of behavior and cognitive processes. The most well-researched profile of development and change within a behavioral phenotype is that of people with Down syndrome. Studies range from descriptions of early infant–mother interactions to the onset and progression of Alzheimer’s disease in adulthood (e.g., Holland, Hon, Huppert, Stevens, & Watson, 1998). More recently, researchers have considered the developmental trajectory of behavior and cognition in a range of genetic syndromes. For example, people with Williams syndrome have been reported to show a decrease in anxiety and compulsions with age, whereas rates of depression and overactivity are thought to increase over time (Elison, Stinton, & Howlin, 2010; Howlin, Elison, Udwin & Stinton, 2010; Stinton, Elison, & Howlin, 2010). In Fragile X syndrome (FXS), the rates of autism spectrum disorder (ASD) and social avoidance behaviors

have been reported to increase with age in males with full-mutation FXS (Hatton et al., 2006; Roberts, Weisenfeld, Hatton, Heath, & Kaufmann, 2007). Deterioration in IQ and adaptive functioning from adolescence has also been reported in this group (e.g. Fisch, Simensen, & Schroer, 2002). The study of developmental trajectories in individuals with neurodevelopmental disorders can enhance understanding of typical and atypical development processes (Cornish, Scerif, & Karmiloff-Smith, 2007; Thomas et al., 2009) and are also important for identifying syndrome-specific, age-related changes. In turn, this enables identification of risk for psychological disorder and may contribute to prevention and intervention strategies.

Cornelia de Lange syndrome (CdLS) is one syndrome in which age-related changes in behavior and mood have been described (Basile, Villa, Selicorni, & Molteni, 2007; Collis, Oliver, & Moss 2006; Kline, Grados, et al., 2007; Kline, Krantz, et al., 2007). CdLS is caused by a deletion in the *NIPBL* gene on chromosome 5 for nearly 60% of individuals, and by mutations on chromosome 10 (*SMC3* gene) and X-linked *SMC1A* and *HDAC8* genes in a smaller proportion of affected individuals (Deardorff et al., 2007; Deardorff et al., 2012;

Gillis et al., 2004; Musio et al., 2006; Tonkin, Wang, Lisgo, Bamshad, & Strachan, 2004). All four genes are involved in the structure and regulation of the cohesin complex, which is crucial for neural maintenance and repair (Dear-dorff et al., 2012; Liu & Krantz, 2008). Recent studies have also indicated down-regulation of proteins involved in the response to oxidative stress and an increase in global oxidative stress in CdLS cell lines (Gimigliano et al., 2012), which may be important for understanding potential age-related changes in the syndrome.

CdLS is characterized by developmental delay, delayed growth, distinctive facial features, and limb abnormalities (Jackson, Kline, Barr, & Koch, 1993). Seizures are reported to occur in approximately 25% of individuals (see Hall et al., 2008); however, research into this aspect of the syndrome is extremely limited. A number of behavioral characteristics are also considered to be associated with CdLS, including self-injurious and compulsive behaviors, aggression, hyperactivity, and ASD-like characteristics (Oliver, Arron, Slo-need, & Hall, 2008; Hyman, Oliver, & Hall, 2002). ASD-like characteristics are particularly prominent within the syndrome. Prevalence estimates range from 43% to 67%, using a range of direct and in-direct assessments (Basile et al., 2007; Berney, Ireland, & Burn, 1999; Bhuyian et al., 2006, Moss et al., 2008; Oliver, Arron, Slo-need, & Hall, 2008). Oliver et al. (2011) identified comparable levels of symptom severity between people with CdLS and those with FXS.

Emerging evidence has suggested that adolescents and adults with CdLS demonstrate an increase in behavioral difficulties and decreases in mood, interest, and pleasure alongside physical signs of premature aging. In the largest study of adolescents and adults with CdLS conducted to date, Kline, Grados, et al. (2007) reported that many people with CdLS evidenced premature graying and changes to the skin and face, giving rise to a more aged appearance compared with their chronological age. Behavioral symptoms including increasing levels of self-injurious behavior, anxiety, hyperactivity, and repetitive behaviors were also reported, and depression was diagnosed in 11% of the sample. Basile et al. (2007) also reported an increase in challenging behaviors and repetitive behaviors with age in a sample of 57 people with CdLS age 1 to 31 years. Sarimski (1997) reported that older children experienced significantly more social isolation,

anxiety, low mood, and frequent changes in mood and became significantly more upset by changes in their routine than younger children. An association between low mood and age was also reported by Berney et al. (1999), who described a cyclical mood disturbance in 27% of 49 individuals with CdLS, with 77% of those affected by this disturbance being age 12 years and over. Finally, Oliver, Berg, Moss, Arron, and Burbidge (2011) reported that adults (over the age of 18) with CdLS were significantly more likely to experience high levels of negative affect and impulsivity compared with younger people with CdLS. This profile of behavior was not reported in any of the other six syndrome groups assessed in this study or in individuals with intellectual disability of heterogeneous cause.

At the biological level, the compromised function of the cohesin pathway (resultant from the genetic mutations that cause CdLS) has been implicated in these behavioral and cognitive changes in CdLS, as a result of the role of this pathway in neural maintenance and repair (Kline, Krantz, et al., 2007). Recent evidence has also indicated down-regulation of proteins involved in the response to oxidative stress and an increase in global oxidative stress in CdLS cell lines, which may be directly linked to the phenotypic changes in the syndrome (Gimigliano et al., 2012).

A small number of studies that have alluded to behavioral factors that may contribute to the low mood reported in CdLS have demonstrated that people with CdLS have a strong preference for predictability and routine. Unexpected changes to routines are thought to lead to episodes of low mood and a loss of interest in activities previously enjoyed (Collis et al., 2006; Jackson et al., 1993; Sarimski, 1997; Van Allen et al., 1993). According to Sarimski (1997), this is significantly more prominent in older children with CdLS. The presence of associated health problems in CdLS may also contribute to levels of mood, interest, and pleasure. Berg, Arron, Burbidge, Moss, and Oliver (2007) reported that people with CdLS with a health problem are approximately three times more likely to experience low mood than those with no health problems.

In the wider literature, an association between low mood and ASD has been demonstrated (Kim, Szatmari, Bryson, Streiner, & Wilson, 2000). The rates of depression in individuals with ASD are reported to increase with age (Ghaziuddin & Greden, 1998; Ghaziuddin, Ghaziudin & Greden,

2002). Given the heightened prevalence of ASD symptomatology in CdLS (Basile et al., 2007; Berney et al., 1999; Bhuiyan et al., 2006; Moss et al., 2008; Moss, Howlin, Magiati, & Oliver, 2012; Oliver et al., 2008; Oliver et al. 2011), the severity of ASD symptomatology may also be an important predictor of low mood in CdLS.

Much of the research conducted to date regarding outcomes in adults with CdLS has involved single-group descriptions of the nature and trajectory of these age-related changes (e.g., Basile et al. 2007; Kline, Grados, et al., 2007; Sarimski, 1997). Few studies have used appropriate contrast groups to identify the specificity of these characteristics—in particular, the degree to which the developmental trajectory is atypical in comparison to other individuals with similar levels of intellectual ability—and none of these studies have examined the factors that might predict low mood, interest, and pleasure in CdLS. Furthermore, no previous studies have used a longitudinal approach, thus limiting the ability to assess the extent to which these changes represent a cohort effect.

Dykens and Hodapp (2001) have stressed the importance of utilizing appropriate contrast groups in behavioral phenotype research. Of utmost importance is the inclusion of a contrast group that is comparable on degree of intellectual disability, age, and gender, to ensure that any findings are not just artifacts of these characteristics. In the current study, two contrast groups were used. People with Cri du Chat syndrome (CdCS) have previously been shown to be comparable to people with CdLS on degree of intellectual disability, age, and gender and have been used as a useful contrast group (Moss et al., 2008; Sarimski, 2002). In addition, given the reports of an association between ASD impairments and low mood (Ghaziuddin & Greden 1998; Ghaziuddin et al., 2002) and the high prevalence of ASD characteristics in CdLS, a second contrast group, people with Fragile X syndrome (FXS), in which a strong association with ASD is well established (for a review, see Moss & Howlin, 2009), was also included in the current study.

CdCS is caused by a partial deletion on the short arm of chromosome 5 and has an estimated prevalence of 1 in 50,000 live births (Neibuhr, 1978). CdCS is associated with severe to profound intellectual disability and a prominent expressive and receptive language discrepancy (Cornish,

Bramble, Munir, & Pigram, 1999; Cornish & Munir, 1998). This profile is similar to that seen in CdLS. However, the groups differ on their association with ASD. People with CdCS show significantly less ASD-related impairments than those with CdLS (Moss et al., 2008).

FXS is the most commonly inherited form of intellectual disability, affecting approximately 1 in 4,000 males and 1 in 6,000 females (Turner, Webb, Wake, & Robinson, 1996). FXS is caused by a mutation on the *FMR1* gene on the long arm of the X chromosome, which causes an abnormal expansion of CGG nucleotide repeats (Kaufmann & Reiss, 1999; Verkerk et al., 1991). Males with FXS typically show more severe cognitive impairments than females and have a mild to moderate intellectual disability (Hatton et al., 2002). An increased prevalence of ASD symptomatology is a prominent feature of the syndrome and is more evident in males with the syndrome (Clifford et al., 2006). Recent prevalence estimates for ASD range from 21% to 50% (for reviews, see Moss & Howlin, 2009, and Moss, Howling, & Oliver, 2011).

In summary, previous findings provide strong evidence that low mood, interest, and pleasure are characteristic of people with CdLS. These difficulties appear to become more pronounced with age and may be related to a preference for routine and predictability, ASD symptomatology, and health problems and may be linked to the specific genotype underlying the syndrome. The current study further evaluates the presence and developmental trajectory of low mood, interest, and pleasure in individuals with CdLS and the factors that predict the reported change with age relative to two contrast groups: FXS and CdCS, which were used because they are comparable with the CdLS group on either intellectual ability or ASD symptom severity, both of which are important confounds to consider.

The current study is a 2-year follow-up of individuals with CdLS, FXS, and CdCS who participated in an extensive survey study (Arron, Oliver, Berg, Moss, & Burbridge, 2011; Moss, Oliver, Arron, Burbridge, & Berg, 2009; Oliver, Berg, Moss, Arron, & Burbridge, 2011). The primary aim of the study was to evaluate changes in mood, interest, and pleasure in individuals with CdLS compared with the FXS and CdCS contrast groups. A secondary aim was to examine the factors that are predictive of these changes in CdLS, including age, insistence on sameness, ASD symptomatology, and health problems. On

the basis of the literature to date, it was predicted that

1. People with CdLS will show significantly lower levels of mood, interest, and pleasure than people with CdCS and FXS at baseline (Time 1) and at follow-up (Time 2).
2. Lower mood will be evidenced more by older individuals with CdLS than younger individuals with CdLS at Time 1 and at Time 2.
3. Analysis of mood, and interest and pleasure scores for participants with CdLS will show that individuals in early adulthood will experience the lowest levels of mood and interest and pleasure.
4. Individuals with CdLS will show a decline in mood and interest and pleasure over a two-year follow-up period.

Method

Participants

People with CdLS, FXS, and CdCS who participated in an extensive questionnaire survey between 2003 and 2004 were invited to participate in the current follow-up study (Time 2), which took place between 2006 and 2007. Ethical approval for the study was obtained from the School of Psychology Ethical Review Board at the University of Birmingham.

At Time 1, 142 parents and/or caregivers of people with CdLS, who had been involved in previous research, were contacted directly and invited to take part in the questionnaire study. The remaining members of the CdLS Foundation (United Kingdom and Ireland) who had not taken part in previous research ($n = 234$), people with CdCS ($n = 180$), and people with FXS¹ ($n = 762$) were invited to take part via the relevant syndrome support groups. At Time 1, 116 people with CdLS, 65 people with CdCS, and 193 people with FXS took part in the study (for further information regarding recruitment at Time 1, Arron et al. 2011; Burbidge et al., 2010; Moss et al., 2009 and Oliver et al., 2011).

At Time 2, participants were invited to take part if they had given consent to be contacted with information about future research. In total, 385 participants (114 with CdLS, 63 with CdCS, and 208 with FXS) were invited to participate at Time 2. Nine participants could not be contacted (three with CdLS, four with CdCS, and two with FXS) as a result of changes of address. Two hundred seventy-four caregivers completed and

returned the questionnaires at Time 2. The return rate for the current study was at least 70% for each group. Participants were included in the current study if they met the following criteria: confirmed diagnosis of the relevant syndrome from an appropriate professional (a pediatrician, a clinical geneticist, general practitioner); no additional chromosomal abnormalities (other than those causing the syndrome); completion of at least 75% of the total questionnaire pack at both Time 1 and Time 2; completion of the Mood, Interest and Pleasure Questionnaire–Short Version (MIPQ-S; Ross, Arron & Oliver, 2008; Ross & Oliver, 2003) at Time 1 and Time 2; and age 4 years or more at Time 1.²

A total of 251 participants (67 with CdLS, 42 with CdCS, and 142 with FXS) met the inclusion criteria for the current study. Table 1 describes the participant characteristics. At Time 1, all participants were between 4 and 47 years of age, and 73.3% were male. There were no significant differences on demographic characteristics between participants taking part at Time 1 and Time 2.

As expected, there were no significant differences between the CdLS group and the CdCS contrast group on chronological age, level of ability, or gender. There were also no significant differences between the CdLS and the FXS contrast group on chronological age and severity of ASD characteristics. These findings support the use of these two contrast groups in the current study and provide some degree of control over the confounds of degree of disability and the presence of ASD throughout the following analyses. The CdLS group evidenced more vision and hearing impairments than both the CdCS and FXS groups, and the FXS group was significantly more able, more mobile, and more likely to be verbal than the CdLS and CdCS groups.

Measures

Given the rarity of the syndromes recruited for this study, a survey approach was conducted in order to maximize the sample sizes and obtain the most representative sample possible. A demographic questionnaire was used to obtain background information about participants including

¹Due to variability between males and females with FXS, and the fact that males with FXS show a more severe degree of disability and a stronger association with ASD, only males with FXS were included in current study.

²Participants were required to be at least four years old at Time 1 because the Autism Screening Questionnaire (ASQ; Berument, Rutter, Lord, Pickles & Bailey, 1999) was administered and this questionnaire contains items regarding the participant's behaviour when aged between four and five years.

Table 1
Demographic Characteristics of Participants in Each Syndrome Group at Time 1 and Time 2

Characteristic	CdLS (n = 67) ^a	CdCS (n = 42)	FXS (n = 142)	F/ χ^2	df	p	Post hoc analyses
% Male	41.8	33.3	100 ^b	120.01	2	< .001	FXS > CdLS, CdCS
Time 1							
Age (years)	.033						
M (SD)	17.33 (9.22)	17.65 (11.75)	17.23 (8.84)	ns			
Range	4-40	4-44	6-47				
Self-help skills (% partly able/able) ^c	50.7	64.3	90.8	43.36	2	< .001	FXS > CdLS, CdCS
Mobility (% fully mobile) ^c	67.2	70.7	95.1	31.46	2	< .001	FXS > CdLS, CdCS
Vision (% normal) ^b	67.2	90.5	90	19.13	2	< .001	FXS, CdCS > CdLS
Hearing (% normal) ^c	62.1	81.0	97.1	43.70	2	< .001	FXS > CdLS, CdCS
Speech (% partly verbal/verbal) ^c	59.1	80.50	97.8	52.07	2	< .001	FXS > CdLS, CdCS
ASQ score							
M (SD)	20.13 (6.35)	13.90 (5.53)	21.30 (6.42)	20.21	2	< .001	FXS, CdLS > CdCS
Time 2							
Age (years)	.06						
M (SD)	20.08 (9.25)	19.89 (11.79)	19.63 (8.60)	ns			
Range	6-43	6-47	9-49				
Self-help skills (% partly able/able) ^c	50.7	61	95	58.36	2	< .001	FXS > CdLS, CdCS
Mobility (% fully mobile) ^c	71.2	65.9	97.1	36.68	2	< .001	FXS > CdLS, CdCS
Vision (% normal) ^c	65.7	90.2	93.5	29.09	2	< .001	FXS, CdCS > CdLS
Hearing (% normal) ^c	64.2	87.8	96.4	39.93	2	< .001	FXS, CdCS > CdLS
Speech (% partly verbal/verbal) ^c	59.1	82.9	95.6	43.38	2	< .001	FXS > CdLS, CdCS
ASQ score							
M (SD)	20.54 (6.51)	14.4 (5.01)	20.79 (6.17)	16.89	2	< .001	FXS, CdLS > CdCS

Note. ASQ = Autism Screening Questionnaire; CdLS = Cornelia de Lange syndrome; CdCS, Cri du Chat syndrome; FXS = Fragile X syndrome.

^an may vary across the groups for the analysis of demographic variables as a result of missing data.

^bFemales with FXS were excluded from the study because the syndrome characteristics vary between males and females in the syndrome (Dykens et al., 2000).

^cInformation obtained from the Wessex Scale (Kushlick et al., 1973).

age, gender, and diagnostic status (whether a diagnosis had been made and by whom the diagnosis was made).

Wessex Scale (Kushlick, Blunden, & Cox, 1973). This informant-based questionnaire is designed to examine social and physical abilities of children and adults with intellectual disability. Subscales include Continence, Mobility (walks unaided or with help), Self-Help Skills (washing, dressing and feeding), and Speech and Literacy (reading, writing, counting). Additional questions regarding vision and hearing are also included in the questionnaire. Informants complete ratings based on a 3-point scale for each question (apart from a question regarding speech comprehensibility). The Wessex scale has good inter-rater reliability at subscale level for both children and adults with intellectual disability (Kushlick et al., 1973; Palmer & Jenkins, 1982).

MIPQ-S (Ross, Arron & Oliver, 2008; Ross & Oliver, 2003). This informant-based questionnaire is used to assess two constructs related to depression: mood and, interest and pleasure. It is designed for use with a range of intellectual disability. Informants rate 12 items describing operationally defined observable behaviors to give a total score, a Mood subscale score and an Interest and Pleasure subscale score. The MIPQ is reported to have good internal consistency, test-retest reliability, and inter-rater reliability (Ross & Oliver, 2003). Each item is rated using a 5-point Likert scale to give a total score of between 0 and 48, where 48 is the maximum score indicating positive affect and elevated interest and pleasure. The two subscale scores range between 0 and 24.

Health Questionnaire (Hall et al., 2008). This informant-based questionnaire measures the presence and severity of 15 health problems. Informants are required to rate the presence and severity (0 = *never occurred* to 3 = *severe problem*) of problems occurring ever in the person's life and over the last month. Scores are summed to produce an Overall Health Score indicating severity of health problems for the previous month and during the person's life. A higher score is indicative of a greater severity of health problems. The total number of health problems during the person's life and the previous month can also be calculated. Inter-rater reliability for health problems ever occurring and for the occurrence of health problems over the last month is good.

The Repetitive Behavior Questionnaire (Moss, Oliver, Arron, Burbidge & Berg, 2009).

This is an informant measure of repetitive behavior for use in children and adults with a range of intellectual disability. The questionnaire consists of 19 items that comprise five subscales: Stereotyped Behavior, Compulsive Behavior, Restricted Preferences, Insistence on Sameness, and Repetitive Use of Language. Informants rate the frequency of each behavior over the preceding month on a 5-point Likert scale ranging from *never* to *more than once a day*. Inter-rater reliability, test-retest reliability, concurrent validity, content validity, and internal consistency are robust (Moss et al., 2009). In this study, only the Insistence on Sameness subscale was used to evaluate whether this variable significantly predicts mood outcome in CdLS. This subscale was selected because adherence to routine and predictability have previously been indicated within the literature to be associated with low mood in CdLS (Collis et al., 2006; Jackson et al., 1993; Sarimski, 1997; Van Allen et al., 1993).

Autism Screening Questionnaire (ASQ; Berument, Rutter, Lord, Pickles, & Bailey, 1999).

This instrument, also known as the Social Communication Questionnaire (Rutter, Bailey, Berument, Lord & Pickles, 2003)³ was developed as a tool for screening for ASD in children and adults and is based on the Autism Diagnostic Interview (Lord, Rutter & Lecouteur, 1994). The measure consists of 40 items which are grouped into three subscales: Communication, Social Interaction, and Repetitive and Stereotyped Patterns of Behaviors. Items are scored for the presence of abnormal behaviors to yield a total score of between 0 and 39 (one item evaluates the current language level of the individual and is not included in the total score), with higher scores indicating the presence of a higher number of abnormal behaviors. The authors identify a cut-off score of 15 as indicative of ASD and a higher cut-off of 22 to differentiate between individuals with autism and those with other pervasive developmental disorders. The ASQ shows moderate concurrent validity with the Autism Diagnostic Interview and with the Autism Diagnostic Observation Schedule (Howlin & Karpf, 2004). Internal consistency is also good ($\alpha = .90$ for the

³The Social Communication Questionnaire was not available when the study began. For consistency, the Autism Screening Questionnaire was utilised at both Time 1 and Time 2 in the current study.

total scale; 26) but inter-rater reliability data are not yet available.

Procedure

At Time 1, each caregiver received a letter of invitation for the study, an information sheet, and a questionnaire pack. Caregivers who gave their permission to be contacted for future research were also invited to participate at Time 2. Reminder letters with new questionnaire packs were sent 4–6 weeks later to those who had not returned their pack.

Data Analysis

The distribution of data was examined via visual inspection of Q-Q plots and by means of the Kolmogorov–Smirnov test. The data were not normally distributed at subscale level or at total score level ($p < .05$). Consequently, nonparametric tests were used throughout the analysis.

The analysis was conducted in three stages. Stage 1 examined group differences on MIPQ-S scores and the effect of age on MIPQ-S scores between and within the syndrome groups. This involved both cross-sectional and longitudinal analyses (Time 1 to Time 2 differences). Kruskal–Wallis tests, with pairwise Mann–Whitney post hoc tests, were used for between-group analyses. Wilcoxon signed-rank tests were used for within-group analyses. A conservative alpha level ($p < .01$) was applied throughout.

Stage 2 was an exploratory analysis that evaluated in more detail, the differences in MIPQ-S scores with age in the CdLS group using pairwise Mann–Whitney tests to evaluate differences across six specified age bands. Because there is no prior research that indicates which age bands are the most vulnerable change periods in CdLS, age bands were chosen that allowed for the most equal distribution of participants across these smaller groups. A more liberal alpha level ($p < .05$) was used as this was an exploratory analysis.

Stage three examined the factors that predicted mood, and interest and pleasure in CdLS. Predictor variables were selected if there was evidence in the literature for an association with mood in CdLS specifically, or if there was evidence for an association with mood in the wider intellectual disability literature. Chronological age, severity of ASD characteristics, insistence on sameness, and severity of health problems were selected as predictor variables. Negative affect and

positive affect were outcome variables. Participants with CdLS who had the lowest third of MIPQ-S total scores were considered to have negative affect, and those who had the top third of MIPQ-S total scores were considered to have positive affect. Mann–Whitney tests were conducted to identify any significant differences between the negative affect and positive affect groups on the four predictor variables. A binary logistic regression, using the *Enter* method, was conducted to examine whether any of the four variables significantly predicted mood, and interest and pleasure in the CdLS group. Data from Time 2 were used for these analyses because information regarding health was available only at this time point.

All analyses on the MIPQ-S were conducted at subscale level (Mood, and Interest and Pleasure). Effect sizes were calculated for any significant differences identified at the post hoc level. Pearson’s correlation coefficient, r , was calculated as an estimation of effect size (see Field, 2005). The relative size of an effect was measured using the following criteria: $r = .1$, small effect size; $r = .3$, medium effect size; and $r = .5$, large effect size (Cohen, 1992).

Results

Group Differences in Mood, and Interest and Pleasure

Table 2 shows the median MIPQ-S subscale scores for each syndrome group at Time 1 and Time 2. Kruskal–Wallis tests revealed an effect of group at both Time 1 and Time 2, with the CdLS group scoring significantly lower than the CdCS and FXS groups on the Mood subscale at Time 1 and Time 2 and the Interest and Pleasure subscale score at Time 1 only. Both the CdLS and the FXS groups scored significantly lower than the CdCS group on the Interest and Pleasure subscale at Time 2. Medium effect sizes were evident in these comparisons. The difference between the CdLS and FXS groups on this subscale at Time 2 approached significance ($p = .02$).

Interaction Between Syndrome Group and Age

For the following analyses, participants were categorized into two age groups (≤ 15 years and > 15 years) according to their age at Time 1. These age bands were chosen because they

Table 2
Median Scores, Interquartile Range, and Results of Statistical Analyses of Subscale Scores on the Mood, Interest and Pleasure Questionnaire-Short Version for Each Syndrome Group at Time 1 and Time 2

Time and subscale	Median (interquartile range)				χ^2	df	p	Post hoc	Post hoc effect size (r)
	CdLS (n = 67)	CdCS (n = 42)	FXS (n = 142)						
Time 1									
Mood	20.00 (17.00–21.00)	21.00 (19.00–22.52)	21.00 (20.00–23.00)		24.2	2	< .001	FXS, CdCS > CdLS	FXS, CdLS: -.34 CdCS, CdLS: -.25
Interest & Pleasure	15.00 (12.00–18.00)	18.50 (15.75–20.25)	17.00 (14.00–20.00)		12.68	2	.005	FXS, CdCS > CdLS	FXS, CdLS: -.18 CdCS, CdLS: -.32
Time 2									
Mood	20.00 (16.00–22.00)	22.00 (19.75–23.66)	22.00 (20.00–23.00)		26.3	2	< .001	FXS, CdCS > CdLS	FXS, CdLS: -.34 CdCS, CdLS: -.36
Interest and Pleasure	14.00 (12.00–19.00)	19.00 (16.75–21.25)	17.00 (14.00–19.25)		19.37	2	< .001	CdCS > CdLS, FXS	CdCS, CdLS: -.40 CdCS, FXS: -.23

Note. CdLS = Cornelia de Lange syndrome; CdCS, Cri du Chat syndrome; FXS = Fragile X syndrome.

allowed for the most equal distribution of participants in each group.

Figure 1 shows the MIPQ-S subscale scores for ≤ 15 - and > 15 -year-olds in CdLS, FXS, and CdCS at Time 1 and Time 2. Mann-Whitney U tests indicated a significant difference in the CdLS group, with those >15 years scoring significantly lower than those ≤ 15 years on the Interest and Pleasure subscale at Time 1 ($U = 241.5, p < .001, r = -.49$) and Time 2 ($U = 319.5, p = .005, r = -.37$). There were no significant age group differences for those with CdLS on the Mood subscale at Time 1 or Time 2 and no significant age group differences in the FXS or CdCS group on either subscale score at Time 1 or Time 2.

Between-groups comparisons using Kruskal-Wallis tests were conducted to evaluate similarities and differences in MIPQ-S scores across > 15 s with CdLS, CdCS, and FXS and, secondly, across ≤ 15 s with CdLS, CdCS, and FXS at Time 1 and Time 2 (Table 3).

Comparison of ≤ 15 s revealed a significant group difference on the Mood subscale at Time 1, with ≤ 15 s CdLS, with scoring lower on the Mood subscale than FXS ≤ 15 s. Comparison of >15 s showed that the > 15 s with CdLS scored significantly lower than both the > 15 s with CdCS and >15 s with FXS on both MIPQ-S subscales at Time 1 and Time 2, with medium-to-large or large effect sizes.

Change in Mood, and Interest and Pleasure Over Time

Wilcoxon signed-rank tests were conducted within each syndrome group in order to examine whether scores on the MIPQ-S changed between Time 1 and Time 2. Analysis was conducted at the total group level. As a result of differences identified between ≤ 15 s and >15 s with CdLS, this analysis was also conducted according to these age bands. The CdCS group showed a significant increase on the Mood subscale ($Z = -2.62, p < .01, r = -.29$) between Time 1 and Time 2. No significant change over time in MIPQ-S scores was identified for the

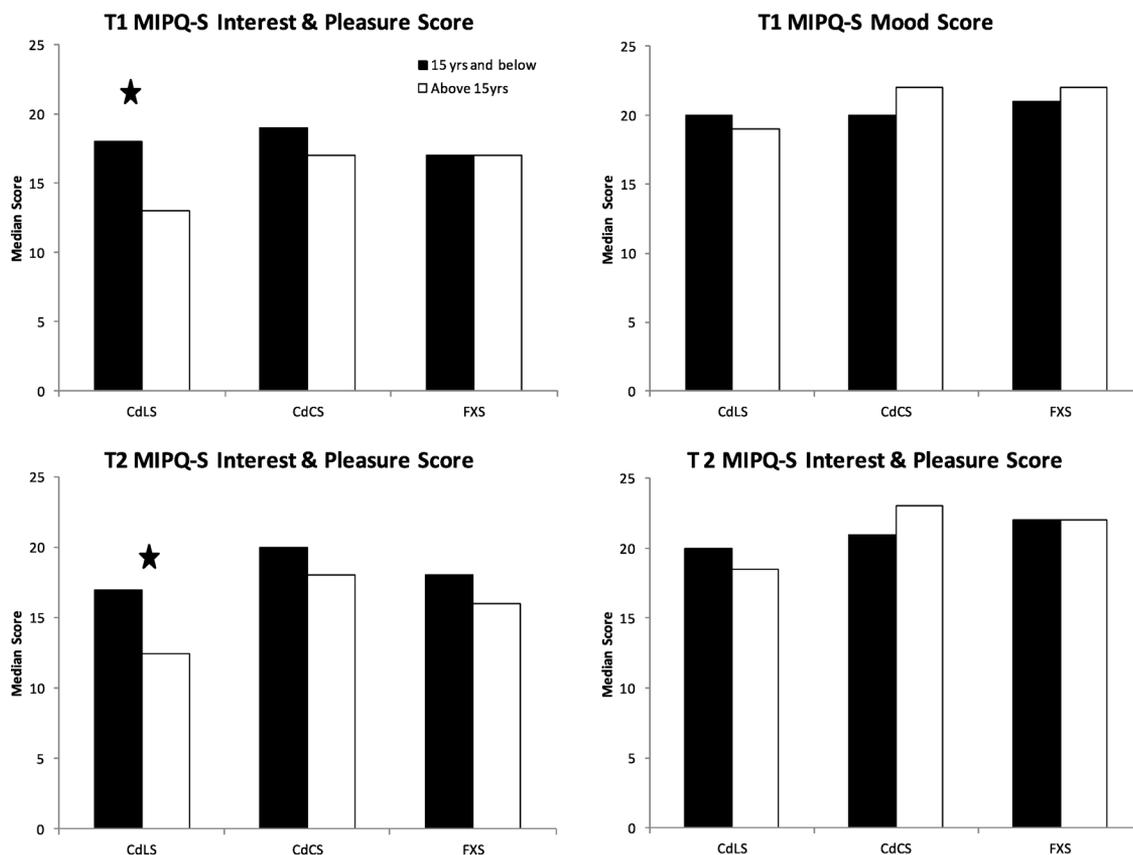


Figure 1. Median scores for ≤ 15 and >15 year olds in each syndrome group on MIPQ-S subscale scores at Time 1 and Time 2 ★ indicates significant age-group difference.

Table 3
Median Scores, Interquartile Range, Statistical Analyses, and Post Hoc Analyses on Subscale-Level Scores on the MIPQ-S for Participants 15 Years and Younger and Older Than 15 Years, in Each Syndrome Group

Time, group, and subscale	Median (interquartile range)			χ^2	df	p	Post hoc	Post hoc effect size (r)
	CdLS (n = 67)	CdCS (n = 42)	FXS (n = 142)					
Time 1								
≤ 15s								
Mood	20.00 (18.00–21.00)	20.00 (18.00–22.00)	21.00 (20.00–23.00)	9.62	2	< .01	FXS > CdLS	FXS, CdLS: -.25
Interest and Pleasure	18.00 (15.00–20.00)	19.00 (18.00–21.00)	17.00 (14.00–20.00)	5.23	2	.07	—	—
> 15s								
Mood	18.50 (15.00–21.00)	23.00 (20.00–24.00)	22.00 (20.00–23.00)	21.65	2	< .001	FXS, CdCS > CdLS	FXS, CdLS: -.42 CdCS, CdLS: -.51
Interest and Pleasure	12.50 (11.00–17.00)	18.00 (16.00–21.00)	16.00 (14.00–19.00)	17.99	2	< .001	FXS, CdCS > CdLS	FXS, CdLS: -.31 CdCS, CdLS: -.54
Time 2								
≤ 15s								
Mood	20.00 (17.00–22.00)	21.00 (19.00–23.00)	22.00 (20.00–23.00)	8.26	2	.02	—	—
Interest and Pleasure	17.00 (13.00–21.00)	20.00 (17.00–22.00)	18.00 (14.00–20.00)	5.43	2	.07	—	—
> 15s								
Mood	18.50 (15.00–21.00)	23.00 (20.00–24.00)	22.00 (20.00–23.00)	21.65	2	< .001	FXS, CdCS > CdLS	FXS, CdLS: -.42 CdCS, CdLS: -.51
Interest and Pleasure	12.50 (11.00–17.00)	18.00 (16.00–21.00)	16.00 (14.00–19.00)	17.99	2	< .001	FXS, CdCS > CdLS	FXS, CdLS: -.31 CdCS, CdLS: -.54

Note. CdLS = Cornelia de Lange syndrome; CdCS, Cri du Chat syndrome; FXS = Fragile X syndrome. ≤ 15s = participants 15 years and younger; > 15s participants older than 15 years.

FXS or CdLS groups as a whole or in either age group (≤ 15 s or > 15 s).

Identifying a More Specific Age Band During Which People With CdLS Are Most at Risk of Showing Low Levels Of Mood and Interest and Pleasure

This analysis focused solely on the CdLS group. Participants with CdLS were split into six age bands in accordance with their age at Time 2: 11 years and under ($n = 12$), 12–15 years ($n = 13$), 16–18 years ($n = 10$), 19–22 years ($n = 9$), 23–28 years ($n = 12$), and 29 years and above ($n = 11$). These age bands allowed for the most equal distribution of participants across groups.

Figure 2 shows the median MIPQ-S subscale scores across the six CdLS age groups. Pairwise comparisons using Mann–Whitney tests across the six age groups revealed that participants with CdLS aged 19–22 years scored significantly lower on the Interest and Pleasure subscale than participants age 11 years and under ($U = 12, p < .005, r = -.66$), 12–15 years ($U = 22, p = .01, r = -.52$), and 23–28 years ($U = 22, p < .05, r = -.50$). Participants age 29 years and above also obtained a significantly lower Interest and Pleasure score than individuals aged 11 years and under ($U = 19.5, p < .005, r = -.60$). Participants with CdLS age 19–22 years also obtained a significantly lower Mood score than those age 12–15 years ($U = 29, p < .05, r = -.42$). A difference in the same direction between participants age 19–22 years and those age 11 years and under approached significance ($U = 26.5, p = .05, r = -.43$). All differences reported for this analysis, including those that approached significance, demonstrated medium-to-large or

large effect sizes, reflecting the magnitude of these findings.

Predictors of Mood and Interest and Pleasure in CdLS

Mann–Whitney tests revealed that participants with CdLS with negative affect showed significantly more insistence on sameness ($U = 117, p < .005, r = -.46$) and a greater number of ASD characteristics ($U = 121.5, p < .05, r = -.34$), and were significantly older ($U = 124, p < .01, r = -.42$) than participants with CdLS with positive affect. Medium-to-large effect sizes were found for comparisons on both insistence on sameness and age, demonstrating the strength of these significant findings. A chi-square test showed no significant association between mood outcome and whether participants met the cut-off for autism on the SCQ (total score > 22). Fourteen of 22 participants with negative affect and 8 out of 22 participants with positive affect scored above the cut-off for autism (total SCQ score ≥ 22). There was no significant difference on the health severity score between those with negative and positive affect.

A binary logistic regression was conducted to examine whether chronological age, SCQ score, Insistence on Sameness score, and Health Severity score significantly predicted negative and positive affect in the CdLS group. The full model produced by the regression analysis was significant ($\chi^2 = 15.96, df = 4, p < .005$). This model accounted for between 32.9% and 43.9% of the variance in mood and interest and pleasure scores. Eighty percent of those with positive affect were successfully predicted, and 65% of those with low mood were successfully predicted. Overall, 72.5%

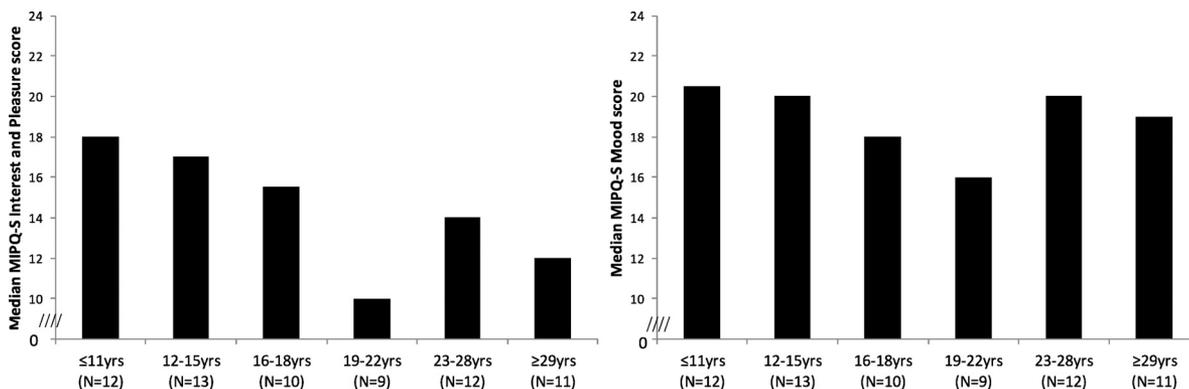


Figure 2. Median MIPQ-S subscale scores for six age bands in the CdLS group.

of predictions were accurate, an increase of 22.5% in accuracy from a model without these factors. Insistence on Sameness score was identified as the only significant predictor of mood and interest and pleasure ($p < .05$); each unit increase in the Insistence on Sameness score was associated with a decrease in the odds of positive affect by a factor of .726.

Discussion

This is the first case-control study to examine the trajectory of mood, and interest and pleasure in participants with CdLS and contrast groups using both cross-sectional and follow-up designs. The broad aims were to examine how mood and, interest and pleasure differed between three syndromes groups (CdLS, FXS, and CdCS) and consider how these scores changed over a 2-year period. Systematic comparisons were used to determine whether low mood and, interest and pleasure was specific to the CdLS group and whether this was associated with chronological age. Using a more fine-grained analysis, the time period during which participants with CdLS showed the lowest levels of mood, and interest and pleasure was examined. This provided a more detailed picture of the developmental trajectory of mood, and interest and pleasure in the syndrome. Finally, an examination of variables that predicted mood, and interest and pleasure in participants with CdLS was undertaken. This study has a number of strengths, including prospective design; the use of appropriate psychometric assessments; the inclusion of appropriate, comparable contrast groups; and a relatively low rate of attrition at follow up.

In line with our predictions, group comparisons of MIPQ-S scores revealed that the CdLS group scored significantly lower than the FXS and CdCS comparison groups on both Mood and Interest and Pleasure subscales at Time 1 and on the Mood subscale at Time 2, whereas interest and pleasure at Time 2 was significantly lower in both the CdLS and FXS groups relative to the CdCS group. Further analysis showed that these differences were accounted for by lower levels of mood and interest and pleasure in older participants (over the age of 15 years) with CdLS. Older participants with CdLS were reported to experience significantly lower mood and interest and pleasure scores than older participants with FXS and those with CdCS. This difference was found

at both Time 1 and Time 2, indicating that this difference was consistent over a 2-year period. The findings suggest that low mood and interest and pleasure are particularly characteristic of older people with CdLS, and this is consistent with previous research findings. Kline, Grados, et al. (2007) reported that 11% of adolescents and adults with CdLS had received a diagnosis of depression. Furthermore, Berney et al. (1999) found an association between low mood and age in CdLS. They reported the presence of a cyclical mood disturbance in 27% of participants with CdLS, with 77% of those participants being over 12 years old. The findings highlight the importance of evaluating behavioral phenotypes from a developmental perspective. It is clear that behavioral phenotypes are not static and that characteristics may change significantly with age. Given that the CdCS and CdLS groups were comparable on degree of intellectual disability and that the FXS and CdLS groups were comparable on severity of ASD characteristics, it is unlikely that these confounds account for the changes observed within the CdLS group.

Further evidence of age-related differences comes from the cross-sectional comparisons of mood and interest and pleasure scores between ≤ 15 s and > 15 s in each syndrome group. The analyses revealed a significant difference in the CdLS group only, suggesting a syndrome-specific, age-related change in interest and pleasures, with > 15 s experiencing significantly lower interest and pleasure than ≤ 15 s. No differences between these age groups were identified on the Mood subscale in CdLS or on either subscale in CdCS and FXS. The results suggest that mood, and interest and pleasure may have different developmental trajectories. Although the findings highlighted a change in interest and pleasure scores only, it is possible that individuals with CdLS show a decline in mood *before* they show a decline in interest and pleasure and the age bands of 15 years and older and younger than 15 years might not accurately capture the age of change in mood scores. Alternatively, mood may generally be lower in people with CdLS, which might account for the lack of between-age-group differences on the Mood subscale. This suggestion is supported by the fact that ≤ 15 s with CdLS were found to have significantly lower mood than ≤ 15 s with FXS.

A more fine-grained analysis of the data indicated that participants with CdLS experienced

both lower mood and, interest and pleasure with age, but the low levels of interest and pleasure were more pronounced. Participants with CdLS age 19–22 years specifically, were reported to experience the lowest levels of interest and pleasure compared with those in other age groups. This analysis was exploratory, and the sample sizes within each given age group were small; therefore, interpretation of these findings should be made cautiously. However, no previous research has sought to identify a specific time period during which these age-related differences might occur in CdLS. Most available evidence is consistent with the current findings and indicates that these differences become apparent in adolescence or adulthood (Basile et al., 2007; Berney et al., 1999; Kline, Grados, et al., 2007). Evidence from other work has also suggested that changes in mood occur around late adolescence or early adulthood, (Collis et al., 2006). Consistent with our predictions, the results from the current study demonstrate low levels of mood and interest and pleasure around early adulthood in people with CdLS.

These findings refer only to the cross-sectional comparisons, so caution must be exercised when interpreting these results, because of potential cohort effects. One characteristic of the CdLS group that might be particularly subject to cohort effects is the heightened number of health problems associated with the syndrome (Hall et al., 2008), in particular gastroesophageal reflux (Luzzani, Macchini, Valade, Milani, & Selicorni, 2003). Research has demonstrated a significant association between health problems and low affect. Specifically, people with a health problem have been found to be approximately three times more likely to experience low affect than those with no health problems (Berg et al., 2007). The extent and severity of health problems associated with CdLS have only begun to be recognized in recent years; therefore, older people with CdLS are more likely to have undiagnosed health problems, which may account for the higher levels of low mood in this age group. However, unlike previous studies, health severity scores in the current study were not found to significantly predict mood, and interest and pleasure in participants with CdLS. Consequently, it is unlikely that any findings from the cross-sectional analysis were accounted for by cohort effects related to health problems. Information regarding seizure disorder and use of medication was not available in this study but may also be

subject to cohort effects and should be considered in future studies of mood and affect in people with CdLS.

The longitudinal analysis of mood and interest and pleasure scores over the 2-year period revealed that the CdCS group showed a significant increase in mood between Time 1 and Time 2. This is an interesting finding as Oliver et al. (2011) also found that adults with CdCS were significantly more likely to show abnormally high levels of positive affect (28.6%) compared to children with CdCS (0%). It may be that this reported increase in mood with age is a protective factor for participants with CdCS, and so this finding should be explored further in future research.

The CdLS group as a whole did not show any significant changes in mood and interest and pleasure over the 2-year follow up and therefore did not provide support for our final prediction. Older (> 15 years) participants with CdLS continued to experience low mood, interest, and pleasure over the follow-up period, suggesting that this characteristic is likely to be relatively stable. Younger participants with CdLS showed no significant change in mood, and interest and pleasure scores over the 2-year period. This was surprising given that the cross-sectional data indicated that there might be a decline in mood with age. It is likely that the 2-year follow-up period was not long enough to detect a significant change in mood, and interest and pleasure within this age group in CdLS. A longer follow-up is needed to fully explore the trajectory of mood and interest and pleasure over time and examine whether the trajectory is the same as that predicted by the cross-sectional analysis.

An investigation of the factors that significantly differentiated participants with CdLS with positive and those with negative affect revealed that those with low mood showed significantly more frequent insistence on sameness behaviors and a greater number of ASD characteristics, and were significantly older than participants in the positive affect group. The binary logistic regression confirmed that insistence on sameness was a significant predictor of mood outcome.

The current findings suggest that insistence on sameness and chronological age are important factors contributing to mood outcome in CdLS. This is consistent with previous studies that have reported that changes in routine or unpredictable environments lead to episodes of low mood and a loss of interest in activities previously enjoyed

(Collis et al., 2006; Jackson et al., 1993; Sarimski, 1997; Van Allen et al., 1993). Similarly, Sarimski (1997) also demonstrated that 61.5% of participants with CdLS became “upset” by changes in routine, and this pattern of behavior was significantly more prominent in older children with the syndrome. Together, these findings demonstrate the importance of both chronological age and insistence on sameness when considering the causal mechanisms of low mood in the syndrome.

An important factor that should be taken into account when considering the findings regarding factors that contribute to mood outcome in CdLS is whether insistence on sameness significantly predicts interest and pleasure because these variables are measuring the same construct. This may indeed be the case and needs exploring in future research. Even if this is the case, the fact that insistence on sameness is a more clearly, defined, observable behavior is an important advancement in identifying the specific age-related changes observed in CdLS. Therefore, rather than a general decline in interest and pleasure with age in CdLS, it may be that there is a specific increase in insistence on sameness, which perhaps is underpinned by cognitive changes with age in the syndrome.

Several factors may limit the interpretation of the findings from the current study. The relatively short follow-up period may have limited the ability to draw conclusions about the developmental trajectory of mood, and interest and pleasure over time. Furthermore, the sampling bias and the attrition rate at follow-up may mean that the results are not generalizable to the wider population of people with these syndromes. However, the survey approach used in this study helped to maximize access to the syndrome populations and thus enabled us to evaluate relatively large sample sizes. Given the rarity of the syndromes, this is a significant strength of the study. Although reliance on this broad, informant-based approach does not provide the same level of in-depth information as direct assessments of behavior, it provides a strong basis from which more detailed, direct assessment can be conducted.

In this study, the confounds of degree of disability and ASD symptom severity were accounted for by comparison with two contrast groups; CdCS and FXS, which were comparable to the CdLS group on these variables (CdCS on intellectual disability and FXS on ASD symptom severity). This cross-syndrome approach is a

strength of the study; however, there were some variables that were not controlled for, including group differences in vision and hearing. It is not clear how these differences might affect the study findings, but these factors should be taken into consideration when interpreting the findings.

Detailed information regarding genetic subtypes was not available for analysis in this study. Although genetic mutations have been identified in approximately 60% of people with CdLS, the underlying causal pathways in CdLS are not yet fully understood. It will be important for further research to consider the impact of different genetic subtypes of CdLS on behavioral outcomes in mood and affect and how these change with age. Finally, the current study utilized group comparisons of median scores rather than evaluating rates of clinically significant levels of low mood. Future research may consider the rates of clinically significant low mood in greater detail.

Despite these limitations, the study presents important research findings. It is the first follow-up study of mood, and interest and pleasure in people with CdLS, which provides important information about the stability of low mood, and interest and pleasure in older people with CdLS over a 2-year period. The cross-sectional data from the study also provide valuable information about the potential developmental trajectory of mood, and interest and pleasure in people with CdLS. The study is the first to identify that the vulnerable time period for people with CdLS is between 19 and 22 years of age, when people experience the lower levels of mood, and interest and pleasure. A consideration of the factors contributing to mood, and interest and pleasure outcome in CdLS have identified that both insistence on sameness and age are important factors that may affect mood outcome. Ultimately, the current findings do allude to a change in mood, and interest and pleasure with age and give rise to the possibility that there are neurological changes occurring in the syndrome that underpin these emotional changes, especially given that the difference in mood, and interest and pleasure appears to be part of a broader difference in behavior and emotion with age (e.g., Oliver et al., 2011). Further research to examine how the genetic and downstream biological mechanisms underlying the syndrome might impact on these differences is crucial to understand why this may be occurring. Specifically, research should evaluate the way in which compromised function of

the cohesin pathway and increased levels of oxidative stress are linked to the phenotypic changes in the syndrome.

The current study has also demonstrated the importance of considering behavioral phenotypes from a developmental perspective and understanding how the trajectory of behavior may differ across syndromes and over time. Further understanding of these age-related changes across the life span in neurodevelopmental disorders will help to identify those who are at greater risk for psychological disorder and help to inform effective prevention and intervention strategies. This may be particularly relevant to people with CdLS and their families. Raising awareness of these changes with age will be important in ensuring that families are prepared for the future and are able to implement preventative strategies and deliver early intervention to mitigate the impact of these changes. The notion of age-related changes in CdLS also indicates that the introduction of regular assessments of behavior and cognition, from birth throughout the lifetime, may be useful in enabling early detection of such changes.

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