Abstract

Despite significant advances in understanding and treating social anxiety in the general population, progress in this area lags behind for individuals with intellectual disability. Fragile X syndrome is the most common cause of inherited intellectual disability and is associated with an elevated prevalence rate of social anxiety. The phenotype of fragile X syndrome encompasses multiple clinically-significant characteristics that are posed as risk markers for social anxiety in other populations. Here, evidence is reviewed that points to physiological hyperarousal, sensory sensitivity, emotion dysregulation, cognitive inflexibility, and intolerance of uncertainty as primary candidates for underlying mechanisms of heightened social anxiety in fragile X syndrome. A multi-level model is presented that provides a framework for future research to test associations.

Keywords*:* social anxiety, risk factors, mechanisms, fragile X syndrome,

Social Anxiety in Neurodevelopmental Disorders: The Case of Fragile X Syndrome

Anxiety disorders are common with an approximate 12-month prevalence of 18% in the general population (Kessler, Chiu, Demler, & Walters, 2005). Children and adults with intellectual disability (ID) are four times more likely to meet criteria for anxiety than those without ID (Green, Berkovits, & Baker, 2015), and individuals with some genetic causes of ID are at even higher risk (Cordeiro, Ballinger, Hagerman, & Hessl, 2011).

Social anxiety disorder is a specific anxiety disorder characterised by persistent fear or anxiety in social situations with exposure to unfamiliar people or possible scrutiny by others. Social situations are either avoided or endured with intense anxiety, which interferes significantly with the person's daily functioning and/or relationships (American Psychiatric Association, 2013). Social anxiety disorder is one of the most common anxiety disorders with a 12-month prevalence rate of 7% (Kessler et al., 2005) in the general population and elevated rates in some genetic syndromes. For example, individuals with fragile X syndrome (FXS) are at particularly high risk of *social* anxiety with almost 60% meeting clinical criteria (Cordeiro et al., 2011). This prevalence rate is almost 35 times higher than that reported in idiopathic ID (Dekker & Koot, 2003).

Despite the substantially heightened prevalence rate, there is a notable lack of evidence-based interventions in people with intellectual disability (Vereenooghe et al., 2018). Multi-level models of anxiety in single disorders can offer a focus for targeted interventions that are informed by the phenotypic characteristics of individual groups. The current review works towards a multi-level model of social anxiety for FXS. In this paper, existing causal models of social anxiety disorder in the general population are summarised. This is followed by an overview of FXS and a review of research on key phenotypic features (i.e. characteristics) of FXS that are identified in general

population models of social anxiety disorders. The explanatory power of these phenotypic characteristics for the elevated prevalence rate of social anxiety in FXS is explored to derive a proposed multi-level model of social anxiety for this population. This model provides a framework for future studies to test explicit hypotheses and pave the way for interventions to ameliorate the negative impacts of anxiety through targeting the contributing mechanisms.

Existing models of social anxiety

Models of social anxiety disorder highlight putative risk factors that enable identification of individuals at high-risk, offering the opportunity for timely identification and preventative interventions. There are a number of causal models with different focal points to explain the development and maintenance of social anxiety disorder in the general population. Cognitive-behavioural models (Clark et al., 1995; Rapee & Heimberg, 1997) and aetiological models (Spence & Rapee, 2016; see Wong & Rapee, 2016 for a review) are summarised below given their potential relevance for the FXS population.

Cognitive models (Clark et al., 1995; Rapee & Heimberg, 1997), state that, upon entering a social situation, individuals with social anxiety disorder engage in self-focussed attention which results in enhanced awareness of their own behaviour and anxiety responses. This information is then used in construction of a negative self-impression. The behavioural element of cognitive-behaviour models focusses on emotion regulation and safety behaviours (e.g. eye gaze avoidance, over-rehearsal, attempts to conceal anxiety). There is clear evidence that cognitive (e.g. information processing biases, focussed attention) and behavioural factors (emotion regulation, safety behaviours) that feature in these models undoubtedly play a role in social anxiety disorder (see Heinrichs & Hofmann, 2001 for a review; McManus, Sacadura, & Clark,

2008). However, it is difficult to accurately capture in-depth information regarding several of these interoceptive factors in many individuals with ID.

Aetiological models, whilst acknowledging cognitive factors, also look to other factors to explain the development of social anxiety disorder and these are more likely to inform causal models in specific neurodevelopmental disorders due to their inclusion of observable factors across multiple levels (biology, behaviour, environment). Spence and Rapee (2016) recently presented convincing evidence for a theoretical model depicting a complex interplay between intrinsic elements, environmental factors, and proximal factors. The authors propose that a genetic or biological predisposition to social anxiety disorder, or the presence of childhood behavioural inhibition (a temperament), coupled with environmental risk factors (parent influences, peer influences, aversive social outcomes, negative life events) influence an individual's acquisition of proximal factors such as social and emotional regulation skills and the development of maladaptive beliefs about the self and others. These maladaptive beliefs contribute to a range of cognitive biases before, during and after a social interaction, which places an individual at heightened risk for social anxiety disorder and its accompanying behavioural, emotional and somatic responses.

Fragile X Syndrome: A 'High-Risk' Population

Affecting approximately 1 in 7,000 males and 1 in 11,000 females, FXS (OMIM Entry: #300624) is the most common cause of inherited ID (Hunter et al., 2014). FXS is a well-characterised monogenic disorder caused by mutations in the 5' untranslated region of the *FMR1* gene (OMIM: 309550) on the Xq27.3 site, which results in an expansion of cytosine-guanine-guanine (CGG) trinucleotide repeats. The CGG segment is typically repeated 5-40 times in the

general population but over 200 times in individuals with the full mutation of FXS. The excessive repeats in FXS causes methylation of the *FMR1* gene, preventing the production of FMRP which helps regulate the production of other proteins and plays a role in the development of synapses. Males and females with FXS are differentially affected due to random X inactivation in females associated with elevated FMRP, which has resulted in the majority of research to date focussing on males. The cognitive phenotype of FXS encompasses moderate ID as well as impulsivity, and compromised sustained attention, inhibition, executive function and language, over and above that expected given the level of ID (see Crawford et al., 2020). The behavioural phenotype of FXS comprises self-injurious behaviour (Crawford, Karakatsani, Singla, & Oliver, 2019), an approach-avoidance socio-behavioural profile (Roberts, Crawford, Hogan, et al., 2019), and the presence of symptomatology associated with autism spectrum disorder, attention-deficit-hyperactivity disorder (ADHD), and anxiety (see Crawford et al., 2020 for an overview).

Anxiety in Fragile X Syndrome

Irrespective of anxiety diagnostic status, the severity of symptomatology associated with social anxiety in males with FXS is comparable to males in the general population with a clinical diagnosis of anxiety (Crawford, Waite, & Oliver, 2017). A study utilising a diagnostic clinical interview based on DSM-IV criteria identified clinically significant anxiety in 82.5% of males with FXS (Cordeiro et al., 2011). Specific phobias and social anxiety were the most common anxiety disorders, with prevalence rates of 60% and 58% respectively, and over 58% of males with FXS met criteria for multiple anxiety disorders (Cordeiro et al., 2011). Ezell et al. (2019), using a different diagnostic measure to Cordeiro et al. (2011) and one that is based on DSM-5,

indicated comparably lower prevalence rates of anxiety (48%) and social anxiety (12%) than those reported by Cordeiro et al. (2011). Ezell et al. (2019) also noted the heterogeneity of participants included in Cordeiro et al. (2011) with regard to age and sex, which may contribute to differences in reported prevalence rates of anxiety.

The substantially elevated prevalence rate of anxiety in FXS, as well as the severity and presence of multiple anxiety disorders, highlights a clinical need for theoretical and empirical developments to further understanding of anxiety, its mechanisms and its risk factors in order to develop effective interventions. The current review culminates in a proposed model that serves as a framework for future research to fill the current gap in theoretical models of anxiety, specifically focussing on social anxiety. Addressing this clinical need is hindered by the challenges associated with measuring anxiety in people with ID, described below, but emerging research shows promise in overcoming these barriers.

Challenges of Studying Anxiety in People with Intellectual Disability

The primary issue facing researchers and clinicians is the accurate assessment and diagnosis of anxiety in individuals who are unable to self-report and/or exhibit a different presentation of anxiety than the general population resulting in diagnostic overshadowing (Appleton, Roberts, & Simpson, 2019). Measuring and characterising anxiety in individuals with ID is difficult due to delay or impairment in communication, which might preclude being able to identify, label, and communicate internal states. Additionally, DSM 5 diagnostic criteria for social anxiety disorder indicate that the person recognises that their fear is unreasonable or excessive, and that the person worries that they might do something that will embarrass them, both of which might not be possible to assess in many individuals with ID which results in under-estimates of diagnoses

(Cordeiro et al., 2011). Given a lack of available alternatives, many studies of anxiety in FXS use measures designed for typically developing populations including informant questionnaires (e.g. Spence Child Anxiety Scale, see Crawford, Waite, et al., 2017) or clinical interview measures (e.g. Cordeiro et al., 2011; Ezell et al., 2019), both of which are reliant on parental insight, which is also likely hindered by limited communication of the person they care for, and are unlikely to capture atypical behavioural expressions of anxiety observed in individuals with ID such as externalising problems (Green et al., 2015), self-injurious and aggressive behaviour (see Wheeler et al., 2014; Woodcock, Oliver, & Humphreys, 2009). Particularly relevant to FXS is the observation of hand-biting, often evoked in response to changes in social-environmental events (Hall, DeBernardis, & Reiss, 2006). These measures are also unlikely to capture the causes of anxiety observed in these individuals where these interact with phenotypic characteristics, a notion clearly documented in the autism literature. Kerns et al. (2021) noted ‘distinct’ anxiety in a proportion of autistic individuals, referring to manifestations of anxiety that commonly arise in ASD but do not match the anxiety disorders specified by the DSM, including “idiosyncratic fears” and “special interest fears”.

Identifying behavioural markers of anxiety in individuals who are unable to self-report holds promise (Crawford, Moss, et al., 2019) but also brings challenges given behavioural overlap between anxiety and other conditions such as autism (see Roberts et al., 2018). Therefore, assessing the stability of overlapping traits (e.g. social avoidance, eye gaze aversion) across different situations, and across development, is crucial for disentangling the mechanistic underpinnings of such behaviours (Crawford, Moss, et al., 2019; Roberts, Crawford, Will, et al., 2019).

Towards a Model of Social Anxiety in Fragile X Syndrome

The clinical need to identify putative risk factors for the substantially heightened social anxiety in FXS highlights the importance of overcoming the barriers of accurate identification and characterisation of social anxiety, described above, particularly given the context that some risk factors identified in other populations are phenotypic of FXS. Existing aetiological models of social anxiety disorder have been developed based on decades of research. In contrast, the study of anxiety in FXS is in its infancy and is hampered by the identification and measurement challenges described above. To date, although the prevalence and phenomenology of social anxiety in FXS have been studied, research into risk factors and associations between phenotypic features of FXS and anxiety has been piecemeal, often investigating variables within one level (e.g. genetic, biological, or cognitive). Thus, as a starting point, a model of social anxiety in FXS requires a more condensed and targeted model than those which have been applied to the general population. In the current review, a model of *intrinsic* factors that contribute to the elevated prevalence and severity of social anxiety in FXS is proposed. As research in this field progresses, additional intrinsic factors as well as environmental and proximal factors can be added.

This review identifies five constructs associated with social anxiety (see Figure 1), either in the general population or in ASD, which may contribute to the elevated prevalence rates of social anxiety in FXS: *physiological arousal, sensory sensitivity, emotion dysregulation, cognitive flexibility and intolerance of uncertainty*. Research demonstrates each of these characteristics as phenotypic of FXS, yet their association to anxiety has not been extensively explored. Whilst the available literature highlights a potential for each of these areas to be implicated in anxiety, it is proposed here that particular gains in effectiveness of anxiety interventions are likely to be made in the areas of physiological hyperarousal, emotion dysregulation and intolerance of uncertainty.

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Physiological Hyperarousal

Physiological hyperarousal is indexed by atypical function of the hypothalamus-pituitary-adrenal (HPA) axis and/or the autonomic nervous system, which both concern responses to stress. The response relevant to the HPA axis is characterised by the hypothalamic release of the corticotropin-releasing hormone, which binds to receptors on the anterior pituitary gland and in turn releases adrenocorticotropic hormone (ACTH). ACTH binds to receptors on the adrenal cortex and stimulates the adrenal release of cortisol. A negative feedback system then promotes the return of homeostasis. The autonomic nervous system response to stress comprises the sympathetic and parasympathetic systems. On presentation of a stressor, the sympathetic nervous system signals to adrenal glands to release adrenaline and cortisol resulting in physiological arousal indexed by increased heart rate and respiration, changes in the digestive process, and increased blood glucose levels, among other physiological responses. The parasympathetic system works to bring physiological functions back to a calm state. In the general population, autonomic dysfunction is implicated in social anxiety disorder via higher baseline sympathetic activity including elevated heart rate and electrodermal activity, as well as lower respiratory sinus arrhythmia, an indicator of lower parasympathetic activation (Krämer et al., 2012; Nikolić, Aktar, Bögels, Colonnesi, & de Vente, 2018; Schmitz, Krämer, Tuschen-Caffier, Heinrichs, & Blechert, 2011). In their aetiological model, Spence and Rapee (2016) indicate that physiological hyperarousal may not be specific to social anxiety disorder and instead may reflect broader anxiety or temperament differences. Whilst this warrants further investigation, it is not a primary feature of their model.

The role of physiological hyperarousal in social anxiety may be more pivotal in neurodevelopmental disorders, particularly those associated with hyperarousal as a core feature. For example, Bellini (2006) showed that, combined with impairments in social skills, physiological hyperarousal predicts social anxiety in people with ASD. A plethora of research documents physiological hyperarousal in FXS through cardiac indices of elevated heart rate, lower heart rate variability, and respiratory sinus arrhythmia indicating diminished vagal tone, as well as heightened salivary cortisol and electrodermal responses (Hardiman & Bratt, 2016; Klusek, Roberts, & Losh, 2015). Evidence indicates that the autonomic dysfunction reported in FXS is not solely a consequence of ID (see Klusek et al., 2015). Together, this research points to both an overactive sympathetic nervous system and an underactive parasympathetic nervous system, which has been demonstrated in infants with FXS as young as 12 months of age (Roberts, Hatton, Long, Anello, & Colombo, 2012).

Research shows that, compared to typically developing individuals, those with FXS evidence physiological dysregulation at baseline *and* throughout social interactions, conversations, toy play, and frustration-eliciting tasks (Belser & Sudhalter, 1995; Hall, Lightbody, Huffman, Lazzeroni, & Reiss, 2009; Klusek, Martin, & Losh, 2013; Roberts et al., 2012). Given that social stressors do not evoke a heightened physiological state above that observed at baseline or in typical development, physiological hyperarousal is believed to be primarily a chronic state in FXS rather than solely dependent on or influenced by context. Although social interaction does not directly evoke heightened arousal, chronic hyperarousal may impair ability to interact with the environment, which may in turn lead to avoidance and anxiety behaviours. An inverse relationship should also be considered whereby social anxiety contributes to physiological hyperarousal.

Associations between physiological hyperarousal and anxiety-related behaviours have yielded mixed findings in FXS. Increased cortisol is associated with behavioural characteristics indicative of social anxiety e.g. more withdrawn behaviour (Hessl et al., 2002), social avoidance (Roberts et al., 2009), and eye gaze aversion although the direction of the latter relationship is unclear (Hall et al., 2006; Hessl, Glaser, Dyer-Friedman, & Reiss, 2006). Despite hyperarousal being a primary putative candidate for underlying social anxiety (Roberts et al., 2018), and evidence of associations between hyperarousal and anxiety-related behaviours noted above, direct associations between *social* anxiety and arousal have not been demonstrated (Keysor, Mazzocco, McLeod, & Hoehn-Saric, 2002; Klusek et al., 2013). However, elevated anxiety is associated with increased HPA activation in FXS (Matherly et al., 2018) and general arousal, indexed by shorter interbeat interval, predicts later anxiety (Hogan et al., 2021). The literature suggests that physiological hyperarousal contributes to social anxiety in FXS but this is a pervasive rather than a context-dependent reaction, and that the relationship between arousal and social anxiety is more complex than that posed by models that do not account for developmental and phenotypic factors that may mediate the relationships. This integrative review poses that sensory sensitivity, emotion dysregulation, cognitive inflexibility, and intolerance of uncertainty also interact and contribute to the relationship between arousal and social anxiety. As such, existing literature in each of these areas is reviewed below.

Sensory Sensitivity

Sensory sensitivities to light, sound, smell, touch, or sensations (e.g. temperature) may provoke anxiety or distress in social settings, and anticipatory anxiety ahead of social settings leading to avoidant behaviours. Although sensory processing sensitivity is associated with social

anxiety disorder in the general population (Hofmann & Bitran, 2007), it is not a factor in prominent causal models. The contribution of atypical sensory processing to social anxiety is likely considerably more notable in neurodevelopmental disorders than the general population given that sensory sensitivity is inversely associated with mental age (Baranek, David, Poe, Stone, & Watson, 2006) and there is an increased prevalence and severity of hypo or hyper-responsiveness to sensory input in neurodevelopmetal disorders. A study of Cornelia de Lange syndrome, Angelman syndrome and FXS showed that each group was associated with a heightened prevalence of unusual sensory processing in comparison with normative data, evidenced in over 80% of all participants, with cross-syndrome differences in profiles (Heald, Adams, & Oliver, 2020). Atypical sensory processing is also a core feature of ASD, and has been associated with social anxiety in this population (Spain, Sin, Linder, McMahon, & Happé, 2018).

Sensory processing differences are well documented in FXS manifesting as auditory, olfactory, tactile, or visual defensiveness, sensitivity or avoidance (Rais, Binder, Razak, & Ethell, 2018; Rogers, Hepburn, & Wehner, 2003) at similar rates and severity to individuals with ASD (Rogers et al., 2003). The behavioural impacts of sensory sensitivity include poor eye contact, avoidance of noisy places, and impaired social reciprocity (Rais et al., 2018), which are all behavioural indicators of anxiety. However, a direct link between sensory processing and anxiety in FXS has not yet been explored.

In working towards a model of social anxiety in FXS, the interplay between features should be considered. Physiological hyperarousal has been noted above as pivotal to the proposed model, and the association between sensory processing and hyperarousal has received attention. Research has shown that a subgroup of children classed as having *severe* sensory processing differences demonstrated lower physiological regulation than typically developing children via

lower vagal tone at baseline and during auditory stimuli presentation (Schaaf et al., 2010). However, a direct link between physiological hyperarousal and sensory profiles in FXS has not been found (Klusek et al., 2015). This may be due to hyperarousal being a chronic state in FXS independent of variation in sensory profiles or vice versa, as is likely the case with hyperarousal not being dependent on social context, as noted in the literature reported above.

In typically developing children, and children with ASD and ADHD, path model analysis has revealed that the intensity of response to sensory stimuli is a mediating variable between baseline arousal levels and anxiety (Lane, Reynolds, & Dumenci, 2012). This suggests that the combination of hyperarousal and sensory sensitivity plays a role in the development and maintenance of anxiety and application of this relationship to social anxiety would be worthwhile to inform causal models more broadly. This is particularly relevant to the FXS population given the presence of hyperarousal and sensory sensitivity as core features. Specifically, it is perhaps the case that whilst hyperarousal does not link directly to anxiety or sensory profiles, the combination of hyperarousal and sensory processing differences interact to influence an individual's experience of anxiety. These mediating relationships likely play a small role in a wider and more complex model. Here, it is proposed that additional factors that are phenotypic of FXS and may interact with hyperarousal and sensory processing abnormalities, such as emotion dysregulation, cognitive flexibility and intolerance of uncertainty, are also involved in the development and maintenance of social anxiety in FXS.

Emotion Dysregulation

Emotion regulation refers to 'extrinsic and intrinsic processes responsible for monitoring, evaluating, and modifying emotional reactions, especially their intensive and temporal features,

to accomplish one's goals' (Thompson, 2019). Emotional regulation can increase and decrease emotional responses, such as anxiety (Cisler, Olatunji, Feldner, & Forsyth, 2010). In the general population, there is empirical evidence for specific emotion regulation deficits that explain the onset and maintenance of social anxiety disorder. Emotion regulation is included in aetiological models of social anxiety disorder where it is proposed that intrinsic factors and environmental factors influence an individuals' emotion regulation skills (Spence & Rapee, 2016). Some emotion regulatory strategies such as attentional deployment and safety behaviours are relevant to factors included in cognitive-behavioural models of social anxiety disorder (Clark et al., 1995; Rapee & Heimberg, 1997). Here it is proposed that emotion dysregulation plays an integral role in social anxiety, particularly for individuals with FXS for whom the sensory input associated with social situations and chronic state of hyperarousal serves as an emotional trigger.

It is argued that individuals with intellectual disability employ a limited repertoire of coping strategies when emotionally aroused (Benson & Fuchs, 1999). Impaired emotion regulation is proposed to underlie many of the behavioural problems commonly seen in children and adults with intellectual disability as well as ASD such as aggression, irritability and anxiety (Mcclure, Halpern, Wolper, & Donahue, 2009; White, Oswald, Ollendick, & Scahill, 2009). The association between these constructs is likely rooted in a failure to employ effective emotional regulation strategies resulting in impulsive reactions including temper tantrums, aggressive and self-injurious behaviour in response to threatening stimuli. However, such behaviours may also reflect behavioural expressions and responses to anxiety in social settings. In support of this notion, social anxiety is reported to predict aggression in ASD (Pugliese, White, White, & Ollendick, 2013) and anxiety is associated with 'problem behaviours' in FXS (Wheeler et al.,

2014). In addition, Woodcock et al. (2009) reported overt displays of anxiety in males with FXS including stereotypical and self-injurious behaviours.

Temperament, which is defined as 'constitutionally based individual differences in reactivity and self-regulation' (Rothbart, Bates, Damon, & Eisenberg, 2006), encompasses affective, attentional and motor reactivity, and is semantically related to emotion regulation. Temperament is a primary feature of existing causal models of social anxiety disorder (Spence & Rapee, 2016) based on decades of empirical evidence in support of the association. Research into temperament in individuals with FXS has identified a profile of features including being more active, less adaptable, and more intense, sad, angry, persistent, and approachable than typically developing peers (Hatton, Bailey, Hargett-Beck, Skinner, & Clark, 1999; Shanahan, Roberts, Hatton, Reznick, & Goldsmith, 2008). Temperament ratings have been associated with anxiety in FXS with early displays of negative affect (composed of fear, anger/frustration, sadness and soothability) predicting later emergence of anxiety (Tonnsen, Malone, Hatton, & Roberts, 2013; Wall et al., 2019).

The autonomic nervous system is involved in the regulation of emotion (Thayer & Lane, 2000) and so it is possible that a chronic heightened state of arousal, as documented in FXS, may result in poor emotion regulation. Whilst the temporal link and causal relationship between arousal and inhibition is not well understood, documented impairments in both the sympathetic and parasympathetic processes indicate that increased acceleration inhibits deceleration processes leading to hyperarousal-induced emotion dysregulation. The close link between physiological hyperarousal and emotional regulation is evidenced by the same physiological markers (e.g. vagal tone) underlying both arousal and emotion regulation. High vagal tone is associated with effective emotion regulation and an ability to attend selectively to aspects of

situations enabling adaptable responses whereas low vagal tone is related to poor regulation (Thayer & Lane, 2000). Dysregulated arousal systems, therefore, likely have a direct impact on the experience and regulation of emotions. In support of this, a recent study has reported vagal nerve stimulation as an effective intervention for temper outbursts in individuals with Prader-Willi syndrome (Manning et al., 2019) and a promising approach to alleviate emotional regulation challenges for people with ASD (Engineer, Hays, & Kilgard, 2017; Jin & Kong, 2017; van Hoorn et al., 2019).

Attentional deployment and cognitive change are processes proposed to be involved in regulation of emotion (Barrett, Ochsner, & Gross, 2007). These skills are compromised in people with FXS due to significant impairments in executive function including cognitive flexibility or attention switching (Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2013; Perry et al., 2022; Wilding, Cornish, & Munir, 2002), which has implications for social anxiety as discussed below. In a given social situation, a chronic state of hyperarousal combined with sensory sensitivity may result in a negative emotional state, which cannot be regulated effectively through redirecting attention, due to impaired cognition.

Cognitive Flexibility

Cognitive flexibility, an emergent property of executive function requiring attention switching, refers to the ability to switch between mental processes to adapt behaviour in response to environmental changes. Broad impairments in executive function, as well as attention switching, have been related to social anxiety (Fujii et al., 2013). Cognitive factors including biased attention for threat and self-focus have been well-documented in social anxiety disorder and are a prominent feature of both cognitive-behavioural (Clark et al., 1995; Rapee &

Heimberg, 1997) and aetiological models (Spence & Rapee, 2016). The ability to shift focus away from the self and from threatening stimuli may be more impaired in individuals with cognitive inflexibility.

Cognitive flexibility is inversely associated with mental age (Campbell et al., 2013) and is compromised in many neurodevelopmental disorders including FXS (Schmitt, Shaffer, Hessl, & Erickson, 2019). Specifically, widespread executive function impairments have been reported in FXS relative to mental age and compared to other neurodevelopmental disorders, particularly on tasks of attention shifting (Perry et al., 2022). This supports other research suggesting particular impairments in attention shifting and inhibition, and delayed development of executive function relative to mental age (see Schmitt et al., 2019 for a review).

One potential route for executive dysfunction to impact social anxiety is through ineffective attention switching leading to disproportionate attention allocation to threatening stimuli, which is widely reported in anxious individuals (see Bishop, 2007 for a review). Indeed, studies using eye-tracking have revealed that heightened social anxiety is associated with more looking, or hypervigilance, to social information in males with FXS (Crawford et al., 2016; Crawford, Moss, Oliver, & Riby, 2017) lending support to the notion that social stimuli such as people and faces are perceived as a threat. In addition, research has shown that individuals with social anxiety have difficulty disengaging from negative social cues (disgust faces) but not positive social cues (happy faces; Buckner, Maner, & Schmidt, 2010). Interestingly, males with FXS show a similar pattern by spending more time looking at disgust versus neutral faces compared to happy versus neutral faces (Crawford, Moss, Anderson, Oliver, & McCleery, 2015). Threat-related attentional biases have been documented in male adolescents with FXS which correspond with anxiety outcomes as a function of age and intensity of fear depicted in stimuli (Kelleher et al., 2020). A

bi-directional relationship should also be considered whereby social anxiety leads to cognitive inflexibility.

An alternative but complementary route for executive dysfunction to impact anxiety is through cognitive-environment interaction. For example, attention switching performance on a go/no-go task is linked to overt displays of anxiety in males with FXS following an unexpected change to daily routine (Woodcock et al., 2009). Interestingly, under the same conditions, individuals with Prader-Willi syndrome demonstrate an association between attention switching deficits and *temper outbursts* rather than anxiety following a change to routine (Woodcock et al., 2009), suggesting a FXS-specific pathway to anxiety downstream from genetic cause. The specificity of this finding to social anxiety warrants further investigation. Links between executive dysfunction and anxiety are also reported in other neurodevelopmental disorders. For example, challenges with planning and working memory are associated with reduced verbalisation, which may be indicative of social anxiety for individuals with Cornelia de Lange syndrome (Crawford, Moss, et al., 2019; Nelson, Crawford, Reid, Moss, & Oliver, 2017; Reid, Moss, Nelson, Groves, & Oliver, 2017).

As well as being linked directly to anxiety, executive function may interact with other features of the FXS phenotype which may also exacerbate social anxiety. For example, poor executive function predicts poor use of adaptive emotion regulation strategies (Andreotti et al., 2013; McRae, Misra, Prasad, Pereira, & Gross, 2012) and mediates the relationship between temperament, linked to emotional regulation described above, and childhood anxiety (Affrunti & Woodruff-Borden, 2015). Similarly, it has been suggested that temperament is more likely to increase risk for social anxiety in children with low attention shifting (Henderson, Pine, & Fox, 2015). Here it is proposed that, in FXS, the negative emotional state experienced in social

situations, induced by a chronic state of hyperarousal combined with sensory sensitivity, cannot be regulated effectively through redirecting attention, due to impaired cognition. It is likely that this inability to process and cope with the social environment would lead to an intolerance of uncertainty or unpredictable events.

Intolerance of Uncertainty

Intolerance of uncertainty refers to a tendency to respond negatively to uncertain or unpredictable situations incorporating two primary constructs; Desire for Predictability (a drive for future events to be certain), and Uncertainty Paralysis (a feeling of being 'stuck' in a cognitive or behavioural sense in the face of uncertainty; Berenbaum, Bredemeier, & Thompson, 2008; Birrell, Meares, Wilkinson, & Freeston, 2011)). Intolerance of uncertainty is well-documented as a risk factor for clinically significant anxiety in the general population (Carleton, 2012) and is linked to many types of anxiety-related disorder, including social anxiety disorder (Boelen & Reijntjes, 2009; Counsell et al., 2017; Whiting et al., 2014). As a relatively new concept, intolerance of uncertainty specifically does not appear in existing causal models of social anxiety disorder. However, it may be viewed as an extension to key factors of cognitive-behavioural models such as interpretation bias (the tendency to interpret ambiguous or neutral stimuli as threatening; Clark et al., 1995; Rapee & Heimberg, 1997). As well as interpreting ambiguous or neutral stimuli as threatening, individuals with social anxiety disorder may have a tendency to interpret uncertain or unpredictable events as threatening. As such, social situations, which are often unpredictable in nature, become feared.

Intolerance of uncertainty has been identified as a predictor and maintaining factor of anxiety in other neurodevelopmental disorders including ASD (see Boulter, Freeston, South, & Rodgers,

2014; Jenkinson, Milne, & Thompson, 2020) and Williams syndrome (Uljarević, Labuschagne, Bobin, Atkinson, & Hocking, 2018). Research supports the notion that intolerance of uncertainty is a direct predictor of anxiety in ASD (Cai, Richdale, Dissanayake, & Uljarević, 2018; Hwang, Arnold, Srasuebkul, & Trollor, 2020; Maisel et al., 2016; Wigham, Rodgers, South, McConachie, & Freeston, 2015) but also that it mediates relationships between other factors, including autism symptomatology, and anxiety (Boulter et al., 2014; Hwang et al., 2020). This mediating pattern is also observed in Williams syndrome (Uljarević et al., 2018). However, this research has not focussed on social anxiety specifically and so further research is required to understand the association of intolerance of uncertainty to social anxiety in such populations.

There is currently no published research on intolerance of uncertainty in FXS. However, pilot data indicate that, much like in idiopathic ASD and Williams syndrome, intolerance of uncertainty is directly linked to anxiety (Perry, 2019). Whether this pattern extends to *social* anxiety warrants investigation. Although intolerance of uncertainty has not been well-explored as a construct, features of the FXS phenotype indicate that intolerance of uncertainty is likely to play an important role in social anxiety. For example, research conducted by Roberts and colleagues indicates that individuals with FXS display a “warm up” effect with high levels of social avoidance on initial encounter with an unfamiliar adult which decreases as the adult becomes more familiar (Roberts et al., 2009; Roberts, Crawford, Hogan, et al., 2019; Roberts, Weisenfeld, Hatton, Heath, & Kaufmann, 2007). In support of this, males with FXS are reported by their parents as more sociable with familiar versus unfamiliar adults (Moss et al., 2016). These findings may reflect avoidance of the uncertainty that comes with interacting with an unfamiliar social partner. The mechanisms of this may be rooted in impaired social

communication, which might lead to an individual to feel incapable of handling challenges and thus fearing potential challenges.

Intolerance of uncertainty mediates the relationship between anxiety and other factors presented in this review. Specifically, intolerance of uncertainty mediates the relationship between emotional regulation and anxiety in ASD (Cai et al., 2018), and is a predictor of sensory sensitivities in children with and without autism (Hwang et al., 2020; MacLennan, Rossw, & Tavassoli, 2021; Neil, Olsson, & Pellicano, 2016). The extent to which intolerance of uncertainty predicts social anxiety and is associated with other features of the FXS phenotype that combine to impact feelings of anxiety is important for future research to consider.

Conclusions and Future Directions

Here, research is presented that highlights features of the FXS phenotype, which are associated with social anxiety in the general population and in individuals with other neurodevelopmental disorders, that have explanatory power for the strikingly heightened rate of social anxiety in this syndrome group. This research has been reviewed in order to move towards the proposal of a model that provides a framework for future studies to explore associations and pave the way for interventions to ameliorate the negative impacts of social anxiety through targeting the contributing mechanisms (Figure 1).

The model presented here highlights a complex and multi-level pathway to social anxiety built around a biologically aroused state that, combined with sensory sensitivity, predisposes individuals with FXS to an inability to regulate negative emotions. In this case, heightened acceleration of physical processes impairs the ability for deceleration of emotional responses. From this state of heightened arousal and emotion, individuals with FXS may be unable to shift

attention away from threatening stimuli resulting in an intolerance for uncertain situations or events as they may be interpreted as threatening. There is a hierarchical element to this model in that emotion dysregulation is downstream of physiological hyperarousal and sensory sensitivity, and cognitive inflexibility and intolerance of uncertainty are downstream of emotion dysregulation.

This model highlights important steps to take towards intervention for this population. First, accurate measurement of the risk factors, triggers and manifestation of social anxiety is crucial. Second, this review represents a move towards a multi-dimensional model of phenotypic outcome and so mediation analyses to explore the proposed contributions of risk factors to social anxiety would enable evidence-based refinement and solidification of a model of social anxiety in FXS. Other factors such as social interaction skills, or autism symptomatology, demographic variables including sex and level of ID, and genetic factors including FMRP levels may contribute to heightened social anxiety in FXS. However, mixed evidence around *how* these factors contribute precludes their inclusion in the proposed model prior to further research being conducted. Rather than being an exhaustive model that incorporates all potential factors, it is a starting point for exploring biological and cognitive mechanisms that are pivotal to improving understanding of social anxiety in the FXS population with the aim of moving towards targeted intervention. In addition, whilst the proposed model ends at social anxiety, social anxiety may lead to some of the pragmatic language difficulties seen in FXS such as poor topic maintenance, perseveration, and rarer cases of selective mutism (Klusek et al., 2013) and future models may build on this as evidence develops. Complementary research should focus on additional factors that are incorporated into existing aetiological models, such as environmental effects, that may contribute to social anxiety. In addition, cross-syndrome comparisons offer valuable insight into

the specificity of risk markers and social anxiety presentation to individual syndromes. Finally, understanding the developmental sequence of social anxiety and its associated risk factors would further inform the relationship between important constructs and identify optimal times for intervention. Whilst these goals are ambitious for any one research site studying single rare genetic syndromes, given the rarity and geographical dispersion of participants, a move towards national and international collaborative efforts, with harmonised and standardised measurement, would enable these steps to be taken with the required statistical power and enable the field of genetic syndromes to be in a prime position for intervention development and evaluation which, to date, has been neglected.

Data from fragile X clinics in the USA shows that between 40% and 90% of individuals with FXS have been prescribed psychotropic medications (Berry-Kravis & Potanos, 2004) and medication use appears stable over time (Laxman et al., 2018). Treatment success, defined as documented clinical report of improvement in behaviour, is between 53% (for anti-depressants) and 62% (for alpha2-agonists) with stimulants and anti-psychotics falling between this range. Data from a national survey in the USA indicated that anxiety is the most common symptom for which medication is given to individuals with FXS (42% of males, 26% of females) yet these medications are described by approximately 70% of parents as not effective, a little effective or somewhat effective (Bailey Jr et al., 2012). Exploring the feasibility and utility of alternative interventions in FXS, such as physiological and behavioural interventions that have grounding in explicitly tested causal models, is important to provide strategies that are more effective than the current pharmacological treatments.

One intervention that has been tested in a small sample of males with FXS is intranasal oxytocin, which resulted in improved eye gaze frequency and reduced cortisol levels but did not

affect heart rate, respiratory sinus arrhythmia or heart rate variability (Hall, Lightbody, McCarthy, Parker, & Reiss, 2012). Recent intervention advances in other neurodevelopmental disorders indicate that vagal nerve stimulation (Manning et al., 2019) and parent-training in intolerance of uncertainty (Rodgers, Herrema, Honey, & Freeston, 2018; Rodgers et al., 2017) have potential to ameliorate characteristics that may be influential in the development and maintenance of social anxiety in FXS. Exploring the predictive power of the proposed risk factors for social anxiety in FXS will afford the opportunity for work towards focused, targeted and timely intervention for anxiety, and highlight the utility of adapting or applying existing interventions (e.g. Manning et al., 2019; Rodgers et al., 2018; Rodgers et al., 2017). In the context of the proposed model, physiologically-improved emotional regulation through vagal nerve stimulation would lower the likelihood of an individual experiencing a negative emotional state, and subsequently put less demand on an already impaired cognitive system to redirect attention as a coping mechanism. More effective regulation of emotions may then improve an individuals' tolerance for uncertainty given less exposure to a negative state in such situations, subsequently leading to less social anxiety symptomatology. Interventions focussed on increasing tolerance for uncertainty would have a more direct impact on social anxiety symptomatology by providing behavioural strategies in situations that cause distress. The proposed model provides a framework, not only to test explicit hypothesis regarding the associative factors contributing to heightened social anxiety in FXS, but also to develop or adapt interventions that are grounded in theory and empirical advances.

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