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Behavioural and physiological indicators of anxiety reflect shared and distinct profiles across individuals with neurogenetic syndromes

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ABSTRACT

Anxiety is heightened in individuals with intellectual disability, particularly in those with specific neurogenetic syndromes. Assessment of anxiety for these individuals is hampered by a lack of appropriate measures that cater for communication impairment, differences in presentation, and overlapping features with co-occurring conditions. Here, we adopt a multi-method approach to identify fine-grained behavioural and physiological (via salivary cortisol) responses to anxiety presses in people with fragile X (FXS; $n = 27$; $M_{age} = 20.11$ years; range 6.32 – 47.04 years) and Cornelia de Lange syndromes (CdLS; $n = 27$; $M_{age} = 18.42$ years; range 4.28 – 41.08 years), two neurogenetic groups at high risk for anxiety, compared to neurotypical children (NT; $n = 21$; $M_{age} = 5.97$ years; range 4.34 – 7.30 years). Results indicate that physical avoidance of feared stimuli and proximity seeking to a familiar adult are prominent behavioural indicators of anxiety/stress in FXS and CdLS. Heightened pervasive physiological arousal was identified in these groups via salivary cortisol. An association between autistic characteristics and anxiety was evident in the FXS group but not in the CdLS group pointing to syndrome-specific nuances in the association between anxiety and autism. This study furthers understanding of the behavioural and physiological presentation of anxiety in individuals with intellectual disability and progresses theoretical developments regarding the development and maintenance of anxiety at the intersection of autism.

1. Introduction

Anxiety disorders are the most prevalent mental disorder with significant impairment associated with elevated symptom severity (Beesdo-Baum and Knappe, 2012; Stein et al., 2017). Mechanistic underpinnings of anxiety have been identified at genetic, biological, cognitive, and behavioural levels (Hudson et al., 2019; Norton and Paulus, 2017; Spence and Rapee, 2016), offering the opportunity to highlight at-risk individuals to facilitate identification, monitoring and early intervention. Specific sub-groups are at substantially higher risk for anxiety including people with intellectual disability for whom the estimated prevalence of anxiety is up to six times greater than that in the general population (Emerson and Hatton, 2007; Reardon et al., 2015).

Despite the elevated presence of anxiety in persons with intellectual disability, there is a tremendous gap in what is known regarding the presentation and underlying mechanisms that are associated with anxiety in this clinical group. These research gaps are due, in large part, to an over-reliance on assessment tools that have questionable validity in characterizing how anxiety presents against the backdrop of lower cognitive ability (Flynn et al., 2017), atypical behavioural expressions of anxiety (Edwards et al., 2022b; Lozano et al., 2022), and other phenotypic characteristics (Talisa et al., 2014). This is documented most widely in the autism literature where autism-sensitive measures have identified manifestations of anxiety that commonly arise in autistic people but do not map onto the anxiety disorders specified in the Diagnostic and Statistical Manual of Mental Disorders (Kerns et al., 2021). The presence of *both* intellectual disability and autistic characteristics poses a particular challenge for identification of anxiety given

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the difficulty in disentangling behavioural features that overlap across both anxiety and autism (e.g. social avoidance). Taken together, these challenges point to a need for novel identification tools and strategies suitable for individuals with intellectual disability such as a multi-method biobehavioral approach.

Several genetic causes of intellectual disability are associated with a substantially heightened risk of anxiety in comparison with both the general population and heterogeneous intellectual disability population (Crawford et al., 2017; Edwards et al., 2022a; Groves et al., 2022). Fragile X syndrome (FXS) is a well-characterised monogenic disorder affecting approximately 1 in 7,000 males and 1 in 11,000 females (Hunter et al., 2014). Nearly all males with FXS have moderate intellectual impairment, and anxiety symptomatology is present in 48–100% of individuals with FXS (Crawford et al., 2017; Edwards et al., 2022a; Groves et al., 2022) with 48–83% of males with FXS meeting criteria for an anxiety diagnosis (Cordeiro et al., 2011; Ezell et al., 2019). Autism is also highly prevalent and is present in approximately 60% of individuals with FXS (Roberts et al., 2020). Cornelia de Lange syndrome (CdLS) is a multi-system disorder associated with moderate intellectual disability and an estimated prevalence of 1:10,000–1:30,000 (Kline et al., 2018). The prevalence of clinical anxiety symptomatology in CdLS is estimated to be 54%−92% (Crawford et al., 2017; Giani et al., 2022; Groves et al., 2022). Autism is also highly prevalent in CdLS with 42% of persons meeting criteria for diagnosis (Richards et al., 2015). The presence of these co-occurring features makes identification of anxiety more challenging, but it also makes these groups ideal candidates for exploring the intersection of anxiety and autism. Of importance to the study of anxiety is the overlapping symptomatology of anxiety, depression and stress. Given that each share affective, cognitive and somatic indicators, dissociation is a challenge, and this is evidenced by the high association between measures of depression and anxiety in FXS (Russo-Ponsaran et al., 2014) as well as the general population (Eysenck and Fajkowska, 2018). Whilst the focus of this manuscript is anxiety, this overlap is important to consider in the evaluation of diverse cognitive and emotional responses in individuals with neurogenetic syndromes.

Interestingly, while there is heightened anxiety in both individuals with FXS and CdLS, the presentation of anxiety differs across these syndromes highlighting the interplay of genetics and intellectual ability. Specifically, informant-report questionnaires and clinical interviews have identified that persons with CdLS exhibit higher separation anxiety and generalised anxiety in comparison to FXS (Crawford et al., 2017), whereas individuals with FXS display elevated social anxiety compared to those with CdLS (Groves et al., 2022). Other sub-types of anxiety disorder (e.g. panic/agoraphobia, phobias) appear similar across the two neurogenetic syndromes. A behavioural observation study identified that heightened social anxiety appears evident in interactions with familiar and unfamiliar social partners in FXS whereas it appears most pronounced in interactions with unfamiliar social partners and in more unstructured settings in CdLS (Crawford et al., 2020b). This cross-syndrome specificity in anxiety profiles is important for identifying cause and prognosis. Such research has led to theoretical developments identifying contributing factors in the development and maintenance of anxiety in CdLS (Groves et al., 2021) and FXS (Crawford, 2023). Differences in profiles of autism characteristics are also evident across these two groups. Using a machine-learning approach, a recent study identified that, despite almost identical mean scores on an autism screening tool, the FXS group was associated with a distinct autism profile that was separable from that of the CdLS group (Bozhilova et al., 2023). Descriptions of FXS and CdLS indicate subtle broader phenotypic differences between these two groups alongside many similarities, which could be important when considering anxiety and autistic traits. For example, mood is lower in people with CdLS compared to those with FXS (Oliver et al., 2011), and interest and pleasure in the environment declines over the lifespan in people with CdLS but not in those with FXS (Groves et al., 2019). People with FXS demonstrate higher levels of impulsive speech (Oliver et al., 2011), repetitive speech and insistence on sameness (Moss et al., 2009) than those with CdLS. People with CdLS and FXS reportedly display similar levels of sociability during some social situations but those with FXS are significantly less sociable in a number of social contexts with unfamiliar adults (Moss et al., 2016).

Research in the general population and in non-syndromic autism has consistently demonstrated that a combination of measures builds refined causal models of anxiety in recognition that biological, psychological, and environmental factors contribute in important ways (Clark and Watson, 1991; Spence and Rapee, 2016; Suveg et al., 2010; White et al., 2014). The value of a multi-method approach to characterizing anxiety has also been demonstrated in FXS as a multi-faceted anxiety composite discriminated adolescents with FXS from autistic participants more strongly than the individual indices did (Roberts et al., 2018). One variable that has been increasingly examined as contributing to anxiety in FXS is physiological hyperarousal (see Klusek et al., 2015 for a review). Physiological arousal can be indexed by atypical function of the hypothalamus-pituitary-adrenal (HPA) axis which regulates stress responsivity via secretion of adrenal glucocorticoid hormones including salivary cortisol, a hormonal response to environmental stressors. Salivary cortisol is, therefore, a key biomarker candidate in the study of anxiety in FXS. Evidence supporting a *direct* association between anxiety and physiological arousal in FXS is mixed as research primarily identifies hyperarousal across both baseline and anxiety-provoking conditions (Hessl et al., 2002). However, heightened salivary cortisol has been associated with some key behavioural indicators of stress or anxiety, including gaze avoidance (Hall et al., 2006, 2009), more withdrawn behaviour (Hessl et al., 2002), and social avoidance (Roberts et al., 2009). Together, this work indicates that physiological arousal contributes to anxiety in FXS but likely in a pervasive, rather than context-dependant, way thus highlighting the importance of a multi-method biobehavioural approach to anxiety identification. The role of physiological arousal contributing to anxiety has not yet been examined in CdLS.

The current study adopts a biobehavioural framework using a multi-method and multi-informant approach to advance understanding of the phenomenology of anxiety in individuals with intellectual disability. This is accomplished by identifying similarities and differences in parental reports as well as behavioural and cortisol responses elicited in a naturalistic experimental paradigm employed with individuals with FXS, CdLS and neurotypical (NT) children matched on receptive language ability. Specifically, we aim to:

A Compare parental reports of anxiety and behavioural and cortisol responses to elicited anxiety presses between all groups. We hypothesise heightened anxiety responses in participants with FXS and CdLS compared to NT children.
B Determine associations between behavioural responses to elicited anxiety presses and cortisol responses, demographic, and clinical characteristics in the genetic syndrome groups, including chronological age, intellectual and functional behaviour skills and autistic characteristics. Hypotheses were not generated for this research question given limited research concerning factors associated with behavioural presentations of anxiety, particularly in the CdLS group.

2. Methods

2.1. Participants

Thirty individuals with FXS, 42 individuals with CdLS, and 21 NT children participated in the study. There were significant group differences in chronological age between all three groups (FXS > CdLS > TD), and in receptive language ability between the CdLS group compared to the FXS and NT groups (FXS = NT > CdLS). Given the possible influence of these characteristics on anxiety presentation, 'matched samples' were formed that were comparable on chronological age (CdLS and FXS only;

NT children were significantly younger as expected), receptive language ability (all groups were comparable) and adaptive behaviour skills (CdLS and FXS only; NT children were not assessed). The matched samples were formed by excluding data from participants with CdLS with the lowest receptive language scores and FXS participants with the highest receptive language scores, until groups were statistically comparable on these variables. These matched samples included 27 participants with FXS, 27 with CdLS and 21 NT children. Participant characteristics for the matched samples are shown in Table 1. Data from the matched samples were used for all analyses except those involving salivary cortisol. As viable samples could not be obtained from all participants, the sample size for cortisol analyses was deemed too small when restricted to the 'matched samples' and so viable samples from the 'full sample' were used for these analyses. Viable samples were obtained at baseline (NT $n = 19$; FXS $n = 22$; CdLS $n = 25$) and post-Anx-DOS (NT $n = 19$; FXS $n = 22$; CdLS $n = 22$). Where participants provided both baseline and post-Anx-DOS samples, cortisol reactivity was calculated by subtracting the baseline cortisol level from post-Anx-DOS level (NT $n = 18$; FXS $n = 22$; CdLS $n = 20$). As anticipated, there was a significant group difference in sex because only males with FXS were recruited for this study due to phenotypic gender differences (see Crawford et al., 2020a).

Table 1
Participant characteristics for the matched samples [a].

	Fragile X Syndrome (FXS; $n = 27$)	Cornelia de Lange Syndrome (CdLS; $n = 27$)	Neurotypical Children (NT; $n = 21$)	p
Chronological age mean years (SD; range)	20.11 (9.35; 6.32–47.04)	18.42 (9.82; 4.28–41.08)	5.97 (.87; 4.35–7.30)	< .001; NT < CdLS=FXS
Gender (% male)	100	37.04	28.57	<.001
Receptive Language (BPVS-III) raw score mean (SD; range)	96.74 (29.30; 31–143)	89.85 (23.27; 43–140)	93.10 (14.90; 58–119)	.571
Adaptive Behaviour (VABS-II) sum of domains standard score mean (SD)	172.11 (53.32; 100–304)	175.33 (63.87; 69–287)	Not assessed	.597
Social Responsiveness Scale (SRS-2) Total t-score mean (SD; range)	72.96 (8.88; 50–90)	71.39 (10.82; 54–90)	Not assessed	.580
Repetitive Behaviour Questionnaire (RBQ) Total Score mean (SD; range)	28.19 (13.79; 6–57)	22.38 (17.32; 0–60)	Not assessed	.118
Anxiety, Depression and Mood Scale Total Score mean (SD; range)	27.31 (13.11; 6–47)	31.11 (13.89; 8–57)	6.15 (4.77; 0–18)	<.001; NT < CdLS=FXS

[a] Chronological age information was not provided for 2 participants with CdLS. Data from the VABS-II are missing for 3 participants with CdLS. Data from the SRS-2 are missing for 1 participant with FXS and 4 participants with CdLS. Data from the ADAMS are missing for 3 participants with FXS, 4 participants with CdLS, and 1 NT child. Data from the RBQ are missing for 3 participants with FXS and 4 participants with CdLS.

2.2. Recruitment

Participants with FXS and CdLS were recruited via a regular participant database held by the Cerebra Centre for Neurodevelopmental Disorders or via the UK syndrome support groups, Cornelia de Lange Syndrome Foundation (UK and Ireland) and the Fragile X Society. NT children were recruited via a community outreach event for families. Participants with FXS or CdLS were included in the study if they were mobile, at least three years old, and had a parent-reported confirmed genetic diagnosis of FXS or a parent-reported confirmed genetic or clinical diagnosis of CdLS. NT children were included in the study if they had no known neurodevelopmental disorder or intellectual disability as reported by their main caregiver.

2.3. Measures

2.3.1. Participant ability measures

The British Picture Vocabulary Scale-Third Edition (BPVS-III; Dunn et al., 2009) was used to assess receptive language ability for all groups. Parents or primary caregivers of participants with FXS and CdLS completed the Vineland Adaptive behavior Scale-Second Edition (VABS-II; Sparrow et al., 2005) to provide an indicator of their child's adaptive behaviour skills. These measures were used to ensure that participant groups were comparable on key indicators of functional ability (see Table 1).

2.3.2. Parental report measures of anxiety and autistic characteristics

Parents or primary caregivers of participants with FXS and CdLS completed the following questionnaire measures: Anxiety, Depression and Mood Scale (ADAMS; Esbensen et al., 2003), Social Responsiveness Scale-Second Edition (SRS-2; Constantino and Gruber, 2012), and Repetitive Behaviour Questionnaire (RBQ; Moss et al., 2009) to provide an indicator of their child's anxiety, autistic characteristics, and repetitive behaviour, respectively. Due to the constraints of collecting data during a community outreach event, parents or primary caregivers of NT children completed the ADAMS only. Missing data from individual items were prorated according to manual instructions.

2.3.3. Behavioural responses to anxiety

All participants completed the Anx-DOS (Mian et al., 2015), which was modified by authors JR, AH, KS in liaison with the original authors (Hogan et al., review), and used in the present study as a natural extension of an ongoing collaboration with HC exploring autism and anxiety in FXS. The Anx-DOS employs a variety of ecologically valid presses designed to elicit a broad range of anxiety responses, behaviours and coping reactions, including clinically relevant manifestations (See Supplementary Material for details). Four conditions are presented to participants: *Toy Spider* (pressing for novelty and present threat), *Auditory Startle* (pressing for biological tendency or involuntary reactivity to a startle), *Mystery Jar* (pressing for novelty, uncertainty and anxiety-related inhibition), and *Parental Separation*. The Anx-DOS was video recorded, and footage was later coded using a manualised coding scheme, developed by the Neurodevelopmental Disorders Laboratory, University of South Carolina (JR, KS, AH). Table 2 shows the behavioural codes scored for each condition and associated range of scores, as well as composite scores and how they are calculated.

Two coders (LB, HC) independently scored 20% of each participant group across all conditions, and intraclass correlation coefficients were used to determine item-level inter-rater reliability. Table 3 shows the Intraclass correlation coefficients for each item of the Anx-DOS coding scheme, ranging from moderate to excellent reliability.

2.3.4. Physiological response

Salivary cortisol was collected using the SalivaBio Children's or Adult's Swab (Salimetrics, State College, PA, USA), depending on the participant's age and level of ability. The swab was placed in the

Table 2
Anx-DOS codes.

Item	Conditions	Score
Behavioural codes [a]		
Facial Fear	Toy Spider; Auditory Startle; Mystery Jar	0 (no sign of facial fear) to 3 (strong facial fear).
Postural Fear	Toy Spider; Auditory Startle; Mystery Jar	0 (no sign of postural fear) to 3 (strong postural fear).
Verbal Fear	Toy Spider; Auditory Startle; Mystery Jar	0 (verbal expressions do not indicate fear) to 3 (verbal expressions indicate high levels of fear).
Physical Avoidance	Toy Spider; Auditory Startle; Mystery Jar	0 (no physical avoidance) to 3 (strong physical avoidance).
Exaggerated Startle	Toy Spider; Auditory Startle	0 (typical response) to 3 (severe response)
Proximity Seeking	Toy Spider; Parental Separation	0 (no proximity seeking) to 3 (strong proximity seeking)
Separation Distress	Parental Separation	0 (no distress) to 3 (strong distress)
Composite scores		
Fear Composite	Toy Spider; Auditory Startle; Mystery Jar	Sum of (highest code given for Facial Fear, Postural Fear and Verbal Fear), Physical Avoidance and Exaggerated Startle[b,c]
Individual Global Composite	Toy Spider; Auditory Startle; Mystery Jar; Parental Separation	0 (no concern) to 3 (atypical), rated using item scores and clinical judgement
Total Anx-DOS Score	Toy Spider; Auditory Startle; Mystery Jar; Parental Separation	Sum of (highest code given for Facial Fear, Postural Fear and Verbal Fear), Physical Avoidance, Exaggerated Startle, Separation Distress and Proximity Seeking[b,c]

[a] A score of 8 was given if response was obscured.
[b] Only items rated in each condition are included in the means.
[c] A score of 8 was treated as a score of 0 when considering 'highest' codes and removed from calculations involving summing of scores.

Table 3
Intraclass correlation coefficients for item-level inter-rater reliability. Intraclass correlation estimates were based on a mean rating ($k = 2$), absolute-agreement, two-way mixed effects model.

Item	Intra-class Correlation Coefficient	Reliability
Facial Fear	.831	Good
Postural Fear	.739	Moderate
Verbal Fear	.876	Good
Physical Avoidance	.918	Excellent
Exaggerated Startle	.796	Good
Separation Distress	.870	Good
Proximity Seeking	.930	Excellent
Global Composite	.896	Good

participant's mouth for 60–90 s and then placed in a storage tube. Two samples were taken, one immediately before the Anx-DOS (baseline) and one 15 min after the end of the Anx-DOS to allow for the delay of cortisol increase in response to a stress event (Blackburn-Munro and Blackburn-Munro, 2003; Dedovic et al., 2009). Cortisol reactivity was calculated by subtracting the baseline cortisol level from the post-Anx-DOS cortisol level, which signifies the extent to which cortisol levels increased or decreased during the Anx-DOS. Both samples were taken during the afternoon (between 13:00–18:00) to mitigate the diurnal pattern of cortisol. The samples were stored in a 4 °C refrigerator during data collection and then transferred in a cool bag alongside a freezer pack for storage in a −80 °C freezer prior to assaying. On the day of analysis, all samples were defrosted, centrifuged and then analysed using a specific cortisol Enzyme ImmunoAssay (EIA) kit. Saliva samples were measured in duplicate for cortisol using a commercially available, high sensitivity salivary cortisol enzyme immunoassay kit (Cat No. #1–3002, Salimetrics, UK). All samples were assayed according to the manufacturer's instructions as described without modification (http://www.salimetrics.com/). Data reduction was performed using Prism (v9.1) software.

2.4. Procedure

Parents or legal guardians provided fully informed written consent on behalf of participants aged under 16 years, and participants aged 16 years and over who were unable to provide fully informed consent themselves. Participants with FXS or CdLS completed the study tasks in a quiet room at their homes or at a syndrome support group family meeting. NT children participated in an indoor room at a community outreach event. Participants provided their first saliva sample, then completed the Anx-DOS, and then provided their second saliva sample after 15 min. Participants completed the BPVS, and other measures as part of a wider study, on the same day either before or after the cortisol/Anx-DOS. Parents or primary caregivers of participants with FXS and CdLS completed the VABS-II via telephone and questionnaire measures via post. Parents or primary caregivers of NT children completed the ADAMS questionnaire whilst their child was participating in the research assessments. Ethical approval was granted by Coventry and Warwickshire NHS Research Ethics Committee (16/WM/0435).

2.5. Data analysis

All data were subjected to the Shapiro-Wilk test for normality. Where data were not normally distributed and could not be transformed to achieve a normal distribution, analyses were conducted with non-parametric tests.

Analyses of variance (ANOVA), or non-parametric equivalents (Kruskal-Wallis), and associated follow-up tests (Bonferroni for normally distributed data, Mann-Whitney tests for non-normally distributed data) were conducted to compare parent-report, and behavioural and physiological responses to anxiety presses between all groups. Viable salivary cortisol samples, obtained from the full participant groups (not matched groups; see Participants section), were used for analyses. Baseline and post-Anx-DOS salivary cortisol data were winsorized to remove outliers identified in box plots.

Correlational analyses were conducted for each group separately to identify associations between Anx-DOS scores with salivary cortisol levels, and demographic and clinical characteristics (chronological age, receptive language ability, adaptive behaviour ability, autistic characteristics, repetitive behaviour; see Table 1 for sample sizes and demographic and participant characteristics).

3. Results

3.1. Parental reported anxiety

Table 1 displays the data from the ADAMS. A one-way ANOVA and Bonferroni post-hoc tests revealed a significant between-groups difference on ADAMS Total Score (F (2, 64) = 28.198, $p < .001$), with NT children scoring significantly lower than participants with CdLS ($p < .001$) and FXS ($p < .001$), but no difference between the CdLS and FXS groups.

3.2. Behavioural response

A Kruskal-Wallis test and follow-up Mann-Whitney tests revealed a significant between-groups difference in the background sound levels of the Auditory Startle condition (χ^2 (2) = 49.544, $p < .001$), such that the background noise was louder in the testing environment for NT participants than participants with CdLS or FXS ($p < .001$). The impact of this on behavioural responses was explored given research showing reduced startle response with increasing background noise (Flaten et al., 2005). Spearman's rho correlations revealed a positive association between Postural Fear and background sound level for the FXS group (r_s (21) =

0.435, $p = .038$). No other associations between background sound level and behavioural codes, or composite scores, for any group, were identified and so this was not considered to be influential on the results reported below.

Fig. 1 displays mean Anx-DOS data for each group. Data are reported here from the matched samples for each behavioural code (Facial Fear, Postural Fear, Verbal Fear, Physical Avoidance, Exaggerated Startle, Separation Distress, and Proximity Seeking) and composite score (Fear Composite, Individual Global Composite) averaged across presses, as well as the Total Anx-DOS score.

A Kruskal-Wallis test revealed a significant between-groups difference in the following behavioural codes and composite scores, averaged across conditions: Facial Fear (χ^2 (2) = 7.696, $p = .021$), Verbal Fear (χ^2 (2) = 7.786, $p = .020$), Physical Avoidance (χ^2 (2) = 14.692, $p < .001$), Proximity Seeking (χ^2 (2) = 10.281, $p = .006$), Fear Composite (χ^2 (2) = 9.405, $p = .009$), Individual Global Composite (χ^2 (2) = 10.530, $p = .005$), and Total Anx-DOS score (χ^2 (2) = 8.349, $p = .015$). Follow-up Mann-Whitney tests revealed that participants with CdLS scored higher than NT participants on each of the behavioural codes (Verbal Fear, Physical Avoidance, Proximity Seeking) and composite scores (all

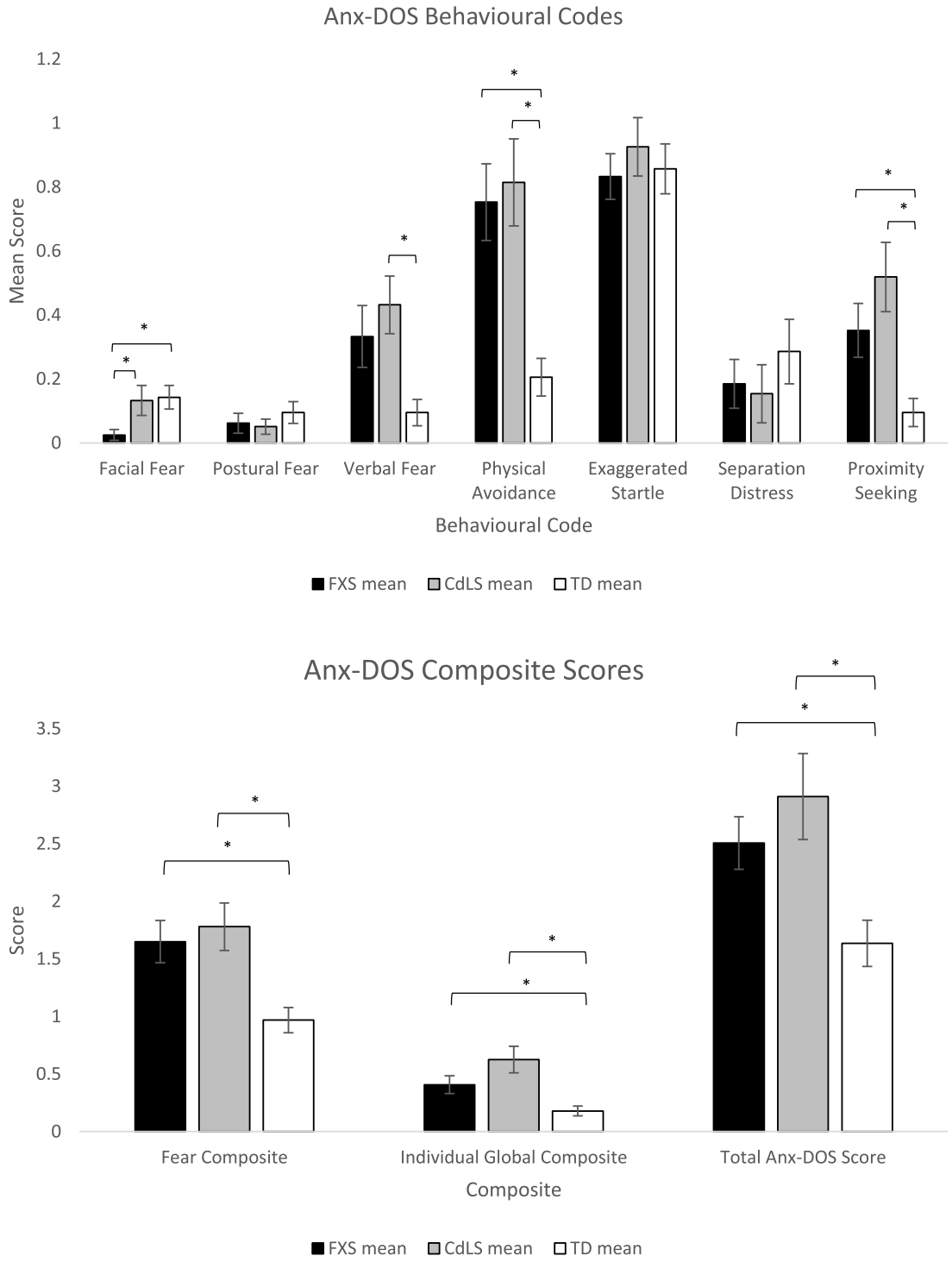

Fig. 1. Mean scores and between-group differences on each behavioural code (a) and composite score (b) of the Anx-DOS for the fragile X syndrome (FXS), Cornelia de Lange syndrome (CdLS) and neurotypical (NT) participant groups.

$p < .019$), except Facial Fear ($p = .502$). In addition, participants with FXS scored higher than NT participants on each of the behavioural codes (Physical Avoidance and Proximity Seeking) and composite scores (all $p < .037$), except Verbal Fear ($p = .079$) where there was no difference between FXS and NT groups, and Facial Fear ($p = .004$) where participants with FXS scored significantly *lower* than NT participants. Participants with CdLS scored higher than participants with FXS on Facial Fear ($p = .044$), but no other differences between the two high-risk anxiety groups emerged.

Due to differences in chronological age between the NT participants and participants with FXS and CdLS, as well as identified within-group associations between age and behavioural anxiety responses (see below), analyses of covariance (ANCOVAs) were conducted to explore between groups differences, as above, but with age as a covariate. ANCOVAs are deemed relatively robust and, therefore, can be used with non-normally distributed data (Olejnik and Algina, 1984). The results confirmed the between-group differences reported above on Facial Fear, Physical Avoidance, Proximity Seeking, Fear Composite, Individual Global Composite, and Total Anx-DOS score. The only behavioural code for which a between-groups difference was not confirmed once age was entered as a covariate was Verbal Fear.

3.3. Physiological response

Fig. 2 displays mean salivary cortisol levels for each group. One-way ANOVAs revealed a significant between groups difference in baseline (F (2, 66) = 6.906, $p = .002$) and post-Anx-DOS (F (2, 62) = 10.752, $p < .001$) salivary cortisol. Bonferroni tests revealed that this difference was driven by participants with FXS and CdLS exhibiting higher salivary cortisol levels than NT children at both baseline (NT vs. FXS: $p = .005$; NT vs. CdLS: $p = .006$) and post-Anx-DOS (NT vs. FXS: $p < 0.001$; NT vs. CdLS: $p = .012$). There was no significant between-groups difference in cortisol reactivity (calculated by subtracting baseline from post-Anx-DOS levels).

Paired-samples t-tests were conducted for each group to determine differences between baseline and post-Anx-DOS salivary cortisol levels. For the NT group only, post-Anx-DOS salivary cortisol levels were significantly lower than the baseline levels (t (18) = .245, $p = .039$), likely reflecting changes in the cortisol diurnal rhythm.

As the full participant groups were not matched on age or receptive language ability, correlational analyses were conducted for each group separately to identify associations between baseline, post-Anx-DOS and reactivity salivary cortisol levels with demographic and clinical characteristics (chronological age, receptive language ability (BPVS-III raw score), and adaptive behaviour ability (VABS-II Sum of Domains Standard Score)). A significant positive correlation between chronological age and baseline salivary cortisol levels (r_s (22) = .444, $p = .030$) was identified for the CdLS group only.

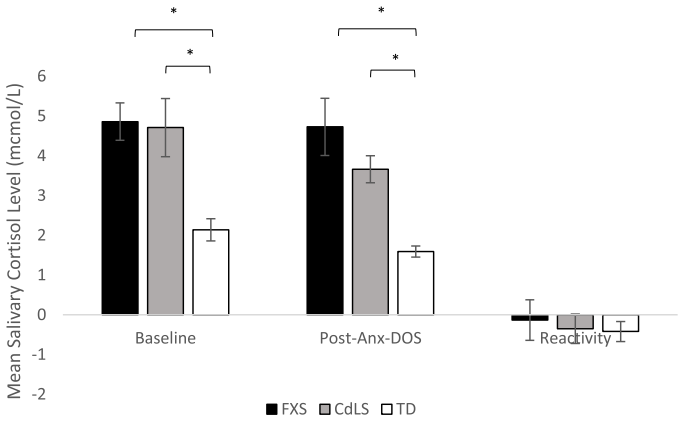

Fig. 2. Mean salivary cortisol levels for each group at baseline (n = 19 NT, 22 FXS, 25 CdLS), post-Anx-DOS (n = 19 NT, 22 FXS, 22 CdLS) and reactivity (post-Anx-DOS minus baseline; n = 18 NT, 22 FXS, 20 CdLS)[a].

[a]To maximise sample sizes for between-group comparisons, mean reactivity is calculated for all participants with both a baseline and post-Anx-DOS sample whereas mean baseline and mean post-Anx-DOS salivary cortisol levels are calculated using all available samples (e.g. where a participant provided one but not both samples). Participants with FXS and CdLS display significantly higher cortisol levels at baseline and post-Anx-DOS compared to the NT group.

3.4. Associations between behavioural and physiological responses

Spearman's rho correlations were conducted for each genetic syndrome group separately to identify associations between behavioural codes and baseline, post Anx-DOS and reactivity salivary cortisol levels. Behavioural codes were used instead of composite scores for these analyses given the additional specificity offered in keeping with the aim to identify fine-grained behavioural and physiological responses to anxiety presses. In the CdLS group, baseline salivary cortisol was negatively associated with Postural Fear (r_s (23) = −.410, $p = .042$). In the FXS group, baseline salivary cortisol was negatively associated with Verbal Fear (r_s (20) = −.449, $p = .036$) and positively correlated with Separation Distress (r_s (20) = .511, $p = .015$). The correlation matrix can be seen in Table 4.

3.5. Associations between behavioural responses and demographic and clinical characteristics

Spearman's rho correlational analyses were conducted for each genetic syndrome group separately to identify associations between the Total Anx-DOS score with demographic (chronological age), intellectual and functional behaviour skills (BPVS-III raw score and VABS-II Sum of Domains Standard Score) and clinical characteristics (SRS-2 and RBQ subscale and total scores). The Total Anx-DOS Score was used for these correlational analyses to minimise the number of tests being conducted. In the FXS group, heightened repetitive language (subscale of RBQ) was positively correlated with the Total Anx-DOS Score (r_s (22) = 0.452, $p = .027$) scores. In the CdLS group, chronological age was negatively correlated with the Total Anx-DOS score (r_s (23) = −0.485, $p = .014$) and adaptive behaviour was positively correlated with the Total Anx-DOS score (r_s (22) = 0.428, $p = .037$). There were no significant correlations between Total Anx-DOS score and subscale scores from the SRS-2 or RBQ.

4. Discussion

The results of the current study are interpreted with consideration to the overlap between anxiety and stress. These indicate that high-risk genetic syndrome groups primarily display anxiety or stress responses through physical avoidance of anxiety-inducing stimuli and proximity seeking to a main caregiver. Salivary cortisol levels were heightened at both baseline and following the Anx-DOS in the high-risk genetic syndrome groups compared to NT children, but there was no cortisol response to the Anx-DOS in any group. Associations were present between salivary cortisol and indices of behavioural anxiety/stress response. In addition, in the CdLS group, younger participants, and those with poorer adaptive behaviour, demonstrated stronger behavioural anxiety/stress responses. More severe autistic characteristics, in the form of repetitive language, was associated with stronger behavioural responses in the FXS group but not in the CdLS group. Taken together, the results indicate that aspects of phenotypes drive the precise manifestation of anxiety/stress in the background of high physiological arousal.

The finding that physical avoidance and proximity seeking were the primary behavioural indicators of anxiety/stress in people with CdLS and FXS is in line with conceptual and theoretical frameworks of anxiety in NT children and adults (Arnaudova et al., 2017; Esbjørn et al., 2012). Operant conditioning models posit that avoidance is learned through

Table 4
Correlation matrix for Anx-DOS behavioural codes and salivary cortisol for the neurotypical (NT), fragile X syndrome (FXS) and Cornelia de Lange syndrome (CdLS) groups.

		Salivary Cortisol Baseline			Post-Anx-DOS			Reactivity		
		NT	FXS	CdLS	NT	FXS	CdLS	NT	FXS	CdLS
Behavioural Code	Facial Fear	**−.627**	.361	−.197	−.014	.224	−.267	**.661**	.155	−.160
		.003	.099	.344	.953	.317	.242	**.002**	.491	.501
	Postural Fear	−.333	−.083	**−.410**	.285	.164	−.155	.412	.283	.381
		.151	.715	**.042**	.224	.465	.501	.080	.202	.097
	Verbal Fear	−.232	**−.449**	−.186	.177	.175	−.350	.444	.397	−.125
		.325	**.036**	.374	.454	.435	.120	.057	.067	.601
	Physical Avoidance	−.249	−.275	−.197	.219	−.008	−.312	.365	.181	−.388
		.305	.216	.344	.368	.971	.169	.137	.420	.091
	Exaggerated Startle	−.187	−.321	−.076	−.103	−.222	.081	.224	−.177	−.235
		.442	.145	.718	.675	.320	.726	.372	.430	.318
	Separation Distress	−.083	**.511**	.103	−.186	.205	.000	−.091	−.158	−.219
		.736	**.015**	.624	.445	.361	1.000	.720	.483	.354
	Proximity Seeking	−.306	−.243	−.090	−.200	−.263	−.212	.283	−.167	−.133
		.202	.275	.669	.411	.238	.356	.255	.459	.575

negative reinforcement as it prevents an anxiety-inducing stimulus from occurring or reduces the potential threat of the stimulus. As such, avoidance is a central feature of multiple anxiety theories (see Hofmann and Hay, 2018 for a review) and is considered a maintaining factor of anxiety (Krypotos et al., 2015). Similarly, proximity-seeking to a caregiver, conceptualised as a safety behaviour in cognitive-behaviour models of anxiety (Blakey and Abramowitz, 2016), and rooted in attachment theory, has long been considered a goal-directed action to alleviate distress (Bowlby, 1969). Interestingly, in the present study, physical avoidance and proximity-seeking were prominent in differentiating an NT group from two highly anxious groups whereas overt behavioural responses (e.g. separation distress, postural fear, facial fear) did not differ between groups. This contrasts with existing literature noting externalising behaviour as a presentation of anxiety (Green et al., 2015). Together this may indicate the emergence of externalising behaviour when a person is *unable* to avoid an anxiety-inducing situation. By describing the most prominent features of anxiety/stress response and where the largest differences from typical development lie (physical avoidance and proximity-seeking), we can move towards a clinical recommendation that new diagnostic screening tools highlight these behaviours.

Interestingly, very few cross-syndrome differences in behavioural responses emerged when the FXS and CdLS groups were compared directly. The only difference was stronger facial fear in the CdLS group (and NT group) compared to the FXS group, which is in line with previous findings of blunted facial fear in FXS (Tonnsen et al., 2017). Cross-syndrome differences were more apparent in the associations between anxiety and demographic and clinical characteristics. Stronger behavioural anxiety/stress responses were associated with younger chronological age and poorer adaptive behaviour in CdLS but not in FXS. In addition, stronger anxiety/stress responses were associated with heightened repetitive language in FXS. This is similar to that seen in idiopathic autism where heightened repetitive behaviour in anxious autistic individuals is seen as a coping mechanism offering increased control of a situation (Rodgers et al., 2012). Conversely, no associations between behavioural responses of anxiety/stress and autistic characteristics were reported in the CdLS group. Given that these groups were comparable on age and ability, the differences in correlates of anxiety/stress point to unique syndrome-sensitive associations between anxiety/stress and autism, likely related to different profiles of autistic characteristics in these groups (Bozhilova et al., 2023). This is crucial to dissect further given the diagnostic challenges in the context of behavioural overlap.

Salivary cortisol was elevated in participants with FXS and CdLS compared to NT children at both baseline and following administration of the Anx-DOS. This contributes to an extensive body of literature pointing to physiological hyperarousal in FXS (see Klusek et al., 2015 for a review), and is the first study to indicate the same in CdLS. In line with existing research, the current study indicates hyperarousal across both baseline and anxiety-inducing conditions contributing to the hypothesis that physiological arousal is linked to anxiety in a pervasive rather than context-dependant way. The current study extends existing research on direct associations between cortisol specific behavioural presentations (Hall et al., 2006, 2009; Hessl et al., 2002; Matherly et al., 2018; Roberts et al., 2009) in FXS by identifying an association between heightened baseline cortisol with reduced verbal fear and elevated separation distress. In CdLS, heightened baseline cortisol was associated with reduced postural fear. Associations between elevated cortisol and blunted behavioural response may indicate a propensity towards adopting a 'freeze' response to stressors. Primate studies indicate high basal cortisol levels being predictive of freeze responses in the presence of immediate threat (Kalin et al., 1998) and human studies indicate heightened trait anxiety as predictive of tonic immobility during a stress challenge (Schmidt et al., 2008).

The association between chronological age and salivary cortisol in CdLS is interesting. First, it indicates a need to interpret CdLS vs. NT group differences in cortisol with caution given the differences in chronological age. Second, it contributes to an extensive body of work on age-related changes in CdLS, which are likely underpinned by a combination of biological, environmental, and cognitive causal factors (Groves et al., 2021). Here, a link between increasing age with elevated salivary cortisol in CdLS, but the absence of an association with behavioural indicators of anxiety/stress, points to a dissociation of behavioural and physiological indicators. This may be indicative of an age-dependant increase in physiological arousal that is specific to trait anxiety but not state or context-dependant anxiety. Higher trait anxiety is associated with lower state anxiety, evidenced through autonomic arousal, in the general population and autistic populations (Endler and Kocovski, 2001; Mertens et al., 2017). The absence of associations in FXS point to differential relationships between these groups and indicate that these effects cannot be explained by IQ/overall ability level but rather by unique downstream effects of genetic aetiology.

The current study is the first to report the administration and results of the Anx-DOS, an observational measure designed to press for behavioural responses of anxiety, in individuals with genetic syndromes and intellectual disability. Whilst high vigilance and caution should be used when administering experimental tasks designed to evoke anxiety/stress responses, we report no adverse effects, no requests for early terminations and a positive response from participants and their families. Many found the tasks interesting and surprising but not a negative experience. We have identified behaviours that are indicative of anxiety/stress in individuals unable to self-report which is critical

information for clinicians assessing and supporting anxious individuals with intellectual disability.

The results of the current study should be considered in light of limitations that are commonplace in research with people with intellectual disability and rare genetic syndromes. To improve similarity of group composition, matched samples were created to generate genetic syndrome groups that were comparable on important characteristics. Participants with genetic syndromes were, however, not matched on all characteristics to NT comparison groups due to level of intellectual ability meaning that groups could not be matched on both ability and age. We opted for groups comparable on age given the association between ability and anxiety (Green et al., 2015). Whilst associations between age and anxiety are inevitable, the current study used a measure designed for young NT children and so data collection of an adult sample to match for age with genetic syndrome groups would not have been appropriate. Additionally, the use of the non-invasive salivary biomarker cortisol, which is known to be elevated with anxiety and reflective of systemic levels, is a marker of hypothalamo-pituitary adrenal (HPA) axis stress. However, given the lack of sensitivity to additional increases following novel stimuli, it may be prudent to examine activation of the sympathetic nervous system (SNS) in future studies using heart rate variability or a similar non-invasive measure. In addition, examining both diurnal and acute cortisol levels in the same sample, particularly in those with CdLS given limited research on physiological arousal, is an important next step to identify more clearly putative risk markers for the maladaptive physiological stress response.

Future research should consider additional risk markers for anxiety that are common across both FXS and CdLS, such as sleep disorders (Agar et al., 2021) and self-injurious behaviour (Arron et al., 2011), and explore the bidirectional associations these have with anxiety. In addition, cognitive domains have been explored in FXS and CdLS with a specific focus on how they relate to social anxiety and behaviour (Crawford, 2023; Nelson et al., 2017). This could be extended to investigate associations between cognition and physiological and behavioural responses to more generalised anxiety/stress. Finally, exploring the association between behavioural responses to anxiety presses with a quality of life assessment would shed light on the impact of these responses in a wider context.

To conclude, the results from the current study can inform the development of multi-level theoretical models explaining the heightened prevalence of anxiety or distress in genetic syndromes associated with intellectual disability. First, heightened physiological arousal provides a background for biological predisposition to rapid learning of associations between stimuli and responses driving a two-factor (operant) conditioning of fear of evolutionary threatening stimuli (biological preparedness; Seligman, 1971). Diverse behavioural responses between different genetic syndrome groups are dependant on syndrome characteristics and interactions with a given phenotype (Woodcock et al., 2009). Overall, this study furthers understanding of the behavioural and physiological presentation of anxiety/stress in individuals unable to self-report which is useful for clinical guidance. In addition, it progresses theoretical developments regarding the emergence and maintenance of anxiety at the intersection of autism, a condition with overlapping behavioural features.

Declaration of Competing Interest

None

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Supplementary materials

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