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Anxiety characteristics in individuals with Williams syndrome

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Abstract

Background: Williams syndrome anxiety research predominantly focuses on disorder prevalence and symptomatology, categorised using standardised mental health classifications. However, the use of these assessments may not fully capture the phenotypic features of anxiety in Williams syndrome. In this study, we examined characteristics of anxiety using a formulation framework.

Method: A semi-structured interview was conducted with thirteen parents of individuals with Williams syndrome (median age: 19, age range: 12–45, 8 females).

Results: Various anxiety triggers were reported, including anxiety triggered by phobias, uncertainty and negative emotions in others. The range of described behaviours was diverse with both avoidant and active coping strategies for anxiety management reported.

Conclusions: Many of the characteristics described were consistent with findings in the intellectual disability and typically developing literature, although novel information was identified. The study demonstrates the utility of a formulation framework to explore anxiety characteristics in atypical populations and has outlined new avenues for research.

KEYWORDS
anxiety, anxiety assessment, behavioural phenotype, formulation framework, intellectual disability, Williams syndrome

1 | BACKGROUND

Williams syndrome is a neurodevelopmental condition caused by a microdeletion of 26–28 genes on chromosome 7q11.23 with an estimated prevalence of between 1 in 7500 and 1 in 20,000 (Ewart et al., 1993; Strømme et al., 2002). Williams syndrome is associated with mild to moderate intellectual disability and a distinct physical, cognitive and behavioural profile (Bellugi et al., 2000; Martens et al., 2008). Physical characteristics include cardiovascular disease, infantile hypercalcaemia, short stature and distinguishing facial features (Donnai & Karmiloff-Smith, 2000; Karmiloff-Smith et al., 2003; Morris & Mervis, 2000; Sindhar et al., 2016; Twite et al., 2019). Individuals with Williams syndrome often have developmental delay and specific cognitive impairments, particularly in the domain of visuospatial processing (Bellugi et al., 2000; Farran & Jarrold, 2003). The behavioural phenotype includes impulsivity, short attention span, hypersociability, 'disruptive' behaviour and anxiety (Klein-Tasman & Lee, 2017; Ng-Cordell et al., 2018; Sampaio et al., 2018; Twite et al., 2019).

The high risk of anxiety disorders for people with Williams syndrome is well documented (Royston et al., 2017). Reported anxiety disorder prevalence rates in the literature vary widely and range from 16% to 82%, although a 2017 meta-analysis estimates a prevalence of 48% (Royston et al., 2017; Stinton et al., 2010; Woodruff-Borden et al., 2010). The most commonly reported anxiety disorders are phobias and generalised anxiety disorder, with a low prevalence of socially related anxiety (Dykens, 2003; Leyfer et al., 2006). Anxiety persists over time, increases with age, and is

experienced across all ages in Williams syndrome (Dodd & Porter, 2009; Einfeld et al., 2001). Although research studies on anxiety have tended to utilise similar methodology and assessments to examine symptomatology, these assessments may not fully conceptualise anxiety in this population. Typically, these studies rely on standardised assessments and classification criteria developed primarily for the general population (Royston et al., 2017). Such measures are rarely validated for individuals with developmental or genetic disorders, and anxiety symptomatology may present atypically in these groups. Deviations from behaviours or symptoms considered as typical features of anxiety may also prevent individuals scoring the threshold criteria indicative of a problem. Therefore, although anxiety may be present, the use of standardised assessments may not fully capture the symptomatology, extent or severity of problems.

Similarly to Williams syndrome, individuals with fragile X syndrome and Cornelia de Lange syndrome have high reported prevalence rates of anxiety (Basile et al., 2007; Cordeiro et al., 2011; Royston et al., 2017). However, there are indications that anxiety may present atypically in these two syndromes. In a study of children with fragile X syndrome, approximately 7% of children displayed behaviours indicative of anxiety, despite all individuals scoring below the anxiety threshold on the Child Behavior Checklist, a standardised measure (Sullivan et al., 2007). Similarly, on the Spence Children's Anxiety Scale, children with Cornelia de Lange syndrome scored comparably to typically developing children without a diagnosed anxiety disorder for social anxiety and scored lower than typically developing children diagnosed with anxiety disorders (Crawford et al., 2017). This is inconsistent with reports of up to 40% of verbal children with Cornelia de Lange syndrome presenting with selective mutism, a disorder associated with social anxiety (Moss et al., 2016). These findings indicate that clusters of behaviours associated with anxiety in genetic syndromes may differ somewhat from behaviours identified in the 'typical' population. Therefore, it is important to examine whether the use of standardised assessments fully captures the phenotypic features of anxiety for people with Williams syndrome.

Williams syndrome research to date focuses on anxiety prevalence and symptoms, based on standard classifications of mental health problems (e.g. Dodd & Porter, 2009; Leyfer et al., 2006). Measures utilised emphasise affect and physiological responses, with minimal focus on other potentially influential factors such as thoughts during anxiety episodes and behavioural expressions of anxiety. Research into antecedents that may precipitate anxiety is also limited. Whilst there are reports of common specific phobia triggers, including loud noises, injections, injury and thunderstorms (Dodd & Porter, 2009; Green et al., 2012; Leyfer et al., 2006), there is less focus on examining triggers relating to broader anxiety topographies, such as social, physical and sensory related anxiety.

The strategies utilised for anxiety management have also been scarcely researched, despite the potential clinical value of this information for anxiety assessment and intervention. Individuals with intellectual disability may be more likely to utilise avoidance strategies (e.g. distraction or escape) to alleviate anxiety, techniques associated with long-term anxiety maintenance (Ben-Zur, 2009; Gonzales et al., 2001; Hartley & Maclean, 2005; Salkovskis, 1991). Conversely, the use of active coping strategies may negate and protect against the persistence and severity of mental health problems (Hartley & Maclean, 2005).

In the present study, we adopted a formulation approach to explore anxiety phenomenology in individuals with Williams syndrome. Formulation is a structured framework that considers events, social relationships, perceptions and beliefs when interpreting and understanding mental health problems, and is routinely applied by practitioner psychologists in clinical services (Johnstone, 2018). It differs from other approaches due to its consideration of cognition and external interactions and can be used to inform models, develop assessment measures and guide interventions (Johnstone & Dallos, 2013). Moreover, this approach has been used effectively in the development of several assessments and interventions (eg cognitive-behavioural therapies) to treat mental health problems in the general population (Albano & Kendall, 2002; Wells, 2005). Given that commonly used standardised assessments may be limited in their scope and sensitivity to identify the broader phenotype of anxiety in Williams syndrome, in this study we aimed to explore more broadly the characteristics of anxiety in Williams syndrome utilising a formulation framework.

2 | METHOD

2.1 | Participants

Families were recruited through the Williams Syndrome Foundation, UK. The study was advertised as focusing on 'emotions and behaviour', and families were informed about the study via email, newsletters and social media. The specific focus on anxiety was not made explicit to potential participants in order to avoid sample bias, to provide the opportunity to examine anxiety symptoms in a range of individuals with Williams syndrome and to limit any preconceived ideas about the anxiety profile. The majority of Williams syndrome anxiety research focuses on child samples, despite evidence for the persistence of anxiety over time (Dodd & Porter, 2009; Einfeld et al., 2001; Ng-Cordell et al., 2018). Therefore, in this study we aimed to explore the anxiety profile in adolescent and adults. Participants who expressed an interest in the study were eligible if they were a parent/carer of a person aged 12 or over, with a confirmed diagnosis of Williams syndrome.

Thirteen parents completed the interview (median age of children: 19 years, range: 12–45, 8 females). Twelve parents completed the Waisman Activities of Daily Living Scale (W-ADL; Maenner et al., 2013), which provides a measure of an individual's level of independence in performing daily living tasks. The maximum possible score is 34; in the present sample, the median score = 26.5 (range: 8–31); all the sample was reported as requiring some assistance in completing daily living tasks. Ethical approval for the study was obtained from the Science, Technology, Engineering and Mathematics

Review Committee at the University of Birmingham (Reference: ERN_12-0018AP19).

2.2 | Procedure

Interviews were conducted over the telephone and recorded. Due to the sensitive nature of some of the interview content, parents were reminded they did not have to answer any questions they felt uncomfortable with and were provided with breaks if requested. Interviews lasted between 30 minutes and an hour.

2.3 | Measures

2.3.1 | Interview development

A combination of the 5Ps and cognitive-behavioural formulation frameworks was chosen for this exploratory study to conceptualise mental health in people with Williams syndrome. The 5Ps formulation framework is atheoretical, comprised of presenting, predisposing, precipitating, perpetuating and protective factors of mental health (Johnstone & Dallos, 2006, 2013). The model is widely used clinically and has utility for defining mental health difficulties, identifying longstanding problems and addressing resilience, triggers and anxiety maintenance (Macneil et al., 2012). The cognitive-behavioural framework conceptualises anxiety as the combination of cognitive, behavioural and physiological components. Interventions utilising this framework have also shown utility in the treatment of anxiety disorders in the general population (James et al., 2020).

Interview items were developed based on the formulation frameworks and Williams syndrome literature, as well as consultation with two qualified clinical psychologists experienced in behavioural phenotype and anxiety research (Table 1). The interview was designed primarily for individuals with Williams syndrome, although also considered aspects relating to broader neurodevelopmental disorders, with the aim of increasing the utility and generalisability of the measure in future work.

Researchers interviewing participants were not clinically trained, and formulation techniques were only utilised in the development of

TABLE 1 Formulation frameworks and incorporation of the models into the interview

Framework	Components	*Explanation*	Items incorporated into interview
The 5Ps[a]	Presenting issues	*Presenting difficulties, addresses behaviours, thoughts and emotions*	Description of recent and typical experiences of anxiety, behaviours, thoughts, frequency, severity and impact
	Predisposing factors	*Internal/external factors that contribute to a person's vulnerability to the presenting issue*	Comorbidity of depressive symptoms and family history, developmental history
	Precipitating factors	*Internal/external factors that trigger the presenting difficulties*	Immediate antecedents of anxiety and triggers surrounding the initial anxiety onset
	Perpetuating factors	*Internal/external factors that maintain problem*	Use of strategies, as these may act to maintain the anxiety cycle (i.e. the continual use of reassurance may act as a reinforcer and may increase the likelihood of a similar anxiety response in the future)
	Protective factors	*Factors that contribute to resilience and strength*	Coping strategies
Cognitive behavioural[b]	Environment	*Situational factors*	Triggers, life events, setting events
	Cognition	*Core beliefs that may be associated with problem* (e.g. *feels safety is threatened*)	Item relating to thoughts during event
	Emotion	*Presenting difficulties*	Event description, severity, frequency, impact
	Behaviour	*Behaviours presented in response to emotion, safety/coping behaviours*	Behavioural responses and strategies used by parents/individuals
	Physiological responses	*Physical sensations*	Physical changes in body in response to anxiety

Note:: Some of the items from the frameworks overlap.

[a]Derived from Johnstone and Dallos (2006).

[b]Derived from Grant et al. (2008).

the interview, not during data collection. Initial questions were followed by more direct questions as prompts. The interview was designed to minimise researcher bias whilst collecting quantifiable information.

The interview was divided into three sections: general introduction, anxiety triggered by specific events and anxiety relating to context (Figure 1). A brief section was also included to address the co-occurrence of depressive symptoms. This enabled the interviewer to ask directly relevant questions and tailor the assessment for each participant, minimising participant burden. For instance, if no depressive symptoms were reported during the introductory section, the depressive symptoms section was not administered. Initial questions were used to determine the relevant sections of the interview for each participant.

A coding scheme was developed to quantify the results and was reviewed by three clinical psychologists for applicability and relevance. Coded information for frequency, severity, triggers, behaviours and the onset of anxiety were derived from existing literature and pre-existing coding schemes in validated measures examining anxiety and behaviour (Broadbent et al., 2006; Charlot et al., 2007; Esbensen et al., 2003; Glen et al., 1993; Hyman et al., 2002; Riddle & Greenhill, 2002; Spence, 1998; Spitzer et al., 2006). Interviews were both conducted and coded by the same researcher. In cases where the information did not fit pre-existing codes, the coding scheme was modified after the interviews were completed. This included the addition of categories that appeared to best fit the data collected.

2.4 | Interview validation

2.4.1 | Inter-rater reliability

Two raters coded interviews independently. The total number of times the raters agreed an item was present was calculated. Percentage agreement for all interview items ranged from 54% to 100%, with 76% of items scoring over 80% agreement. Cohen's Kappa statistics were also calculated for all interview items, and agreement was substantial (Kappa = 0.68). Inter-rater weighted kappa was also calculated for coded items. Agreement ranged from moderate to good (weighted kappa = 0.41–0.83; Viera & Garrett, 2005).

2.5 | Convergent validity

To examine convergent validity, coded interview results were examined in relation to the Spence Children's Anxiety Scale (SCAS-P; Spence, 1998), a measure used extensively within Williams syndrome research and in broader anxiety research (e.g. Crawford et al., 2017; Dodd & Porter, 2011; Ng-Cordell et al., 2018; Reardon et al., 2019; Rodgers et al., 2012). The suggested clinical cut-off is 24. In the present study, the mean score was 21 (SD: 9.42). Associations between interview items and the corresponding subscales of the SCAS-P were assessed using point biserial correlations and rank-biserial correlations. Spearman's rho correlations were conducted to identify associations between frequency/severity and the SCAS total score. The majority of correlations were weak and non-significant, although the correlation between the SCAS physical subscale and aversive settings was moderate (r_{rb}=.56). Further comment on validity is outlined in the discussion. See Supporting Information for full table of correlations.

3 | RESULTS

All parents reported anxiety to be the most difficult negative emotion experienced by their child. Depressive symptomatology was reported for nine individuals and frustration/anger for two. Eleven parents reported anxiety triggered by specific events, and three parents reported a generalised type of anxiety, occurring across multiple contexts and situations.

3.1 | Anxiety onset

Most (11) parents reported anxiety onset before age 12. The life events reported to precede anxiety onset were variable, although some described anxiety events relating to relationship disruption, including friendship difficulties (*n* = 2), parental marital difficulty (*n* = 1) and the death of a loved one (*n* = 1). Three parents reported anxiety onset after the age of 15, perceiving this as being related to transitions (e.g. increased independence and transitioning to

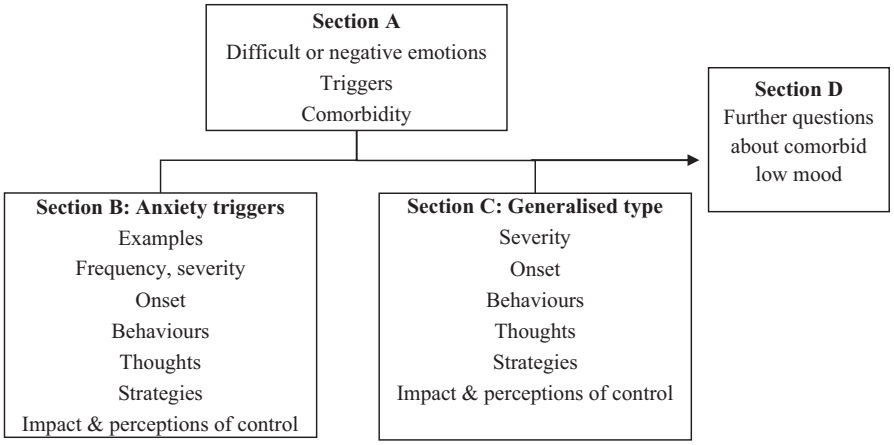

FIGURE 1 Interview format

adulthood). All parents reported generalised-type anxiety as having a gradual onset, as did five parents reporting triggered anxiety.

3.2 | Antecedents/triggers

Parents reported between two and eight triggers of anxiety (median = 4) for their child (Figure 2). Commonalities in parental responses led to the addition of two new coding categories, 'negative emotions in others' and 'unpredictability'. The most frequently reported triggers were specific phobias (*n* = 8), new situations (*n* = 7), sensory sensitivities (*n* = 6) and negative emotions in others (*n* = 5).

These triggers were then categorised further (see Figure 2). Health worries, lack of sleep, sensory sensitivities and pain were categorised as physically related. New situations, unpredictability and routine changes were grouped together based on associations with uncertainty. Triggers relating to the welfare of others, negative emotions in others and separation anxiety were considered to be socially related; those associated with aversive settings were grouped under specific phobias. Anxiety related to every day events was retained as an individual category; anticipatory worry was placed in the miscellaneous category.

For the topographies of specific phobias, parents reported phobias of noise (*n* = 5), blood/needles/injections (*n* = 2), storms/earthquakes (*n* = 2), heights (*n* = 1), animals (*n* = 1) and young children (*n* = 1). Four individuals experienced anxiety related to specific settings, namely doctors and hospitals (*n* = 3) and transportation (*n* = 2). Parents were also asked why they believed these triggers were difficult for their child. Responses included lack of understanding (*n* = 3), regimented thinking or difficulty with change (*n* = 2), syndrome or health-related issues (*n* = 6) and family-related factors (*n* = 1).

3.3 | Behaviours

Parents reported a diverse range of behaviours associated with anxiety (see Figure 3). All parents reported communication changes, such as increased communication with others (*n* = 7) and self-reporting anxiety feelings (*n* = 6). Body movements were variable, although responses included crying (*n* = 5), seeking proximity (*n* = 5), repetitive behaviours (*n* = 4) and pacing (*n* = 4). Seven parents reported physiological symptoms of anxiety, such as increased sweating (*n* = 3) and trembling (*n* = 3). Muscle tension was described in all individuals who were reported to experience generalised-type anxiety (*n* = 3).

3.4 | Cognitions

Parents found it difficult to comment on what they believed their child was thinking when they were feeling anxious and as very few individuals were able to provide answers to this section, it was not possible to analyse the data systematically. However, some examples of responses included '[my child is] thinking of how to get away', 'trying to understand why' and 'doesn't feel safe and wants to feel safe'.

3.5 | Frequency, severity and impact

Parents generally reported anxiety as infrequent, mild and with minimal lasting impact. Eight parents believed anxiety had a minimal impact on their child and their family. However, the three parents who reported generalised-type anxiety felt it had a significant negative impact on their child's routine and/or relationships.

3.6 | Strategies

Parents reported their children used both active and avoidant styles of coping. Distraction (*n* = 6) and escape (*n* = 5) were the most commonly utilised strategies, followed by emotion-focused strategies such as reassurance seeking (*n* = 4) and talking through worries with others (*n* = 4). Parents reported they mostly used active coping styles, such as giving reassurance (*n* = 11) and avoidant strategies

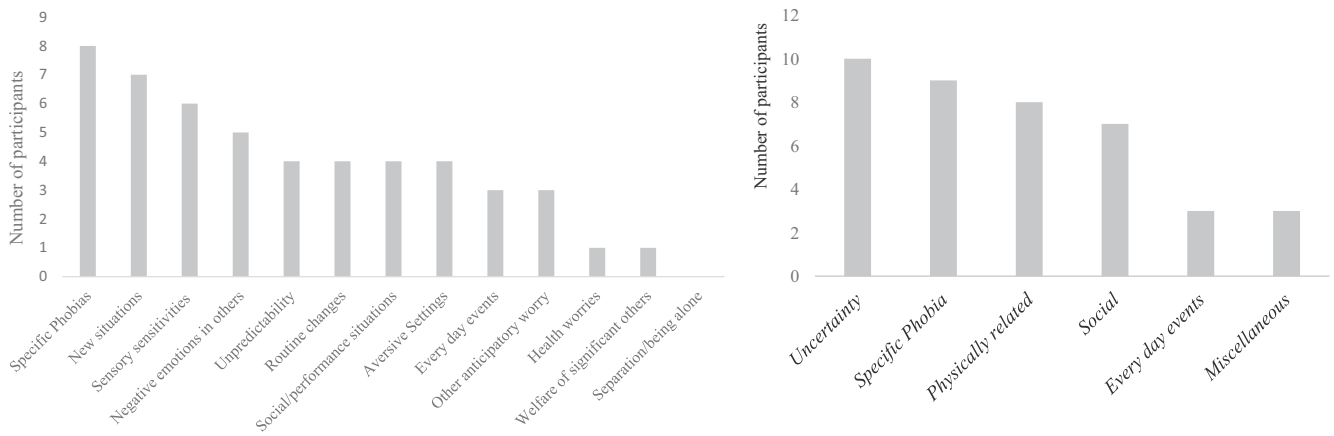

FIGURE 2 Number of participants reporting each anxiety trigger (left panel; *n* = 13) and triggers categorised into themes (right panel)

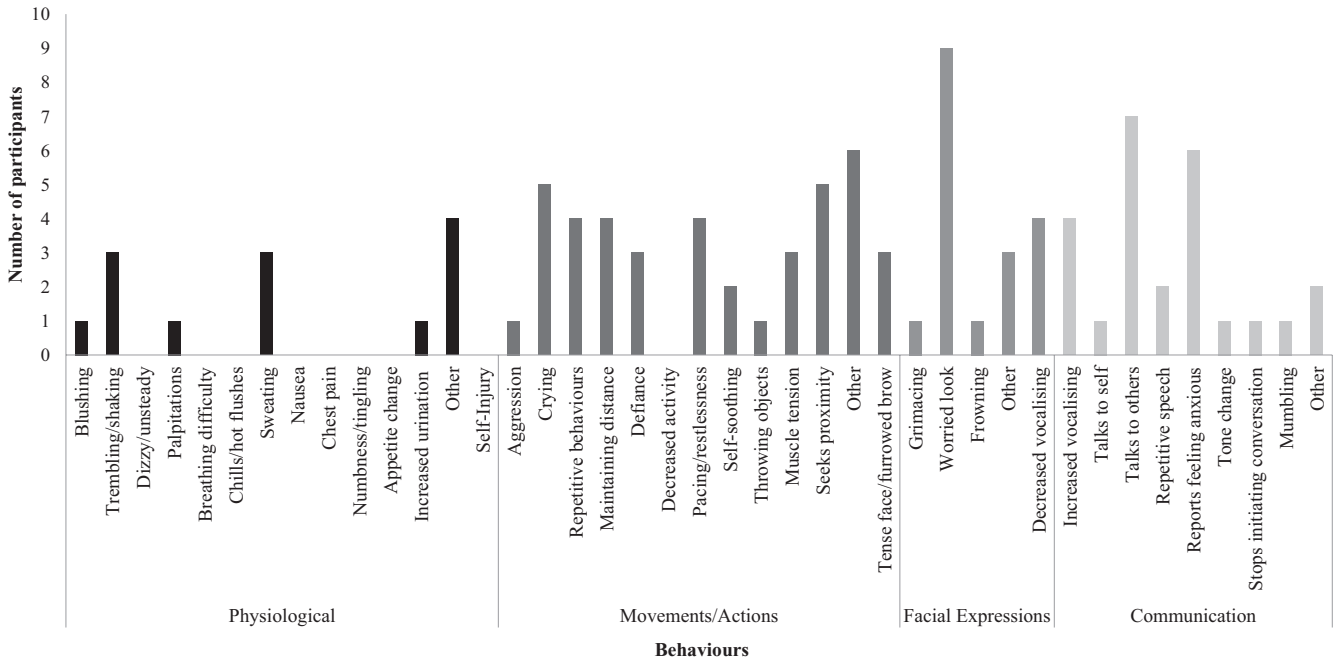

FIGURE 3 Behaviours associated with anxiety reported in the interview

(*n* = 9). Parents also perceived themselves as having a reasonable level of control over the impact of this anxiety (maximum score of full control=10: median: 7, range: 0–8.5).

3.7 | Anxiety profiles

Figure 4 presents each individual's anxiety profile. Triggers were variable across participants and only three parents reported setting events of poor sleep and pain. These are events not specifically related to anxiety but may increase the likelihood of anxiety occurring. For some individuals, primary responses such as withdrawal were described and the majority of people showed some form of physiological response when anxious (e.g. tension, sweating, trembling). Secondary behaviours such as crying, repetitive behaviours and changes in communication were common. Various strategies were utilised by participants to alleviate and reduce anxiety (e.g. distraction, seeking proximity or reassurance), and these were all rated as being effective at least 75% of the time. Four parents reported the duration of anxiety as being 10 min or less; five described anxiety as diminishing and reappearing in a cyclical fashion and three reported that anxiety dissipated only after the removal of the triggering stimulus.

4 | DISCUSSION

This is the first study to employ a formulation driven framework to explore the nature and phenomenology of anxiety in Williams syndrome. The interview focused on examining triggers, behaviours and strategies, as well as the frequency, severity, onset and impact of anxiety. The utilisation of a formulation approach also facilitated the mapping of anxiety profiles for each participant, providing a visual depiction of the triggers, behaviours and strategies utilised by individuals with Williams syndrome and their families.

Consistent with the existing literature, the interview highlighted anxiety as being the most prevalent mental health problem for individuals with Williams syndrome (Dodd & Porter, 2009; Leyfer et al., 2006). Anxiety was triggered by multiple precipitating factors for all individuals. Several triggers outlined in the interview, including routine changes and unpredictability, have been described in Williams syndrome, as well as in other neurodevelopmental disorders associated with intellectual disability, including autism spectrum disorder, Prader-Willi syndrome and fragile X syndrome (Davies et al., 1998; Moskowitz et al., 2013; Oliver et al., 2010; Ozsivadjian et al., 2012; Woodcock et al., 2009). Anxiety related to 'negative emotions in others' has not been reported previously in the Williams syndrome literature, although may reflect the highly empathic nature of people with Williams syndrome (Klein-Tasman & Mervis, 2003). This trigger could also be considered socially related, which is a surprising finding considering the low reported rates of social anxiety in Williams syndrome (Royston et al., 2017). This novel finding requires further investigation but highlights the benefits of using alternative assessment methodologies, such as formulation, to explore mental health.

Reported triggers could also be considered and categorised in a broader context. Many of the reported specific phobias (i.e. storms, noise, babies and animals) fall under the umbrella of uncertainty. Likewise, noise phobias, sensory sensitivities, fear of young children and thunderstorms could be accounted for by the pervasiveness of hyperacusis in Williams syndrome (Levitin et al., 2005; Leyfer et al., 2006). Reports of these triggers are generally consistent with

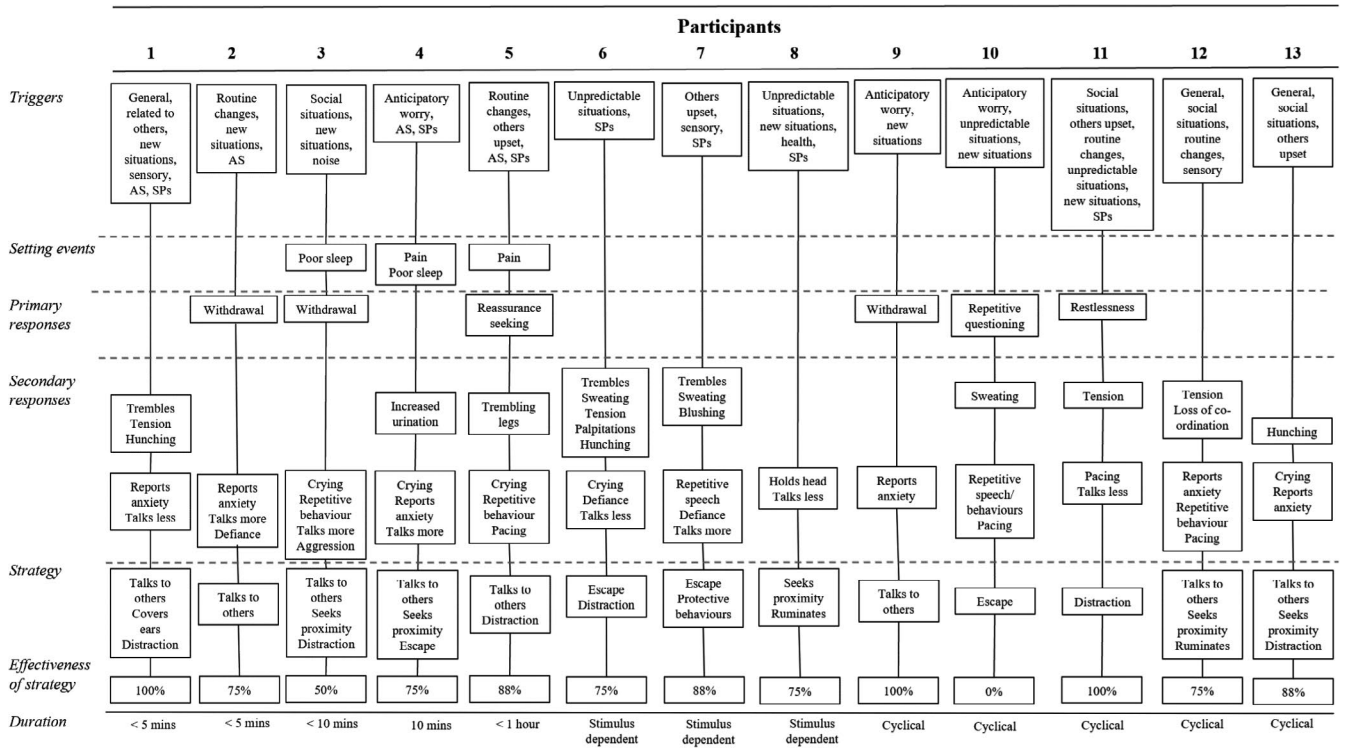

FIGURE 4 A diagram to show anxiety triggers and setting events, physiological responses, behavioural responses and coping strategies utilised

previous Williams syndrome research (e.g. Dykens, 2003; Leyfer et al., 2006) and may be associated with certain core phenotypic difficulties in Williams syndrome. Hence, identification of these factors may inform understanding of the genotype-phenotype relationship.

Many of the behaviours reported could be considered typical anxiety responses, including crying, seeking proximity and restlessness (Eley et al., 2003). Repetitive behaviours in response to anxiety have also been reported in other conditions, such as autism spectrum disorder and fragile X syndrome (Adams et al., 2019; Glod et al., 2019; Janes et al., 2014; Rodgers et al., 2012; Sullivan et al., 2007). Parents reported far fewer physiological symptoms than other more directly observable behaviours. This is similar to the findings of Stinton et al. (2010), indicating parents may find it more challenging to report on physiological symptoms. Further examination of these symptoms may require more experimental and self-report focused studies.

Contrary to expectations, and other clinical and research reports (e.g. Ng-Cordell et al., 2018; Royston et al., 2017; Uljarević et al., 2018), anxiety was generally reported as mild, infrequent and minimal in terms of impact. This may be due to several different factors. For example, since the specific focus of the study was not revealed during recruitment, our participants may constitute a more representative sample of the Williams syndrome population, rather than just those experiencing high anxiety. It is also possible that parents may underreport the extent of anxiety problems compared to the accounts of individuals themselves (Stinton et al., 2010). Moreover, the persistence of anxiety over a prolonged period of time may lead to lifestyle adjustments and the adoption of coping strategies perceived as successful, which, in turn, may influence parental perceptions regarding anxiety frequency and severity.

The frequent use of avoidant coping strategies in response to anxiety is comparable with findings in other groups of individuals with intellectual disability (Hartley & Maclean, 2005). Parents in this study also reported the frequent and effective use of support and reassurance seeking behaviour. Nevertheless, despite parental perceptions of effectiveness, these strategies may only provide short-term alleviation and may contribute to anxiety maintenance in the long term (Rector et al., 2011). Identification of more successful and adaptive coping strategies will assist in the development of interventions to guide individuals and parents on the most effective anxiety management methods.

There are a number of limitations to this study. Several interview questions required parents to interpret the thoughts and behaviours of their child and to recall information retrospectively. As noted above, individuals with Williams syndrome tend to report higher levels of anxiety than their parents (Stinton et al., 2010); hence, reliance on parental report may result in unduly low estimates of severity and impact. Due to the flexibility and open-ended nature of the interview, less salient but relevant information may have not been reported by the parent. Additionally, several of the topographies of anxiety that were classified as 'triggers' may not necessarily reflect more pervasive types of anxiety, such as social related anxiety, that can occur across multiple contexts and situations. This potentially confounds the conceptual distinction between the two types of anxiety (i.e. triggered by specific events or relating to context) examined in the interview. However, the anxiety reported in this interview is

consistent with previous Williams syndrome research demonstrating elevated anxiety in this group (e.g. Leyfer et al., 2006; Royston et al., 2017).

A further issue relates to the lack of association between the interview and the SCAS. Although inter-rater reliability was good, correlations between interview items and the corresponding subscales of the SCAS-P were low. This may be due to the small sample size or the emphasis on certain SCAS-P items that are less relevant for individuals with Williams syndrome. For instance, the social subscale of the SCAS-P includes items such as worrying about the use of public toilets and taking tests. However, parents in the interviews reported more people-oriented social anxieties, such as worry about other's expectations and receiving criticism. This suggests that some symptoms may not be effectively captured by the SCAS-P and that different symptoms are more reflective of anxiety problems for people with Williams syndrome.

Despite these limitations, the study findings add to our understanding of the characteristics of anxiety in Williams syndrome and have identified important areas for future research. These include the need for increased use of self-report assessments, the use of formulation interview techniques with larger samples of both children and adults and further investigation, in particular, of the trigger relating to negative emotions in others.

To summarise, the use of a formulation framework has been valuable for exploring and describing the phenomenology of anxiety in a small sample of individuals with Williams syndrome. The interview highlighted many features that correspond with existing literature, including common symptoms and triggers. It has also proved valuable in identifying avenues for future research such as studies focusing on anxiety related to negative emotions in others and anxiety management strategies. Further exploration of these findings and investigations with larger samples of participants will further elucidate the contributions of these factors to the anxiety profile in Williams syndrome.

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CONFLICT OF INTEREST

No conflicts of interest have been declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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