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ORIGINAL PAPER

A Behavioural Assessment of Social Anxiety and Social Motivation in Fragile X, Cornelia de Lange and Rubinstein-Taybi Syndromes

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Abstract

Unique socio-behavioural phenotypes are reported for individuals with different neurodevelopmental disorders. Here, the effects of adult familiarity and nature of interaction on social anxiety and social motivation were investigated in individuals with fragile X (FXS; n = 20), Cornelia de Lange (CdLS; n = 20) and Rubinstein-Taybi (RTS; n = 20) syndromes, compared to individuals with Down syndrome (DS; n = 20). The Social Anxiety and Motivation Rating Scale was employed whilst participants completed four social tasks, each administered separately by a familiar adult, and also by an unfamiliar adult. Compared to participants with DS, those with FXS and RTS exhibited high levels of social anxiety but similar levels of social motivation. Participants with CdLS showed heightened social anxiety and reduced social motivation only during interactions with an unfamiliar adult when active participation was voluntary.

Keywords Social anxiety · social motivation · Cornelia de Lange syndrome · Rubinstein-Taybi syndrome · Fragile X syndrome · Down syndrome

There has been growing interest in the delineation of social phenotypes with literature highlighting divergent profiles of sociability in children and adults with different neurodevelopmental disorders. Most commonly reported in the literature are the social impairments displayed by individuals with autism spectrum disorder (ASD). Often considered at the opposite end of the sociability continuum (Tager-Flusberg et al. 2006), Williams syndrome is associated with hyper-sociability, a strong drive to interact with others, and overfriendliness with strangers (Jones et al. 2000). The behavioural phenotype of Angelman syndrome also includes heightened levels of sociability and smiling in social situations (Oliver et al. 2007). Whilst the study of behavioural phenotypes highlights the link between genetic disorders and behaviours or characteristics, evidence of within syndrome variability alludes to the importance of considering the role of the environment in the presentation of behaviours (Tunnicliffe and Oliver 2011; Langthorne et al. 2013; Oliver et al. 2013). For example, systematic manipulation of aspects of a social interaction has been shown to govern levels of laughing and smiling behaviour in children with Angelman syndrome (Horsler and Oliver 2006).

Specific profiles of social functioning have been reported in children and adults with fragile X (FXS), Cornelia de Lange (CdLS), and Rubinstein-Taybi (RTS) syndromes, which are characterised by a complex profile of social behaviours incorporating both social anxiety and social motivation. To date, there are few studies investigating the parameters of social interactions that drive these behavioural characteristics in each of these syndrome groups, and little is known about the interplay between social anxiety and social motivation.

FXS is the most common cause of inherited intellectual disability (Crawford et al. 2001) affecting approximately 1 in

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2500–5000 males and 1 in 4000–6000 females (Coffee et al. 2009; Hirst et al. 1993). FXS is caused by abnormalities in the *FMR1* gene located at Xq27.3 resulting in excessive cytosine-guanine-guanine (CGG) repeats. Females with FXS are often less severely affected than males due to having a second, normally functioning, X chromosome (Hagerman and Hagerman 2002). Clinically significant features of social anxiety are present in approximately 60% of participants (Cordeiro et al. 2011), and the severity of social anxiety symptomatology in FXS is comparable to individuals in the general population who have received a clinical diagnosis of anxiety (Crawford et al. 2017). Social avoidance is also elevated in this population and, interestingly, a "warm up" effect is evident whereby males with FXS demonstrate reduced avoidance over the course of an interaction (Roberts et al. 2007, 2009, 2019). Despite heightened social anxiety and avoidance, individuals with FXS are also reported to show behaviours suggestive of their willingness or desire to interact with others. The 'fragile X handshake' describes how individuals with FXS display a wish to initiate social interaction by approaching a social partner and offering a handshake whilst simultaneously avoiding eye contact (Cornish et al. 2008).

CdLS affects approximately 1 in 40,000 live births (Beck 1976) and is primarily caused by a deletion in the NIPBL gene located on chromosome 5 (Gillis et al. 2004; Krantz et al. 2004; Miyake et al. 2005). Fewer cases are caused by mutations on the SMC3 gene on chromosome 10 (Deardorff et al. 2007), the SMC1A gene (Musio et al. 2006), the RAD21 gene (Minor et al. 2014), and the HDAC8 gene (Deardorff et al. 2012). The social impairment in CdLS has been characterised by social communication impairments, selective mutism, social anxiety, and shyness (Goodban 1993; Moss et al. 2008; Richards et al. 2009; Moss et al. 2016), alongside behavioural indicators of intact social motivation including appropriate eye contact (Moss et al. 2013b; Nelson et al. 2017). Social anxiety has been reported to occur particularly during times of high social demand, and when verbalisation is required (Richards et al. 2009; Nelson et al. 2017). Interestingly, individuals with CdLS scored lower on an informant report measure of social anxiety than individuals without CdLS who have a diagnosis of anxiety (Crawford et al. 2017). This indicates that social anxiety is not generally heightened in this group but, rather, is a product of particular social demands.

RTS affects approximately one in 100,000–125,000 live births (Hennekam et al. 1990) and is caused by mutations within chromosome 16p13.3 (Lacombe et al. 1992), the CBP gene and in the E1A Binding Protein, P300, located at 22q13.2 (Coupry et al. 2002; Hennekam 2006; Kalkhoven et al. 2003; Petrif et al. 1995; Roelfsema et al. 2005). Research suggests that individuals with RTS are sociable. For example, a recent parental-report study demonstrated a level of sociability in individuals with RTS that was comparable to that of individuals with Angelman and Down syndromes, two neurodevelopmental disorders noted for their comparatively heightened sociability (Moss et al. 2016). This corroborates reports of children with RTS displaying higher levels of social interest and social contact compared to children matched for chronological age, sex and developmental level (Galéra et al. 2009). Some studies of adults with RTS do, however, highlight difficulties with social interactions. For example, difficulty relating to peers has been reported in 47% of adults with RTS (Stevens et al. 2011). In addition, parental reports of adolescents aged over 14 years with RTS indicated clinically significant levels of social problems (Yagihashi et al. 2012).

Research studies manipulating social interactions offer valuable insight into the role of the environment on social behaviours in individuals with genetic syndromes. Hall and colleagues reported more social escape behaviours in individuals with FXS during an interview and singing task compared to an oral reading and silent reading task (Hall et al. 2006). During the same social tasks, Hessl et al. reported higher levels of behaviours indicative of social anxiety in individuals with FXS compared to their non-affected siblings (Hessl et al. 2006). However, as these studies did not incorporate well-matched comparison groups, it is difficult to determine whether these behaviours were FXS-specific or more broadly associated with intellectual impairment. In addition, the social tasks in both studies were administered by unfamiliar adults only. Evidence suggests that the familiarity of a social partner may impact on social anxiety. Specifically, individuals with FXS, CdLS and RTS have been rated as significantly more sociable during interactions with a familiar versus unfamiliar person (Moss et al. 2016). In addition, males with FXS demonstrate reduced social avoidance over the time course of an interaction as a social partner becomes more familiar (Roberts et al. 2007, 2009, 2019). This extends to other populations as children self-report higher symptoms of social anxiety in situations with unfamiliar versus familiar people (Beidel et al. 1995). The effect that familiarity of social partner has on social anxiety and social motivation is crucial to understand, particularly for educational and clinical services whereby building a rapport with an individual prior to placing demands on them may be of critical importance.

Tools typically used to assess social anxiety include psychiatric interviews, clinician rating scales and self and proxy report measures (Bernstein et al. 1996). Therefore, the diagnosis of anxiety disorders in individuals with intellectual disability can be particularly challenging due to the reliance on self-report. In addition, proxy report measures often require informants to access the individual's internal states, which is difficult for caregivers of individuals with limited communication. Rating scales have

provided a useful tool for investigating social behaviours. For example, the Social Performance Rating Scale (SPRS) was designed to assess the behaviours and social skills of people with social phobia and could be applied to conversations between two people (Fydrich et al. 1998). Assessment of the psychometric properties of the SPRS yielded excellent inter-rater reliability and evidence for convergent, divergent and criterion-related validity. In addition, the Child Sociability Rating Scale (CSRS; Moss et al. 2013a) demonstrates robust reliability and convergent validity, and was designed to assess social behaviour with a particular focus on social enjoyment and social motivation in individuals with intellectual disability.

Here, we report the development of a novel rating scale based on the SPRS (Fydrich et al. 1998) and CSRS (Moss et al. 2013a), the Social Anxiety and Motivation Rating Scale (SAMS), employed to investigate behaviours indicative of social anxiety and social motivation in individuals with FXS, CdLS and RTS during the administration of Social Tasks; four naturalistic social interactions, which vary in the nature of social demand and were administered separately by an unfamiliar adult and also by a familiar adult. Data from these syndrome groups will be compared to data from individuals with Down syndrome (DS) due to the similar levels of intellectual ability, with most individuals meeting criteria for mild to severe intellectual disability (Chapman and Hesketh 2000), and a well-delineated social phenotype comprising relative strengths in social skills (Gibbs and Thorpe 1983; Wishart and Johnston 1990; Dykens 2007; Fidler et al. 2009). As such, social anxiety is unlikely to be elevated in individuals with DS who do not have comorbid ASD, and social motivation appears typical or a relative strength.

The aims of the current study are to:

1. Develop a novel rating scale designed to assess behaviours indicative of social anxiety and social motivation in individuals with intellectual disability, and to assess the psychometric properties. The Social Anxiety and Motivation Rating Scale was developed to achieve this aim (see "Measures" section).
2. Investigate the effect of familiarity and type of social interaction on social anxiety in individuals with FXS, CdLS and RTS, compared to those with DS. The relationship between participant characteristics (age, autism symptomatology and ability level) and social anxiety will also be explored.
3. Investigate the effect of familiarity and type of social interaction on social motivation in individuals with FXS, CdLS and RTS, compared to those with DS. The relationship between participant characteristics (age, autism symptomatology and ability level) and social motivation will also be explored.
4. Investigate the relationship between social anxiety and social motivation in individuals with FXS, CdLS, RTS and DS.

It was hypothesised that participants with FXS, CdLS and RTS would demonstrate heightened social anxiety during interactions with unfamiliar versus familiar partners (based on Moss et al. 2016). In addition, it was hypothesised that participants with FXS would display anxiety-related behaviours during all social conditions, whereas participants with CdLS would display social anxiety that is mediated by the nature of the Social Tasks presented. Due to the naturalistic conditions in the Social Tasks, the hypothesis for the FXS group was based on literature characterising generally elevated social anxiety during typical daily interactions (Cordeiro et al. 2011; Crawford et al. 2017). A hypothesis was not generated for the RTS group due to the lack of existing literature exploring social anxiety. It was hypothesised that participants with FXS, CdLS and RTS would demonstrate elevated social motivation during conditions administered by a familiar versus unfamiliar partner. No hypothesis was generated for (a) how the type of social interaction would mediate social motivation (Aim 3), and (b) the relationship between social anxiety and social motivation in each participant group (Aim 4), due to limited literature in these areas.

Methods

Participants and Recruitment

Twenty individuals with FXS (0 female, $M_{age} = 23.68$, $SD = 7.65$) and 20 individuals with RTS (10 female, $M_{age} = 25.52$, $SD = 9.72$) were included in the analyses. In addition, 20 individuals with CdLS (10 female, $M_{age} = 22.62$, $SD = 9.11$) and 20 individuals with DS (7 female, $M_{age} = 23.67$, $SD = 5.87$) whose video footage during the Social Tasks was collected for a different study were included in the analyses (Nelson et al. 2017). Participants with FXS and RTS were recruited through the participant database held at the Cerebra Centre for Neurodevelopmental Disorders, University of Birmingham, and had agreed to be contacted for future research studies. As reported in a previous study (Nelson et al. 2017), participants with CdLS and DS were also recruited from the Cerebra Centre for Neurodevelopmental Disorders participant database and Cornelia de Lange Foundation UK and Ireland, the family support group. This study was reviewed and approved by the Science, Technology, Engineering and Mathematics Ethical Review Committee at the University of Birmingham. All participants aged 16 years and above, and parents of children under 16 years of age, provided written consent before taking part in the study.

Participants with FXS and RTS were included in the study if they met the following criteria: a confirmed diagnosis from a professional (paediatrician or clinical geneticist), a self-help score on the Wessex Scale (Kushlick et al. 1973) of 6 or above, were mobile (could walk unaided), were verbal (could speak more than 30 words), were aged 11 years or above, could provide informed consent if aged 16 or above, and lived within 3 h of the research base. Participants with CdLS and DS from the previous study conducted by Nelson et al. (2017) were selected for the current study based on being comparable on chronological age (CA), receptive language and adaptive behaviour, at a group level, to participants with FXS and RTS. To achieve this, data from five participants with CdLS that were originally reported in Nelson et al. (2017) were excluded from the present study.

Table 1 shows that participants were comparable on receptive language age equivalence, adaptive behaviour, and CA. Due to the documented sex differences in FXS, all participants with FXS are male and therefore do not match other participant groups on sex.

Measures

A demographic questionnaire was included to provide information about the participant's sex, date of birth, and diagnosis including the specific diagnosis given, who gave the diagnosis, and when. The British Picture Vocabulary Scale-II (BPVS; Dunn et al. 1997) was used to assess receptive language abilities, and the Vineland Adaptive Behavior Scale (VABS; Sparrow et al. 2005) was used to assess adaptive behaviour skills. Parents of participants completed the Social Communication Questionnaire to provide an indicator of their child's autism symptomatology (SCQ; Rutter et al. 2003).

Social Tasks

Behaviours indicative of social anxiety and social motivation were examined using the Social Anxiety and Motivation Rating Scale (described below) to code behaviours exhibited during the Social Tasks. The conditions of the Social Tasks were designed by Nelson et al. (2017) to assess behaviours indicative of social anxiety across four different social conditions in which the nature of social demand is manipulated systematically. The Social Tasks consist of one control condition (*No Social Interaction*) and three experimental conditions (*Voluntary Social Interaction*, *Required Social Interaction* and *Performance*). Each condition is administered separately with a researcher that is unfamiliar to the participant and with an adult that is familiar to the participant (someone who sees the participant at least three times a week). The term 'experimenter' will be used to refer to the interacting adult, whether they are familiar or unfamiliar to the participant. All conditions were administered on the same day with the experimenter and participant sat at a table. The order in which participants completed the conditions of the Social Tasks was counterbalanced. The four social conditions are outlined below:

1. The *No Social Interaction* condition was adapted from the break condition in modules 3 and 4 of the Autism Diagnostic Observation Schedule (ADOS; Lord et al. 1999). This condition requires the participant to independently engage with the materials provided in the ADOS testing kit (pens, paper, spinning top, magazines, radio and puzzles) whilst the experimenter makes notes or reads a newspaper for approximately 4 min. During this condition, the experimenter is in close proximity to the participant, to control for experimenter presence, but does not engage with the participant. If the participant

Table 1 Participant characteristics for each participant group

	Fragile X syndrome	Rubinstein-Taybi syndrome	Cornelia de Lange syndrome	Down syndrome	*p*
Chronological age mean in years (SD)	23.68 (7.65) (n = 20)	25.52 (9.72) (n = 20)	23.67 (9.11) (n = 20)	24.76 (5.87) (n = 20)	.87
Receptive language age equivalence mean in months (SD)	100.25 (35.71) (n = 20)	75.11 (32.38) (n = 19*)	87.85 (20.76) (n = 20)	82.75 (31.44) (n = 20)	.08
Adaptive behavior composite score mean (SD)	46.45 (16.32) (n = 20)	41.65 (15.70) (n = 20)	52.45 (15.93) (n = 20)	51.33 (18.68) (n = 15**)	.17
Social communication questionnaire total score mean (SD)	18.15 (6.47) (n = 20)	17.53 (7.22) (n = 16***)	16.36 (6.42) (n = 16***)	8.33 (6.70) (n = 16***)	<.001

*Receptive language age equivalence could not be calculated for one participant with RTS due to non-completion of the BPVS-II

**The Adaptive Behavior Composite score could not be calculated for five participants with DS due to these data not being available in Nelson et al. (2017)

***Parents of four participants with RTS did not complete the SCQ. These data were also not available in Nelson et al. (2017) for four participants with CdLS and four participants with DS

initiates interaction with the experimenter, they respond briefly but positively and encourage the participant to continue engaging with the materials.

2. During the *Voluntary Social Interaction* condition, the experimenter shows the participant twenty holiday photographs of objects, buildings, landscapes and animals. The experimenter makes a predetermined comment on alternate photographs. Example comments include: "the weather was terrible and we had to wait in the airport for ages" [when shown a photo of an airport], and "this is the hotel we stayed in, it was amazing" [when shown a photo of a hotel building]. The order in which the photographs are shown, and the comments on the photographs, are the same for each participant. There are two sets of holiday photographs, one for the familiar experimenter to use and one for the unfamiliar experimenter to use. This is described as a *voluntary* social interaction as there is no requirement for the participant to respond or initiate an interaction with the experimenter, but the opportunity to do so, if they wish, is present. The expectation to interact is, therefore, an implicit one. There is no time limit for this condition.
3. The *Required Social Interaction* condition requires the experimenter and participant to have a conversation for approximately 4 min. This is described as a *required* social interaction because the participant is expected to answer the open and closed ended questions asked by the experimenter. To ensure that the *Required Social Interaction* condition reflected a naturalistic conversation, there were no specific prompts. However, examiners tended to ask participants questions regarding hobbies, siblings, pets, school (if age appropriate), specific interests and favourite television shows. This condition also gives participants the opportunity to initiate interactions by asking the experimenter questions if they so wish.
4. The *Performance* condition is adapted from the cartoons social press administered in modules 3 and 4 of the ADOS. This condition requires the experimenter to tell the participant a story from six cartoon cards provided in the ADOS testing kit. The participant is then asked to stand up and re-tell the story. For the purpose of the Social Tasks, this is conducted with two different cartoon stories. There is no time limit to this condition.

Procedure

Following the consent procedure, a research visit to the participant's home or school was scheduled. The Social Tasks were conducted during this research visit in a quiet room. Parents/primary caregivers completed the VABS either in person or via telephone following the research visit. Participants completed the BPVS either during the research visit or during a separate visit to the research base shortly before the visit to the participant's home or school.

The Social Anxiety and Motivation Rating Scale

The Social Anxiety and Motivation Rating Scale (SAMS; Table 2) was developed to assess behavioural indicators of social anxiety and social motivation in children and adults during their involvement in a range of social situations. For the present study, the SAMS was used to code behaviours observed from video footage of the Social Tasks. However the SAMS could be used in any naturalistic social situation. The SAMS includes ten items (six items in the social anxiety subscale, four items in the social motivation subscale), each rated on a five-point Likert Scale. The items in the social anxiety subscale were selected based on the SPRS and previous literature that has investigated behaviours indicative of social anxiety in typical development and people with genetic syndromes (Lesniak-Karpiak et al. 2003; Fydrich et al. 1998; Hessl et al. 2006; Hall et al. 2006). All behaviours were operationally defined in the rating scale. The behaviours included to assess social motivation were adapted from the behaviours indicative of social motivation in the CSRS (Moss et al. 2013a).

Each item yields a score from 0 to 4 with a higher score indicating higher levels of social anxiety and social motivation. The score for the Social Anxiety and Social Motivation subscales is calculated from the mean score of all items within each subscale. Therefore, the maximum possible score for each subscale is four. The following items cannot be scored for the *No Social Interaction* conditions with a familiar and unfamiliar experimenter: gaze, vocal length, time to first utterance, avoidance of social interaction, spontaneous positive affect, and social responsiveness. This is because a lack of these behaviours in the *No Social Interaction* conditions would not be indicative of social anxiety or motivation. For example, vocal length cannot be scored in the control condition as a lack of vocalisation would not indicate social anxiety, rather it would indicate adherence to the task instructions. Minimal training, beyond experience of behavioural coding, is required to score the SAMS.

Intraclass correlation coefficients were used to determine subscale and item level inter-rater reliability for 20% of participants in each participant group across all conditions. Intraclass correlation estimates were based on a mean rating ($k = 2$), absolute-agreement, two-way random effects model. For the present study, one item (negative emotional affect) was excluded from reliability analyses due to low frequency of occurrence. Subscale coefficients were .82 and .93 for social anxiety and social motivation, respectively, indicating excellent reliability (Fleiss 1981). The item level coefficients ranged from .64 to .90, indicating good to excellent reliability (Fleiss 1981). Table 3

Table 2 The social anxiety and motivation rating scale

Social anxiety subscale	4	3	2	1	0
Gaze	*Very poor* Participant completely avoids looking at adult or stares continuously	*Poor* Participant avoids eye contact (or stares) for majority of time	*Fair* Participant frequently avoids eye contact (or stares)	*Good* Participant occasionally avoids eye contact or tends to look too much (stares) while adult is speaking or during shifts of conversation	*Very good* Participant keeps eye contact during the conversation, does not stare; shifts focus during pauses and conversation
Vocal length	*Very poor* Does not speak; or monosyllabic ('hmmm', 'yeah', 'OK') speech turns; or responses so long that adult must interrupt or cannot utter reply	*Poor* Participant makes mostly short statements with very long pauses; or speaks in long phrases that monopolize the conversation	*Fair* Participant mostly speaks one sentence at a time with occasional long pauses between sentences; or s/he tends to talk excessively (or tangentially) most of the time but allows some responses from adult	*Good* Participant mostly speaks in statements of one or two sentences without any major pauses, but there are other occasions where speech is short or excessive or tangential	*Very good* At most times, participant's utterances are two or more sentences long. Participant acknowledges partner's remarks without taking over and monopolizing the conversation
Time to first utterance	*Very poor* Participant does not produce an utterance when it is socially appropriate to do so	*Poor* Participant occasionally produces an utterance following long and awkward pauses from when it is socially appropriate to do so	*Fair* Participant often responds to adult following moderate pauses from when it is socially appropriate to do so	*Good* Participant is responsive to adult following mostly brief but comfortable pauses from when it is socially appropriate to do so	*Very good* Participant is responsive to adult each time it is socially appropriate to do so
Avoidance of social interaction Avoidance includes aversion to gaze or touch, refusing to talk, turning back on interacting adult, covering face with hands or object, or removing self from proximity of interacting adult.	*Very high* Participant demonstrates continuous avoidance of social interaction. S/he leaves the room or fervently attempts to flee the situation	*High* Participant frequently attempts to avoid social interaction. S/he does not make serious attempts at fleeing the situation	*Moderate* Participant cooperates for the most part. S/he only shows mild attempts to avoid about half of the attempts made to socially interact	*Low* Participant demonstrates occasional, brief instances of avoiding social interaction	*Very low* Participant does not avoid social interaction and cooperates fully

Table 2 (continued)

Social anxiety subscale	4	3	2	1	0
Discomfort Rigidity: part or all of the body is held unusually stiff or motionless for more than 10 s (examples: clenched jaw, arms clasped tightly around body, clenched fists, interlocked fingers) Fidgeting: non-stereotyped movement of body or part of body	*Very high* Complete rigidity of arms, legs or whole body. Constant leg movements or fidgeting with hands, hair or clothing. Extremely stiff face or constant facial tics. Frequent nervous throat clearing, swallowing, or stuttering. Frequent inappropriate giggling or laughing. Look of extreme discomfort and desire to flee situation shown by 2 or more breaks in social tasks. Participant does not pay attention to the social tasks most of the time	*High* Rigidity or fidgeting for majority of time. Difficulty sitting still is somewhat disruptive to conversation. Stiff face or frequent facial tics. Some nervous throat clearing or swallowing. Some inappropriate giggling or laughing. Participant shows signs of discomfort by frequently looking around. There is no more than 1 break in the social tasks	*Moderate* No rigidity. Slight movement of legs, fidgeting, throat clearing, or swallowing. Participant shows only brief periods of discomfort. Focuses on the social tasks most of the time. There are no interruptions in the social tasks	*Low* No rigidity, nervous throat clearing, or swallowing. Minimal fidgeting that is not disruptive to performance. No notable signs of discomfort. Remains focussed on the social tasks throughout the interaction. At times may appear relaxed and at ease (smiling or gesturing)	*Very low* Relaxed body posture and natural body movement. Participant laughs and smiles at appropriate times. S/he shows effective gesturing (to be distinguished from fidgeting). Participant focuses on the social tasks all the time, does not appear at all uncomfortable, but at ease in situation
Negative emotional affect Example: negative facial expressions, vocalisations and/or manner (such as crying and frowning). Participant may appear distressed or angry	*Very high* Affect generally negative throughout and often sustained between expressions of negative affect in response to particular activities	*High* Affect negative most of the time. May cry in response to particular activities for example, but also sometimes sustained between these instances	*Moderate* Affect negative about half of the time. May cry in response to particular activities for example, but affect not sustained between these instances	*Low* Some examples of negative affect but only tentative or occasional	*Very low* No examples of negative affect at any stage
Social motivation subscale	**0**	**1**	**2**	**3**	**4**
Spontaneous positive emotional affect Example: positive facial expressions, vocalisations and/or manner (such as smiling, laughing and/or clapping hands)	*Very low* No spontaneous positive affect at any stage when appropriate. Or spontaneous positive affect only when inappropriate	*Low* Some examples of spontaneous positive affect when appropriate but only tentative or occasional	*Moderate* Spontaneous positive affect about half of the time when appropriate. May consist of brief expressions of positive affect in response to particular activities for example	*High* Spontaneous positive affect most of the time when appropriate. May consist of brief expressions of positive affect in response to particular activities for example	*Very high* Spontaneous positive affect each time it is appropriate
Focus of attention Object focus versus people focus	*Very poor* Focus of the participant's attention either unclear or entirely object focussed. Participant does not attend to or show any interest in other people	*Poor* Focus of participant's attention mostly objects. Some attention paid to other people even if only for monitoring purposes	*Moderate* Focus of participant's attention shared between people and objects	*High* Focus of participant's attention mostly on people. Attention appears to be socially motivated at least some of the time and not simply for purpose of monitoring.	*Very high* Focus of participant's attention almost entirely on people perhaps to an excessive degree. Attention appears to be socially motivated.

Table 2 (continued)

Social motivation subscale	0	1	2	3	4
Social responsiveness Responds: responds to specific behavioural requests, suggestions, questions or their name (if used) Elaboration: when the participant spontaneously builds on what is expected of them	*Very poor* Unresponsive and disinterested. Does not respond. Largely ignores what the adult is doing	*Poor* Unresponsive but some interest. May not respond but attends to what adult is doing (this must be more than a fleeting glance)	*Fair* Interested and occasionally responsive. Responds at least once but interactions are adult led and not reciprocal. Participant mostly attentive to adult.	*Good* Interested and highly responsive. Responds more often than not. Interactions are reciprocal. At least one or two examples of a back and forth exchange of several steps but participant does not elaborate beyond initial adult suggestions (interaction not necessarily verbal)	*Very good* Interested and elaborately responsive. Responds more often than not. More than two examples of back and forth exchanges of several steps. Participant elaborates on initial adult suggestions (interaction not necessarily verbal)
Socially motivated initiation of social interaction Initiation of interaction may be verbal or non-verbal (e.g. turning to the adult, speaking or signing to the adult (not in response), touching the adult to attempt to gain their attention. Behaviour must appear socially motivated e.g. for the purpose of being friendly	*Very low* No clear spontaneous initiation of interaction with adult, which appears to be socially motivated (e.g. for the purpose of being friendly) rather than for personal demands (e.g. giving or showing an object)	*Low* One example of spontaneous initiation of interaction with adult, which appears to be socially motivated (e.g. for the purpose of being friendly) and not merely for personal demands (e.g. giving or showing an object)	*Moderate* Two examples of spontaneous initiation of interaction with adult, which appears to be socially motivated (e.g. for the purpose of being friendly) and not merely for personal demands (e.g. giving or showing an object)	*High* Three examples of spontaneous initiation of interaction with the adult, which appears to be socially motivated (e.g. for the purpose of being friendly) and not merely for personal demands (e.g. giving or showing an object)	*Very high* Four or more examples of spontaneous initiation of interaction with the adult which appear to be socially motivated (e.g. for the purpose of being friendly) and not merely for personal demands (e.g. giving or showing an object)

Table 3 The single measures intraclass correlation coefficients of inter-rater reliability for the social anxiety and motivation rating scale

Social anxiety and motivation rating scale item	Correlation coefficient
Gaze	.68
Vocal length	.81
Time to first utterance	.66
Avoidance of social interaction	.85
Discomfort	.73
Spontaneous positive affect	.90
Focus of attention	.69
Social responsiveness	.64
Socially motivated initiation of interaction	.84
Social anxiety subscale	.82
Social motivation subscale	.93

Table 4 The Spearman coefficients for the social anxiety and motivation rating scale and frequency of observable behaviours

Social anxiety and motivation rating scale item	Spearman coefficient
Gaze (familiar conditions)	.85
Gaze (unfamiliar conditions)	.70
Vocal length (familiar conditions)	.74
Vocal length (unfamiliar conditions)	.81
Spontaneous positive affect (familiar conditions)	.59
Spontaneous positive affect (unfamiliar conditions)	.60

shows the Intraclass correlation coefficients for each item of the SAMS included in the reliability analyses.

The Cronbach's alpha coefficients, used to calculate the internal consistency of the SAMS subscales, were $\alpha = .74$ for the social anxiety subscale and $\alpha = .62$ for the social motivation subscale.

Validity was assessed using Spearman correlations to investigate the relationship between the mean score on items on the SAMS and the frequency of corresponding behaviours that had previously been coded using observational coding for participants with CdLS and DS (Nelson et al. 2017). These items were: gaze, vocal length and spontaneous positive affect. Table 4 shows the correlation coefficients for the items included in this validity analysis and indicate moderate to strong correlations. Convergent validity of the social motivation subscale was assessed using a Spearman correlation between mean social motivation scores during the experimental conditions and scores on the Reciprocal Social Interaction subscale of the SCQ, used to measure autism symptomatology, for all four participant groups combined. This revealed a significant negative correlation between social motivation and autism symptomatology ($r_s\ (64) = -.278$, $p = .024$).

Data Analysis

Data were analysed at subscale level. 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 parametric tests and significant effects were confirmed with the equivalent non-parametric tests. Where there were no meaningful differences between the outcomes of the two types of tests, results from parametric tests are reported. For correlational analyses, Pearson's correlations were used for normally distributed data and Spearman's rank correlations were used for not normally distributed data.

Preliminary analyses were conducted to ensure that scores on the SAMS were evoked by the social demands presented in the experimental conditions of the Social Tasks. To achieve this, paired samples t-tests were conducted separately for each group to compare social anxiety and social motivation ratings between the control condition (*No Social Interaction*) and each of the experimental conditions (*Voluntary Social Interaction, Required Social Interaction, Performance*). All comparisons were significant (all $p \leq .003$) demonstrating that social anxiety and social motivation scores were evoked by the social demands of the experimental conditions. Therefore, all remaining analyses include only the experimental conditions of the Social Tasks.

Analyses of variance (ANOVA), and associated follow-up tests, were conducted to assess the effects of condition, familiarity of experimenter, and syndrome group, on social anxiety and social motivation scores. The alpha level for statistical tests conducted to assess differences between groups or conditions was .05. The alpha level for correlational analyses was .025 to account for multiple comparisons.

Due to a technical issue reported by Nelson et al. (2017), data from one participant with DS were missing for all conditions carried out with a familiar experimenter and data from another participant with DS were missing for the unfamiliar experimenter *Performance* condition. In addition, data from one participant with RTS were missing for the familiar experimenter *Voluntary Social Interaction* condition. In order to avoid these participants being excluded from the ANOVAs reported below, missing data were replaced with group means for all analyses except correlational analyses.

Results

Social Anxiety

Aim 2 was to investigate the effect of familiarity and type of social interaction on social anxiety in individuals with FXS, CdLS and RTS, compared to those with DS. Figure 1 depicts the mean social anxiety scores during interactions

with familiar and unfamiliar experimenters during the control condition and each of the three experimental conditions of the Social Tasks for participants with DS (a), CdLS (b), FXS (c) and RTS (d).

A 3 (condition) × 2 (familiarity of experimenter) × 4 (syndrome group) mixed ANOVA was conducted using the mean social anxiety subscale scores. The ANOVA revealed a main effect of condition (F (2, 152) = 13.086, $p < .001$, $\eta^2 = .147$), a main effect of syndrome group (F (3, 76) = 7.088, $p < .001$, $\eta^2 = .219$), a condition × syndrome group interaction (F (6, 152) = 3.802, $p = .001$, $\eta^2 = .130$), and a three-way interaction between condition, familiarity and syndrome group (F (5, 129) = 2.494, $p = .033$, $\eta^2 = .090$). The three-way interaction indicates that the relationship between familiarity of experimenter and nature of social demand in their effect on social anxiety differed according to syndrome group and consequently is explored using a one-way ANOVA to investigate between-group differences in mean social anxiety levels collapsed across all conditions of the Social Tasks, and four 2 × 3 ANOVAs to investigate the effect of familiarity of experimenter and nature of social interaction on social anxiety for each syndrome group separately. Between-group comparisons were not made for each condition separately in order to reduce the number of analyses conducted.

Between-Groups Comparison

Table 5 presents mean scores of social anxiety. The one-way ANOVA revealed a significant between-groups difference in mean levels of social anxiety (F (3, 79) = 7.088, $p < .001$). Bonferroni post hoc comparisons indicated that this difference was driven by participants with FXS and RTS scoring higher on social anxiety than participants with DS (FXS vs. DS: $p < .001$; RTS vs. DS: $p = .006$).

Down syndrome

The two-way ANOVA revealed a main effect of condition (F (2, 38) = 5.868, $p = .006$, $\eta^2 = .236$). Bonferroni-corrected post hoc comparisons revealed that social anxiety scores were higher in the *Voluntary Social Interaction* condition compared to the *Required Social Interaction* condition ($p = .007$). There were no differences in social anxiety across other conditions, or between conditions administered by a familiar and unfamiliar experimenter.

Cornelia de Lange Syndrome

The two-way ANOVA revealed a main effect of condition (F (2, 33) = 22.726, $p < .001$, $\eta^2 = .545$). Bonferroni-corrected post hoc comparisons revealed that social anxiety scores were highest in the *Voluntary Social Interaction* condition

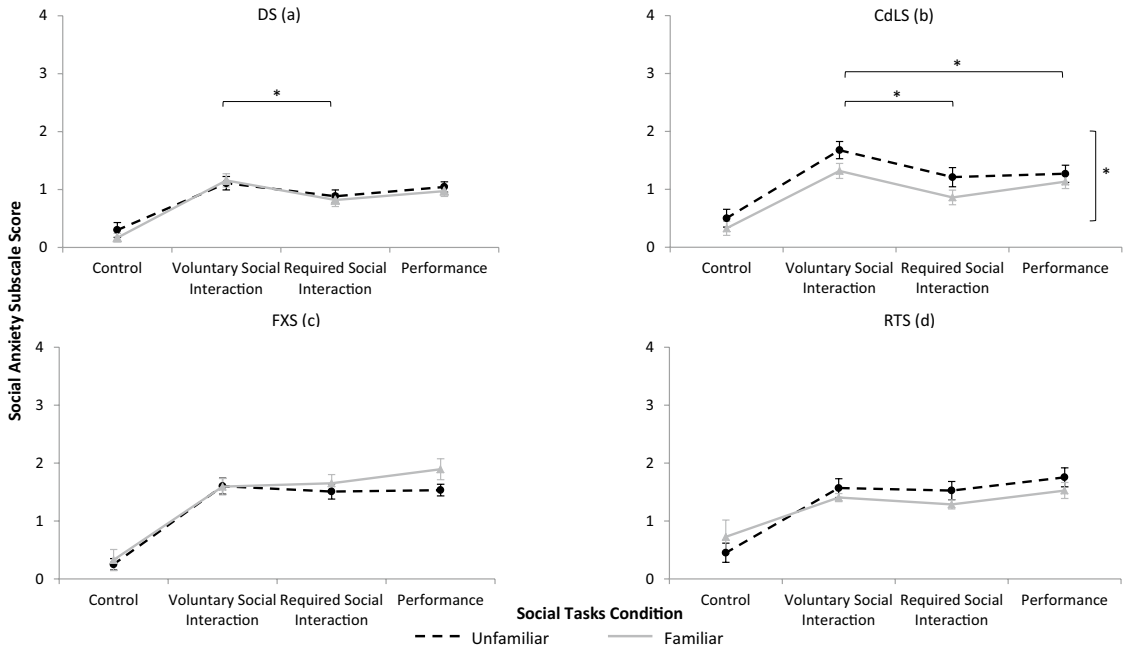

Fig. 1 Mean social anxiety subscale scores for each participant group during each condition of the Social Tasks. Scores for the control condition are included in this figure to highlight the difference in scores between the control and experimental conditions. The control condition was not included in analyses and so indicators of significant differences are not present for this condition

Table 5 Mean social anxiety scores and between-group differences for each experimental condition of the social tasks

Condition	Experimenter	Down syndrome	Cornelia de Lange syndrome	Fragile X syndrome	Rubinstein-Taybi syndrome	Group differences
Voluntary social interaction mean (SD)	Familiar	1.16 (0.51)	1.32 (0.58)	1.59 (0.63)	1.40 (0.31)	NA
	Unfamiliar	1.11 (0.52)	1.68 (0.67)	1.60 (0.62)	1.57 (0.72)	NA
Required social interaction mean (SD)	Familiar	0.82 (0.50)	0.86 (0.56)	1.65 (0.66)	1.28 (0.35)	NA
	Unfamiliar	0.88 (0.48)	1.21 (0.74)	1.51 (0.59)	1.53 (0.70)	NA
Performance mean (SD)	Familiar	0.97 (0.41)	1.13 (0.54)	1.89 (0.81)	1.53 (0.62)	NA
	Unfamiliar	1.04 (0.40)	1.27 (0.67)	1.53 (0.44)	1.75 (0.74)	NA
Total social anxiety mean score (SD)	NA	1.00 (.40)	1.24 (.56)	1.63 (.47)	1.51 (.45)	FXS > DS; RTS > DS

compared to all others ($p < .001$). The ANOVA also revealed a main effect of familiarity (F (1, 19) = 13.767, $p = .001$, $\eta^2 = .420$), which was driven by higher social anxiety scores during interactions with an unfamiliar experimenter compared to a familiar experimenter.

Fragile X Syndrome

The two-way ANOVA revealed no main effect of condition or familiarity, nor a condition × familiarity interaction (all $p > .05$).

Rubinstein-Taybi Syndrome

The two-way ANOVA revealed no main effect of condition or familiarity, nor a condition × familiarity interaction (all $p > .05$).

To summarise, participants with FXS and RTS demonstrated higher levels of social anxiety than those with DS and, for these two groups, social anxiety was not mediated by the nature of the interaction or the familiarity of the social partner. In contrast, these factors did influence social anxiety in participants with CdLS as social anxiety was heightened during interactions with an unfamiliar versus familiar adult and during the *Voluntary Social Interaction* condition compared to other conditions.

Relationship Between Participant Characteristics and Social Anxiety

Included in Aim 2 was to explore the relationship between social anxiety and participant characteristics. Correlations between the mean social anxiety score across the three experimental conditions and participant characteristics (age, adaptive behaviour standard score, autism symptomatology, and receptive language age equivalence in months) were conducted for each participant group separately. The correlational analyses revealed a moderate negative association between social anxiety and adaptive behaviour in the DS group (r_p (11) = −.632, $p = .020$). Analyses also revealed a moderate negative association between social anxiety and CA in the FXS group (r_p (18) = −.606, $p = .005$), and between social anxiety and receptive language age equivalence in the FXS group only (r_p (18) = −.620, $p = .004$). Due to the likely relationship between age and receptive language, a partial correlation was conducted that revealed no association between social anxiety and CA when receptive language age equivalence was controlled for or between social anxiety and receptive language age equivalence when CA was controlled for (p's > .05). The correlation between SCQ total score and social anxiety subscale score was not significant. Therefore, differences in autism symptomatology are unrelated to the social anxiety-related behaviours observed in the current study.

Social Motivation

Aim 3 was to investigate the effect of familiarity and type of social interaction on social motivation in individuals with FXS, CdLS and RTS, compared to those with DS. Figure 2 depicts the mean social motivation subscale scores during interactions with familiar and unfamiliar experimenters during the control condition and each of the three experimental conditions of the Social Tasks for participants with DS (a), CdLS (b), FXS (c) and RTS (d).

A 3 (condition) × 2 (familiarity of experimenter) × 4 (syndrome group) mixed ANOVA was conducted using the mean scores from the social motivation subscale. This revealed a main effect of condition (F (2, 137) = 128.990, $p < .001$, $\eta^2 = .629$), a condition × syndrome interaction (F (5, 137) = 3.820, $p = .002$, $\eta^2 = .131$), a familiarity × syndrome interaction (F (3, 76) = 3.664, $p = .016$, $\eta^2 = .126$), and a three-way condition × familiarity × syndrome interaction (F (5, 144) = 3.949, $p = .001$, $\eta^2 = .135$). The three-way interaction indicated that the familiarity of the experimenter modulates the between-groups difference across conditions on the social motivation subscale. To investigate this interaction, a one-way ANOVA

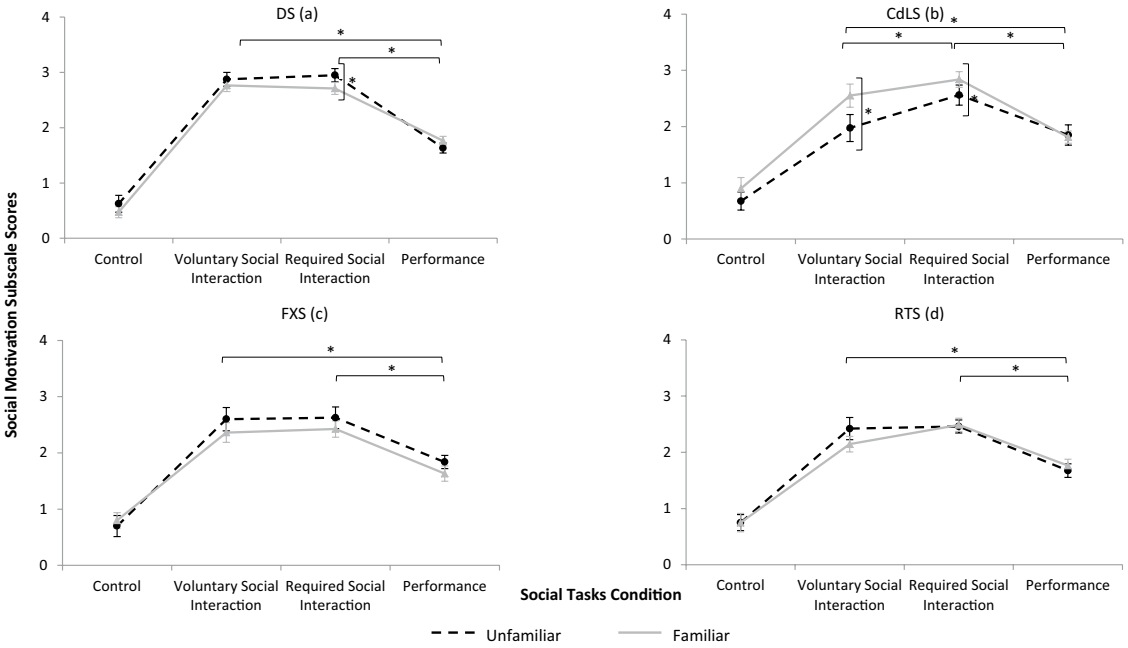

Fig. 2 Mean social motivation subscale scores for each participant group during the Social Tasks. Scores for the control condition are included in this figure to highlight the difference in scores between the control and experimental conditions. The control condition was not included in analyses and so indicators of significant differences are not present for this condition

using mean social motivation scores was used to assess between-group differences across all experimental conditions of the Social Tasks collapsed, and four 3 (condition) × 2 (familiarity of experimenter) ANOVAs were conducted, to assess the effect of condition and familiarity on social motivation for each syndrome group separately.

Between-Groups Comparison

Mean social motivation scores are presented in Table 6. The one-way ANOVA revealed no significant difference between groups for mean social motivation scores (F (3, 79) = 1.160, p = .331).

Down Syndrome

The two-way ANOVA revealed a main effect of condition (F (2, 38) = 67.558, p < .001, η^2 = .780). A condition x familiarity interaction (F (2, 38) = 4.266, p = .021, η^2 = .183) was also revealed. Social motivation scores were lowest in the *Performance* condition compared to the other two conditions for both familiar and unfamiliar interactions (p's < .001). In the *Required Social Interaction* condition, social motivation scores were significantly higher when participants were interacting with an unfamiliar versus a familiar social partner (t (19) = 2.105, p = .049).

Table 6 Mean social motivation scores and between-group comparisons for each experimental condition of the social tasks

Condition	Experimenter	Down syndrome	Cornelia de Lange syndrome	Fragile X syndrome	Rubinstein-Taybi syndrome	Group differences
Voluntary social interaction mean (SD)	Familiar	2.76 (.50)	2.55 (.93)	2.36 (.79)	2.14 (.62)	NA
	Unfamiliar	2.88 (.55)	1.98 (1.07)	2.60 (.93)	2.42 (.86)	NA
Required social interaction mean (SD)	Familiar	2.71 (0.48)	2.84 (.62)	2.43 (.65)	2.49 (.52)	NA
	Unfamiliar	2.95 (.53)	2.56 (.80)	2.63 (.86)	2.46 (.51)	NA
Performance mean (SD)	Familiar	1.76 (.36)	1.81 (.49)	1.63 (.61)	1.77 (.50)	NA
	Unfamiliar	1.63 (.41)	1.85 (.80)	1.84 (.52)	1.68 (.54)	NA
Total social motivation mean score (SD)	NA	2.45 (.31)	2.26 (.58)	2.25 (.62)	2.16 (46)	NS

Cornelia de Lange Syndrome

The two-way ANOVA revealed a main effect of condition (F (2, 38) = 18.795, $p < .001$, $\eta^2 = .497$) and a condition x familiarity interaction (F (2, 38) = 4.740, p = .015, $\eta^2 = .200$). During unfamiliar interactions, social motivation scores were highest in the *Required Social Interaction* condition compared to the other two conditions (p's ≥ .003). During familiar interactions, scores were lowest in the *Performance* condition compared to the other conditions (p's ≥ .001). Social motivation scores were also significantly higher in the *Voluntary Social Interaction* and *Required Social Interaction* conditions when participants were interacting with a familiar versus an unfamiliar social partner (*Voluntary Social Interaction: t* (19) = × 2.475, $p = .023$; *Required Social Interaction: t* (19) = × 2.238, $p = .037$).

Fragile X Syndrome

The two-way ANOVA revealed a main effect of condition (F (2, 38) = 47.406, $p < .001$, $\eta^2 = .704$). Bonferroni-corrected post hoc comparisons revealed that social motivation scores were lowest in the *Performance* condition compared to the other two conditions (p's > .001).

Rubinstein-Taybi Syndrome

The two-way ANOVA revealed a main effect of condition (F (1, 38) = 22.050, $p < .001$, $\eta^2 = .537$). Bonferroni-corrected post hoc comparisons revealed that social motivation scores were lowest in the *Performance* condition compared to the other two conditions (p's < .001).

To summarise, participants with DS, FXS and RTS demonstrated less social motivation in the *Performance* conditions compared to other conditions. Participants with CdLS only demonstrated this pattern of results during conditions with a familiar experimenter. When interacting with an unfamiliar experimenter, participants with CdLS demonstrated higher social motivation during the *Required Social Interaction* compared to the other conditions. In addition, participants with CdLS demonstrated less social motivation with unfamiliar versus familiar social partners. Although there were no between-group differences in mean social motivation levels, the nature of social situation and familiarity of social partner modulated social motivation for participants with CdLS more than other participant groups.

The Relationship between Participant Characteristics and Social Motivation

Included in Aim 3 was to explore the relationship between social motivation and participant characteristics. Correlations between the mean social motivation subscale scores across the three experimental conditions and participant characteristics (age, adaptive behaviour standard score, autism symptomatology, and receptive language age equivalence in months) were conducted for each participant group separately. A strong positive relationship was revealed between social motivation and adaptive behaviour (r_p (11) = .747, p = .003) for the DS group. For the FXS group, moderate positive relationships were revealed between social motivation and CA (r_p (17) = .555, p = .014), and between social motivation and receptive language age equivalence (r_p (17) = .603, p = .006). Due to the likely relationship between age and receptive language ability, partial correlations were conducted for the FXS. These revealed that age was not significantly correlated with social motivation when receptive language was controlled for, and receptive language was not significantly correlated with social motivation when age was controlled for. In summary, social motivation was related to adaptive behaviour ability in participants with DS, and with age and/or receptive language ability in participants with FXS.

The Relationship Between Social Anxiety and Social Motivation

The final aim of this study was to delineate the relationship between social anxiety and social motivation in FXS, CdLS, RTS and DS. To achieve this, correlational analyses were conducted to investigate the relationship between social anxiety and social motivation mean subscale scores, which revealed negative correlations between social anxiety and social motivation for participants with DS, CdLS and FXS (all $p = \leq .016$), but no association between these two constructs for participants with RTS ($p > .025$).

Discussion

In this study, Social Tasks, in which the nature of social interaction and familiarity of the experimenter varied systematically, were presented to children and adults with FXS, CdLS, RTS and DS. Behaviours indicative of social anxiety and social motivation during the Social Tasks were investigated using the SAMS, a rating scale developed for the current study. The internal consistency of the social anxiety and social motivation subscales, and the inter-rater reliability at subscale and item level, were good. In addition, the validity of ratings on a number of items had a moderate to strong correlation with data obtained from behavioural observation coding. This is the first study to: (a) directly compare behavioural indicators of social anxiety and social motivation across FXS, CdLS and RTS, (b) assess the effect of the nature of social interaction and the

familiarity of interacting adult on social anxiety and social motivation in these groups, and (c) contrast the findings with those reported for a chronological and mental age matched group of individuals with DS. Results are consistent with the notion that the nature of social demand, participants' syndrome group, and the familiarity of the experimenter are interacting factors that mediate social anxiety. The results indicated that social anxiety was generally heightened in individuals with FXS and RTS compared to those with DS. In addition, social anxiety was largely unaffected by the type of social interaction and familiarity of experimenter in individuals with DS, FXS and RTS. In contrast, social anxiety in participants with CdLS *was* mediated by the nature of the interaction *and* by the familiarity of the experimenter. Specifically, participants with CdLS demonstrated more anxiety-related behaviours during the *Voluntary Social Interaction* condition compared to all other conditions and during interactions with an unfamiliar experimenter compared to a familiar experimenter. The results also indicated that, although there were no overall between-group differences in mean social motivation levels, the nature of the social interaction and the familiarity of the experimenter influenced social motivation differentially across groups. Taken together, these results suggest that the familiarity of a social partner and the type of social interaction have differential effects on social anxiety and social motivation between syndrome groups.

Interestingly, levels of anxiety-related behaviours in social situations were not related to severity of autism symptomatology. Some of the behaviours indicative of social anxiety, such as reduced eye gaze, may also reflect social communicative impairments. However, the results suggest that the combination of behaviours rated in the SAMS does indeed reflect social anxiety as opposed to autism symptomatology, and that these two constructs are unlikely to be related to one another in FXS, CdLS and RTS. In addition, although the first three items of the SAMS (eye gaze, vocal length, time to first utterance) on their own may be indicative of a lack of social interest, as reported in ASD, they may also capture a 'shut down' response to anxiety. This is compared to the final three items (social avoidance, discomfort, negative emotional affect), which describe an overt distress response to anxiety. Symptoms of anxiety that include overt distress responses (e.g. crying, oppositional defiant disorder) are more likely to be observed in younger children, whereas a 'shut-down' response (e.g. withdrawal, shyness) may be seen in older children (Beesdo-Baum and Knappe 2012). Both expressions of anxiety are important to capture, particularly when studying groups with a wide range of ages and ability levels.

Fragile X Syndrome

The results of the current study support the hypothesis that individuals with FXS would display generally heightened social anxiety that is not necessarily governed by the nature of social interaction. Interestingly, a positive correlation between social anxiety and IQ has previously been reported (Hessl et al. 2006). Although groups in the present study were matched for receptive language and adaptive behaviour ability, a positive correlation between receptive language ability and social anxiety was present in the FXS group only when CA was not accounted for. Therefore, it remains unclear whether social anxiety is related to ability levels in FXS. The current study indicates that individuals with FXS demonstrate social anxiety with familiar as well as unfamiliar people. This is not supported by parental reports of sociability across familiar and unfamiliar interactions (Moss et al. 2016) or behavioural observations of reduced avoidance with familiar partners (Roberts et al. 2007; Cohen et al. 1989, 1991). The results reported here might, therefore, be indicative of heightened social anxiety during interactions with a familiar person when unfamiliar adults are also present within the participants' home environment, compared to everyday social situations. In addition, although the Social Tasks are designed to be naturalistic interactions, they are structured, and this type of structured interaction between participants and parents may be unusual, resulting in heightened social anxiety with a familiar partner.

Previous literature indicates that individuals with FXS display a willingness to interact with others, alongside the heightened social anxiety (Cornish et al. 2008). This study highlights that behavioural indicators of social motivation did not differ in people with FXS from people with DS, supporting the notion that individuals with FXS show a willingness to interact with others. Between-group comparisons revealed that whilst social anxiety was heightened compared to those with DS, social motivation was similar. Therefore, the relationship between social anxiety and social motivation for individuals with FXS is more likely to represent the divergent facets of the socio-behavioural phenotypes of FXS, which encompass both social anxiety and social motivation simultaneously.

Cornelia de Lange Syndrome

The results regarding social anxiety in CdLS support our hypothesis and previous literature indicating the presence of social anxiety related behaviours, which are mediated by particular social demands, including verbalisation (Richards et al. 2009; Nelson et al. 2017). Here, it is reported that individuals with CdLS did not display higher levels of social anxiety compared to individuals with DS, overall. Rather, individuals with CdLS were significantly

more likely to display social anxiety related behaviours when there was no explicit expectation to verbalise *(Voluntary Social Interaction)* compared to when the expectation was explicit (*Required Social Interaction, Performance*). Therefore, it may be the uncertainty, and lack of ability to generate planned responses, that led to heightened social anxiety in this condition. Interestingly, previous literature investigating the executive function profile in individuals with CdLS has reported specific impairments on tasks that require 'generativity', or verbal fluency (Reid et al. 2017), and reduced verbalisation has also been noted in this group (Nelson et al. 2017). Generating verbal responses may be most challenging during a social situation in which the nature of the interaction is unpredictable and expectations to interact are not explicit. Therefore, executive function deficits may be related to anxiety in such situations, particularly with unfamiliar people.

Although mean levels of social motivation between participants with CdLS did not differ to other groups when scores were collapsed across conditions, social motivation was modulated by the nature of the social interaction more so for this group than others. In addition, Fig. 2 indicates that participants with CdLS demonstrated lower levels of social motivation than did participants with DS in the *Voluntary Social Interaction* condition with an unfamiliar social partner. Item-level scores indicate that this result is primarily driven by the item assessing socially motivated initiation of interaction as opposed to positive affect, focus of attention and social responsiveness. Participants with CdLS also showed particularly high social anxiety in this condition compared to other conditions and thus withdrawing from the interaction through reduced initiation of interaction may reflect the selective mutism that is commonly reported in CdLS (Moss et al. 2016). Existing literature on this topic has suggested that mutism may be an avoidance strategy, which serves as a coping mechanism to reduce anxiety in typically developing children (Yeganeh et al. 2006). An alternative yet complementary interpretation of these results is that the specific impairments in tasks requiring generation, as reported above, may also contribute to lower levels of initiation during situations where the social expectations are unclear. Participants also showed higher social motivation with familiar versus unfamiliar adults in two of the three experimental conditions, indicating that the familiarity of a social partner is an important factor in both anxiety and social motivation for this population. A negative association between social anxiety and social motivation was reported for participants with CdLS, suggesting that these two constructs are contingent on one another in in this group, such that as social anxiety increases, social motivation decreases.

Rubinstein-Taybi Syndrome

The results for participants with RTS are the first to indicate heightened levels of observable behaviours indicative of anxiety in this participant group across a range of social situations with familiar and unfamiliar interacting adults. Previous studies have primarily used parental report measures, which have mostly reported intact social skills and heightened sociability in this group. Although social anxiety has not been investigated in RTS until now, previous studies do describe the presence of behaviours that may be linked to social anxiety, such as a preference to spend time alone (Hennekam et al. 1992), and clinging to adults, alongside an increase of anxiety with age (Yagihashi et al. 2012). The results of the current study support some previous findings indicating the presence of social anxiety-related behaviours in individuals with RTS. However, due to the mixed literature, further research is warranted to better define the social phenotype in this group.

Behavioural indicators of social motivation did not differ between those with RTS and those with DS. Higher social interest has been reported in individuals with RTS compared to others matched for age and developmental ability (Galéra et al. 2009). However, the results from the present study suggest that social interest in RTS does not differ to a comparison group matched for receptive language and adaptive behaviour abilities. For participants with RTS, social anxiety and social motivation also appear to present simultaneously.

The strengths of the present study include the development of a robust tool to assess social anxiety and social motivation in individuals with intellectual disability through behavioural observation, and detailed examination of syndrome specific profiles of social anxiety and social motivation in individuals with FXS, CdLS, RTS and DS across a range of naturalistic social situations. However, this study did not include female participants in the FXS sample, which is a significant limitation that should be addressed in future research to further understanding of the behavioural phenotype of females with FXS. The groups in this study were statistically similar on important characteristics such as age, receptive language, and adaptive behaviour, indicating that differences in the genetic landscapes result in different downstream pathways from genetics through to behaviour.

Conclusions

In summary, the present study highlighted that the familiarity of a social partner and the type of social interaction influences social anxiety and social motivation in different ways for different syndrome groups. Heightened social anxiety but similar social motivation was reported in FXS and RTS compared to a contrast group of individuals with DS matched on

chronological and mental age. Furthermore, individuals with CdLS displayed heightened social anxiety but this was mediated by the nature of the interaction, rather than occurring across all social situations. Overall, the results from the present study support the summary of the social impairments in FXS that describe a combination of motivation to interact with others, alongside anxiety. The results from the present study refine the CdLS phenotype further by proposing that social anxiety in CdLS is specific to unpredictable social situations with unfamiliar people, and that social motivation is reduced during these times. For RTS, this is the first study to demonstrate through behavioural observation that whilst social motivation may be developmentally typical, social anxiety is heightened, which should be confirmed with future research to promote awareness of co-morbid anxieties in this group. To our knowledge, this is the first study to investigate the interplay of social anxiety and social motivation, two seemingly contrasting social constructs that interact differentially in individuals with genetic syndromes associated with unique socio-behavioural profiles. The association between social anxiety and social motivation differed by group thus extending the notion that individuals with neurodevelopmental disorders display different behavioural expressions of anxiety to typically developing individuals by indicating that individuals with *different* neurodevelopmental disorders express anxiety in different ways.

Awareness of the conditions under which social anxiety is induced in people with an intellectual disability has implications for intervention planning. This study indicates that unpredictable social situations with unfamiliar social partners are likely to induce heightened social anxiety and reduced motivation to interact in individuals with CdLS, which is important for clinical practice. The results from this study go some way towards delineating the interaction between genetic influences and the role of the environment in the mediation of behavioural indicators of social anxiety and social motivation. This enhances understanding of the social phenotype of FXS, CdLS and RTS, which is important both for the research community and for families with children and adults with genetic syndromes.

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Author Contributions HC was involved in study design, data collection, data analysis, data interpretation and drafting of the manuscript. JM was involved in study design and editing the manuscript. LG was involved in participant recruitment, data collection and data coding. RD was involved in participant recruitment and data collection. LN was involved in task development, and recruitment and data collection of the CdLS and DS participant groups. DR was involved in recruitment and data collection of the CdLS and DS participant groups. CO was involved in study design, data analysis, data interpretation and editing of the manuscript.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study. Participants aged 16 and above provided written consent to participate. Parents of children aged below 16 years provided written consent on behalf of their children.

References

Beck, B. (1976). Epidemiology of Cornelia de Lange's syndrome. *Acta Paediatrica, 65*(4), 631–638.

Beesdo-Baum, K., & Knappe, S. (2012). Developmental epidemiology of anxiety disorders. *Child and Adolescent Psychiatric Clinics, 21*(3), 457–478.

Beidel, D. C., Turner, S. M., & Morris, T. L. (1995). A new inventory to assess childhood social anxiety and phobia: The social phobia and anxiety inventory for children. *Psychological Assessment, 7*(1), 73–79.

Bernstein, G. A., Borchardt, C. M., & Perwien, A. R. (1996). Anxiety disorders in children and adolescents: A review of the past 10 years. *Journal of the American Academy of Child and Adolescent Psychiatry, 35*(9), 1110–1119.

Chapman, R., & Hesketh, L. (2000). Behavioural phenotype of individuals with Down syndrome. *Mental Retardation and Developmental Disabilities Research Reviews, 6,* 84–95.

Coffee, B., Keith, K., AlbizuaMalone, T., Mowrey, J., Sherman, S. L., et al. (2009). Incidence of Fragile X syndrome by newborn screening for methylated FMR1 DNA. *The American Journal of Human Genetics, 85*(4), 503–514.

Cohen, I. L., Vietze, P. M., Sudhalter, V., Jenkins, E. C., & Brown, W. T. (1989). Parent-child dyadic gaze patterns in fragile X males and in non-fragile X males with autistic disorder. *Journal of Child Psychology and Psychiatry, 30*(6), 845–856.

Cohen, I. L., Vietze, P. M., Sudhalter, V., Jenkins, E. C., & Brown, W. T. (1991). Effects of age and communication level on eye contact in fragile X males and non-fragile X autistic males. *American Journal of Medical Genetics Part A, 38*(2–3), 498–502.

Cordeiro, L., Ballinger, E., Hagerman, R., & Hessl, D. (2011). Clinical assessment of DSM-IV anxiety disorders in fragile X syndrome: Prevalence and characterization. *Journal of Neurodevelopmental Disorders, 3*(1), 57–67.

Cornish, K., Turk, J., & Hagerman, R. (2008). The fragile X continuum: New advances and perspectives. *Journal of Intellectual Disability Research, 52*(6), 469–482.

Coupry, I., Roudaut, C., Stef, M., Delrue, M. A., Marche, M., Burgelin, I., et al. (2002). Molecular analysis of the CBP gene in 60 patients

with Rubinstein-Taybi syndrome. *Journal of Medical Genetics, 39*(6), 415–421.

Crawford, D. C., Acuna, J. M., & Sherman, S. L. (2001). FMR1 and the fragile X syndrome: Human genome epidemiology review. *Genetics in Medicine, 3*(5), 359–371.

Crawford, H., Waite, J., & Oliver, C. (2017). Diverse profiles of anxiety in Fragile X, Cornelia de Lange and Rubinstein-Taybi syndromes. *Journal of Autism and Developmental Disorders, 47*(12), 3728–3750.

Deardorff, M. A., Bando, M., Nakato, R., Watrin, E., Itoh, T., Minamino, M., et al. (2012). HDAC8 mutations in Cornelia de Lange syndrome affect the cohesin acetylation cycle. *Nature, 489*(7415), 313–317.

Deardorff, M. A., Kaur, M., Yaeger, D., Rampuria, A., Korolev, S., Pie, J., et al. (2007). Mutations in cohesin complex members SMC3 and SMC1A cause a mild variant of Cornelia de Lange syndrome with predominant mental retardation. *The American Journal of Human Genetics, 80*(3), 485–494.

Dunn, L. M., Whetton, C., & Burley, J. (1997). *The British Picture Vocabulary Scale, Second Edition Testbook*. Windsor: NFER.

Dykens, E. M. (2007). Psychiatric and behavioral disorders in persons with Down syndrome. *Mental Retardation and Developmental Disabilities Research Reviews, 13*(3), 272–278.

Fidler, D., Most, D., & Philofsky, A. (2009). The Down syndrome behavioural phenotype: Taking a developmental approach. *Down's Syndrome, Research and Practice, 12*(3), 37–44.

Fleiss, J. L. (1981). *Statistical methods for rates and proportions* (2nd ed.). New York: Wiley.

Fydrich, T., Chambless, D. L., Perry, K. J., Buergener, F., & Beazley, M. B. (1998). Behavioral assessment of social performance: A rating system for social phobia. *Behaviour Research and Therapy, 36*(10), 995–1010.

Galéra, C., Taupiac, E., Fraisse, S., Naudion, S., Toussaint, E., Rooryck-Thambo, C., et al. (2009). Socio-behavioral characteristics of children with Rubinstein-Taybi syndrome. *Journal of Autism and Developmental Disorders, 39*(9), 1252–1260.

Gibbs, M. V., & Thorpe, J. G. (1983). Personality stereotype of noninstitutionalized Down syndrome children. *American Journal of Mental Deficiency, 102*(3), 228–237.

Gillis, L. A., McCallum, J., Kaur, M., DeScipio, C., Yaeger, D., Mariani, A., et al. (2004). NIPBL mutational analysis in 120 individuals with Cornelia de Lange syndrome and evaluation of genotype-phenotype correlations. *The American Journal of Human Genetics, 75*(4), 610–623.

Goodban, M. T. (1993). Survey of speech and language skills with prognostic indicators in 116 patients with Cornelia de Lange syndrome. *American Journal of Medical Genetics, 47*(7), 1059–1063.

Hagerman, R. J., & Hagerman, P. J. (2002). *Fragile X syndrome: Diagnosis, treatment, and research*. US: Taylor & Francis.

Hall, S., DeBernardis, M., & Reiss, A. L. (2006). Social escape behaviors in children with fragile X syndrome. *Journal of Autism and Developmental Disorders, 36*(7), 935–947.

Hennekam, R. C. (2006). Rubinstein-Taybi syndrome. *European Journal of Human Genetics, 14*(9), 981–985.

Hennekam, R. C., Baselier, A. C., Beyaert, E., & Bos, A. (1992). Psychological and speech studies in Rubinstein-Taybi syndrome. *American Journal on Mental Retardation, 96*(6), 645–660.

Hennekam, R. C., Van Den Boogaard, M.-J., Sibbles, B. J., & Van Spijker, H. G. (1990). Rubinstein-Taybi syndrome in the Netherlands. *American Journal of Medical Genetics, 37*(56), 17–29.

Hessl, D., Glaser, B., Dyer-Friedman, J., & Reiss, A. L. (2006). Social behavior and cortisol reactivity in children with fragile X syndrome. *Journal of Child Psychology and Psychiatry, 47*(6), 602–610.

Hirst, M. C., Knight, S. J., Christodoulou, Z., Grewal, P. K., Fryns, J. P., & Davies, K. E. (1993). Origins of the fragile X syndrome mutation. *Journal of Medical Genetics, 30,* 647–650.

Horsler, K., & Oliver, C. (2006). Environmental influences on the behavioural phenotype of Angelman syndrome. *American Journal on Mental Retardation, 111*(5), 311–321.

Jones, W., Bellugi, U., Lai, Z., Chiles, M., Reilly, J., Lincoln, A., et al. (2000). II. Hypersociability in Williams syndrome. *Cognitive Neuroscience, 12*(1), 30–46.

Kalkhoven, E., Roelfsema, J. H., Teunissen, H., den Boer, A., Ariyurek, Y., Zantema, A., et al. (2003). Loss of CBP acetyltransferase activity by PHD finger mutations in Rubinstein-Taybi syndrome. *Human Molecular Genetics, 12*(4), 441–450.

Krantz, I. D., McCallum, J., DeScipio, C., Kaur, M., Gillis, L. A., Yaeger, D., et al. (2004). Cornelia de Lange syndrome is caused by mutations in NIPBL, the human homolog of Drosophila melanogaster Nipped-B. *Nature Genetics, 36*(6), 631–635.

Kushlick, A., Blunden, R., & Cox, C. (1973). A method of rating behaviour characteristics for use in large scale surveys of mental handicap. *Psychological Medicine, 3,* 466–478.

Lacombe, D., Saura, R., Taine, L., & Battin, J. (1992). Confirmation of assignment of a locus for Rubinstein-Taybi syndrome gene to 16p13.3. *American Journal of Medical Genetics, 44*(1), 126–128.

Langthorne, P., McGill, P., & Oliver, C. (2013). The motivating operation and negatively reinforced problem behaviour: A systematic review. *Behaviour Modification, 38*(1), 107–159.

Lesniak-Karpiak, K., Mazzocco, M. M. M., & Ross, J. L. (2003). Behavioral assessment of social anxiety in females with Turner or fragile X syndrome. *Journal of Autism and Developmental Disorders, 33*(1), 55–67.

Lord, C., Rutter, M., DiLavore, P., & Risi, S. (1999). *Autism diagnostic observation schedule: Manual*. Los Angeles: Western Psychological Services.

Minor, A., Shinawi, M., Hogue, J. S., Vineyard, M., Hamlin, D. R., Tan, C., et al. (2014). Two novel RAD21 mutations in patients with mild Cornelia de Lange syndrome-like presentation and report of the first familial case. *Genetics in Medicine, 537*(2), 279–284.

Miyake, N., Visser, R., Kinoshita, A., Yoshiura, K.-I., Niikawa, N., Kondoh, T., et al. (2005). Four novel NIPBL mutations in Japanese patients with Cornelia de Lange syndrome. *American Journal of Medical Genetics Part A, 135*(1), 103–105.

Moss, J., Howlin, P., Hastings, R. P., Beaumont, S., Griffith, G. M., Petty, J., et al. (2013a). Social behavior and characteristics of autism spectrum disorder in Angelman, Cornelia de Lange, and Cri du Chat syndromes. *American Journal on Intellectual and Developmental Disabilities, 118*(4), 262–283.

Moss, J., Nelson, L., Powis, L., Waite, J., Richards, C., & Oliver, C. (2016). A comparative study of sociability in Angelman, Cornelia de Lange, Fragile X, Down and Rubinstein-Taybi syndromes and autism spectrum disorder. *American Journal on Intellectual and Developmental Disabilities, 121*(6), 465–486.

Moss, J., Oliver, C., Berg, K., Kaur, G., Jephcott, L., & Cornish, K. (2008). Prevalence of autism spectrum phenomenology in Cornelia de Lange and Cri du Chat syndromes. *American Journal of Mental Retardation, 113*(4), 278–291.

Moss, J., Oliver, C., Nelson, L., Richards, C., & Hall, S. (2013b). Delineating the profile of autism spectrum disorder characteristics in Cornelia de Lange and fragile X syndromes. *American Journal on Intellectual and Developmental Disabilities, 118*(1), 55–73.

Musio, A., Selicorni, A., Focarelli, M. L., Gervasini, C., Milani, D., Russo, S., et al. (2006). X-linked Cornelia de Lange syndrome owing to SMC1L1 mutations. *Nature Genetics, 38*(5), 528–530.

Nelson, L., Crawford, H., Reid, D., Moss, J., & Oliver, C. (2017). An experimental study of executive function and social impairment

in Cornelia de Lange syndrome. *Journal of Neurodevelopmental Disorders, 9,* 33.

Oliver, C., Adams, D., Allen, D., Bull, L., Heald, M., Moss, J., et al. (2013). Causal models of clinically significant behaviors in Angelman, Cornelia de Lange, Prader-Willi and Smith-Magenis syndromes. *International Review of Research in Developmental Disabilities, 44,* 167–212.

Oliver, C., Horsler, K., Berg, K., Bellamy, G., Dick, K., & Griffiths, E. (2007). Genomic imprinting and the expression of affect in Angelman syndrome What's in the smile? *Journal of Child Psychology and Psychiatry, 48*(6), 571–579.

Petrif, F., Giles, R. H., Dauwerse, H. G., Saris, J. J., Hennekam, R. C., Masuno, M., et al. (1995). Rubinstein-Taybi syndrome caused by mutations in the transcriptional co-activator CBP. *Nature, 376*(6538), 348–351.

Reid, D., Moss, J., Nelson, L., Groves, L., & Oliver, C. (2017). Executive functioning in Cornelia de Lange syndrome: Domain asynchrony and age-related performance. *Journal of Neurodevelopmental Disorders, 9,* 29.

Richards, C., Moss, J., O'Farrell, L., Kaur, G., & Oliver, C. (2009). Social anxiety in Cornelia de Lange syndrome. *Journal of Autism and Developmental Disorders, 39*(8), 1155–1162.

Roberts, J. E., Crawford, H., Hogan, A. L., Fairchild, A., Tonnsen, B., Brewe, A., et al. (2019). Social avoidance emerges in infancy and persists into adulthood in fragile X syndrome. *Journal of Autism and Developmental Disorders, 49*(9), 3753–3766.

Roberts, J. E., Clarke, M. A., Alcorn, K., Carter, J. C., Long, A. C. J. & Kaufmann, W. E. (2009). Autistic behavior in boys with fragile X syndrome: Social approach and HPA-axis dysfunction. *Journal of Neurodevelopmental Disorders, 1*(4), 283–291.

Roberts, J. E., Weisenfeld, L. A. H., Hatton, D. D., Heath, M., & Kaufmann, W. E. (2007). Social approach and autistic behavior in children with fragile X syndrome. *Journal of Autism and Developmental Disorders, 37*(9), 1748–1760.

Roelfsema, J. H., White, S. J., Ariyürek, Y., Bartholdi, D., Niedrist, D., Papadia, F., et al. (2005). Genetic heterogeneity in Rubinstein-Taybi syndrome: Mutations in both the CBP and EP300 genes cause disease. *The American Journal of Human Genetics, 76*(4), 572–580.

Rutter, M., Bailey, A., & Lord, C. (2003). *The Social Communication Questionnaire*. Los Angeles: Western Psychological Services.

Sparrow, S. S., Cicchetti, D. V., & Balla, D. A. (2005). *Vineland-II Adaptive Behavior Scales: Survey forms manual*. Circle Pines: AGS Publishing.

Stevens, C. A., Pouncey, J., & Knowles, D. (2011). Adults with Rubinstein-Taybi syndrome. *American Journal of Medical Genetics Part A, 155*(7), 1680–1684.

Tager-Flusberg, H., Skwerer, D. P., & Joseph, R. M. (2006). Model syndromes for investigating social cognitive and affective neurosciene: A comparison of autism and Williams syndrome. *Social Cognitive and Affective Neuroscience, 1*(3), 175–182.

Tunnicliffe, P., & Oliver, C. (2011). Phenotype-environment interactions in genetic syndromes associated with severe or profound intellectual disability. *Research in Developmental Disabilities, 32,* 404–418.

Wishart, J. G., & Johnston, F. H. (1990). The effects of experience on attribution of a stereotyped personality to children with Down's syndrome. *Journal of Intellectual Disability Research, 34*(5), 409–420.

Yagihashi, T., Kenjiro, K., Nobuhiko, O., Mizuno, S., Kenji, K., Takao, T., et al. (2012). Age-dependent change in behavioural feature in Rubinstein-Taybi syndrome. *Congenital Anomalies, 52*(2), 82–86.

Yeganeh, R., Beidel, D. C., & Turner, S. M. (2006). Selective mutism: More than social anxiety? *Depression and Anxiety, 23*(3), 117–123.