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Hyper-reactivity in fragile X syndrome females: Generalised or specific to socially-salient stimuli? A skin conductance study

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ABSTRACT

Fragile X syndrome (FXS) is characterised by hyper-reactivity, autistic tendencies and social anxiety. It has been hypothesised that the FXS social phenotype is secondary to a generalised hyper-reactivity that leads to social avoidance. No study, however, has investigated whether hyperarousal in FXS is generalised or more specific to socially salient information. We recorded skin conductance responses (SCRs) while females with FXS, as well as chronological age-(CA-) and mental age-(MA-) matched controls, viewed two sets of visual images: direct-gaze emotional faces and affectively arousing scenes. Explicit emotion recognition and subjective ratings of emotions aroused by images were also recorded. Overall, females with FXS displayed hyper-reactivity only when viewing the more socially salient stimuli (emotional faces), compared to CA-matched controls, but not MA-matched controls. Moreover, females with FXS also displayed atypical emotion recognition abilities and subjective ratings of their own emotional states. These findings suggest that any hyper-reactivity observed in FXS may be more specific to socially salient stimuli, rather than generalised.

1. Introduction

Females with fragile X syndrome (FXS) display the symptoms of attention-deficit hyperactivity disorder (ADHD), autistic tendencies, social anxiety, excessive shyness and social avoidance (Freund et al., 1993; Hagerman, 2002; Lachiewicz, 1992; Mazzocco et al., 1997) to a similar, yet more varied degree than males with FXS. In fact, although females with FXS typically display milder levels of intellectual impairment than their male counterparts, significant socio-emotional difficulties still remain apparent (see Keysor and Mazzocco, 2002). For example, one third of females with the FXS full mutation meet criteria for ADHD (Freund et al., 1993; Hagerman et al., 1992) with many other females with FXS presenting with notable ADHD symptoms despite their not meeting criteria for a formal diagnosis (Keysor and Mazzocco, 2002). In addition, females with FXS are reported to display significantly more autistic behaviours than gender- and chronological age-(CA-) matched controls (Mazzocco et al., 1997; Reiss and Freund, 1992); atypically high rates of social anxiety disorder (Cordeiro et al., 2011; Franke et al., 1996; Tsiouris and Brown, 2004) and avoidant personality disorder (Freund et al., 1993); as well as abnormal social behaviours consistent with schizotypal personality disorder, such as social oddness, avoidance of direct eye contact, and difficulty building rapport (Sobesky et al., 1994). Evidence of emotion recognition deficits in FXS has also begun to emerge, particularly for ambiguous and negative emotional expressions (Cornish et al., 2005; Hagan et al., 2008; Shaw and Porter, in press).

With these aforementioned reports of heightened levels of hyper-reactivity and social difficulties in FXS, researchers have hypothesised that autonomic hyperarousal may explain, at least to some degree, the FXS socio-behavioural phenotype. More specifically, it has been asserted that the autistic features and social anxiety seen in FXS are secondary to generalised hyperarousal that leads to an avoidance of, or withdrawal from, social stimuli (Cohen, 1995; Cornish et al., 2004; Hagerman, 2002). While there has recently been an increase in the number of psychophysiological studies which have investigated autonomic hyperarousal in FXS, the nature and degree of this hyperarousal remains unclear. Moreover, it is particularly relevant to explore autonomic arousal levels to different types of stimuli in FXS individuals. That is, the critical question is whether any apparent hyperarousal in FXS is specific to socially salient stimuli, or more generalised, as suggested by some previous research (e.g., Cornish et al., 2004; Hagerman, 2002; Hirstein et al., 2001).

1.1. Psychophysiology in fragile X syndrome

Early psychophysiological research in FXS focussed primarily on males. Belser and Sudhalter (1995) were the first to use skin conductance measures to empirically explore arousal levels in FXS in a pilot study. The tonic SCLs of two males with FXS, one ADHD male and one

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male with Down syndrome (DS) were measured while the participants engaged in conversations with a stranger. Results revealed that the two males with FXS displayed significantly higher SCLs during conversations which involved eye contact with the stranger compared to both the ADHD and DS males. Their results provided initial support for social hyperarousal in FXS, as well as a possible link between eye contact, arousal and anxiety. However, these early results need to be interpreted with caution due to the small sample size, unmatched comparison groups, and use of tonic non-specific SCLs rather than SCR to index autonomic arousal.

Miller et al. (1999) extended Belser and Sudhalter's (1995) work with males with FXS to systematically compare the SCRs of 15 males with FXS and 15 chronological age-(CA-) and gender-matched typically developing controls during a sensory challenge protocol containing olfactory, auditory, visual, tactile and vestibular stimuli. The FXS individuals displayed SCRs of greater magnitude, more responses per stimulation, greater SCR frequency, and reduced habituation compared to controls across all sensory stimuli; providing support for generalised hyperarousal in FXS. However, using the same sensory challenge protocol, Hagerman et al. (2002) later reported that another group of FXS children and adolescents (84% male), who were taking part in a treatment study using stimulant medication, displayed similar SCR patterns to CA- and IQ-matched developmentally delayed controls at baseline testing. Unlike the developmentally delayed control group, who showed no differences in SCR patterns from time 1 to time 2, the FXS group did, however, show significant decreases in mean SCR frequency and mean SCR peak amplitude after treatment with stimulant medication (Hagerman et al., 2002).

Keysor et al. (2002) were the first to extend this line of research to explore arousal and anxiety levels in adolescent and young adult females with FXS. SCLs were measured initially, while participants were not engaged in any tasks, and then during performance on three cognitive tasks. The females with FXS were compared to females with Turner syndrome and a CA- and gender-matched control group. Results indicated that the females with FXS had a significantly higher skin conductance range at initial baseline compared to the CA-matched controls, but not compared to the females with Turner syndrome; and no other significant differences were observed between the FXS group and the Turner syndrome or CA-matched control group. The researchers suggested, however, that the lack of any increased arousal in the FXS group during performance of the cognitive tasks could be accounted for by the hyperarousal observed at baseline (Keysor et al., 2002). Interestingly, heart rate studies have also reported similar findings of increased arousal at baseline in young males and females with FXS (Hall et al., 2009; Roberts et al., 2001). For example, Hall et al. (2009) reported increased heart rate at baseline *and* during a social interaction task in their large sample of males and females with FXS, compared to a gender-matched sibling control group (Hall et al., 2009). This hyper-reactivity was observed in addition to, but was not associated with, eye gaze aversion. Farzin et al. (2009, 2011) have also reported increased pupillary reactivity, another index of ANS activity, in both males and females with FXS compared to CA-matched controls when the participants passively viewed emotional faces (Farzin et al., 2009, 2011). In contrast to Hall et al. (2009), however, this increased pupillary response was significantly associated with eye gaze aversion in the FXS group, but not the CA-matched control group (Farzin et al., 2009).

Together, these previous psychophysiological studies indicate that individuals with FXS display significant hyper-reactivity compared to CA-matched controls (e.g., Farzin et al., 2009; Miller et al., 1999). Some of these studies also suggest that this autonomic hyperarousal in FXS can be seen at baseline (Hall et al., 2009; Keysor et al., 2002; Roberts et al., 2001), as well as when responding to both social (Farzin et al., 2009, 2011; Hall et al., 2009) and non-social (Hagerman et al., 2002; Miller et al., 1999) stimuli. However, findings regarding hyperarousal in FXS individuals compared to mental age-(MA-) or IQ-matched controls are less conclusive; and previous studies have neglected to include both a CA- and a MA-matched control group for better comparison. Furthermore, no study to date has directly compared SCRs to different types of arousing stimuli in the same participants, thus making it difficult to conclusively determine whether any apparent hyper-reactivity observed in FXS individuals is stimulus-dependent, in particular, more associated with social stimuli, or, instead, stimulus-independent, and thus a chronic feature of FXS. The current study aimed to address these issues.

1.2. Study predictions

We recorded SCRs while a FXS group and both a CA- and a MA-matched control group were presented with two sets of visual images of arousing stimuli, one of which is considered to be more socially salient than the other. That is, one set contained images of faces with direct eye-gaze and the other set contained affectively arousing scenes, which occasionally depicted people's bodies but none of which depicted direct faces.[1] It was hypothesised that the FXS group would display significantly larger SCR magnitudes and increased SCR frequencies compared to both control groups, irrespective of the stimulus set. However, we also predicted that these differences between groups would be more marked for the direct-gaze faces compared to the affective scenes. Thus, we hypothesised that, while the FXS group would display generalised hyper-reactivity, this would be particularly heightened when the participants viewed more socially salient information.

Additionally, based on the emerging evidence of emotion recognition difficulties in FXS, we also manipulated the emotion within each stimulus set. That is, the direct-gaze faces varied with respect to emotional expression (angry, disgusted, fearful, happy, sad and neutral) and the affective scenes varied in the emotional state being elicited. We predicted that females with FXS may display larger SCRs for negative faces and scenes relative to controls. Furthermore, possible group differences in subjective ratings of both the direct-gaze emotional facial expressions and the emotions evoked by affective scenes were also examined; and it was predicted that the FXS group would display significant emotion recognition difficulties for ambiguous and negative emotional expression as seen in previous studies.

2. Materials and method

2.1. Participants

Participants were 12 females with FXS, 12 CA- and gender-matched typically developing controls, and 12 MA- and gender-matched typically developing controls. All participants displayed normal or corrected to normal vision.

2.1.1. Fragile X syndrome (FXS) participants

FXS participants were recruited through the Fragile X Association of Australia, the Western Australian Fragile X Support Group and the GOLD Service, Hunter Genetics. All FXS participants exhibited the medical and clinical phenotype associated with FXS, had a clear family history of X-linked inheritance, and had previous genetic testing to confirm the FXS diagnosis (6 Southern Blot, 6 Cytogenic). FXS participants were screened for a history of neurological compromise that was not a part of their FXS profile (e.g. brain injury). MA and IQ were established using the Wechsler Abbreviated Intelligence Scale (WASI; Psychological Corporation, 1999). As can be seen from Table 1, the average FSIQ of our

[1] We initially aimed to have all affective scenes contain no social information; however, this proved to be difficult for specific affective categories (e.g., sad and happy) when trying to choose images that suited individuals across the lifespan. A total of 29% of our affective images contained some degree of social information, with the sad affective image set containing the majority (77%). There was a mean of 1.86 prominent people per scenes that included social information. Importantly, no affective images contained faces with direct-gaze.