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Abstract

In this study we assessed the behavioral presentation of social anxiety in Cornelia de Lange syndrome (CdLS) using a contrast group of Cri du Chat syndrome (CdCS). Behaviors indicative of social anxiety were recorded in twelve children with CdLS (mean age = 11.00; SD = 5.15) and twelve children with CdCS (8.20; SD = 2.86) during social interaction. Lag sequential analysis revealed that participants with CdLS were significantly more likely to evidence behavior indicative of anxiety in close temporal proximity to the point at which they maintained eye contact or spoke. Individuals with CdLS demonstrate a heightened probability of anxiety related behavior during social interaction but only at the point at which social demand is high.

Introduction

Cornelia de Lange syndrome (CdLS) is a rare genetic syndrome with an estimated prevalence of 1:50,000 births (Beck, 1976; Beck & Fenger, 1985) and is caused by a deletions on chromosomes 5, 10 and X (Gillis *et al.,* 2004; Krantz *et al.,* 2004; Tonkin, Wang, Lisgo, Bamshad & Strachan, 2004; Musio *et al.,* 2006; Deardorff *et al.,* 2007). The physical phenotype includes growth retardation, upper limb abnormalities, hypertrichosis and facial dysmorphism (Jackson, Kline, Barr & Koch, 1993). CdLS is associated with intellectual disability ranging from mild to profound, health problems including vision and hearing impairments and gastro-oesophageal reflux (Berney, Ireland & Burn, 1999; Jackson *et al,* 1993; Collis et al., 2008; Hall, Arron, Sloneem and Oliver, 2008; Oliver, Arron, Hall & Sloneem, 2008). Behavioral problems associated with CdLS include impulsivity, repetitive and self injurious behaviors (Berney *et al.*, 1999; Hyman, Oliver and Hall, 2002, Moss *et al,* In press).

Recent research indicates a heightened prevalence of autism spectrum disorder (ASD), in CdLS with estimates ranging from 55 to 66% (Basile, Villa, Selicorni & Molteni, 2007; Bhyuian *et al.,* 2006; Moss *et al.*, 2008; Oliver, et al., 2008; Moss *et al,* In press). Fine-grained investigation has indicated that the presentation of the triad of impairments in CdLS may not be typical of that observed in idiopathic ASD. Specifically, social impairment in CdLS may be characterised by selective mutism, extreme shyness and social anxiety (Goodban, 1993; Collis, Oliver & Moss, 2006; Moss *et al.*, 2008). This presentation of social impairment appears similar to the social anxiety and shyness that is reported in Fragile X syndrome (Dykens & Volkmar, 1997). Arron *et al.* (2006) also described a high prevalence of socially avoidant behaviors such as 'wriggling out of physical contact' and 'attempting to move away

during an interaction' in fourteen out of sixteen individuals with CdLS. Collectively these studies indicate that social anxiety and social avoidance may be evident in individuals with CdLS. Additionally social anxiety has been found to be prevalent in individuals with ASD (Simonoff *et al.* 2008). However, unlike in CdLS, selective mutism is a less common expression of social anxiety, and social anxiety itself is not a core feature or diagnostic symptom of ASD.

Social anxiety is difficult to assess in individuals with developmental disorders as introspection and self report may be compromised (Kim, Szatmari, Bryson, Streiner & Wilson, 2000; Gillott, Furniss & Walter, 2001). Consequently, observation of behavioral markers of social anxiety has been employed in empirical studies. Hall, DeBernadis & Reiss (2006) manipulated social and performance demands in order to examine social escape behaviours in 114 children with Fragile X syndrome. All children were exposed to four video taped conditions of varying social demand ranging from silent reading to an interview condition. In the interview condition, participants had to converse with an experimenter and particular emphasis was placed on the participant maintaining eye contact to increase social interaction. Social escape behaviours such as fidgeting and low levels of eye contact were coded, and were found to be most prevalent in the interview condition. The presence of these behaviours was also associated with increased levels of salivary cortisol suggesting that an interaction between biological and environmental factors may contribute to social escape behaviours in Fragile X syndrome.

Lesniak-Karpiak, Mazzocco and Ross (2003) used a similar methodology to assess social withdrawal and avoidance of social interaction in Turner syndrome and Fragile

X syndrome, compared to social interaction in typically developing individuals. They constructed eight behavioural markers of social anxiety which included eye contact avoidance, fidgeting and wringing of hands, and measured the occurrence of these in role play interactions. The role play interactions included conditions of conversing with familiar adults and unfamiliar adults. Again, individuals with Fragile X syndrome, engaged in more hand movements during social interaction than the group with Turner syndrome, or the typically developing control group. This methodology is promising and is used in this study to assess social anxiety in children with CdLS.

Contrasts between syndrome groups are useful for determining the specificity of behavioral phentoypes (Hodapp & Dykens, 2001). In this study a matched comparison group of children with Cri du Chat syndrome (CdCS) was employed. CdCS is caused by a deletion on the short arm of chromosome 5 (5p15; Goodhart *et al*., 1994; Overhauser *et al*., 1994) and occurs in approximately 1 in 50,000 births. Individuals with CdCS have similar levels of intellectual disability, expressive and receptive communication to those identified in CdLS (Cornish & Munir, 1988; Cornish, Bramble, Munir & Pigram, 1999). In contrast to individuals with CdLS, nonverbal communication skills and social interaction skills are reported to be a relative strength in CdCS (Cornish & Pigram, 1996; Cornish, Munir & Bramble, 1998; Sarimski, 2002) although, as is the case in CdLS, speech is compromised. These shared general and specific characteristics, makes CdCS an appropriate contrast group for this study. In this study we use fined grained observations of social interaction to investigate the behavioral indicators of social anxiety in children with CdLS and CdCS during periods of high social demand.

Method

Recruitment and Particpants

Participants were recruited from a study of nerve function in CdLS and CdCS (Oliver *et al.*, 2007)[1]. The twelve most able participants with CdLS from this group were selected based on Vineland Adaptive Behavior Scales composite standard scores (VABS; Sparrow, Balla & Cicchetti, 1994). Twelve participants with CdCS were selected based on the matching criteria of age (+/- 2 years), gender and VABS scores. A measure of cognitive functioning derived from scores on the British Picture Vocabulary Scale (BPVS; Dunn, Dunn, Whetton & Burley, 1997) was available for some participants. However, these data were missing for three participants with CdLS and one participant with CdCS. In addition, two further participants with CdLS and four further participants with CdCS scored at floor level on the BPVS. Consequently, meaningful data was only available for fourteen of the total twenty four participants. Therefore, as no other data were available on cognitive functioning, it was determined that VABS data would be more useful to match the groups. Table 1 shows participants characteristics. The CdLS group did not differ from the CdCS group on any variables.

(Insert table 1 about here)

Measures

     Structured social interactions. Participant behaviour was coded from video recordings made during an experimental analogue situation (similar to those described by Carr and Durand, 1985). As previous literature had indicated that social anxiety behaviours were most prevalent during periods of conversation with researchers,

participants were observed during high attention conditions of the analogue situation (Hall *et al.*, 2006; Lesniak-Karpiak *et al.*, 2003). Two, ten minute high attention conditions were assessed, during which the researcher maintained high levels of verbal attention toward the participant, whilst sustaining physical proximity. No task demands were placed on the participant during this condition. This condition was deemed to present the participants with high levels of social expectation and social demand since this condition involved the examiner repeatedly directing conversation towards the participant providing frequent opportunities for the participant to engage in social interaction. Participant behaviors during these interactions were operationally defined and coded from video recorded observations. In order to confirm that individuals in each participant group were given a comparable opportunity to engage in social interaction during this condition, the percentage duration of examiner communication during the 10 minute high attention conditions was compared between participant groups. No significant differences in examiner communication were identified (CdLS mean=71.10, SD=9.05; CdCS mean=72.08, SD=9.85). Participant behaviors during these interactions were operationally defined and coded from video recorded observations.

Behavior Definitions and Video Coding

Definitions of behavior indicative of social anxiety were constructed from reviewing studies that used similar methods (Hall *et al.*, 2006; Lesniak-Karpiak *et al.*, 2003). Behavioral codes focused on verbal and eye contact, and hand movements, these had been identified as indicators of anxiety in previous studies, with levels of the behavior differing significantly between those experiencing social anxiety, and those not (Hall *et al.*, 2006; Lesniak-Karpiak *et al.*, 2003). According to Hall *et al.* (2006), the increased

salivary cortisol levels associated with fidgeting in individuals with Fragile X syndrome give a physiological indication that this type of non-functional, non-rhythmic motor movement behavior is related to anxiety rather than any other underlying variable. Consequently the behavior code for hand movement in this study identified only hand movement behaviour that was non-functional and did not include stereotypic or repetitive rhythmic behaviors.

Table 2 shows the behaviors and operational definitions employed. Behaviors were either coded as duration variables (eye contact, participant and examiner communication), where the behavior onset and offset was recorded, or as event variables, where only the behavior occurrence was recorded (moving hands). Using these behavioral codes, each session was coded in real time using Obswin software (Martin, Oliver & Hall, 2000).

(Insert table 2 about here)

In order to analyse the relationship between social demand and social anxiety behaviors, behaviors were analysed as criterion or target variables. A criterion variable indicates a behavior which may increase the experience of social demand or pressure. Therefore, participant communication is a criterion variable. When a participant is engaging in verbal communication, social demand to communicate effectively is high. Likewise, participant eye contact is also a criterion variable, as engaging in eye contact increases social demand to participate in a verbally communicative manner. However, eye contact is also analysed as a target variable as it is identified by Hall *et al.,* (2006) to indicate anxiety in social encounters. Target variables are behaviors which are

predicted to change when social demand is high, indicating anxiety. Consequently, in addition to eye contact, hand movement behaviour is also a target behavior.

Interrater Reliability

20% of the video footage, an equal amount from both participant groups, was independently coded by a second observer. Kappa coefficients for 3s time windows were calculated for all coded behaviors (see Table 2). The mean Kappa score for behavioral codes was .88 (range .80 − .96) which indicates a good level of interrater reliability.

Data Analysis

Lag sequential analyses were used to investigate temporal relationships between points of high social demand and social anxiety behaviors. The analysis considers the unconditional probability of the participant engaging in the target behavior (e.g. moving hands) against the conditional probability of the participant engaging in the target behavior *given* the presence of a criterion behavior (e.g. moving hands *given* eye contact). Lags were examined for six, 3s intervals prior to and after the presence of the target behavior. Lag zero indicates the display of the criterion behavior. The lag analyses were *restricted* to the next occurrence of the criterion behavior. Consequently any association with the target behavior indicative of social anxiety can be isolated to that display of the criterion behavior. A significant degree of difference between the unconditional and conditional probabilities was deemed evident by a z score of greater than 4.5 (p<.00001) to avoid type 1 errors (see Moss *et al.*, 2005).

Results

Analysis of behaviors indicative of social anxiety

Analyses were conducted to test for differences in the frequency and duration of social anxiety behaviors between the CdLS and CdCS groups. No significant differences were found between the groups for any behaviors (See Table 3 for results).

(Insert table 3 about here)

The effects of social interaction upon behaviors indicative of social anxiety

Lag sequential analyses investigated the temporal relationship between eye contact and engaging in verbal communication with the examiner (points of high social demand) and participant hand movements. The results are shown in Figure 1.

(Insert figure 1 about here)

The upper panels of Figure 1 display the unconditional probability of each group engaging in eye contact and the conditional probability of each group engaging in eye contact *given* that they are engaging in verbal communication. The graphs show that both groups (CdLS and CdCS) engage in eye contact immediately prior to speaking to the researcher, and continue to engage in eye contact whilst speaking, only ceasing the eye contact after they have finished speaking. However, for the participants with CdLS, significant increases in eye contact occur closer to communicating and cease earlier after communicating. This suggests that the participants with CdLS engage in eye contact as temporally close to communicating as possible, rather than before or after. This analysis also identifies this point as characterised by high social demand i.e. there is both eye contact and the participant speaks

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The central panels of Figure 1 display the unconditional probability of each group moving their hands, plotted alongside the conditional probability of each group moving their hands *given* that they are engaging in eye contact. The graphs indicate that the participants with CdLS move their hands immediately prior to and after engaging in eye contact significantly more frequently than they would usually move their hands. They continue to move their hands whilst engaging in eye contact although the probability decreases slightly, suggesting that the most anxiety provoking time is just prior to and after the social engagement. This contrasts with the graph for the participants with CdCS, who do not show a pronounced relationship between hand moving and engaging in eye contact.

Finally, the lower panels of Figure 1 display the unconditional probability of each group moving their hands, plotted against the conditional probability of each group moving their hands *given* that they are engaging in verbal communication. The participants with CdLS display a consistent pattern of increasing hand movements prior to engaging in verbal communication with the examiner, this peaks during communication and decreases after the social interaction has finished. The participants with CdCS show a less pronounced pattern and display no difference between the unconditional and conditional probabilities.

Discussion

In this study we examined behavioral indicators of social anxiety in a group of participants with CdLS and a matched contrast group of participants with CdCS. The use of the contrast group with similar characteristics and, specifically, restricted speech

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enabled the specificity of these behavioral indicators to be evaluated in CdLS. We employed observational assessments of behavioral indicators of social anxiety similar to those used by Hall *et al* (2006) and Lesniak-Karpiak *et al* (2003) in order to investigate the prevalence of these behaviors and their association with high social demand. No significant differences were identified between behavioral indicators of social anxiety displayed by individuals with CdLS compared to those with CdCS in terms of overall levels. However, more detailed investigation of the pattern of behavioral responses before and after points of high social demand revealed that individuals with CdLS were significantly more likely to display behaviors indicative of social anxiety, such as hand movements, in close temporal proximity to periods of social interaction. The findings also demonstrated that the use of eye contact in CdLS was far more fleeting during these points of high social demand in comparison to individuals with CdCS. Given that communicative ability is thought to be comparable between the two participant groups (Cornish & Munir, 1988; Cornish *et al.,* 1999) it is assumed that any differences in communication between the groups are not attributable simply to communication impairment, but rather reflect group differences in response to social demand.

The results of this study add to a growing body of literature describing the presence of social anxiety in CdLS and demonstrate a more refined methodology for evaluating behavioral indices of social anxiety. Previous research had demonstrated that during periods of social interaction, individuals with CdLS engaged in socially avoidant behaviors in order to terminate social interaction (Arron *et al.,* 2006). The present study has added to this research by further delineating social behavior in CdLS with two characteristic findings. Firstly, that there is no quantitative difference in the amount of behaviors indicative of social anxiety displayed by children with CdLS

compared to children with CdCS. This is in marked contrast to the profile of social anxiety in other genetic syndromes such as Fragile X (Lesniak-Karpiak *et al.*, 2003) where the prevalence of social anxiety behaviors are reported to be heightened in comparison to those with Turner syndrome and typically developing individuals. The comparable nature of social interaction in CdLS and CdCS is further highlighted by the initial lag analyses which demonstrate that the pattern or sequence of social interaction behaviors in CdLS appears to be very similar to that of individuals with CdCS. Both groups of children engage in eye contact prior to and during verbal communication with a researcher. However, this analysis also revealed that although the participants with CdLS can and do engage in eye contact whilst communicating, they only do so in close temporal proximity to their verbal communication. This may indicate that social interaction combining eye contact and verbal communication is anxiety provoking for individuals with CdLS, and therefore they avoid engaging in it until the last possible moment and as briefly as possible.

This initial difference between the two experimental groups becomes more apparent when the behavior of 'moving hands' was analysed. Previous literature in people with Fragile X indicated that this behavior (or behaviors similar to this; 'fidgeting', 'wringing hands') was indicative of social anxiety (Lesniak-Karpiak *et al.*, 2003; Hall *et al.*, 2006). The lag analyses revealed that in the CdLS group, hand movements indicative of social anxiety were more likely to occur when social demand was heightened, specifically when the individual was engaging in eye contact or verbal communication with the examiner. This pattern of behaviour was not observed in the CdCS group. Whilst the two groups displayed a comparable frequency and duration of this behavioral indicator of anxiety, the participants with CdLS displayed hand movement differentially during social interaction. This may suggest that individuals

with CdLS experience heightened levels of anxiety during periods of high social demand. The finding that children with CdLS display social anxiety through small, non verbal behaviours should not be surprising, given that due to deficits in expressive communication, individuals with CdLS tend to rely on nonverbal communicative acts to express themselves (Sarimski, 1997).

This study was limited by two factors. Firstly the sample size of the groups was relatively small, and the participants were young. Previous studies have indicated that social anxiety in CdLS may be more prevalent amongst young adults with CdLS (Collis *et al.*, 2006). It may be the case that the subtle indicators of social anxiety identified in the current study sample of younger individuals may become stronger with age and this should be investigated. Secondly, the presence of hand movements as indicative of anxiety has been assumed, in part based on the clustering of these behaviors around periods of high social demand. However, previous studies have used physiological assessment to validate the presence of hand moving behaviors as indicative of social anxiety (Hall *et al.*, 2006). This type of validation was not possible in this study but should be considered in future studies of social anxiety in CdLS.

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Footnotes

1. The recruitment procedure for the larger study sample is described in detail in Moss *et al.* (2008).

Tables

Table 1: Participant characteristics and comparative analysis

		CdLS (N=12)	CdCS (N=12)	Independent t-test value	P Value
Chronological Age (Years)	Mean (SD)	11:00 (5.15)	8:20 (2.86)	17.17	.11
	range	*5.00-18.00*	*5.00-14.00*		
Gender	N Male	4	4		
VABS ABC standard score	Mean (SD)	45.83 (12.50)	36.83 (9.10)	2.01	.12
	range	*31.00 – 68.00*	*23.00 – 54.00*		
VABS Classification	N Mild	3	1		
	N Moderate	5	3		
	N Severe	4	8		

Table 2: Operational Definitions of Behaviors and Cohen's Kappa values.

Behavior	Operational Definition	Kappa
Behaviors Indicative of Social Anxiety		
Eye contact	Participant looks up/or at the examiner and fixates on the examiners eyes or face.	.80
Participant – communication	Any verbal communication or use of formal signs directed towards the examiner. This includes prompting, offering information and response to a question.	.90
Moving of hands	Moving of hands to face, head, or another part of the body. For example scratching or touching face, hair, arm, which has no obvious function. Excluding any forms of self-injury, or any communicative gestures.	.86
Examiner Behavior		
Examiner – communication	Any verbal communication directed towards the participant. This includes prompting, offering information and response to a question.	.96

Table 3. Mean frequencies, durations and comparative analyses for behaviors

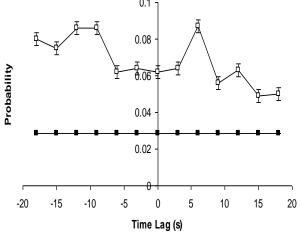**indicative of social anxiety for the CdLS group and CdCS group.** 25

Behavior	CdLS	CdCS	Mann Whitney U	P Value
Eye Contact duration	19.33	15.73	68.00	.82
Participant Communication duration	13.06	9.70	57.00	.39
Moving Hand frequency (per minute)	1.03	.39	52.50	.26

Figure Captions

Figure 1. Mean unconditional probability (filled squares) of the child engaging in the

target behavior and conditional probability (unfilled squares) of the child engaging in

the target behavior given that they are engaging in the criterion behavior, for 21s

before and after the target behavior occurs for the CdLS group and the CdCS group (*
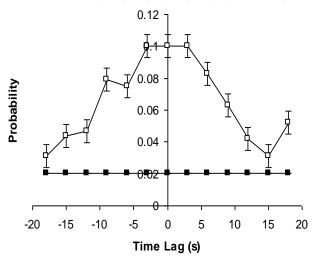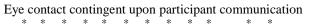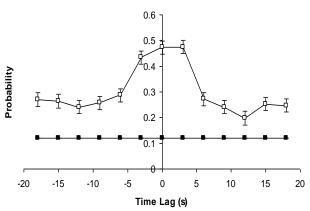
= p<.00001, $z > 4.5$).

Figure 1 Top

CdLS
Eye contact contingent upon participant communication

CdCS
Eye contact contingent upon participant communication

CdLS
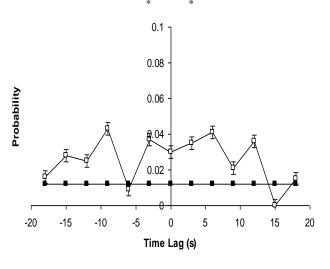Moving hands contingent upon eye contact

CdCS
Moving hands contingent upon eye contact

CdLS
Moving hands contingent upon participant communication

CdCS
Moving hands contingent upon participant communication